Advances in Clinical Medicine 临床医学进展, 2026, 16(4), 4579-4585
Published Online April 2026 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2026.1641729

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一例双侧颌下腺Warthin样黏液表皮样癌的诊断与治疗

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收稿日期：2026年3月23日；录用日期：2026年4月18日；发布日期：2026年4月23日

摘　要

目的：报告1例双侧颌下腺Warthin样黏液表皮样癌(WL-MEC)病例，探讨其临床特征及诊疗策略。方法：回顾分析1例41岁女性双侧颌下腺WL-MEC患者，结合影像学、病理学、免疫组化及FISH检测MAML2基因重排明确诊断。患者接受“右侧颌下腺摘除术 + 双侧颌下肿物切除术”并行术后调强放疗(200 cGy/30次，共6000 cGy)，随访评估预后。结果：患者双侧颌下腺肿物，影像学提示囊实性病变，病理示双侧病灶囊性变并缺乏典型的Warthin瘤双层嗜酸性上皮结构，免疫组化显示Ki-67增殖指数约10%。FISH检测MAML2基因易位阳性。放疗过程顺利，术后28个月随访未见复发或转移。结论：双侧颌下腺WL-MEC为罕见病例，MAML2基因易位是诊断及鉴别诊断的关键。对于高危病例，术后辅助放疗能有效巩固局部控制。

关键词

Warthin样黏液表皮样癌，双侧颌下腺肿瘤，放疗

Diagnosis and Treatment of Bilateral Warthin-Like Mucoepidermoid Carcinoma of the Submandibular Glands: A Case Report

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Received: March 23, 2026; accepted: April 18, 2026; published: April 23, 2026

Abstract

Objective: To report a case of bilateral Warthin-like mucoepidermoid carcinoma (WL-MEC) of the

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文章引用: 夏顺贤, 谭叶, 陆海军. 一例双侧颌下腺 Warthin 样黏液表皮样癌的诊断与治疗[J]. 临床医学进展, 2026, 16(4): 4579-4585. DOI: 10.12677/acm.2026.1641729

submandibular glands and to investigate its clinical characteristics, diagnostic approaches, and therapeutic strategies. Methods: A retrospective analysis was conducted on a 41-year-old female patient with bilateral WL-MEC of the submandibular glands. The diagnosis was confirmed through a combination of imaging, histopathology, immunohistochemistry, and fluorescence in situ hybridization (FISH) detection of MAML2 gene rearrangement. The patient underwent "right submandibular gland resection combined with bilateral submandibular mass excision", followed by postoperative intensity-modulated radiotherapy (200 cGy per fraction, 30 fractions, total dose 6000 cGy). Prognosis was evaluated through follow-up. Results: The patient presented with bilateral submandibular gland masses. Imaging suggested cystic and solid lesions. Histopathology revealed cystic changes in bilateral lesions and the absence of the typical bilayered oncocytic epithelium characteristic of Warthin tumor. Immunohistochemistry showed a Ki-67 proliferation index of approximately 10%. FISH detection was positive for MAML2 gene translocation. The radiotherapy course was uneventful. At the 28-month postoperative follow-up, no recurrence or metastasis was observed. Conclusion: Bilateral WL-MEC of the submandibular glands is a rare entity. MAML2 gene translocation is pivotal for its diagnosis and differential diagnosis. For high-risk cases, postoperative adjuvant radiotherapy can effectively consolidate local control.

Keywords

WL-MEC, Bilateral Submandibular Gland Neoplasms, Radiotherapy

1. 引言

黏液表皮样癌(Mucoepidermoid carcinoma, MEC)是唾液腺最常见的恶性肿瘤，占所有唾液腺恶性肿瘤的约 30%~35%，可发生于大、小唾液腺，以腮腺最常见[1]-[3]。近年来研究证实，CRTC1-MAML2 基因融合是 MEC 的关键分子驱动因素，在低级别 MEC 中发生率较高，且现在该融合基因被认为可有效预测 MEC 生物行为，为其精准治疗和预后评估提供了重要证据[4]-[6]。Warthin 样黏液表皮样癌(Warthin-like mucoepidermoid carcinoma, WL-MEC)是 MEC 的罕见亚型，2011 年被首次报道，2015 年被明确界定并命名[7] [8]。其组织学特征与 Warthin 瘤(WT)及黏液化生型 Warthin 瘤(mWT)高度相似，均表现为富含淋巴细胞的间质和嗜酸性上皮样结构，易导致误诊；但 WL-MEC 缺乏 WT 典型的双层嗜酸性上皮结构，代之以化生或不典型的上皮，这是其核心鉴别要点[7] [9] [10]。本病具有明显的发病部位倾向性，既往报道以腮腺最常见[11]，腭、颌下腺、淋巴结等腮腺外部位仅有零星报道，整体病例数仍有限[12]-[15]。作为低级别恶性肿瘤，WL-MEC 的罕见性和诊断复杂性使其在临床上面临诸多挑战。

本研究报告了一例双侧颌下腺 WL-MEC 病例。该病例的双侧发作特征及术后辅助放疗为其扩展了诊断和治疗的认识。通过总结该病例的临床、病理及分子特征，结合术后放疗及长期随访，进一步丰富对 WL-MEC 的临床谱系，为类似罕见病例的诊断与治疗提供参考。

2. 病例介绍

患者女性，41 岁，2023 年 6 月 22 日因“发现下颌肿块 1 月”就诊于我院。2 年前患者发现右侧颌下痛性包块，数日后感冒，口服头孢后疼痛消失，肿物未觉明显改变。1 个月前发现左侧颌下区无痛性包块，因感冒口服头孢数日，肿物未觉明显改变。体格检查右侧颌下区肿物约 2.5 × 2.0 cm，质软，界清，

无活动度。左侧颌下区肿物约 3.0 × 4.0 cm 大小，表面光滑，质韧，界清，无活动度。彩色多普勒超声检查结果：双侧颌下腺下方低回声结节(见图 1(A))。结节穿刺活检：囊肿性病变，囊壁构成于增生的纤维结缔组织呈慢性炎症，被覆柱状上皮；穿刺术后结节明显增大成“鸡蛋”大小，伴局部轻微胀痛。超声造影检查：双侧颌下腺下方囊性为主囊实性结节，考虑良性病变(见图 1(B))。CT 检查：双侧颌下肿物边界清楚类圆形肿物，颈部未见明显转移淋巴结(见图 2)。患者于 2023 年 7 月 5 日行“双侧颌下肿物切除术 + 右侧颌下腺摘除术”。术中见颌下区有一肿大淋巴结，完整摘除一并送病理。

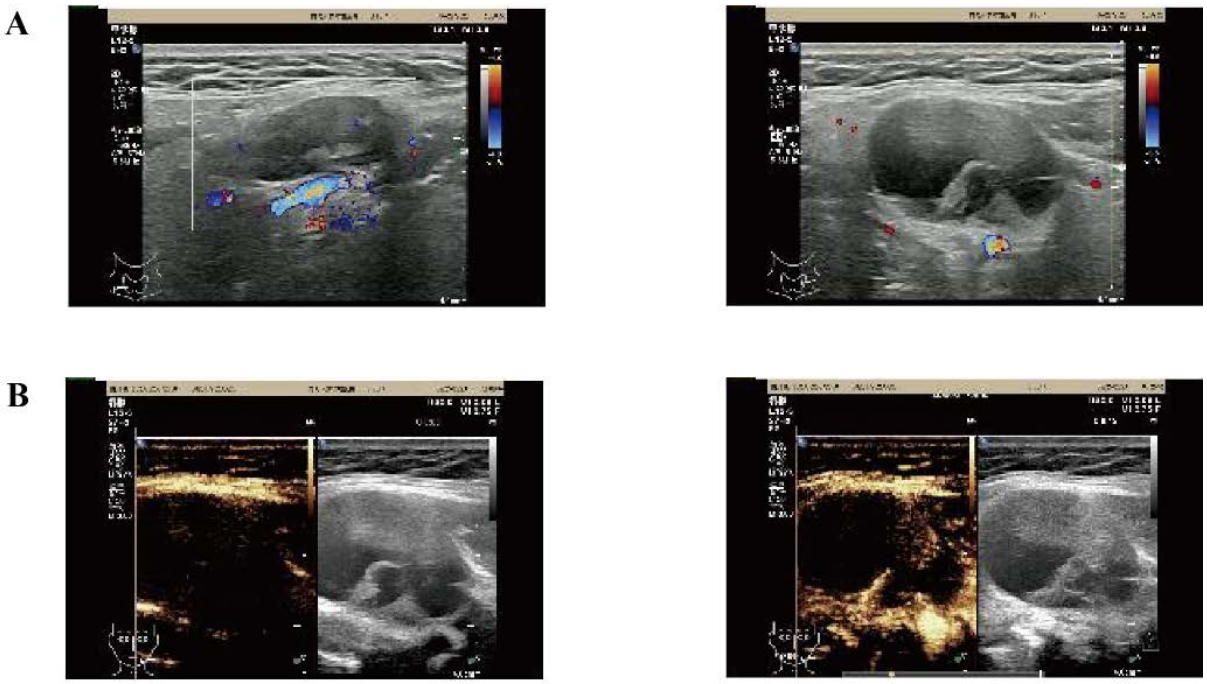

Figure 1. Ultrasound examination
图 1. 超声检查

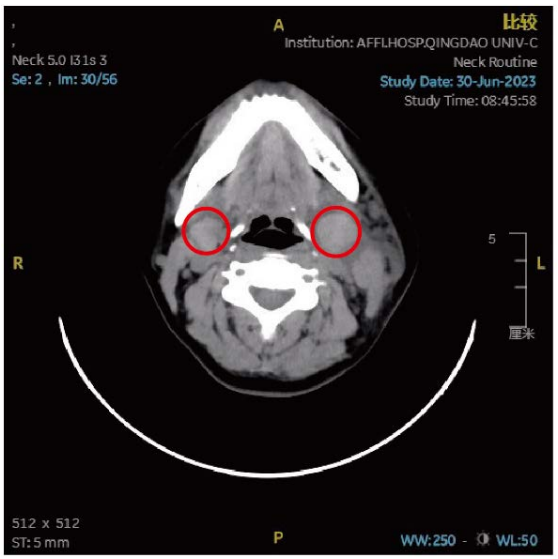

Figure 2. Preoperative CT, with enlarged bilateral submandibular glands circled in red
图 2. 术前 CT，红色圈出肿大的双侧颌下腺

大体观：左侧颌下肿物大小 3.0 × 2.5 × 2.5 cm，切面呈灰白灰黄色，部分区域呈胶冻样；右侧颌下肿物 4.5 × 4.5 × 3.0 cm，内见 2.5 × 1.5 cm 胶冻样结节(灰白质脆)，其余组织灰黄质韧。组织病理检查：镜下双侧均为囊性病变，间质伴显著淋巴组织增生及淋巴滤泡形成，左侧病灶部分区域衬覆复层上皮，部分区域上皮增生呈乳头状、筛状伴不典型性增生，见较多黏液细胞；右侧囊性部分区域内衬复层上皮，局灶区域上皮呈筛状增生。与典型 Warthin 瘤相比，缺乏特征性的双层嗜酸性上皮结构及乳头状囊腔排列方式。免疫组织化学：CK7 (+)，p63 (+)，CK8/18 (+)，CK19 (+)，CD117 (−)，Calponin (−)，S100 (−)，CK14 (+)，CK5/6 (+)，p40 (+)，Ki-67 (+，约 10%)。特殊染色结果：黏液卡红(+)。荧光免疫杂交(fluorescence in situ hybridization, FISH)检测 MAML2 重排(+)。送检颌下区淋巴结内未见肿瘤转移。结合组织形态学表现及 MAML2 融合阳性诊断为双侧颌下腺 WL-MEC。

鉴于术中肿物剥离困难，且未进行根治性切除，增值指标 Ki-67 偏高(约 10%)，经肿瘤放疗科、口腔颌面外科、病理科等多学科团队(MDT)联合讨论，结合《唾液腺恶性肿瘤诊疗指南》及相关临床研究证据，综合评估肿瘤切除范围、增殖活性、病理亚型等高危风险因素的权重，排除单纯手术随访、化疗等替代方案后，一致决定实施调强放射治疗(IMRT)，靶区覆盖双侧颌下腺床，放疗计划剂量 200 cGy/30 次，共 6000 cGy。治疗全程顺利，未出现严重急性或晚期放射毒性。放疗后定期复查，28 个月内未见复发或转移。

3. 文献复习与讨论

WL-MEC 作为黏液表皮样癌(MEC)的一个罕见亚型，2015 年被明确界定并命名[7]。截至目前报道的 84 例(含本例) WL-MEC 中，女性 51 例，男性 33 例，男女比例 1.54:1，患者年龄跨度 8~75 岁，中位年龄 42 岁。从发病部位来看，WL-MEC 也具有明显的解剖学倾向性，腮腺是最常见的发病部位，但是近年来腮腺外发病的报道逐渐增多，腭、颌下腺、淋巴结等部位均有零星报道，提示该亚型的发病谱更广泛[12] [13] [15] [16]。

本病通常表现为痛性或无痛性肿块，也有病例伴随上呼吸道感染或淋巴结肿大[12]。本例双侧肿物伴发上感症状，感染缓解后肿物稳定，可能与 WL-MEC 富含淋巴组织间质特征有关——上呼吸道感染引起局部淋巴组织反应性增生，刺激肿瘤细胞增殖或促使隐匿病灶显现。结合 WL-MEC 富含淋巴组织间质的核心病理特征，其肿瘤发生发展或与局部免疫微环境重塑、慢性炎症调控密切相关。本例患者有上呼吸道感染史，感染后局部淋巴组织反应性增生、病灶显现，提示上呼吸道感染或为 WL-MEC 病灶显现的潜在诱因：慢性炎症刺激或引发颌下腺导管上皮反复损伤与修复，诱导上皮化生与不典型增生，其产生的活性氧易造成 DNA 损伤，可能增加染色体易位概率，为 MAML2 基因重排(CRTC1::MAML2 融合)创造分子条件[3]；而该融合基因或可激活 NF-κB 通路，放大局部促炎效应，或形成“炎症启动–分子驱动–炎症强化”的正反馈循环，推动肿瘤发生发展[17]。同时，WL-MEC 间质淋巴滤泡形成的免疫微环境，并非单纯炎症细胞浸润，更可能是以淋巴细胞、M2 型肿瘤相关巨噬细胞、调节性 T 细胞为主的免疫抑制微环境，这类细胞或通过分泌 IL-10、TGF-β 等抑炎因子抑制 $CD8^+$ T 细胞的抗肿瘤功能，使肿瘤细胞免疫逃逸，基质细胞分泌的趋化因子又可能进一步招募免疫细胞，维持局部免疫抑制状态，为肿瘤增殖提供适宜条件[18]。此外，本例患者 Ki-67 增殖指数达 10%，显著高于 WL-MEC 普遍的<5%水平[18]，推测或与局部炎症因子过度分泌、免疫抑制微环境失衡相关，这种失衡或使肿瘤细胞摆脱免疫监视、增殖活性升高，也成为术后行辅助放疗巩固局部控制的重要考量因素。而放疗作为唾液腺恶性肿瘤高危病例术后的重要治疗手段，既可直接杀伤残留肿瘤细胞，又可能通过诱导肿瘤细胞免疫原性死亡、抑制免疫抑制细胞活性，一定程度逆转局部免疫微环境，实现放疗与免疫的协同抗肿瘤效应[19]，也为本例术后放疗的良好疗效提供了机制层面的合理解释。

在诊断过程中，WL-MEC 常因其显著的淋巴组织背景和嗜酸性上皮外观而与良性 Warthin 瘤或黏液化生型 Warthin 瘤(mWT)混淆[14] [20] [21]。需仔细观察其关键鉴别特征：缺乏 Warthin 瘤典型的双层嗜酸性上皮结构，代之以排列紊乱的上皮成分，可见上皮呈筛状、乳头状或腺样增生并伴黏液细胞存在[11]。部分肿瘤可同时含有 WT 与 MEC 成分，因此在富含淋巴组织的病灶中应充分取材，以免漏检 MEC 成分而导致误诊。作为低级别 MEC，该亚型的核心分子驱动事件为 MAML2 基因重排(多表现为 CRTC1::MAML2 融合)，这一特征与 Warthin 瘤(WT)呈完全互斥关系，成为两者鉴别诊断的关键分子标志物[7] [22]。并且 FISH 检测因为可以敏感地检出 MAML2 重排，并且方便确定重排基因的位置，有望成为该疾病诊断的标准方法之一[23]。

免疫组化可辅助评估分级和鉴别诊断。WL-MEC 可见 CK5/6、CK7、CK8/18 及 p63、p40、阳性，S100 及 SMA 阴性，并且 KI-67 普遍小于 5% [18]。最新研究发现，BSND 免疫组化被认为 10%阳性阈值 ≥ 可区分 WT 与 WT-MEC，可作为区分两者的特异性辅助标志物[24]。FNA 可检测到嗜酸性细胞的缺失，因此可以作为与其他低级别 MEC 的鉴别参考，但是对本病的诊断准确率较低(不足 50%)，且 FNA 可能引发炎症或病灶破溃，需谨慎评估适应症[15] [25]。CT 在判断低级别和高级别 MEC 中具有一定价值[26]。超声可提示病变边界、血供等特征[27]。但影像学无法替代病理确诊，仅适用于初步筛查与手术规划。

手术切除被认为是治疗 Warthin 样黏液表皮样癌(WL-MEC)的首选方案，特别是对于切缘阴性的病例，单纯手术已能获得良好的预后[28]。然而，某些特殊病例接受术后放疗，并取得良好效果。例如，Basak 曾报道过一例术中病理切缘阳性的病例，该患者在全腮腺切除术后立即接受术后放疗，随访 28 个月未见复发[21]。Kajo 报道了一例右侧腮腺肿物(大小约为 6.0 × 5.0 × 5.0 cm)，其边界不清，并伴有双侧颈部淋巴结肿大(最大可达 3.0 × 2.0 cm)，该患者接受了腮腺切除术和颈部淋巴结清扫术后，进行了辅助放疗，十年随访未见复发[29]。这提示术后放疗可能在高风险病例中起到巩固局部控制改善预后的作用。

4. 结论

本例报道的 41 岁女性患者表现为双侧颌下腺 WL-MEC，一侧痛一侧无痛。该病例具有多重罕见特征：其一，发病部位特殊，既往报道以单侧腮腺为主，而双侧颌下腺在已报道过的病例中相当罕见；其二，Ki-67 增殖指数约为 10%，显著高于 WL-MEC 普遍存在的<5%水平，更高的增殖活性可能增加局部复发的风险；其三，除手术切除外，进行了术后放疗。这个病例的报道可以扩展对 WL-MEC 这一少见疾病的理解与放疗的应用场景。

声　明

该病例报道已获得患者知情同意与青岛大学附属医院伦理审核通过(伦理批件号：QYFYWZLL 42304)。

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