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无痛性泪腺腺样囊性癌一例

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摘 要

目的：探讨无痛性泪腺腺样囊性癌(Adenoid cystic carcinoma of lacrimal gland, LGACC)的临床特征，以提升对该罕见肿瘤的认识。方法：回顾性分析1例LGACC患者的临床资料，并结合国内外文献进行复习探讨。结果：患者因发现左眼进行性突出伴上睑下垂就诊，无疼痛等不适，影像学检查提示左眼眶内肿物，行眶内肿物摘除术，病理诊断为腺样囊性癌。术后接受全身化疗，随访6月未见肿瘤复发或转移。结论：无痛性泪腺腺样囊性癌罕见，因解剖位置隐匿导致诊断困难，需尽早手术干预并结合病理明确诊断。

关键词

泪腺，腺样囊性癌，病例报告，病理学，免疫组织化学

A Case of Painless Adenoid Cystic Carcinoma of Lacrimal Gland

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Abstract

Objective: To investigate the clinical features of painless adenoid cystic carcinoma of lacrimal gland (LGACC) in order to improve the understanding of this rare tumor. Methods: The clinical data of 1 patient with LGACC of lacrimal gland adenoid cystic carcinoma were analyzed retrospectively, and

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the literature at home and abroad was reviewed. Results: The patient presented with progressive proptosis of the left eye accompanied by ptosis, without experiencing pain or other discomfort. Imaging examination revealed left orbital mass and resection of orbital mass was performed. The postoperative pathology revealed adenoid cystic carcinoma. The patients received systemic chemotherapy after surgery, and no tumor recurrence or metastasis was found in 36 months of follow-up. Conclusion: Painless adenoid cystic carcinoma of lacrimal gland is rare and difficult to diagnose due to hidden anatomical location. Early surgical intervention and pathological diagnosis are necessary.

Keywords

Lacrimal Gland, Adenoid Cystic Carcinoma, Case Report, Pathology, Immunohistochemistry

1. 引言

腺样囊性癌(Adenoid cystic carcinoma, ACC)是一种罕见的分泌性腺癌类型的恶性肿瘤，多发于头颈部，尤其在唾液腺和泪腺中较为常见[1] [2]。泪腺腺样囊性癌(adenoid cystic carcinoma of lacrimal gland, LGACC)是发生在泪腺部位的 ACC，典型的临床表现包括眼部症状和神经侵犯症状，如单侧性眼球突出、上睑下垂、视力下降等，以及疼痛、麻木等。疼痛提示伴随骨破坏和神经侵犯，是 LGACC 的一个常见特征[3]。本文报道了一例无痛性 LGACC 患者，旨在通过分析其临床特征，提高对该肿瘤的诊断和治疗能力。

2. 临床资料

患者女，38 岁，因发现左眼进行性突出伴上睑下垂就诊，无疼痛等不适，既往体健，全身浅表淋巴结未触及肿大。左眼颞上侧眼眶触及一约 3 cm × 4 cm 的肿物，边界不清，质地韧，无压痛。视力眼压前节无特殊。突眼计显示左眼 15 mm，右眼 11 mm，眶间距 95 mm。

眼部彩超提示左眼球后存在一大小约 2.04 cm × 2.81 cm 的不规则低回声光团，边界不清，内回声尚均匀，可见粗大血流信号，但未侵犯视神经(图 1)。磁共振成像(Magnetic Resonance Imaging, MRI)检查显示左眼眶内眼球外上方有一椭圆形病灶，与泪腺局部似相连，边界清楚，大小约 2.7 cm × 2.3 cm，病灶内信号略欠均匀，T1 加权成像(T1WI)呈等信号，T2 加权成像(T2WI)大部分呈高信号，内见条状低信号，增强后可见明显强化，局部与上直肌及外直肌关系密切。两侧视神经及眼外肌大小、信号和走形无殊，两侧眼球信号未见异常，脑实质扫描亦未见异常(图 2)。

患者入院后，在静吸复合全身麻醉下接受了左眼眶内肿物切除。术中发现左眼泪腺区实性肿物，与周围组织粘连紧密，大小约 3 cm × 4 cm。手术过程顺利，未出现并发症，术后进行了抗感染、抗炎等治疗。病理学检查显示肿瘤细胞排列成筛状、管状混合型，瘤细胞异型，可见神经侵犯及脉管癌栓(图 3)。进一步的免疫组织化学染色结果显示广谱细胞角蛋白(Cytokeratin, pan (CK pan)) (+)，S-100 蛋白(+)，抗平滑肌抗体(Smooth muscle actin, SMA) (+)，CD117 (c-kit) (+)，CD43 (−)，胶质纤维酸性蛋白(Glial fibrillary acidic protein, GFAP) (−)，P63 (+)，经荧光原位杂交和苏木精－伊红染色提示存在 MYB-NFIB 基因融合。(图 4)。结合免疫组化及分子病理检测结果，最终诊断为腺样囊性癌。

术后患者恢复良好，出院后前往肿瘤内科门诊就诊，Illumina 高通量测序(Next-generation Sequencing, NGS)检测结果显示 EP300 c.3671 + 1G > A 14.19%；人类白细胞抗原-I (Human leukocyte antigen-I, HLA-I)

类分子基因分型结果显示 HLA-I (A、B、C)部分纯合，HLA-I 类分子进化多样性评分分别为 HLA-A:6.232、HLA-B:7.613、HLA-C:0，HED Mean Score 为 4.615。鉴于肿瘤恶性程度较高，患者在手术后半个月接受了全身化疗。术后随访 6 个月，未见肿瘤复发，视力也未出现明显下降。

本案例报道已征得患者知情同意。

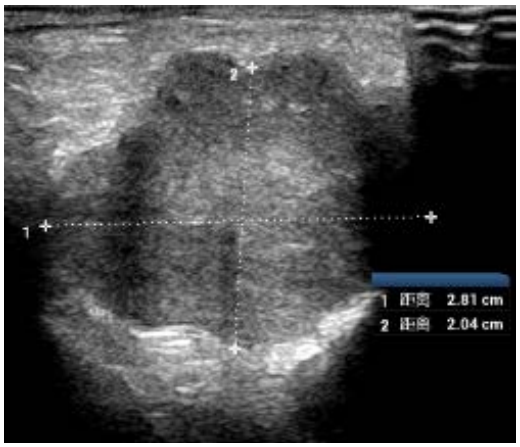

Figure 1. An irregular low-echo cluster with a size of 2.04 cm × 2.81 cm can be seen behind the left eye bulb, with unclear boundaries, even internal echo, and coarse blood flow signal
图 1. 左眼球后可见大小约 2.04 cm × 2.81 cm 的不规则型低回声光团，边界不清，内回声尚均匀，内可见粗大血流信号

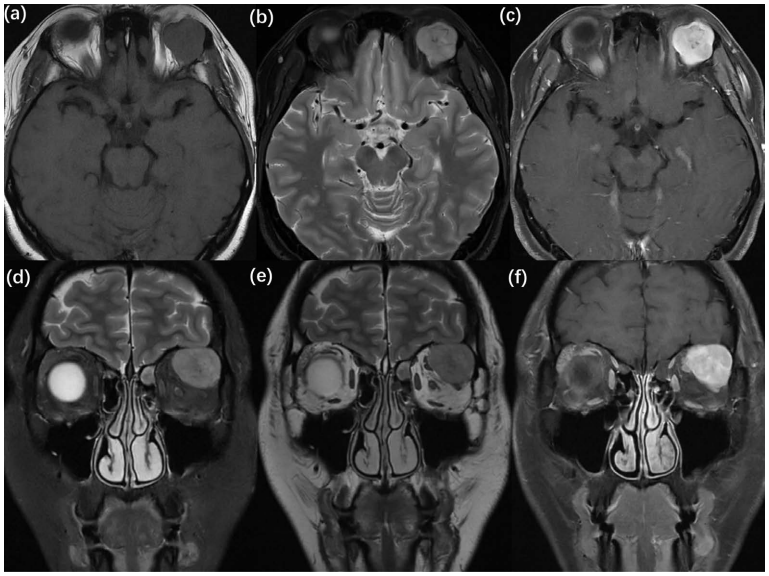

Figure 2. Orbital MRI: There was an oval lesion in the left orbit, which was locally connected to the lacrimal gland, about 2.7 cm × 2.3 cm in size, closely related locally to the superior rectus muscle and the external rectus muscle, and the signals in the lesion were slightly uneven. T1WI sequence level (a): The lesion shows isosignal (similar to muscle signal). Horizontal position (b) of T2WI sequence: Most of the lesions showed high signal, with low signal strip inside. Coronal position (c) of T1WI enhanced sequence: The lesion showed obvious enhancement and internal separation. Coronal position (d) of T1WI sequence: Same as (a). Coronal position (e) of T2WI sequence: Same as (b). Coronal position (f) of T2WI enhanced sequence: Same as (c)
图 2. 眼眶 MRI：左眼眶内眼球外上方可见一椭圆形病灶，与泪腺局部相连，大小约 2.7 cm × 2.3 cm，局部与上直肌及外直肌关系密切，病灶内信号略欠均匀。T1WI 序列水平位(a)：病灶呈等信号(与肌肉信号相仿)。T2WI 序列水平位(b)：病灶大部分呈高信号，内见条状低信号。T1WI 增强序列冠状位(c)：病灶呈明显强化，内见分隔。T1WI 序列冠状位(d)：同(a)。T2WI 序列冠状位(e)：同(b)。T2WI 增强序列冠状位(f)：同(c)

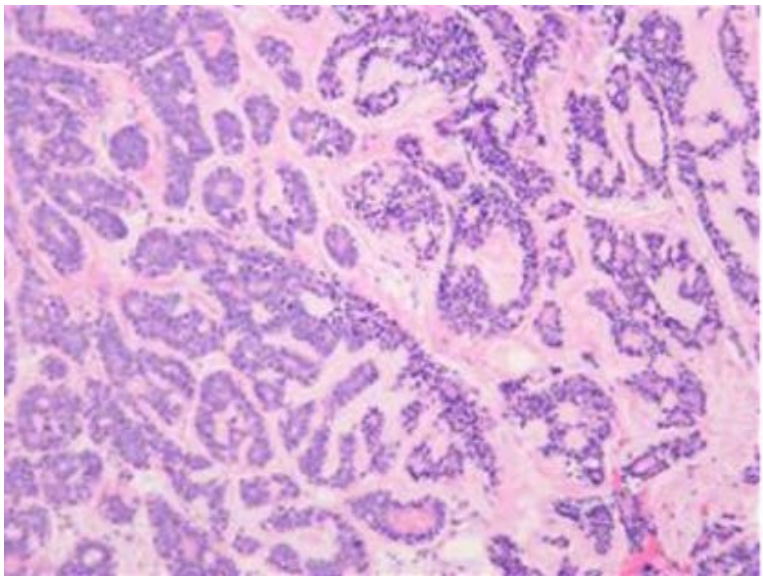

Figure 3. Pathological examination results: The tumor cells were arranged into a mixed type of sieve and tube, and the tumor cells were heterogeneous, with nerve invasion and vascular cancer thrombus (+) (HE × 100)
图 3. 患者组织病理学检查结果：肿瘤细胞排列成筛状、管状混合型，瘤细胞异型，可见神经侵犯，脉管癌栓(+) (HE × 100)

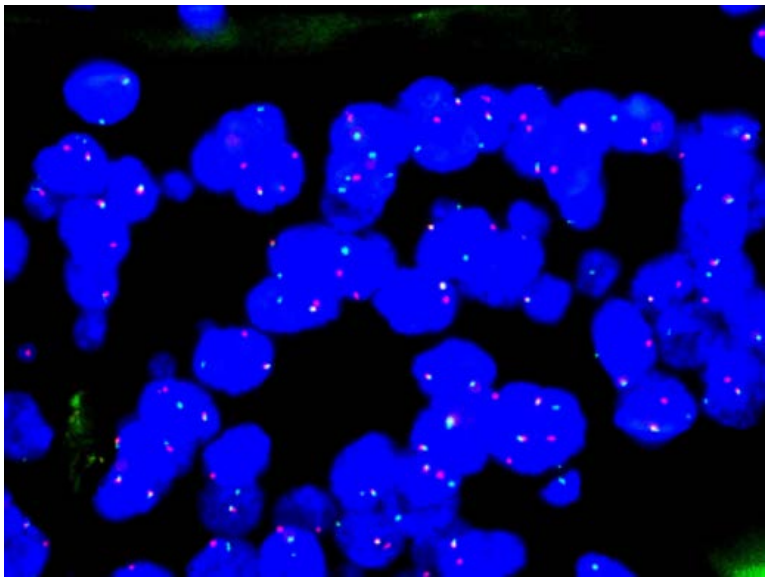

Figure 4. The fluorescence in situ hybridization (FISH) assay of the patient revealed the following signaling patterns in tumor cells with MYB gene probes (red labeled 5' end, green labeled 3' end): 70 (70%) tumor cells exhibited red-green signal separation, while 25 (25%) cells displayed yellow fusion signals along with separate red or green signals. According to the interpretation criteria (red and green signal isolated cells accounted for ≥15% as positive), the result for this patient was determined to be positive for MYB gene mutation
图 4. 患者荧光原位杂交(FISH)检测结果，MYB 基因探针(红色标记 5'端，绿色标记 3'端)在肿瘤细胞中存在以下信号模式：70 个(70%)肿瘤细胞显示红绿信号分离，25 个(25%)细胞显示黄色融合信号伴单独红色或绿色信号。根据判读标准(红绿信号分离细胞占比 ≥ 15%即为阳性)，本例结果判定为 MYB 基因突变阳性

3. 讨论

本文报道了一例无痛性 LGACC 患者，通过分析其临床特征，提高临床对该肿瘤的诊断和治疗能力。

ACC 是最常见的泪腺恶性上皮肿瘤，约占泪腺上皮肿瘤的 25%~40%，约占所有眼眶肿瘤的 1.6% [3]-[8]。LGACC 的中位发病年龄在 38.9 岁到 41 岁之间[6] [7] [9]。女性患者通常多于男性，占比 58%~70% [3] [6] [7]。本例患者为 38 岁青年女性，与既往研究结果较为一致。另有研究[4]发现，年轻 LGACC 患者的预后优于成年患者，这可能是由于他们的肿瘤具有较弱的侵袭性组织学特征。Malen 等人[10]发现，诊断年龄是总体生存的独立预后因素。

由于 LGACC 较为少见，且临床症状缺乏特异性，因此需要与其他泪腺肿瘤如泪腺多形性腺癌、泪腺炎性假瘤、泪腺混合瘤等进行鉴别诊断。LGACC 的典型临床表现包括眼部症状和神经侵犯症状，眼部症状包括：单侧性眼球突出、上睑下垂、视力下降等，神经侵犯症状包括疼痛、麻木等，尤其是疼痛常提示伴随骨破坏和神经侵犯[3]。本例患者表现为无痛性 LGACC，且病理结果提示存在周围神经浸润。这在 LGACC 中较为罕见，因此需要结合影像学检查、早期手术病理检测等帮助鉴别。

术前影像学检查在确定肿瘤大小、位置、范围及特征方面具有重要作用。良性泪腺肿瘤通常表现为边界清晰的肿块，而恶性病变则常伴有钙化、骨破坏及邻近结构侵犯等特征[11]。因此，术前影像学检查在手术方案的选择中具有重要的指导意义。MRI 因其优越的软组织分辨率，能够清晰显示肿瘤与周围组织的关系，也为 LGACC 的鉴别提供参考依据。在 LGACC 中，MRI 通常表现为 T1WI 中低信号强度、T2WI 中高信号强度，对比增强可突出显示囊性变化区域[12]。计算机断层扫描(Computed Tomography, CT)在检测骨骼受累方面具有显著优势。LGACC 的 CT 通常显示眶内不规则形状的病变，内部密度不均，可伴有钙化和坏死区域，并呈现中度至显著的对比增强，提示肿瘤的侵袭性。肿瘤的生长模式常沿眶壁向眶内甚至眶尖延伸，可能累及邻近的眼外肌和眶骨，也可通过眶上裂或眶尖侵犯颅内。临床上往往需要结合 CT 和 MRI 综合评估。Williams 等人[13]的研究表明，在接受 MRI 和 CT 检查的患者中，87.5%的患者通过影像提示存在骨受累的证据，对于这些病例，需采用更广泛的手术方式切除受累骨壁。本病例在 T1WI 呈等信号，T2WI 大部分呈高信号，内见条状低信号，增强可见明显强化，内见分隔，局部与上直肌及外直肌关系密切。是较为典型的影像学表现。

LGACC 生长缓慢，但具有晚期复发、骨破坏和远处转移的高风险[14] [15]。因此，早期诊断和治疗尤为关键。LGACC 最常见的远处转移部位是肺，其次是骨和肝。此外，LGACC 具有不可预测的生长速度、频繁复发和/或转移、逆行性神经周围浸润(Perineural Invasion, PNI)、软组织浸润和骨浸润[16] [17]的特点。其中，PNI 通常在没有血管或淋巴浸润的情况下观察到，是肿瘤细胞增殖的途径[18] [19]。PNI 是指癌细胞浸润到神经纤维鞘中或癌细胞包裹在神经纤维周围达到其周长的 33% [20]。最近的一项回顾性研究[21]发现，PNI 患者和非 PNI 患者的局部复发率有显著差异。PNI 患者局部复发率高，预后差，转移性肿瘤发生率高[22]。然而，由于该病的罕见性和恶性，目前尚无前瞻性研究讨论 PNI 与 LGACC 预后的关系。本例患者的病理结果提示存在周围神经浸润及脉管癌栓，术后需要进行进一步治疗改善预后。

ACC 肿瘤表现出三种不同的结构模式，即管状型、筛状型、实体型，在每个肿瘤中可见不同数量的结构模式[23]。管状型是分化程度最高的组织学模式，由结构良好的导管或管状结构组成，与较低的远处转移率和较高的总生存率(管状组 9 年，筛状组 8 年，实体型 5 年)相关[24]。筛状型是典型的 ACC，预后介于管状型和实体型之间[25]。若实体型占肿瘤组织 30%及以上，则预后较差[26]。研究还表明[21] [27]实体型患者的 5 年生存率显著低于非实体型患者(21% vs. 71%)，且与疾病特异性生存率显著相关。本例患者的病理表现为筛状、管状混合型，是预后较好的类型。

LGACC 缺乏特异性的免疫组织化学标记物。但由于其在组织学和生物学行为上与唾液腺腺样囊性癌(Salivary adenoid cystic carcinoma, SACC)相似，诊断时通常参考 SACC 的相关指标。根据既往研究，CK14、S-100 蛋白、SMA、CD117、CD43、GFAP 和 P63 等蛋白在 SACC 中均呈现阳性表达，这些标志物在 ACC 的诊断中具有重要价值[28]-[34]。此外，在分子层面，研究发现 MYB-NFIB 基因融合是包括

LGACC 在内的多种 ACC 的重要特征，这一基因融合通过激活 IGF1R 信号通路促进肿瘤生长，为 ACC 的治疗提供了潜在靶点[35]-[38]。本例患者的免疫组织化学染色结果显示 CK (pan) (+)，S-100 蛋白(+)，SMA (平滑肌+)，CD117 (+)，CD43 (−)，GFAP (−)，P63 (+)，经荧光原位杂交和苏木精－伊红染色提示存在 MYB-NFIB 基因融合。这些检测结果与目前已知的 LAGCC 的免疫组化特征高度一致，进一步支持了 LGACC 的诊断，并为治疗提供了重要的参考依据。

目前，不同机构对 LGACC 的治疗方法差异很大，尚未建立统一的治疗方案[6] [8] [13] [27] [39]-[44]。在过去，眶内容物剜除术是主要的手术方式，并伴随术后放疗。然而，研究表明，根治性手术(如眼眶内容物剜除术伴随周围骨质去除)并未显著减少疾病的复发、转移或死亡率[9]，反而可能导致功能障碍和毁容，影响患者的生活质量[8] [45]。对于不同分期阶段的肿瘤，研究发现，肿瘤分期 > T3 (美国癌症联合委员会(American Joint Committee on Cancer, AJCC)癌症分期手册，第六版分类为 2.5~5 cm)的患者具有较高的局部复发率、淋巴结累及、远处转移和较差的总生存期[6] [46]。因此，对于肿瘤 ＜T3 的患者，通常推荐保眼手术加放疗，而≥T3 的患者可能需要眼眶内容物剜除术。早期 T1 或 T2 肿瘤患者也可以考虑微创手术。此外，研究发现在≥T3 肿瘤患者中，术后未接受辅助放射治疗的患者局部复发风险增加[6]。根据最新 2017 年 AJCC 第八版分类[47]，本例患者的分期为 T2aN0M0，采取保眼手术治疗及术后辅助化疗，与既往研究的治疗方案基本一致。

近年来，新辅助动脉内化疗、质子放疗、立体定向放射外科、等辅助治疗[8] [13] [40]-[44]被引入，在 LGACC 尤其是广泛累及眼眶软组织的 LGACC 晚期病例中显示出较好的局部控制效果[8] [48]。例如，NIAC 治疗组的 5 年生存率高达 83.3%，累计 5 年复发率降至 23.8% [6]。最新的研究发现[49]在泪动脉完好的患者行 NIAC 治疗后 10 年和 15 年生存率均为 87.5%。

目前，关于 ACC 的化疗研究主要借鉴头颈部腺样囊性癌(Head and Neck Adenoid Cystic Carcinoma, HNACC)的经验。顺铂和阿霉素等铂类药物和蒽环类药物显示出显著的抗肿瘤活性，但由于其较高的毒性反应，临床应用受到限制[50]-[52]。根据本例患者 Illumina 高通量测序(NGS)的结果，在化疗药物敏感性方面，铂类的化疗方案(2B)可能较为敏感，毒副作用可能居中的药物有伊立替康(1A)、甲氨蝶呤(2A)，毒副作用可能较低的药物为氟尿嘧啶(1A)。

本例患者为青年女性，因发现左眼进行性突出伴上睑下垂就诊，无疼痛等不适，影像学检查提示左眼眶内肿物，病理学显示：神经侵犯(+)，但患者未出现疼痛症状，肿瘤分期为 T2aN0M0。本病例表示，即使患者并未表现出疼痛，仍需警惕泪腺部位恶性肿瘤的可能，及时明确诊断并行手术切除，积极治疗，改善预后。

4. 结论

综上所述，ACC 是最常见的泪腺恶性上皮肿瘤，预后较差，需早期手术切除联合术后放疗或化疗。充分认识其临床、影像学检查、病理形态及免疫表型特征，对该病的临床诊断、治疗及预后评估具有重要价值。通过本例案例的学习，我们认识到综合个性化诊治的重要性，以避免漏诊并弥补不足。例如，术前可增加 CT 检查，术中结合冰冻检查以辅助诊断和治疗。此外，由于该病临床较为罕见，仍需更多病例的积累和观察，以进一步优化诊疗策略。

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