Incidentally Discovered Adenoid Cystic Carcinoma of the Lacrimal Gland with Isolated Liver Metastases

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Established Facts

- Adenoid cystic carcinoma of the lacrimal gland is an aggressive malignancy that is often associated with local recurrence and late distant metastasis.

Novel Insights

- Primary adenoid cystic carcinoma of the lacrimal gland may rarely present with metastatic lesions isolated to the liver at initial diagnosis.

Keywords

Adenoid cystic carcinoma of the lacrimal gland · Adenoid cystic carcinoma · Lacrimal gland carcinoma · Orbital tumor · Metastasis · Lacrimal/orbit

Abstract

Aim: To report a rare presentation of adenoid cystic carcinoma (ACC) of the lacrimal gland. **Method:** This is a case report presenting clinical, radiographic, and histopathologic findings. **Results:** A 72-year-old female with no reported ocular symptoms was found to have an incidental right orbital mass on imaging. Additional studies revealed multiple liver lesions, which were biopsied and found to be consistent with ACC. She was then referred to the ophthalmology service, where ocular examination demonstrated 2.5 mm of right proptosis with elevation and abduction deficits. Diplopia could be elicited in extreme upgaze and right lateral gaze. An excisional biopsy of the orbital mass was performed,

with histopathology confirming the diagnosis of primary ACC of the lacrimal gland, thereby also supporting the initial suspicion that the hepatic ACC lesions represented metastases. **Conclusion:** The authors describe a rare presentation of ACC of the lacrimal gland, initially asymptomatic, with metastatic lesions restricted to the liver at the time of diagnosis. Three previous cases of ACC with isolated metastatic hepatic lesions at the time of diagnosis have been reported; all of these cases localized the primary tumor to the salivary glands.

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Introduction

Adenoid cystic carcinoma (ACC) is an aggressive malignancy originating from the epithelial cells of the salivary and lacrimal glands [1]. Accounting for approximately 1% of all orbital tumors, ACC is the most common

epithelial malignancy of the lacrimal gland [2]. As compared to other lacrimal gland carcinomas, patients with ACC of the lacrimal gland are typically diagnosed at younger ages, report earlier and more frequent periocular pain, and experience local recurrence or distant metastasis even after long quiescent periods [3]. The difficulties in localized control and the high tendency for regional recurrences in ACC are attributed to perineural infiltration and bone invasion [4]. Distant metastasis is seen in up to 50% of patients with ACC, with the lungs, bone, and liver reported as the most commonly affected sites [1, 5–7]. In this report, we describe an unusual presentation of ACC of the lacrimal gland with isolated distant single-organ metastasis.

Case Report

A previously healthy 72-year-old Caucasian female was admitted to the hospital for altered mental status. She was found to have a urinary tract infection, as well as electroencephalographic findings suggestive of seizures. Her mental status improved to baseline with initiation of anti-seizure medication and treatment of the urinary tract infection. During the inpatient workup, CT and MRI scans of the brain showed no signs of any acute intracranial process. However, an incidental orbital mass was found in the right lacrimal gland fossa measuring $1.7 \times 2.0 \times 2.2$ cm. The lesion appeared well demarcated without obvious bony erosion (Fig. 1a). She denied any ocular symptoms at that time, and also reported a normal eye examination that was performed 2 months earlier. Further investigation with chest, abdomen, and pelvis CT scan showed multiple lesions in the liver involving the right hepatic lobe (Fig. 1b). No other lesions were visualized in the chest, lymph nodes, or remaining abdominal regions. Whole-body PET scan demonstrated focal uptake within the right lacrimal gland mass and increased uptake within at least one liver lesion. An ultrasound-guided liver biopsy was performed with the histopathology showing nests of tumor cells in a tubular to cribriform pattern (Fig. 2a), with foci of mucinous material in the surrounding stroma and in the lumen of some of the glandular structures. Immunostaining showed the tumor cells to be uniformly positive for CD117 (c-Kit proto-oncogene) (Fig. 2b). Additionally, the cell nuclei in the periphery of the tumor nests (consistent with myoepithelial cells) were positive for p63 (not shown). In the setting of the lacrimal gland mass, the histopathology and immunophenotype were most suggestive of ACC.

Subsequently, the oncology division referred the patient to the ophthalmology service for further evaluation of the right orbital mass. At her initial visit (6 weeks after presentation), she admitted to momentary episodes of diplopia and occasional mild headaches localized to the right superolateral orbit. On examination, extraocular motility of the right eye was mildly limited in elevation and abduction. Diplopia was present in extreme upgaze and right gaze. There was 2.5 mm of right proptosis with deep induration and tenderness of the right lacrimal gland fossa.

Fig. 1. Radiologic imaging. **a** Contrast-enhanced coronal T1-weighted MRI of the orbit demonstrates an enhancing extraconal mass in the right lacrimal gland fossa. **b** Delayed post-contrast T1-weighted MRI of the abdomen with multiple hepatic lesions (white arrows) that did not retain contrast.

Fig. 2. Histopathology and immunohistochemical staining of the hepatic biopsy. **a** Hematoxylin-eosin stain. Nests of tumor cells are seen arranged in a tubular to cribriform pattern (original magnification, $\times 200$). The bottom right inset shows a magnified view ($\times 1,000$) of the dotted-boxed area, with tumor cells demonstrating nuclear hyperchromasia and pleomorphism, with a mitotic figure in the field (arrow). **b** CD117 (c-Kit proto-oncogene) immunohistochemical stain. The tumor cells exhibit uniformly positive staining for CD117 (original magnification, $\times 200$).

An orbitotomy was performed, and the decision was made intraoperatively to complete an excisional rather than incisional biopsy of the mass as it appeared to be well demarcated from the adjacent tissue. Microscopic evaluation revealed tumor morphology similar to what had been observed in the prior hepatic biopsy: nests of tumor cells arranged in a cribriform (“Swiss cheese”) to tubular pattern, with mucinous material present within the lumen of some of the glandular structures and in the surrounding stroma (Fig. 3a). There were approximately 3 mitoses per high-power field. The neoplasm was adjacent to normal lacrimal gland tissue, with some admixture of normal lacrimal gland with tumor in the transition zone, providing strong evidence that the malignancy

arose primarily from the lacrimal gland (Fig. 3b). Perineural spread (Fig. 3c), intravascular invasion (Fig. 3d), and tumor extension to the surgical margins were all seen. Similar to the hepatic biopsy, the tumor cells were positive for CD117 immunostain, whereas only minimal/faint positivity for CD117 was seen in the normal lacrimal gland, with patchy positivity seen in the transition zone (Fig. 3e). Combining the clinical and imaging findings with the histological results, it was concluded that the hepatic masses likely represented metastatic lesions from the primary lacrimal gland ACC.

Four months after initial presentation, the patient underwent palliative transarterial chemoembolization of the right hepatic lobe with doxorubicin-loaded drug-eluting beads without any complications. One month later, MRI imaging of the orbit and liver showed stable hepatic lesions and postsurgical orbital findings. The most recent whole-body PET study, performed 5 months after chemoembolization therapy, showed the known hepatic lesions with one lesion slightly increased in size, another showing minimal interval increase in uptake, and no evidence of any new hepatic or orbital lesions.

At the most recent clinic visit, 10 months after initial presentation, the patient reported no ocular symptoms, and clinical examination remained stable without any findings suggestive of orbital tumor recurrence. Orbital radiation therapy was recommended due to the increased risk for local tumor recurrence given the presence of tumor at the orbital biopsy margins; however, the patient chose to defer radiation treatment due to the absence of orbital tumor recurrence on surveillance imaging and the associated risk of vision loss with radiation. The patient is scheduled for surveillance whole-body PET imaging every 4 months to monitor tumor progression.

Discussion

Lacrimal gland ACC is a rare, aggressive malignancy characterized by multiple episodes of local recurrence with variable quiescent periods and late distant metastasis [1, 5]. Presence of perineural invasion and positive surgical margins have been associated with local recurrence and decreased survival rates [6, 7]. Additionally, Rapidis et al. [8] showed a statistically significant relationship between early perineural invasion and late distant metastasis, whereby 100% of the patients with distant metastases initially presented with perineural invasion. In the present case, perineural invasion, intravascular invasion, and positive biopsy margins were all found on histopathologic examination.

Due to the poor prognosis, aggressive treatment of localized ACC of the lacrimal gland has typically involved a combination of total exenteration, adjuvant radiation therapy, and systemic chemotherapy [1, 7]. More recently, a protocol evaluated by Tse et al. [9] using neoadjuvant intra-arterial chemotherapy has reported improved overall survival and a decreased incidence of disease recur-

Fig. 3. Histopathology and immunohistochemical staining of the right orbital biopsy. **a–d** Hematoxylin-eosin stain; **e** CD117 immunohistochemical stain. **a** In the orbital biopsy, tumor cells are arranged (similar to the hepatic biopsy) predominantly in a cribriform (dotted-boxed region) to tubular pattern, with some of the luminal structures appearing mucin-filled (lightly basophilic) (original magnification, $\times 100$). **b** In this field, a transition from normal lacrimal gland (arrow) to tumor (asterisk) is evident, thereby establishing the lacrimal gland as the primary site of malignan-

cy (original magnification, $\times 200$). **c** In this section, perineural invasion by tumor cells is evident (arrow) (original magnification, $\times 200$). **d** Intravascular invasion is evident in this section, displaying a cluster of tumor cells (arrow) adjacent to red blood cells within the lumen of a blood vessel (original magnification, $\times 400$). **e** Immunostaining with CD117 exhibits uniformly prominent positivity in the tumor cells (asterisk), patchy positivity in the transition zone (arrow), and minimal positivity in the normal lacrimal gland (L) (original magnification, $\times 20$).

rence in patients with lacrimal gland ACC without metastasis.

Many reports of ACC have documented the late complication of metastatic lesions to the liver, in addition to the lungs, bones, and kidneys [5, 6, 8]. Infrequently, metastatic lesions can be found at the time of diagnosis of ACC; however, these cases almost always originate from salivary gland ACC [10–12]. Three previous reports have described isolated liver metastases found at the time of

diagnosis of ACC, with all of them initially presenting with abdominal symptoms; all three of these cases found the primary malignancy to originate from the submandibular glands [13–15]. We report a rare case of primary ACC of the lacrimal gland diagnosed concurrently with isolated metastatic liver lesions. Additionally, we describe an unusual presentation of metastatic ACC found incidentally on imaging, prior to the patient reporting any symptoms from the orbital or hepatic lesions.

Statement of Ethics

This study adhered to the principles of the Declaration of Helsinki, and the authors have maintained Health Insurance Portability and Accountability Act compliance.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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