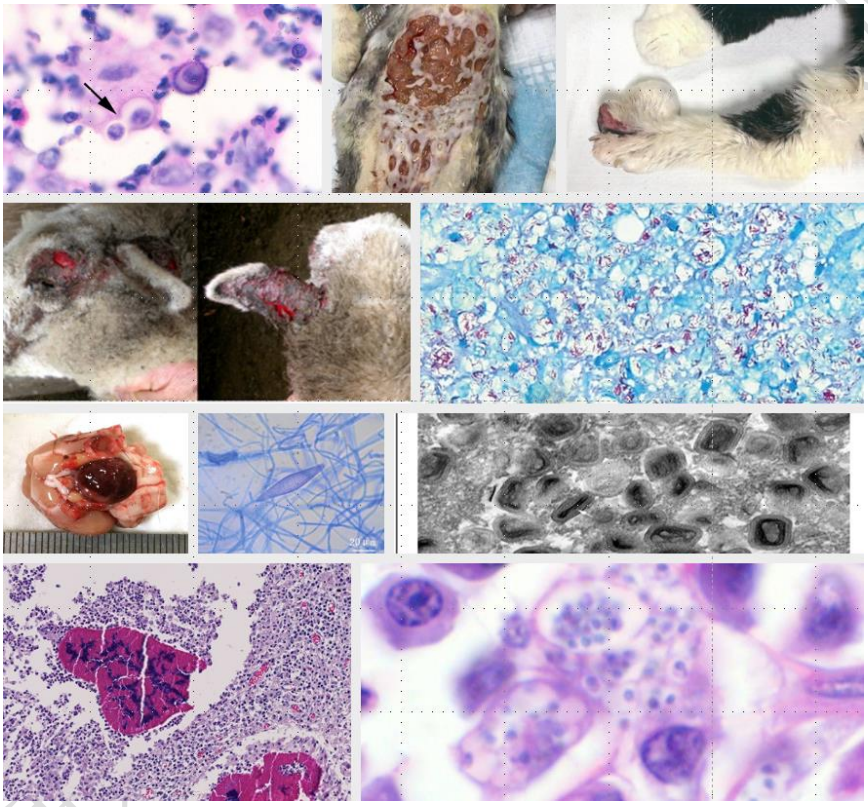
2022 年度第 31 次实验病理学公益网络学习会

第十次比较病理学讨论会-皮肤及乳腺疾病专题

Proceedings of the 10th Comparative Pathology Conference

Diseases of skin and mammary glands



日期: 2022 年 7 月 2 日 (星期六)

时间: 8:25-18:00

主办: 中国毒理学会毒性病理学专委会，深圳市专家人才联合会，广东省药品监督管理局实验病理学重点实验室，深圳市实验动物管理委员会

承办: 深圳市药品检验研究院

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承办: 深圳市药品检验研究院

议程表		
8:25-8:30	开幕致词	
8:30-9:00	病例 83	CP2022-83（高俊，四川省疾病预防控制中心）
9:00-9:30	病例 84	CP2022-84（陈会丛，同仁堂研究院）
9:30-10:00	病例 85	CP2022-85（裴天仙，天津药物研究院）
10:00-10:30	病例 86	CP2022-86（王彦武，广西壮族自治区疾病预防控制中心）
10:30-11:00	病例 87	CP2022-87（杨洪宝，中国药科大学新药安评中心）
11:00-11:30	病例 88	CP2022-88（英永，山东省药学科学院新药安评中心）
11:30-12:00	病例 89	CP2022-89 （冯雪建，郑州大学药物安全性评价研究中心）
12:00-13:30	午休	
13:30-14:00	病例 90	CP2022-90 (陈云珂，中国农大动物医院）
14:00-14:30	病例 91	CP2022-91 (马莹，吉林大学动物医学院)
14:30-15:00	病例 92	CP2022-92（张兴娟，山东牧业经济学院）
15:00-15:30	病例 93	CP2022-93（吴彩霞，广东省科学院生物与医学工程研究所）
15:30-16:00	病例 94	CP2022-94（张卓，哈尔滨兽医研究所）
16:00-16:30	病例 95	CP2022-95 (李一帆，中国农大动物医院）
16:30-17:00	病例 96	CP2022-96 (李浩运，中国农大动物医院）

17:00-17:30	病例 97	CP2022-97 (金毅，深圳市药品检验研究院/深圳市医疗械检测中心)
17:30-18:00	综合讨论	

临床病史摘要

病例 83	CP2022-83（高俊，四川省疾病预防控制中心） 拳师犬（Boxer），雄性，2 岁；体重不足，鼻部平面角化过度，口腔黏膜皮肤交界处溃疡，足部有红斑及水肿病变。 切片连结： https://www.askjpc.org/vspo/show_page.php?id=NEUzY25rSTdpaTBvWEJCWHgwSGZwZz09
病例 84	CP2022-84（陈会丛，同仁堂研究院） 14 月龄纽芬兰犬。 切片连结： https://www.askjpc.org/vspo/show_page.php?id=eGRFOHJ3UkNIYUZVMGtvejhuK01ldz09
病例 85	CP2022-85（裴天仙，天津药物研究院） 动物园 4 周大的雌性火烈鸟，在右侧胫跗关节的皮肤上出现多结节、溃疡、疣状增生，大小约 5 x 4 x 3 厘米。手术切除增生的组织，10%中性福尔马林缓冲液固定，做组织学检查。 切片连结： https://www.askjpc.org/wsco/wsc_showcase2.php?id=OC9CZUdmdHpUUXRMWGI2d3NEWjZEdz09
病例 86	CP2022-86（王彦武，广西壮族自治区疾病预防控制中心） 猫多处多发皮肤结节。 切片连结： https://www.askjpc.org/vspo/show_page.php?id=ZWJQdVBoZVVvSnBUQzhzUUdZNUdNZz09
病例 87	CP2022-87（杨洪宝，中国药科大学新药安评中心） 8 个月大的母羊（白羊）。这只小羊一直生长良好，直到 4 周前才被发现耳朵水肿，白天躺在阴凉处。在接下来的 4 周里，小羊体重逐渐减轻，眼睛周围、双耳背侧和面部的皮肤脱落。主人出于人道的考虑选择安乐死，因为这只小羊没有任何好转的迹象，而且一直在摩擦它的脸和耳朵。 切片连结： https://www.askjpc.org/wsco/wsc_showcase2.php?id=dnc1c0hjOG5Da2FIS3ITa1BJQzRsdz09
病例 88	CP2022-88（英永，山东省药学科学院新药安评中心） 14 岁雌性绝育家养短毛猫。患病动物表现为后肢进行性瘫痪，后脚和面部引流性皮肤损伤。体检时，患畜消瘦（3.08 kg），抑郁沮丧，但对触摸有反应。无法用后肢站立，不发烧。瞳孔大小不等（左侧大于右侧）。后脚足趾均出现非常坚硬的结节性肿胀，几个脚趾末端有很深的溃疡，并伴有血和脓性分泌物。前足也有类似的、不那么明显的结节性溃疡，也累及右上唇。 此外，在左侧第五肋骨和右侧前臂远端及跖骨区域可触诊到坚硬骨性肿块。听诊支气管肺泡音增

	加，弥漫性分布，在右侧颅底和背腹象限尤为明显。。 切片连结： https://www.askjpc.org/wsco/wsc_showcase2.php?id=TlY5OGl4RXM2RUxaVWhKcVZGdU5Odz09
病例 89	CP2022-89（冯雪建，郑州大学药物安全性评价研究中心） Long Evans 大鼠（*Rattus norvegicus*），雌性，18 个月。右侧腋窝皮下有一个大而坚硬的肿块。 切片连结： https://www.askjpc.org/wsco/wsc_showcase2.php?id=K0JRTEJKcUMrRFNC8xT1daK3JTdz09
病例 90	CP2022-90 (陈云珂，中国农大动物医院) 流浪猫，雄性，5 岁，腹部皮肤大面积溃烂，在外院使用头孢类抗生素未见好转，使用糖皮质激素轻度好转，FNA 可见大量退行性中性粒细胞。
病例 91	CP2022-91 (马莹，吉林大学动物医学院) 柯基犬，6 个月零 1 天,雌性，未绝育。主诉近期发现宠物肘部有肿物。刚出生时发生肺炎，带回家中饲养两个多月，咳嗽，拍片诊断为肺炎，进行输液治疗。近期洗澡后，观察到颈部有化脓，将患宠毛发剔除，发现背部有大量脓包（疖子）。中间更换过一次粮，大概半个月时间，最近饮食及精神状态均无异常。于 2021 年 3 月 17 日手术切除皮肤肿物。
病例 92	CP2022-92（张兴娟，山东牧业经济学院） 7 岁奶牛，品种不明，4-5 个月前产下犊牛，此后一直在牧场上。死前无任何征兆。 切片连结： https://www.askjpc.org/wsco/wsc_showcase2.php?id=K0tiRWlob1dTA1Snp0c3BxWXVUZz09
病例 93	CP2022-93（吴彩霞，广东省科学院生物与医学工程研究所） 6 岁雄性恒河猴（*Macaca mulatta*），在右侧乳头附近发现一个皮下肿块。肿块摘除后提交分析。体格检查时未见其他异常。 切片连结： https://www.askjpc.org/wsco/wsc_showcase2.php?id=cElxWnhLOTNNGQzNnNhQThBT3hmdz09
病例 94	CP2022-94（张卓，哈尔滨兽医研究所） 切片 A: 猫，该病例整个乳腺弥漫性肿大。 切片 B (JPC #4154528)：9 岁雌性节育暹罗猫，左乳腺多个链状排列肿物，持续时间未知。 切片连结： https://www.askjpc.org/vspo/show_page.php?id=YlBRNitLN01qTjh1c1SnM5R3Mxdz09

病例 95	CP2022-95 (李一帆，中国农大动物医院) 性 犬，多灶性脱毛、结痂，头部和躯干处的皮肤色素沉着。 切片连结: https://www.askjpc.org/vspo/show_page.php?id=aHltV1lBbFptR1RRMHRrNEpPazBLdz09
病例 96	CP2022-96 (李浩运，中国农大动物医院) 犬，蛋白尿，组织活检于鼻平面。 切片连结: https://www.askjpc.org/vspo/show_page.php?id=anZmeWluTXd4SS9kMk5pbEVDNDF3dz09
病例 97	CP2022-97 (金毅，深圳市药品检验研究院/深圳市医疗器械检测中心) 5 岁，雄性，恒河猴 (*Macaca mulatta*)，非人类灵长类动物。这只猴子于 2005 年 8 月 25 日通过扁桃体途径接种了猴免疫缺陷病毒 (SIVmac239)。感染两周后病毒载量很高。 扁桃体攻击后 25 周，动物出现脓疱性皮疹，全身状况恶化，食欲下降。由于预后不良，这只猴子于 2006 年 2 月 15 日被安乐死。 切片连结: https://www.askjpc.org/wsco/wsc_showcase2.php?id=SUl4cTczYVRhVXViZWxGQnNZbS95QT09

病例 83 CP2022-83

切片原病理编号：(JPC# 2277382)

演讲及翻译人（Presenter and Translator）：

高俊 主管医师 四川省疾病预防控制中心

临床病史(Clinical History)：拳师犬（Boxer），雄性，2 岁；体重不足，鼻部平面角化过度，口腔黏膜皮肤交界处溃疡，足部有红斑及水肿病变。

大体检查(Gross Findings)：无

组织病理学检查(Histopathologic Description)：

切片 A：被覆毛发的皮肤及皮下组织：真皮层可见大量炎细胞弥漫浸润：并向轻度角化过度的表皮延伸；包围、分离和破坏胶原束及其附件；且深入皮下呈多灶性分布；炎细胞种类较多：包括大量吞噬病原体的巨噬细胞、浆细胞、较少的淋巴细胞和嗜酸性粒细胞，偶有多核巨细胞（Langhans 型）。原虫的无鞭毛体常见于组织细胞内，偶见透明寄生泡，少见于细胞外。虫体直径约为 2-3μm，胞浆清亮；单核，嗜碱性，核直径约为 1μm。真皮浅层因水肿及纤维蛋白而呈多灶性轻度扩张，真皮胶原呈多灶性损伤。真皮深层和皮下组织有中度纤维化，及多灶性微小角化过度。脂膜肌中的肌细胞通常体积缩小（萎缩），或肌浆空泡状肿胀（变性），或萎缩伴肌浆嗜酸性变及核固缩（坏死）。

切片 B：被覆毛发的皮肤及皮下组织（Giemsa 染色）：深紫色无鞭毛体大量分布于组织细胞内，细胞外较少；直径 2-3 微米，胞浆清亮；单胞核，其直径为 1 微米，相邻处常有一个体积较小的垂直动基体。

提供者形态学诊断（Morphological Diagnosis）：拳师犬（Boxer），被覆毛发的皮肤及皮下组织(未指定具体部位)：肉芽肿性及浆细胞性皮炎及脂膜炎，查见大量多灶聚集分布于组织细胞内的无鞭毛体，另少量分布于细胞外。

病因学（Etiology）：利什曼原虫（*Leishmania* sp.)

病因学诊断（Etiologic Diagnosis）：皮肤利什曼病（Cutaneous leishmaniasis)

概述（General）：

•由专性细胞内寄生的双相性原生生物引起的具有皮肤及全身表现的人畜共患疾病。

•类：动基体门；锥虫科；

•婴儿利什曼原虫（L.chagasi）最为常见的；还有杜氏利什曼原虫（L.donovani），巴西利什曼原虫（L.braziliensis）

•属于地中海国家、非洲部分地区、印度、中南美洲以及德克萨斯州、俄克拉荷马州、密歇根州和俄亥俄州的地方病

•犬是自然宿主，是人类感染的主要家庭宿主

•疾病的三种形式：皮肤性、黏膜性以及内脏性；犬通常只有皮肤和内脏表现，类似于组织胞浆菌病
•利什曼病通常与其他皮肤病相关，如机会性感染（细菌性、蠕形螨病）、自身免疫性疾病或肿瘤；利什曼原虫感染可引起免疫功能障碍；
•在纤维肉瘤、T 细胞淋巴瘤、犬阴道传染性性病肿瘤和肾上腺皮质腺瘤的肿瘤细胞中发现利什曼原虫的无鞭毛体
•其他伴随感染（可能是由于免疫抑制）：埃立克体、巴贝斯体、无浆体、肝簇虫、锥虫、恶丝虫、蠕形螨、疥螨、螺旋体；
•由于细胞介导免疫缺陷，易患全身蠕形螨病
•同时报告有并发自身免疫性疾病（叶状天疱疮、系统性红斑狼疮 SLE）及内分泌疾病（甲状腺功能减退）

发病机制和生命周期（Pathogenesis and Life Cycle）：
• 有鞭毛的纤毛体（前鞭毛体）形式在雌性白蛉（Phlebotomous sp.，Lutzomia sp.）中肠里通过二元分裂进行增殖>白蛉摄食期间的反流将前鞭毛体转移到宿主皮肤>前鞭毛体被巨噬细胞吞噬>在吞噬细胞中以无鞭毛的无鞭毛体繁殖（利什曼原虫形式），可将其与宿主细胞防御机制分离>巨噬细胞破裂（增殖的机械后果）>释放的无鞭毛体穿透宿主细胞，主要通过血液淋巴系统传播>白蛉从受感染的宿主身上吸食血液>摄取含有无鞭毛体的单核细胞> 无鞭毛体转化为有鞭毛的前鞭毛体
• 感染后 3 个月至 7 年可能出现临床症状
• 感染的结果取决于宿主的免疫反应、遗传背景和并发症；
• 主要的细胞介导免疫反应：通常无症状——对感染（通过细胞介导的免疫机制从体内清除的寄生虫）的抵抗力依赖于 TH1（IL-2、IFN-γ、TNF-α）
•无毛型的生物体较少，与 TH1 反应有关
• 主要的体液反应：通常有症状
- 易感染：TH2 依赖性 (IL-4)
• B 细胞活化>以 IgG 为主>杀虫率低且寄生虫负荷较高；+/-抗原：抗体复合物（III 型超敏反应）
• 结节型含有大量巨噬细胞，及大量病原体，与 TH2 反应有关
• 保护性免疫很可能由活化的 T 细胞分泌的 TNF-a、IL-2 和 IFN-y 介导，通过产生一氧化氮上调巨噬细胞的抗利什曼原虫活性，一氧化氮负责通过启动细胞凋亡杀死寄生虫
• 受感染的巨噬细胞也会被 $CD8^+$ 细胞毒性 T 细胞在组织兼容性复合物受限的过程中裂解，这种过程可以在具有高寄生虫负荷的有症状犬中得到抑制；
• 伴随免疫复合物沉积的 III 型超敏反应历来被认为是肾小球肾炎（以及多发性关节炎、血管炎、葡萄膜炎）的主要机制，但有证据表明 $CD4^+$ T 细胞的迁移和粘附分子表达增加（如 ICAM-1 和 P-选择素）也参与其中；
• 在寒冷的天气中，可能会产生冷球蛋白，沉淀在四肢血管中；导致缺血性坏死
• 临床症状是由于肉芽肿性炎症（例如结节性皮炎）、自身抗体（例如免疫介导的血小板减少症）、抗组蛋白抗体（例如肾小球肾炎）和/或循环免疫复合物（例如关节炎）的产生

•多诺瓦尼乳杆菌（L. donovani）需要主动转运质子外排泵（LDH1A 和 LDHIB），才能在巨噬细胞吞噬体空泡的酸性环境中存活，并维持营养素摄取的电动氢梯度
•传播：
• 雌性白蛉的叮咬（Phlebotomous sp.、Lutzomia sp.）
• 机械载体
• 输血
• 垂直、子宫内传播
•已有从受感染的雄犬到健康雌犬的性病传播的记录
•寄生虫载量、组织病理学变化的严重程度和免疫检测之间存在相关性（Silva 等人，J Comp Pathol 2019）

典型临床表现(Typical Clinical Findings)：
• 无痛、无瘙痒、全身性、干性剥脱性皮炎伴脱发、反复眼鼻分泌物、鼻痂、鼻衄
• 全身症状：发烧、嗜睡、恶病质、身体状况不佳、毛发粗糙、腹泻、淋巴结肿大、脾肿大
• 最常见的实验室检查结果是高蛋白血症伴高丙种球蛋白血症和低白蛋白血症； 还有蛋白尿、氮质血症、ALP 和 ALT 升高、轻度非再生性贫血、淋巴细胞减少
• 已显示由于利什曼原虫感染导致肾损伤的犬的尿凝聚素（一种糖蛋白生物标志物）增加（Garcia-Martinez，J Vet Diagn Invest 2012）
• 超过 80% 的犬会出现皮肤损伤，内脏受累
• 皮损通常是全身性的而不是局部的

典型的大体表现（Typical Gross Findings)：
皮肤：
• 脱发、溃疡、结节或脓疱
• 剥脱性皮炎伴银白色鳞屑
• 口吻、眶周（“眼周月牙”）和听觉区域（白蛉觅食区）最严重； 结节性黏膜利什曼病也有报道
• 淋巴结病
• 棘爪畸形（肥大和爪弯曲度增加）伴轻度至重度苔藓样和界面性单核细胞皮炎
内脏：
• 全身淋巴结肿大、肝脾肿大
• 肝脾肿大，呈深褐色； 肝脏含有大量肉芽肿
• 肾脏通常轮廓正常但比正常颜色深
• 犬的结节性和溃疡性口腔病变（Blume 等人，J Comp Pathol 2019）
• 病例报告：法国斗牛犬的喉肉芽肿（Torrent 等人，J Comp Pathol 2018）

典型的临床病理表现（Typical Clinical Pathology Findings）
• 巨噬细胞为主，但可能存在淋巴细胞、浆细胞和偶尔出现的多核巨细胞
• 细胞内无鞭毛体约为 1.5 *2.5-5.0μm，具有红色的细胞核和特征性的条形

动基体。
- 骨髓和淋巴系统受累常见
- 可能患有多克隆或单克隆丙种球蛋白病和非再生性贫血

典型的光镜检查结果（Typical Microscopic Findings）：
- 在巨噬细胞（偶有其他白细胞、内皮细胞、成纤维细胞或肿瘤细胞）中发现无鞭毛体阶段，在 50% 的病例中发现细胞外无鞭毛体阶段：圆形至椭圆形，直径 2-4μm，具有棒状的动基体（巨型线粒体），据报道，它的方向垂直于细胞核；当在细胞内时，无鞭毛体通常位于寄生空泡内

皮肤：
- 角化过度角化和毛囊角化，结节性至弥漫性，浅表和深部脓性肉芽肿到肉芽肿性浆细胞性皮炎
- 炎症模式可能是血管周围、滤泡周围或间质，有体积较大的泡沫状巨噬细胞（其内含有大量虫体）和少量淋巴细胞；或有大量淋巴细胞和浆细胞（由于 CMI 反应所致）
- 溃疡性皮炎，病变边缘有表皮增生及中性粒细胞浸润；巨噬细胞、淋巴细胞、中性粒细胞和嗜酸性粒细胞比例不等的弥漫性皮炎

内脏：
- 广泛的浆细胞、淋巴细胞或组织细胞炎症，其中脾脏、肝脏、淋巴结最严重
- 肾脏：系膜增生性或膜增生性肾小球肾炎和间质性肾炎是内脏利什曼病最常见的肾脏表现（Aresu 等人，Vet Pathol 2013）
- 心脏：一项研究发现，利什曼病犬普遍存在心脏病变，如淋巴浆细胞性或肉芽肿性心肌炎（尤其是右心房）、心肌坏死和间质胶原增加（即使没有心脏病的临床症状）（Rosa Vet Pathol 2014）
- 肌肉：单核性肌炎、肌坏死、纤维化
- 眼部炎症/生物体：结膜、角膜缘、睫状体、虹膜、角膜、巩膜
- 中枢神经系统：脑膜脑炎、血管炎、脊髓炎的罕见报告

超威结构（Ultrastructure）：
- 无鞭毛体，通常在寄生泡内，呈卵圆形，具有双膜结合核
- 动基体（线粒体复合体）通常垂直于细胞核

其他诊断测试（Additional Diagnostic Tests）：
- 淋巴结或骨髓涂片；活检；免疫组化；原位杂交；皮内皮试；
- 白蛉优先觅食地点的无鞭毛体负荷疑似增加；口吻皮肤的活检可能具有最高的寄生虫载量
- 骨髓细胞块技术
- 骨髓离心，细胞沉淀后固定，石蜡包埋，类似组织标本一样处理。然后进行组织学和免疫组化 IHC。 （梅内塞斯等人，2016）
- Giemsa：将细胞质染成蓝色、细胞核染成红色和动基体染成紫色
- 血清学上的抗利什曼原虫抗体（IFA、ELISA）
- 利什曼原虫 IHC：抗原（Casanova 等人，J Comp Pathol 2019）
- 聚合酶链反应

鉴别诊断（Differential Diagnosis）：

大体：

- 疥癣（I-P06）、蠕形螨（I-P07）、皮脂溢、叶性天疱疮（I-M26）、皮肤/系统性红斑狼疮（I-M28）、细菌感染、浅表坏死性皮炎（I-M16）、锌反应性皮炎（I-M18）、肿瘤

显微镜下观：

- 克氏锥虫（C-P06，组织期/无鞭毛体形式）：心肌细胞内的无鞭毛体；有趣的是，动基体倾向于平行于细胞核平行
- 荚膜组织胞浆菌：2-5μm，细胞内，窄基出芽；主要是组织细胞炎症
- 弓形虫：2-6μm 速殖子；坏死
- 犬新孢子虫（I-P17）：4-7μm 速殖子
- 新型隐球菌（I-F08）：2-20μm，粘液胭脂红阳性荚膜
- 皮炎芽生菌（I-F06）：10-20μm，广泛出芽
- 申克孢子丝菌（I-F07）：4-10μm，椭圆形至雪茄状

比较病理学（Comparative Pathology）：

- 野生啮齿动物：人类皮肤/粘膜皮肤形式的宿主
- 野生犬科动物（狐狸和豺狼）：人类内脏形态的主要宿主
- 猫、马、骡子、驴和负鼠：易感，但被认为是偶然宿主——罕见，病变类似于犬；耳廓、头部和颈部结痂、溃疡结节；肉芽肿性、淋巴浆细胞性皮炎
- 野生动物：在狼、麝猫、圈养红袋鼠、蹄兔、蝙蝠鬣狗、蝙蝠和刺猬也有报道（Terio 等人，eds，2018）。

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表 1：切片 A

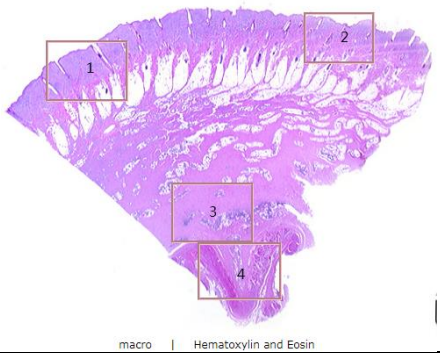	
图 1. 皮肤，拳师犬	

被覆毛发皮肤的亚大体视图。 HE ｜ macro	
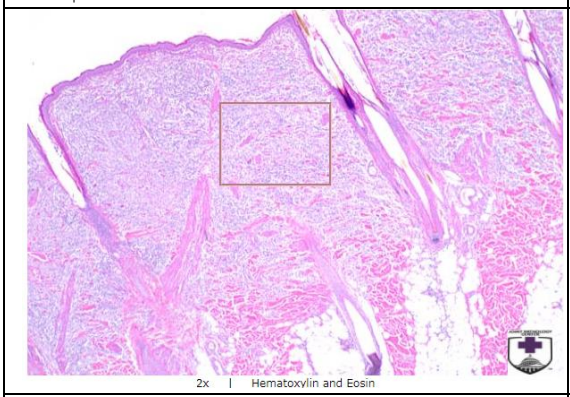	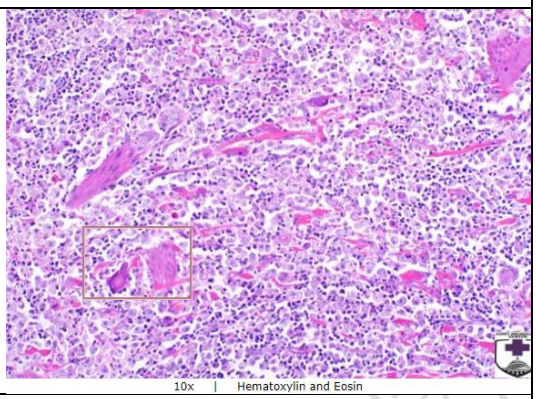
图 2. 皮肤，拳师犬 视野 1：浅层真皮因细胞浸润而扩张，细胞浸润分离并包围毛囊并取代皮脂腺。HE ｜ 2X	图:3. 皮肤，拳师犬 视野 1：炎细胞分离并包绕胶原纤维。HE ｜ 10X
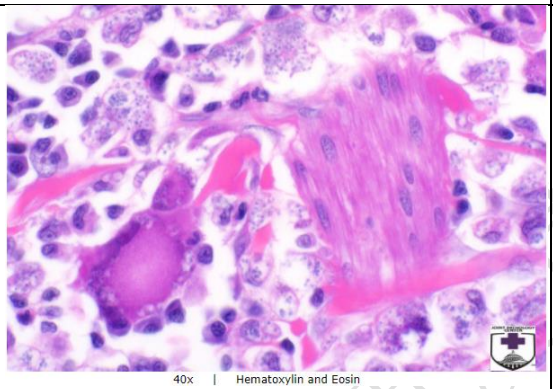	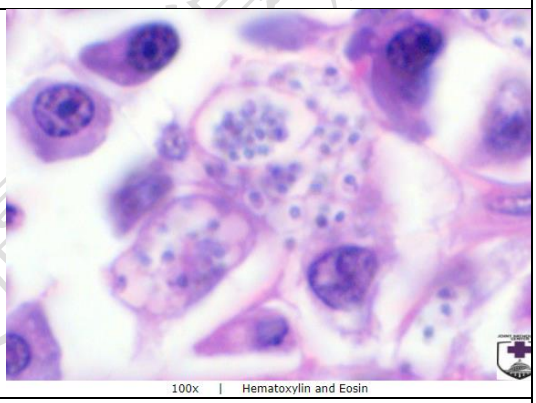
图 3. 皮肤，拳师犬 视野 1：平滑肌束旁边的多核巨细胞（朗汉斯型）。 许多巨噬细胞内充满了直径为 2-3 微米的原生动物。 HE ｜ 40X	图 4 皮肤，拳师犬 视野 1：巨噬细胞的细胞质中充满了直径为 2-3um 的无鞭毛体，其外壁清晰，核呈嗜碱性。 HE ｜ 100X
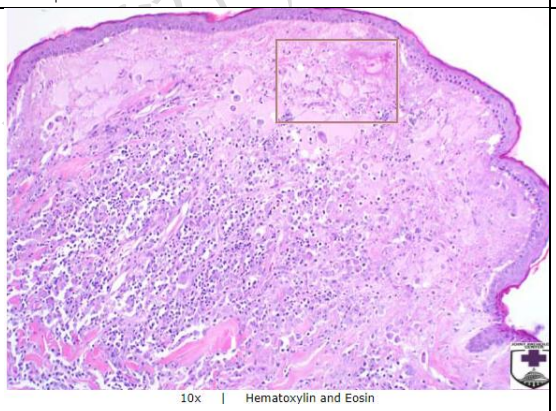	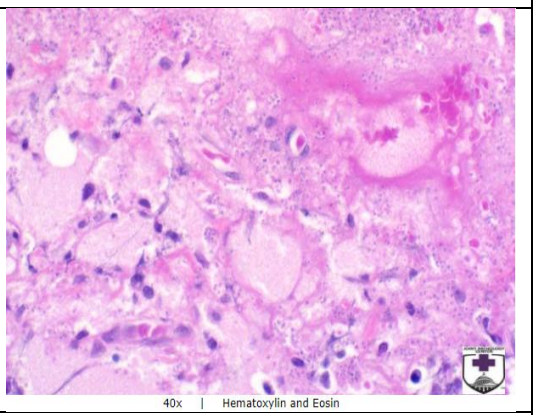
图 5. 皮肤，拳师犬 视野 2：表皮失去了各层结构，并有细胞浸润。HE ｜ 10X	图 6. 皮肤，拳师犬 视野 2：真皮浅层坏死，伴有溶细胞性和核裂性碎片。HE ｜ 40X

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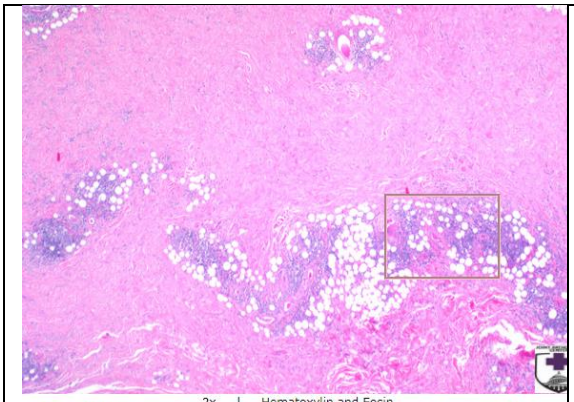
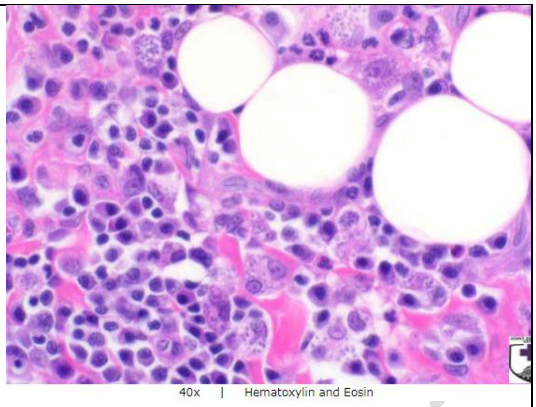
<tr><td> 
</td><td> 
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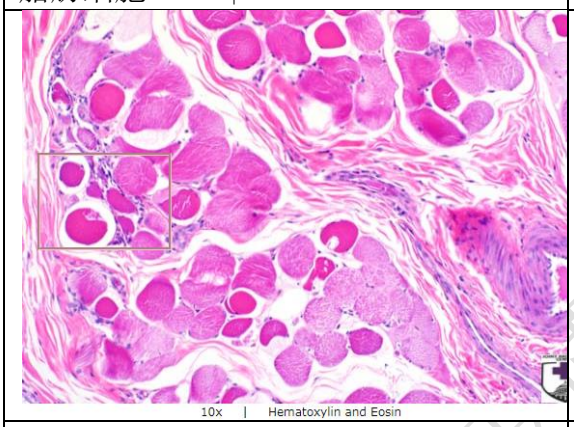
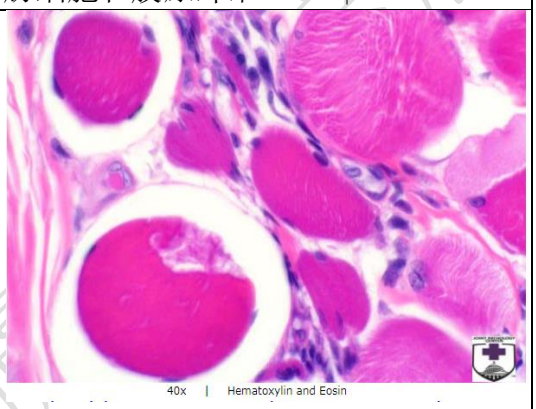
<tr><td>图 7. 皮肤，拳师犬
视野 3：炎症包绕脂肪脂膜和真皮的脂肪细胞。HE ｜ 2X</td><td>图 8. 皮肤，拳师犬
视野 3：巨噬细胞和浆细胞围绕着脂肪细胞和胶原纤维。HE ｜ 40X</td></tr>
<tr><td> 
</td><td> 
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<tr><td>图 9. 皮肤，拳师犬
视野 4：个别肌肉纤维呈明显的嗜酸性，偶被炎症包围。HE ｜ 10X</td><td>图 10. 皮肤，拳师犬
视野 4：肌纤维透明化，横纹缺失和细胞质空泡化。肌纤维之间可见巨噬细胞和淋巴细胞。HE ｜ 40X</td></tr>
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以上图片均来自
JPC SYSTEMIC PATHOLOGY INTEGUMENTARY SYSTEM October 2019 I-P15

表 2：利什曼原虫症（Leishmaniasis）

病原特性：病原体是利什曼属（Leishmania spp.）的原虫类引起，已知的三十种中约有 21 种可同时感染人和动物，种类繁多且形态学上无法区分，故实用上以临床症状分类：

分型	地理分布	保虫动物
皮肤型 （cutaneous Leishmaniasis ）	地中海沿岸、非洲、中东地区及中南美洲	沙鼠为保虫宿主
黏膜皮肤型 （mucocutaneous Leishmaniasis）	中南美洲的森林地区	狗、森林中的啮齿类和哺乳类动物
内脏型 （visceral Leishmaniasis）	印度、孟加拉国、尼泊尔、苏丹和巴西，为 90%以上的病例发生地	动物宿主（犬科、鼠类），在苏丹，鼠类为主要宿主；东非则为松鼠

其中由杜氏利什曼原虫（Leishmania donovani）感染引起的内脏利什曼病，临床上以长期不规则发热、消瘦、肝脾肿大（脾大更显着）、全血细胞减少及血清球蛋白增多为特征，此外，可出现面部、手、足及腹部皮肤色素沉着为特征，又称黑热病（Kala-azar）；

以上内容来自于：

刘振轩等主编《人畜共通传染病临床指引》第二版

李兰娟等主编《传染病》第 9 版 人卫出版社

利什曼病流行分布（世界）：亚洲主要流行于印度、中国、孟加拉国和尼泊尔；东非、北非、欧洲的地中海沿岸地区及国际；中亚、中南美洲部分国家；	利什曼病流行分布（中国）：1949 年以前，我国流行广泛；近年来，主要发生于新疆、内蒙古、甘薯、四川、陕西、山西 6 个省、自治区；

表 7-1 常见医学原虫及其分类

纲(Class)	目(Order)	科(Family)	虫种	主要寄生部位
动鞭纲	动基体目	锥虫科	杜氏利什曼原虫	单核吞噬系统
Zoomastigophora	Kinetoplastida	Trypanosomatidae	*Leishmania donovani*	
			热带利什曼原虫	
			Leishmania tropica	
			巴西利什曼原虫	
			Leishmania braziliensis	
			布氏冈比亚锥虫	
			Trypanosoma brucei gambiense	
			布氏罗得西亚锥虫	
			T.brucei rhodesiense	
	毛滴虫目	毛滴虫科	阴道毛滴虫	泌尿生殖道
	Trichomonadida	Trichomonadidae	*Trichomonas vaginalis*	
			口腔毛滴虫	口腔
			Trichomonas tenax	
			人毛滴虫	肠
			Trichomonas hominis	
			脆弱双核阿米巴	
			Dientamoeba fragilis	

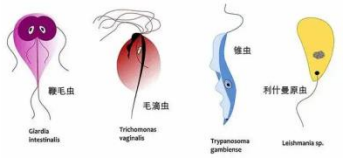

图 1：利什曼原虫：属动鞭纲 动基体目 锥虫科；

该图来自于人卫的《人体寄生虫学》（第 8 版）

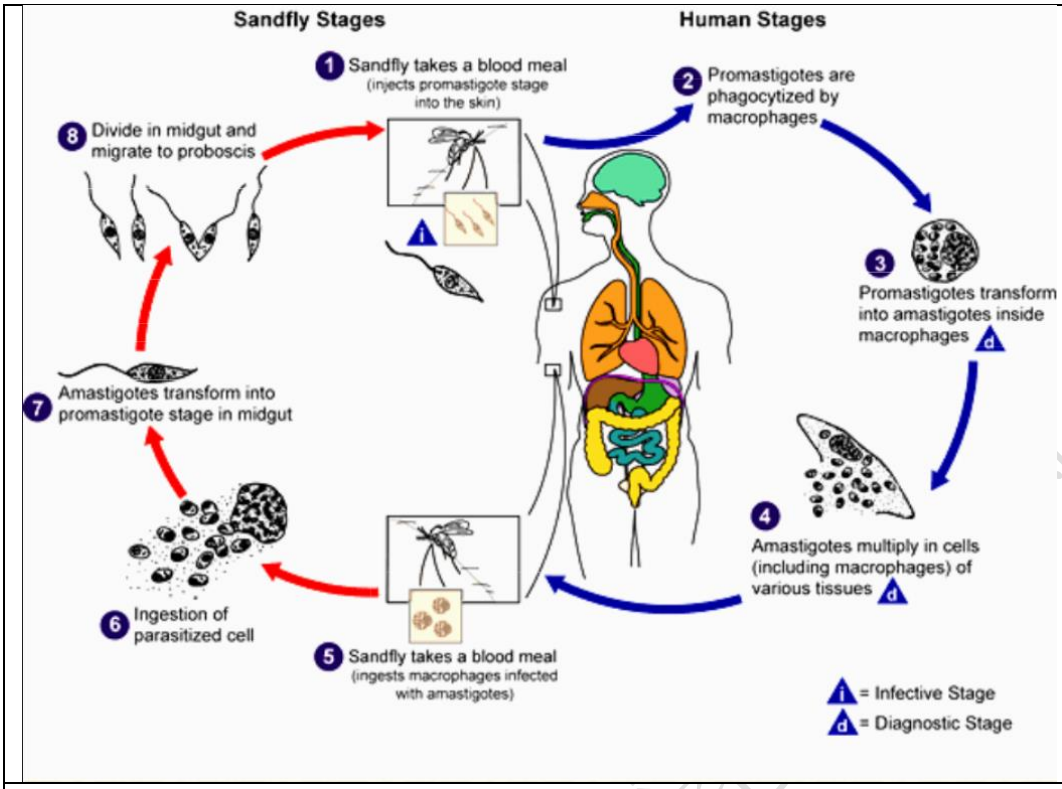

图 2：利什曼原虫生活史:白蛉体内（红色箭头）；病人及保虫宿主体内（蓝色箭头）；该病主要传染媒介为白蛉，蜱和其他蚊虫类可造成机械性传播；（图片来自于 courtesy of CDC/Alexander J.da Silva,PhD/Melanie Moser）

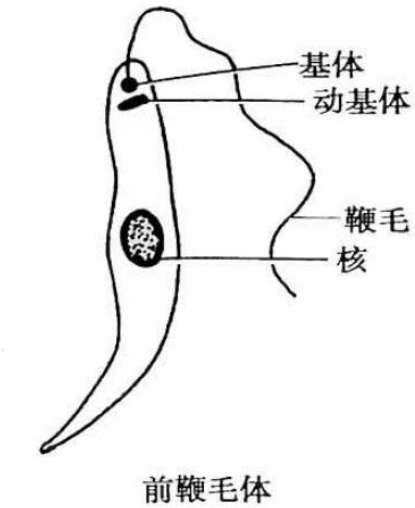

图 3：利什曼原虫前鞭毛体简图：虫体呈梭性，大小 14.3-20）μm*（1.5-1.8）μm，核位于虫体中部，动基体在前部，基体发出一鞭毛，长与虫体相近，弯曲。（Sandfly stage）
（图片来自于网络）

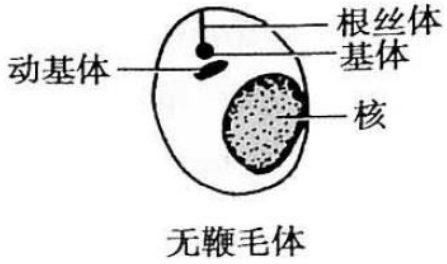

图 4：利什曼原虫无鞭毛体（利杜体）简图：卵圆形，（2.9-5.7）μm*（1.8-4.0）μm，大而圆细胞核，动基体位于核旁，细小、杆状；（Human stage）
（图片来自于网络）

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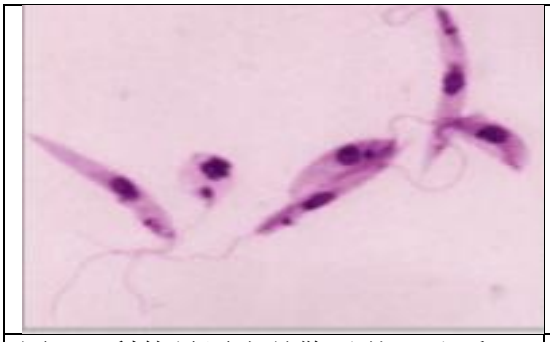
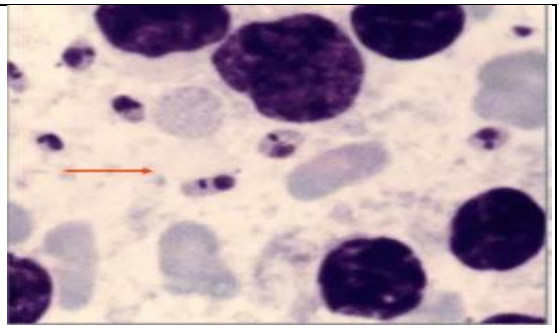
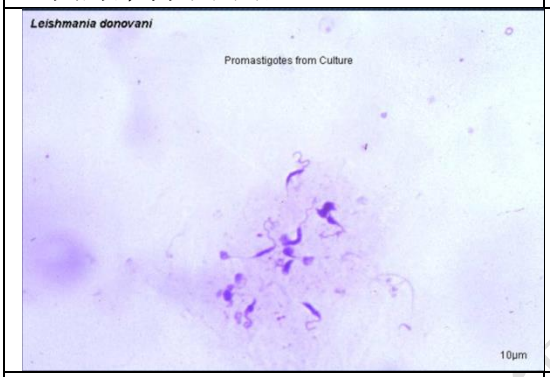
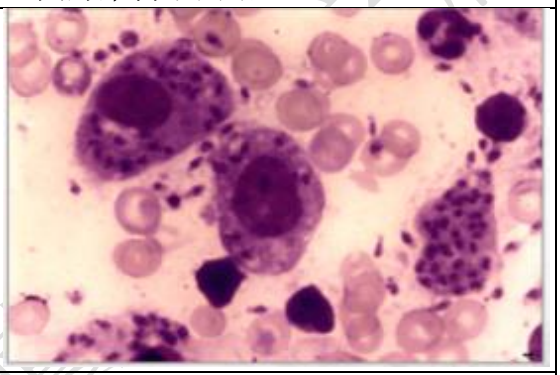
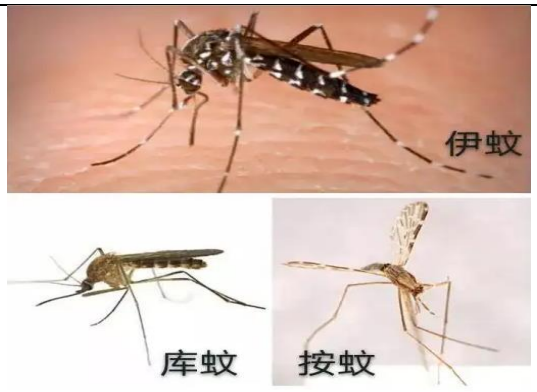
<tr><td>  </td><td>  </td></tr>
<tr><td>图 5：利什曼原虫前鞭毛体：胞质呈蓝色，核呈紫红色；（Sandfly stage）
Giemsa 染色。
（图片来自于网络）</td><td>图 6：利什曼原虫无鞭毛体（利杜体）胞质淡蓝色，核呈红色或紫红色，动基体紫红色；（Human stage）
骨髓涂片 Giemsa 染色。
（图片来自于网络）</td></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td>图 7：利什曼原虫前鞭毛体（Sandfly stage）。
（图片来自于网络）</td><td>图 8：利什曼原虫无鞭毛体（利杜体）无鞭毛体寄生于人和其它哺乳动物单核巨噬细胞内（Human stage）。
（图片来自于网络）</td></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td>图 9：白蛉（Sandfly）
（该图片来自于网络）</td><td>图 10：常见三类蚊：伊蚊、库蚊、按蚊
（图片来自于网络）</td></tr>
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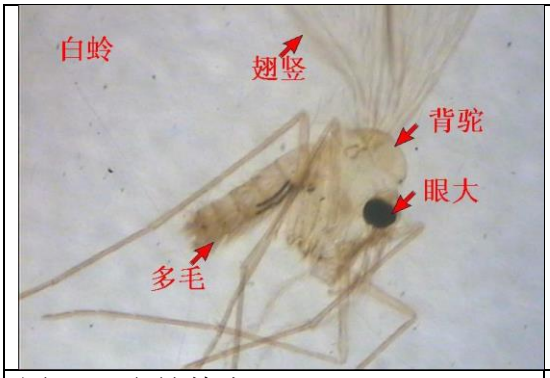
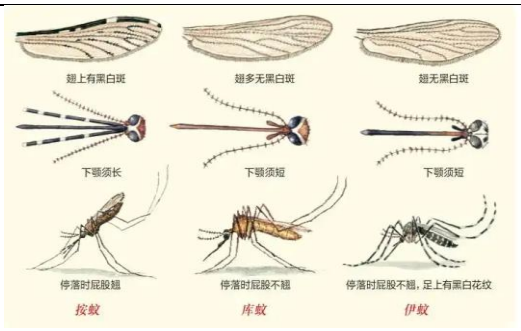
<tr><td> 
</td><td> 
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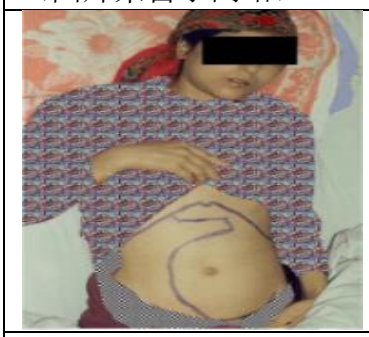
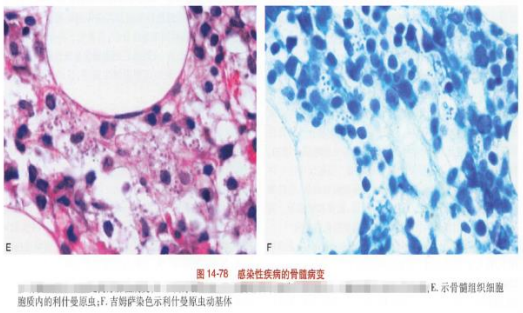
<tr><td>图 11：白蛉特点
（图片来自于网络）</td><td>图 12：常见三类蚊的特点
（图片来自于网络）</td></tr>
<tr><td>  </td><td> 
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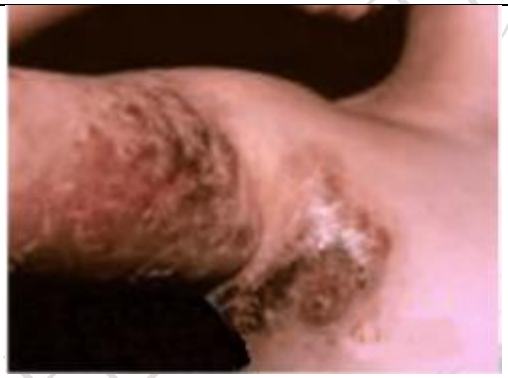
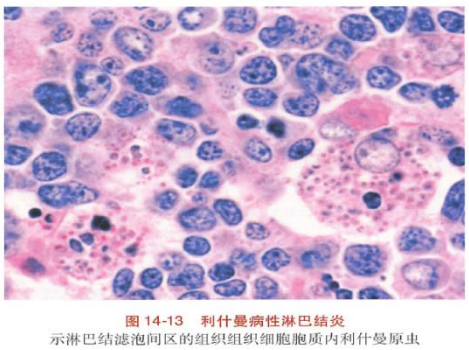
<tr><td>图 13：内脏利什曼病（黑热病）的肝脾肿大；其临床三大特点：
1、长期不规则发热；
2、肝脾肿大（脾大更显着）；
3、贫血（全血细胞减少）
（图片来自于网络）</td><td>图 14：人骨髓涂片中利什曼原虫
（图片来自刘彤华《诊断病理》第 4 版）</td></tr>
<tr><td>  </td><td> 
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<tr><td>图 15：黑热病其他临床类型：
淋巴结型黑热病（腋下淋巴结）：腹股沟、股部最常见；其次为颈部及腋下；
（图片来自于网络）</td><td>图 16：人淋巴结中利什曼原虫
（图片来自刘彤华《诊断病理》第 4 版）</td></tr>
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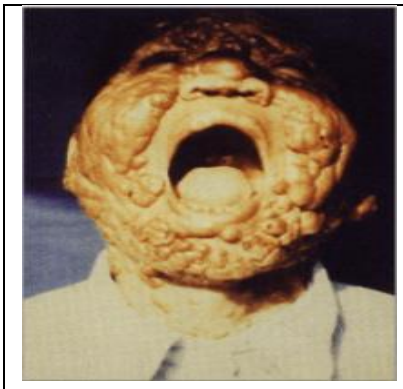	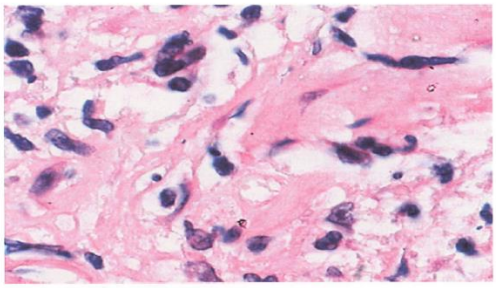 图 19-16 皮肤利什曼病 组织细胞内或外均可见利什曼原虫或利什曼小体，利什曼小体大小为 2～3μm
图 17：黑热病其他临床类型： 皮肤黑热病：多分布于平原地区，多数患者有黑热病史：面部、四肢或躯干等部位出现含有利什曼原虫的皮肤结节，为大小不等的肉芽肿，呈暗色丘疹状，位于面部及颈部，连成片状，酷似瘤型麻风。 （图片来自于网络）	图 18：人皮肤中利什曼原虫。 （图片来自刘彤华《诊断病理》第 4 版）

JPC SYSTEMIC PATHOLOGY
INTEGUMENTARY SYSTEM
October 2019
I-P15

Signalment (JPC# 2277382): Two-year-old male boxer

HISTORY: This dog was underweight and had hyperkeratosis of the planum nasale, ulceration of the oral mucocutaneous junction, and erythematous and edematous lesions on the feet.

HISTOPATHOLOGIC DESCRIPTION: Slide A: Haired skin and subcutis: Diffusely infiltrating the dermis; extending to and elevating the mildly hyperkeratotic epidermis; surrounding, separating, and replacing collagen bundles and adnexa; and multifocally extending deeply into the subcutis are numerous often protozoa-laden macrophages, plasma cells, fewer lymphocytes and eosinophils, and occasional multinucleated giant cells (Langhans type). Protozoal amastigotes are often intrahistiocytic within an occasionally apparent clear parasitophorous vacuole and to a lesser extent free within the extracellular space. They are 2-3 um in diameter with clear cytoplasm and a single 1 um diameter basophilic nucleus. The superficial dermis is multifocally mildly expanded by edema and fibrin, and dermal collagen is multifocally smudged. There is moderate fibrosis within the deep dermis and subcutis. There is multifocal minimal orthokeratotic hyperkeratosis. Myocytes in the panniculus carnosus are often either shrunken (atrophy), swollen with vacuolated sarcoplasm (degeneration), or shrunken with hypereosinophilic sarcoplasm and pyknotic nuclei (necrosis).

Slide B: Haired skin and subcutis (Giemsa): There are numerous intrahistiocytic and fewer extracellular 2-3 um diameter, deeply-purple amastigotes with clear cytoplasm and a 1 um diameter nucleus with a smaller adjacent, often perpendicular kinetoplast.

MORPHOLOGIC DIAGNOSIS: Haired skin and subcutis, site not specified: Dermatitis and panniculitis, granulomatous and plasmacytic, multifocal to coalescing, marked, with numerous intrahistiocytic and fewer extracellular amastigotes, boxer, canine.

ETIOLOGY: *Leishmania* sp.

ETIOLOGIC DIAGNOSIS: Cutaneous leishmaniasis

GENERAL:

Zoonotic disease with cutaneous and systemic manifestations caused by obligate intracellular diphasic protozoa

Class: Kinetoplasta; Family: *Trypanosomatidae*

L. infantum (*L. chagasi*) is the most common; also *L. donovani*, *L. braziliensis*

Endemic in Mediterranean countries, parts of Africa, India, and Central and South America as well as Texas, Oklahoma, Michigan, and Ohio

Dogs are natural hosts and the primary domestic reservoir for human infection

Three forms of the disease: Cutaneous, mucocutaneous, and visceral; **dogs usually only have cutaneous and visceral** manifestations (mimics histoplasmosis)

Leishmaniasis is **often associated with other dermatoses** such as opportunistic infections (bacterial, demodicosis), autoimmune disease or neoplasia; infection with *Leishmania* sp. may induce immune dysfunction

***Leishmania* amastigotes** have been found **within neoplastic cells** of a fibrosarcoma, a T-cell lymphoma, a vaginal canine transmissible venereal tumor, and an adrenocortical adenoma

Other concomitant infections (possibly due to immunosuppression): *Ehrlichia, Babesia, Anaplasma, Hepatozoon, Trypanosoma, Dirofilaria, Demodex, Sarcoptes, Spirocerca*

Predisposed to generalized demodicosis due to cell-mediated immunodeficiency

Also reports of concurrent autoimmune diseases (pemphigus foliaceus, SLE) and endocrinopathies (hypothyroidism)

PATHOGENESIS AND LIFE CYCLE:

Flagellated leptomonad (promastigote) form proliferates via binary fission in the midgut of the female sandfly (*Phlebotomous* sp., *Lutzomia* sp.) > regurgitation during sandfly feeding transfers **promastigotes** to the host skin > promastigotes are phagocytized by macrophages > multiply as **non-flagellated amastigotes (leishmanial form)** within phagolysosomes that separate

them from host cell defense mechanisms > macrophages rupture (a mechanical consequence of proliferation) > freed amastigotes penetrate additional host cells and disseminate primarily through hemolymphatic system> sandfly takes a blood meal from infected host > ingests mononuclear cells containing amastigotes > amastigotes transform into flagellated promastigotes

Clinical signs may develop 3-months to 7-years after infection

The outcome of infection is determined by the host immune response, genetic background and concurrent disease:

Predominant **cell-mediated immune response**:

Usually **asymptomatic** – **resistance** to infections (parasites cleared from the body by cell-mediated immune mechanisms)

is **TH1** dependent (IL-2, IFN-gamma, TNF-alpha)

Alopecic form has fewer organisms & is associated with TH1 response

Predominant humoral response: Usually symptomatic – **susceptible** to infection: **TH2** dependent (IL-4)

B-cell activation > IgG predominates > inefficient killing with higher parasitic burden; +/- antigen:antibody complexes (type III hypersensitivity)

Nodular form has numerous macrophages containing **large numbers of organisms** and is associated with **TH2 response**

Protective immunity is most likely mediated by **TNF-a, IL-2 and IFN-y** secreted by activated T cells to upregulate the anti-leishmanial activity of macrophages through **nitric oxide** production that is responsible for the parasite killing by apoptosis

Infected macrophages are also **lysed by CD8+ cytotoxic T cells** in a histocompatibility complex-restricted process that can be suppressed in symptomatic dogs with a high parasitic load

Type III hypersensitivity with immune complex deposition has historically been accepted as the primary mechanism of glomerulonephritis (and polyarthritis, vasculitis, uveitis), but there is evidence that migration of CD4+ T-cells and increased expression of adhesion molecules such as ICAM-1 and P-selectin are also involved

In cold weather, cryoglobulins may be generated, which precipitate in the blood vessels of the extremities; results in ischemic necrosis

Clinical signs are due to generation of **granulomatous inflammation** (e.g. nodular dermatitis), **autoantibodies** (e.g. immune-mediated thrombocytopenia), **antihistone antibodies** (e.g. glomerulonephritis), and/or **circulating immune complexes** (e.g. arthritis)

L. donovani requires actively transporting proton efflux pumps (*LDH1A* and *LDH1B*) to survive the acidic environment of macrophage phagolysosomal vacuoles and to maintain an electrogenic hydrogen gradient for nutrient uptake

Transmission:

Bite of a female sandfly (*Phlebotomous* sp., *Lutzomia* sp.)

Mechanical vectors (*Rhipicephalus*)

Blood transfusions

Vertical, *in utero* transmission

Venereal transmission from infected males to healthy bitches is documented

There is a correlation between parasite load, severity of histopathologic changes, and immunodetection (Silva et al, *J Comp Pathol* 2019)

TYPICAL CLINICAL FINDINGS:

Non-painful, nonpruritic, generalized, dry exfoliative dermatitis with alopecia, recurrent oculonasal discharge, nasal crusting, epistaxis

Systemic signs: Fever, lethargy, cachexia, poor body condition, rough haircoat, diarrhea, lymphadenomegaly, splenomegaly

Most common laboratory finding is hyperproteinemia with hypergammaglobulinemia and hypoalbuminemia; also proteinuria, azotemia, elevated ALP and ALT, mild nonregenerative anemia, lymphopenia

Urinary **clusterin** (a glycoprotein biomarker) has been shown to increase in dogs with renal damage due to *Leishmania* infection (Garcia-Martinez, *J Vet Diagn Invest* 2012)

Skin lesions occur in over 80% of dogs with visceral involvement

Skin lesions usually generalized instead of local

TYPICAL GROSS FINDINGS:

Cutaneous:

Alopecia, ulcers, nodules, or pustules

Exfoliative dermatitis with silvery-white scales

Most severe on **muzzle, periorbital** ("periocular lunettes")**, and aural regions** (where sandflies feed); nodular mucosal leishmaniasis is also reported

Lymphadenopathy

Oncychogryphosis (hypertrophy and increased curvature of the claws) with mild to severe lichenoid and interface mononuclear dermatitis

Visceral:

Generalized **lymphadenopathy**, **hepatosplenomegaly**

Liver and spleen are enlarged and dark brown; liver contains numerous granulomas

Kidneys usually normal contour but darker than normal

Nodular and ulcerative oral lesions in dogs (Blume et al, *J Comp Pathol* 2019)

Case report: laryngeal granuloma in a French bulldog (Torrent et al, *J Comp Pathol* 2018)

TYPICAL CLINICAL PATHOLOGY FINDINGS:

Macrophages predominate, but lymphocytes, plasma cells, and occasional multinucleated giant cells may be present

Intracellular amastigotes measure approximately 1.5 x 2.5-5.0 um, with red nucleus and characteristic bar-shaped kinetoplasts.

Bone marrow and lymphoid involvement common

May have a polyclonal or monoclonal gammopathy and non-regenerative anemia

TYPICAL MICROSCOPIC FINDINGS:

Amastigote stage found **in macrophages** (and occasionally other leukocytes, endothelial cells, fibroblasts or neoplastic cells), and extracellular in 50% of cases**:** Round to oval, 2-4um in diameter with a rod-shaped **kinetoplast** (giant mitochondria) that is anectdotally reported to be oriented perpendicular to the nucleus; when intracellular, amastigote is typically within a parasitophorous vacuole

Cutaneous:

Orthokeratotic **hyperkeratosis** and follicular keratosis, nodular to diffuse, superficial and deep pyogranulomatous to **granulomatous** to **plasmacytic dermatitis**

Inflammatory pattern may be perivascular, perifollicular, or interstitial composed of large, foamy macrophages with numerous organisms and few lymphocytes or large numbers of lymphocytes and plasma cells (due to effective CMI response)

Ulcerative dermatitis with epidermal hyperplasia and neutrophil exocytosis at the border of the lesion; diffuse dermatitis with macrophages, lymphocytes, neutrophils and eosinophils in variable proportions

Visceral:

Widespread plasmacytic, lymphocytic, or histiocytic inflammation, most severe in spleen, liver, lymph nodes

Kidneys: Mesangioproliferative or membranoproliferative **glomerulonephritis** and interstitial nephritis are the most common renal manifestations of visceral leishmaniasis (Aresu et al, *Vet Pathol* 2013)

Heart: A study found that **cardiac lesions**, such as lymphoplasmacytic or granulomatous myocarditis (especially in the **right atrium**), myocardial necrosis and increased interstitial collagen, are prevalent in dogs with leishmaniasis (even if there are no clinical signs of cardiac disease) (Rosa *Vet Pathol* 2014)

Muscle: Mononuclear myositis, myonecrosis, fibrosis

Ocular inflammation/organisms: Conjunctiva, limbus, ciliary body, iris, cornea, sclera

Central nervous system: Rare reports of meningoencephalitis, vasculitis, myelitis

ULTRASTRUCTURE:

Often within parasitophorous vacuole, amastigote is ovoid with a double membrane-bound nucleus

Kinetoplast (mitochondrial complex) is often perpendicular to the nucleus

ADDITIONAL DIAGNOSTIC TESTS:

Lymph node or bone marrow smears; biopsy; immunohistochemistry; in situ hybridization; intradermal skin test

Amastigote load seems to increase in the preferential feeding sites of sandflies; biopsies of the skin of the muzzle may have highest parasite yield

Bone marrow cell-block technique

Marrow is centrifuged, cellular pellet is fixed, paraffin embedded, and treated like a tissue specimen. Histology and IHC are then performed. (Menezes et al, 2016)

Giemsa: Stains cytoplasm blue, nucleus red, and kinetoplast purple

Anti-*Leishmania* antibodies on serology (IFA, ELISA)

IHC for *Leishmania* spp. antigen (Casanova et al, *J Comp Pathol* 2019)

PCR

DIFFERENTIAL DIAGNOSIS:

Gross:

Sarcoptic mange (I-P06), demodectic mange (I-P07), seborrhea, pemphigus foliaceus (I-M26), cutaneous/systemic lupus erythematosus (I-M28), bacterial infection, superficial necrolytic dermatitis (I-M16), Zn-responsive dermatitis (I-M18), neoplasia

Microscopic:

Trypanosoma cruzi (C-P06, tissue phase/amastigote form): Amastigotes within cardiomyocytes; **anecdotally, kinetoplast tends to be oriented parallel to the nucleus**

Histoplasma capsulatum: 2-5um, intracellular, narrow-based budding; predominantly histiocytic inflammation

Toxoplasma gondii: 2-6um tachyzoites; necrosis

Neospora caninum (I-P17): 4-7um tachyzoites

Cryptococcus neoformans (I-F08): 2-20um, mucicarmine-positive capsule

Blastomyces dermatitidis (I-F06): 10-20um, broad-based budding

Sporothrix schenckii (I-F07): 4-10um, oval to cigar shaped yeast

COMPARATIVE PATHOLOGY:

Wild rodents: Reservoir host for cutaneous / mucocutaneous forms in humans

Wild canids (foxes and jackals): Main reservoirs for visceral form in humans

Cats, horses, mules, donkeys, and opossums: Susceptible but considered accidental hosts – **rare,** lesions similar to those in dog; crusted,

ulcerated nodules on the pinna, head, and neck; granulomatous, lymphoplasmacytic dermatitis

Wildlife: Also reported in wolves, genets, captive red kangaroos, hyrax, bats, and agouti (Terio et al, eds, 2018).

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病例 CP2022-84

简介：芽生菌病(Blastomycosis)

本病又称皮炎芽生菌病(Blastomycosisdermatitidis)、北美芽生菌病(North American blastomycosis)或 Gilchrist 病，系由皮炎芽生菌引起。

皮炎芽生菌系土壤和木材的腐生菌，但是从自然界尚未分离成功。本菌可感染人和低等动物，然尚未见人与人之间的传播。在组织内和 37 ℃下为酵母型，室温下则为菌丝型。

本病见于北美、非洲和以色列等地，中国已见 2 例，1 例在旅居美国时得病，另 1 例原发于四川。

【临床表现】

本病主要侵犯皮肤、肺和骨骼等器官，是一种慢性化脓性肉芽肿性疾病。其感染途径多经由皮肤、呼吸道侵入，进而借血行播散至骨、关节、前列腺、睾丸、中枢神经或皮肤等。临床上可分为:①皮肤芽生菌病;②肺芽生菌病;③系统性芽生菌病。皮肤芽生菌病多继发于肺部病变，偶见原发性，属接种感染。初发皮损呈硬下疳样，渐次形成结节或肉芽肿，常伴发淋巴管炎，似淋巴管型孢子丝菌病。继发性病变常表现为疣状结节或皮下结节，可自行破溃，中央结疤，边缘呈堤状，逐渐向周围扩展，不伴发淋巴管炎。病灶部直接镜检可见直径 8 ~ 15μm 的球形、厚壁、单芽生孢子。

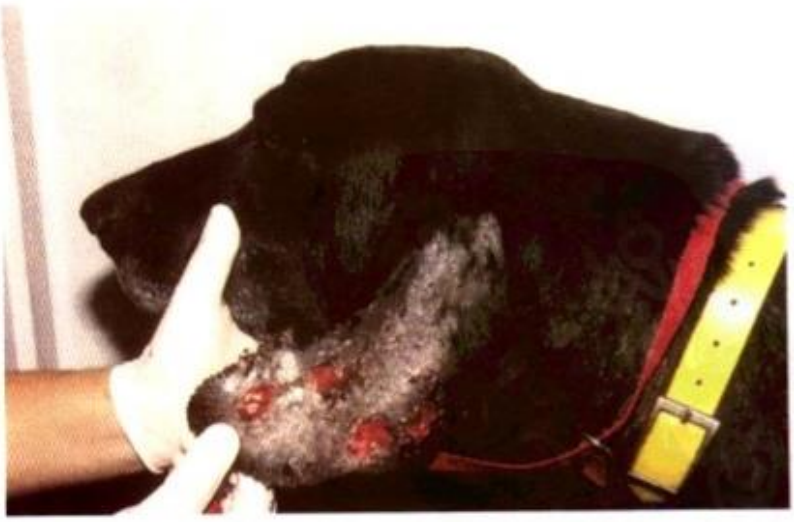
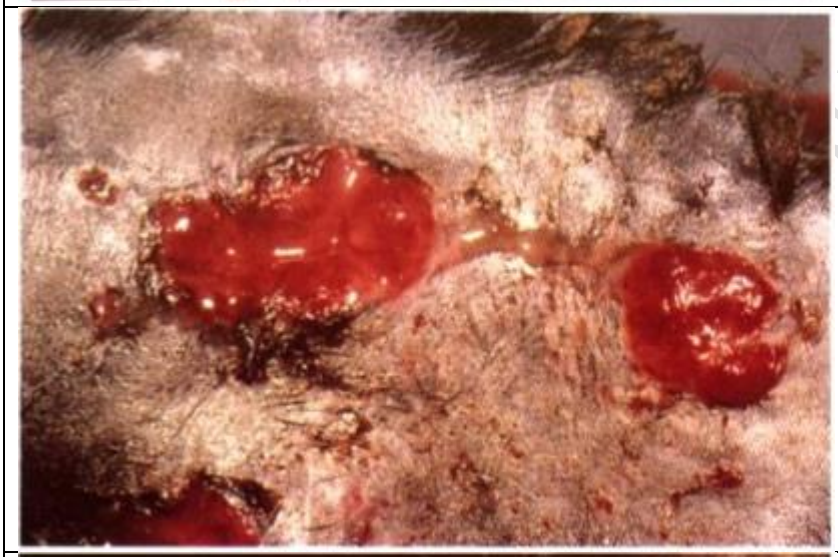
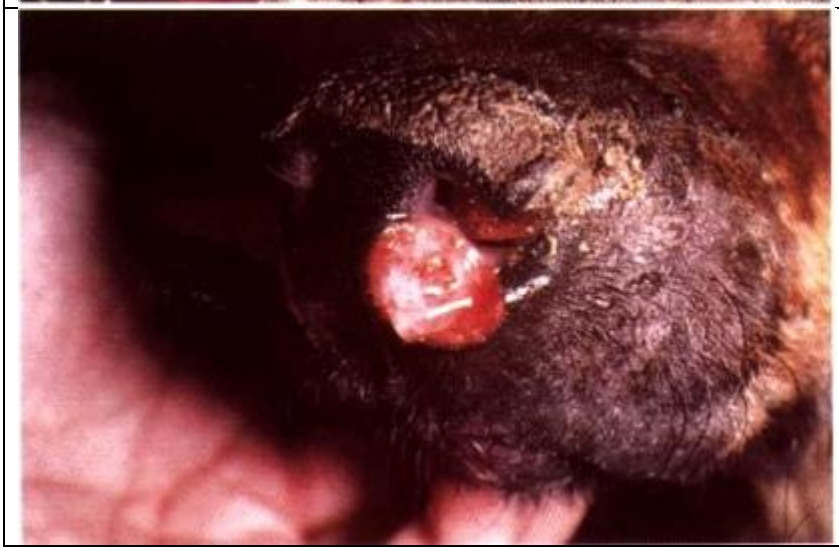
【组织病理】

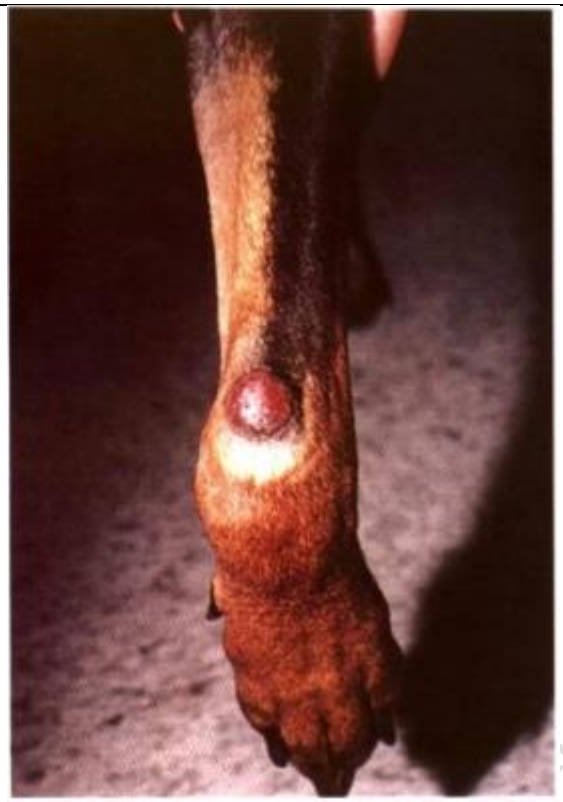
本病的基本病理改变呈现化脓性与肉芽肿性混合型炎症，具体表现视病期和部位而定。疾病早期多见化脓性炎症，有中性粒细胞浸润和脓肿。晚期病变可发展成为混有多核巨细胞的上皮样细胞肉芽肿，限局性，间或融合成不整形，有的伴有干酪样坏死或脓肿。

本病常见棘层肥厚、乳头瘤样增生，并常有表皮内微脓肿。如累及真皮及皮下组织，则可见多形性炎细胞浸润直至肉芽肿形成。在肉芽肿内散在有多个微脓肿。陈旧性病灶中，化脓过程为肉芽肿所取代，伴有轻度纤维化，间或见有结核样结构，然无干酪样坏死。

皮炎芽生菌在组织内的寄生形态表现为圆形或卵圆形酵母细胞，呈双层厚壁，直径 6 ~ 15um，并可见单芽，芽颈较粗。菌体多位于脓肿内或巨细胞中。HE 染色时可发现本菌，呈嗜碱性或双染性，唯菌量少时需作连续切片。PAS 或 Grocott 染色更易查见。特异性免疫荧光、酶标技术对鉴定本菌很有价值。

下表为犬芽生菌病大体所见：

	**芽生菌病** 犬耳廓处有多个破溃病灶（自D.Angarano）
	**芽生菌病** 上图的近观，整个耳廓发生蜂窝织炎和破溃（自D.Angarano）
	**芽生菌病** 犬鼻梁的溃疡病灶（自D.Angarano）



芽生菌病
杜宾犬腕部的单个糜烂性病灶。患部隆起、脱毛。注意该病变与肢端舔舐性肉芽肿相似
（自 D.Angarano）

JPC 系统性皮肤系统病理学 August 2019　I-F06
病例 JPC # 3104239

演讲及翻译人（Presenter and translator）：
陈会丛，同仁堂研究院

特征描述: 14 月龄纽芬兰犬。

病史:无。

组织病理学描述:
A 面:毛皮:真皮多灶性扩张,分离和包围附件结构，并延伸到显着增生和角化过度的表皮,多个合并结节是由大量上皮样巨噬细胞和中性粒细胞与较少的淋巴细胞组成，浆细胞和罕见的嗜酸性粒细胞,常被排列松散的成纤维细胞包围。浸润物内有许多椭圆形，直径 10-20μm，具有 1μm 明显的双层细胞壁和颗粒原生质的酵母，偶尔出现广泛的出芽。上覆上皮明显增生，有许多网状网脊,丰富的基底细胞有丝分裂，中度棘层增生，500 um 厚的角化过度和角化不全过度。炎性结节常将棘层与角质层(表皮内脓肿)分开；可见多灶性角膜内脓疱，由退化的中性粒细胞和坏死碎片组成。多灶性大汗腺扩张，内皮内衬血管轻度肥大(反应性)。

B 面(PAS): 毛皮: 多灶性，有 PAS 阳性 10-20 微米直径的卵圆形酵母，双层细胞壁，真皮和表皮有广泛的基底出芽。

形态学诊断:皮炎，化脓性肉芽肿，多灶性融合，明显，表皮内脓肿，表皮增生，酵母，病因与皮炎芽孢杆菌一致，纽芬兰，犬。

病因诊断: 皮肤芽孢菌病

病因: 皮炎芽生菌

疾病: 芽生菌病

同义词: 吉尔克里斯病，芝加哥病，北美芽孢菌病

常规讨论：

皮炎芽生菌为双相型土壤腐生菌，在土壤中以菌丝形式存在，在组织中以酵母形式存在。

初级致病性双态性真菌：

皮炎芽生菌

粗球孢子菌

荚膜组织胞浆菌

巴西副球孢子菌（巴西芽生菌）

申克氏孢子丝菌

马尔尼菲青霉菌

（好发于）大型运动品种的年轻雄犬。

秋季病例增加；常与接近水和酸性沙土有关。

主要是北美的一种疾病(特别是五大湖、密苏里州、俄亥俄州、密西西比河流域)；在非洲、印度、中东和欧洲也有发现。

犬的感染率是人的 10 倍，因此犬是人类芽孢菌病的重要流行病学标志物

犬类眼内真菌病的最常见原因。

发病机制：

原发性肺部感染(最常见)

吸入分生孢子种子至末端细支气管和肺泡。

分生孢子迅速萌发成酵母形态，通过表达和分泌芽孢杆菌粘附分子 1(BAD1)(原 WI-1)诱导酵母相特异性毒力基因。

BAD1 介导与吞噬细胞(CR3 和 CD14)的粘附，并抑制 TNF-α的生成。

细胞壁多糖α-葡聚糖可以防止巨噬细胞的杀伤作用。

酵母在肺内增殖并通过血液和淋巴管传播，但不具有传染性。

播散性病变：通过淋巴管和血管通道发生，在犬类中，最常见的肺外扩散部位是淋巴结、眼睛、皮肤、皮下组织、骨骼和关节；不太常见的是中枢神经系统、泌尿生殖道、脾脏和乳腺。

局部皮肤感染：皮肤感染应被认为是潜在的弥散性内脏疾病的表现，很少是直接接种引起的。

典型的临床表现:

厌食、体重减轻、咳嗽、呼吸困难、眼疾、跛足、皮肤病。

皮肤损伤包括丘疹、结节、斑块、溃疡、引流管（Draining tracts）和皮下脓肿；多见于鼻平面、面部和甲床。

由巨噬细胞过量产生的 1,25 二羟基胆钙化醇引起的肉芽肿性疾病的高钙血症。

伴有血浆纤维蛋白原浓度升高的系统性芽生菌病的高凝状态。

肉眼检查:

皮肤溃疡性肉芽肿性丘疹和结节。

有浆液性至脓性渗出物的引流管。

偶见广泛性淋巴结病变。

肺是最常受累部位，可见弥漫性、多灶性分布大小不一的灰白色结节。

光镜检查：

混合性肉芽肿到化脓性肉芽肿的炎症反应取决于部位和病程。

表皮常呈棘皮状或溃烂、渗出，并可能有脓肿。

可见互不相连的肉芽肿或化脓性肉芽肿性病灶。

常见坏死。

酵母为 5-15 微米，圆形，无包被，壁清晰，原生质颗粒状

宽基芽生出子细胞。

游离于组织和巨噬细胞中，常位于炎症灶中心。

玻片压片或细胞学标本描述为一个圆形的嗜碱性酵母，直径为 6-15um(大约和红细胞大小至略大于中性粒细胞)，细胞壁厚，透明，可折射；有机体通常染成深蓝色，并显示出广泛的芽殖。

附加的诊断检查:

PAS 染色。

格莫瑞六亚甲基四胺银 (GMS)染色。

Gridley 染色。

琼脂凝胶免疫扩散(AGID)和酶联免疫吸附试验(ELISA)商品化试剂盒用于 A 抗原(囊状抗原)的检测。

放射免疫分析法(RIA)用于抗 WI-1 抗原的抗体，具有高敏感性和特异性。

不建议在医院实验室进行细胞学标本的培养，因为这种微生物的菌丝形式有感染的危险。

鉴别诊断:

大体所见的肺和其他器官内的多结节性病变:

转移性肿瘤:结节通常更大，大小变化更大。

组织学检查结果:

新型隐球菌:直径 2-20 um， 厚度 2-10 um 粘多糖囊壁，粘蛋白卡红阳性，窄基出芽。

球虫病:球形体直径 20-200um；内生孢子直径 2-5um。

巴西副球虫病(南美芽孢菌病): 直径 5-60 um，显示多个窄基出芽，呈现“轮辐状”外观。

荚膜组织胞浆菌杜波氏变种:直径 8- 15um，大小相似，但芽来自狭窄的基部，沙漏状，单核，液泡状细胞质。

荚膜组织胞浆菌荚膜变种: 直径 2-5 um；细胞内。

申克氏孢子丝菌：比 B 型皮炎芽生菌更小，通常更多形性；通常为“雪茄形状”。

无绿藻:藻类；较大，具有典型的“梅赛德斯-奔驰”内孢子形态的原囊藻属。

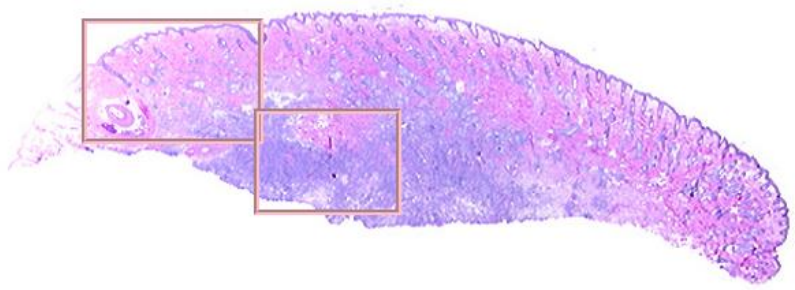
Lacazia (Loboa) loboi（疤痕芽生菌病，又称 Lobo 病）：酵母经常联结在一起，形成“珍珠串”的外观。

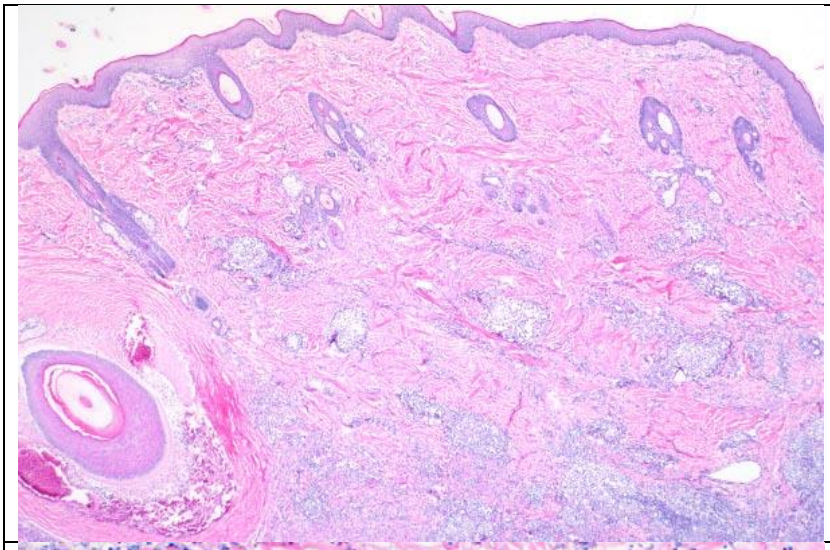
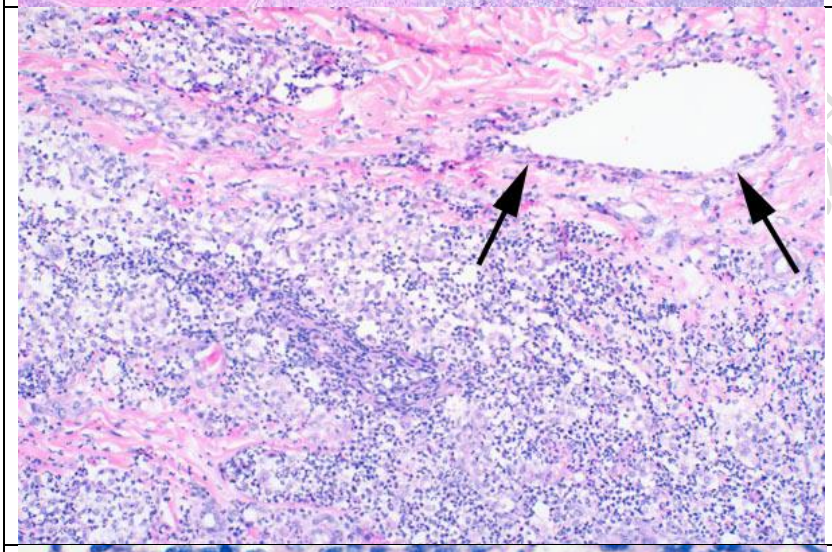
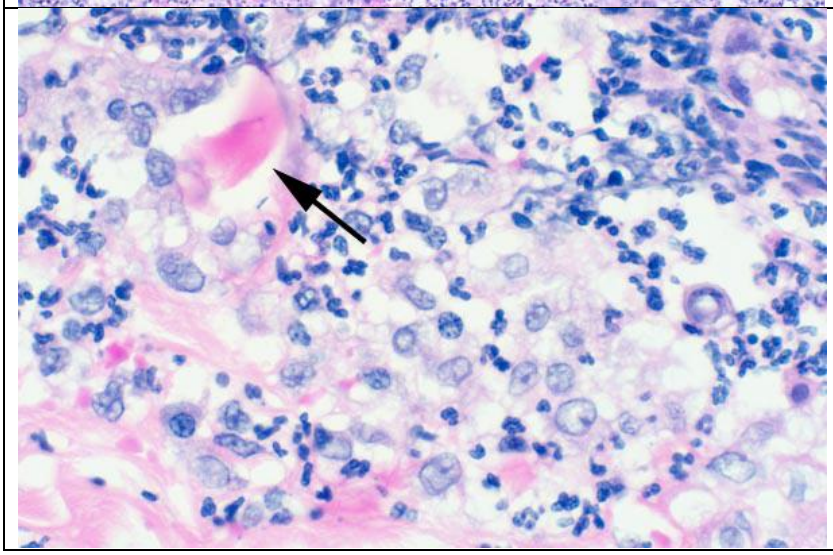
比较病理学:

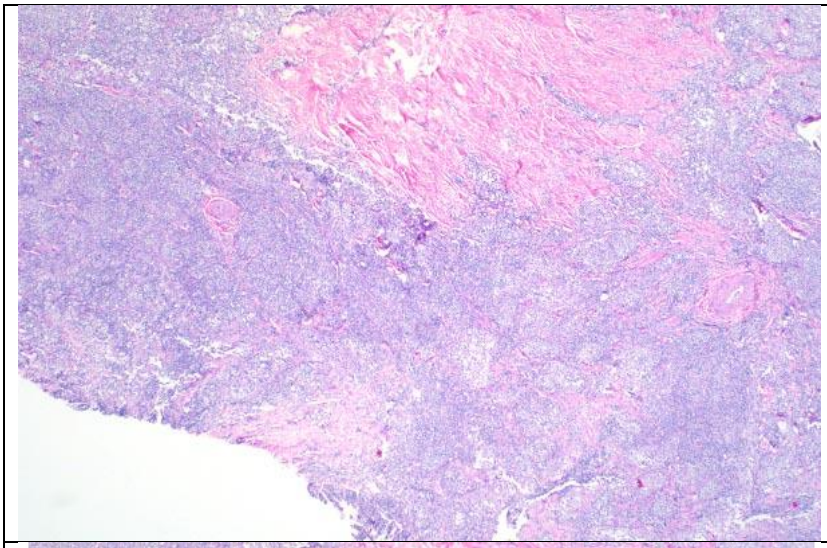
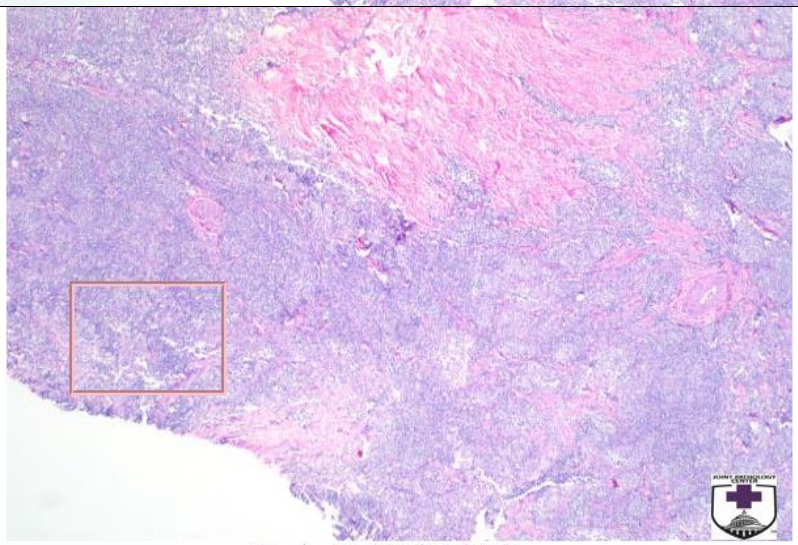
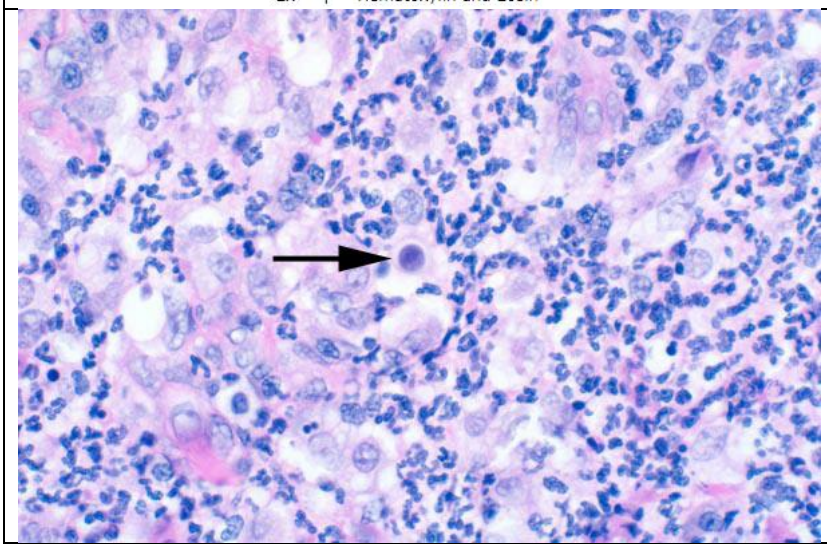
偶尔发生在猫。

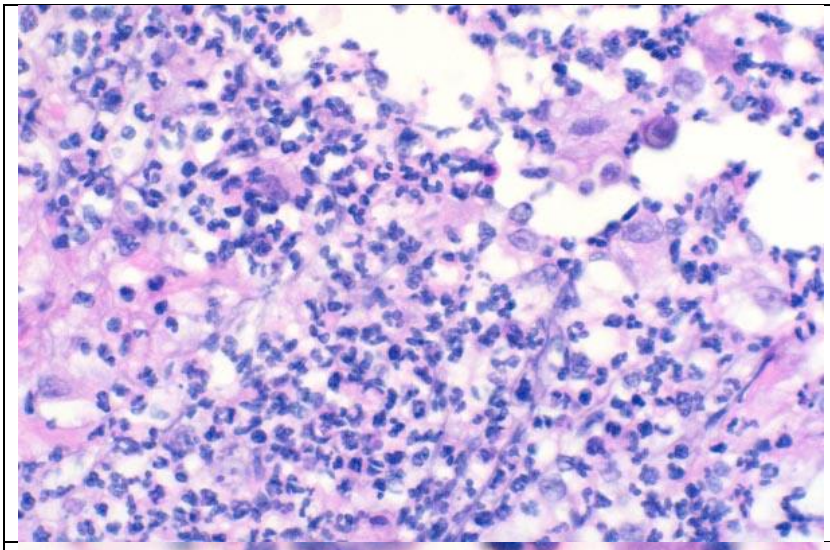
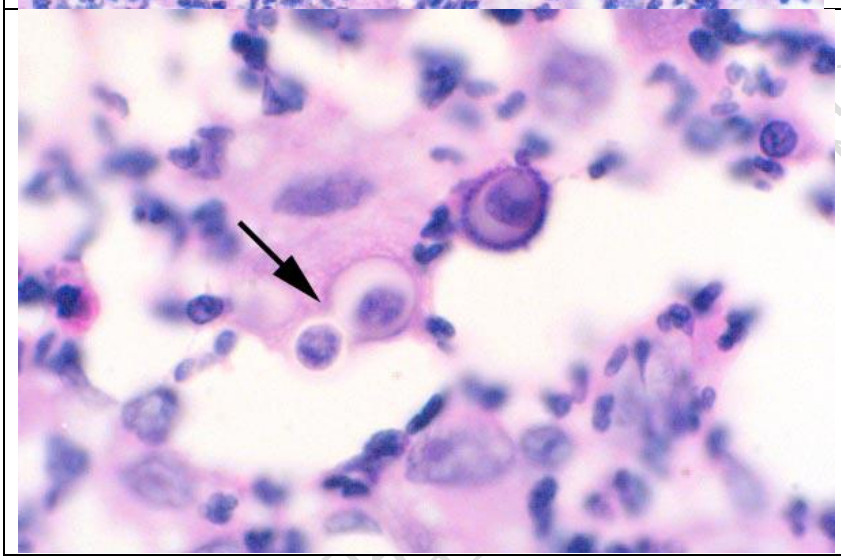
已在恒河猴、马、非洲和亚洲狮子、西伯利亚虎、印度豹、雪豹、北极熊、狼、印度果蝠、雪貂、大西洋宽吻海豚、虎头狮和加利福尼亚海狮、老鼠和栗鼠(大多数为传播病例)中被报道。

下表中为芽生菌病镜下表现:

	重点观察区。

	2× HE 染色（分区 1）真皮及皮下组织炎细胞浸润。
	10× HE 染色淋巴管扩张（箭头）提示水肿。
	40× HE 染色胶原纤维（箭头所示）被脓肉芽肿性炎症包围，嗜酸性粒细胞增多并变性（火焰图）。

	2× HE 染色 真皮层内有密集的炎性浸润。
 2x | Hematoxylin and Eosin	10× HE 染色 重点观察方框内组织学特点。
	40× HE 染色 （左上视野）脓肉芽肿性炎症包围着直径为 8 微米、细胞壁厚为 1-2 微米的酵母（箭头所示）。

	40× HE 染色（右下视野）。
	100× HE 染色（右下视野）偶尔会有酵母，其细胞壁清晰，1-2 微米，呈现出宽基出芽产生子细胞（箭头）。

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10.《小动物皮肤病彩色图谱与治疗指南》

JPC SYSTEMIC PATHOLOGY
INTEGUMENT SYSTEM
August 2019
I-F06

Signalment (JPC # 3104239): 14-month-old Newfoundland dog

HISTORY: None

HISTOPATHOLOGIC DESCRIPTION: SLIDE A: Haired skin: Multifocally expanding the dermis, separating and surrounding adnexal structures and extending into the markedly hyperplastic and hyperkeratotic epidermis, are multiple coalescing nodules composed of numerous epithelioid macrophages and neutrophils with fewer lymphocytes, plasma cells, and rare eosinophils, often surrounded by loosely arranged fibroblasts. Within this infiltrate are many oval, 10-20 um in diameter, yeast with a 1 um distinct double-contoured cell wall and granular protoplasm, which occasionally exhibit broad-based budding. The overlying epithelium is markedly hyperplastic with numerous anastomosing rete ridges, abundant basilar mitoses, moderate acanthosis, and a 500 um thick layer of orthokeratotic and parakeratotic hyperkeratosis. The inflammatory nodules often separate the stratum spinosum from the stratum corneum (intraepidermal abscesses); there are also multifocal intracorneal pustules, composed of degenerate neutrophils and necrotic debris. Multifocally, apocrine glands are ectatic and endothelium lining vessels is mildly hypertrophied (reactive).

Slide B (PAS): Haired Skin: Multifocally, there are PAS positive 10-20 um diameter oval yeasts with double contoured walls and broad based budding within the dermis and epidermis.

MORPHOLOGICAL DIAGNOSIS: Haired Skin: Dermatitis, pyogranulomatous, multifocal to coalescing, marked, with intraepidermal abscesses, epidermal hyperplasia, and yeast, etiology consistent with *Blastomyces dermatitidis*, Newfoundland, canine.

ETIOLOGIC DIAGNOSIS: Cutaneous blastomycosis

CAUSE: *Blastomyces dermatitidis*

CONDITION: Blastomycosis

SYNONYMS: Gilchrist's disease, Chicago disease, North American blastomycosis

GENERAL DISCUSSION:

Dimorphic soil saprophyte that exists in **mycelial form in soil** and **yeast form in tissue**

Primary pathogenic dimorphic fungi:

Blastomyces dermatitidis

Coccidioides immitis

Histoplasma capsulatum

Paracoccidioides brasiliensis

Sporothrix schenkii

Penicillium marneffei

Young male dogs of large and sporting breeds

Increased numbers of cases in the fall; frequently associated with proximity to water and acidic sandy soil

Principally a disease of North America (especially Great Lakes, Missouri, Ohio, Mississippi river valleys); has also been identified in Africa, India, Middle East and Europe

Infection rate is 10 times greater in dogs than in man, hence the dog is important epidemiologic marker for human blastomycosis

Most common cause of intraocular mycosis in dogs

PATHOGENESIS:

Primary pulmonary infection (most common)

Inhaled conidia seed terminal bronchioles and alveoli

Conidia rapidly germinate into yeast form and yeast phase specific virulence genes are induced with expression and secretion of **blastomyces adhesion 1 (BAD 1)** (formerly WI-1)

BAD 1 mediates adhesion to phagocytic cells (CR3 and CD14), and suppresses generation of TNF alpha

Cell wall polysaccharide alpha-glucan protects against killing by macrophages

Yeast forms proliferate within the lungs and disseminate via the blood and lymphatic vessels, but **are not contagious**

Disseminated disease

Occurs via lymphatic and vascular channels

In dogs, the most common sites of extrapulmonary dissemination are the lymph nodes, **eyes, skin**, subcutaneous tissues, **bones**, and joints; less common are the central nervous system, urogenital tract, spleen and mammary gland

Localized cutaneous infection

Cutaneous infection should be considered a manifestation of underlying disseminated visceral disease

Rarely, can be caused by direct inoculation

TYPICAL CLINICAL FINDINGS:

Anorexia, weight loss, coughing, dyspnea, ocular disease, lameness, skin disease

Skin lesions include papules, nodules, plaques, ulcers, draining tracts and abscesses in the subcutis; usually multiple, frequently found on nasal planum, face, and nail beds

Hypercalcemia of granulomatous disease due to the excessive production of 1,25 dihydroxycholecalciferol by macrophages

Hypercoagulability in systemic blastomycosis with elevations in plasma fibrinogen concentration

TYPICAL GROSS FINDINGS:

Ulcerated, cutaneous granulomatous papules and nodules

Draining tracts with a serosanguinous to purulent exudate

Occasional generalized lymphadenopathy

The lung is the most consistently affected site with diffuse, multifocal distribution of variably sized grey-white nodules

TYPICAL LIGHT MICROSCOPIC FINDINGS*:*

Mixed granulomatous to pyogranulomatous inflammatory reaction depending on site and chronicity

Epidermis is often acanthotic or ulcerated and exudative and may contain abscesses

Discrete granulomas or pyogranulomatous foci may be present

Necrosis is often present

Yeast are **5-15 um**, round, non-encapsulated, **distinct wall**, and a granular protoplasm

Broad based budding

Found free in tissue and in macrophages often at the center of inflammatory focus

Touch impression or cytologic preparations describe a round, basophilic yeast that measures 6-15 um in diameter (approximately the size of a RBC to slightly larger than a neutrophil) and has a **thick, clear, refractile cell wall**; organism usually stains dark blue and exhibits broad based budding

ADDITIONAL DIAGNOSTIC TESTS*:*

Periodic acid-Schiff (PAS) reaction

Gomori's methenamine silver (GMS)

Gridley's stain

Agar gel immunodiffusion (AGID) and ELISA commercial kits available for demonstration of A-antigen (capsular antigen)

Radioimmunoassay (RIA) for antibodies against WI-1 antigen - high sensitivity and specificity

Culture of cytologic specimens is not recommended for in-hospital laboratories because of the danger of infection from the mycelial form of the organism

DIFFERENTIAL DIAGNOSIS:

For gross finding of multinodular lesions within the lung and other organs:

Metastatic neoplasia: Nodules often larger and more variable in size

For histological findings:

Cryptococcus neoformans: 2-20 um in diameter, **thick 2-10 um mucopolysaccharide capsule that is mucicarmine positive**, **narrow-based budding**

Coccidioides immitis: **Spherules 20-200 um diameter; endospores 2-5 um in diameter**

Paracoccidioides brasiliensis (South American blastomycosis): 5-60 um diameter, **exhibit multiple narrow based budding giving the appearance of a "spoke wheel"**

Histoplasma capsulatum var. duboisii: 8-15 um diameter, size is similar but bud from a narrow base, hourglass shape, uninucleate, vacuolated cytoplasm

Histoplasma capsulatum var. capsulatum: **2-5 um diameter**; **intracellular**

Sporothrix schenckii: Smaller and generally more pleomorphic than *B. dermatitidis*; often **"cigar-shaped"**

Prototheca: Algae; larger with characteristic **"Mercedes Benz" endospore morphology**

Lacazia (Loboa) loboi: Yeast often associate to produce **"string of pearls" appearance**

COMPARATIVE PATHOLOGY:

Occasionally in cats

Has been reported in rhesus monkey, horses, African and Asian lions, Siberian tiger, cheetah, snow leopard, polar bear, wolves, Indian fruit bat, ferret, Atlantic bottlenose dolphin, Steller's and California sea lions, mice, and chinchillas (most of them are disseminated cases)

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病例 CP2022-85

切片连结：
https://www.askjpc.org/wsco/wsc_showcase2.php?id=OC9CZUdmdHpUUXRMWGl2d3NEWjZEdz09

演讲及翻译人：

裴天仙，副研究员 天津药物研究院（天津天诚新药评价有限公司）

特征描述：
4 周大，雌性，智利火烈鸟，智利凤凰，鸟类。

病史：
动物园 4 周大的雌性火烈鸟，在右侧胫跗关节的皮肤上出现多结节、溃疡、疣状增生，大小约 5 x 4 x 3 厘米。手术切除增生的组织，10%中性福尔马林缓冲液固定，做组织学检查。

大体观察描述：
提交的组织局部溃疡，呈棕褐色，在切面上呈多叶状。

组织病理学描述：
无毛皮肤：表皮不规则增生并明显增厚，以棘细胞层增厚为主（棘皮病）。表皮多灶状浅表或完全缺失，伴有出血和少量异嗜粒细胞浸润。角质层下面的部分，可见多个由变性的异嗜性粒细胞、红细胞、蛋白液和细菌组成的病灶。棘层细胞弥漫性肥大、细胞内水肿（水变性），细胞质中存在直径达 15μm 的嗜酸性包涵体（Bollinger 包涵体）。
真皮内轻度至中度弥漫性异嗜性粒细胞浸润和少量巨噬细胞。此外，可见血管扩张、充血，多灶状出血和纤维蛋白渗出。

形态学诊断（提供者）：
皮肤：皮炎，糜烂、溃疡，急性，弥漫性，严重者伴有表皮增生，脓疱，角质细胞水肿变性，可见胞浆嗜酸性包涵体(Bollinger 包涵体)，与痘病毒感染一致。

实验室结果：
福尔马林固定石蜡包埋组织 (FFPE) 用于对编码 4b 蛋白的基因进行分子测序。系统发育分析显示与金丝雀痘 ATCC 株(属：禽痘病毒)序列同源性为

99.9%。。

提供者评论：

形态学结果与透射电镜结果一致，均证明为痘病毒感染；分子分析揭示为禽痘病毒（APV)属的一个金丝雀痘病毒株。

组织学上的主要病变包括表皮增生和角质细胞的水样变性，角质细胞胞质含有大量嗜酸性包涵体。透射电子显微镜显示，可见大小为 250 x 320 nm 的双凹砖状病毒颗粒。根据切片平面的不同，病毒颗粒显示出一个双凹核心、两个侧体和一个与禽痘病毒粒子一致的包膜。

肉眼观察，胫跗关节无羽毛皮肤上出现外生溃疡性多结节增生。这种疣状病变代表着 APV 感染的增生或皮肤形式（“干痘”）。它的特征是无羽毛皮肤上的结节状增生，如腿、脚、眼睑和喙基部，在恢复和愈合后可见瘢痕。APV 感染的另一种表现形式被称为白喉/类白喉或“湿”型，其特征是粘膜的增生性和纤维蛋白坏死性病变，主要发生在舌、咽和喉。鸟类也可能同时出现这两种形态。据报道，白喉型的死亡率高于皮肤型。然而，继发性细菌感染可能显着增加皮肤型的死亡率。以羽毛皱褶、嗜睡、发绀和厌食为特征的败血症，很罕见，但是这种形式可能导致高达 99%的死亡率，主要见于金丝雀和金丝雀杂交。

禽痘病毒，属于禽痘病毒属，它是痘病毒科脊痘病毒亚科的成员。禽痘病毒是具有双链 DNA 的大型砖形包膜病毒。在受感染的细胞中，它们在细胞质中复制。通过潜伏感染的鸟类和叮咬的节肢动物传播，通过皮肤、黏膜伤口感染，或痘痂脱落破散直接传播。此外，病毒可通过气溶胶、眼睛粘膜或上呼吸道和消化道传播。蚊子可在唾液腺内保留传染性病毒 2-8 周，干痂可以携带病毒长达数月之久。所有年龄段的鸟类都是易感的，然而，主要是年轻的个体受到影响。潜伏期由 7 至 14 天不等。这种病毒通常根据最初分离出来的种类来命名。大多数关于 APV 感染的死亡率和发病率的研究都是基于单个 APV 分离株，这使得很难找到特定 APV 分离株在不同物种中的致病性的一般信息。例如，金丝雀对金丝雀痘病毒高度敏感，但它们对鸽痘、火鸡痘和鸡痘具有抗性。然而，APV 也可以跨越物种屏障，并可能感染不同的物种。禽痘病毒在世界范围内分布，在 23 目 232 多种鸟类中均有感染。疾病可能出现在许多不同物种的家禽、宠物和野生鸟类中。

禽痘病毒感染已在世界不同国家的各种火烈鸟物种中报道过。美国和葡萄牙感染了美洲火烈鸟，南非感染了小火烈鸟，日本感染了大火烈鸟。在本案例中，是一只智利火烈鸟被感染。在所有已发表的病例中，感染发生在年龄不超过 4.5 个月的年轻动物。他们都是皮肤型禽痘病毒感染。在葡萄牙、日本和美国，个别动物受到了影响，而在南非，30 %的刚出生的火烈鸟表现出皮肤型的症状。

各种禽痘病毒种类的鉴定和分化主要基于 4b 核心多肽的测序。该基因由 1971 个核苷酸组成，编码一种分子量为 75.2 kDa 的蛋白质。为了分离禽痘病毒，对无特定病原体鸡胚的绒毛尿囊膜（CAM）进行了接种。在这种培养体系中，病毒形成 A 型细胞质包涵体。

作为增生的形态学鉴别诊断，必须考虑与肉芽肿性炎症及肉芽组织鉴别。

JPC 诊断：

皮肤：皮炎，坏死、增生性，多灶状，严重，伴有气球样变性，胞浆内嗜酸性病毒包涵体（Bollinger 体），智利火烈鸟（*Phoenicopterus chilensis*），鸟类。

会议点评：

禽痘一词最初用于描述所有鸟类的痘病毒感染，但随着受影响物种数量的增加，它专门用于鸡的疾病。禽痘是一种古老的疾病，以前被认为与人类天花和水痘有关。虽然这种疾病不会影响人类种群，但它确实会影响我们所知道的许多鸟类（鸡、火鸡、鸽子、金丝雀、鹦鹉和野鸟），但也许所有鸟类都易感。

美国农业部为禽类产品颁发的第一个许可证是 1918 年的禽痘疫苗。迄今为止，痘疫苗是疾病控制和预防的主要方法，在 4 周龄或必要时在任何年龄进行初始疫苗接种。禽痘疫苗由于其功效和优越性，目前正被用作重组疫苗的载体。痘病毒的特征包涵体（如上所述）代表了感染性病毒颗粒的 DNA 合成和加工位置。

禽痘病毒包含许多 DNA 复制、修复和加工的基因，以及一种利用可见光作为能量来源修复紫外线诱导的 DNA 损伤的特定酶（CPD 光解酶）。这可能有助于解释病毒的环境适应性。痘病毒编码影响宿主细胞的蛋白，如痘苗病毒生长因子(VGF)，通过表皮生长因子受体(EGFR)刺激角质形成细胞增殖。另外一些蛋白抑制补体介导的细胞裂解和宿主的炎症反应。所有这些因素的作用不仅为病毒提供了安全的复制环境，而且为继发细菌感染提供了肥沃的土壤。

在大体病变上，皮肤(干性)痘主要需要与螨虫感染和细菌性足跖皮炎进行鉴别。突变革螨(“鳞状腿螨”)主要生活在没有羽毛的皮肤上，导致小腿表皮增厚、角化过度，可见白色的鳞状外壳；而鸡革螨（“脱羽螨”）生活在基部的羽轴上，导致羽毛断裂或缺失。最后，最常由金黄色葡萄球菌引起的细菌性足皮炎（“禽掌炎”）会因穿透性伤口导致足底表面出现化脓性脓肿。

参会者注意到在一些切片中形成了不同的血清细胞结痂，其中有明显的表面细菌菌落并伴有出血。

表 1：选择痘病毒科的属

属	**病毒/疾病**	**主要宿主**
正痘病毒	牛痘病毒 水牛痘/兔痘病毒*	数量众多:牛，水牛，猪，兔子
	牛痘*	啮齿动物(水库)，牛，猫，大象，犀牛
	骆驼痘	骆驼

	畸形(鼠痘)	老鼠、田鼠
	猴痘*	非人灵长类动物、松鼠、食蚁兽
	山羊痘	山羊、绵羊
山羊痘病毒	羊痘	绵羊、山羊
	块状皮肤病病毒	牛，水牛角
猪痘病毒	猪瘟病毒	猪（载体=猪血红蛋白）
	粘液瘤病毒	兔子 (穴兔属&棉尾兔属种.)
兔痘病毒	兔纤维瘤病毒、野兔纤维瘤病毒	兔子
	松鼠纤维瘤病毒	灰松鼠和红松鼠
鸟痘病毒	禽痘、金丝雀痘、鹌鹑痘等	鸡、火鸡、孔雀等
	山羊副痘病毒（羊痘；传染性膿疮）*	绵羊、山羊
副痘病毒	牛痘(牛丘疹性口炎病毒) *	牛
	假牛痘*	牛
	水痘*	海豹
	马鹿副痘病毒	马鹿
软体虫痘病毒	传染性软疣病毒*	非人灵长类动物，鸟，狗，袋鼠，马
亚痘病毒	亚巴痘病毒&坦痘病毒*	坦痘病毒
未分类	松鼠痘病毒，鱼(鲤鱼水肿)，马痘	

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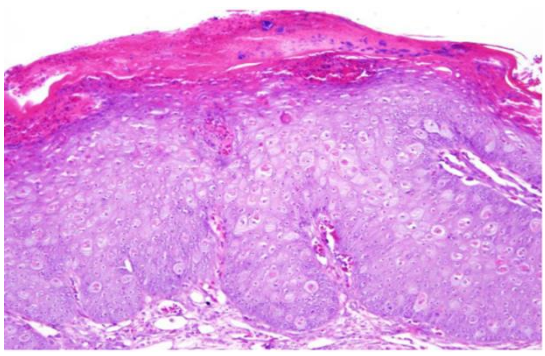
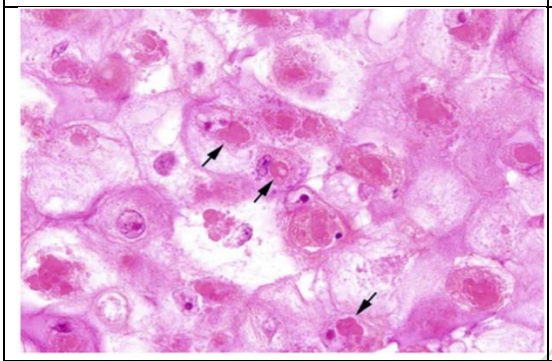
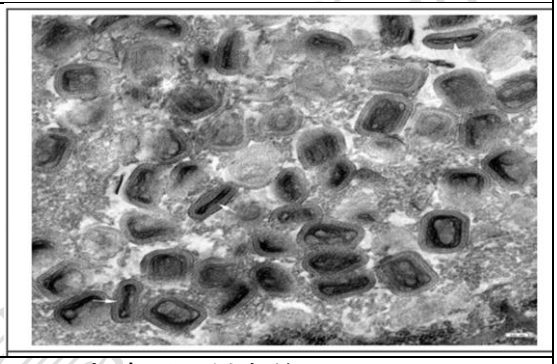
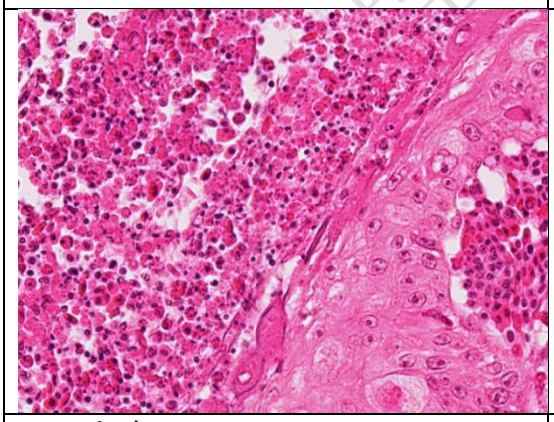
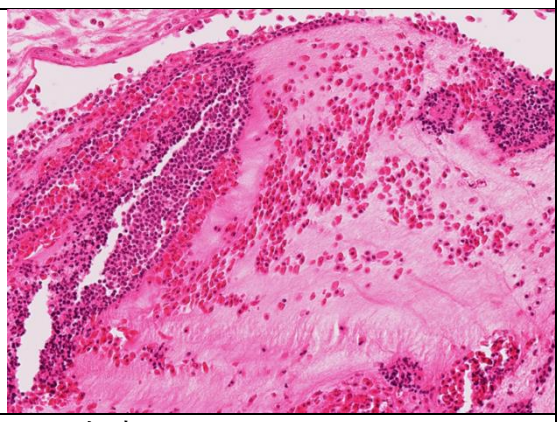
<tr><td>  </td><td>  </td></tr>
<tr><td>图 1 胫跗关节（大体所见）
多结节、溃疡性、疣状增生。</td><td>图 2 皮肤
皮肤上覆盖痂皮，表皮不规则增生，明显增厚，以棘细胞层细胞增多为主</td></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td>图 3 皮肤
棘层细胞弥漫性肥大、细胞内水肿（水变性），细胞质中存在直径达 15μm 的嗜酸性包涵体，如箭头所示。</td><td>图 4 皮肤（透射电镜）
在超威结构上，感染性角质细胞含有多个大小为 250x320nm 的双凹砖状的病毒颗粒。</td></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td>图 5 皮肤
变性、坏死的异嗜性粒细胞</td><td>图 6 皮肤
由变性的异嗜性粒细胞、红细胞、蛋白液和细菌组成的病灶</td></tr>
</table>

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2017-2018
Conference 15
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CASE II: E 6940/16 (JPC 4100856).

Signalment: 4-week-old, female, Chilean flamingo, *Phoenicopterus chilensis*, avian.

History: A 4-week-old, female flamingo from the zoo showed a multinodular, ulcerated, wart-like proliferation of approximately 5 x 4 x 3 cm extension in the skin at the right tibiotarsal joint. The proliferated tissue was surgically resected, fixed in 10% neutral buffered formalin and submitted for histological examination.

Gross Pathology: The submitted tissue was partially ulcerated and had a tan color. On cut surface it appeared multilobulated.

Laboratory results:
Formalin-fixed paraffin-embedded tissue (FFPE) was used for molecular sequencing of the gene encoding the 4b-protein. Phylogenetic analysis revealed a sequence homology of 99.9% with the ATCC strain of canarypox (genus: avipoxvirus).

Microscopic Description: Glaborous skin: The epidermis of the featherless skin is irregularly proliferated and severely thickened with increased layers of spinosum cells (acanthosis). There are multifocal superficial or complete losses of the epidermis associated with extravascular erythrocytes and few heterophilic granulocytes. Underneath the stratum corneum there are multifocal accumulations of partly degenerated heterophilic granulocytes, erythrocytes, proteinaceous fluid and bacteria. Particularly, cells of the spinosum layer display severe diffuse hypertrophy with intracellular edema (hydropic degeneration). Eosinophilic inclusion bodies up to 15 µm in diameter are present in the cytoplasm (Bollinger's inclusion bodies).

Within the dermis, there is a diffuse mild to moderate infiltration of heterophilic granulocytes and few macrophages. Furthermore, numerous blood vessels are markedly extended and filled with red blood cells. Multifocally there are moderate accumulations of extravascular erythrocytes (hemorrhages) and eosinophilic, fibrillary material (fibrin).

Contributor's Morphologic Diagnosis: Skin: Dermatitis, erosive and ulcerative, heterophilic, acute, diffuse, severe with epidermal hyperplasia, pustules, hydropic degeneration of keratinocytes and cytoplasmic, eosinophilic inclusion bodies (Bollinger's inclusion bodies) consistent with poxvirus infection.

Contributor's Comment: The morphological findings are consistent with a poxvirus infection that was confirmed by transmission electron microscopy. Molecular analysis revealed a canarypox strain of the genus avipoxvirus (APV).

The histologic key lesions include epidermal hyperplasia and hydropic degeneration of keratinocytes with large, cytoplasmic, eosinophilic inclusion bodies (Bollinger's inclusion bodies). Using the pop-off technique,[11] transmission electron microscopy (TEM) revealed biconcave brick-shaped virions measuring 250 x 320 nm. Virus particles exhibited, depending of the sectioning plane, a biconcave core, two lateral bodies and an envelope consistent with avipox virions.[15]Macroscopically, an exophytic ulcerated multinodular proliferation was present on the featherless skin at the tibiotarsal joint. This wart-like lesion represents the proliferative or cutaneous form of an APV infection ("dry pox").[8] It is characterized by nodular proliferations on featherless skin such as legs, feet, eyelids and base of the beak. Scars may be visible after recovery and healing. Another manifestation of APV infections is termed diphtheritic/diphtheroid or "wet" form that is characterized by proliferative and fibrino-necrotic lesions of the mucous membranes, predominantly of the tongue, pharynx and larynx.[4,8,20] Birds may also show both forms. The mortality rate of the diphtheritic form is reported to be higher compared to the cutaneous form. However, secondary bacterial infections may significantly increase the mortality rate in the cutaneous form.[20] Rarely, a septicemic form develops that is characterized by acute onset of ruffled plumage, somnolence, cyanosis and anorexia. This form may cause mortality rates of up to 99% and is seen predominantly in canaries and canary-finch crosses.[8]

Avian poxviruses belong to the genus *Avipoxvirus* which is a member of the subfamily *Chordopoxvirinae* with the family of *Poxviridae*. Avian poxviruses are

large, brick-shaped, enveloped viruses with a double-stranded DNA. In infected cells, they replicate in the cytoplasm.[10,19] Transmission occurs through latently infected birds and biting arthropods. In addition, direct transmission of the virus may be facilitated by small traumatic injuries caused by territorial behavior. Furthermore, virus may be transmitted through aerosols via mucous membranes of the eyes or the upper respiratory and digestive tracts.[4,8,10,12] Mosquitos may retain infectious virus in the salivary glands for 2 to 8 weeks.[8] Dry scabs can harbor the virus for many months.[15] Birds of all ages are susceptible, however, mostly young individuals are affected. The incubation period varies from 7 to 14 days.[14] The virus is usually named by the species in which it was originally isolated. Most investigations about mortality and morbidity of APV infections are based on single APV isolates, which make it difficult to find general information on pathogenicity of particular APV isolates in different species. For example, canaries are highly susceptible to canary poxviruses but they are resistant to pigeon pox, turkey pox and fowl pox.[19] Nevertheless, APV can also cross species barriers and may infect taxonomically different species.[10] Avian poxvirus has a worldwide distribution and infection is described in over 232 avian species in 23 orders.[2] Disease can arise in domestic, pet and wild birds of many different species.[19]

Avipoxvirus infections have been described in various flamingo species in different countries of the world.[10,13,16,20] American flamingos (*Phoeniconais ruber*) were infected in the USA and Portugal,[10,13] Lesser flamingos (*Phoenicopterus minor*) in South Africa,[16] and Greater flamingos (*Phoenicopterus roseus*) in Japan.[16] In the presented case, a Chilean flamingo (*Phoenicopterus chilensis*) was affected. In all published cases, infection occurred in young individuals up to 4.5 months of age. They all suffered from the cutaneous form of avian poxvirus infection.[8,11,16,20] In Portugal, Japan and the USA, single animals were affected,[4,10,13] whereas in South Africa 30% of the fledgling flamingos displayed the cutaneous form.[20]

Identification and differentiation of various Avipoxvirus species is mainly based on sequencing of the 4b core polypeptide. This gene is composed of 1971 nucleotides and encodes a protein that has a molecular weight of 75.2 kDa.[1,18] For the isolation of Avipoxvirus, the chorioallantoic membrane (CAM) of specific-pathogen-free (SPF) chicken embryos is inoculated. Within this culture system the virus forms type A cytoplasmic inclusions.[2,10,13]

As morphological differential diagnoses neoplastic proliferations, granulomatous inflammation as well as exuberant granulation tissue have to be considered.

JPC Diagnosis: Skin: Dermatitis, necrotizing and proliferative, focally extensive, severe, with ballooning degeneration, and intracytoplasmic eosinophilic viral inclusion bodies (Bollinger bodies), Chilean flamingo (*Phoenicopterus chilensis)*, avian.

Conference Comment: The term fowlpox was initially used to describe poxvirus infections of all birds, but as the number of species affected grew, it became used specifically for the disease in chickens.[3] Avianpox is an old disease that was previously thought to be related to human small pox and chicken pox. While this disease does not affect the human population, it does affect numerous avian species that we know of (chickens, turkeys, pigeons, canaries, psittacines, and wild birds) but perhaps all bird species are susceptible.[17]

The first USDA license issued for a poultry product was for the fowlpox vaccine in 1918.[5] To this day, the pox vaccine is the primary method of disease control and prevention with initial vaccination of birds at 4 weeks of age or at any age if necessary. The fowl pox vaccine is currently being used as a vector for recombinant vaccines due to its efficacy and prevalence.[17] The characteristic inclusion bodies of poxviruses (described above) represent the site of DNA synthesis and packing of the infectious virus particles.

Avianpox viruses contain numerous genes for DNA replication, repair, and processing, as well as a specific enzyme (CPD photolyase) that repairs UV-induced DNA damage using visible light as a source of energy. This may help explain the virus' environmental durability. Poxviruses encode proteins that affect host cells such as vaccinia virus growth factor (VGF) which stimulates proliferation of keratinocytes using epidermal growth factor receptors (EGFRs). Still other proteins inhibit complement mediated cell lysis and the host inflammatory response. All of these factors function to not only provide the virus a safe environment to replicate in, but also provide fertile soil for secondary bacterial infections.[3]

Gross differentials for cutaneous (dry) pox include mite infections and bacterial pododermatitis. *Cnemidokoptes mutans* ("scaley leg mite") lives primarily in unfeathered skin and causes thick, hyperkeratotic shanks with white, scaly crusts, and *Cnemidokoptes gallinae* ("depluming mites") lives in basal feather shafts and

causes breakage or complete loss of feathers and intense irritation.[6] Finally, bacterial pododermatitis ("bumblefoot") most commonly caused by *Staphylococcus aureus* results in purulent abscesses on the plantar surface of the foot due to penetrating wounds.[7]

Conference participants noted variable serocellular crust formation in some sections with prominent colonies of superficial bacteria admixed with hemorrhage.

Table 1: Select genera of the family Poxviridae.[9,12]

Genus	Virus/Disease	Major Hosts
Orthopoxvirus	Vaccinia virus	Numerous: cattle, buffalo, swine, rabbits
	Buffalopox/Rabbitpox virus*	
	Cowpox*	Rodents (reservoir), cattle, cats, elephants, rhinos
	Camelpox	Camels
	Ectromelia (Mousepox)	Mice, voles
	Monkeypox*	NHPs, squirrels, anteaters
Capripoxvirus	Goatpox	Goats, sheep
	Sheeppox	Sheep, goats
	Lumpy skin disease virus	Cattle, cape buffalo
Suispoxvirus	Swinepox virus	Swine (vector= *Hematopinus suis*)
Leporipoxvirus	Myxoma virus	Rabbits (*Oryctolagus* & *Sylvilagus* spp.)
	Rabbit fibroma virus, Hare fibroma virus	Rabbits
	Squirrel fibroma virus	Grey and red squirrels
Avipoxvirus	Fowlpox, canarypox, quailpox, etc	Chickens, turkeys, peacocks, etc.
Parapoxvirus	Caprine parapoxvirus (Orf; contagious ecthyma)*	Sheep, goats
	Bovine parapox (bovine papular stomatitis virus)*	Cattle
	Pseudocowpox*	Cattle

	Sealpox*	Seals
	Parapoxvirus of red deer	Red deer
Molluscipoxvirus	Molluscum contagiosum virus*	NHPs, birds, dogs, kangaroos, equids
Yatapoxvirus	Yabapox virus & tanapoxvirus*	NHPs
Unclassified	Squirrel poxvirus, fish (carp edema), horsepox	

*zoonotic

Contributing Institution:

http://www.tiho-hannover.de/kliniken-institute/institute/institut-fuer-pathologie

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病例 CP2022-86

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演讲及翻译人（Presenter and translator）：

王彦武 广西壮族自治区疾病预防控制中心毒理所

病史(History)：猫多处多发皮肤结节。

组织病理学描述(Histopathologic Description)：有毛皮肤：真皮、皮下组织扩张，附近肌脂层的骨骼肌纤维分离，上覆表皮轻度增生和局灶性溃疡，附属结构广泛分离，多灶性到融合，5～15mm 直径的化脓性肉芽肿性炎症结节。炎性结节通常包括凝固性坏死区域(差异染色丧失和组织结构保留)和溶解性坏死区域(正常结构丧失，取而代之的是混杂着嗜酸性粒细胞、活的、退化的中性粒细胞、出血和核碎片等)。坏死灶周围有大量上皮样细胞、中性粒细胞、少量多核巨细胞(Langhans 型和异体型)、散在淋巴细胞、浆细胞、成纤维细胞和纤维结缔组织。在化脓性肉芽肿结节的边缘血管周围有许多淋巴细胞和浆细胞聚集。残存的淋巴管呈中度扩张。多灶性、单个炎症细胞围绕肌层的肌细胞；受累的肌纤维细胞有时肿胀，伴有胞浆苍白、空泡样 (变性)。上覆表皮局部大面积溃疡，取而代之的是由大量退化中性粒细胞与嗜酸性粒细胞、核碎片、红细胞、嗜酸性纤维、珠状物(纤维蛋白)混合而成的血细胞痂(serocellular crust)。溃疡附近的表皮呈轻度的棘皮状和皮肤棘细胞层水肿，伴有轻微角化过度。

切片 B: 有毛皮肤(抗酸):在上皮样细胞和多核巨噬细胞的胞浆中，可见中等量 3～5um 大小的抗酸杆菌，常呈平行束状排列。

形态学诊断(Morphologic Diagnosis)：有毛皮肤和皮下：皮炎和脂膜炎，化脓性肉芽肿和溃疡，多灶性融合，组织细胞内明显抗酸杆菌，品种不详，猫。

病因诊断(Etiologic Diagnosis): 皮肤分枝杆菌病。

病原(Cause)：鼠麻风分枝杆菌（*Mycobacterium lepraemurium*）

疾病(Condition)：猫麻风病综合征（Feline leprosy syndrome）

讨论 (General Discussion)：

1. 最常见生活于温带海洋性气候，包括：新西兰，澳大利亚，北美(如美国西北部)和欧洲。

2. 猫皮肤分枝杆菌病，现在已知是由几个不同种类的分枝杆菌引起的，它们的临床症状和组织学特征重叠，妨碍了简单的分类方案；然而，三种经典临床表现被描述了。

3. 猫麻风病综合征:罕见；由难以培养的分枝杆菌种类而引起的；分枝杆菌种类包括 *M. lepraemurium* 鼠麻风分枝杆菌， *M. visible*, *M.* spp. strain Tarwin， 以及新西兰和澳大利亚东海岸的一种新菌种。

4. 非典型分枝杆菌病(机会性分枝杆菌肉芽肿):慢性或复发性瘘管、溃疡、筋膜炎和溃疡性结节，最常发生在尾腹部、腹股沟或腰部；致病微生物在脂肪组织中大量繁殖；通常由腐生和非腐生分枝杆菌污染伤口引起；大多数病例由快速生长的菌种(如 ***M. fortuitum*** 偶然分枝杆菌， *M. phlei* 草分枝杆菌， *M. smegmatis* 耻垢分枝杆菌， *M. chelonae* 龟分枝杆菌)或很少由缓慢生长的菌种(*M. avium* 鸟分枝杆菌, *M. chitae* 千田分枝杆菌, *M. xenopi* 蟾蜍分枝杆菌, *M. ulcerans* 溃疡分枝杆菌)引起；用容易培养来区分非典型分枝杆菌病和猫麻风病。

4.1 组织学上可见多灶性化脓性肉芽肿性皮炎和/或脂膜炎，有大量被中性粒细胞包围的透明空泡；透明胞质中罕见有抗酸性细菌(细胞成分较少(paucicellular))。

4.2 公认的三种综合征:

① 分枝杆菌性脂膜炎伴慢性感染、皮炎和皮下炎。

② 化脓性肉芽肿性大叶性肺炎。

③ 免疫功能低下的动物的播散性疾病。

5. 皮肤结核(“典型结核”):多发性溃疡、斑块、结节和脓肿，由化脓性肉芽肿性炎症和干酪样坏死组成的大量渗出物；猫常患下颌下淋巴结病；由牛分枝杆菌、结核分枝杆菌引起，很少由鸟分枝杆菌或鼠分枝杆菌引起；主要通过口腔感染，以及通过受感染的啮齿动物/肉类，未经巴氏消毒的牛奶感染。

发病机制(Pathogenesis)：

• 猫或大鼠咬伤(疑似传播方式)>进入巨噬细胞>阻断吞噬体和溶酶体的融合>细胞内复制>抗原在组织中的持续存在>通过细胞介导的炎症反应破坏组织。

• 免疫抑制已被提出有助于感染，特别是发生在老年猫，由一种新的分枝杆菌引起的瘤型麻风病；然而，没有相关的并发感染被证实(如： FIV 猫免疫缺陷病毒，Feels 猫白血病毒)。

• 结核样型麻风病的特征是 TH1 反应，产生 IL-2 和 IFN-γ(激活巨噬细胞)；IL-12 在 TH1 应答的产生中起重要作用，而 IL-12 的缺乏可能导致瘤型麻风病。

• 瘤型麻风病的特征是 TH1 应答缺陷或 TH2 应答主导，产生 IL-4、IL-5 和 IL-10，可能抑制巨噬细胞的激活。

典型临床表现（Typical Clinical Findings）：

• 年轻的雄性户外猫占多数。

• 进行性和经常侵袭性的临床感染过程，取决于宿主免疫，分枝杆菌种类，和感染接种物的数量。

典型的大体检查（Typical Gross Findings）：

• 局灶性到多灶性皮肤丘疹和硬结、边界清楚、脱毛、不同程度溃疡性结节，直径为 2mm ~ 40mm。

• 淋巴结肿大常见。

典型的光学显微镜检查结果（Typical Light Microscopic Findings）：

• 猫麻风综合征：两种不同的形态学模式

1. 结核样型麻风病：真皮到皮下肉芽肿伴有中央干酪样坏死，化脓性肉芽肿炎症周围环绕上皮样细胞，偶尔有多核巨噬细胞。

1.1 见相对较少至中度抗酸杆菌，通常局限于坏死区域。

2. 瘤型麻风病：通常指示在宿主免疫后。

2.1 结节性到弥漫性肉芽肿性皮炎和无坏死性脂膜炎。

2.2 片状或大的结节，泡沫状巨噬细胞伴有稀少的巨细胞。

2.3 不等数量的散在淋巴细胞、浆细胞、多核巨噬细胞和中性粒细胞。

2.4 细胞内大量的抗酸杆菌（多杆菌），密集、平行排列于组织细胞胞浆内，取代细胞核。

3. 矿化和被夹(encapsulation) 不明显。

4. +/-表皮棘皮状和/或溃疡。

• 结核病：结节状→弥漫性肉芽肿性皮炎→化脓性肉芽肿性皮炎和脂膜炎，伴有中央干酪样坏死。

其他的诊断测试(Additional Diagnoctic Tests)：

1. 抗酸染色：Ziehl-Neelsen (标准)、Fite-Farraco (改良)、Kinyoun's (改良)。

2. 极难培养：需要强化的蛋黄培养基；可能需要几周到几个月才能生长。

3. 分枝杆菌的存在及结核分枝杆菌培养阴性支持对猫麻风病的诊断，但不是决定性的。

4. PCR (聚合酶链反应)。

5.实验动物的实验性感染。

鉴别诊断（Differential Diagnosis）：

1. 皮肤结核(牛分枝杆菌和鼠分枝杆菌)和非典型分枝杆菌/非结核分枝杆菌(鸟分枝杆菌复合体)：肉眼和显微镜下的病变可能类似猫麻风病；必须要用培养、PCR 相鉴别。

2. 黄色瘤：由泡沫状巨噬细胞组成的无菌肉芽肿；类似瘤型麻风病，但缺乏大量的抗酸杆菌。

3. 真菌感染(如孢子丝菌病(I-F07)，隐球菌病(I-F08)和其他全身性霉菌病):通过真菌染色、培养进行鉴别。

4. 无菌肉芽肿和化脓性肉芽肿综合征(pyogranuloma syndrome)。

5. 异物肉芽肿/反应。

6. 慢性细菌感染。

7. 进行性树突状细胞/组织细胞增多症。

比较病理学（Comparative Pathology）

1. 犬麻风病肉芽肿：皮肤和皮下肉芽肿性疾病，由一种尚未命名的物种引起，与 *M.tilburgii*, *M.simiae* 和 *M.genavense* 有关；被认为是通过创伤或节肢动物的咬伤进入；免疫能力强的狗通常会自我限制；偏好对短毛犬的繁殖 (尤其是拳击犬)；通常在头部(耳廓最常见) ；可见多少不等的抗酸杆菌。

2. 牛皮肤结核(牛条件性皮肤分枝杆菌病)：主要在小腿真皮和皮下的结节性病变(可向近端扩散)，无淋巴结受累；认为是腐生分枝杆菌通过皮肤的擦伤感染(堪萨斯分枝杆菌在一些病例中被报道)；牛结核菌素皮肤试验可能导致假阳性反应。

3. 大鼠和小鼠(鼠麻风病):由麻风病分枝杆菌引起的麻风病样病变；主要在内脏和皮肤(很少在周围神经)。

4. 麻风分枝杆菌感染人类、黑猩猩、黑白眉猴和犰狳；与人类麻风病不同，猫麻风病的典型特征不是周围神经受累(见 I-B04)。

5. 田鼠分枝杆菌：田鼠结核病；野鼠是维持宿主，由于对野鼠的不利影响，该病具有生态学意义；随着年龄的增长，皮肤损伤只发生在疾病的晚期；通常是全身性疾病；皮下和皮肤损伤几乎只发生在头部；在感染的动物，90%的肝脏和80%脾脏出现结核病灶；在无全身性病变时(肝、脾受累)，肺部未发现结核病灶。

6.红松鼠：在赖特岛的红松鼠中发现了麻风杆菌病。

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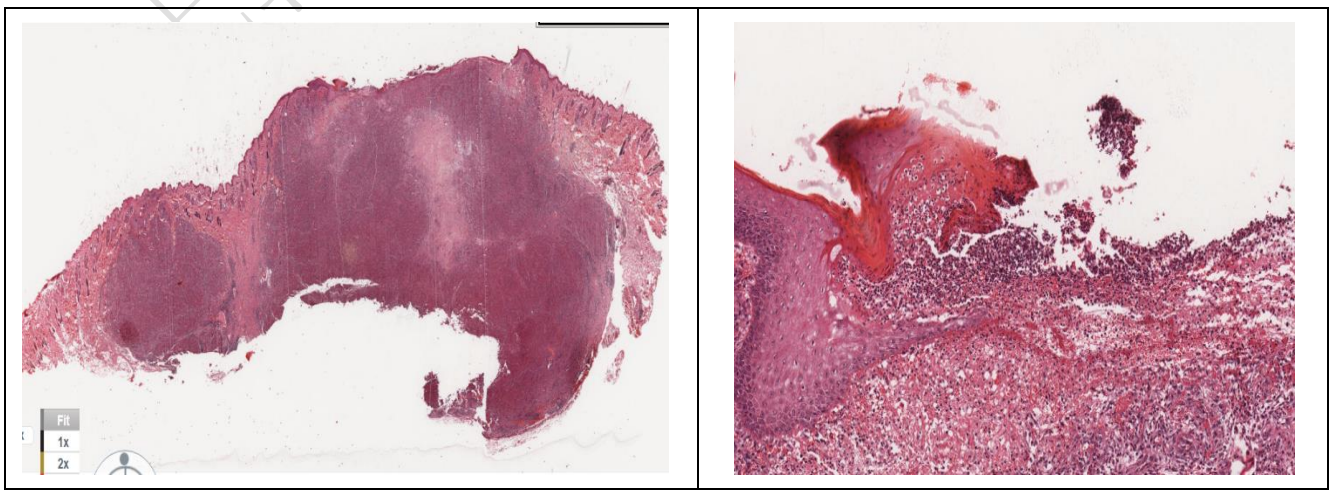

图 1　低倍镜下皮下多个结节（HE ×1）	图 2 表皮轻度增生和局灶性溃疡（HE ×4）
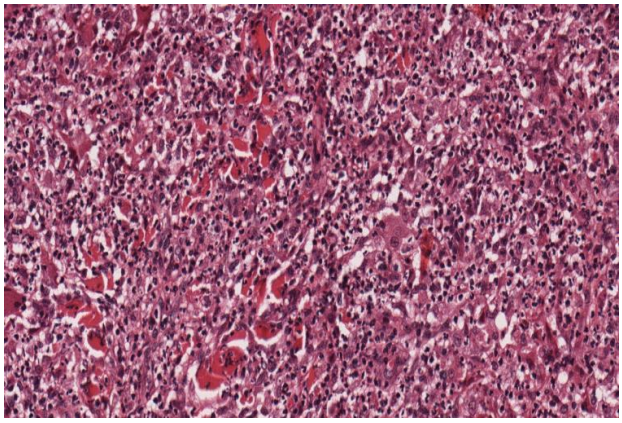	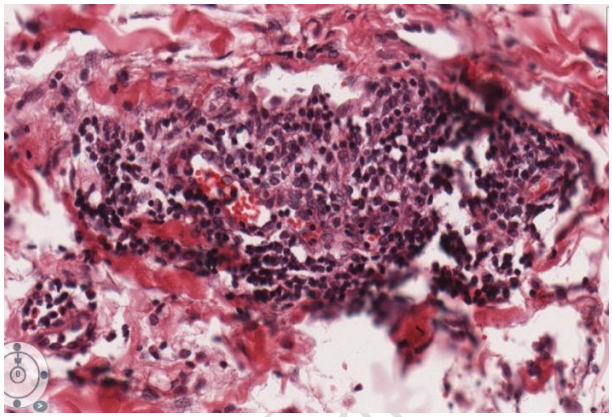
图 3　化脓性肉芽组织（HE ×10）	图 4 血管周围淋巴细胞和浆细胞聚集（HE ×20）
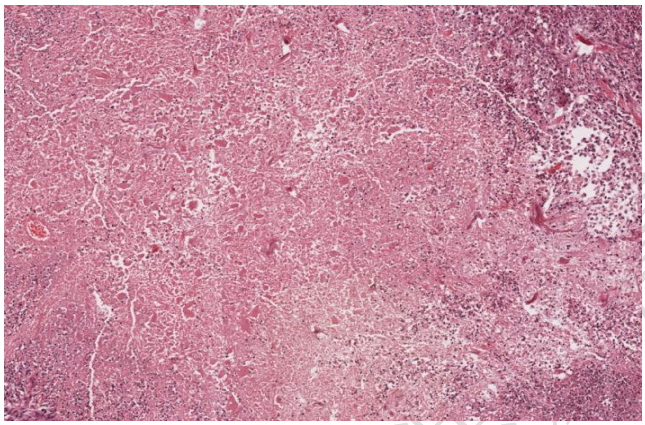	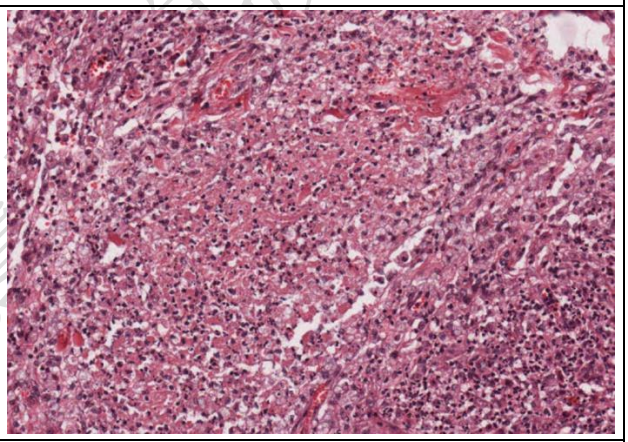
图 5 凝固性坏死区域（HE ×4）	图 6 溶解性坏死区域（HE ×10）
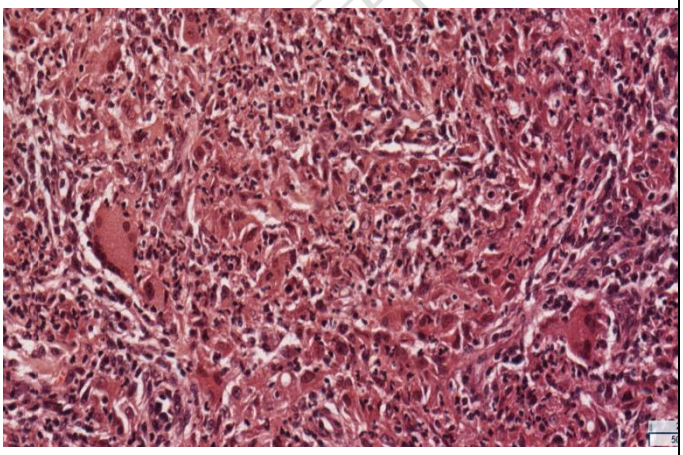	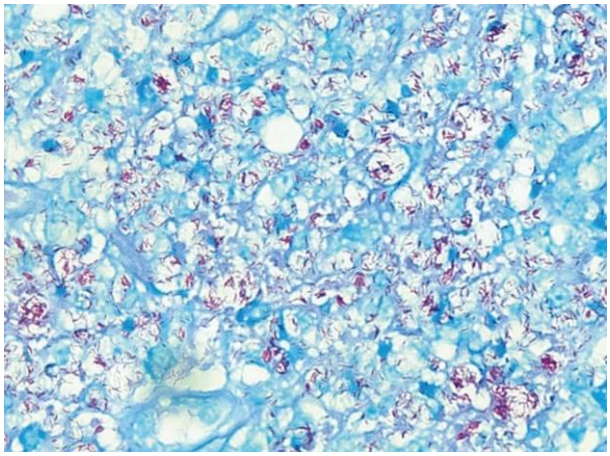
图 7 多核巨细胞(Langhans 型和异体型)（HE ×20）	图 8 Ziehl-Neelsens 尼氏抗酸染色（HE ×10）

JPC SYSTEMIC PATHOLOGY
INTEGUMENTARY SYSTEM
August 2019
I-B03 (NP)

Signalment (JPC #1113469): Cat

HISTORY: This cat presented with multiple skin nodules.

HISTOPATHOLOGIC DESCRIPTION: Haired skin: Expanding the dermis, subcutis, separating and surrounding skeletal myofibers of the panniculus carnosus, elevating the overlying mildly hyperplastic and focally ulcerated epidermis, and widely separating adnexa, are multifocal to coalescing, 5-15 mm diameter nodules of pyogranulomatous inflammation. Inflammatory nodules are often centered on areas of coagulative (with loss of differential staining and retention of tissue architecture) and lytic (loss of normal architecture with replacement by eosinophilic cellular and karyorhectic debris admixed with viable and degenerate neutrophils and hemorrhage) necrosis. Necrotic foci are surrounded by numerous epithelioid macrophages, neutrophils, fewer multinucleate giant cells (Langhans' and foreign body types), scattered lymphocytes, plasma cells, fibroblasts and fibrous connective tissue. There are multiple, often perivascular aggregates of lymphocytes and plasma cells at the periphery of the pyogranulomatous nodules. Entrapped lymphatics are moderately ectatic. Multifocally, inflammatory cells separate and surround skeletal myocytes of the panniculus carnosus; affected myofibers are occasionally swollen, with pale, vacuolated sarcoplasm (degeneration). The overlying epidermis is focally extensively ulcerated and replaced by a serocellular crust composed of abundant degenerate neutrophils admixed with eosinophilic cellular and karyorrhectic debris, erythrocytes and eosinophilic, fibrillar, beaded material (fibrin). The epidermis adjacent to the ulcer is mildly acanthotic and spongiotic, with minimal orthokeratotic hyperkeratosis.

Slide B: Haired skin (acid fast): There are moderate numbers of 3-5 um acid-fast bacilli, often arranged in parallel bundles present within the cytoplasm of epithelioid macrophages and multinucleate giant cells.

MORPHOLOGIC DIAGNOSIS: Haired skin and subcutis: Dermatitis and panniculitis, pyogranulomatous and ulcerative, multifocal to coalescing, marked, with intrahistiocytic acid-fast bacilli, breed unspecified, feline.

ETIOLOGIC DIAGNOSIS: Cutaneous mycobacteriosis

CAUSE: *Mycobacterium lepraemurium*

CONDITION: Feline leprosy syndrome

GENERAL DISCUSSION:

Most prevalent in temperate maritime climates of New Zealand, Australia, North America (e.g. northwest US), and Europe

Feline cutaneous mycobacteriosis is now known to be caused by several different species of *Mycobacterium* with overlapping clinical and histological features precluding development of a simple classification scheme; however, three manifestations are classically described:

Feline leprosy syndrome: **Rare**; **caused by mycobacteria species that are difficult to culture**; mycobacterial species include *M. lepraemurium*, *M. visible*, *M.* spp. strain Tarwin, and a novel species in New Zealand and the East Coast of Australia

Atypical mycobacteriosis (opportunistic mycobacterial granulomas): Chronic or recurrent fistulous tracts, ulcers, fasciitis, and ulcerative nodules most frequently on **caudal abdomen, inguinal or lumbar regions**; **causative organisms thrive in fatty tissues;** typically caused by wound contamination with saprophytic and non-saprophytic mycobacteria; most cases caused by rapidly growing species (e.g. ***M. fortuitum***, *M. phlei*, *M. smegmatis*, *M. chelonae*) or rarely, slowly growing species (*M. avium*, *M. chitae*, *M. xenopi*, *M. ulcerans*); ease of culture differentiates atypical mycobacteriosis from feline leprosy

Histologically there is multifocal pyogranulomatous dermatitis and/or panniculitis with numerous **clear vacuoles surrounded by neutrophils**; clear vacuoles contain **rare acid-fast bacteria** (paucicellular)

Three syndromes are recognized:

Mycobacterial panniculitis with chronic infection or skin and subcutis

Pyogranulomatous lobar pneumonia

Disseminated disease in immunocompromised animals

Cutaneous tuberculosis ("classic tuberculosis"): Multiple ulcers, plaques, nodules, and abscesses that discharge a thick exudate composed of pyogranulomatous inflammation with caseous necrosis; **cats often develop submandibular lymphadenopathy**; caused by *M. bovis*, *M. tuberculosis*, or rarely, *M. avium* or *M. microti*; typically, oral route of infection, les often via infected rodents/meat, unpasteurized milk

PATHOGENESIS:

Cat or rat bite (suspected mode of transmission) > enters macrophages > **blocks fusion of phagosome and lysosome** > intracellular replication > persistence of antigen in tissue > tissue destruction via cell mediated inflammatory response

Immunosuppression has been proposed to contribute to infection, particularly in lepromatous leprosy caused by a novel mycobacterial species in older cats; however, no association concurrent infection (e.g. FIV, FeLV) has been proven

Tuberculoid leprosy is characterized by a TH1 response with production of IL-2 and IFN-γ (which activates macrophages); IL-12 is important in the generation of a TH1 response, and lack of IL-12 may lead to lepromatous leprosy

Lepromatous leprosy is characterized by a defective TH1 response or a dominant TH2 response with production of IL-4, IL-5, and IL-10 that may suppress macrophage activation

TYPICAL CLINICAL FINDINGS:

Young, male outdoor cats overrepresented

Progressive and often aggressive clinical course of infection, dependent on host immunity, the mycobacteria species, and size of the infective inoculum

TYPICAL GROSS FINDINGS:

Focal to multifocal cutaneous papules and firm, well circumscribed, alopecic, and variably ulcerated nodules, 2mm to 40mm in diameter

Lymphadenopathy common

TYPICAL LIGHT MICROSCOPIC FINDINGS:

Feline leprosy syndrome: Two distinct morphologic patterns

Tuberculoid leprosy:

Dermal to subcutaneous granulomas with central caseation, surrounded by pyogranulomatous inflammation with epithelioid macrophages and occasional multinucleated giant macrophages

Relatively few to moderate AFB, often confined to necrotic areas

Lepromatous leprosy: **Generally, indicates a post host immunity**

Nodular to diffuse granulomatous dermatitis and panniculitis **without necrosis**

Sheets or nodules **of large, foamy macrophages** with sparse giant cells

Variable numbers of scattered lymphocytes, plasma cells, multinucleate giant macrophages, and neutrophils

Abundant intracellular AFB (multibacillary) arranged in dense parallel intrahistiocytic intracytoplasmic accumulations which displace the nucleus

Mineralization and encapsulation not typically observed

+/- Acanthosis and/or ulceration in overlying epidermis

Tuberculosis: **Nodular to diffuse granulomatous to pyogranulomatous dermatitis and panniculitis, with caseous central necrosis**

ADDITIONAL DIAGNOSTIC TESTS:

Acid fast stains: Ziehl-Neelsen (standard), Fite-Farraco (modified), Kinyoun's (modified)

Extremely difficult to culture; requires an enriched egg yolk medium; may take weeks to months to grow

Presence of AFB with a negative mycobacterial culture supports the diagnosis of feline leprosy, but is not definitive

PCR

Transmission of the disease to laboratory animals

DIFFERENTIAL DIAGNOSIS:

Cutaneous tuberculosis (*M. bovis and M. microti*) and atypical mycobacteria/nontuberculosis mycobacteria (*M. avium* complex: Gross and microscopic lesions may resemble feline leprosy; must differentiate with culture, PCR

Xanthoma: Sterile granulomas composed of foamy macrophages; resemble lepromatous leprosy but lack the numerous AFB

Mycotic infections (e.g. sporotrichosis (I-F07), cryptococcosis (I-F08) and other systemic mycoses): Differentiate with fungal stains, culture

Sterile granuloma and pyogranuloma syndrome

Foreign body granulomas/reactions

Chronic bacterial infection

Progressive dendritic cell histiocytosis

COMPARATIVE PATHOLOGY:

Canine leproid granuloma: Granulomatous disease of skin and subcutis caused by an as yet unnamed species related to *M. tilburgii*, *M. simiae*, and *M. genavense*; thought to enter via **trauma or biting arthropods**; often self-limiting in immunocompetent dogs; breed predilection for short-haired breeds (especially **boxers**); variable number of AFB seen; often on the head (**pinna** most common)

Bovine cutaneous tuberculosis (cutaneous opportunistic mycobacteriosis): Nodular lesions in the dermis and subcutis primarily of lower legs (may spread proximally) without lymph node involvement; saprophytic mycobacterial implicated and thought to enter via abrasions (***M. kansasii*** has been reported in some cases); may cause **false positive reaction to bovine tuberculin skin tests**

Rats and mice (murine leprosy): Leprosy-like disease caused by *M. lepraemurium*; primarily viscera and skin (rarely peripheral nerves)

Mycobacterium leprae infects humans, chimpanzees, sooty mangabeys, and armadillos; in contrast to human leprosy, feline leprosy is not typified by peripheral nerve involvement (see I-B04)

Mycobacterium microti: Vole tuberculosis; field vole is the maintenance host, the disease is of ecological interest due to adverse effects on field voles; increasing prevalence with age, skin lesions only occur in advanced stages of disease; generally a systemic disease; subcutaneous and skin lesions are almost exclusively in the cranial part of the body; tuberculosis lesions were noted in the liver and spleen in 90% and 80% of affected animals; never found tuberculosis lesions in lungs without systemic disease (involvement of liver and spleen)

Red squirrels: *M. lepramatosis* has been identified in Isle of Wright red squirrels

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病例 CP2022-87

切片连结：
https://www.askjpc.org/wsco/wsc_showcase2.php?id=dnc1c0hjOG5Da2FIS3lTa1BJQzRsdz09

演讲及翻译人（Presenter and translator）：
杨洪宝，中国药科大学新药安评中心

信息：

8 个月大的母羊（白羊）。这只小羊一直生长良好，直到 4 周前才被发现耳朵水肿，白天躺在阴凉处。在接下来的 4 周里，小羊体重逐渐减轻，眼睛周围、双耳背侧和面部的皮肤脱落。主人出于人道的考虑选择安乐死，因为这只小羊没有任何好转的迹象，而且一直在摩擦它的脸和耳朵。

大体描述：

尸检显示，整个尸体的脂肪组织呈淡黄色。肝脏形状正常，但稍硬，呈青铜色。没有其他明显异常。

组织病理描述:

在整个切片中，门静脉三联因胆管数量的增加和疏松的纤维结缔组织(浸润有适量的淋巴细胞和浆细胞)而不同程度地扩大。许多大中型胆管内衬发育不良的上皮细胞，周围有水肿的外膜，外膜含有毛细血管和反应性成纤维细胞。有些大导管要么完全被水肿的肉芽组织所取代，要么有明显衰减的管腔。门脉区偶尔有大血管在受损胆管旁发生管壁分段增厚。实质可见散在聚集的中性粒细胞和偶见的纤维化灶，但肝细胞不受影响。

形态学诊断:

亚急性淋巴细胞/浆细胞性胆管炎伴管周水肿、代偿性纤维化和再通。

条件：

孢子丝蛋白中毒

贡献者的评论:

这些肝损伤是典型的由接触孢子菌素引起的，孢子菌素是一种由菌类石孢菌产生的毒素。这种真菌很容易在黑麦草牧场的死亡植物上生长，含有孢子素的孢子在温暖潮湿的天气(通常发生在秋天)可以达到很高的水平。芽孢杆菌毒性是新西兰北岛反刍动物和骆驼科动物产量损失、病俭甚至死亡的一个重要原因。澳大利亚南部和南非也报告了这种疾病。该疾病的特点是肝源性光敏，在

新西兰通常被称为面部湿疹。

大、中型肝内、肝外胆管是毒素的主要靶点，严重者可减弱或完全闭塞。这些导管的改变实际上是孢子虫毒性的特征，(3,4,6)门脉纤维化和胆管增生代表了大导管堵塞后的非特异性继发性改变。

虽然病变遍及整个肝脏，但左(腹)叶比右叶受影响更严重。在慢性病例中，特别是那些暴露于亚致死剂量超过一年的动物，左叶可能明显萎缩，仅以纤维残余存在，有时含有小的增厚肝细胞残余。在这种情况下，右叶是典型的肥厚，肝脏呈圆形。

亚急性孢子虫素毒性的特征是血清中 GGT 活性显着增加(通常远高于 1000 IU/L)，在暴露于毒素后几个月仍保持升高。

JPC 诊断:

肝:胆道增生，弥漫性，明显，反应性发育不良，中度门静脉和桥接纤维化，轻度淋巴浆细胞性门静脉肝炎。

会议评论：

虽然会议参与者没有提供大体尸检结果或面部湿疹的临床病史，但大多数人怀疑是由于存在门脉和桥接纤维化引起的中毒性病因。此外，显着的胆道增生导致许多参与者考虑针对胆道上皮的毒素，特别是真菌毒素孢子体蛋白；然而，这些病变的鉴别诊断还必须包括 phomopsin、Lantana、黄曲霉毒素和吡咯里嗪生物碱肝毒性，以及南非称为 geeldikkop 的疾病。视磷素、兰塔纳、黄曲霉毒素和吡罗里西定生物碱肝毒性

Phomopsin 是一种由腐生真菌 *Phomopsis leptostromiformis* 产生的真菌毒素，通常感染羽扇豆；它是一种有效的微管抑制剂，可导致中期有丝分裂停滞。因此，除了胆汁增生和肝纤维化外，这种情况的显微镜特征是存在许多奇异的有丝分裂。光敏素中毒也与肝源性光敏性有关。从马缨丹灌木中提取的有毒五环三萜（尤其是马缨丹 A、B 和 C）可在反刍动物（主要是牛）中诱发肝胆汁淤积、黄疸和肝源性光敏反应。马缨丹肝中毒的组织学特征是巨核细胞增多、胆汁积聚和胆管增生。南非植物蒺藜的皂甙（单独或与孢子虫素结合）可能是导致绵羊 geeldikkop（黄色大头）的原因，其特征是急性中毒时肝细胞空泡化和枯否细胞增生，慢性中毒时胆管内存在结晶物质。

黄曲霉毒素病和吡咯里西啶生物碱毒性与绵羊光敏性的相关性较低，在这种情况下被认为是不太可能的原因。在报告的众多黄曲霉毒素类型中，最常见的是黄曲霉毒素 B1，它通常由曲霉属产生。在肝细胞色素 p450 酶代谢后，在缺乏足够谷胱甘肽-s-转移酶的物种中，有毒代谢物会引起多种致癌、毒性和致畸作用。肝脏的组织学特征包括急性肝细胞坏死，慢性肝纤维化、肝细胞巨核细胞增生和胆管增生。千里光、巴豆和太阳花中的吡咯利嗪生物碱通过肝细胞色素 p450 酶代谢为脱氢吡咯利嗪（DHP）衍生物，可引起与黄曲霉毒素类似的

肝损伤。绵羊被认为对黄曲霉毒素和吡咯里西啶生物碱毒性具有相对抗性；牛、马、家养鹿和猪最易受感染。

光敏化通常分为三大类：类型 1、2 和 3（见附表）。1 型或初级光敏作用发生在摄入预先形成的光动力毒素后，如圣约翰草中的金丝桃素、荞麦中的荞麦苷和某些药物，包括吩噻嗪和四环素。2 型光敏化是由于先天性酶缺乏导致内源性色素积累所致。牛先天性造血卟啉症是由于尿卟啉原 III 协同合成酶（血红素生物合成的关键酶）水平不足所致。卟啉随后在牙本质和骨骼中积聚，导致牙齿和骨骼在紫外线照射下呈粉红色并发出荧光。卟啉也会积聚在皮肤中，导致皮肤坏死，可能是通过诱导活性氧物种或黄嘌呤氧化酶。受影响的牛贫血，积聚的色素在尿液中排出，尿液呈棕色。另一方面，牛红细胞生成性原卟啉病是利木赞牛的常染色体隐性疾病，由铁螯合酶缺陷引起，导致原卟啉 IX 在血液和组织中积聚。这种疾病的特征是旋旋光性皮炎。没有贫血，牙齿、骨骼和尿液没有变色。如本例所示，面部湿疹与 3 型或肝源性光敏相关。这是最常见的形式。它与原发性肝细胞损伤（或不太常见的胆管梗阻）同时发生，是由于强效光动力剂叶绿蓟素的肝脏排泄受损所致。叶绿蓟素是叶绿素的分解产物，由胃肠道中的微生物形成，通过门静脉循环运输；肝细胞通常吸收叶菊酯并将其排泄到胆汁中。在食用富含叶绿素的食物和全身性肝损伤的动物中，叶菊酯在各种组织中积累，包括皮肤。光敏性皮炎在所有类型光敏剂中的分布相似；它通常局限于头发稀疏、肤色浅、阳光照射的皮肤区域。

图 1 毛皮 这只 8 个月大的母羊体重逐渐减轻，眼睛周围、双耳背侧和面部的皮肤脱落。

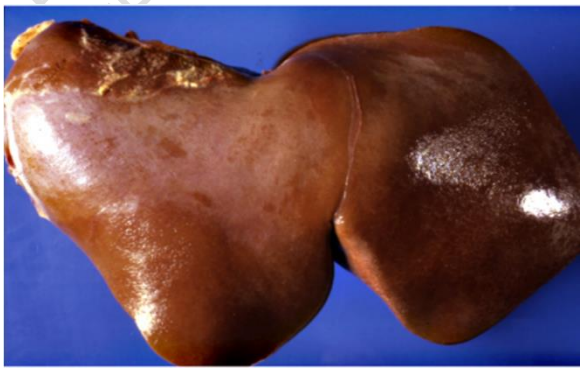
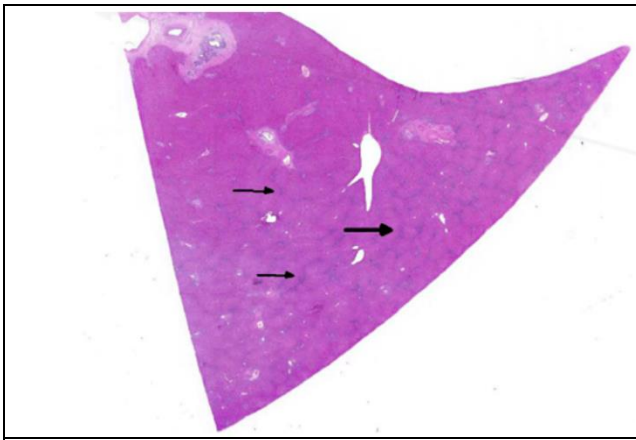
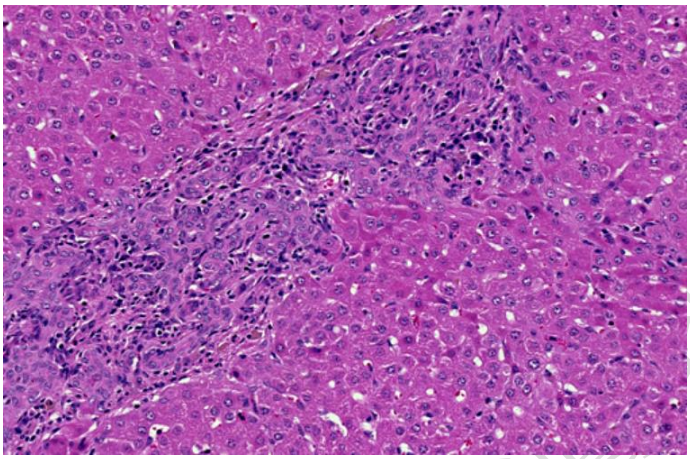
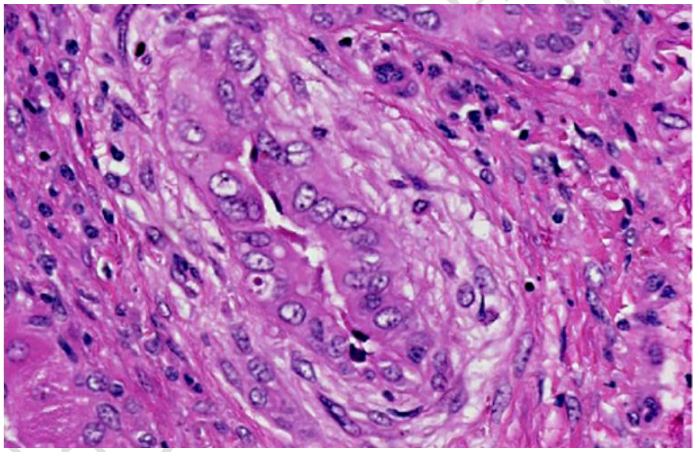


图 2 肝脏形状正常，但稍硬，呈青铜色。

	图 3 肝脏 HE 染色 在切面内，胆管外周水肿，门静脉三联管因其细胞增生而突出（箭头）。0.63×
	图 4 肝脏 门静脉三联管因明显的胆道重叠而扩大，轻度纤维化常突破界板并桥接邻近的门静脉区。118x
	图 5 肝脏 胆管内衬发育不良的上皮细胞，可见明显增大的不等核和多核细胞。288x

Signalment:
8-month-old female sheep, (*Ovis aries*).The lamb had been growing well until 4 weeks earlier when it was noticed to have edematous ears and was lying in the shade during the day. Over the following 4 weeks the lamb progressively lost weight and skin sloughed from around the eyes, the dorsal aspect of both ears, and on the face. The owner elected euthanasia on humane grounds because the lamb had not shown any signs of improvement and was constantly rubbing its face and ears.

Gross Description:
On post-mortem examination, adipose tissue throughout the carcass was pale yellow. The liver was normal in shape, but slightly firm and had a bronze discoloration. No other gross abnormalities were apparent.

Histopathologic Description:
Throughout the section, portal triads are variably expanded by increased numbers of bile ductules and loose fibrous connective tissue infiltrated with moderate numbers of lymphocytes and plasma cells. Many large and medium-sized bile ductules are lined by dysplastic epithelial cells and surrounded by an edematous adventitia containing capillaries and reactive fibroblasts. Some large ducts have been either completely replaced by edematous granulation tissue or are represented by a markedly attenuated lumen. Occasional large blood vessels in portal regions have segmental thickening of their wall adjacent to damaged bile ducts. Scattered aggregates of neutrophils and occasional foci of fibrosis are present in the parenchyma but hepatocytes are unaffected.

Morphologic Diagnosis:
Subacute lymphocytic/plasmacytic cholangitis with periductular edema, replacement fibrosis and recanalization.

Condition:
Sporodesmin toxicosis

Contributor Comment:

These hepatic lesions are typical of those caused by exposure to sporidesmin, a toxin produced by the fungus *Pithomyces chart arum*. This fungus grows readily on dead plant material in ryegrass pastures and spores containing sporidesmin can reach high levels during periods of warm, moist weather, as often occurs during the fall. Sporidesmin toxicity is an important cause of production loss, ill thrift and sometimes death in ruminants and camelids in the North Island of New Zealand. The disease is also reported in southern Australia and South Africa. The disease is characterized by hepatogenous photosensitivity and is commonly known in New Zealand as facial eczema.

Large and medium-sized intrahepatic and extrahepatic bile ducts are the primary target of the toxin and may become attenuated or completely occluded in severe cases. The changes in these ducts is virtually pathognomonic for sporidesmin toxicity,(3,4,6) the portal fibrosis and biliary ductular hyperplasia representing non-specific secondary changes following blockage of larger ducts.

Although lesions occur throughout the liver, the left (ventral) lobe is affected more severely than the right lobe. In chronic cases, especially those where animals are exposed to sublethal doses over more than one year, the left lobe may be markedly atrophic and exist only as a fibrous remnant, sometimes containing small remnants of hyperplastic hepatocytes. In such cases, the right lobe is typically hypertrophic and the liver is rounded in shape.

Subacute sporidesmin toxicity is characterized by a marked increase in the serum activity of GGT (often well above 1000 IU/L), which remains elevated for several months following exposure to the toxin.

JPC Diagnosis:
Liver: Biliary hyperplasia, diffuse, marked, with reactive dysplasia, moderate portal and bridging fibrosis and mild lymphoplasmacytic portal hepatitis.

Conference Comment:

Although conference participants were not provided with gross necropsy findings or the clinical history of facial eczema, most suspected a toxic etiology based upon the presence of portal and bridging fibrosis. Moreover, the prominent biliary hyperplasia led many participants to consider toxins that target the biliary epithelium, specifically the mycotoxin sporidesmin; however, the differential diagnosis for these lesions must also include phomopsin, *Lantana*, aflatoxin and pyrrolizidine alkaloid hepatotoxicity, as well as the South African condition known as geeldikkop.

Phomopsin is a mycotoxin produced by the saprophytic fungus *Phomopsis leptostromiformis*, which commonly infects lupines; it is a potent microtubule inhibitor that results in mitotic arrest during metaphase. Thus, in addition to biliary hyperplasia and hepatic fibrosis, this condition is characterized microscopically by the presence of numerous bizarre mitoses. Phomopsin toxicosis is also associated with hepatogenous photosensitivity.(1,5) Toxic pentacyclic triterpenes (especially Lantadene A, B, and C) from the shrub *Lantana camara* induce hepatic cholestasis, icterus and hepatogenous photosensitization in ruminants, primarily cattle. *Lantana* hepatotoxicosis is distinguished histologically by megalocytosis, bile accumulation and bile duct proliferation.(5) Saponins of the South African plant Tribulus terrestris (alone or in combination with sporidesmin) are likely responsible for geeldikkop (yellow bighead) in sheep, which is characterized by hepatocyte vacuolation and Kupffer cell hyperplasia in acute toxicosis, and the presence of crystalline material within bile ducts in chronic intoxication.(5)

Aflatoxicosis and pyrrolizidine alkaloid toxicity are less commonly associated with photosensitivity in sheep and are considered less likely causes in this case. Of the numerous types of aflatoxin reported, the most common is aflatoxin B1, which is typically produced by *Aspergillus* sp. Following metabolism by hepatic cytochrome p450 enzymes, in species that lack adequate glutathione-s-transferase, toxic metabolites cause multiple carcinogenic, toxic and teratogenic effects. In the liver, histological features include hepatocellular necrosis in acute cases, and hepatic fibrosis, hepatocellular megalocytosis and

biliary hyperplasia in more chronic cases. Pyrrolizidine alkaloids from *Senecio, Crotalaria* and *Heliotropium* sp. are metabolized via hepatic cytochrome p450 enzymes into dehydropyrrolizidine (DHP) derivatives, which cause similar hepatic lesions to those described for aflatoxicosis. Sheep are thought to be relatively resistant to both aflatoxin and pyrrolizidine alkaloid toxicity; cattle, horses, farmed deer, and pigs are most susceptible.(1,5)

Photosensitization is generally classified into three broad categories: types 1, 2 and 3 (see included table). Type 1, or primary photosensitization occurs following ingestion of preformed photodynamic toxins, such as hypericin in St. John's Wort, fagopyrin in buckwheat, and certain drugs, including phenothiazine and tetracycline. Type 2 photosensitization is due to congenital enzyme deficiencies resulting in endogenous pigment accumulation. Bovine congenital hematopoietic porphyria results from deficient levels of uroporphyrinogen III cosynthetase, a key enzyme in heme biosynthesis. Porphyrins subsequently accumulate in dentin and bone, causing the teeth and bone to appear pink and fluoresce upon exposure to ultraviolet radiation. Porphyrins also accumulate in the skin, where they cause necrosis, likely via induction of reactive oxygen species or xanthine oxidase. Affected cattle are anemic, and the accumulated pigments are excreted in the urine, which appears brown. Bovine erythropoietic protoporphyria, on the other hand, is an autosomal recessive condition in Limousin cattle caused by a defect in ferrochelatase, which allows accumulation of protoporphyrin IX in the blood and tissue. This disease is characterized solely by the presence of photodermatitis. There is no anemia, and the teeth, bones and urine are not discolored. Facial eczema, as demonstrated in this case, is associated with type 3, or hepatogenous, photosensitization. This is the most common form. It occurs in conjunction with primary hepatocellular damage (or, less commonly, bile duct obstruction) and is due to impaired hepatic excretion of the potent photodynamic agent, phylloerythrin. Phylloerythrin is a breakdown product of chlorophyll, formed by microbes in the gastrointestinal tract and transported via portal circulation; hepatocytes normally take up phylloerythrin and excrete it into bile. In animals on a chlorophyll-rich diet and generalized hepatic damage, phylloerythrin builds up in various tissues,

including the skin. The distribution of the photodermatitis is similar in all types of photosensitization; it is generally confined to sparsely-haired, lightly pigmented, sunlight exposed areas of the skin.(2)

Table: Categories of photosensitization.(2)

Type	**Causes**
Type 1: Primary	Ingestion of preformed **photodynamic toxins** in plants and drugs: • St. John's Wort (hypericin) • Buckwheat (fagopyrin) • Phenothiazine
Type 2	Congenital **enzyme deficiencies** resulting in endogenous pigment accumulation: • Uroporphyrinogen III cosynthetase deficiency (bovine congenital hematopoietic porphyria) • Ferrochelatase deficiency (bovine erythropoietic protoporphyria)
Type 3: Hepatogenous	Build-up of **phylloerythrin** due to generalized hepatocellular damage or bile duct obstruction

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病例 CSCP2022-88

切片原病理号：CASE 2: 19F156892 (JPC 4155173-00)

演讲及翻译人（Presenter and translator）：

英永，山东省药学科学院新药安评中心

Signalment（特征）：

14 岁雌性绝育家养短毛猫

病史（History）：

患病动物表现为后肢进行性瘫痪，后脚和面部引流性皮肤损伤。在过去的几月里，患畜在其他三家诊所接受了兽医的检查和治疗，但都均未成功。患畜是一只只在室内活动的猫，目前正在接种疫苗，喂食商业干猫粮，并与她的主人从北卡罗来纳州搬到了怀俄明州。

体检时，患畜消瘦（3.08 kg），抑郁沮丧，但对触摸有反应。 无法用后肢站立，宁愿用肘部和前臂支撑休息，也不愿用前脚站立。不发烧（温度=100.3 华氏度，即 37.9 摄氏度）。两后腿有退缩和深痛反射，但尾巴感觉减退，膀胱大而易见。 肛门张力有所降低。瞳孔大小不等（左侧大于右侧）。后脚足趾均出现非常坚硬的结节性肿胀，几个脚趾末端有很深的溃疡，并伴有血和脓性分泌物。前足也有类似的、不那么明显的结节性溃疡，也累及右上唇。 此外，在左侧第五肋骨和右侧前臂远端及跖骨区域可触诊到坚硬骨性肿块。听诊支气管肺泡音增加，弥漫性分布，在右侧颅底和背腹象限尤为明显。最初的鉴别诊断清单包括肺肥大性骨病、转移性肿瘤和全身性真菌病（包括孢子丝菌病）。

大体病变（Gross Pathology）：

一只 14 岁绝育母猫，体重 3.08kg，在尸检良好且自溶极少的情况下进行下尸检。猫身体瘦弱，内脏和皮下脂肪组织储存略有减少。外部检查，右上颌犬齿上方的皮肤上有一开放性创口，引流管形成瘘管，向上延伸至右鼻孔外侧。伤口的特征是周围边缘有慢性出血，并有一条中央道延伸穿过皮下和下面的肌肉组织。下颌骨及喙缺失，牙槽窝内右侧上颌犬齿变色、松动。双后肢多指远端有类似的外伤处，有表面溃疡和穿透性溃疡。前肢在有毛皮肤和爪垫交界处的脚趾表面有不太严重的溃疡。 开放性病灶渗出浆液和/或少量脓性渗出物。不规则的环状骨增生使趾骨肿大至正常直径的 10 倍。 此外，右侧跖骨和左侧胫骨干骺端也有类似的骨质扩张。 胸部左侧第 5 至第 7 肋骨中部被一圆形骨性病变局灶性破坏，中央有空洞。

胸腔含有约 10mL 浆性游离液。所有肺叶被离散性或融合性结节，多灶性破裂，结节呈淡褐色至白色，实性至囊性或空洞状，切面上偶渗出脓性至粘液性物质。约 60%肺实质受累，结节大小约 3mm ~ 3cm。胸膜表面的小结节呈脐状外观，中央凹陷，周边变白色。肺叶边缘有肺气肿性改变。气管\、气管淋巴结肿大至正常 20 倍，被类似囊性、实性结节完全占据。

双侧肾脏被膜表面有多灶性、不规则凹陷，延伸到皮质实质深处（与慢性梗死一致）。肝脏弥漫性充血，轻度硬化。 胃内和小肠肠腔是空的。远端结肠适度扩张，含有大量成形的粪便。

实验室结果（Laboratory results）：

生化（Chemistry Panel）

指标	结果	正常范围	备注
总蛋	9.5	5.7 - 8.0	>range g/dl > 正常范围
白蛋白	4.7	2.4 - 3.8	>range g/dl
球蛋白	4.8	2.4 - 4.7	>range g/dl
白球比	1	0.6 - 1.1	in range
碱性磷酸酶	21	12.0 - 65.0	in range U/l
谷丙转氨酶（转氨酶）	20	8.3 - 53.0	in range U/l
胆红素，总胆	4.4	0.1 - 0.5	>range mg/dl
葡萄糖	120	61 - 124	in range mg/dl
胆固醇	160	71.0 - 161.0	in range mg/dl
淀粉酶	322	371 - 1193.0	<="" span="">
脂肪酶	< 10	0.0 ? 76	in range U/l
肌酐	0.5	0.5 - 1.9	in range mg/dl
尿素氮	15.4	15.0 - 31.1	in range mg/dl
钠	> 250	146.0 - 159.0	>range meq/l
氯	> 175	108.0 - 130.0	>range meq/l
钾	2.5	3.8 - 5.3	<="" span="">
钙	7.5	7.9 - 10.9	<range< span=""></range<>
磷	5.5	4.0 - 7.3	in range mg/dl
二氧化碳总量	33.1	16.0 - 22	>range
阴离子间隙	****	7 - 17	

中等溶血

血细胞计数（CBC）

指标	结果	正常范围	备注
WBC 计数，手动	3.6	5.5 - 19.5	<="" span="">
杆状嗜中性粒细胞	6	0 - 3	>range %
中性粒细胞	75	35 - 75	in range %
淋巴细胞	14	20 - 55	<="" span="">
单核细胞	4	1 ? 4	in range %
嗜酸性粒细胞	1	2 - 12	<="" span="">

嗜碱性粒细胞	0	0 - 0.5	in range %
血小板	109	300 - 700	<="" span="">
轻度血小板聚集			
红细胞计数	4.93	5.0 - 10.0	<="" span="">
红细胞压积	18.7	30.0 - 45.0	<="" span="">
血红蛋白	5.8	8.0 - 15.0	<="" span="">
平均红细胞体积	37.8	39.0 - 55.0	<="" span="">
平均红细胞血红蛋白浓度	31.0	30.0 - 36.0	in range g/dl
平均红细胞血红蛋白含量	11.7	13.0 - 17.0	<="" span="">
红细胞分布宽度	19.7	14.0 - 19.0	>range %.

微观描述（Microscopic description）：

远端指骨：远端指骨脱钙后切片特征是软组织明显扩张和消失，广泛浸润，骨膜和骨的界限不清， 中等异型性的肿瘤细胞由呼吸上皮细胞组成，排列成不同的腺样结构中，间质致密。肿瘤细胞呈柱状到立方形，顶端表面可见数量不一的纤毛。细胞边界明显，适量的嗜酸性胞浆，圆形至椭圆形的基底核，具有精细点状染色质和一突出的核仁。细胞及细胞核大小不等。核分裂象是每 10 个高倍视野 13 个，400 倍。有许多大的、离散的或融合的囊性结构，含有嗜酸性分泌物质中央湖，混合固缩或核碎裂碎片，内衬单层肿瘤性呼吸性上皮。有些囊性结构含有变性的中性粒细胞的聚集物。肿瘤侵蚀骨膜和皮质骨，并浸润骨髓髓腔。部分坏死性骨的骨针经常衬有前面所描述的肿瘤细胞和/或衬有少量多核破骨细胞。 肿瘤间质中有中等数量的中性粒细胞、巨噬细胞，偶尔有淋巴细胞和浆细胞松散聚集。. 肿瘤明显扩张皮下和深处真皮，并多病灶延伸至真皮浅层。

贡献者的形态学诊断（Contributor's morphologic diagnosis）：

骨，远节指骨：转移性支气管来源的腺癌。

贡献者评论（Contributor's comment）：

猫肺趾综合征（FLDS）最初是由摩尔和米德尔顿在 1982.9 年从一系列三个病例中描述的 。主要特征是在面对非呼吸系统体征（例如，呼吸困难、咳嗽等）时对原发性肺腺癌进行死后检测。两名患畜出现肢体远端疼痛和肿胀，并在随后几周内出现呼吸症状。第三例患畜有非特异性的临床表现（缺氧和体重减轻），由于生活质量恶化，在接下来的一周被安乐死。2 例软组织肿胀的病例在生前活检后被诊断为转移性腺癌。2000 年一项对另外 36 只猫的回顾性研究创造了“FLDS”这个绰号。 所有猫均患有转移性指癌。同样，无呼吸症状。

虽然临床上典型的 FLDS 是通过转移到四肢来确认的，但也存在变异。指是最常见的部位，但也有转移骨骼肌、骨骼、眼睛和皮肤的记录。偏好转移脚趾的可能与肿瘤的血管侵袭行为以及猫脚趾的高血管性质有关，有助于散热。肿瘤栓塞可能与通常归因于原发性心脏病的主动脉血栓栓塞（ATE）相似。 对 127 例 ATE 的回顾性研究发现 6% ATE 是由肿瘤引起的，是猫的第二大常见病因，远端肢体缺血和坏死也可能是血栓栓塞的结果。最终，血栓栓塞的大小决定于它们可能定居的位置和病理生理学。

根据肿瘤的大小，通过活检或细针抽吸浅表肿块和胸片最容易诊断。原发肿瘤常因缺少呼吸症状而漏诊。 更多的现代成像技术，如计算机断层摄影术在检测原发肿瘤更敏感。很难治疗。化疗并不经常进行，因为其疗效尚未得到充分的证明。受影响的脚趾或肢体的截肢，在实施时，很少是姑息性的。 增加的 CK 可作为骨骼肌转移的标志物。即使进行肺叶切除术，预后较差。从最初症状开始，平均生存时间为 34-58 天。目前还未发现品种或性别偏好。

一般来说，原发性肺部肿瘤在猫身上很少见。其中腺癌最为常见。88%的脚趾癌是原发性肺癌转移的结果，尽管鳞状细胞癌在这些病例中占一小部分。跛行通常是一种常见的主诉，而第三节指骨松解应该引起高度怀疑。然而，应考虑其他差异，包括细菌性和真菌性骨髓炎。1/8 一的猫指甲和甲床疾病是肿瘤。鉴于其他病因有更好的预后和通常对截肢的反应（如细菌性/真菌性骨髓炎）或有更高的平均生存时间(如鳞状细胞癌? 207 天)，建议在手术前诊断或排除原发性肺癌的临床体征。

Contributing Institution: 贡献的机构:

怀俄明大学/怀俄明州立兽医实验室
http://www.uwyo.edu/vetsci/

J PC 诊断（JPC diagnosis）：

脚趾：转移性肺癌

JPC 评论（JPC comment）：

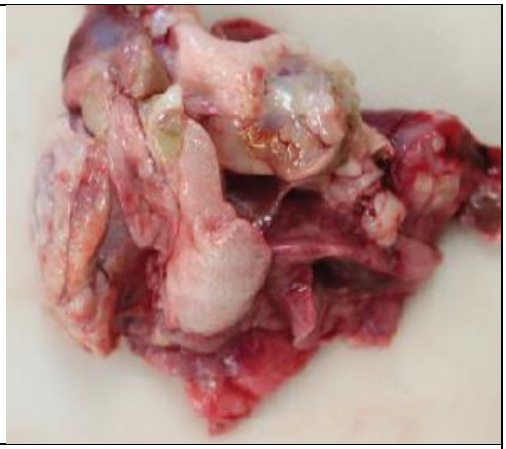
猫肺趾综合征（FLDS）发生时，最常见的转移部位之一是远节指骨背侧及足垫表皮下真皮。

一个重要的鉴别诊断是外分泌腺癌。外分泌腺瘤和腺癌在狗身上已经有文献记载，而外分泌腺瘤在猫身上通常是恶性的。虽然是人类的一种常见疾病，但外分泌腺局限于狗和猫的足垫，这是唯一发生外分泌腺瘤的部位。重要的是，外分泌腺瘤和肺部肿瘤具有不同的免疫组织化学特征。除 napsin A 和角蛋白 7 外，甲状腺转录因子 1（TTF-1）在原发性肺癌/腺癌中表达。大约 50%的外分泌腺癌表达 S100，大约 25%的外分泌腺和大汗腺肿瘤细胞表达 p63，并且尚未在皮肤转移性腺癌中记录。

人类原发性肿瘤常发生转移，但可能报道不足。大约 20-70%死于恶性疾病的患者在尸检时有骨转移的组织学证据，但只有 2%足部有转移性病灶。据报道，这些病变 CK7 和 CDX2（尾型同源框转录因子 2）免疫阳性，与支气管腺癌一致

主持人就狗和猫脚趾病变最常见的区别进行了讨论。在狗中，最常见的包括甲下黑色素瘤、甲下鳞状细胞癌、甲下角化棘皮瘤、小汗腺癌、软组织肉瘤、肥大细胞瘤、创伤/感染和红斑狼疮性甲营养不良。在猫，最常见的脚趾病变包括肺趾综合征、鳞状细胞癌、各种肉瘤、浆细胞足跖皮炎和动静脉瘘

附图

	
图 02-1 指，猫。肿大正常的 5 倍，相邻的指也肿胀。 （图片由怀俄明州大学/怀俄明州州立兽医实验室提供。http://www.uwyo.edu/vetsci/）	图 02-2 指，猫。所有的肺叶都有苍白的肿瘤组织结节，切开时渗出粘液。（照片由怀俄明州大学/怀俄明州州立兽医实验室提供 http://www.uwyo.edu/vetsci/）

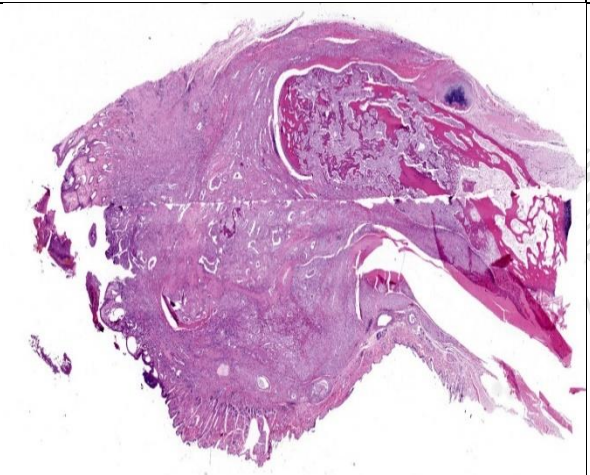
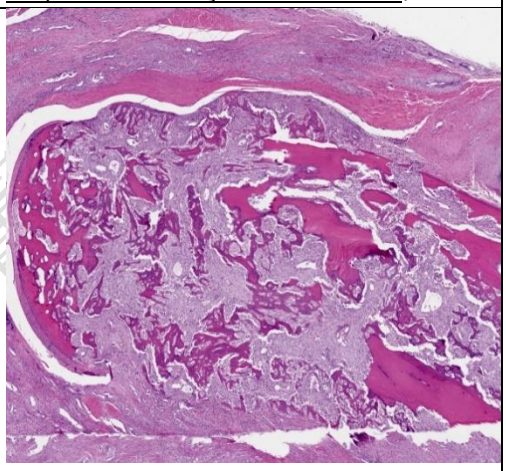

	

图 02-1 指，猫，HE 5X。指矢状切面及第二节指骨进行检查。 第三指骨未呈现。指骨及其腹侧和近端软组织因肿瘤扩张而消失，形成大的囊性腺体。	图 02-4 指，猫，HE 24X。第二节指骨骨肿瘤细胞浸润，大量纤维组织取代骨髓腔，髓质骨吸收形成薄的编织骨小梁，腹侧板层骨吸收，形成少量骨膜编织骨。

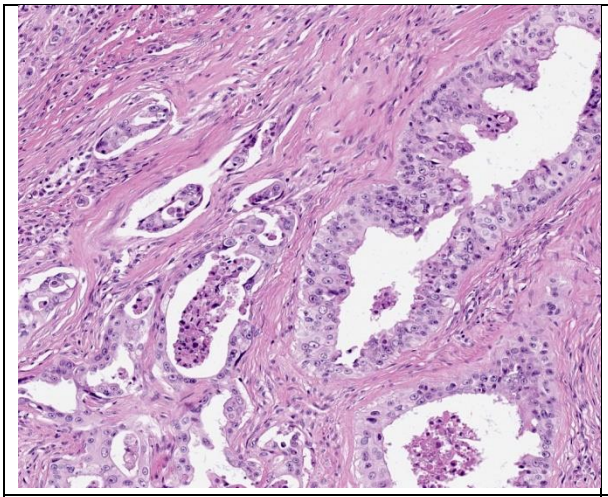
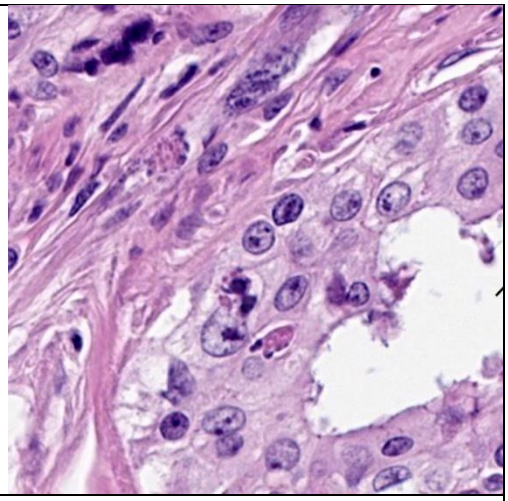
	

图 02-5 指，猫，HE 150X。癌浸润第二节指骨近端及腹侧软组织，形成巢状、索状，最终形成大小不一的复层小管。	02-6. 图 02-1 指，猫，HE 300X。管内衬的肿瘤细胞偶尔显示纤毛(箭头)。

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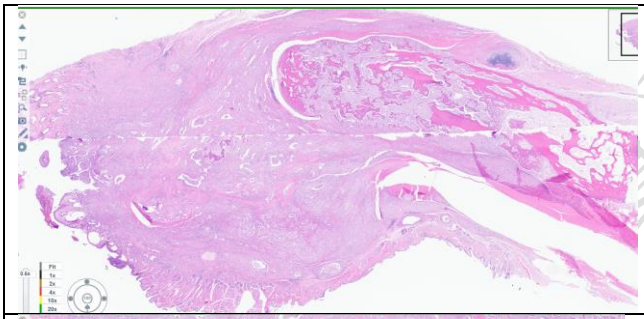
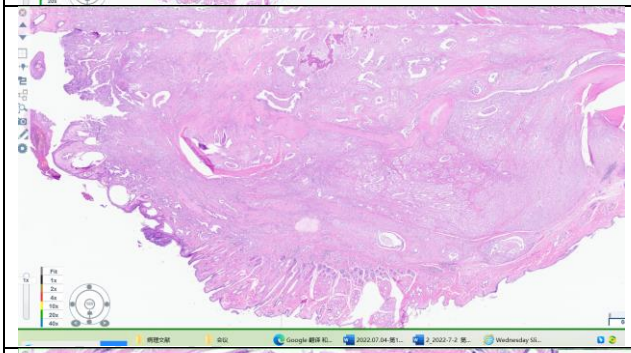
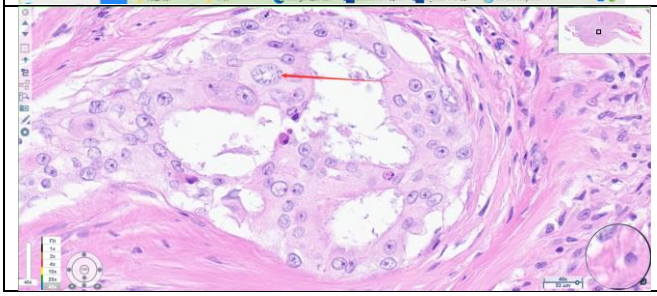
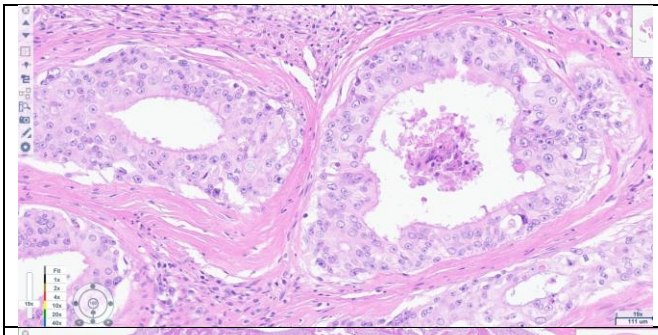
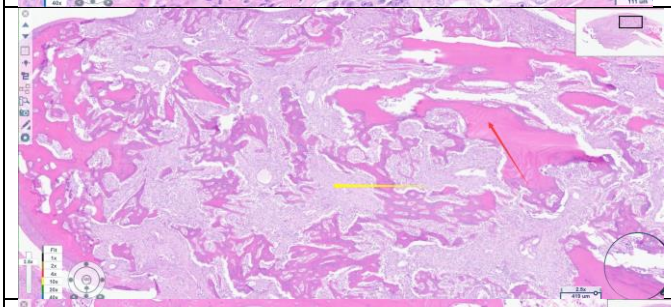
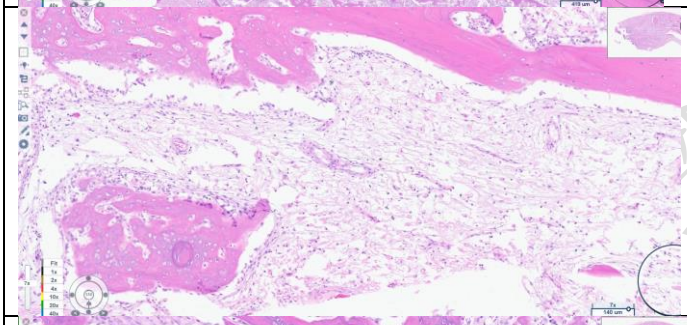
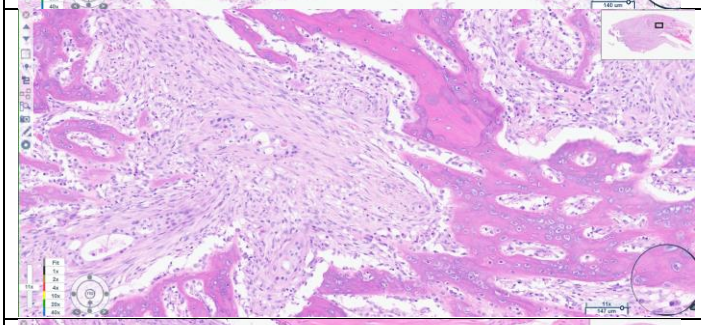
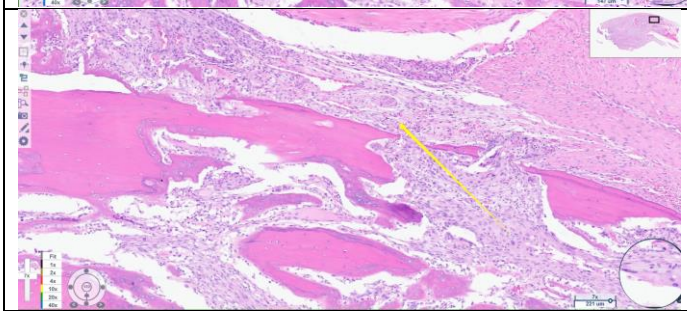
	整体切片（低倍镜）。
	指骨腹侧面（下面是皮肤组织）。
	肿瘤巨核细胞。

	管状细胞层数双侧或多层。
	红色箭头 骨组织，黄色箭头肿瘤组织，骨髓腔不明显。
	髓腔造血细胞不明显，造血细胞减少/缺失。
	髓腔造血细胞不明显，造血细胞减少/缺失、纤维化。
	髓腔造血细胞不明显，造血细胞减少/缺失，纤维化。

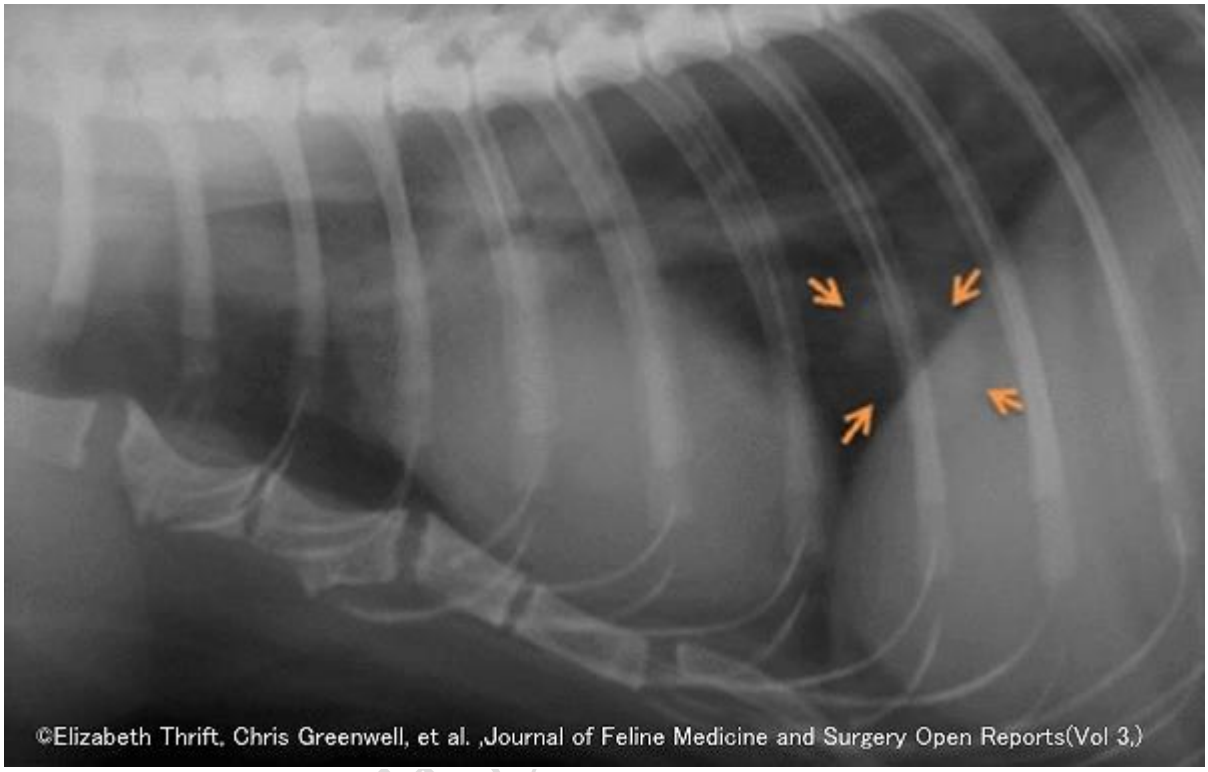
知识拓展:

1、报告了肺癌转移导致指尖肉瘤的“肺趾综合征”的病例报告（2017.3.16/澳大利亚）

猫肺趾综合征（猫呼吸系统，FLDS）是指发生在肺部的癌细胞通过血流等移动，并转移到前腿或后脚趾的疾病。 自 1982 年报告三只猫的原发性肺癌转移到指尖以来，它逐渐引起了人们的关注，现在它们被确认为一种疾病。 虽然疾

病名称中包含“脚趾”，但转移目标不仅仅限于脚趾，而且存在脊柱、肌肉和眼睛的变化。 2017 年，澳大利亚二级诊所的医生报告了 7 例“猫肺趾综合征”病例。

临床表现：1）肺部病变：在许多情况下，没有呼吸困难、咳嗽或胸腔积水等症状，如原发性肺癌。 有的可以通过 X 光检查为明显的肿瘤性病变，有的不能确认。 CT 扫描可以确认难以看到的病变。



2）指尖病变：它经常表现为手腕或脚踝的疼痛和肿胀，有时是单侧性的，也可以是两侧的。 具体来说，手腕（腕骨）、脚踝（足根骨）、手掌（中手骨）、脚底（中足骨）、脚趾（指骨）、脚趾（肋骨）、脚趾之间等。 在 x 射线中，骨的溶解和关节的渗透往往可以确认。

3）肿瘤病变：小腿、大腿、背部、腹部、侧腹、颈部、肩部、眼睑、脸颊、嘴唇、侧头、口腔（味觉）

4）急性后肢瘫痪：主诉猫的后腿突然停止移动”。 具体表现为与腹部主动脉栓塞一致的症状，如急性后腿瘫痪、后肢尖端寒冷、、股动脉跳动两侧缺失等。

在许多情况下，即使进行超声心动图或 x 光检查，也无法确认最常见的心脏病（心肌病）的发现，这是腹部主动脉栓塞的原因。

2、Feline lung-digit syndrome: unusual metastatic patterns of primary lung tumours in cats。

N. Goldfinch, D. Argyle，Published 27 February 2012，Medicine，Journal of Feline Medicine and Surgery

猫“肺趾综合征”描述了一种不寻常的转移模式，这种转移模式在各种类型的原发性肺肿瘤中见，特别是支气管和细支气管肺泡腺癌。肿瘤转移见于非典型部位，尤其是四肢远端指骨；负重指最常受累，多指多肢受累多见。由于与原发性肿瘤相关的临床症状，通常无法检测到猫的原发性肺肿瘤；相反，许多病例出现与远处转移有关的迹象。猫原发性肺肿瘤的其他转移部位包括皮肤、眼

睛、骨骼肌和骨骼，以及多个胸部和腹部器官。这些病变被认为是由肿瘤的直接动脉栓塞引起的。事实上，主动脉三分叉处的肿瘤栓塞是可能的。
原发性肺肿瘤在猫中并不常见。年龄较大的动物受影响最大（出现时的平均年龄为 12 岁，范围为 2-20 岁）。没有明显的性别或品种偏好。
临床挑战：猫肺趾综合征对诊断提出了挑战。通常会出现脚趾肿胀和发红，甲床有脓性分泌物，以及相关指甲的发育不良或固定外鞘。虽然这些迹象可能暗示感染，但这可能继发于指部转移性病变，特别是在中年或老年猫中。远端指骨广泛骨溶解的放射影像学证据，可以跨关节到第二指骨，提高了临床怀疑原发性肺肿瘤转移的指数。在任何手术或数字截肢之前都需要进行胸部 X 光检查，因为患有这种综合征的猫的预后通常很严重，平均存活时间在发病后仅 58 天。

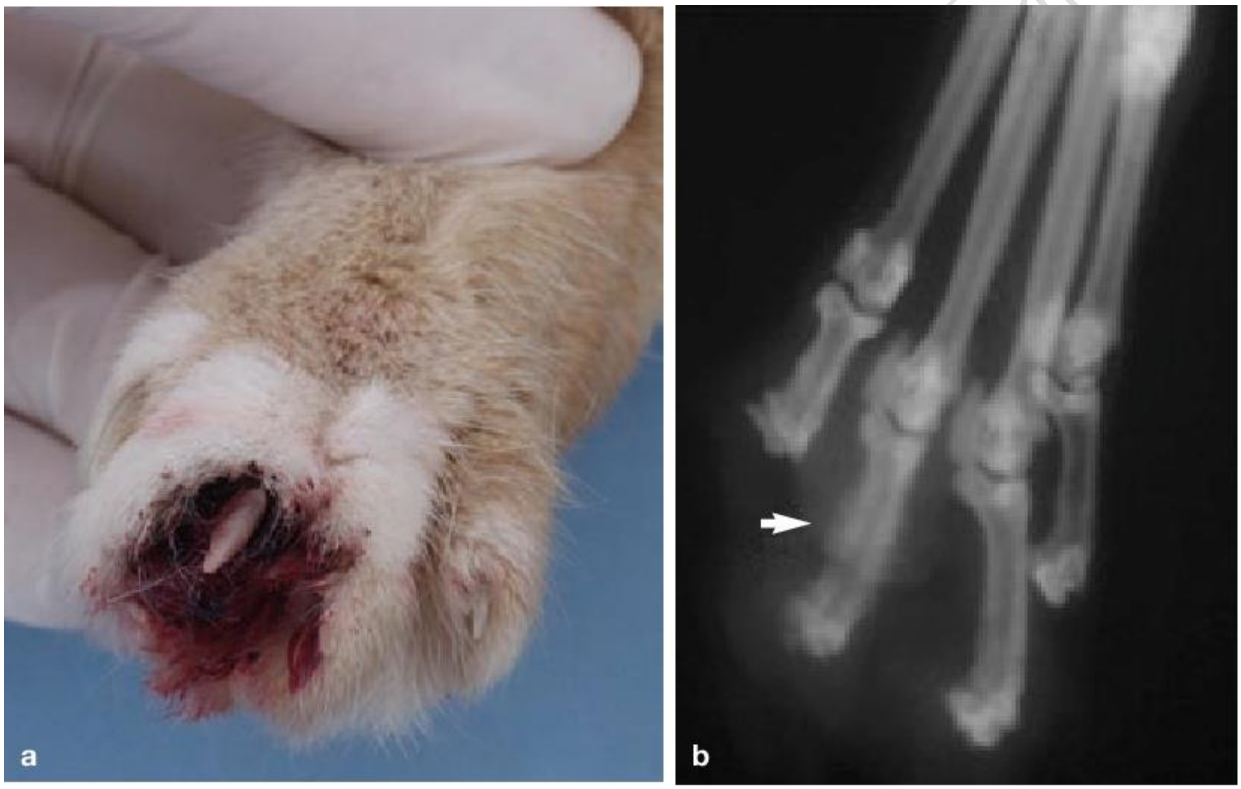


Figure 1 (a) Metastatic lesion from a primary pulmonary adenocarcinoma in the digit of an elderly cat. The cat presented with lameness and clinically evident deviation of the nail, local

图 1 (a) 老年猫脚趾原发性肺腺癌的转移性病变。 这只猫表现出跛足和临床上明显的指甲偏离、局部软组织炎症和甲床的血清血性分泌物。(b) 射线照相显示相关指骨的骨质溶解（箭头）

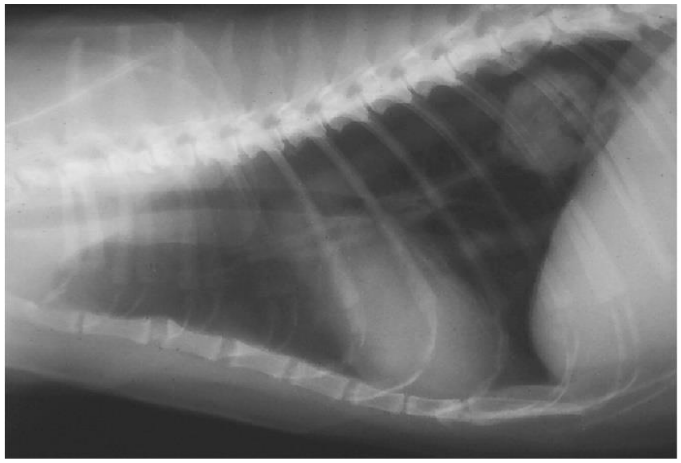


Figure 2 A primary pulmonary neoplasm is evident within the caudal lung fields of the same cat

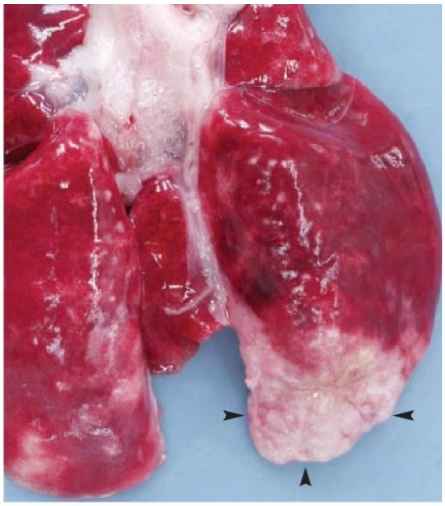
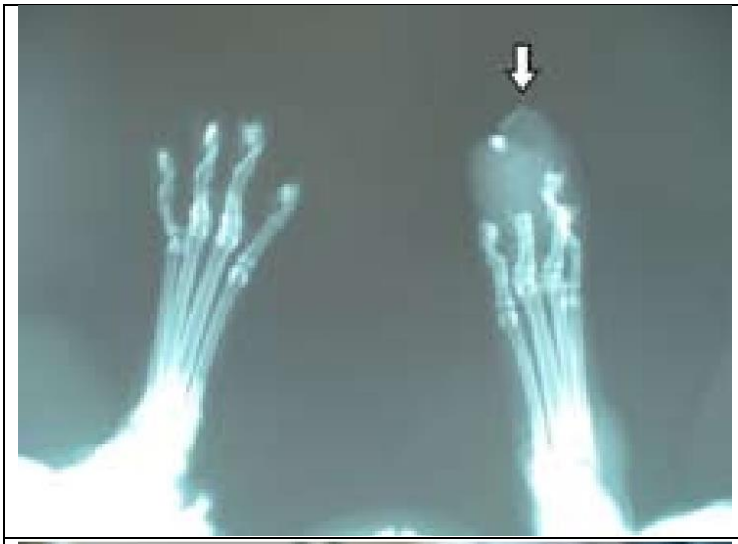
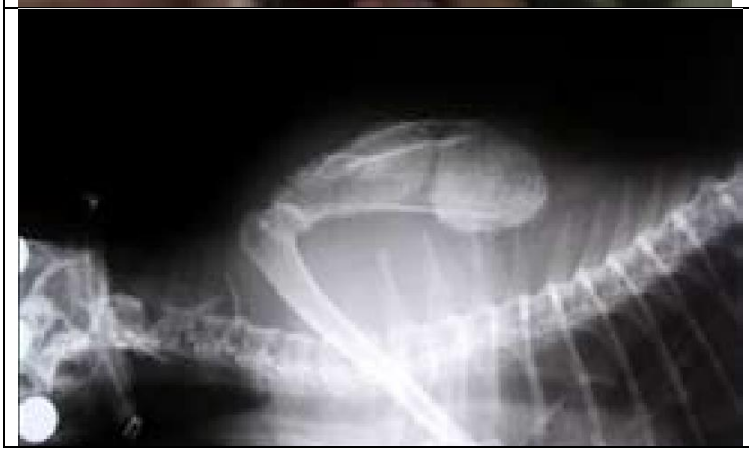


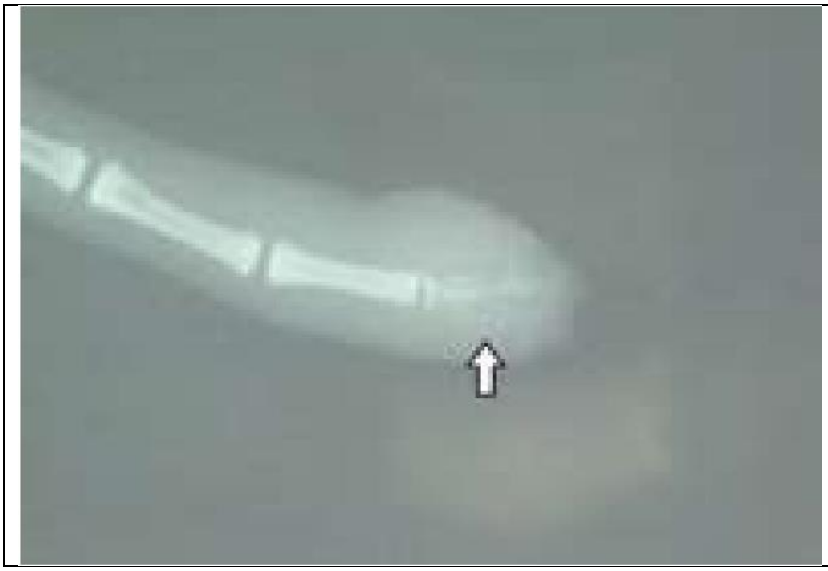
Figure 3 Gross appearance of neoplastic proliferation

图 3 图 1 和图 2 中猫的尾肺区域内肿瘤增殖（箭头）的总体外观。

3、Clinical findings in lung-digit syndrome in five cats。

Hiroki Sugiyama1），Takuya Maruo1），Takuo Shida1,2），Takeshi Ishikawa1） Kayo Kanakubo1），Hiroo Madarame1），Hideki Kayanuma1,2），and Tsunenori Suganuma1,2

	猫 2 后肢的 X 射线图像。可见明显的骨质溶解。
	猫 2 右后肢的照片。可见肿胀、溃疡和腐烂涉及多个脚趾。
	Cat 3 肩胛骨的 X 线图像。可见软组织肿胀和骨质溶解。

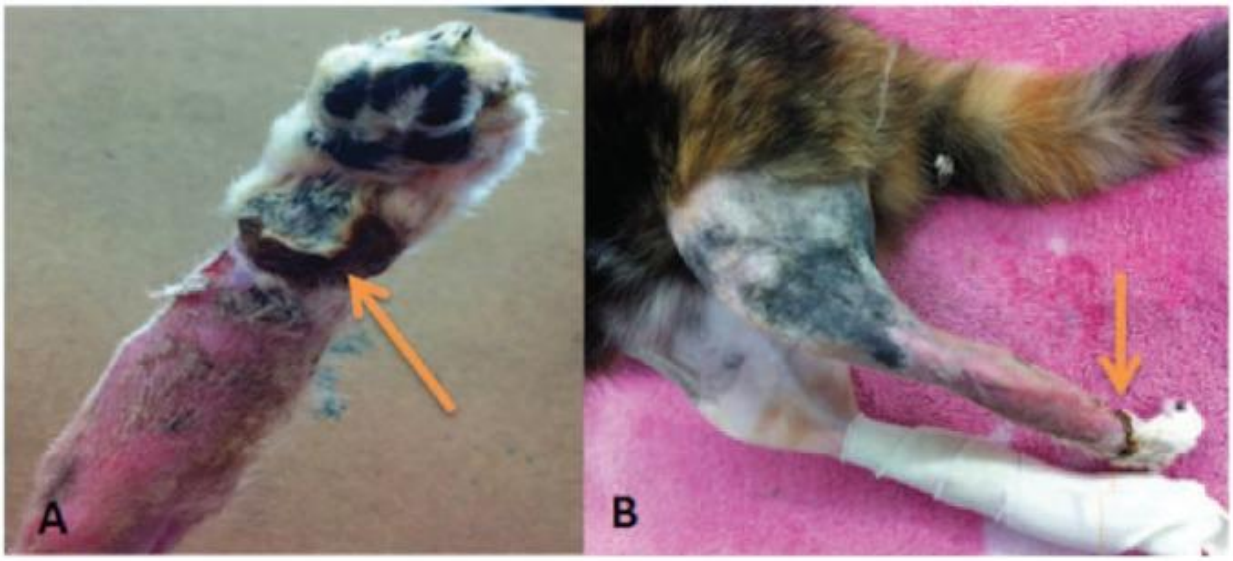


Cat 4 尾巴的 X 射线图像。可见尾椎骨溶解。

4、Metastatic pulmonary carcinomas in cats ('feline lung–digit syndrome'): further variations on a theme

Elizabeth Thrift,1 Chris Greenwell,2 Audra-Lynne Turner,3 Andrea M Harvey,2 Donna Maher,4 and Richard Malik5

JFMS Open Rep. 2017 Jan-Jun; 3(1)



病例 1.(a) 截肢前右后肢远端出现； 足底方面。 (b) 截肢前两个后肢的外观。 注意神经源性肌肉萎缩和后肢挛缩。 (a) 和 (b) 中的橙色箭头突出显示皮肤坏死区域。

CASE 2: 19F156892 (JPC 4155173-00)

Signalment:
14-year-old female spayed domestic short haired cat (*Felis catus*)

History:
The patient presented with complaints of progressive paralysis in the hind limbs and draining skin lesions of the hind feet and face. The patient had been examined and treated unsuccessfully by veterinarians at three other clinics over the last several months. The patient was an indoor-only cat, was current on vaccinations, was fed a commercial dry cat food, and had moved with her owners to Wyoming from North Carolina.

On physical exam, the patient was thin (3.08 kg) and somewhat depressed but responsive to handling. She was unable to stand on her hind limbs and preferred to rest on her elbows and forearms rather than stand on her front feet. She was afebrile (temp = 100.3 F). Withdrawal and deep pain reflexes were present in both hind legs, but her tail had reduced sensation and her bladder was large and easily expressed. Anal tone was judged to be somewhat reduced. Anisocoria (L > R) was noted. Very firm, nodular swellings of all the digits of the hind feet were present, and the ends of several of the toes were deeply ulcerated and matted with blood and purulent-type discharge. Similar, less dramatic nodular ulcers were present in the front feet and also involved the right upper lip. Additionally, hard, bony masses could be palpated on the left 5th rib and the distal right antebrachium and metatarsal regions. Increased bronchovesicular pulmonary sounds were ausculted diffusely but were particularly prominent in the right cranial and dorsocaudal quadrants. The initial differential diagnostic list included pulmonary hypertrophic osteopathy, metastatic neoplasia, and systemic mycotic disease (including sporotrichosis).

Gross Pathology:
A 14-year-old female spayed domestic short haired cat weighing 3.08 kg was presented for necropsy in excellent postmortem condition with minimal autolysis. The cat was in thin body condition with mildly reduced stores of visceral and subcutaneous adipose tissue. On external exam, there was an open wound with a fistulous draining tract in the skin overlying the right maxillary canine, extending upward to the lateral aspect of the right nostril. The wound was characterized by a peripheral rim of chronic hemorrhage with a central tract extending through the

subcutis and the underlying musculature. There was loss of the underlying maxillary bone and rostrum, with dark discoloration and loosening of the right maxillary canine in the alveolar socket. The distal aspects of multiple digits on both hindlimbs had similar external wounds with surface ulceration and deep penetrating tracts. The front limbs had less severe ulcerations on the digital surfaces at the junction of the haired skin and the paw pad. Open lesions oozed serous fluid and/or small amounts of purulent exudate. The phalanges were expanded up to 10 times the normal diameter by irregular, circumferential bony proliferations. Additionally, there was similar bony expansion of the right metatarsal bones and the left tibial metaphysis. The mid-bodies of ribs 5 through 7 on the left side of the thorax were focally disrupted by a circular bony lesion with central cavitation.

The thorax contained approximately 10mL of serosanguineous free fluid. All lung lobes were multifocally disrupted by discrete to coalescing nodules that were pale tan to white, solid to cystic or cavitated, and occasionally oozed purulent to mucinous material on cut section. Approximately 60% of the lung parenchyma was affected, and nodules ranged in size from ~3mm to 3cm. Small nodules on the pleural surface had an umbilicated appearance with central depressions and peripheral rims of white discoloration. There was emphysematous change at the borders of the lung lobes. The tracheobronchial lymph nodes were expanded up to 20 times normal and were completely effaced by similar solid to cystic nodules.

Bilaterally, the kidneys had multifocal, irregularly shaped pitted depressions on capsular surface that extended deep into the cortical parenchyma (consistent with chronic infarcts). The liver was diffusely congested and moderately firm. The stomach and small intestines were empty. The distal colon was moderately dilated and contained a large amount of formed feces.

Laboratory results:

Chemistry Panel

Test	Result	Normal Range	High or Low Units
Total Protein	9.5	5.7 - 8.0	>range g/dl
Albumin	4.7	2.4 - 3.8	>range g/dl

Globulin	4.8	2.4 - 4.7	>range g/dl
A/G Ratio	1	0.6 - 1.1	in range
ALP	21	12.0 - 65.0	in range U/l
ALT (SGPT)	20	8.3 - 53.0	in range U/l
Bilirubin, total	4.4	0.1 - 0.5	>range mg/dl
Glucose	120	61 - 124	in range mg/dl
Cholesterol	160	71.0 - 161.0	in range mg/dl
Amylase	322	371 - 1193.0	<="" span="">
Lipase	< 10	0.0 ? 76	in range U/l
Creatinine	0.5	0.5 - 1.9	in range mg/dl
BUN	15.4	15.0 - 31.1	in range mg/dl
Sodium	> 250	146.0 - 159.0	>range meq/l
Chloride	> 175	108.0 - 130.0	>range meq/l
Potassium	2.5	3.8 - 5.3	<="" span="">
Calcium	7.5	7.9 - 10.9	<range< span=""></range<>
Phos	5.5	4.0 - 7.3	in range mg/dl
TCO2	33.1	16.0 - 22	>range
Anion Gap	****	7 - 17	

Hemolysis
Moderate

CBC

Test	Result	Normal Range	High or Low Units
WBC Count, Manual	3.6	5.5 - 19.5	<="" span="">
Bands	6	0 - 3	>range %
Neutrophils	75	35 - 75	in range %
Lymphocytes	14	20 - 55	<="" span="">
Monocytes	4	1 ? 4	in range %
Eosinophils	1	2 - 12	<="" span="">
Basophils	0	0 - 0.5	in range %
Platelets	109	300 - 700	<="" span="">
Mild Platelet Clumping			
RBC Count	4.93	5.0 - 10.0	<="" span="">
PCV	18.7	30.0 - 45.0	<="" span="">
Hemoglobin	5.8	8.0 - 15.0	<="" span="">
MCV	37.8	39.0 - 55.0	<="" span="">
MCHC	31.0	30.0 - 36.0	in range g/dl
MCH	11.7	13.0 - 17.0	<="" span="">
RDW	19.7	14.0 - 19.0	>range %.

Microscopic description:

Distal phalanx: Decalcified sections of the distal phalanx are characterized by marked expansion and effacement of the soft tissue and extensive infiltration and of periosteum and bone by a poorly demarcated, moderately cellular neoplasm comprised of respiratory epithelial cells arranged in variably ectatic glandular

structures supported and subdivided by a dense desmoplastic stroma. Neoplastic cells are columnar to cuboidal with variably discernible cilia that line the apical surface. Cells have distinct cell borders, moderate amounts of eosinophilic cytoplasm, and round to oval, basilar nuclei with finely stippled chromatin and one prominent nucleolus. There is marked anisocytosis and anisokaryosis. The mitotic count is 13 per 10 high powered fields, 400x. There are many large, discrete to coalescing cystic structures containing central lakes of eosinophilic secretory material admixed with pyknotic to karyorrhectic debris and lined by a single layer of neoplastic respiratory epithelium. Some cystic structures contain aggregates of degenerate neutrophils. The neoplasm effaces the periosteum and cortical bone and infiltrates the medullary cavity. Spicules of partially necrotic bone are frequently lined by the previously described neoplastic cells and/or less frequently lined by few multinucleated osteoclasts. Within the desmoplastic stroma of the neoplasm, there are moderate numbers of neutrophils, macrophages, and occasional loose aggregates of lymphocytes and plasma cells. The neoplasm markedly expands the subcutis and deep dermis and extends to the superficial dermis multifocally.

Contributor's morphologic diagnosis:

Bone, distal phalanx: Metastatic bronchogenic adenocarcinoma.

Contributor's comment:

Feline lung-digit syndrome (FLDS) was originally described by Moore and Middleton from a series of three cases in 1982.[9] The main feature was postmortem detection of a primary pulmonary adenocarcinoma, in the face of non-respiratory signs (e.g., dyspnea, coughing, etc). Two presented with pain and swelling of distal extremities and eventually developed respiratory signs in the following weeks. The third case had non-specific clinical findings (hyporexia and weight loss) and was euthanized the following week due to deteriorating quality of life. The two cases with soft tissue swelling were diagnosed as metastatic adenocarcinoma following antemortem biopsy. A retrospective study of 36 additional cats coined the moniker FLDS in 2000.[7] All cats presented with metastatic digital carcinoma; again, none had respiratory signs.

While FLDS is classically acknowledged clinically by metastases to extremities, variations exist. Digits are the most common site, but metastases have been documented in skeletal muscle, bone, eye, and skin.[5,12] The predilection for digit metastasis may be related to the angioinvasive behavior of the neoplasm, and the

highly vascular nature of feline digits, which helps to dissipate heat.[5,9] Tumor emboli may mimic aortic thromboembolism (ATE) that is usually attributed to primary cardiac disease. Retrospective studies of 127 cases of ATE identified neoplasia as the cause of 6% of ATE, representing the second most common cause in cats.[8] Ischemia and necrosis of the distal limbs may also manifest as a result of thromboemboli.[11] Ultimately, the size of thromboemboli dictates where they might settle and the pathophysiology.

Diagnosis is most easily accomplished through biopsy or fine needle aspirate of superficial masses and thoracic radiographs depending on the size of the tumor. The primary tumor often escapes detection due to absence of respiratory signs. More modern imaging technique such as computed tomography may be more sensitive in detecting the primary tumor.[12] FLDS is difficult to treat; chemotherapy is not often pursued, as efficacy has not been well documented.[12] Amputation of affected digits or limbs, while performed, is rarely palliative.[7,10] Increased CK may be useful as a marker of metastases to skeletal muscle. Prognosis is poor to grave, even with pulmonary lobectomy. Mean survival time from initial presentation is 34-58 days.[7,13] No breed or sex predilection has been identified.[7]

In general, primary pulmonary tumors are rare in cats. Of these, adenocarcinoma is most common. Eighty-eight percent of carcinomas in digits are the result of metastases from primary pulmonary carcinomas, although squamous cell carcinomas contribute to a fraction of these cases.[13] Lameness is often a common presenting complaint, and lysis of the third phalanx should provide a high index of suspicion;[12] however, other differentials should be considered including bacterial and fungal osteomyelitis. One in eight feline nail and nail bed disorders are neoplastic.[5] Given that other etiologies have better prognoses and generally response to amputation (i.e., bacterial/fungal osteomyelitis) or have a higher mean survival time (i.e., squamous cell carcinoma ? 207 days), it is advisable to diagnose or rule out primary pulmonary carcinoma as a cause of clinical signs before pursuing surgery.[7,13]

Contributing Institution:
University of Wyoming/Wyoming State Veterinary Laboratory
http://www.uwyo.edu/vetsci/

JPC diagnosis:
Digit: Metastatic pulmonary carcinoma.

JPC comment:

When feline lung digit syndrome (FLDS) occurs, one of the most common sites of metastasis is to the dermis on the dorsum of the distal phalanx and under the footpad epidermis.[2]

An important differential to consider is eccrine gland carcinoma.[6] Eccrine adenomas and adenocarcinomas have been documents in dogs, while eccrine tumors are usually malignant in cats.[4] While a common disease in humans, eccrine glands are confined to the footpads of dogs and cats, and this is the only site at which eccrine neoplasia occurs. Importantly, eccrine and pulmonary tumors have different immunohistochemical profiles. Thyroid transcription factor 1 (TTF-1) is expressed by primary pulmonary carcinoma/adenocarcinoma, in addition to napsin A and keratin 7.[3] Approximately 50% of eccrine carcinomas express S100, and about 25% of eccrine and apocrine tumors cells express p63 and has not been documented in metastatic adenocarcinomas in the skin.[3]

Human primary tumors often metastasize but are likely under reported. Approximately 20-70% of patients who died of their malignant disease had histologic evidence of osseous metastasis at autopsy, but only 2% have metastatic lesions to the foot. These lesions are reported to be CK7 and CDX2 (caudal type homeobox transcription factor 2) immunopositive, consistent with bronchogenic adenocarcinoma.[1]

The moderator led a discussion about the most common differentials for digital lesions in dogs and cats. In dogs, the most common include subungual melanoma, subungual squamous cell carcinoma, subungual keratoacanthoma, eccrine carcinoma, soft tissue sarcoma, mast cell tumor, trauma/infection, and lupoid onychodystrophy.[14] In the cat, the most common digital lesions include lung-digit syndrome, squamous cell carcinoma, various sarcomas, plasma cell pododermatitis, and arteriovenous fistula.[15]

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病例　CP2022-89

切片原病理编号：无

演讲及翻译人（Presenter and Translator）：

冯雪建　病理诊断师　郑州大学药物安全性评价研究中心

临床病史(Clinical History)：

Long Evans 大鼠 (Rattus norvegicus)，雌性，18 个月。右侧腋窝皮下有一个大而坚硬的肿块。

大体检查(Gross Findings)：

1、腋窝皮下肿块

位置:在右侧腋窝区域皮下。

性状：质地坚硬，界限清楚，分叶状。

直径大小:3.5 厘米。

2、颅腔结节性肿块

位置:大脑腹侧，垂体位置。

性状：深红棕色。

直径大小:1 厘米。

组织病理学检查(Histopathologic Description)：

1、腋窝皮下肿块

肿块：肿瘤上皮，单层立方形，胞质中等丰富，空泡状，排列形成大小不一的腺泡或小管。并被结缔组织分开，形成大小不一，形状不规则的小叶。小间间结缔组织丰富，且主要有胶原蛋白组成。

肿瘤上皮细胞空泡大小数量不一，使细胞扩张和胞核边移且略变形，呈囊泡状或细粒状，有一小的核仁，核异型性较小，未见分裂象。

腺泡腔内有蛋白性的分泌物，多灶性，在某些情况下显示出内层（淀粉体）。其它部分的切片（网站上未提供）镜下观察显示：上皮细胞形成的大的囊肿内充满分泌物。

2、颅腔结节性肿块

被膜较薄，实心，由血管和纤维结缔组织分割成多个岛峪状。(颜色为深红色)。

肿瘤细胞，界限不明显，胞质呈中等的嗜酸性和轻度的嗜双色性，胞核呈不规则的圆形、囊泡状或细粒状，核仁较小。可观察到核异型和一些核分裂象。在肿瘤的边缘分散有大量的巨细胞（ka-ryomegalic cells.)。肿瘤内有数量较多的大而充满血液的空间。

在肿块的一侧可能残留有腺垂体组织。

形态学诊断 (Morphologic Diagnosis)：

腋窝肿块：乳腺纤维腺瘤

垂体（腺垂体)：腺瘤

实验室结果（Laboratory Results）：

无。

疾病诊断（Disease Diagnosis）：

大鼠，垂体腺瘤，乳腺纤维腺瘤，

作者注释（Contributor Comment）：

乳腺纤维腺瘤：乳腺肿瘤是老年雌性大鼠最常见的肿瘤之一[1]， 特别是在 SD 品系中，即使在 lifetime studies 研究中，对照组自发性肿瘤的发生率都通常接近 50%[4]。大多数是乳腺上皮细胞和结缔组织组成的良性肿瘤。大多数是良性纤维腺瘤，由乳腺上皮细胞和结缔组织的数量。不同品系大鼠之间乳腺纤维腺瘤的发生率差异很大，这表明遗传背景是其发生的重要因素。影响其发生率的还有饮食、环境和毒理学研究时乳腺的分化程度和动物的激素水平。

乳腺肿瘤在 1 岁之前很少见，通常在 18 个月大之后发现[1]。雄性大鼠也偶尔会发生乳腺纤维腺瘤[5]。

纤维腺瘤中腺体和结缔组织的比例是不同的，在组织学上根据其比例的不同又将纤维腺瘤他为不同的亚型。然面，在一个肿瘤中，通常又包含几种亚型[1, 4]，这种分类方式似乎又没什么实际价值。动物长期暴露于雌激素和催乳素会增加肿瘤发生率，而胎次的增加和卵巢切除后会降低大鼠乳腺肿瘤的发生率[1, 5]。然而，发现在患有垂体瘤的大鼠身上乳腺肿瘤患病率增加，高水平的催乳素被认为是其一个促成因素，但很难确定这种影响是否有必然的联系[1,5]。雌激素会诱发垂体瘤和乳腺肿瘤，并且这两种肿瘤都与体重相关[1]。

乳腺纤维腺瘤可能会变得非常大，但通常它们只是局部浸润，很少发生转移。宠物大鼠或具有实验价值的动物可以进行手术切除[5]。自发性乳腺腺癌在 SD 大鼠中最常见，在其他品系中不常见。乳腺腺癌可能从乳腺纤维腺瘤发展而来，但这种情况很少见，并通常不发生转移[1]。

垂体腺瘤在老年大鼠中非常常见，尤其是 Wistar 品系。但是在一些参考文献中关于它们在不同品系大鼠中的发生率的报道却存在相互矛盾的信息：根据 Boorman 和 Everitt[1]报道在 F344 大鼠中很常见，在 SD 大鼠中不常见，而 Percy 和 Barthold[5]却报道说在 SD 大鼠中很常见。一些研究表明雌性的发病率略高。除了年龄外，遗传背景、饮食和繁殖历史也被认为影响肿瘤的发生。减少采食量会降低其发病率，并且根据有研究发现，未交配过的雌性比发生过交配的雌性更易患这些肿瘤[5]。临床症状也不尽相同，从无症状到严重抑郁不等，通常伴有动作不协调[5]。神经症状主要是由于垂体腺瘤对脑压迫所致。

组织学上，周围实质的压迫和结节边缘清晰的轮廓是腺瘤的标志。

肿瘤细胞通常比正常细胞大，细胞质丰富，通常呈苍白或微弱嗜碱性。有丝分裂指数通常较低。通常存在由内皮细胞或肿瘤性垂体细胞排列而形成的明显扩张的血管通道，这被称为血管瘤性或海绵状图案。这些地方通常有巨细胞和坏死区域[3]。大多数垂体肿瘤被认为起源于远端部分，并根据 HE 染色结果被诊断为嫌色细胞腺瘤[1,5]。 也有嗜酸细胞和嗜碱性细胞肿瘤。该资料未提供有关嫌色细胞腺瘤的肿瘤内分泌状态信息[1]。通过免疫组化方法研究，在垂体肿瘤中催乳激素细胞的肿瘤是最常见的类型[5]，但生长激素细胞、促肾上腺皮质激素细胞、促甲状腺激素细胞、促性腺激素细胞也有报道[1]。通常认为老龄大鼠发生泌

乳现象是功能性垂体瘤的征兆[1]。

垂体腺瘤应与增生性和肥厚性病变相鉴别。在增生性病变中，增殖的细胞是正常大小，没有假包膜形成的迹象，也没有对相邻垂体组织的显着压迫。体积大的细胞虽形成结节状，但其外面没有形成包膜[1,3]。垂体癌是比较罕见的，需要有侵袭或向远处转移的证据才能诊断。

JPC 诊断 (JPC Diagnosis)：

1.垂体：垂体远端腺瘤。

2.乳腺：乳腺纤维腺瘤。

讨论 (General Discussion)：

乳腺纤维腺瘤是最常见的大鼠乳腺肿瘤之一。它在雌性大鼠中更常见，并且在 SD 大鼠中发生率特别高。它通常是明确定义为由增生的腺体组织及其周围增生的纤维组织组成，可能累及大部或整个乳腺。

它可能具小叶生长模式特点，每个小叶的大小和组成不同。分泌性上皮单层排列，可能存在多形性细胞形成的小病灶，但分裂相不常见。增生与腺瘤的主要区别在于纤维结缔组织。

腺癌可能来源于乳腺纤维腺瘤[6]。大鼠中其他不太常见的乳腺肿瘤包括导管癌和囊腺瘤。另一个必须与良性乳腺肿瘤相鉴别的病变是小叶增生。这种情况可称为假孕，具有正常的乳腺小叶组织结构，特别是各种乳腺组织成分（包括导管、腺上皮、基质和肌上皮）之间的关系与瘤形成区别开来。

不存在细胞多形性；然而，可能发生局灶性鳞状化生，增生性病变可能是局灶性或弥漫性的[6]。弥漫性乳腺增生与妊娠晚期和哺乳期激素引起的生理变化有关。局灶性增生可能伴有因纤维增生形成的分割腺泡小叶，但小叶结构正常，对周围组织不产生压迫，这有助于将其与乳腺纤维腺瘤区分开来[6]。

已知限制饮食可降低大鼠垂体和乳腺肿瘤的发生率。催乳素是大鼠乳腺瘤形成的主要刺激因素，限制饮食的大鼠的催乳素水平较低。尽管尚未在所有病例中证明明确的联系，且并非所有大鼠垂体瘤都是催乳素阳性的。但发生垂体肿瘤的大多数大鼠是催乳素呈免疫阳性的，并认为其与乳腺肿瘤的发展有关[2]。

有趣的是，由于热量摄入减少而导致体重减轻与大鼠子宫肿瘤的增加有关。推测这种效应与催乳素对卵巢和黄体功能的影响有关。在大鼠中，催乳素促进排卵后黄体中孕酮的产生，这与雌激素对子宫生长的促进作用相反。因此，催乳素的减少会导致雌激素水平升高，从而刺激子宫内膜的生长[2]。

长期给大鼠使用雌激素也会导致产生催乳素的垂体腺瘤。这些诱发的肿瘤也可能产生其他激素，如促甲状腺激素[7]。

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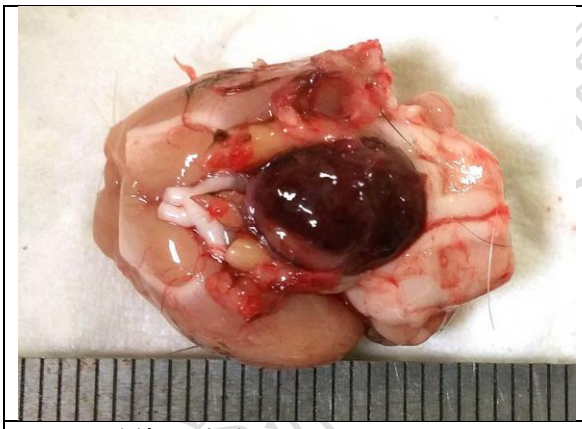


图 1. 垂体，大鼠
垂体处有一个直径约 1 厘米的深红棕色结节性肿块。

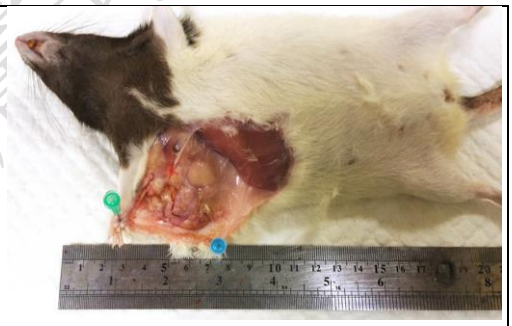
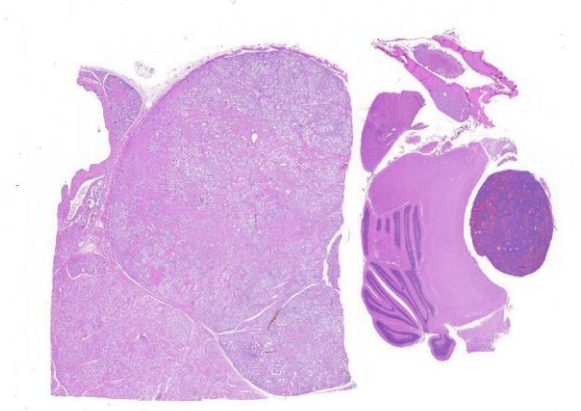


图 2. 乳腺，大鼠
腋窝区域皮下，有一质地坚硬，界限清楚，分叶状，直径约 3.5 厘米的肿块。



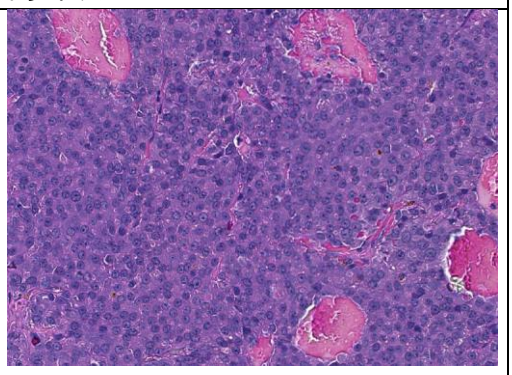


图 3. 组织，大鼠. 乳腺（左），垂体（右）。HE	6X	图 4. 垂体，大鼠 肿瘤细胞呈巢状或包状排列在纤维血管基质上，整个肿块内有许多充满血液的空间。 细胞核大小呈轻度变化和低分裂相。

Signalment:

An 18-month-old, female, LongEvans rat (*Rattus norvegicus*).

The investigator noticed a large, firm, subcutaneous mass in the right axilla.

Gross Description:

At necropsy, a firm, circumscribed and lobulated subcutaneous mass approximately 3.5 cm in diameter, was attached to the skin in the axillary area. On removing the brain, a dark red-brown nodular mass, approximately 1 cm in diameter, was present in the ventral aspect of the brain, replacing the pituitary gland.

Histopathologic Description:

Axillary mass - Part of a multilobular mass composed of disorganized epithelial pro-liferation and connective tissue. The neoplastic epithelium forms variably sized acini and tubuli which are aggregated into lobules dissected and separated by moderate to abundant dense, collagen-rich, connective tissue. The neoplastic cells are cuboidal to irregular and arranged as a monolayer; they have moderate to abundant cytoplasm which is often vacuolated.

Vacuoles vary from numerous and small (microvesicular vacuolation) to large, single, lipid vacuoles which lead to significant expansion of the cytoplasm and peripheral displacement of the nucleus. Nuclei are round to slightly irregular, vesicular to finely granular, and have a small nucleolus. There is slight anisocytosis and anisokaryosis. Mitotic fi-gures are not observed.

Multifocally, the lumen of acini contains proteinaceous secretory material, which in some cases shows internal layers (corpora amylacea). In other parts of the mass, not submitted, there are large cysts filled with secretory material and lined by epithelial cells as described. Pituitary mass- Compressing the medulla there is a small, discrete, thinly encapsulated and densely cellular nodular mass composed of a uniform population of polygonal cells arranged into solid islands separated by fine fibrovascular stoma.

The neoplastic cells have a moderate amount of eosinophilic to lightly amphophilic cytoplasm, relatively indistinct cytoplasmic margins, and round to slightly irregular, vesicular to finely granular nuclei with a small nucleolus. There is anisocytosis and anisokaryosis. A few mitotic figures are observed. At the edge of the mass there are scattered giant ka-ryomegalic cells. There are numerous large, blood-filled spaces lined by neoplastic pituitary cells.

At one edge of the mass there are possible remnants of the pre-existing adeno-hypophsis

Morphologic Diagnosis:

Axillary mass: Mammary gland fibro-adenoma
Pituitary gland (adenohypophysis): Adenoma

Lab Results:

None.

Condition:

Pituitary adenoma, mammary fibroadenoma, rat

Contributor Comment:

Mammary fibroadenoma: Mammary tumors are one of the most common tumors in old female rats,1 especially in the SD strain where the incidence of spontaneous tumors often approaches 50% in lifetime studies of control animals.[4] Most are benign fib-roadenoma which are composed of mammary epithelial cells and connective tissue.[4] The incidence of these tumors varies considerably between different rat strains, suggesting that genetic background is an important factor in their development. Other factors which influence their occurrence are diet, environment, and in the case of toxiclogic studies, the degree of differentiation of the mammary glands, and physiologic and hormonal status at the time of chemical exposure.[4]

Mammary tumors are rare before 1 year of age, and are generally found after 18 months of age.1 Mammary fibroadenomas also occur occasionally in male rats.[5]

Histologically, the proportion of glandular and connective tissue in fibroadenomas is variable, and this has led to their sub-classification. However, since several subtypes are commonly encountered in a single tumor, this division appears to be of little merit.[1,4] Exposure to estrogen and prolonged exposure to prolactin increase tumor frequency, whereas parity and ovariectomy decrease the incidence of mammary gland tumors in rats.[1,5] Although increased mammary gland tumors are found in rats with pituitary tumors and high levels of prolactin are considered a contributing factor, a casual effect is difficult to determine.[1,5] Estrogens induce both pituitary and mammary tumors, and the incidence of both types of tumors correlates with body weight.[1]

Mammary fibroadenomas may become very large, but as a rule, they are only locally infiltrative and rarely metastasize. Surgical excision is possible in pet rats or experimentally valuable animals.[5] Sp-ontaneous mammary adenocarcinomas are most common in SD rats and uncommon in other strains. They may develop in existing fibroadenoma, but this is rare. They generally do not metastasize.[1]

Pituitary adenoma is very common in older rats, especially of the Wistar strain. There is conflicting information in standard ref-erences regarding their incidence in other strains: according to Boorman and Everitt 1 they are common in F344 and uncommon in SD, while according to Percy and Barthold 5 they are common in the SD strain. Some studies suggest a slightly higher incidence in females. Other than age, genetic ba-ckground, diet, and breeding history are thought to play a role in tumor development. Reduction of food intake reduces their incidence and, according to one study, mated females are less prone to these tumors than virgin females.[5] Clinical signs vary from asymptomatic to severe depression, often with incoordination.[5] The neurologic signs are due to compression of the brain.

Histologically, the hallmark of adenoma is compression of the surrounding parenchyma and sharp delineation at the margins of the nodule. The neoplastic cells are generally larger than normal and have more abundant cytoplasm, which is usually pale or faintly basophilic. The mitotic index is usually low. Often, there are prominently dilated vascular channels which may be lined by endothelial cells or neoplastic pituitary cells; this has been referred to as angiomatous or cavernous pattern. Giant cells and areas of necrosis may be present.[3] Most pituitary tumors are thought to arise from the pars distalis and are diagnosed as chromophobe adenomas based on HE-stained sections.[1,5] Acidophil and basophil tumors have also been described. The diagnosis of chromophobe adenoma pro-vides no information regarding the endocrine status of the tumor.[1] In pituitary tumors studied by immunocytochemistry, prolactin-producing tumors are the most common type,5 but growth hormone, ACTH, TSH and FSH-secreting tumors have also been described.[1] Lactation in an aging rat is often a sign of a functional pituitary tumor.[1]

Pituitary adenomas should be differentiated from hyperplastic and hypertrophic lesions. In hyperplastic lesions there is proliferation of cells of normal size, no evidence of pseudocapsule formation, and no significant compression of adjacent pituitary tissue. Nodules of hypertrophic cells form islands of large cells without evidence of encapsulation.[1,3] Pituitary carcinomas are rare and require evidence of invasion or distant metastasis for their diagnosis.

JPC Diagnosis:

1. Pituitary gland: Pituitary pars distalis adenoma.
2. Mammary gland: Mammary fibroadenoma.

Conference Comment:

Mammary gland fibroadenoma is one of the most common rat mammary tumors. It is more commonly seen in female rats and has an especially high incidence in Sprague Dawley rats as mentioned above. It is generally well defined and composed of proliferating glandular tissue surrounded by a proliferation of fibrous tissue. Large sections or an entire mammary gland may be involved.

It may have a lobular growth pattern with variation in size and composition of individual lobules. Secretory epithelium is arranged in a single layer, and small foci of pleomorphic cells may be present, but mitoses are uncommon. It is differentiated from adenoma by the conspicuous con-tribution of a fibrous connective tissue component.

Adenocarcinoma may arise fr-om within mammary fibroadenoma.[6] Other less common mammary neoplasms in the rat include ductular carcinoma and cystadenoma. Another lesion which must be differentiated from benign mammary neoplasia is lob-uloalveolar hyperplasia. This condition may be referred to as pseudopregnancy, and is differentiated from neoplasia by maintaining the normal lobular histologic architecture, specifically the relationships among the various mammary tissue components in-cluding ducts, glandular epithelium, stroma, and myoepithelium.

Cellular pleomorphism is absent; however, focal squamous met-aplasia can occur and hyperplastic lesions may be focal or diffuse.[6] Diffuse mammary hyperplasia is associated with hormonally-induced physiologic changes during late gestation and lactation. Focal hyperplasia may be accompanied by fibrous pro-liferation separating acini, but the lobular architecture is maintained and the lesion is not compressive, which aids in dif-ferentiating it from mammary fibroadenoma.[6]

Dietary food restriction is known to decrease the incidence of both pituitary and mam-mary tumors in rats. Lower levels of prolactin are present in rats on a restricted diet, and prolactin is a primary stimulus for the development of mammary neoplasia in rats. Most rat pituitary neoplasms are prolactin-

immunopositive and are postulated to be involved in the development of mammary tumors,[2] although a definitive link has not been demonstrated in all cases. Furthermore, not all rat pituitary tumors are prolactin positive.

Interestingly, reduction in body weight from decreased caloric intake is paradoxically associated with an increase in uterine neoplasia in rats; this effect is postulated to be related to prolactins influence on function of the ovary and corpora lutea. In the rat prolactin promotes progesterone production in the corpus luteum post ovulation, which opposes estrogens promotion of uterine growth. Therefore, a decrease in prolactin results in elevated levels of estrogen, which stimulates endometrial growth.[2]

Long term administration of estrogen to rats also results in prolactin producing pituitary adenomas. These induced tumors may also produce other hormones, such as thyroid stimulating hormone.[7]

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病例　CP2022-90

切片原病理编号：CAU21-2134. 22 June 2021. CAU VTH, Clinical Laboratory Diagnostic Center

提供者（Contributor）：

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临床病史(Clinical History)：

流浪猫，雄性，5 岁，腹部皮肤大面积溃烂，在外院使用头孢类抗生素未见好转，使用糖皮质激素轻度好转，FNA 可见大量退行性中性粒细胞。

大体检查(Gross Findings)：

腹部皮肤肿胀，表面破溃。

组织病理学检查(Histopathologic Description)：

HE 染色：真皮组织水肿，存在大量炎性细胞浸润，以巨噬细胞和中性粒细胞为主，可见大量巨噬细胞呈片状分布，具有反应性变化，细胞核大小不等，可见多核巨细胞，细胞内含有大量嗜酸性细胞质，胞质中存在数量不等的空泡。真皮深层可见多处肉芽肿性病变，包含大量无定形真菌菌丝聚集体。可见巨噬细胞吞噬真菌孢子、真菌菌丝。

PAS 染色：可见巨噬细胞聚集区域内存在大量分隔菌丝、真菌孢子样结构，呈紫红色。

提供者形态学诊断（Morphologic Diagnosis)：

猫，脓性肉芽肿性炎症（pyogranulomatous inflammation)；真菌性肉芽肿（fungal granuloma)；皮肤癣菌假足菌肿（dermatophytic pseudomycetoma）

提供者描述（Contributor Comment)：

皮肤癣菌通常寄生在机体表面，多数情况下侵犯皮肤的角质层以及含有角蛋白的附属器，包括甲和毛发，引起浅表性皮肤病变，表现为对称或非对称性的脱毛斑、丘疹、鳞屑和结痂等，当宿主存在免疫受损或其他情况时，皮肤癣菌会侵犯皮下组织，引起皮肤癣菌肉芽肿。人的深在型皮肤癣菌感染分为 3 种类型，即 Majocchi 肉芽肿、真皮深部皮肤癣菌病和播散性皮肤癣菌病[1]。Majocchi 肉芽肿是皮肤癣菌肉芽肿最常见的类型，包括毛囊周围炎型和皮下结节型[2]。真皮深部皮肤癣菌病常累及免疫受损者，可侵犯真皮、皮下组织，临床上可呈现结节、脓肿等多种表现，严重患者致病真菌可播散至内脏器官，累及

淋巴结、骨、肌肉、肝脏等[3]。在多数病例中，患者存在免疫抑制的情况，如重症肌无力、系统性红斑狼疮、特应性皮炎和糖尿病等[4]。

皮肤癣菌假足菌肿（dermatophytic pseudomycetoma）于 1993 年由 Chen 等首次提出[5]。在此之前，该病被归入足菌肿。足菌肿（mycetoma）是指皮肤、皮下组织和骨骼的一种慢性局限性破坏性感染，通常累及手足，表现为无痛性皮下肿物、多发性窦道和包含颗粒的脓性渗出物 3 种特征，又称足菌肿三联征[6]。通常是由不同种类的真菌（真菌性足菌肿）或放线菌（放线菌性足菌肿）通过伤口接种到皮下组织中引起，颗粒是由真菌或放线菌成分形成致密的团块，并通过窦道排出。足菌肿的颗粒（grains）在组织病理学上表现为无定型基质中紧密黏合的放射状菌丝团块，直径约 0.3~1mm，光镜下易见，根据不同致病病原体，颗粒的颜色可以为白色、黑色、红色、黄色或棕色[7]。然而，假足菌肿在临床上缺少皮肤窦道表现，亦无颗粒排出；在组织病理学上，菌丝形成的”颗粒“状结构与足菌肿的颗粒存在多处不同：①假性颗粒具有菌丝-小簇集性菌落-大簇集性菌落的顺序变化；②周围可见大量 Splendore-Hoeppli 现象；③相比真性颗粒，假性颗粒的菌丝数量和连接紧密性均较低；④缺少黏合成分；⑤毛囊破坏可能与 Majocchi 肉芽肿有关。因此，假足菌肿的“颗粒”结构被命名为假性颗粒（pseudoganule）。皮肤癣菌假足菌肿鉴别诊断要点见表 1。

表 1. 皮肤假足菌肿鉴别要点

	假足菌肿	足菌肿	Majocchi 肉芽肿
流行地区	非洲，世界各地	非洲、印度	世界各地
病因	不明，可能与头癣有关	外伤	外伤，多见于刮剃腿毛时足部病原菌接种感染
好发人群	儿童多见	20~40 岁	青中年女性
常见受累部位	头皮	足背	小腿
临床表现	结节、脓肿，通常无窦道	窦道、流脓、瘢痕化	小结节和斑块
组织病理特征	假性颗粒	颗粒	毛囊内菌丝或孢子毛囊周围炎症
最常见致病菌	犬小孢子菌	真菌或放线菌	红色毛癣菌（80%~90%）
治疗	抗真菌药物+手术	抗真菌或抗细菌药物+手术	抗真菌药物
治疗反应	差	差	好

皮肤癣菌假足菌肿常见的临床表现为多发性结节性皮损，不同于真菌性足

菌肿，该病通常不出现窦道、流脓等表现，但免疫功能受损患者可出现皮肤泛发性感染。假足菌肿临床表现具有非特异性，需要结合组织病理以明确诊断。

假足菌肿组织学病理表现为弥散性混合炎性细胞浸润。在真皮全层散在分布多数成群的肉芽肿，在每个肉芽肿中央有假性颗粒结构，其中包含致病真菌的微小菌落。假性颗粒在组织病理上排列有序，缺乏粘合性，周围可见明显嗜酸性物质沉积，主要为坏死组织和免疫球蛋白沉积所形成，即 Splenore-Hoeppli 现象。该现象多见于铜绿假单胞菌和金黄色葡萄球菌导致的葡萄状菌病，也可见于球孢子菌等真菌感染[4]。周围包绕朗格汉斯巨细胞和多种炎性细胞浸润，包含中性粒细胞、嗜酸性粒细胞、淋巴细胞和浆细胞[8]。每个肉芽肿的中心过碘酸-希夫染色（PAS）和六铵银染色（GMS）均可清楚显示菌丝成分[9]，使用兔抗小孢子菌抗血清的免疫组织化学方法可进一步确定真菌的种类[10]。

除了组织病理学，也可收集组织或患处分泌物进行真菌培养，进一步通过 PCR 扩增和序列测定或质谱鉴定确定菌种。

犬小孢子菌是假足菌肿最常见的致病真菌，其他病原体还包括铁锈色小孢子菌（*M. ferrugineum*）、奥杜盎小孢子菌（*M. audouinii*）、红色毛癣菌（*T. rubrum*）、须毛癣菌（*T. mentagrophytes*）、断发毛癣菌（*T. tonsurans*）和许兰毛癣菌（*T. schoenleinii*）[9]。我国报道的 2 例人类和 1 例猫的皮肤癣菌假足菌肿致病菌经 DNA 分子学测序和基质辅助激光解吸电离飞行时间质谱法（MALDI-TOFMS)检测均为犬小孢子菌[10][11]。

皮肤癣菌假足菌肿的具体发病机制尚未明确，该病发病前通常无明显皮肤外伤史，表明不通过破损皮肤接种感染。在人类中，由于皮损常位于头皮等毛囊丰富部位，且好发于长期患头癣患儿，推测可能为真菌菌丝通过毛囊侵入真皮及皮下组织引起的免疫炎症反应。此发病过程与 Majocchi 肉芽肿发病机制类似，可能为同一病理过程中的不同严重程度[4][14]。

研究表明，皮肤癣菌假足菌肿在犬猫等动物均可发生，有一定的品种倾向性（如波斯猫和约克夏犬），主要发病机制不详，可能与特异性的免疫缺陷有关[15]。在现有报道中发现，多数患猫为长毛猫（波斯猫），但也有病例为美国短毛猫[13]，说明短毛猫也有患皮肤癣菌假足菌肿的风险。

表 2. 不同物种中的假足菌肿

	猫	犬	马	雪貂	人类	仓鼠
发病率	均罕见					
倾向性	长毛猫（尤其是波斯猫）	约克夏（可能易感）			长期患头癣的非洲裔儿童；免疫受损者	
部位	背部；尾部	背部；尾部			头皮；	爪部

致病菌	犬小孢子菌	犬小孢子菌（须毛癣菌）	马毛癣菌	小孢子菌属；毛癣菌属	小孢子菌属；毛癣菌属；	葡萄球菌

治疗皮肤癣菌假足菌肿一般采用手术切除和抗真菌治疗相结合的方法[16]。如果病变早期为单一的结节，及时进行手术切除可提高治愈的可能性。口服药物推荐伊曲康唑，也可根据药敏结果选择抗真菌药。一项对 28 株犬小孢子菌的药物敏感性检测研究显示，灰黄霉素、伊曲康唑、特比奈芬、泊沙康唑等抗真菌药物对犬小孢子菌均有抗菌活性[17]。但也有文献表明，与浅表性的皮肤癣菌病不同，皮肤癣菌假足菌肿对灰黄霉素和酮康唑等多数抗真菌药物反应欠佳[18]。多数病例需要长期治疗，且常见复发，预后不良。

Contributing Institution:

China Agricultural University Veterinary Teaching Hospital, Beijing

http://www.cauvet.com/

提供病例的机构： 北京中国农业大学教学动物医院

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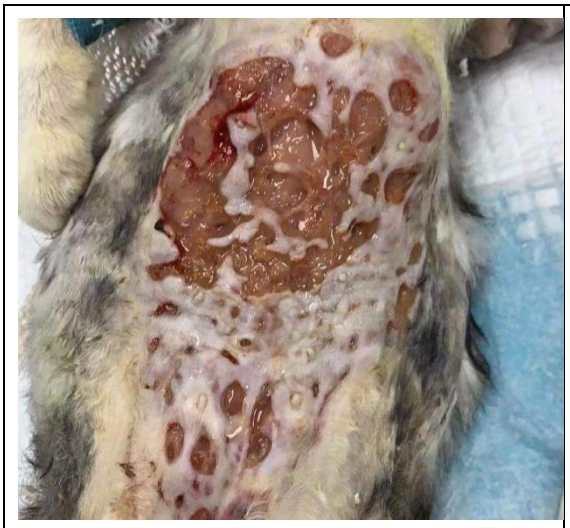


图 1. 腹部皮肤，猫
皮肤肿胀，大面积溃疡，有脓性分泌物。

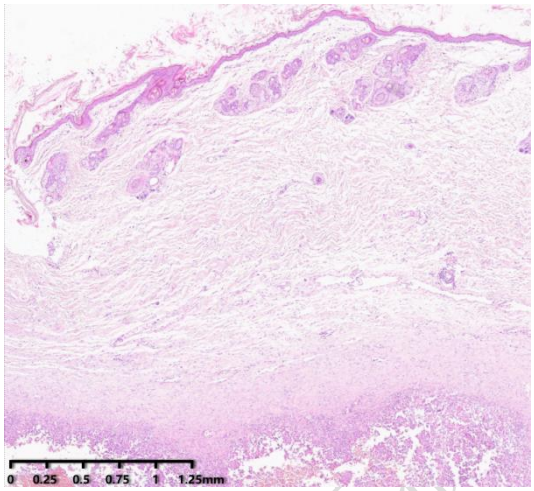


图 2. 皮肤，猫
表皮、真皮结构较完整，病变位于真皮深层及皮下组织。HE |2X。

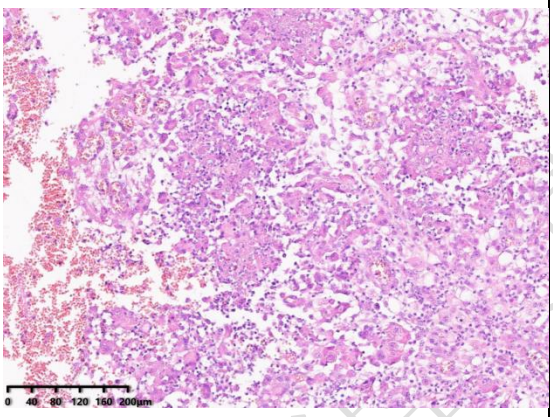


图 3.皮肤，猫
皮下组织出血、多灶性的肉芽肿性病变，包含分隔的真菌菌丝、上皮样巨噬细胞、中性粒细胞、浆细胞和多核巨细胞等。
HE |10X。

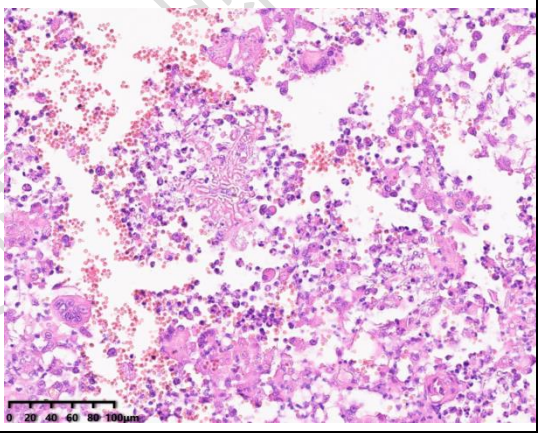
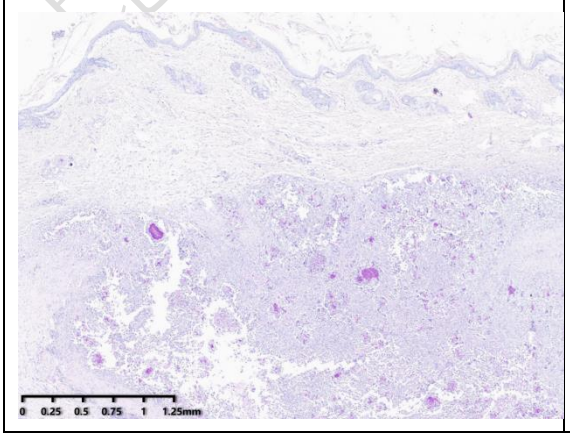


图 4.皮肤，猫
真菌菌丝有不平行的壁、不规则的分枝和球状隆起。HE |20X。



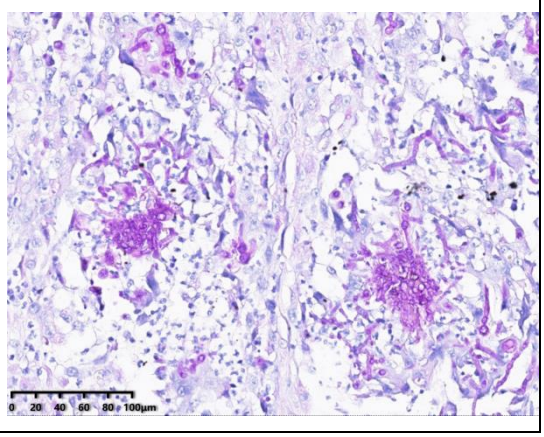


图 5. 皮肤，猫 表皮、真皮及皮下的肉芽肿，可见散在紫红色团块。PAS | 2X	图 6. 皮肤，猫 成簇的紫红色物质，为无定型的真菌菌丝聚集体。PAS |20X。

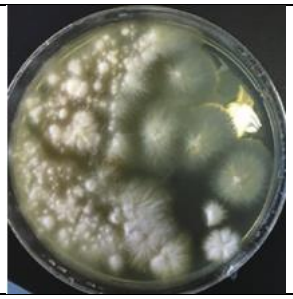



图 7.SDA 培养基生长的真菌菌落。	图 8.DTM 培养基生长的真菌菌落。
	
图 9.犬小孢子菌的大分生孢子。 棉蓝染色 | 100X	

病例 CP2022-91

切片原病理编号：JLU2021-28

提供者（Contributor）：

马 莹 本科毕业生 准硕士研究生 吉林大学动物医学学院

临床病史（Clinical History）：

柯基犬，6 个月零 1 天,雌性，未绝育。主诉近期发现宠物肘部有肿物。刚出生时发生肺炎，带回家中饲养两个多月，咳嗽，拍片诊断为肺炎，进行输液治疗。近期洗澡后，观察到颈部有化脓，将患宠毛发剔除，发现背部有大量脓包（疖子）。中间更换过一次粮，大概半个月时间，最近饮食及精神状态均无异常。于 2021 年 3 月 17 日手术切除皮肤肿物。

诊断（Diagnosis）：

局限性钙盐沉着症（Calcinosis circumscripta），肘部皮肤肿物。

肉眼检查（Gross Findings）：

送检肿物无皮肤包被，表面呈乳白色，质地比较坚实（Fig.1A），切面为乳白色（Fig.1B）

组织病理学检查（Histopathological Findings）：

低倍镜下未见上皮组织，皮下组织中包含许多大小不一的无定形到颗粒状的嗜碱性物质沉积，散在分布或融合成团块的病灶，周围的结缔纤维组织排列比较致密（Fig.2A）；高倍镜下，病灶由无细胞性钙化物质组成，部分钙化区域有纤维组织包裹，周围排列有巨噬细胞、多核巨细胞及类上皮细胞（Fig.2B）。周围组织中可见嗜碱性染色的黏液样变性（Fig.2C），在纤维结缔组织内可见表现为圆形、层片状的沙粒样小体（Fig.2D）。

讨论（Discussion）：

局限性钙盐沉着症是一种不常见的疾病，又称肿瘤钙质沉着症、皮肤钙质沉着症、脂钙质沉着症、钙质性痛风，系发生于皮肤皮下组织及真皮层内的一种异常钙化作用，其特征为软组织内的钙沉积。钙盐沉着的病因包括营养不良、转移性或特发性钙化。营养不良型钙质沉着发生在组织损伤的特定区域，可能是由于损伤、坏死、炎症或肿瘤，患宠血清钙、磷水平正常；转移性钙质沉着与钙或磷酸盐代谢异常有关，如慢性肾衰竭、终末期肾病或维生素 D 中毒引起的高钙血症或高磷血症；特发性钙质沉着没有明确的病因，通常带有遗传成分，有人推测其为磷酸钙沉积于变性的胶原的现象，亦有认为其源自于一些顶浆腺 (apocrine gland) 如汗腺的腔中。在小动物中，营养不良和特发性钙质沉着比转移性钙质沉着更容易发生。而在生长快速的大型犬只，如德国牧羊犬，由于其钙化代谢功能活化，这种钙化不良的现象更加严重。

局限性钙盐沉着病变常呈单发结节团块突出于皮肤上，大小可达 10 公

分，当团块较大时，表面可能发生溃疡，并排出白色砂砾样物质，常见于受压力较多及曾遭受创伤的皮肤，如四肢肌肉较少的部位（跖骨侧、趾骨、肘部、第 4～6 颈椎）、剪耳后的耳壳周缘及舌头等，此外，在拳师犬及波士顿梗中，病变较常发生于耳根部及脸颊，同时一些报告指出，当此病变呈对称性发生时，常与肥大性骨营养不良症（hypertrophic osteodystrophy）及特发性多发性关节炎（idiopathic polyarthritis）有关。本病例在周围组织中可见嗜碱性染色的黏液样变性以及呈圆形、层片状的沙粒样小体，提示患犬发生的局限性钙盐沉着症系营养不良性钙化。

部分病例中在毛囊及顶浆腺中可见钙化结节，本病钙化不良的病灶区，以 PAS 及 Alcian blue 染色呈阳性反应，少数病例会化生形成骨组织。

实验室检查可发现有无结缔组织疾患存在，包括血清酶、肌酸和肌酐值，血钙、磷、碱性磷酸酶和尿钙排出量。X 线摄影可以确定病变的范围，有无骨和血管钙化等。

临床治疗局限性钙盐沉着症一般通过外科切除钙化组织，术后极少复发且预后良好，但如果诱发钙质沉着的主要原因没有解决，即使手术切除也需要定期追踪其预后情况。

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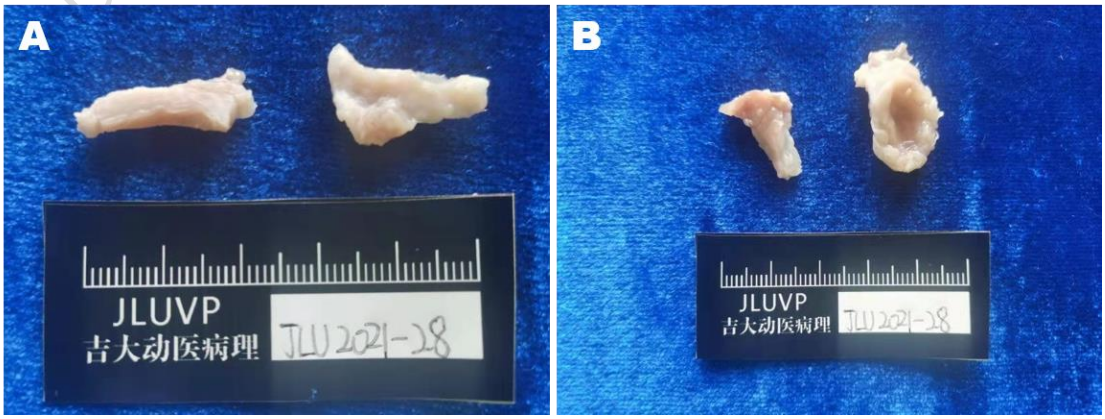

图 1 送检组织经 10%中性福尔马林溶液固定后的病理图片

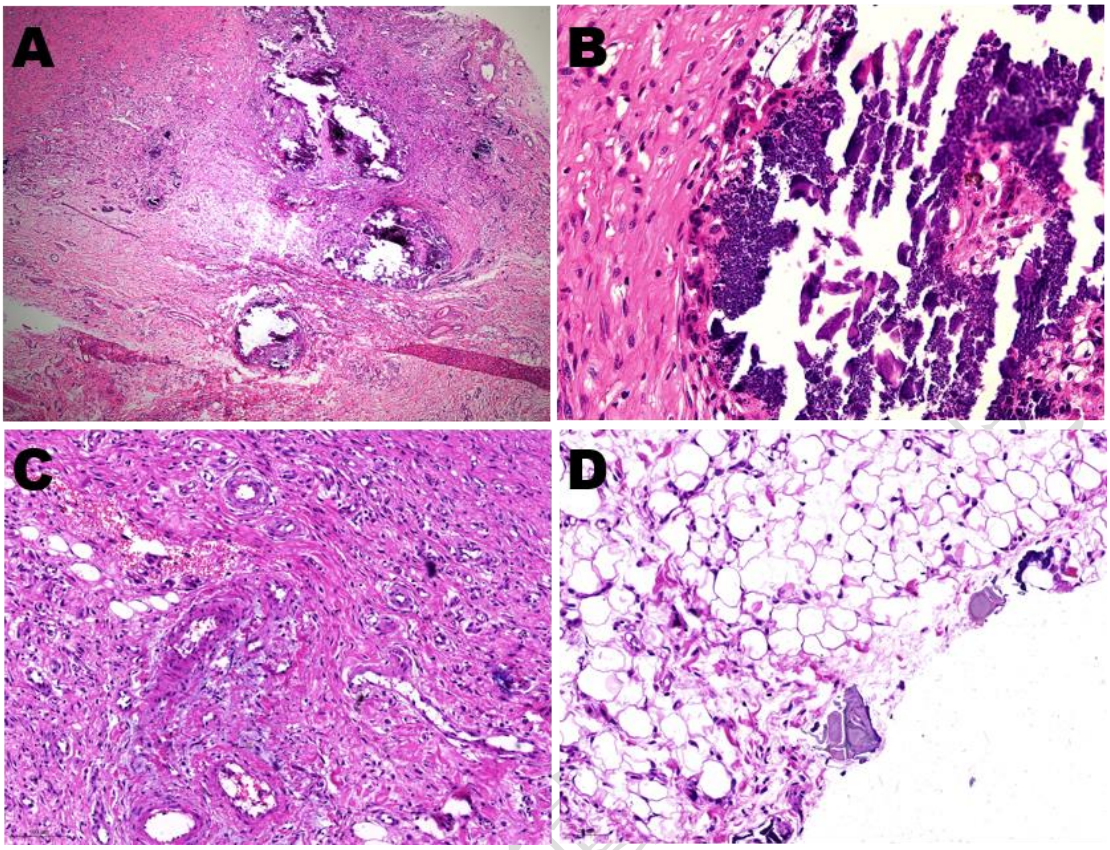

图 2 送检组织切片后 HE 染色结果

A. 皮下组织中散在分布或融合成团块的嗜碱性物质沉积；B. 部分钙化区域周围排列有巨噬细胞、多核巨细胞及类上皮细胞；C.周围组织中可见嗜碱性染色的黏液样化生；D.组织内可见沙粒样小体。

病例 CP2022-92

切片病理编号(JPC#)**：无**

演讲及翻译人（Presenter and Translator）：

张兴娟 山东畜牧兽医职业学院

临床病史(Clinical History)：

7 岁奶牛，品种不明，4-5 个月前产下犊牛，此后一直在牧场上。死前无任何征兆。

大体检查(Gross Findings)：

尸体保存较差，但动物体况良好。大体病变局限于泌尿道、乳腺和乳腺上淋巴结。

1. 肾脏：双侧严重的慢性、纤维素性脓性肾盂肾炎；
2. 膀胱：慢性坏死性化脓性膀胱炎；尿石症；
3. 乳腺：左前乳腺有硬结，无法挤出乳汁。在切面上，腺体实质明显纤维化，有 2-3 mm 多灶性化脓区。左乳上淋巴结肿大，有直径 1 厘米的化脓灶。

组织病理学检查(Histopathologic Description)：

乳腺：萎缩腺泡被成熟的纤维结缔组织分割呈小叶状，其中包含直径 10 mm 的多灶性至合并性的脓性肉芽肿。肉芽肿的中心聚集有革兰氏阳性球菌菌落，菌落周围可见放射状嗜酸性物质（Splendore-Hoeppli），偶尔可见大面积的坏死区。菌落及嗜酸性物质被嗜中性粒细胞包围，外围可见大量巨噬细胞和不同数量的多核巨细胞，并混合淋巴细胞、浆细胞和少量中性粒细胞，以同心圆排列的纤维组织结缔组织带为边界。

形态学诊断(Morphologic Diagnosis)：

乳腺：脓肉芽肿性乳腺炎

实验室结果 (Laboratory Results)：

从乳腺上淋巴结分离出β溶血性、凝固酶阳性金黄色葡萄球菌；从肾脏中分离出肾棒状杆菌。

疾病诊断 (Disease Diagnosis)：

葡萄球菌性乳腺炎

作者注释（Contributor Comment）：

本例死亡原因为肾盂肾炎所致肾功能衰竭。慢性乳腺炎被认为是偶然发现的。从乳腺上淋巴结分离出金黄色葡萄球菌。虽然没有对乳腺组织进行细菌培养，但病变内球菌的革兰氏阳性性质与葡萄球菌一致。

金黄色葡萄球菌是引起奶牛乳腺炎的最常见原因之一。临床上，葡萄球菌性乳腺炎可能是超急性和暴发性的，也可能是较轻和更慢性的。急性乳腺炎通常发生在分娩后不久，往往会导致坏疽，死亡率很高。慢性或亚临床形式更常见，对养殖业造成严重的损失。临床表现与金黄色葡萄球菌株有关;菌株在畜群内传播的能力不同，导致体细胞数升高、持续感染或产奶量减少的能力也不同。在体外，不同菌株抵抗中性粒细胞的杀伤或入侵乳腺上皮细胞的能力不同。

金黄色葡萄球菌一旦污染乳头，可在进入乳头管和乳头窦前持续繁殖，并扩散至乳腺内部。细菌可以通过粘附到上皮细胞表面的特定受体实现乳腺远端定植。每个细胞粘附的细菌数量从极低到极高不等。细菌定植处上皮细胞发生变性和坏死，间质内及腺泡内中性粒细胞渗出。如果渗出物大量且病原具有高度的毒性，则会发生急性和坏疽性乳腺炎。金黄色葡萄球菌也可以入侵更深入腺泡间组织并建立持久的感染病灶,引起肉芽肿反应与纤维结缔组织增生。乳腺腺泡萎缩可能是由于间质纤维化、渗出物或肉芽肿的压力，造成乳汁排出受阻。

JPC 诊断 (JPC Diagnosis)：

乳腺：多灶性脓性肉芽肿性乳腺炎，伴有大量球菌和 Splendore-Hoeppli 物质

讨论 (General Discussion)：

本例中的组织切片主要由乳腺导管组成;乳腺腺泡大部分萎缩或消失，可能是大量炎症渗出物及增生的纤维结缔组织压迫所致。乳腺炎是成年奶牛最常见的疾病。感染途径包括乳头管上行感染(最常见)、血行感染或经皮感染。最常分离到的细菌是链球菌属、葡萄球菌属和革兰氏阴性大肠菌群，尤其是大肠杆菌(也包括产气肠杆菌、肺炎克雷伯菌、多杀巴氏杆菌、铜绿假单胞菌、沙雷氏菌属和变形杆菌属)。乳腺是某些细菌(包括无乳链球菌、金黄色葡萄球菌和牛支原体)持续存在和储存的主要场所，而大肠菌群的感染通常是由于外界环境而造成乳头的污染 (例如，粪便污染的垫料、土壤或水)。乳房链球菌和无乳链球菌可以在任何一个位置持续存在。与牛乳腺炎相关的其他病原体包括化脓棒状杆菌，*Prototheca zopfii*、*Nocardia asteroides*、分枝杆菌属，以及不太常见的，流产布鲁氏菌，溶血性曼氏菌，沙门氏菌属，新型隐球菌，念珠菌属。

金黄色葡萄球菌从非致病性到高致病性不等，是乳腺炎最常见的病因。过氧化氢酶和溶血毒素的产生是细菌致病性的特征性指标，在正常牛奶中抑制细

菌生长的物质列在表 1 中，金黄色葡萄球菌已经发展出多种毒力因素来克服这些防御机制，这些防御机制列在表 2 中。

表 1 乳汁中的抗菌物质

乳汁中的抗菌物质	
吞噬细胞	在牛奶中的吞噬作用不如在血清中有效
乳铁蛋白	抑制细菌繁殖的铁结合蛋白
溶菌酶	溶解细菌细胞壁的肽聚糖
乳过氧化物酶	可抑制 S.Â 金黄色葡萄球菌和链球菌
过氧化氢	一种弱氧化剂，是牛奶碳水化合物细菌发酵的副产品
免疫球蛋白	主要是促进调理作用的 IgG;较少的 IgA，这可能会减少细菌在上皮表面的粘附

表 2 金黄色葡萄球菌的毒力因子

金黄色葡萄球菌的毒力因子	
杀白细胞素	对牛白细胞有溶解作用
α毒素	结合细胞膜形成六聚孔;不是所有的金黄色葡萄球菌都能产生
β毒素	神经磷脂酶 C 或鞘磷脂酶
蛋白 A	是一种与 IgG Fc 片段结合的抗吞噬因子
胞外酶	凝固酶、透明质酸酶、磷酸酶、脂肪酶、过氧化氢酶、纤溶酶、超抗原和蛋白酶
细菌包膜	干扰调理作用、吞噬作用和补体活性，并非所有菌株都存在
青霉素酶	分解青霉素的β-内酰胺环

乳腺炎在牛中最常见，但也会发生于其他动物。从患有坏死性或坏疽性乳腺炎的绵羊和山羊身上分离到的主要病原体是金黄色葡萄球菌和溶血性曼氏菌。对于支原体乳腺炎，典型的病原体是无乳支原体。此外，山羊和绵羊感染小反刍动物慢病毒、山羊关节炎和脑炎病毒以及梅迪-维斯纳病毒，会导致乳房变硬并伴有无乳。马乳腺炎是散发性的，主要是由兽疫链球菌引起。在猪中，乳腺炎通常发生在哺乳期或刚断奶不久的母猪。最常见的分离的病原是革兰氏阴性大肠菌群，革兰氏阳性菌如链球菌、葡萄球菌和气球菌属的报道较少。狗和猫的乳腺炎并不常见，狗更容易出现乳腺肿瘤。狗或猫发生乳腺炎时，往往见于哺乳早期，由于葡萄球菌属，链球菌属或大肠杆菌通过乳头进入输乳管。大肠杆菌、肺炎克雷伯菌和兽疫链球菌在豚鼠乳腺炎中常见，而金黄色葡萄球菌（C 型）和多杀性巴氏杆菌倾向于影响兔子。在大鼠（通常是由于嗜肺巴斯

德氏菌、金黄色葡萄球菌、棒状杆菌属或假单胞菌属）和仓鼠（β-溶血性链球菌属、嗜肺假单胞菌、大肠杆菌）中也有乳腺炎的报道。

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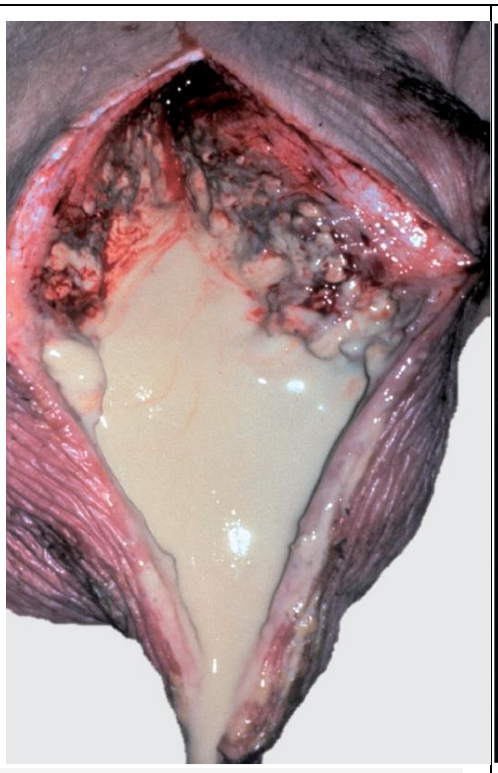

图 1 化脓性乳房炎 乳池和乳导管充满脓汁。

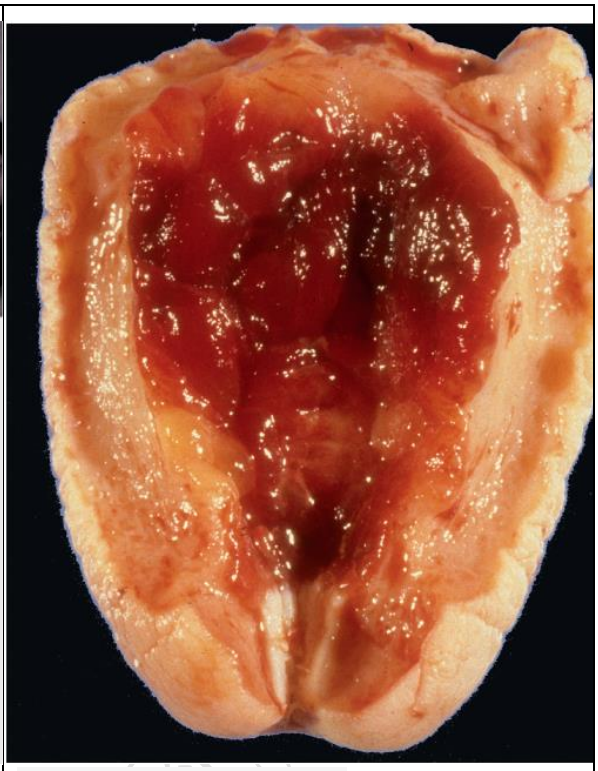

图 2 奶牛发炎的乳池。

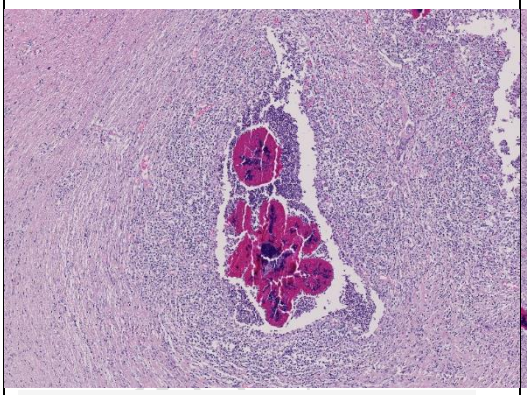

图 3 葡萄球菌感染形成的脓性肉芽肿。

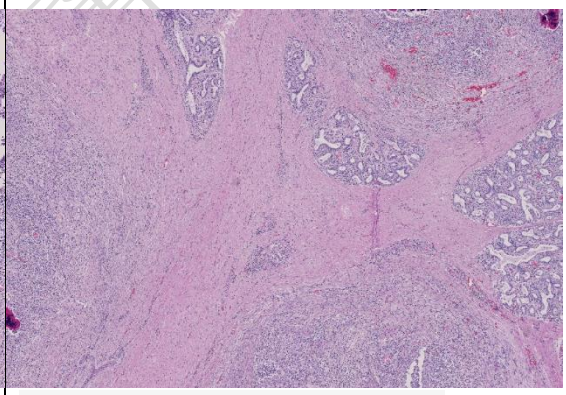

图 4 间质纤维结缔组织增生。

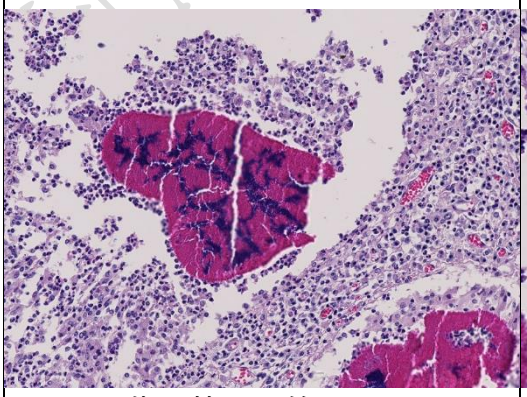

图 5 细菌及其周围的 splendore-hoeppli 物质。

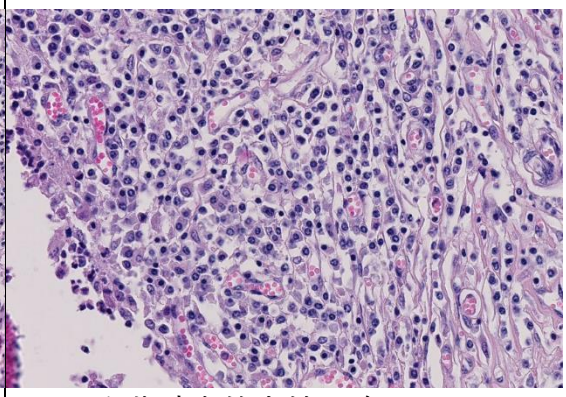

图 6 肉芽肿中的炎性细胞。

Signalment:

7-year-old female breed unspecified ox, (*Bos taurus*).This 7-year-old cow calved 4-5 months previously, and had been at pasture since. Found dead without premonitory signs.

Gross Description:

Carcass preservation is poor, but the animal is in good body condition.Â Gross lesions are confined to urinary tract, mammary gland and supramammary lymph nodes: bilateral, chronic, fibrinopurulent and severe pyelonephritis; chronic, necrosuppurative, severe cystitis; urolithiasis due to multiple sand-like calculi; and induration of the left-fore mammary gland quarter.Â No milk could be expressed.Â On cut surface, the gland parenchyma was markedly fibrosed with multifocal 2-3 mm areas of suppuration.Â The left supramammary lymph node was enlarged with a 1 cm diameter focus of suppuration.Â

Histopathologic Description:

Mammary gland.Â Separating lobules of atrophic acini are extensive bands of mature fibrous tissue which contain multifocal to coalescing pyogranulomas up to 10 mm in diameter.Â Pyogranulomas are centered on colonies of gram-positive cocci (gram-stained section not submitted) within up to 100 Î¼m long radiating columns of hyaline eosinophilic material (Splendore-Hoeppli material).Â These in turn are surrounded by variably sized zones of viable and degenerate neutrophils, occasionally within a large area of necrosis, bounded by large numbers of macrophages and varying numbers of multinucleated giant cells mixed with lymphocytes, plasma cells and small numbers of neutrophils, bounded by concentric bands of fibrous tissue.Â Mammary acini are devoid of secretory product and are lined by cuboidal to low columnar epithelium which is multifocally vacuolated or necrotic and sloughing.Â Multifocally there is exocytosis of low numbers of neutrophils and lymphocytes into acinar epithelium and multifocally acini contain small amounts of eosinophilic fibrillar material (fibrin) and small numbers of neutrophils and/or macrophages.Â Within the

interstitium of the secretory tissue there is vascular congestion and a diffuse mild infiltration of lymphocytes, plasma cells and fewer macrophages and a diffuse mild fibroplasia.Â

Morphologic Diagnosis:

Mammary gland: pyogranulomatous mastitis, chronic with intra-lesional bacteria.Â

Lab Results:

Beta-haemolytic, coagulase-positive *Staphylococcus aureus* was isolated from the supramammary lymph node.Â *Corynebacterium renale* was isolated from the kidney.

Condition:

Mammary gland botryomycosis

Contributor Comment:

The cause of death in this case was renal failure due to pyelonephritis.Â The chronic mastitis was judged to be incidental with respect to the presentation of sudden, unexpected death.Â *Staphylococcus aureus* was isolated from the supramammary lymph node.Â Although culture was not performed on the mammary gland, gram positive nature of the intralesional cocci would be consistent with *Staphylococcus* spp.Â

S.Â aureus is one of the most common causes of bovine mastitis.Â Clinically, staphylococcal mastitis may be peracute and fulminating or milder and more chronic.Â The acute forms of disease generally occur shortly after parturition and tend to produce gangrene of the affected quarters with high mortality.(9) The chronic or subclinical forms are more common and thus associated with the most

important economic losses.Â The clinical presentation may be related to the strain of *S.Â aureus*; strains differ in their ability to spread within herds, and to cause somatic cell count elevation, clinical mastitis, or persistent infections or loss in milk production.Â In vitro, strains differ in their ability to withstand killing by neutrophils or invade mammary epithelial cells.(1)

The main reservoirs of infection are infected quarters and lesions on the skin of the udder and teat.Â Once *S.Â aureus* contaminates the teat orifice, it can persist and multiply before entering the teat canal and sinus and disseminating within the mammary gland.Â Colonization of the distal part of the mammary gland may be achieved by adhesion to specific receptors on the surface of epithelial cells.Â The adhesion varies from very low to extremely high numbers of bacteria per cell.Â In vitro adhesion depends on multiple factors including strain and origin of mammary epithelial cells.(5) The host response to the penetration includes degeneration and necrosis of epithelial cells and exudation of neutrophils into the interlobular tissue and secretory acini.Â If the exudation is massive and the organisms highly toxigenic, the acute and gangrenous forms of the disease occur.Â *S.Â aureus* can also invade more deeply into the inter-acinar tissue and establish persistent foci of infection that provoke botryomycotic granulomatous reactions associated with marked fibroplasia.(9) Acinar atrophy may be due to pressure from this fibrosis and also from occlusion of small ducts by exudate or granulation tissue causing obstruction of milk flow from unaffected lobules.(9)

JPC Diagnosis:

Mammary gland: Mastitis, pyogranulomatous, multifocal, severe, with numerous cocci and Splendore-Hoeppli material.

Conference Comment:

The tissue sections examined in this case are composed primarily of lobules of mammary ducts; mammary glands/acini are largely

atrophied or lost, likely due to pressure necrosis secondary to abundant inflammation.Â Mastitis is the single most common disease syndrome of adult dairy cows.Â Routes of infection vary from ascending infection of the teat canal (most common) to hematogenous or percutaneous.Â The most commonly bacterial isolates are *Streptococcus* spp., *Staphylococcus* spp., and gram-negative coliforms, especially *Escherichia coli* (also *Enterobacter aerogenes, Klebsiella pneumoniae, Citrobacter* spp., *Pasteurella multocida, Pseudomonas aeruginosa, Serratia* spp., and *Proteus* spp.).Â The mammary gland is the principal site of persistence or reservoir for certain bacterial species, including *Streptococcus agalactiae, Staphylococcus aureus* and *Mycoplasma bovis*, while infection with coliforms is typically acquired via teat contamination from the external environment (e.g., fecal contaminated bedding, soil or water).Â *Streptococcus uberis* and *S.Â dysagalactiae* can persist in either location.Â Other pathogens associated with bovine mastitis include *Trueperella pyogenes, Prototheca zopfii, Nocardia asteroides, Mycobacterium* spp., and less commonly, *Brucella abortus, Mannheimia haemolytica, Salmonella* spp., *Cryptococcus neoformans*, and *Candida* spp.(4,7,9)

Staphylococcus aureus is the most commonly reported etiology of mastitis.Â *S.Â aureus* isolates range from nonpathogenic to highly pathogenic; catalase and hemolysin production are the best indicators of bacterial pathogenicity.(4,9) Factors in normal milk which inhibit bacterial growth are listed in table one.(7,9) *S.Â aureus* has developed multiple virulence factors to overcome these defense mechanisms, which are listed in table two.(2-5,7)

Although most problematic in cattle, mastitis also affects many other domestic animal species.Â The major agents recovered from sheep and goats with necrotizing or gangrenous mastitis are *S.Â aureus* and *Mannheimia haemolytica*.Â For mycoplasmal mastitis, the typical causative agents are *Mycoplasma agalactiae* or *M.Â mycoides*.Â Additionally, goats and sheep infected with the small ruminant lentiviruses, caprine arthritis and encephalitis virus and maedi-visna virus, respectively, develop hard udders with agalactia.Â Equine mastitis is sporadic, and *Streptococcus*

zooepidemicus is the typical cause.(4,7,9) In swine, mastitis usually occurs in lactating or recently weaned sows.Â Gram-negative coliforms are the most commonly isolated etiologic agents; gram-positive bacteria such as *Streptcoccus,*
Staphylococcus and *Aerococcus* spp.Â are reported less frequently.(6) In dogs and cats mastitis is uncommon; dogs are more likely to present with mammary neoplasia, while fibroadenomatous hyperplasia (mammary hyptertrophy) is the most prevalent mammary lesion in cats.Â When present in dogs or cats, mastitis tends to occur in early lactation, due
to *Staphylococcus* spp., *Streptococcus* spp.Â or *E.Â coli* entering lactiferous ducts via fissures in nipples.(4) *E.Â coli, Klebsiella pneumoniae* and *Streptococcus zooepidemicus* are commonly encountered in guinea pig mastitis, while *S.Â aureus* (type C) and *Pasturella multocida* tend to affect rabbits.Â Mastitis is also reported in rats (typically due to *Pasteurella pneumotropica*, *S.Â aureus, Corynebacterium* spp., or *Pseudomonas* spp.), and hamsters (beta-hemolytic *Streptococcus* spp., *P.Â pneumotropica, E.Â coli*).(8)

Table 1.Â Antibacterial factors in milk.Â (7,9)

Antibacterial Factor	
Phagocytic cells	Phagocytosis is less efficient in milk than in serum
Lactoferrin	Iron-binding protein that inhibits bacterial multiplication
Lysozyme	Lyses bacterial cell wall peptidoglycan
Lactoperoxidase	May inhibit *S.Â aureus* and streptococci
Hydrogen peroxide	A weak oxidizing agent that is a byproduct of bacterial fermentation of milk carbohydrates
Immunoglobulins	Primarily IgG, which promotes opsonization; less IgA, which may reduce bacterial adherence at epithelial surfaces

Table 2.Â Select virulence factors of S.Â aureus.(2-5,7)

Virulence Factor	

Leucocidin	Cytolytic to bovine leukocytes
Alpha-toxin	Binds cell membranes forming hexameric pores; not produced by all *S.Â aureus* isolates
Beta-toxin	A phospholipase C or sphingomyelinase
Protein A	Antiphagocytic factor that binds to the F_c fragment of IgG
Extracellular enzymes	Coagulase, hyaluronidase, phosphatase, nuclease, lipase, catalase, staphylokinase (fibrinolysin), superantigens and proteases
Bacterial capsule	Interferes with opsonization, phagocytosis, and complement activity; not present in all strains of *S.Â aureus*
Penicillinase	Splits beta-lactam ring of penicillin

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病例 CP2022-93

切片连结(JPC#)：

https://www.askjpc.org/vspo/show_page.php?id=YlBRNitLN01qTjh1d0c1SnM5R3Mxdz09

演讲及翻译人（Presenter and Translator）：

吴彩霞，广东省科学院生物与医学工程研究所

背景描述（Signalment）：

6 岁雄性恒河猴（*Macaca mulatta*），在右侧乳头附近发现一个皮下肿块。肿块摘除后提交分析。体格检查时未见其他异常。

大体所见（Gross Description）：

组织样本（活检）测得肿块大小为 1.8 x 1.5 x 1.0 cm。肿块呈结节状，似有包膜，切面为黄色至白色、质坚硬。

镜下描述（Histopathologic Description）：

肿瘤界限清晰，周围包绕一层内衬有一层扁平上皮细胞的平滑肌。在周围的软组织中有一些正常的乳腺组织。肿瘤结节大部分为实性，具有罕见的导管和管状结构。导管结构内衬失去极性的多形上皮细胞，而且有多层细胞堆积。(图 2-1, 2-2) 部分细胞有明显的胞质空泡。细胞内胞核为单个核仁，且有斑点染色质。每 40 倍视野大约可见 1 个有丝分裂象。该肿瘤的多个切片内未见有周围软组织的浸润。对所有肿瘤切片进行细分，以备用于制作会议切片。

组织形态学诊断（Morphologic Diagnosis）：

乳腺：导管原位癌（DCIS）

疾病（Condition）：

导管原位癌

提供者评论（Contributor Comment）：

乳腺肿瘤在猕猴中并不常见。目前尚不清楚猕猴中观察到的低癌症发病率是因为对癌症的不易感性，还是因为对生命周期的监测不足难以确定在老年猕猴中是否会有较高的癌症发生率。(8) 导管原位癌（DCIS）是肿瘤细胞局限于导管的肿瘤。这与细胞延伸进小叶中的小叶原位癌（LCIS）不同。有时很难从形态学上

区分小叶原位癌（LCIS）和导管原位癌（DCIS）。区分 DCIS 和 LCIS 的潜在标志物是 E-钙粘蛋白，因为 E-钙粘蛋白在 LCIS 中表达缺失，而在 DCIS 中仍有表达。（6,8）

DCIS 和 LCIS 之间的区别对人类至关重要，因为这两种癌的管理策略差异很大。（7）在人类当中，雌激素被认为有助于乳腺肿瘤的形成。不分性别，雌激素都会刺激乳腺上皮细胞的有丝分裂，并能促进乳腺组织不受调控的增长。这个特殊的病例很有趣，因为它代表了一种罕见的男性乳腺癌。在一项对未经治疗的动物进行的长期研究中，有一份报告给出了 1.1%的发病率。（8）该发病率与男性乳腺癌发病率相似，占所有乳腺癌病例的 0.8%。大多数男性乳腺癌起源于导管，且多为浸润性。据报道，男性乳腺癌与睾丸异常、Klinefelter 综合征、乳腺癌家族史、不育症和乳腺分泌物有关。他们的雌激素和孕激素受体往往趋向于高表达。

JPC 诊断（JPC Diagnosis）：

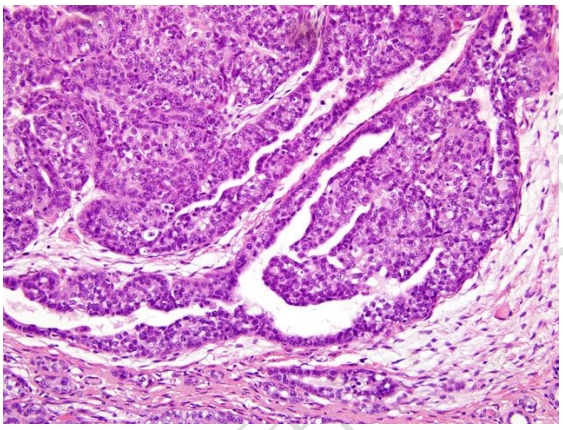
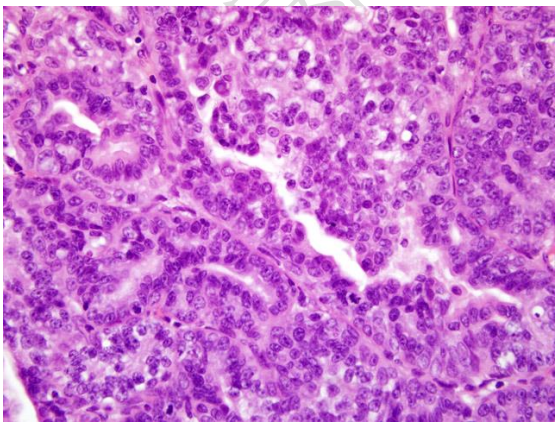
乳腺导管原

会议评论（Conference Comment）：

该病例在咨询 AFIP 妇科和乳腺病理科后进行了复审，AFIP 妇科和乳腺病理科同意提供者的诊断，并进一步评论说 DCIS 似乎会引起导管内乳头状瘤，基于病变内乳头状结构的存在，其内衬有与 DCIS 一致的单一增殖排列的上皮细胞。他们还注意到一些乳头状结构局部存在肌上皮细胞。会后，部分讨论集中在区分良恶性肿瘤的一般特征上。这些特征包括多形性、核形态、有丝分裂的出现、总体有丝分裂率、极性和侵袭性等。在恶性肿瘤中，细胞和细胞核的大小和形状变化通常比良性肿瘤大。细胞可以比相邻细胞大或小，细胞核大小变化相似。这些变化分别称为细胞异形性和核异形性。在恶性肿瘤中，细胞核通常含有丰富的 DNA，染色更暗（深染）。核质比也可以从正常的 1:4 到 1:6 接近 1:1。恶性肿瘤中的有丝分裂比良性肿瘤中的有丝分裂更丰富。通常，恶性肿瘤也有异常的有丝分裂，也就是病理性核分裂，可形成与正常染色体有丝分裂不同的异常形状和模式。这些细胞通常产生多极纺锤体，这些纺锤体可以产生与相邻细胞相关的异常细胞外观。恶性肿瘤通常是生长速度较快的肿瘤，其生长方式更无序、随意（通常称为极性丧失）。恶性肿瘤也倾向于侵入周围组织并转移到区域淋巴结和其他器官系统，而良性肿瘤则停留在起源位置。根据肿瘤的具体类型和所涉及的组织，肿瘤内可能有各种各样的形态学表现，因此，这些指南是作为一项一般规则，并且根据不同类型的肿瘤而有所不同。(4)在许多实验室动物和家养物种中已经报告了乳腺病变，其中一些更常见的病变在会后会议中进行了讨论。下面是一张图表，列出了本次会议讨论的物种以及每个物种的变化。

Species 种属	Mammary change 乳腺变化	Cause 原因

Rat 大鼠	Fibroadenoma (S-D strain) 纤维腺瘤	Increase in prolactin 催乳素增加
Rabbit 兔	Mammary dysplasia 乳腺异常增生	Pituitary tumor 垂体瘤
Mouse 小鼠	FVB/N mice hyperplasia of mammary glands FVB/N 小鼠乳腺增生 Mammary tumors 乳腺瘤	Proliferation of prolactin secreting cells in pars distalis 在远侧部的泌乳素分泌细胞增殖 Mammary tumor viruses (MMTVs) 乳腺肿瘤病毒
Cat 猫	Fibroepithelial hyperplasia 纤维上皮增生	Progesterone administration 孕酮给药 (Ovaban other iatrogenic hormones) 其他医源性激素
Canine 犬	Gynecomastia 乳房发育	Sertoli cell tumor 支持细胞瘤

	肿瘤细胞形成微乳头状突起，充满导管腔。
	肿瘤由多边形至立方形细胞组成，具有不同的细胞边界，中等数量的嗜酸性细胞浆，圆形至椭圆形的细胞核，有细点状染色质，通常有 1-3 个核仁。有丝分裂率视野部位而异，在某些高倍视野中可达 4-5 个。

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3. Giordano SH, Buzdar AU, Hortobagyi GN: Breast cancer in men. Annals of Internal Medicine 137:678-687. Primatology 2001; 30:121126
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7. Schnitt SJ, Morrow M: Lobular carcinoma in situ: current concepts and controversies. Semin Diagn Pathol 16:20923, 1999
8. Wood CE, Usborne A, Tarara R, Starost MF: Hyperplastic and neoplastic lesions of the mammary gland in macaques. Vet Pathol 43:471483, 2006

Signalment:

6-year-old male, Rhesus Macaque, (*Macaca mulatta*). An encapsulated subcutaneous mass was noted near the right nipple. It was removed and submitted for analysis. On physical exam no other abnormalities were noted.

Gross Description:

The tissue sample (biopsy) measured 1.8 x 1.5 x 1.0 cm. The mass is firm, slightly nodular and yellow to white in color. It is encapsulated in a well demarcated capsule.

Histopathologic Description:

The slide consists of a well demarcated neoplasm surrounded by a layer of smooth muscle lined by flattened epithelial cell. There are some pockets of normal glandular tissue in the surrounding soft tissue. The neoplastic nodules appear to be mostly solid with rare ductal and tubular structures. The ductal structures are lined by pleomorphic epithelial cells with loss of polarity and piling up of cells (**Figs. 2-1, 2-2**). Some cells have clear cytoplasmic vacuoles.Â The nuclei have stippled chromatin with single nucleoli and are centralized in the cell. Roughly 1 mitotic figure per 40X field is seen. Multiple sections of the neoplasm fail to show invasion into surrounding soft tissue. Original tumor sections were subdivided to prepare conference slides.

Morphologic Diagnosis:

Mammary Gland: ductular carcinoma in situ (DCIS)

Condition:

Ductular carcinoma in-situ

Contributor Comment:

Mammary gland tumors are uncommon in macaques. It is still unclear whether the low cancer rate observed in macaques is true resistance or if insufficient lifespan studies have been conducted to see whether higher cancer rates occur in aged populations.(8) Ductular carcinoma in situ (DCIS) are neoplasms that have neoplastic cells limited to ducts. This is distinguished from lobular carcinoma in situ (LCIS) where cells extend into lobules. Occasionally it is difficult to morphologically distinguish LCIS from ductular carcinoma in situ DCIS. A potential marker to distinguish DCIS from LCIS is E-cadherin since E-cadherin protein expression is lost in LCIS, while it remains in cases of DCIS.(6,8)

Differentiation between DCIS and LCIS is crucial in humans because management strategies differ greatly between the two types.(7) In humans, estrogens have been hypothesized as contributing to the formation of mammary tumors. Estrogen stimulates the mitosis of breast epithelial cells regardless of the gender and can enhance unregulated growth of mammary tissue.(1) This particular case is interesting because it represents a mammary gland carcinoma in a male, which has been rarely reported. One report gives an incidence rate of 1.1% in a long term study of untreated animals.(8) This rate is similar to that seen in men, accounting for 0.8% of all the cases of mammary carcinoma. Most mammary carcinoma in human males is ductal in origin with the majority being invasive. Mammary gland carcinoma in men has been reported to be linked to testicular abnormalities, Klinefelter syndrome, familial history of breast cancer, infertility and breast discharge. They tend to be estrogen and progesterone receptor positive.(3)

JPC Diagnosis:

Mammary gland: Ductular carcinoma in-situ

Conference Comment:

This case was reviewed in consultation with the AFIP Department of Gynecologic and Breast Pathology, who agreed with the contributors diagnosis, and further commented that the DCIS appeared to involve a papilloma, based on the presence of papillary cores within the lesion which are lined by a monotonous proliferation of epithelial cells consistent with DCIS. They also noted the focal presence of myoepithelial cells in some of the papillary cores.

During the post conference, part of the discussion focused on general features distinguishing benign from malignant tumors. These features include pleomorphism, nuclear morphology, appearance of mitotic figures and overall mitotic rate, polarity, and invasiveness.

In malignant tumors, both cells and nuclei generally display greater variation in size and shape than do their benign counterparts. Cells can be much larger or smaller than adjacent cells, with similar variation in nuclear size. These changes are referred to as anisocytosis and anisokaryosis, respectively. In malignant tumors, nuclei often contain an abundance of DNA and stain much darker (hyperchromatic). The nuclear to cytoplasmic ratio can also approach a 1:1 ratio from the normal 1:4 to 1:6 ratio. Mitotic figures are more abundant in malignant tumors than in benign tumors. Often, malignant tumors also have bizarre mitotic figures forming abnormal shapes and patterns that do not resemble the normal mitotic rearrangement of chromosomes. These cells often produce multipolar spindles, which c create an a highly unusual cellular appearance in relation to neighboring cells. Malignant tumors are generally faster growing neoplasms with growth occurring in a more disorganized, haphazard fashion (often referred to as loss of polarity). Malignant tumors also tend to invade surrounding tissue and metastasize to regional lymph nodes and other organ systems, whereas benign tumors stay in the location of origin. There can be a wide range of morphologic appearances within tumors depending on the specific type of tumor and the tissue involved, so these guidelines are meant as a general rule and are subject to vary from one type of neoplasm to the next. (4)

Mammary gland lesions have been reported in numerous lab animals and domestic species, and a few of the more common of these were discussed during the post-conference session.Â A chart listing the species discussed during this session and the changes in each species is included below.

Species	**Mammary change**	**Cause**
Rat	Fibroadenoma (S-D strain)	Increase in prolactin
Rabbit	Mammary dysplasia	Pituitary tumor
Mouse	FVB/N mice hyperplasia of mammary glands Mammary tumors	Proliferation of prolactin secreting cells in pars distalis Mammary tumor viruses (MMTVs)

Cat	Fibroepithelial hyperplasia	Progesterone administration (Ovaban other iatrogenic hormones)
Canine	Gynecomastia	Sertoli cell tumor

(2,5)

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1. Clemons M, Goss P: Estrogen and the risk of breast cancer. N Engl J Med **344**:276-285, 2001

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6.Moll R, Mitze M, Frixen UH: Differential loss of E-cadherin expression in infiltrating ductal and lobular breast carcinomas.Am J Pathol **143**:173142, 1993

7.Schnitt SJ, Morrow M: Lobular carcinoma in situ: current concepts and controversies. Semin Diagn Pathol **16**:20923, 1999

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病例 CP2022-94

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演讲及翻译人（Presenter and Translator）：

张卓 哈尔滨兽医研究所

切片 A: 猫

病史：该病例整个乳腺弥漫性肿大。

组织病理学:

乳腺：弥漫性乳腺小叶增生，增生小叶大小不同，其中增生性导管被多层肌成纤维细胞包围，外包疏松结缔组织，最外层包绕致密胶原纤维。 导管壁由 1-3 层柱状上皮细胞组成。周围的梭形细胞(肌上皮细胞)边界不清，胞浆呈轻度嗜酸性，细胞核椭圆形，染色质呈点状分布，1-2 个核仁。多处管腔内充满坏死细胞碎片、脱落的上皮细胞和少量嗜中性粒细胞。导管周间质可见少量泡沫样巨噬细胞、少量淋巴细胞和浆细胞。

真皮浅层可见空白区域可淋巴管扩张（水肿）。

表皮轻度角化过度。

形态学诊断:乳腺:增生，纤维上皮，弥漫性，中度，品种不详的猫，猫科动物。

原因：孕酮水平长期升高

疾病：乳腺纤维腺瘤样增生

鉴别：纤维上皮增生，猫科动物乳房肥大

切片 B(JPC #4154528):9 岁节育暹罗猫，母。

病史:左乳腺多个链状排列肿物，持续时间未知。

组织病理描述:

- 毛皮、皮下和乳腺:皮下和真皮层扩张，压迫其被覆附件，表皮膨隆。肿瘤组织细胞密集、边界清楚，外有包膜，瘤细胞为上皮细胞，瘤细胞呈腺管状排列，腺管轻度扩张，多屈曲。少数部位可见瘤细胞巢状排列，由密度不同维管支撑，偶见结缔组织增生或硬质间质（硬癌）。

  肿瘤上皮细胞边缘清晰 ，细胞质嗜酸性，核圆至卵圆形，染色质呈粗大颗粒至囊泡状，一个明显红色核仁。 每 10 个高倍场(2.37mm²）可见 72 个核分裂像。 小管通常由单层柱状至立方状的肿瘤上皮细胞构成，细胞核常呈栅栏状。在某些区域，小管厚达 4 个细胞(复层化)，基底方向缺失(细胞异型性)，核多形性明显，或衬有细长的上皮细胞。 小管腔内充满轻度嗜碱性至中性的均质液体(分泌产物)、胞浆嗜酸性泡沫状巨噬细胞、胞浆嗜酸性高、核固缩的坏死上皮细胞。纤维间质因出血、纤维蛋白渗出和水肿而呈多灶性扩张。 可见局 灶性大面积坏死，表现为差异性染色消失、细胞结构保留(凝固性坏死)和坏死灶中央细胞结构缺失(溶解性坏死); 在肿瘤细胞的其余区域也发现了类似的较小坏死灶。 邻近皮下组织可见肿瘤细胞多灶性浸润，并被含有大量梭形细胞(肌成纤维细胞)的致密胶原间质所分隔和包围。肿瘤旁皮下组织可见多灶性淋巴细胞和浆细胞浸润，淋巴管扩张。

  形态学诊断：皮肤、皮下和乳腺：癌，管状，III 级，浸润性，暹罗，猫。

  疾病：导管性乳腺癌

  讨论

  乳腺纤维瘤样增生:

  乳腺导管和结缔组织的良性，非肿瘤增生的年轻未绝育母猫(<2 岁)，怀孕的猫，或老年绝育的公猫和母猫长期孕酮治疗(醋酸甲孕酮)

  最常见的发生在春天和前几个发情周期

  卵巢子宫切除术或终止妊娠或孕激素治疗

- 猫科动物乳腺瘤

- 猫比狗少见

  雌性多见，但也发生于雄性

  75-90%为癌，大多数最终转移

  暹罗和其他短毛纯种犬更倾向于此

  未绝育动物风险略高; 1 岁前切除卵巢的猫的风险要小得多(尽管子宫切除和发病率之间的联系不像狗那么强); 7-9 岁患病风险低。

乳腺相关恶性肿瘤诊断标准:

局部淋巴结转移(提示为恶性)

淋巴浸润(常提示为恶性)

周围组织浸润伴结缔组织增生/硬化反应

肿瘤组织类型(如实体癌、粉刺癌、腺鳞癌等)

明显的核和细胞多形性(即明显的异型细胞增多/异型核增多，细胞深染，细胞质少(导管肿瘤没有此特征)

核分裂计数≥6 / 2.37 mm^2用于区分某些良恶性肿瘤

随机分布的多发性坏死(不要与缺血坏死区域相混淆)

复层化，基底膜缺失，核多形性

-

猫乳腺癌分级标准

-

存在两个分级系统(诺丁汉人类分级系统(NHG)和 2015 年引入的三层“Mills 系统”); 目前对于哪种分级体系应该用于猫的乳腺癌还没有达成共识; 建议联合使用

诺丁汉人类分级系统

组织学特征	
腺管状结构	评分
构成肿瘤大部 (>75%)	1
呈中等程度分布(10-75%)	2
很少或不见(<10%)	3
核多形性	评分
小而规则	1
中等程度体积增大、呈囊泡状、形状多变	2
大小形状变化显着	3
核分裂计数 (2.37$mm^{2)}$	评分
0-8 个分裂相 (0-50*)	1
9-16 个分裂相 (51-70*)	2
≥17 分裂相 (≥71*)	3
组织学评级	总分
I 级 (低级)	3-5
II (中级)	6-7
III (高级)	8-9

3-tier Grading System (Mills system)

-

3 层分级系统(MILLS 系统)

组织学特征	
淋巴管血管侵袭	评分
无	0
有	1
核形态*	评分
≤5%异常	0
>5% 异常	1
分裂相计数 (2.37mm^2)**	Score
≤62	0
>62	1
组织学分级	总分
一级 (低级)	0
二级 (中级)	1
三级 (高级)	2-3

*肿瘤分化程度最低和/或侵袭性最强部位的异常核形态。正常细胞核表面光滑，圆形或椭圆形。异常核形态包括凹陷、棱角、波纹或变形虫样。 估算异常核形态的细胞数，计算其在给定视野中细胞总量的百分比。

**在肿瘤周围或大部分有丝分裂活性的部位评估。

发病机理:

乳腺纤维瘤样增生:

黄体期的发情期、怀孕早期或孕激素治疗后

IGF-1 和生长激素诱导增生

长期暴露于内源性或外源性孕激素

机制不明

-

猫科动物乳腺癌:

雌激素和孕激素均增加乳腺上皮恶性转化的风险; 确切的机制未知

与健康组织相比，Wnt/β-catenin 和 Hippo 通路异常(狗和人类似)

侵袭性与渗透性糖蛋白(P-gp)和金属硫蛋白(MT)的表达相关

典型的临床表现:

乳腺纤维瘤样增生:

一个或多个乳腺突然、迅速、均匀的增大

硬而无痛，排除溃疡

-

猫科动物乳腺癌:

一个或多个乳腺内的硬结节性肿物，发病时间与发情无关

受累乳头可能出现红斑和肿大; 可能会渗出黄褐色或黄色的液体

常见皮肤溃疡

与皮肤或腹壁黏连

+ / -淋巴结肿大

典型的大体病变:

乳腺纤维瘤样增生:

一个或全部乳腺明显增大

皮肤:粉色到蓝色，+/-坏死

切面:白色至粉红色，突起，结节状伴蓝色纤维间隔形成网状，水肿，出血，坏死

管腔内增生:管腔内可见息肉状或穹隆状的肿块或围绕管腔中央环状生增生

猫科动物乳腺癌:

单发肿块与多发肿瘤均常见; 在多发性肿瘤的情况下，肿块通常发现整个乳腺

原发肿瘤通常靠近乳头

一般直径 >3cm

典型的光学显微镜结果:

乳腺纤维瘤样增生:

无包被的肿块，由分支导管结构的小叶组成，上皮细胞包围着水肿的肌成纤维细胞间质

导管状结构，由几层具有小泡核的立方到柱状上皮细胞排列

在导管和肌成纤维细胞中均多见分裂相

管状乳腺癌:

小管是主要特征，但也可能与其他模式共存(如实性或乳头状)

管状管腔可在宽度上变化，并可由一层以上的细胞排列，通常是多形性的; 细胞核的范围从低染到常染到深染

核分裂计数≥6 每 2.37mm2(通常为>30)

常见多灶性坏死

侵入邻近乳腺组织引起纤维母细胞广泛增殖，结缔组织增厚/硬化反应

鉴别诊断:

乳腺纤维瘤样增生:

肿瘤:通常不累及所有腺体; 通常是一个离散的结节; 上皮成分无组织和/或侵袭性

其他非肿瘤性乳腺增生

乳腺导管囊性扩张:因导管阻塞导致扩张; 常见于猫和狗

正常小叶增生:小叶内导管和腺泡增生; 上皮细胞无异型性

具有分泌活性的小叶增生(哺乳期):腺泡因分泌旺盛的立方细胞而不同程度地膨胀和排列(哺乳期变化); 腺泡细胞常有胞浆内空泡(脂质)，上皮细胞顶端表面突起(起泡)。

小叶增生伴纤维化; 突出的小叶间和小叶内纤维结缔组织

非典型性小叶增生:上皮细胞表现为核色变、异核、异细胞增多和少量分裂相; 小叶结构排列略不规律

上皮增生(导管内上皮增生):规则，明显异型性(可进展为癌); 根据核多形性、核分裂增多和/或坏死作出癌诊断

乳头状瘤病:导管内红色上皮增生，形成乳头状突起

乳汁淤积:乳潴留导致乳房充血、发热、疼痛(催产素释放抑制失败)

猫的原发性乳腺瘤(部分):

导管状

导管腺瘤:猫科动物最常见的良性乳腺肿瘤; CK8+/18+管腔上皮细胞；圆形至椭圆形基底上层细胞或圆形至椭圆形间质肌间质细胞，表达肌上皮标记物(CK5、CK6、CK14、平滑肌肌动蛋白、钙调蛋白); 轻度的异核症和异红细胞增多症; 少见分裂相(每 2.37mm^2 <6)

导管癌:肿瘤细胞排列成索状、小管状和实性区域，但实性区域比导管腺瘤大; 不同的是，管腔呈裂隙状，常由双层管腔上皮细胞和肌上皮细胞组成，基质很少或没有; 与导管腺瘤的区别在于更广泛异核细胞增多，有丝分裂计数增加(≥6 / 2.37mm^2)，没有分化良好的导管结构，取而代之的是鳞状上皮。

单纯瘤:由上皮构成肿瘤成分

单纯性腺瘤:猫科动物非常罕见的良性乳腺肿瘤; 由小管状上皮细胞组成的结节性、边界清楚、无浸润性病变; 细胞异形和核异形极少，分裂相很少(每 2.37mm^2 <6)。

小管癌:常见于猫; 见“镜下发现”的描述。

管状乳头状癌:在猫中很常见; 与小管癌相似，但 20%的小管有由纤维血管结缔组织间质支撑的乳头状突起，突入管腔

实体癌:常见于猫; 上皮细胞呈巢状、岛状排列，无腔管，间质致密;中度至重度核异形和细胞异形，分裂相不定; 注:实性癌在小管形成上不可能为 1 分。

粉刺癌:常见于猫; 以单个肿瘤内的多结节为特征的; 肿瘤结节内可见大小不等、界限清楚的由肿瘤细胞包围的中央圆形坏死区域; 外周上皮细胞可能有多种增殖模式，包括实性、管状乳头状、管状和微乳头状; 分裂相不定，但通常是中等到高(每 2.37mm^2 >20); 诊断时常见的淋巴浸润和淋巴结转移

注:虽然罕见，猫的由恶性上皮细胞和肌上皮细胞组成的肿瘤也有报道。

比较病理:

其他物种乳腺增生:

小鼠：未交配雌性 FVB/N 小鼠发生小叶增生，腺泡和导管内有分泌产物;进展程度与年龄正相关，且与垂体远侧部泌乳素分泌细胞相关; FVB/N 小鼠垂体腺瘤发生率高; 在没有垂体失调的情况下也可出现持续性增生

兔子：使用环孢霉素可引起乳腺增生

水牛：乳腺纤维腺瘤样增生; 可能受激素影响而引起。

其他物种的乳腺肿瘤

狗：超过 35 种表型; 7 种为良性，其余为组织学上的恶性; 50%的病例是良性的，有上皮或混合上皮和肌上皮成分; 单纯性癌、实体癌和复合癌是最常见的乳腺恶性肿瘤; 乳腺癌的分级方案与用于猫乳腺癌的诺丁汉人类分级系统相似(但不相同); 诊断后生存时间短的乳腺肿瘤包括乳腺骨肉瘤、间变性癌、富脂质癌、微乳头浸润癌、炎性癌、粉刺癌和鳞状细胞癌。

小鼠：:与内源性和外源性乳腺肿瘤病毒基因插入突变有关; 倾向于钝性扩张而不是浸润性增殖; 60%转移至肺，尽管通常具有良性形态学特征; 高达 100%的 C3H 雌性鼠在 9 个月大时发生乳腺肿瘤; 常见于经产 FVB/N 小鼠; BALB / c 不多见

大鼠：:乳腺良性纤维腺瘤; 泌乳素升高; 常见于老年雌性 Sprague-Dawley 大鼠; 去卵巢大鼠发病明显减少; 恶性乳腺肿瘤很少见

豚鼠：雄性和雌性均可发生乳腺腺癌; 多数为导管性; 可能转移到区域淋巴结，此外可见低级别的局部恶性肿瘤; 也有乳腺腺瘤和恶性混合性乳腺肿瘤的报道

兔：多品种受累，包括实验兔; 一般在 3-4 岁左右出现; 大多数为管状、乳头状、管状乳头状、实性、腺鳞状、粉刺状、复合体、导管状、筛状、间变和梭形细胞癌; 囊性乳腺炎被认为是良性腺瘤向腺癌转变的前奏; 有淋巴结、肺及其他器官转移的报道

鳍足类：乳腺癌是圈养海狮最常见的肿瘤之一

美洲狮：在最近报道乳腺癌较常见。

有关于美洲驼、羊驼，单峰骆驼，野猪、野生猫科动物、白鲸、蝙蝠和一只雄性猩猩的乳腺癌报告

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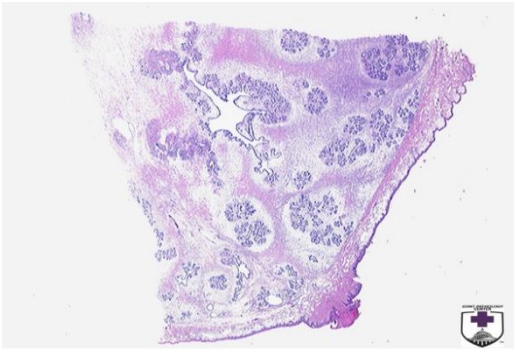
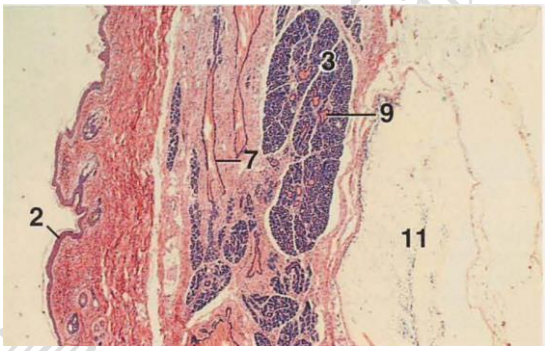
<tr><td>  </td><td> 
</td></tr>
<tr><td>增生乳腺（猫）</td><td>正常乳腺（猫）
《Color Atlas of Veternary Histology》</td></tr>
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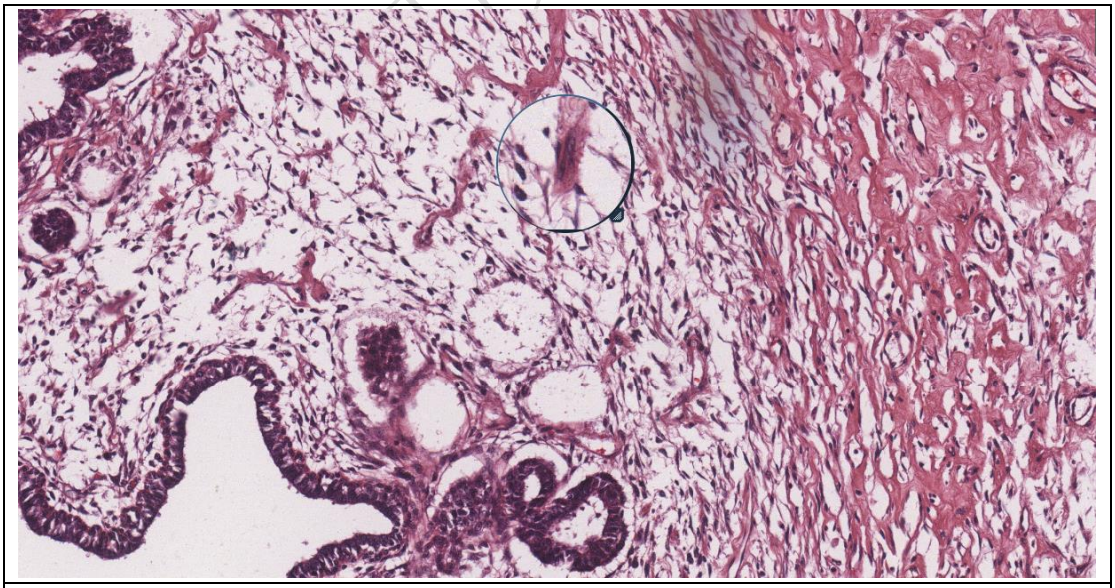
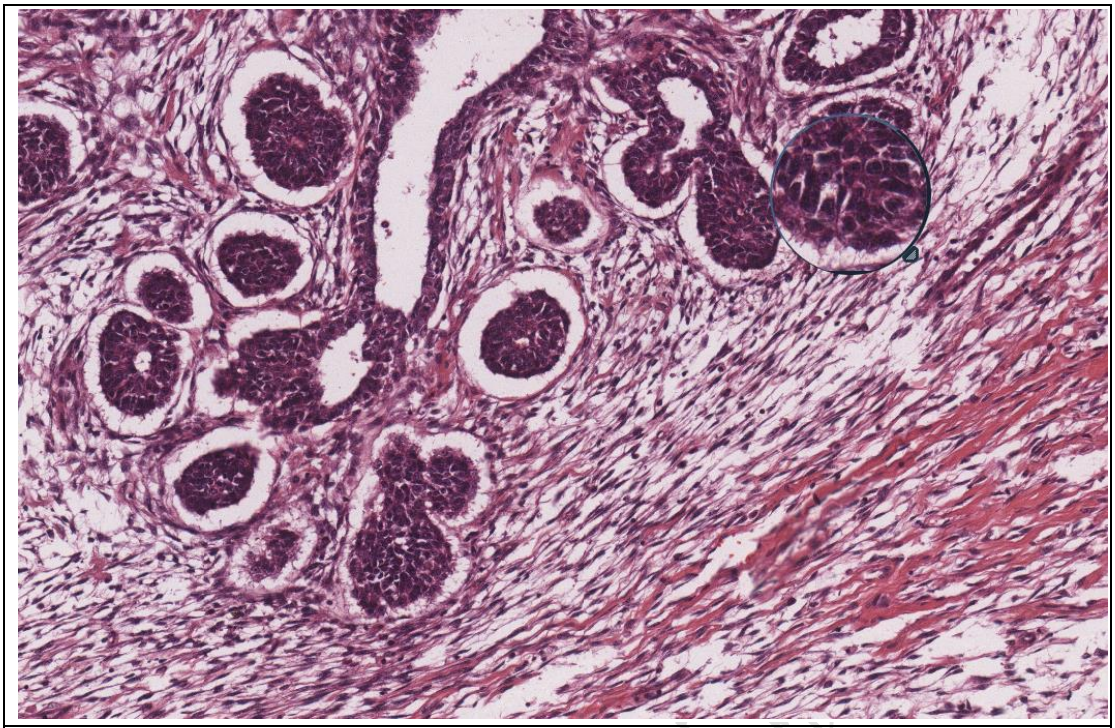


导管壁由 1-3 层柱状上皮细胞组成。周围的梭形细胞(肌上皮细胞)边界不清，胞浆呈轻度嗜酸性，细胞核椭圆形，染色质呈点状分布，1-2 个核仁。



多处（并非）管腔内充满坏死细胞碎片、脱落的上皮细胞和少量嗜中性粒细胞。

JPC SYSTEMIC PATHOLOGY
ENDOCRINE SYSTEM
January 2022
R-N10

Slide A: Signalment (JPC #2026123): A cat

HISTORY: This cat had diffusely swollen and enlarged mammary glands along the entire mammary chain.

HISTOPATHOLOGIC DESCRIPTION: Mammary gland: Diffusely, the mammary gland is expanded by variably sized lobules composed of hyperplastic ducts surrounded by multiple layers of myofibroblasts embedded within loose stroma that blends peripherally into dense bands of collagenous stroma. Ducts are lined by 1-3 layers of cuboidal to columnar epithelial cells. The surrounding spindle cells (myoepithelial cells) have indistinct cell borders, a scant amount of eosinophilic fibrillar cytoplasm, and an oval nucleus with finely stippled chromatin and 1-2 nucleoli. Multifocally ducts are filled with small amounts of necrotic debris, sloughed epithelial cells, and few neutrophils. Within the periductal stroma there are moderate numbers of foamy macrophages and fewer lymphocytes and plasma cells. Diffusely the superficial dermis is mildly expanded by increased clear space and ectatic lymphatics (edema). The epidermis is mildly hyperkeratotic.

MORPHOLOGIC DIAGNOSIS: Mammary gland: Hyperplasia, fibroepithelial, diffuse, moderate, breed unspecified cat, feline.

CAUSE: Prolonged elevated levels of progesterone

CONDITION: Mammary fibroadenomatous hyperplasia

SYNONYMS: Fibroepithelial hyperplasia, feline mammary hypertrophy

Slide B: Signalment (JPC #4154528): A nine-year-old spayed-female Siamese cat.

HISTORY: This cat had multiple left mammary chain masses for an unknown duration.

HISTOPATHOLOGIC DESCRIPTION: Haired skin, subcutis, and mammary gland: Expanding the subcutis and dermis, compressing overlying adnexa, and elevating the overlying epidermis is an encapsulated, well demarcated, densely cellular neoplasm composed of neoplastic epithelial cells predominantly arranged in mildly ectactic ectatic and tortuous tubules and fewer solidly cellular areas supported by a variably dense fibrovascular to occasionally desmoplastic/scirrhous stroma. Neoplastic epithelial cells have distinct cell borders, a moderate amount of eosinophilic cytoplasm, and a round to oval nucleus with coarse to vesiculated chromatin and one prominent magenta nucleolus. Anisocytosis and anisokaryosis are marked and there are 72 mitotic figures per 10 high power fields ($2.37mm^2$). Tubules are typically lined by a single layer of columnar to cuboidal neoplastic epithelial cells that frequently have palisading nuclei. In other regions tubules are up to four cells thick (pluristratification) with loss of basilar orientation (cellular atypia) and marked nuclear pleomorphism, or are lined by attenuated epithelium. Tubule lumens are variably expanded by lightly basophilic to amphophilic homogenous fluid (secretory product), macrophages with eosinophilic foamy cytoplasm, and sloughed necrotic epithelial cells characterized by hypereosinophilic cytoplasm and pyknotic nuclei. The fibrovascular stroma is multifocally expanded by hemorrhage, fibrin, and edema. There is a focally extensive region of necrosis characterized by both loss of differential staining and retention of cellular architecture (coagulative necrosis) and loss of cellular architecture (lytic necrosis) within the central aspect of the mass; similar smaller necrotic foci are found throughout the remaining regions of viable neoplastic cells. Neoplastic cells multifocally infiltrate into the adjacent subcutis and are separated and surrounded by dense collagenous stroma that contains numerous spindle cells (myofibroblasts). The subcutis adjacent to the neoplasm is multifocally infiltrated by few lymphocytes and plasma cells, and lymphatics are ectatic.

MORPHOLOGIC DIAGNOSIS: Haired skin, subcutis, and mammary gland: Carcinoma, tubular, grade III, infiltrative, Siamese, feline.

CONDITION: Tubular mammary carcinoma

GENERAL DISCUSSION:

Mammary fibroadenomatous hyperplasia:

- Benign, **nonneoplastic proliferation** of mammary ducts and connective tissue of **young intact female cats (<2yrs old),** pregnant cats**,** or older neutered male and female cats on prolonged progesterone therapy (megestrol acetate)
- Most commonly occurs in the spring and with first several estrus cycles
- Regression following ovariohysterectomy or termination of pregnancy or progesterone therapy

Feline mammary neoplasia

- Much less common in cats than dogs
- Predominantly occurs in queens but also occurs in males
- 75-90% are carcinomas and majority eventually metastasize
- Siamese and other short-haired pure breeds are predisposed
- Intact animals at slightly greater risk; cats spayed prior to 1 year of age have much less risk (although association between ovariohysterectomy and incidence is not as strong as in the dog); 7-9 year risk plateau

Criteria of malignancy associated with mammary neoplasms:

- Metastasis to regional lymph node(s) (always indicative of malignancy)
- Lymphatic invasion (always indicative of malignancy)
- Infiltration of surrounding tissue with desmoplasia/scirrhous reaction
- Tumor histotype (e.g. solid carcinoma, comedocarcinoma, adenosquamous carcinoma, etc.)
- Marked nuclear and cellular pleomorphism (i.e. prominent anisocytosis/anisokaryosis, hyperchromatic cells, and loss of cytoplasm (not in ductal tumors)
- **Mitotic count with ≥ 6 per 2.37 mm² used to distinguish between some benign and malignant tumors**

- Randomly distributed areas of necrosis (not to be confused with central regions of ischemic necrosis)
- Pluristratification with loss of cellular orientation with the basement membrane and nuclear pleomorphism

Feline mammary carcinoma grading systems

- Two grading systems exist (Nottingham Human Grading System (NHG) and Three-Tiered "Mills System" introduced in 2015); no current consensus on which should be used for feline mammary carcinomas; combined use suggested (Avallone et al, *Vet Pathol.* 2021)
- Nottingham Human Grading System

Histologic feature	
Tubule formation	Score
Comprises majority of tumor (>75%)	1
Present to a moderate degree (10-75%)	2
Little or none present (<10%)	3
Nuclear pleomorphism	Score
Small regular uniform nuclei	1
Moderate increase in size, vesiculation, and variability	2
Vesicular nuclei with marked variation in size and shape	3
Mitotic count ($2.37mm^{2}$)	Score
0-8 mitoses (0-50*)	1
9-16 mitoses (51-70*)	2
⩾17 mitoses (⩾71*)	3
Histological grade	Total Score
Grade I (low grade)	3-5
Grade 2 (medium grade)	6-7
Grade 3 (high grade)	8-9

*Assessed at periphery or in most mitotically active parts of the tumor. Recently proposed modifications to the mitotic cutoffs are reported in parentheses (Mills et al.)

- 3-tier Grading System (Mills system)

Histologic feature	
Lymphovascular invasion	Score
Absent	0
Present	1
Nuclear shape*	Score
⩽5% abnormal	0
>5% abnormal	1
Mitotic count (2.37mm^2)**	Score
⩽62	0
>62	1
Histological grade	Total Score
Grade 1 (low grade)	0
Grade 2 (medium grade)	1
Grade 3 (high grade)	2-3

* Abnormal nuclear from includes any deviation from smooth nuclear contour or round/oval nuclear shape, such as clefting, angularity, corrugation, or ameboid morphology assessed at high power in the least differentiated and/or most invasive portion of the tumor. The number of nuclei exhibiting the abnormal nuclear form is estimated and expressed as a percentage of the total number of nuclei within any given field.

**Assessed at periphery or in most mitotically active parts of the tumor.

PATHOGENESIS:

Mammary fibroadenomatous hyperplasia:

- **Coincides with the luteal phase of estrus, early in pregnancy, or after progestin therapy**

The mechanism for progesterone induced hyperplasia involves IGF-1 and growth hormone

- Prolonged exposure to endogenous or exogenous progesterone
- Exact mechanism unknown

Feline mammary carcinoma:

- Both estrogen and progesterone increase risk of malignant transformation of mammary epithelium; exact mechanism is unknown
- Deregulation of the Wnt/β-catenin and Hippo pathways compared to healthy tissues (similar in dogs and humans) (Sammarco et al, *Vet Pathol.* 2020)
- Aggressiveness correlated with expression of permeability glycoprotein (P-gp) and metallothionein (MT) (Manoel et al, *J Comp Pathol.* 2021)

TYPICAL CLINICAL FINDINGS:

Mammary fibroadenomatous hyperplasia:

- Sudden, rapid, uniform enlargement of one or more mammary glands
- Firm and painless, unless ulcerated

Feline mammary carcinoma:

- Firm, nodular masses in one or more mammary glands with the time of onset unrelated to estrus
- Involved nipples may be erythematous and swollen; may exude a tan or yellow fluid
- Ulceration of the overlying skin is common
- May be adhered to overlying skin or underyling abdominal wall
- +/- lymphadenopathy

TYPICAL GROSS FINDINGS:

Mammary fibroadenomatous hyperplasia:

- **One** or **all mammary glands markedly enlarged**
- Overlying skin: Pink to blue, +/- necrosis
- Cut surface: White to pink, bulges, multinodular with blue fibrous septa forming a reticulated pattern, edema, hemorrhage, necrosis
- Intraductal pattern: Project from wall of fluid-filled space as a polypoid or dome shaped mass or more annular growth around a central cavity

Feline mammary carcinomas:

- Solitary masses are as common as multiple tumors; in cases of multiple tumors, masses are commonly found throughout the mammary chains
- Primary tumor is usually adjacent to the nipple
- May be >3cm diameter

TYPICAL LIGHT MICROSCOPIC FINDINGS:

Mammary fibroadenomatous hyperplasia:

- Unencapsulated mass composed of lobules of branching ductal structures lined by epithelial cells surrounded by edematous myofibroblastic stroma
- Duct-like structures lined by several layers of cuboidal to columnar epithelial cells with vesiculate nuclei
- Mitoses may be common in both ductal and myofibroblast populations

Tubular mammary carcinoma:

- Tubules are predominant feature but may coexist with other patterns (e.g. solid or papillary)
- Tubular lumina may vary in width and may be lined by more than one layer of cells, which are often pleomorphic; nuclei range from hypo- to normo- to hyperchromatic
- Mitotic count is ⩾6 per 2.37mm^2 (often >30)
- Multifocal regions of necrosis are common
- Invasion into adjacent mammary tissue elicits a desmoplastic/scirrhous response with extensive proliferation of (myo)fibroblasts

DIFFERENTIAL DIAGNOSIS:

Mammary fibroadenomatous hyperplasia:

- Neoplasia: Usually does not involve all glands; usually a discrete nodule; epithelial component disorganized and/or invasive
- Other non-neoplastic mammary gland proliferations

- Cystic dilation of mammary ducts: due to obstruction of duct leading to dilation; common in dogs and cats
- Regular lobular hyperplasia: proliferation of intralobular ducts and alveoli; epithelial cells exhibit no atypia
- Lobular hyperplasia with secretory activity (lactational): alveoli variably distended and lined by actively secreting cuboidal cells (lactational change); alveolar cells often have intracytoplasmic vacuoles (lipid) and apical surface of epithelial cells may protrude (blebbing)
- Lobular hyperplasia with fibrosis; prominent interlobular and intralobular fibrous connective tissue
- Lobular hyperplasia with atypia: epithelial cells exhibit changes including nuclear hyperchromasia, anisokaryosis, anisocytosis, and variable numbers of mitoses; lobular architecture may be slightly disorganized
- Epitheliosis (epithelial proliferation in ducts): regular, with marked atypia (may progress to carcinoma); carcinoma diagnosis made based on nuclear pleomorphism, increased mitoses, and/or necrosis
- Papillomatosis: florid epithelial proliferation in ducts forming papillary projections
- Galactostasis: engorged, hot, painful mammae secondary to milk retention (failure of let-down d/t inhibition of oxytocin release)

<u>Primary mammary gland neoplasia in felines (not all encompassing):</u>

- Ductular
- **Ductal adenoma:** most common benign feline mammary tumor; bilayered epithelium of CK8+/18+ luminal epithelial cells and round to oval suprabasal or or round to oval interstitial myointerstitial cells which express myoepithelial markers (CK5, CK6, CK14, smooth muscle actin, calponin); minimal ansiokaryosis and anisocytosis; few mitoses (<6 per 2.37mm^2)
- **Ductal carcinoma**: neoplastic cells arranged in cords, tubules, and solid areas, but solid areas are larger than ductal adenomas; variably present slit-like lumina often lined by double layer of luminal epithelial and myoepithelial cells with little to no matrix;

differentiated from ductal adenoma by more extensive anisokaryosis and anisocytosis, an increased mitotic count (⩾6 per 2.37mm^2), and loss of well-differentiated ductal architecture which are replaced by sheets of neoplastic luminal epithelial cells with occasional foci of squamous differentiation

- Simple: neoplastic component composed of epithelium
- **Simple adenoma**: very rare benign mammary tumor in felines; nodular, well-demarcated, non-infiltrative lesion composed of luminal epithelial cells arranged in tubules; anisocytosis and anisokaryosis are minimal with few mitotic figures (<6 per 2.37mm^2)
- **Tubular carcinoma**: common in cats; see description under "light microscopic findings"
- **Tubulopapillary carcinoma**: very common in cats; similar to tubular carcinoma but >20% of tubules have papillae supported by fibrovascular connective tissue stroma protruding into lumina
- **Solid carcinoma**: common in cats; epithelial cells arranged in nests and islands without lumina and are separated by delicate stroma; anisokaryosis and anisocytosis are moderate to severe and number of mitoses is variable; note: solid carcinomas can never score a 1 for tubule formation
- **Comedocarcinoma**: common in cats; characterized by a multinodular pattern within a single tumor; within tumor nodules there are variably sized and very well defined, central, circular areas of necrosis surrounded by neoplastic cells; peripheral epithelial cells may have multiple growth patterns, including solid, tubulopapillary, tubular, and micropapillary; mitotic count is variable but is typically medium to high (>20 per 2.37mm^2); lymphatic vessel infiltration and lymph node metastasis common at time of diagnosis
- Note: Although rare, tumors composed of malignant epithelial cells and myoepithelial cells have been reported in cats (Sammarco et al, *Vet Pathol.* 2020)

COMPARATIVE PATHOLOGY:

Mammary hyperplasia in other species:

- **Mice**: virgin female FVB/N develop lobuloalveolar hyperplasia with secretory product in alveoli and ducts; increases with age and associated with prolactin secreting cells in pars distalis of pituitary; high incidence of pituitary adenomas in FVB/N mice; persistent hyperplasia may be present in absence of pituitary signs
- **Rabbits:** mammary hyperplasia can be caused by the administration of cyclosporine
- **Water Buffalo:** mammary gland fibroadenomatoid hyperplasia; probable hormone influence

Mammary neoplasia in other species

- **Dogs:** More than 35 phenotypes described; 7 are benign with remaining considered histologically malignant; >50% of cases are benign with either an epithelial or mixed epithelial and myoepithelial components; simple carcinomas, solid carcinomas, and complex carcinomas are the most common malignant mammary neoplasms; grading scheme for mammary carcinomas is similar (but not identical) to Nottingham Human Grading System used for feline mammary carcinomas; mammary neoplasms associated with short survival times following diagnosis include mammary osteosarcoma, anaplastic carcinoma, lipid-rich carcinoma, micropapillary invasive carcinoma, inflammatory carcinoma, comedocarcinoma, and squamous cell carcinoma
- **Mice**: Related to insertional mutagenesis of endogenous and exogenous mammary tumor viruses; tend to grow by blunt expansion rather than invasion; 60% metastasize to lung despite commonly having morphologically benign features; up to 100% C3H females develop mammary tumors by 9mo of age; common in multiparous FVB/N mice; BALB/c strain resistant
- **Rats:** Mammary gland benign **fibroadenomas**; elevated prolactin; common in older female Sprague-Dawley rats; markedly reduced in ovariectomized rats; malignant mammary tumors are rare
- **Guinea pigs**: Mammary adenocarcinomas occur in both males and females; majority are ductal in origin; may metastasize to regional lymph nodes while others are low grade local malignancy; mammary gland adenoma and malignant mixed mammary tumors also reported

- **Rabbits**: Multiple breeds affected, including laboratory rabbits; typically arise around 3-4yrs of age; majority are carcinomas, including tubular, papillary, tubulopapillary, solid, adenosquamous, comedo, complex, ductal, cribriform, anaplastic, and spindle cell; cystic mastitis thought to be a prelude to neoplastic transformation from benign adenomas to adenocarcinomas; lymph node, lung, and other organ metastasis reported
- Pinnipeds: Mammary carcinoma among the most common neoplasias of captive sea lions
- Panthers: Mammary carcinoma was the most commonly reported neoplasm in a recent study (Kloft et al, *J Comp Pathol.* 2019)
- Reports of mammary carcinoma in llamas, alpacas, dromedary camels, suids, wild felids, beluga whales, bats, and a male orangutan

病例　CP2022-95

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演讲及翻译人（Presenter and Translator）：

李一帆　病理诊断兽医师　中国农业大学动物医院

临床病史(Clinical History)：

犬，多灶性脱毛（multifocal alopecia）、结痂，头部和躯干处的皮肤色素沉着。

组织病理学检查(Histopathologic Description)：

有毛皮肤：角质层下方有多个脓疱，横跨数个毛囊，脓疱由大量中性粒细胞、中等数量的棘层松解细胞和少量嗜酸性粒细胞构成，其中，棘层松解细胞单个散在分布，呈圆形，细胞核居中，含有深嗜酸性的细胞质。表皮棘层增厚，角质形成细胞表现出明显的细胞间桥(海绵状增生)和细胞质空泡化(细胞内水肿)，伴有中度的中性粒细胞浸润。邻近受影响较轻的表皮表现为轻度棘层增生、海绵状增生和正角化性角化过度。真皮与表皮交界处存在弥漫性浸润的炎性细胞，表现为苔藓样病变（带状），可见中等数量的中性粒细胞和淋巴细胞，少量的浆细胞、嗜酸性粒细胞和巨噬细胞。真皮深层和附属器周围偶见炎性细胞浸润。毛囊上皮罕见中性粒细胞，真皮胶原纤维束被透明空隙隔开，淋巴管扩张（水肿），顶浆分泌腺轻度扩张。

形态学诊断 (Morphologic Diagnosis)：

犬，品种不明，有毛皮肤：角质层下脓疱，多个，中度，明显棘层松解和中度中性粒细胞性皮炎。

病因学诊断 (Etiologic Diagnosis)：

自体免疫性皮炎（Autoimmune dermatitis）

疾病（Condition）：

落叶型天疱疮（Pemphigus foliaceus）

讨论（General Discussion）：

- **天疱疮：**一类自体免疫性皮肤病，主要表现为脓疱、小水泡、大疱、糜烂和溃疡，组织学上表现为棘层松解(上皮细胞间失去粘附)。
- **落叶型天疱疮（Pemphigus foliaceus ，PF）**较少发生，但在家畜天疱疮中疾病是最常见的类型，其次是盘状红斑狼疮和系统性红斑狼疮。
- PF 通常好发于中年犬，无性别差异。
- 遗传易感性：秋田、粗毛柯利犬（bearded collie）、松狮犬、腊肠犬、杜宾犬、芬兰猎犬、 纽芬兰犬、 沙皮犬、英国可卡犬和舒伯齐犬。
- 三种发生形式：
  - 自发：秋田和松狮
  - 药物诱导：拉布拉多和杜宾
  - 疾病相关：患有慢性过敏或瘙痒性皮肤病的犬

发病机制（Pathogenesis）

- 桥粒处的细胞黏附分子协助角质形成细胞间产生黏附，循环天疱疮自身抗体就是以细胞黏附分子为靶点。
- 天疱疮只发生在有毛皮肤上，抗体的靶标是位于表皮上层的桥粒糖蛋白(II 型超敏反应)。
  - 犬的主要自身抗原是桥粒胶蛋白(desmocollins-1 ,DSC1)，一种跨膜钙依赖的桥粒糖蛋白，参与细胞内粘连。
    - 只有少数患有 PF 的犬会对另一种桥粒黏附蛋白桥粒芯糖蛋白（desmoglin-1，DSG1)产生抗体，DSG1 是人类的自身抗原。
    - 马、山羊和猫中发生的 PF（以及其它报道过 PF 的动物）尚未有自体抗体相关的研究。
    - 通常是自发产生的，但也会因药物不良反应引起，如跳蚤和蜱虫预防性用药。

- 自身抗体与 DSC1 结合→抗体诱导的细胞外结构域 DSC1 的裂解→角质形成细胞间失去黏附力（棘层松解）→形成浅表皮小泡→形成脓疱和结痂
- 也有人认为，与黏附分子结合的自身抗体可能刺激尿激酶型纤溶酶原激活剂（urokinase-type plasminogen activator，uPa）的分泌→激活纤溶酶原→：角质形成细胞间失去黏附力

典型的临床症状（Typical Clinical Findings）

- 约 25%的病例瘙痒明显
- 全身性症状见于全身性疾病，包括厌食、抑郁、发热、体重减轻

典型的大体病变（Typical Gross Findings）

- 小泡迅速转变为脓疱并结痂，病变通常两侧对称，好发于面部（尤其是鼻平面）、耳朵、脚垫、爪垫和/或腹股沟。超过 50%的病例可能出现全身性症状。
- 脓疱存在时间短，容易破裂，并变成厚的痂壳，伴有脱毛和糜烂
- 鼻褪色导致感光过敏

典型的组织学变化（Typical Light Microscopic Findings）

- 表浅皮内(角质层下方和颗粒层)脓疱性皮炎，通常累及角质层和颗粒细胞层
  - 破裂的脓疱可形成厚的炎性痂壳，其中含有棘层松解细胞
  - 脓疱跨越数个毛囊，含有大量中性粒细胞，大多数情况下还可见嗜酸性粒细胞。
  - 棘层松解细胞：脓疱中含有大量散在的棘层松解的角质形成细胞、部分粘附或附着在角质层上，这些仅在 PF 中出现，痂壳可能包含棘层松解细胞，因此可用于评估。
- 毛囊的外毛根鞘存在棘层松解角质形成细胞
- 苔藓样变（带状）或浅表血管周围至间质炎症
- 脚垫损伤包括绒毛状角化过度、肿胀和龟裂

额外的诊断检测（Additional Diagnostic Tests）

- 免疫荧光或免疫组化(IHC)可显示表皮各层细胞间或表皮内存在的免疫球蛋白(IgG)，但对 PF 是非特异的，因此经常出现假阳性和假阴性的结果

鉴别诊断（Differential Diagnosis）

- **大体病变（脓疱性和结痂性皮炎）**
  - 浅表性细菌性毛囊炎是 PF 最主要的鉴别诊断:剥脱性毒素可裂解桥粒芯糖蛋白-1 从而产生棘层松解细胞
    - ✓ PF 的脓疱跨越多个毛囊，而细菌性毛囊炎的脓疱通常集中于单个毛囊
    - ✓ PF 的棘层松解细胞较浅表毛囊炎多
    - ✓ 黏附颗粒层细胞仅存在 PF 中
  - 大疱性脓疱病：较年轻的犬通常在腹侧发生
    - ✓ 脓疱不涉及毛囊
  - 浅表弥漫性脓皮病：小脓疱和浅表角质层的嗜碱性碎片
  - 浅表脓疱性皮肤病：年轻动物好发
  - 蠕形螨
  - 脂溢性皮炎
  - 盘状和系统性红斑狼疮
  - 锌反应性皮肤病
  - 皮脂腺炎
  - 蕈样肉芽肿：不对称
- **镜检（角质层下脓疱）**
  - 水泡性脓皮病：球菌，棘层松解不严重
  - 棘层松解性皮肤真菌病- GMS, PAS 显示菌丝
  - 红斑性天疱疮：通常局限于面部病变(而不是脚垫)，病变程度较轻，IgG/IgM 沿基膜和细胞间沉积;，主要表现为基底细胞损伤(界面皮炎)

比较病理学（Comparative Pathology）

- 猫——面部和耳廓经常出现两侧对称的厚结痂
- 马——PF 是马最常见的自体免疫性皮肤疾病，起于面部和四肢末端，或局限于蹄冠，无性别年龄差异，阿帕卢萨马（Appaloosas）可能更易患病，超过 50%的患马同时有全身临床症状。
- 山羊——脸部、腹部、四肢、会阴、尾巴
- 大角野绵羊

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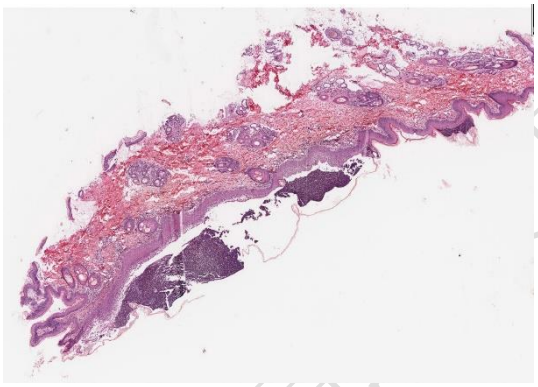


图 1. 皮肤组织，犬.
表皮层失去正常组织结构，角质层下可见脓疱，横跨数个毛囊，棘细胞层增厚。
HE | 1X

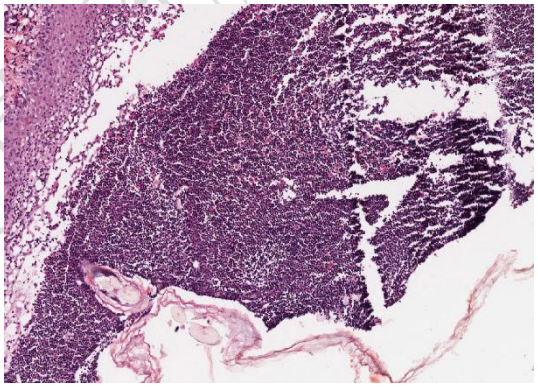


图 2. 角质层下脓疱，犬.
脓疱由大量炎性细胞组成。
HE | 8X

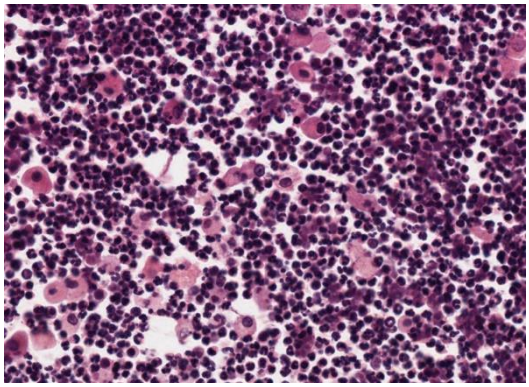
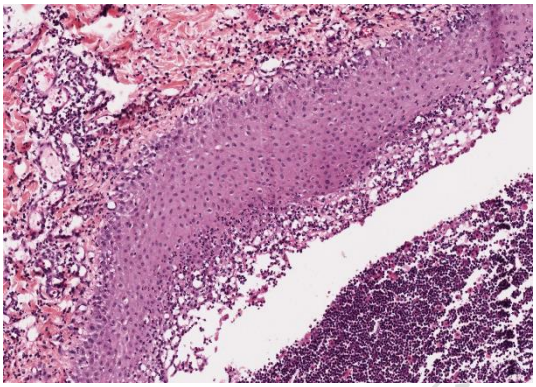
	

图 3. 角质层下脓疱的细胞类型，犬. 大量中性粒细胞、中等数量的棘层松解细胞和少量嗜酸性粒细胞。 HE | 40X	图 4. 增厚的棘细胞层，犬.。 HE | 15X

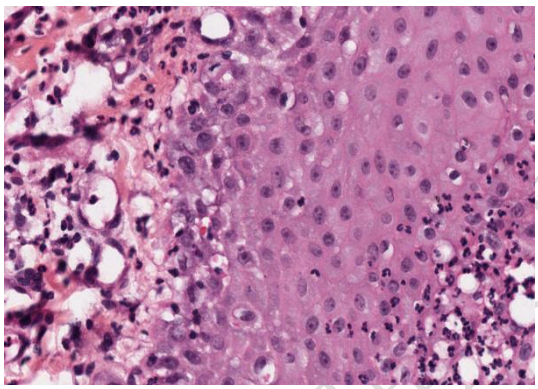
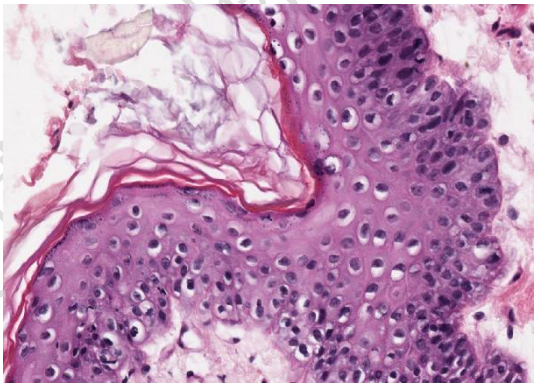

	

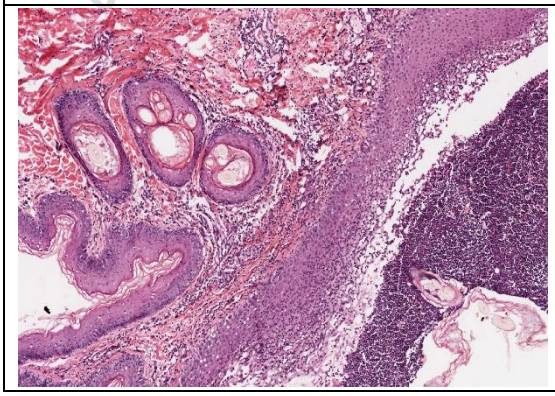
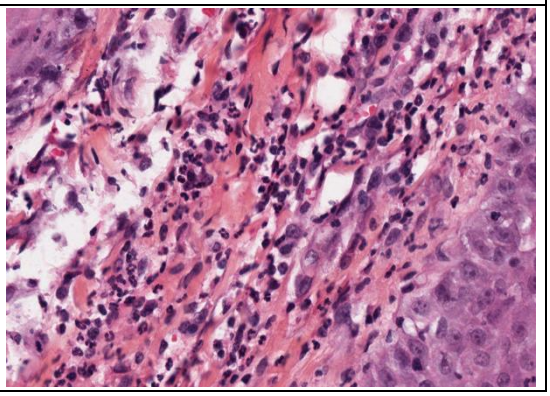
图 5. 增厚的棘细胞层，犬. 细胞间桥（海绵状增生）和细胞质空泡化（细胞内水肿），有中性粒细胞浸润。 HE | 40X	图 6. 邻近受影响较轻的表皮，犬. 轻度棘层增生、海绵状增生和正角化性角化过度。 HE | 33X
	

图 7. 苔藓样病变，犬. 真皮与表皮交界处炎性细胞浸润。 HE | 6X	图 8. 苔藓样病变，犬. 以中性粒细胞和淋巴细胞为主，少量的浆细胞、嗜酸性粒细胞和巨噬细胞。 HE | 40X

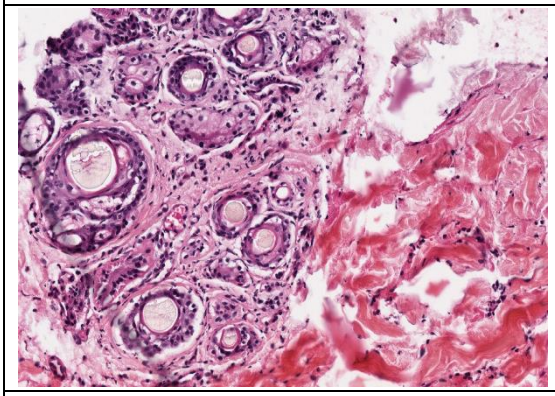
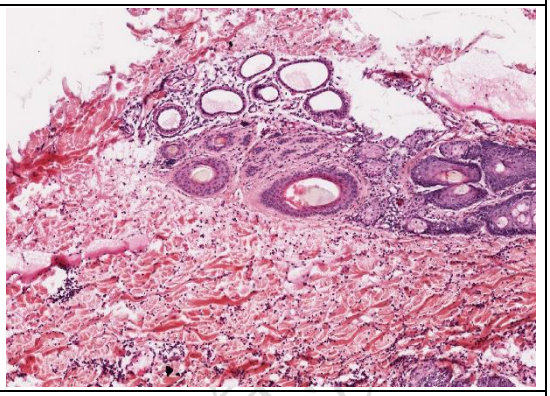

	

图 9. 真皮深层及附属器，犬. 少量炎性细胞浸润。 HE | 18X	图 9. 毛囊、顶浆分泌腺和真皮胶原纤维束，犬. 。 毛囊上皮少量炎性细胞浸润，顶浆分泌腺扩张，真皮胶原纤维束被透明空隙隔开，淋巴管扩张。 HE | 7X

JPC SYSTEMIC PATHOLOGY
INTEGUMENTARY SYSTEM
September 2019
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Signalment (JPC #2152K): Dog

HISTORY: This dog had multifocal alopecia, crusting, and hyperpigmentation of the skin of the head and trunk.

HISTOPATHOLOGIC DESCRIPTION: Haired skin: There are multifocal to confluent subcorneal pustules that span several hair follicles and are filled with numerous neutrophils, few eosinophils, and moderate numbers of individualized acantholytic keratinocytes with a central nucleus, rounded margins, and deeply eosinophilic cytoplasm. The underlying epidermis is acanthotic; these keratinocytes exhibit prominent intercellular bridging (spongiosis) and cytoplasmic vacuolation (intracellular edema). There is a moderate neutrophilic exocytosis. The less-affected adjacent epidermis is characterized by mild acanthosis, spongiosis, and orthokeratotic hyperkeratosis. Diffusely at the dermal-epidermal junction there is a lichenoid band of inflammation composed of moderate numbers of neutrophils and lymphocytes with fewer plasma cells, eosinophils, and macrophages. These inflammatory cells occasionally infiltrate the deeper dermis and surround adnexae. Rare neutrophils are also within follicular epithelium. Dermal collagen bundles are separated by clear space and there are dilated lymphatics (edema). Apocrine glands are mildly ectatic.

MORPHOLOGIC DIAGNOSIS: Haired skin: Subcorneal pustules, multifocal, moderate, with marked acantholysis and moderate neutrophilic dermatitis, breed unspecified, canine.

ETIOLOGIC DIAGNOSIS: Autoimmune dermatitis

CONDITION: Pemphigus foliaceus

GENERAL DISCUSSION:

Pemphigus: A group of autoimmune skin diseases characterized grossly by the formation of pustules, vesicles, bullae, erosions, ulcers and histologically by acantholysis (loss of adhesion between epithelial cells)

Pemphigus foliaceus (PF), although uncommon, is the most common form of pemphigus in domestic animals, followed by discoid and systemic lupus erythematosus

PF typically occurs in middle-aged dogs, with no sex predilection

Genetic predisposition in Akita, bearded collie, chow chow, dachshund, Doberman pinscher, Finnish spitz, Newfoundland, Chinese shar-pei, English springer spaniel and schipperke

There are three forms:

Spontaneous: Akitas and chow chows

Drug induced: Labrador retrievers and Doberman pinschers

Disease associated: Dogs with chronic allergic or pruritic skin disease

PATHOGENESIS:

Circulating pemphigus autoantibodies target cell-adhesion molecules which assists in binding keratinocytes together at the desmosome

Pemphigus foliaceus lesions occur only on haired skin, where the antibody targets a desmosomal glycoprotein that resides in the upper layers of the epidermis (type II hypersensitivity reaction)

The major autoantigen in dogs is desmocollin-1 (DSC1), a transmembrane calcium-dependent desmosomal glycoprotein involved in intracellular adhesions

Only a minority of dogs with PF will have against another desmosomal cadherin, desmoglein-1 (DSG1), which is the autoantigen in humans

Autoantibodies have not been studied in PF in horses, goats, or cats, the other species in which PF has been reported

Often arises spontaneously, but can be triggered by adverse drug reactions as well as topical flea and tick preventatives

Autoantibody binding to **DSC1**> antibody-induced cleavage of extracellular domain DSC1 > **loss of cohesion** between **keratinocytes (acantholysis**) > formation of superficial epidermal vesicles > formation of pustules and crusts

It is also thought that autoantibody binding to adhesion molecules may stimulate the secretion of urokinase-type plasminogen activator (**uPa**) > activates plasminogen> loss of cohesion between keratinocytes

TYPICAL CLINICAL FINDINGS:

Pruritis is evident in approximately 25% of cases

Systemic signs are often seen in cases with generalized disease, including anorexia, depression, fever, weight loss

TYPICAL GROSS FINDINGS:

Vesicles that rapidly transition into **pustules** with **crusting, often bilaterally symmetrical** on the **face** (especially **nasal planum**), **ears**, **footpads**, clawbeds, and/or groin; may be generalized in >50% of cases

Pustules are transient, easily rupture, and lead to **thick crusts** with variable scaling, alopecia, and erosions

Nasal depigmentation leads to photosensitization

TYPICAL LIGHT MICROSCOPIC FINDINGS:

Superficial intraepidermal (subcorneal and intragranular) pustular dermatitis that typically involves the corneal layer and granular cell layer

Ruptured pustules can form a thick inflammatory crust that contains acantholytic cells

Pustules often span several follicles and contain myriad **neutrophils** and often **eosinophils**

Acantholytic cells: pustules contain numerous acantholytic keratinocytes that are free, partially adherent or **adhered to the overlying stratum corneum;** these "cling-ons" are only seen in PF; the **crust** is useful to assess as it likely contains acantholytic cells

External root sheath of hair follicle can have acantholytic keratinocytes

Lichenoid (band-like) or superficial perivascular to interstitial dermal inflammation possible

Footpad lesions include villous hyperkeratosis, swelling, and fissures

ADDITIONAL DIAGNOSTIC TESTS:

Immunofluorescence or Immunohistochemistry (IHC) may demonstrate immunoglobulin (IgG) in the intercellular space in all layers of the suprabasilar epidermis or in the superficial epidermis; this is not specific for PF, and there are frequent false positive and false negative results

DIFFERENTIAL DIAGNOSIS:

For gross findings (pustular and crusting dermatitis):

Superficial bacterial folliculitis is the top differential diagnosis for PF: exfoliative toxins may cleave desmoglein 1 resulting in acantholytic cells

In PF the pustules span multiple hair follicles whereas in bacterial folliculitis are usually centered on single follicles

Acantholytic cells are more numerous in PF than in superficial folliculitis

"Cling-on" stratum granulosum cells are only present in PF

Bullous impetigo: Usually ventral abdominal in pubescent dogs

- Impetigo does not involve hair follicles

Superficial spreading pyoderma: Smaller pustules and Dunstan's blue line of basophilic debris in superficial keratin layers

Superficial pustular dermatophytosis: Usually young animals

Demodicosis

Seborrhea

Discoid and systemic lupus erythematosus

Zinc responsive dermatosis

Sebaceous adenitis

Mycosis fungoides: Less symmetry

For microscopic findings (subcorneal pustules):

Bullous impetigo: Cocci; less severe acantholysis

Acantholytic dermatophytosis - GMS, PAS reveals hyphae

Pemphigus erythematosus: Milder form usually limited to facial lesions (not footpads); deposits of IgG/IgM along the basement membrane and intercellular spaces; basal cell damage (interface dermatitis) is prominent

COMPARATIVE PATHOLOGY:

Cat – thick crusts are often bilaterally symmetrical on the face and ears (pinnal margin)

Horse – **PF is the most common autoimmune skin disease in equids**; begins on the face or distal extremities, or may be localized to coronets; no age or sex predilections; **Appaloosas** may be predisposed; over 50% have concurrent systemic clinical signs

Goat – face, abdomen, limbs, perineal region, tail

Barbary sheep

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病例 CP2022-96

切片连结：

https://www.askjpc.org/vspo/show_page.php?id=anZmeWluTXd4SS9kMk5pbEVDNDF3dz09

演讲及翻译人：

李浩运 中国农业大学动物医院

临床病史（Clinical History）：

犬，蛋白尿，组织活检于鼻平面。

诊断（Diagnosis）：

系统性红斑狼疮（Systemic lupus erythematosus，SLE）

组织病理学检查（Histopathological Findings）：

表皮真皮交界处、血管周围、附属器周围可见多灶性炎性细胞浸润，形成苔藓样条带，浸润的炎性细胞以浆细胞、淋巴细胞为主，可见少量巨噬细胞和中性粒细胞（界面性皮炎）。中性粒细胞浸润于表皮角化层附近，形成表皮内脓疱。可见多灶性表皮溃疡，表皮层全层消失，伴有浆液性渗出物和坏死的细胞碎片。表皮层及毛囊囊壁可见棘层增厚，伴网锥状结构形成，可见中等程度的不完全角化上皮增生。基底层可见细胞水肿变性和凋亡，排列紊乱。真皮浅层可见巨噬细胞吞噬黑色素颗粒（色素失禁）。可见轻度、弥散性顶浆分泌腺扩张、淋巴管扩张（水肿）。

淋巴结髓系血窦轻度扩张，组织细胞增多，可见胞质内吞噬红细胞及含铁血黄素。髓索内可见浆细胞增多。

形态学诊断（MORPHOLOGIC DIAGNOSIS）：

1. 黏膜皮肤交界处：皮炎、黏膜炎；界面性、淋巴浆细胞性、弥散性、重度，伴散在基底细胞凋亡（Civatte bodies），中度表皮、毛囊上皮增生，角化上皮增生、角化异常。

淋巴结：轻度、弥散性出血。

病因学诊断（ETIOLOGIC DIAGNOSIS）：

免疫介导性皮肤病

疾病（CONDITION）：

系统性红斑狼疮

综合讨论（GENERAL DISCUSSION）：

红斑狼疮属于一系列疾病的总成，其发病程度从局限于皮肤症状至威胁生

命的系统性疾病（SLE）不等。皮肤红斑狼疮（CLE）主要指红斑狼疮的皮肤发病情况，无论是否有其他系统性疾病牵涉。

系统性红斑狼疮（SLE）

- 属于罕见的、多系统受累的免疫介导性疾病，发病种属见于犬、猫、马、人、非人灵长类、小鼠、蛇、以及鬃蜥。
- 疾病以循环血中抗原抗体复合物增加为特征，对组织造成的主要损伤均因抗原抗体复合物在多处组织的积聚引起 III 型超敏反应所至，II 型、IV 型超敏反应在本病发病机制中作用较小。
- SLE 中的皮肤症状曾被认为是常见病变形式，然而实际病例中，SLE 的皮肤症状可能表现的非常轻微。
- 无年龄、性别特异性，柯利犬、苏牧、泰迪、德牧、暹罗猫、喜马拉雅猫和波斯猫为好发品种。

皮肤红斑狼疮（CLE）

- 在犬中最常诊断的皮肤自体免疫性疾病类型。
- 发病症状局限于皮肤的红斑狼疮曾经被称为盘状红斑狼疮（DLE），然而家养动物中的 DLE 发病特征与人医中的 DLE，目前更加推荐使用皮肤红斑狼疮（CLE）一词。
- CLE 在家养动物中通常较少发展为 SLE。
- 在犬中典型的 CLE 通常具有品种特异性，与遗传因素有关。
    - 扩散性盘状红斑狼疮（Disseminated discoid lupus erythematosus）-中国冠毛犬、尖嘴丝毛犬。
    - 剥脱性皮肤红斑狼疮（Exfoliative cutaneous lupus erythematosus）-德国短毛指示犬。
    - 血管性皮肤红斑狼疮（Vesicular cutaneous lupus erythematosus）-粗毛柯利犬、苏牧、边牧。
    - 黏膜皮肤型红斑狼疮（Mucocutaneous lupus erythematosus）-德牧最具代表性。

病理机制（PATHOGENESIS）

T 淋巴细胞与 B 淋巴细胞调控自身耐受性的机能异常导致机体产生一系列针对自身细胞成分（如组蛋白、双链 DNA、无组蛋白连接的 RNA 以及细胞核抗原等）的自身抗体。

导致机体不断正向激活自体免疫、形成抗原抗体复合物的本质原因是调控性 T 细胞的数量减少或缺失（调控性 T 细胞在正常免疫反应中具有负向调控作用）。

自身抗原抗体复合物在机体内广泛分布，引起 III 型超敏反应，造成关节、皮肤、肾脏的炎症反应（既关节炎、皮炎、肾小球肾炎）。

相对 III 型超敏反应，还有一小部分组织损伤是由于血液成分（红细胞、白细胞、血小板）作为抗原被自身抗体攻击，引发 II 性超敏反应或细胞介导型免疫反应（IV 性超敏反应）。

提到的发病因素包括遗传、环境以及传播等，SLE 的确切病因仍处于位置状态，目前推测的发病因素包括：

- 内源性（遗传、激素、代谢）
- 外源性（紫外、药物、传染性病原）

紫外线加剧的皮肤病灶（人类）：正常分布于角质形成细胞之间的蛋白质发生抗原易位。损伤的细胞继而释放出 IL-1、IL2、IL-6 以及 TNF-α，进一步扩大损伤作用；紫外线同时也会诱导 ICAM-1 表达，ICAM-1 是 LFA-1 的主要基团，后者是白细胞粘附分子（炎症中的白细胞离开血管到达组织需要粘附分子参与）。

异常的细胞免疫导致淋巴细胞减少，以 CD4+淋巴细胞与 CD8+淋巴细胞的比值升高为特征（SLE 患犬可升高至 6，正常犬小于 2）

典型临床表现（TYPICAL CLINICAL FINDINGS）

多样化，可能与多种疾病相似。

以阶段性加重或消退为特征的慢性病程。

相关综合征：皮炎，关节肿大、疼痛导致交替性跛行（非侵蚀性多发性关节炎），肾小球肾炎，胃炎，黏膜皮肤病灶，心包膜炎，心肌炎，多发性肌炎，肺炎，胸膜炎，脑膜炎，脊髓炎，多发性神经症状，淋巴水肿。

- 不明原因嗜睡、食欲不振、发热。
- SLE 病例中约 1/3 存在皮肤症状。

临床病理学：提示系统性疾病，包括蛋白尿、溶血性贫血、血小板减少症、骨髓坏死。

典型大体外观(TYPICAL GROSS FINDINGS)

皮肤病变的大体外观差异极大，典型病变包括非特异性红斑、脱毛、结痂、渗出，溃疡性皮肤病灶多分布于毛发稀少的面部区域（尤其鼻部、唇部、耳廓）、四肢（尤其前肢头侧）、腋窝、腹股沟和腹侧。

典型光镜下外观(TYPICAL LIGHT MICROSCOPIC FINDINGS)

苔藓样（界面性）皮炎：单核样细胞浸润于表皮真皮交界处，以淋巴细胞为主。

- 相对于细胞较少的（界面性）皮炎：表皮真皮交界处病变伴有轻度表皮炎症，见于苏牧/柯利犬的皮肌炎。

基底细胞水肿样变，可能牵涉毛囊，伴色素失禁。

Civatte 小体（基底细胞凋亡）。

表皮与真皮之间形成裂痕和大疱伴表皮细胞严重空泡化。

可能出现血管炎。

基底膜增厚。

进一步诊断性检查(ADDITIONAL DIAGNOSTIC TESTS)

抗核抗体（ANA）：检测血清中针对细胞核成分的抗体。

- 对 SLE 敏感性高，特异性低（对利士曼原虫感染、巴通氏症、埃立克体病或恶性肿瘤的患病动物也可能呈阳性）
- CLE 通常呈阴性。

组织化学染色：PAS 染色评估肾脏及皮肤基底膜增厚程度。

细胞学：对于 SLE 患犬进行关节液评估小概率可见红斑狼疮细胞或类风湿关节炎细胞，诊断自体免疫性疾病不可靠。

鉴别诊断(DIFFERENTIAL DIAGNOSIS)

获得性大疱性表皮松解症（Epidermolysis bullosa acquisita）：可能组织学表现完全相同，需要根据 SLE 的特征相鉴别，对胶原蛋白 IV 的免疫组化提示阳性信号位于表皮内空泡的上方，而其他自体免疫性皮肤病均位于表皮内空泡下方。

狼疮样药物反应：可能非常相似，需要结合病史及治疗反应（停药）。

多形性红斑：角质形成细胞凋亡存在于表皮全层，伴界面性皮炎和基底细胞退行性病变。

犬皮肌炎（柯利犬、苏牧）：一种与 35 号染色体有关的常染色体疾病，皮肤病变的基础上，患犬还表现出肌炎、淋巴组织增大、结膜炎，组织学表现包括毛囊萎缩，毛囊周围炎症/纤维化，基底层角质细胞水肿变性引发表皮真皮间裂痕或空泡化。

比较病理学(COMPARATIVE PATHOLOGY)

小鼠：SLE 模型（NZB/W/F1）。

猫：罕见，病灶与犬相似，主要以发热、肾小球肾炎、溶血性贫血、表皮内棘层松解性脓疱为主，SLE 引起的皮肤炎症相比于犬、马更加常见。

马：最常见的病征为眼睛、嘴唇、鼻平面、生殖器、肛周、会阴等皮肤区域出现边界清楚的色素丢失性病灶。

人类：与犬表现相似，更常见于女性。

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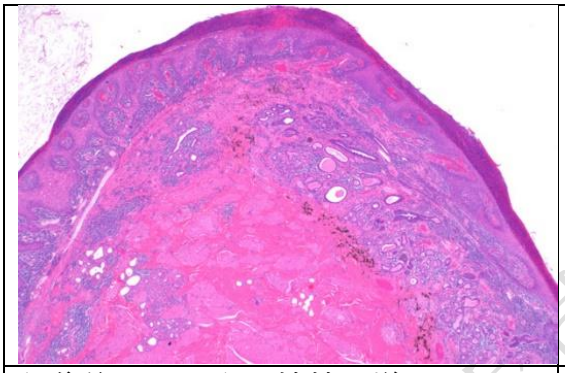
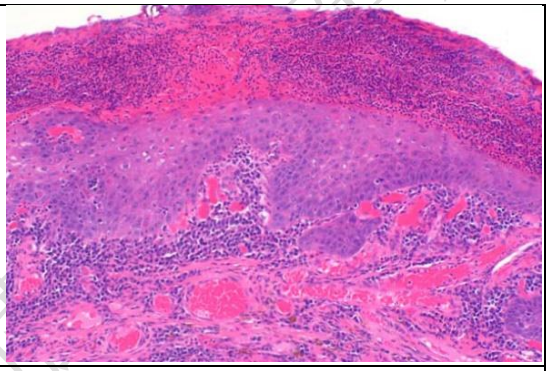
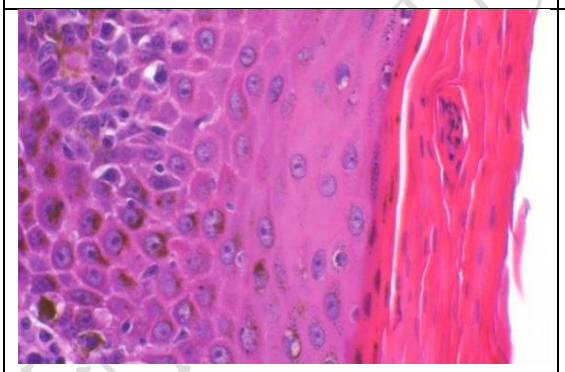
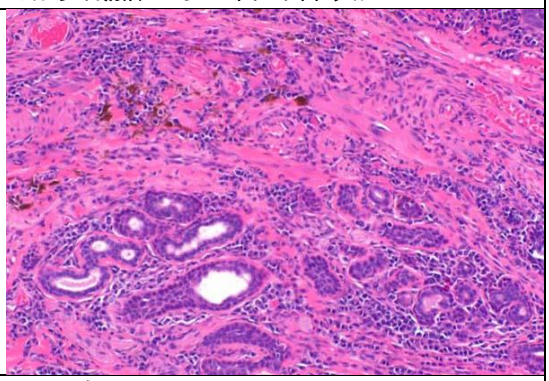
	
低倍镜下可见广泛性棘层增厚。	不规则增厚的表皮表面存在血细胞形成的结痂，可见苔藓样皮炎。
	
表皮层存在角化不良性增生，表皮全层细胞均可见色素颗粒。	真皮浅层可见色素颗粒和炎症。

JPC SYSTEMIC PATHOLOGY
INTEGUMENTRY SYSTEM
September 2019
I-M28

Signalment (JPC 2602974): Dog.

HISTORY: Tissue from the nose of a dog with proteinuria.

HISTOPATHOLOGIC DESCRIPTION: Planum nasale, mucocutaneous junction: Diffusely within the superficial dermis, surrounding blood vessels and adnexa, multifocally obscuring the dermal-epidermal junction, and forming a lichenoid band is a dense infiltrate of predominantly plasma cells, lymphocytes, fewer macrophages, and rare neutrophils (interface dermatitis). Inflammatory cells, predominantly neutrophils, often transmigrate the epidermis frequently forming variably sized intracorneal and rare intraepidermal pustules. Multifocally, there are several erosions and ulcers characterized by partial to complete loss of epithelium with replacement by a serocellular crust composed of serum and necrotic cellular debris. Diffusely the epidermis and superficial follicular epithelium are moderately spongiotic and hyperplastic with acanthosis and anastomosing rete ridges, and there is moderate parakeratotic hyperkeratosis. Within the stratum basale there is occasional hydropic degeneration and apoptosis (Civatte bodies), and basal keratinocytes are often disorganized or jumbled. Within the superficial dermis, scattered macrophages contain melanin (pigmentary incontinence). There is mild, diffuse apocrine gland ectasia and lymphatics are ectatic (edema).

Lymph node: Diffusely the medullary sinuses are mildly expanded by increased numbers of histiocytes that often contain phagocytized erythrocytes and hemosiderin, and extravasated erythrocytes (draining hemorrhage). There are moderate numbers of plasma cells within the medullary cords.

MORPHOLOGIC DIAGNOSIS: 1. Planum nasale, mucocutaneous junction: Dermatitis and mucositis, interface, lymphoplasmacytic, diffuse, severe, with scattered basal cell apoptosis (Civatte bodies), moderate epidermal and follicular hyperplasia, and parakeratotic hyperkeratosis, breed not specified, canine.
2. Lymph node: Draining hemorrhage, diffuse, mild.

ETIOLOGIC DIAGNOSIS: Immune-mediated dermatosis

CONDITION: Systemic lupus erythematosus (SLE)

GENERAL DISCUSSION:

Lupus erythematosus (LE) refers to a spectrum of inflammatory disorders that varies from mild skin-limited conditions to life-threatening systemic disease (systemic lupus erythematosus (SLE)); **cutaneous lupus erythematosus (CLE)** refers to the **skin-specific effects of LE, regardless of whether or not there is systemic involvement**

SLE:

Rare, multisystemic immune-mediated disease that affects **dogs, cats, horses, humans,** nonhuman primates, mice, snakes, and iguanas

Characterized by high levels of circulating antigen-antibody complexes; the main tissue damage is caused by antigen-antibody complexes that deposit at various sites throughout the body and incite a **type III hypersensitivity** reaction; type II and type IV hypersensitivities play a lesser role

SLE is historically thought to include dermatitis as a common lesion; **true cutaneous manifestations of SLE are probably rare**

No age or sex predilection for SLE; collies, Shetland sheepdogs, poodles, German shepherd dogs, and Siamese, Himalayan and Persian cats appear to be predisposed

CLE:

The most frequently diagnosed autoimmune skin disease in the dog

Historically, LE restricted to skin was termed discoid lupus erythematosus (DLE); however, DLE in domestic animals is not comparable to that in humans, and the term CLE is now preferred

CLE in domestic animals generally does not precede the onset of SLE

Well-described CLE disorders in dogs are often breed specific and presumed hereditary

Disseminated discoid lupus erythematosus – Chinese crested, spitz

Exfoliative cutaneous lupus erythematosus – German shorthaired pointer

Vesicular cutaneous lupus erythematosus – rough-coated collies, Shetland sheepdogs, border collies

Mucocutaneous lupus erythematosus – GSD overrepresented

PATHOGENESIS:

Failure of mechanisms that maintain B- and T-cell self-tolerance results in production of **autoantibodies against a range of nuclear and cytoplasmic components of the cell** (e.g. histones, double-stranded DNA, nonhistone proteins bound to RNA, and nucleolar antigens)

Regulatory T-cell response is reduced or absent, essentially allowing a positive feedback loop of immunoreactivity to autoantibody-antigen complexes

Autoantigen-antibody complexes deposit throughout the body, inciting a **type III hypersensitivity** reaction, resulting in inflammation of **joints, skin, and kidney** (i.e. arthritis [nonerosive], dermatitis, glomerulonephritis)

To a lesser extent, tissue damage is induced by antibodies directed toward self-antigen on erythrocytes, leukocytes, and thrombocytes initiating a type II hypersensitivity reaction, or cell-mediated immunity (type IV hypersensitivity)

Genetic, environmental, and transmissible factors have been implicated; the definitive cause of SLE remains unknown; proposed triggers include:

Endogenous (genetic, hormonal, metabolic)

Exogenous (UV light, drugs, infectious agents)

Ultraviolet-exacerbated cutaneous lesion (humans): Induces the translocation of antigens normally expressed only intracellularly to the keratinocyte cell membrane; damaged cells then release IL-1, IL-2, IL-6, and TNF-alpha that increase damage; UV light also induces ICAM-1 expression, which is the major ligand for LFA-1, an adhesion molecule found on all leukocytes

Abnormality in cellular immunity includes a **lymphopenia** that is characterized by a **high CD4+:CD8+ ratio** (as high as 6 in dogs with SLE versus <2 in normal dogs)

TYPICAL CLINICAL FINDINGS:

Variable; may mimic numerous diseases

Chronic illness characterized by periods of progression and remission

Associated syndromes: **Dermatitis,** shifting leg lameness with swollen and painful joints **(nonerosive polyarthritis)**, **glomerulonephritis,** stomatitis, mucocutaneous lesions, pericarditis, myocarditis, generalized muscle

wasting (polymyositis), pneumonitis, pleuritis, meningitis, myelitis, polyneuropathy, and lymphedema

Lethargy, anorexia, fever of unknown origin

Dermatologic signs occur in approximately 1/3 of the cases of SLE

Clinical pathology: suggestive of systemic disease, including **proteinuria**, hemolytic anemia, thrombocytopenia, bone marrow necrosis

TYPICAL GROSS FINDINGS:

Gross skin lesions are extremely variable; more classic lesions consist of non-specific distribution of erythematous, alopecic, crusting, oozing, ulcerative skin lesions affecting sparsely haired areas of the face (especially the nose, lips, pinnae), limbs (especially the cranial aspect of the thoracic limbs), axilla, groin, and ventral abdomen

TYPICAL LIGHT MICROSCOPIC FINDINGS:

Lichenoid (interface) dermatitis: band of mononuclear cell infiltrate at dermoepidermal junction, lymphocytes predominate

Versus cell-poor (interface) dermatitis: interface changes with **minimal** superficial dermal inflammation; seen in dermatomyositis of Collies/Shetland Sheepdogs

Basal cell hydropic degeneration that may involve follicles and **pigmentary incontinence**

Civatte bodies (**basal cell apoptosis**)

Cleft and bulla formation between epidermis and dermis with severe subepidermal vacuolization

Vasculitis (leukocytoclastic) may occur

Basement membrane thickening

ADDITIONAL DIAGNOSTIC TESTS:

Antinuclear antibody (ANA): Identifies serum antibodies to nuclear material

High sensitivity for SLE, less specificity (i.e. may also be positive in animals with leishmaniasis, bartonellosis, ehrlichiosis, or malignancies)

CLE is usually ANA negative

Histochemical stains: PAS to demonstrate thickened basement membranes in the kidney or skin

Cytology: Evaluation of synovial fluid from animals with SLE may rarely yield lupus erythematosus (LE) cells or ragocytes; not a reliable method of

diagnosing immune-mediated disease (Barger, *Canine and Feline Cytology* 2016)

DIFFERENTIAL DIAGNOSIS:

For histologic lesions:

Epidermolysis bullosa acquisita: May be histologically identical and requires identification of criteria compatible with SLE for differentiation; IHC staining of collagen IV is ABOVE the subepidermal vesicles, whereas in all other autoimmune blistering diseases the staining is below the vesicle

Lupoid drug reactions: May be essentially identical; history of treatment

Erythema multiforme (I-M29): Individual keratinocyte apoptosis in **all** layers of epidermis in addition to interface dermatitis and basal cell degeneration

Canine dermatomyositis (Shetland sheepdogs and collies): An autosomal dominant disease linked to chromosome 35; in addition to skin lesions, dogs develop myositis, lymphadenomegaly, and conjunctivitis; histopathologic lesions include follicular atrophy, perifollicular inflammation/fibrosis, and hydropic degeneration of basal keratinocytes leading to dermal-epidermal clefts and vesiculation.

COMPARATIVE PATHOLOGY:

Mouse model of SLE: **NZB/W/F1**

Cats: Rare; lesions similar to those in dogs; primarily fever, glomerulonephritis, and hemolytic anemia; intraepidermal acantholytic pustular dermatitis; true SLE dermatitis is more often present than in dogs or horses

Horses: The most common presenting sign in horses with SLE is a sharply demarcated zone of depigmentation of the skin around the eyes, lips, nostrils, genitalia, and skin of the perianal and perineal regions

Humans: Similar presentation to dogs; more common in females

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病例 CP2022-97

切片连结：

https://www.askjpc.org/wsco/wsc_showcase2.php?id=SUI4cTczYVRhVXViZWxGQnNZbS95QT09

演讲及翻译人：

金毅，主任药师 深圳市药品检验研究院/深圳市医疗器械检测中心

临床信息:

5 岁，雄性未绝育，恒河猴（*Macaca mulatta*），非人类灵长类动物。这只猴子于 2005 年 8 月 25 日通过扁桃体途径接种了猴免疫缺陷病毒(SIVmac239)。感染两周后病毒载量很高。 扁桃体接种后 25 周，动物出现脓疱性皮疹，全身状况恶化，食欲下降。由于预后不良，这只猴子于 2006 年 2 月 15 日被安乐死。

大体描述:

尸检时，恒河猴的营养状况良好。皮肤上覆盖着多个单一到合并的脐状脓疱。 脓疱主要可见于腹股沟区域、嘴唇、手和脚，也累及舌、牙龈和口咽粘膜。皮肤脓疱呈脐状，被中央内陷的痂皮覆盖，周围为外周充血。

还可见的病变包括严重的坏死性肺炎和脾炎、淋巴结的广泛增生和脾脏的严重滤泡增生。

组织病理学描述:

显微镜观察，皮肤和粘膜可见局灶性表皮水泡、表皮棘层肥厚、棘层松解和气球样变性以及全层表皮坏死和溃疡。中性粒细胞和嗜酸性粒细胞为主的混合炎性细胞浸润，伴有少量组织细胞和淋巴细胞。在某些区域，毛囊和皮脂腺病变累及。受累细胞中主要为囊泡或边缘有单个圆形至椭圆形胞浆内包涵体是顾氏小体 (Guarnieri bodies)。 顾氏小体呈嗜酸性，靠近受感染细胞的细胞核。它们随机分布在病变的上皮细胞内。在基底上皮层附近可见罕见的合胞体形成 (syncytia formations)。在足底和手掌的皮肤处，病变停滞在水泡阶段，覆盖有厚的完整表皮细胞层（未呈现在所有切片中）。 皮肤样本的透射电子显微镜显示角质形成细胞的细胞质中有单个正痘样颗粒。 通过 PCR 和细胞培养诊断猴痘病毒。

形态学诊断:

舌：亚急性多灶性严重糜烂性溃疡性皮炎，伴有单个胞浆内嗜酸性包涵体，恒河猴（*Macaca mulatta*），非人类灵长类动物。

皮肤：亚急性多灶性严重脓疱性增殖性皮炎，伴有单个嗜酸性胞浆内嗜碱性包涵体和罕见的合胞体、恒河猴（*Macaca mulatta*），非人类灵长类动物。

实验室结果：

免疫组化：单纯疱疹 1 型和 2 型：阴性

疾病：

猴痘

提供者评论：

猴痘是一种罕见的病毒性疾病，主要在中非和西非的热带雨林国家发现。这种疾病被称为猴痘，它于 1958 年首次在实验室猴子身上发现。

猴痘病毒属于痘病毒的正痘病毒组。其他可导致人类和非人类灵长类动物感染的正痘病毒包括天花病毒（天花）、牛痘病毒（用于天花疫苗）和牛痘病毒。痘病毒是大型、复杂的双链 DNA 病毒。

自然感染猴痘病毒只出现在西非和中非的热带雨林中，它会在几种非人类灵长类动物 (NHP) 物种中引起亚临床地方性感染。过去曾报道过圈养非人灵长类动物爆发疫情，主要是恒河猴和食蟹猴，涉及进口大量猕猴的机构。但在狨猴、松鼠猴、叶猴、狒狒、猩猩、大猩猩、长臂猿和黑猩猩中也报道过该疾病。 6,7,10 1970 年报道了第一例人类猴痘病例。至此，出现了几例人类猴痘病例，在西非和中非的热带雨林地区作为孤立病例或小流行。在这些地区，这种感染会在年轻人中引起严重的、有时甚至是致命的天花样疾病。传播可能通过咬或其他接触气源性发生。人们可以通过咬伤或直接接触受感染动物的血液、体液或病变（丛林肉 bush meat）从受感染的动物身上感染猴痘。 2003 年，报导几名美国居民在与生病的进口草原土拨鼠接触后患病。这种疾病也可在人与人之间传播，但它的传染性远低于天花。

在非人类灵长类动物中，该疾病通常表现出高发病率和低死亡率。临床症状不明显或动物可表现为发热、淋巴结病和皮疹。除了幼猴之外，死亡并不常见。典型的痘表现为直径 1 至 4 毫米的丘疹，然后发展成含有细胞碎片的脓疱。脓疱变成脐状并被结痂覆盖。猴最常见的痘形成部位是面部、手足、口腔黏膜和生殖道，也常累及咽、喉气管、肺、脾和淋巴结。

本次，我们在免疫功能低下的猴子身上获得了该疾病结果的经验。此处描述的免疫功能低下动物中的猴痘偶发病例，特征是严重的水泡性皮疹。皮疹伴有严重的呼吸道受累，疾病进展是致命的。到目前为止，尚不清楚这种情况下是如何传播的。由于感染的猴痘病毒的包涵体含量极少，不易诊断。通过电子显微镜可以证明典型的正痘病毒颗粒。疱疹性湿疹被认为是鉴别诊断，但单纯疱疹 1 型和 2 型的免疫组化结果为阴性。

JPC 诊断：

1. 无毛皮肤：局部广泛性明显水泡性脓疱性皮炎，伴有棘层和气球样变性，恒河猴（*Macaca mulatta*），灵长类 **(Fig. 4-1)**.。

2. 有毛皮肤：中性粒细胞和嗜酸性粒细胞为主的局部广泛性严重坏死溃疡性皮炎，伴有气球样变性。

3. 舌：中性粒细胞和嗜酸性粒细胞为主的多灶性明显坏死溃疡性舌炎，伴有气球样变和病灶内球菌**(Fig. 4-2 and 4-3)**。

会议评论:

2003 年，美国中西部有数人被确诊感染猴痘病毒。所有受影响的个体都与来自加纳的圈养土拨鼠有关，这些土拨鼠与冈比亚巨型袋鼠（*Cricetomys* sp.)、绳松鼠（*Funiscuirus* spp.）和/或睡鼠（*Graphiurus* sp.）一起饲养。截至 2003 年 7 月 30 日，已报告 72 例人类猴痘病毒感染病例。受影响的个人包括兽医、宠物店工作人员、动物经销商以及购买受感染啮齿动物的儿童和父母。

在超威结构上，正痘病毒是 375 X 200 nm 的颗粒，位于细胞质中，由一个外膜组成，该外膜包裹着一个特征性的哑铃形电子透明核心，该核心由两个侧体包围。

表格来自 Ginn et al.3

Orthopoxvirus 正痘病毒	Key points 要点
Camelpox virus 骆驼痘病毒	单峰骆驼； 临床上与骆驼传染性臁疮（副痘）相同
Cowpox virus 牛痘病毒	家猫的皮肤和偶尔的呼吸道病变，可累及面部和前爪； 广泛感染野生和家养猫科动物、牛、狗、啮齿动物、人类； 牛没有地方病，牛感染并不常见； 野生啮齿动物是病原储存宿主； 大象：严重致命的肺炎。
Ectromelia virus (mousepox virus) 8 鼠痘病毒（鼠痘病毒）8	存活小鼠需肢体截肢； 全身感染
Monkeypox virus 猴痘病毒	啮齿动物、新大陆猴子和类人猿； 全身性疾病
Buffalopox virus 水牛痘病毒	感染印度水牛；印度瘤牛(Zebu cattle)明显不易感染； 与牛痘病毒密切相关
Uasin Gishu disease virus (unassigned) 瓦森伊修病病毒（未确定）	马痘在 19 世纪自然灭绝； 最近从患有马丘疹性皮炎的马和肯尼亚患有瓦森伊修病的马中分离出的未鉴定的正痘病毒； 发现与牛痘病毒和牛痘病毒（Vaccinia virus and cowpox virus）密切相关

Vaccinia virus 牛痘病毒	不会导致家畜自然感染
Variola virus (human smallpox) 天花病毒（人类天花）	影响人类和非人类灵长类动物； 根除?

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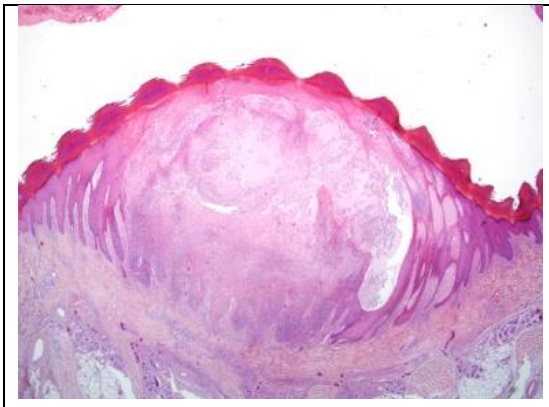

图 4-1 足 （HE，20x）
在表皮内可见局灶性巨大水泡样脓疱。

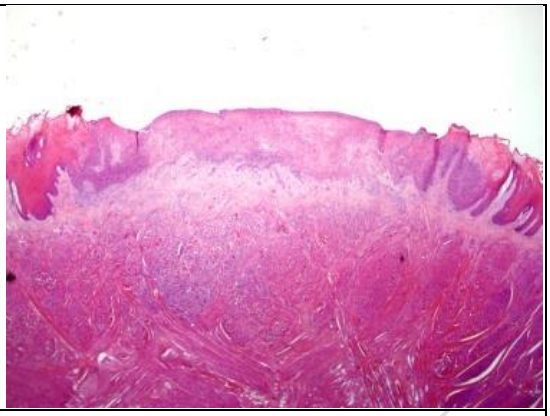

图 4-2 舌（HE，20x）
黏膜上皮里可见局灶性巨大溃疡。

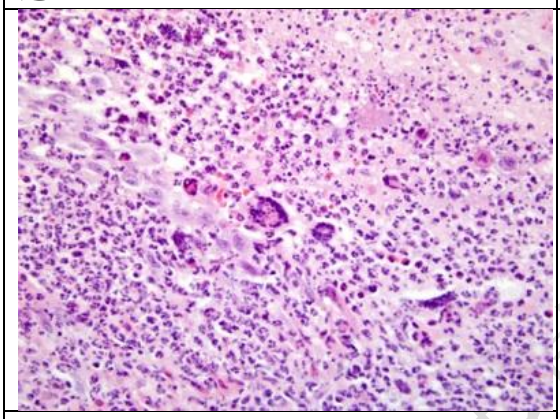

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图 4-3 舌 （HE，20x）

在坏死区域可见大量未退行性变的中性粒细胞以及少量组织细胞，淋巴细胞，嗜酸性粒细胞及偶见多核合胞体细胞。

Signalment:

5-year-old, intact male, rhesus macaque (*Macaca mulatta*), non-human primate. This monkey was inoculated with simian immunodeficiency virus (SIVmac239) on 25/08/05 via the tonsillar route. There was a high virus load after two weeks post infection. Twenty-five weeks after the tonsillar challenge the animal showed a pustular skin rash, deteriorating general condition and reduced appetite. The monkey was euthanized on 15/02/06 due to a poor prognosis.

Gross Description:

At necropsy the rhesus macaque was in a good nutritional condition. The skin was covered with multiple single to coalescing umbilicated pustules. Pustules were preferentially found within the inguinal region, the lips, the hands and feet but they also affected the tongue, the gingiva and the oropharyngeal mucosa. The skin pustules were umbilicated, covered with a central invaginated crust and surrounded by peripheral hyperemia.

Further findings included a severe necrotising pneumonia and splenitis, a generalized hyperplasia of the lymph nodes and severe follicular hyperplasia of the spleen.

Histopathologic Description:

At microscopic examination the skin and the mucous membranes revealed focal areas with epidermal vesiculation, epidermal acanthosis, acantholysis and ballooning degeneration as well as full thickness epidermal necrosis and ulceration. A mixed inflammatory infiltrate composed of neutrophilic and eosinophilic granulocytes, few histiocytes and lymphocytes accompanied the process. In some locations hair follicles and sebaceous glands were involved in the dermal process. Intact affected cells of the vesicle base or margin contained single round to oval intracytoplasmatic inclusion bodies identical with Guarnieri bodies. The Guarnieri bodies were eosinophilic and lay close to the nuclei of infected cells. They were randomly distributed within the altered epithelium. Rare syncytia formations were found close to the basal epithelial layer. At the skin of soles and palms the lesion was arrested in the vesicular stage, covered with a thick intact epidermal cell layer (not included in all sections).

Transmission electron microscopy of skin samples revealed single orthopox like particles in the cytoplasma of keratinocytes.

Monkey pox virus was diagnosed by PCR and cell culture.

Morphologic Diagnosis:

Tongue: Dermatitis, erosive-ulcerative, subacute, multifocal, severe, with single intracytoplasmatic eosinophilic inclusion bodies, rhesus macaque (*Macaca mulatta*), non-human primate.
Skin: Dermatitis, proliferative, pustular, subacute, multifocal, severe, with single eosinophilic intracytoplasmatic basophilic inclusion bodies and rare syncytia, rhesus macaque (*Macaca mulatta*), non-human primate.

Lab Results:

Immunohistochemistry: Herpes simplex Type 1 and 2: negative

Condition:

Monkeypox

Contributor Comment:

Monkeypox is a rare viral disease that is found mostly in the rainforest countries of Central and West Africa. The disease is called monkeypox because it was first discovered in laboratory monkeys in 1958.

Monkeypox virus belongs to the orthopox virus group of pox-viruses. Other orthopox viruses that can cause infection in humans and non-human primates include variola (smallpox), vaccinia (used in smallpox vaccine), and cowpox viruses. Pox-viruses are large, complex double stranded DNA viruses.

Naturally monkeypox virus only occurs in the tropical rain forest of Western and Central Africa, where it causes subclinical endemic infections in several non-human primate (NHP) species. In the past outbreaks have been reported in captive NHPs, primarily rhesus and cynomolgus, involving institutes importing large numbers of macaques. But the disease has also been reported in marmosets, squirrel monkeys, langurs, baboons, orangutans, gorillas, gibbons and chimpanzees.[6,7,10] The first human case of monkeypox was reported in

1970. Till then several human cases of monkeypox appeared in the tropical rain forest areas of West and Central Africa as isolated cases or as small epidemics. In these regions the infection causes a serious, sometimes fatal smallpox-like disease among young people. Transmission occurs probably aerogenously, by biting or other contacts. People can get monkeypox from an infected animal through a bite or direct contact with the infected animals blood, body fluids, or lesions (bush meet problem). In 2003 monkeypox was reported among several residents in the United States who became ill after having contact with sick imported prairie dogs. The disease can be spread from person to person too, but it is much less infectious than smallpox.

In non-human primates the disease in usually exhibit a high morbidity and low mortality.Â Clinical signs may be inapparent or animals may ehibit fever, lymphadenopathy and cutaneous eruptions. Death is uncommon except in infant monkeys. Typical pocks appear as papules of 1 to 4 mm in diameter, which then develop into pustules containing cell debris. The pustules become umbilicated and covered by crusts. The most common sites of pock formation in the monkes are the face, hands and feet, the mucous membranes of the oral cavity and the genital tract, but also pharynx, larynx trachea, lung, spleen and lymph nodes are commonly involved.

Today we gained experience with the outcome of the disease in immunocompromised monkeys.Â This accidental case of monkeypox in an immunocompromsed animal described here showed that the disease outcome was characterized by severe vesicular exanthema. The skin rash was accompanied by severe respiratory tract involvement and progression of the disease was fatal. Till now it is not clear how transmission occurred in this case. Diagnosis was complicated due to the minimal content of inclusion bodies indicative for poxvirus infection. By electron microscopy typical orthopox like viral particles were demonstrable. An *Eczema herpeticatum* was considered as differential diagnosis, but immunohistochemistry for *Herpes simplex* type 1 and 2 was negative.

JPC Diagnosis:

1. Glabrous skin: Dermatitis, vesiculopustular, focally extensive, marked, with acanthosis and ballooning degeneration, rhesus macaque (*Macaca mulatta*), primate **(Fig. 4-1)**.
2. Haired skin: Dermatitis, necroulcerative, neutrophilic and eosinophilic, focally extensive, severe with ballooning degeneration.
3. Tongue: Glossitis, necroulcerative, neutrophilic and eosinophilic, multifocal,

marked, with ballooning degeneration and intralesional cocci **(Fig. 4-2 and 4-3)**.

Conference Comment:

In 2003, several people in the Midwestern United States were diagnosed with monkeypox virus infection. All affected individuals were associated with exposure to captive prairie dogs that had been housed with Gambian giant pouched rats (*Cricetomys* sp.), rope squirrels (*Funiscuirus* spp.), and/or dormice (*Graphiurus* sp.) that originated from Ghana.[2,4] As of 30 July 2003, 72 human cases had been reported of human monkeypox virus infection.[2] Affected individuals included veterinarians, pet store personnel, an animal distributor, and children and parents that bought the infected rodents.[2]

Ultrastructurally, orthopox viruses are 375 X 200 nm particles, located free in the cytoplasm, composed of an outer membrane enclosing a characteristic dumbell-shaped inner electron lucent core that is bounded by two lateral bodies.[4]

Table extracted from Ginn et al.[3]

Orthopoxvirus	**Key points**
Camelpox virus	Dromedary camels; clinically identical to camel contagious ecthyma (parapox)
Cowpox virus	Cutaneous and occasionally respiratory lesions in domestic cats; on face and forepaws; affects wild and domestic Felidae, cattle, dogs, rodents, humans; not endemic in cattle, and infections in cattle are uncommon; wild rodents are the reservoir; severe fatal pneumonia in elephants
Ectromelia virus (mousepox virus)[8]	Limb amputation in surviving mice; systemic infection
Monkeypox virus	Rodents, New World monkeys, and great apes; systemic disease
Buffalopox virus	Affects waterbuffalo in India; Zebu cattle apparently refractory to infection; closely related to Vaccinia virus
Uasin Gishu disease virus (unassigned)	Horsepox became naturally extinct in 19th century; recent uncharacterized orthopox viruses isolated from horses with equine papular dermatitis, and in equines with Uasin

	Gishu disease in Kenya; are found closely related to Vaccinia virus and cowpox virus
Vaccinia virus	Does not cause natural infection in domestic animals
Variola virus (human smallpox)	Affects humans and non-human primates; irradicated?

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比较病理学讨论会病例分类一览表（2021/2/27-）

病例编号	场次	诊断	动物种属	提供机构
肿瘤				
VP2021-2	1	羊肺腺癌（Ovine pulmonary adenocarcinoma, Ovine pulmonary adenomatosis, Jaagsiekte）	绵羊	内蒙古农业大兽医学院
VP2021-3	1	山羊地方性鼻内腺癌（Enzootic nasal adenocarcinoma of sheep and goats, ENA）	山羊	南京农业大学动物医学院
VP2021-8	2	病例 8-1: 软组织软骨瘤（Soft tissue chondromas），肠系膜 病例 8-2: 腹腔囊性异位骨化伴有出血（Heterotrophic celiac cystic ossification with hemorrhage），膀胱背侧	犬	陕西省动物研究所
VP2021-9	2	混合型肝癌（肝细胞癌和胆管细胞癌）（Mixed hepatocellular and cholangiocellular carcinomas）	犬	河南牧业经济学院动物医药学院
VP2021-16	3	脊髓肾母细胞瘤（Spinal cord nephroblastoma）	犬	中国农业大学动物医院
CP2021-17	4	精原细胞瘤（Seminoma），也称生殖细胞癌（Germ cell carcinoma）	大熊猫	四川农业大学动物医学院
CP2021-18	4	蕨类植物导致的牛膀胱肿瘤（Bracken-fern-induced bovine urinary bladder tumors）	牛	成都里来生物科技有限公司
CP2021-20	4	卵巢畸胎瘤（Ovarian teratoma）	猫	中国农业大学动物医院
CP2021-22	4	1. 子宫内膜增生（Endometrial hyperplasia）	兔	吉林大学动物医学学院

		2. 乳腺癌（Adenocarcinoma）		
CP2021-23	5	脾脏平滑肌肉瘤（Splenic leiomyosarcoma）	犬	东北农业大学动物医学学院
CP2021-24	5	趋上皮型皮肤淋巴瘤（Epitheliotrophic cutaneous lymphoma）	犬	中国农业大学动物医院
CP2021-25	5	脾脏淋巴组织结节性增生（Nodules of lymphoid hyperplasia）	犬	浙江省食品药品检验研究院
CP2021-30	5	急性肿瘤溶解综合征；白血病(Acute tumor lysis syndrome, Leukemia)	大鼠	JPC 及山西省药品检验所
CP2021-31	5	恶性肥大细胞瘤伴胸腺上皮增生（Malignant mast cell tumor with thymic epithelial hyperplasia)	大鼠	JPC 及中山大学实验动物中心
CP2021-26	5	T 淋巴细胞瘤(T cell lymphoma)	熊	内蒙古农业大学兽医学院
CP2021-27	5	皮肤型髓外浆细胞瘤（Cutaneous extramedullary plasmacytoma）	犬	吉林大学动物医学学院
CP2021-40	6	间皮细胞瘤(Mesothelioma)	犬	中国农业大学动物医院
CP2022-58	8	脊索瘤（Chordoma)	雪貂	中国农业大学动物医院
CP2022-59	8	间质细胞瘤（Interstitial cell tumor）伴骨外骨肉瘤（Extraskeletal osteosarcoma)，睾丸	犬	中国农业大学动物医院
CP2022-60	8	肺泡型横纹肌肉瘤(Alveolar rhabdomyosarcoma)，左侧上颊肿物	犬	吉林大学动物医学学院

CP2022-61	8	软骨肉瘤（Chondrosarcoma）	犬	中国农业大学动物医院
CP2022-66	8	平滑肌肉瘤（Leiomyosarcoma）	犬	吉林大学动物医学学院
CP2022-68	8	多小叶骨肿瘤（Multilobular tumor of bone）	犬	JPC 及上海市食品药物检验研究院
CP2022-88	10	猫肺趾综合征（Feline lung-digit syndrome）	猫	JPC 令山东省药学科学院新药安评中心
CP2022-89	10	乳腺纤维腺瘤(Mammary fibroadenoma) 及垂体（腺垂体）腺瘤(Pituitary adenoma)	大鼠	JPC 及郑州大学药物安全性评价研究中心
CP2022-93	10	乳腺导管原位癌(Mammary Gland: ductular carcinoma in situ, DCIS)	猴	JPC 及广东省科学院生物与医学工程研究所
CP2022-94	10	切片 A: 乳腺纤维腺瘤样增生(Mammary fibroadenomatous hyperplasia) 切片 B：导管性乳腺癌(**Tubular mammary carcinoma)**	猫	JPC 及哈尔滨兽医研究所
细菌				
VP2021-1	1	全身粟粒性结核（Disseminated 196ilitary tuberculosis）	牛	中国农业大学动物医学院
VP2021-13	3	李斯特杆菌脑炎（*Listeria* encephalitis）	牛	中国农业大学动物医学院
VP2021-15	3	猪链球菌症（*Streptococcus suis* infection）	猪	JPC 及东北农业大学动物医学院

CP2021-32	5	炭疽 (Anthrax)	牛	JPC 及广西兽医研究所
CP2021-33	5	兔热病 (Tularemia)	兔	JPC 及北京协和建昊医药技术开发有限责任公司
CP2022-51	7	脑膜布鲁氏菌病 (Meningeal brucellosis)	牛	JPC 及广东省实验动物监测所
CP2022-62	8	禽掌炎（Bumblefoot）	鸭	山东畜牧兽医职业学院
CP2022-86	10	猫麻风病综合征 (Feline leprosy syndrome)	猫	JPC 没广西壮族自治区疾病预防控制中心毒理所
CP2022-92	10	葡萄球菌性乳腺炎 (Mammary gland botryomycosis)	牛	JPC 及山东畜牧兽医职业学院
霉菌				
VP2021-4	1	播散性毛霉菌病（Disseminated mucormycosis）	海豚	西北农林科技大学动物医学院
VP2021-5	1	新型隐球菌性鼻炎（Cryptococcal rhinitis）	猫	中国农业大学动物医院
CP2022-84	10	芽生菌病 (Blastomycosis)	犬	JPC 及同仁堂研究院
CP2022-90	10	皮肤癣菌假足菌肿（Dermatophytic pseudomycetoma	猫	中农大动物医院
病毒				
VP2021-7	2	禽戊型肝炎病毒（Avian hepatitis E virus）感染	鸡	东北农业大学动物医学院
VP2021-10	2	猫传染性腹膜炎 (Feline infectious peritonitis)	猫	中国农业大学动物医院

CP2021-19	4	传染性造血组织坏死症 (Infectious hematopoietic necrosis)	虹鳟	四川农业大学动物科技学院水产养殖系
CP2021-28	5	马立克病 (Marek's disease)	孔雀	JPC 及江西农业大学动物科学技术学院
CP2021-29	5	非洲猪瘟 (African swine fever)	猪	JPC 及中国农业大学动物医学院
CP2021-39	6	小病毒性心肌炎 (Parvoviral myocarditis)	犬	JPC 及中国农业大学动物医学院
CP2021-43	6	口蹄疫 (Foot and mouth disease)	大捻角羚	JPC 及海南医学院海南省药物安全性评价研究中心
CP2022-46	7	狂犬病 (Rabies)	牛	内蒙古农业大学兽医学院
CP2022-47	7	小反刍兽疫 (Peste des petitis ruminants)	羊	内蒙古农业大学兽医学院
CP2022-48	7	猪流行性腹泻 (Porcine Epidermic Diarrhea)	猪	JPC 及江苏鼎泰药物研究股份有限公司
CP2022-49	7	非洲马瘟 (African Horse Sickness)	马	JPC 及深圳市药品检验研究院
CP2022-50	7	羊痘 (Sheep pox)	羊	吉林大学动物医学学院
CP2022-52	7	高致病性禽流感 (Highly pathogenic avian influenza, HPAI)	鸡	JPC 及天津药物研究院
CP2022-54	7	埃博拉病毒感染 (Ebola virus infection)	小鼠	JPC 及上海食品药物检验研究院)
CP2022-56	7	猴疱疹病毒 1 感染 (Herpesvirus simiae (B virus) infection)	猴	JPC 及湖南普瑞玛公司

CP2022-57	7	亨德拉病毒感染（Hendra virus infection)	马	JPC 及昭衍（北京）新药研究中心有限公司
CP2022-85	10	禽痘(Avian pox)	智利火烈鸟	JPC 及天津天诚新药评价有限公司
CP2022-97	10	猴痘（Monkeypox)	猴	JPC 及深圳市药品检验研究院/深圳市医疗器械检测中心
朊蛋白				
CP2022-53	7	羊痒病（Scrapie)	羊	JPC 及中国农业大学动物医学院
		传染性水貂脑病(Transmissible mink encephalopathy)	水貂	
寄生虫				
VP2021-6	2	组织滴虫病（Histomoniasis)	孔雀	吉林大学动物医学学院
VP2021-11	3	脑胞虫症（Coenurosis)	羊	内蒙古农业大学兽医学院
VP2021-16	3	弓浆虫症（Toxoplasmosis)	犬	JPC 及西北农林科技大学动物医学院
CP2021-34	6	新孢子虫病（Neosporosis）	牛	JPC 及中国农业大学动物医学院
CP2021-35	6	心丝虫病(Dirofilariasis)	犬	JPC 及中国农业大学动物医院
CP2021-41	6	旋尾线虫病（Spirocercosis)	犬	JPC 及中国农业大学动物医学院
CP2021-42	6	锥虫性心肌炎(Trypanosoma myocarditis)	犬	JPC 及中国农业大学动物医学院
CP2022-55	7	脑孢子虫病(Encephalitozoonosis)	免	JPC 及广州质量监督检测研究院

CP2022-64	8	新孢子虫病（Neosporosis）	牛	内蒙古农业大学兽医学院
C)2022-83	10	皮肤利什曼病 (Cutaneous leishmaniasis)	犬	JPC 及四川省疾病预防控制中心
代谢及中毒				
CP2021-38	6	维生素 E/硒缺乏（Vitamin E/Selenium deficiency）	猪	JPC 及山东畜牧兽医职业学院
CP2022-63	8	佝偻病(Rickets)	绵羊	JPC 及天津市医药科学研究所
CP2022-65	8	食盐中毒 (Salt poisoning)	猪	JPC 及山西省药品检验技术研究所
CP2022-67	8	维生素 E/硒缺乏 (Vitamin E/selenium deficiency)	大蓝鹭	JPC 及深圳市药品检验研究院/深圳市医疗器械检测中心
CP2022-70	9	三聚氰胺/三聚氰酸中毒 (melamine/cyanuric acid toxicosis)	犬	JPC 及西北农林科技大学动物医学院
CP2022-71	9	乙二醇中毒(Ethylene glycol toxicosis)	犬	JPC 及深圳市药品检验研究院
CP2022-72	9	胶性甲状腺肿 (Colloid goiter), 上皮萎缩伴随脱毛(Epidermal atrophy with alopecia)	羊	JPC 及炼朴生物
CP2022-73	9	联吡啶（百草枯）中毒 (Bipyridilium(paraquat) toxicity)	犬	JPC 及天津有济医药科技发展有限公司
CP2022-74	9	营养性脑软化 (Nutritional encephalomalacia)	火鸡	JPC 及深圳市药品检验研究院/河南牧业经济学院

CP2022-75	9	肝门静脉分流 (Portosystemic shunts)	犬	JPC 及山东省药学科学院新药安评中心
CP2022-76	9	食盐中毒 (Salt poisoning)	猪	JPC 及深圳赛赋
CP2022-77	9	B1 缺乏导致灰质脑软化 (Thiamine deficiency induced polioencephalomalacia)	牛	JPC 及上海市疾病预防控制中心
CP2022-78	9	Acetaminophen 中毒	犬	JPC 及江苏省农业科学院兽医研究所
CP2022-79	9	Ionophore (Monensin) toxicosis	鸡	JPC 及黑龙江省中医药大学安评中心
CP2022-80	9	橡树芽肾病 (Oak bud nephrosis)	牛	JPC 及陕西省食品药品检验研究院
CP2022-81	9	Encephalomalacia due to *Trema micrantha* poisoning	马	JPC 及上海市疾病预防控制中心
CP2022-82	9	B1 缺乏导致灰质脑软化 (Thiamine deficiency induced polioencephalomalacia)	猫	JPC 及山东欣博
		B1 缺乏导致灰质脑软化 (Thiamine deficiency induced polioencephalomalacia)	牛	
CP2022-87	10	孢子丝蛋白中毒 (Sporodesmin toxicosis)	羊	JPC 及中国药科大学新药安评中心
CP2022-91	10	局限性钙盐沉着症 （Calcinosis circumscripta）	犬	吉林大学动物医学学院
其他				
VP2021-12	3	脑水肿 (Cerebral edema)	犬	中国农业大学动物医学院

CP2021-22	4	伪胎盘子宫内膜增生（Pseudo-placentational endometrial hyperplasia, PHE)；又名节段性子宫内膜增生（Segmental endometrial hyperplasia）	犬	中国农业大学动物医学院
CP2021-36	6	结节性多发动脉炎 (Polyarteritis nodosa)	鼠	JPC 及湖北天勤生物科技有限公司
CP2021-37	6	全身性动脉粥样硬化 (Atherosclerosis)	犬	JPC 及湖南安生美药物研究院
CP2021-44	6	高血压肾病(Hypertensive nephropathy)	鼠	JPC 及山东欣博药物研究有限公司
CP2021-45	6	肥大性心肌病 (Hypertrophic cardiomyopathy)	猫	JPC 及宁波海关技术中心
CP2022-69	8	Slide A: 咀嚼性肌炎 (Masticatory myositis)	犬	JPC 及江苏鼎泰药物研究（集团）股份有限公司
		Slide B: 肉孢子虫性肌炎 (Sarcocystic myositis)	牛	
CP2022-95	10	落叶型天疱疮（Pemphigus foliaceus）	犬	JPC 及中国农业大学动物医院
CP2022-96	10	系统性红斑狼疮 (Systemic lupus erythematosus，SLE）	犬	JPC 及中国农业大学动物医院