Lacrimal Gland Adenoid Cystic Carcinoma with High-Grade Transformation to Myoepithelial Carcinoma: Report of a Case and Review of Literature

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Abstract Adenoid cystic carcinoma (AdCC) is the most frequent malignant neoplasm of the lacrimal glands. Like its salivary gland counterpart, lacrimal AdCC can rarely undergo high-grade transformation (“dedifferentiation”). We herein report the clinical, radiographic and microscopic findings of a lacrimal gland AdCC with high grade transformation, occurring in a 39-year-old female patient. In contrast to salivary gland AdCC with high-grade transformation, which usually shows a high grade component with “ductal” differentiation, in the case presented, the “dedifferentiated” component showed morphologic and immunohistochemical features of myoepithelial differentiation.

Keywords Adenoid cystic carcinoma · High grade transformation · Lacrimal gland · Pathology · Immunohistochemistry

Introduction

Primary epithelial neoplasms represent 23–70 % of histologically examined lacrimal gland lesions [1]. Although up to 70 % of lacrimal gland epithelial neoplasms are pleomorphic adenomas [1], and the majority of the remainder is represented by adenoid cystic carcinomas and carcinomas ex-pleomorphic adenoma, rare cases of a wide variety of other histologic types analogous to their salivary gland counterparts, have also been described, mostly as individual case reports. Such rare tumors of the lacrimal glands include basal cell adenocarcinoma, ductal carcinoma, acinic cell carcinoma, mucoepidermoid carcinoma, oncocytoma and oncocytic carcinoma, polymorphous low-grade adenocarcinoma, myoepithelioma and myoepithelial carcinoma [2]. The data from 19 series [1, 3] reported from 1954 to 2010, comprising 1,366 primary epithelial neoplasms of the lacrimal gland, show that adenoid cystic carcinomas represent about 20 % (range 6–75 %) of all epithelial tumors and about 65 % (range 29–93 %) of all malignant epithelial tumors of the lacrimal gland. It is likely, however, that this is an overestimation of their frequency, since many of these series are from large tertiary cancer centers and from consultation files and show an overrepresentation of malignant tumors. The histologic features of adenoid cystic carcinomas of the lacrimal gland are similar to their major and minor salivary gland counterparts and are composed of a dual population of epithelial (adluminal) and myoepithelial (abluminal) small hyperchromatic cells that show tubular, cribriform and solid growth patterns, which may be present

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in various proportions in a tumor. As with adenoid cystic carcinomas from other sites, the prognosis of tumors showing a predominantly solid growth pattern is worse than that of tumors with predominantly tubular or cribriform growth patterns. Apart from these classic histologic types of adenoid cystic carcinoma, another type, which shows areas of classic adenoid cystic carcinoma with a gradual or sharp transition to areas of high-grade carcinoma has been recently described. To date, about 35 such tumors arising from major and minor salivary glands have been described under different designations, initially as “hybrid tumors”, between adenoid cystic carcinoma and salivary duct carcinoma [4–8], subsequently as “dedifferentiated” adenoid cystic carcinomas [9–13] and most recently as adenoid cystic carcinomas with high-grade transformation [14, 15]. The lacrimal gland counterpart of this tumor has, to our knowledge, only been described in two individual case reports [16, 17]; two additional cases were included in a recent multi-

institutional histopathologic review of lacrimal gland tumors but not described in detail [2]. Herein we present the clinical, imaging, histopathologic and immunohistochemical features of an additional example of lacrimal AdCC with high grade transformation.

Case Report

A 39-year-old woman with no relevant prior history presented to the ophthalmologist complaining of increased periorbital pressure and progressive swelling of her left eye. Ophthalmologic examination revealed a 3 mm proptosis, visual acuity of 20/20 in both eyes, along with normal pupils, color vision and extraocular motility. CT and MRI were performed and showed a $3 \times 2.2 \times 2$ cm extraconal mass effacing the lacrimal gland and displacing the left lateral rectus, optic nerve and globe (Fig. 1a, b). A wide

Fig. 1 Imaging features of the primary lacrimal gland tumor and its recurrence. **a, b.** Initial presentation: T1 & T2 MRI scan of the orbit exhibiting a well-defined, round, $3 \times 2.2 \times 2$ cm extraconal mass displacing the left lateral rectus, optic nerve—sheath complex and optic globe with effacement of the homolateral lacrimal gland. **c,**

d Recurrent lesion: T1 & T2 MRI demonstrating a developing $1.6 \times 1.1 \times 1.3$ cm extraconal mass of the lateral superior left orbit attached to the superior and lateral recti muscles with erosion of the underlying bone

differential diagnosis was suggested, including lacrimal gland neoplasms, pseudotumors, hemangioma, lymphoma and metastatic processes. The tumor was resected under the presumption that it represented a pleomorphic adenoma.

On macroscopic examination, the specimen consisted of pink, rubbery $3.2 \times 1.9 \times 1.6$ cm nodular mass with a small amount of attached adipose tissue. On section, it revealed a tan center exhibiting cystic degeneration and small necrotic foci. The tumor infiltrated the remaining adjacent benign lacrimal gland tissue and was extending to the margins. After seeking expert consultation, the outside pathologist diagnosed the mass as carcinoma ex-pleomorphic adenoma. No

immunohistochemical stains were initially performed. No residual neoplastic tissue was identified in the subsequent wide local excision and resection of the residual non-neoplastic lacrimal gland. The patient presented an uneventful postoperative course with improvement of her vision. However, 2 years later, follow-up magnetic resonance imaging revealed a mildly enhancing $1.6 \times 1.1 \times 1.3$ cm extraconal mass, localized in the lateral superior left orbit (Fig. 1c, d). The lesion was attached to the superior and lateral recti muscles and had eroded the underlying bone.

Review of the histologic sections of the tumor at our institution, showed two distinct morphologic patterns

Fig. 2 Scanning and low-power histologic appearance of the two components of the tumor. **a** Scanning power appearance of a section of the tumor composed the less cellular low grade component (*right side of the image*) surrounded by large cellular nests of tumor. **b** Section of the tumor composed exclusively of the high grade component with large areas of necrosis (H&E stain, original

magnification $\times 1$). **c, d** Low grade component of AdCC with a predominantly cribriform architectural surrounded by dense hyalinized fibrous tissue (H&E stain, original magnification $\times 40$). **e, f** High grade/dedifferentiated component characterized by a comedocarcinoma-like pattern (H&E stain, original magnification $\times 40$)

(Fig. 2a, b). The first pattern, which made up the minority of the tumor had a low-grade appearance (Fig. 2c, d) and was sharply demarcated from the second, high-grade pattern (Fig. 2e, f). The low-grade component revealed typical morphologic features of AdCC characterized by small hyperchromatic neoplastic cells forming solid nests, duct-like structures, cords and sheets invested within abundant dense fibrous and hyalinized connective tissue stroma. No myxoid or chondroid areas were present. The tubular structures were formed by two layers of cells: an outer layer of uniform cells with scant, indistinct, focally clear cytoplasm and hyperchromatic ovoid or triangular nuclei measuring 7–10 μm in largest diameter and an inner, adluminal layer composed of slightly larger cells with more distinct, eosinophilic cytoplasm and round to ovoid nuclei measuring 8–11 μm in diameter (Fig. 3a, b). Neoplastic cell nests exhibited prominent neurotropism with perineural and intraneural infiltration. The high grade component of the tumor was composed of larger (18–20 μm) round, cuboidal or polygonal cells with larger (10–15 μm), more pleomorphic nuclei with vesicular or coarsely granular chromatin, irregular, thick nuclear membranes, nuclear grooves and indentations, prominent nucleoli and moderate amounts of eosinophilic cytoplasm. The neoplastic cells were arranged in large solid cell nests with central necrosis (Fig. 3c, d). The large cell nests were surrounded by a

variably thick deeply eosinophilic collagenous rim and were separated from each other by a scant desmoplastic stroma (Fig. 4a). Within these solid neoplastic cell nodules, the cells were arranged in sheets or trabeculae (Fig. 4b). No ductal (tubular) structures were seen. Small areas with focal collagen spherule production and small foci of squamous or squamoid differentiation, with tumor cells showing more abundant glassy eosinophilic cytoplasm or forming pearls were also present (Fig. 4c). Mitoses and apoptotic bodies were easily appreciated (Fig. 4d). The mitotic count was 6/10 HPF, whereas no mitosis was identified in the low-grade component. The cytologic and histologic features of both patterns are summarized in Table 1.

Immunohistochemical staining (Table 2) was performed on a Ventana NexES automated system (Ventana Medical Systems, Tucson, AZ). In the typical AdCC areas, luminal cells demonstrated intense positivity against AE1/AE3, CK 8/18, EMA, CD117, and focal positivity against p16. Very rare nuclei (<1 %) stained for p53 and for Ki67. The myoepithelial component was diffusely decorated by AE1/AE3, CK 5/6, EMA, SMA, S-100, calponin and p63 and stained focally for p16 and cyclin-D1.

The poorly differentiated component exhibited strong and diffuse positivity for cytokeratin AE1-AE3, CK 5/6, EMA, p16, SMA, S-100, calponin and p63, but not for CK

Fig. 3 Medium power histologic appearance of the two components of the tumor. **a, b** Low grade component of AdCC characterized by ovoid or cuboidal cells with hyperchromatic nuclei arranged in a tubular and cribriform pattern. **c, d** High grade component of AdCC

with neoplastic cells arranging in bands separated by thin fibrous septa (**c**) and focal collagen formation (**d**) (all images, original magnification $\times 100$)

Fig. 4 Higher power appearance of the high grade component of AdCC. **a** Thick deeply eosinophilic collagenous stroma surrounding the neoplastic cell nodules. **b** Trabecular pattern. **c** Focal squamoid

differentiation. **d** Prominent cytologic atypia and mitotic activity (original magnification **a** $\times 200$, **b**, **c** $\times 400$, **d** $\times 1,000$)

Table 1 Histologic features of the low-grade and high-grade components of the tumor

Histologic feature	AdCC/LG component Abluminal cells	AdCC/LG component Luminal cells	AdCC/HG component
Growth pattern	Predominantly tubular with focal cribriform areas		Solid nests with comedo necrosis
Stroma	Abundant, hypocellular, hyalinized		Scant, desmoplastic
Extracellular matrix production	Present		Focal
Cell size	Small (diameter $<10\ \mu$)	Small (diameter $<12\ \mu$)	Larger (diameter $18\text{--}20\ \mu$)
Cytoplasm	Very scant, eosinophilic or clear	Scant, eosinophilic	Moderate amounts, eosinophilic, focally squamoid
Nuclear shape	Ovoid	Rounded	Rounded or ovoid, pleomorphic
Nuclear size	$7\text{--}10 \times 6\text{--}7\ \mu$	$8\text{--}11 \times 7\text{--}8\ \mu$	$11\text{--}15 \times 10\text{--}12\ \mu$
Nuclear chromatin	Very hyperchromatic	Hyperchromatic	More open, coarsely granular
Nucleoli	Rarely visible	Occasionally visible	Prominent $1\text{--}2\ \mu$
Mitoses	0/10 HPF	0/10 HPF	6/10 HPF
Apoptotic cells	None	None	Frequent
Necrosis	Absent		Prominent comedo-type

8/18, demonstrating a myoepithelial immunophenotype. Ki-67 nuclear staining was observed in approximately 20 % of the neoplastic cells and p53 showed diffuse nuclear positivity (Fig. 5). Based on these histopathologic and immunohistochemical characteristics, the tumor was diagnosed as AdCC with high grade transformation to myoepithelial carcinoma.

Discussion

Lacrimal AdCC affects middle age patients (mean 40 years) [18] and manifests with a variety of symptoms and signs, including pain, numbness, disturbed motility, ptosis, and diplopia [19]. Imaging reveals usually a round mass with irregular, ill-defined margins and variable

Table 2 Antibodies used and results of immunohistochemistry

Antibody	Source	Clone	AdCC/LG component		AdCC/HG component
			Abluminal (myoepithelial cells)	Luminal (ductal) cells	
CK AE1/AE3	Dako	AE1, AE3	+ (weak)	+ (strong)	+ (weak)
CK 5/6	Ventana	D5/16B4	+ (strong)	–	+ (strong)
CK 8/18	Biocare Medical	5D3	–	+ (strong)	–
EMA	Ventana	E29	+	+	+
α -SMA	Dako	1A4	+	–	+ (80 %)
S-100	Ventana	Polyclonal	+ (weak)	–	+ (20–50 %) ^a
Calponin	Dako	CALP	+	–	+
Synaptophysin	Leica	27G12	–	–	–
CD117	Biocare Medical	Y145	–	+	–
p16	Cintec	INK4a	–	F+ (10 %)	+ (50 %) ^a
p53	Ventana	Bp-53-11	–	F+ (<1 %)	+ (70 %)
p63	Biocare Medical	BC4A4	+	–	+ (100 %)
Cyclin-D1	Ventana	SP4	F+ (10 %)	F+ (10 %)	+ (50 %)
Ki-67 (%)	Leica	MM1	0	<1 %	20 %

AdCC/LG adenoid cystic carcinoma low grade, *AdCC/HG* adenoid cystic carcinoma high grade, *CK* cytokeratin, *EMA* epithelial membrane antigen, *α -SMA* α -smooth muscle actin, *F+* focally positive

^a Heterogeneous staining of different tumor nodules

Fig. 5 High grade AdCC transformation showing lack of CK 8/18 staining (**a**), strong diffuse staining with CK 5/6 (**b**), nuclear staining for Ki67 in about 20 % of tumor cells (**c**) and diffuse staining for p53 (**d**) (original magnification **a**, **b** $\times 40$, **c**, **d** $\times 200$)

presence of intralesional focal dystrophic calcifications [17, 19]. Although AdCC can be slow growing, imaging studies may show peri- and intraneural infiltration, bone invasion

and intracranial spread in 4–36 % of cases [16, 18]. Local recurrences and distant metastases are common, accounting for the poor long-term prognosis of this tumor [12, 16–18].

The prognosis of lacrimal gland AdCC may be worse than that of AdCC of the major salivary glands [20].

Histopathologically, lacrimal AdCC is characterized by the presence of small basaloid neoplastic cells with hyperchromatic nuclei which form nests, cords, sheets, as well as cribriform, cyst- or duct-like structures containing amorphous, eosinophilic material. Areas of necrosis may occasionally be seen in the solid type of AdCC. The epithelial component is invested in a densely collagenized or hyalinized connective tissue stroma. Among the classic patterns of growth of lacrimal AdCC, the most frequent is the cribriform [21], followed by basaloid/solid and tubular/ductal patterns. Tumors with a basaloid-solid pattern are the most infiltrative and are associated with a 5-year survival rate of only 21 % [22].

High grade transformation or “dedifferentiation”, similar to that seen in salivary gland AdCC, can also be encountered in lacrimal tumors. In general, high grade transformation of AdCC is rare and is associated with aggressive clinical course, including a frequency of high lymph node metastases (57 %) and distant metastases [23]. Thirty-five cases of AdCC with high grade transformation have been described, demonstrating a strong predilection for the 6th decade and a slight male predominance. Common sites of occurrence have been the sinonasal seromucinous glands, the submandibular gland and the minor salivary glands of the hard palate [24]. Histologically, two architectural patterns are appreciated; one low grade, conventional AdCC with minimal cellular atypia, the other a high grade or “dedifferentiated” characterized by pleomorphism and numerous mitoses. The demarcation between the two components is usually sharp, but in some cases, a more gradual transition between the low and the high-grade areas of the tumor may be observed [12, 15]. In addition, high grade areas may show squamous and/or micropapillary morphology as well as loss of the myoepithelial layer surrounding the tumor nests [14, 23]. Rarely, the “dedifferentiated” neoplastic cells may acquire spindle, sarcomatoid or large basaloid phenotype and occur in solid nests or show a comedocarcinoma pattern [4]. The high-grade component of most of the reported cases has morphologic and immunohistochemical features of a high-grade malignant epithelial neoplasm with ductal differentiation, and loss of myoepithelial differentiation as demonstrated by the lack of SMA, SMM,

S100, calponin, and p63 staining. While this high grade component is reminiscent of salivary duct carcinoma, it shows no androgen receptor or Her2/neu staining.

The presence of a high-grade (“dedifferentiated”) component with myoepithelial differentiation, as seen in our case, has only been rarely reported in minor or major salivary gland tumors [9].

High grade transformation of lacrimal AdCC is rare, with only two reports recorded thus far in the English literature (Table 3). The high grade component showed myoepithelial dedifferentiation in both published cases, and was composed of atypical solid nests of neoplastic cells with limited necrotic foci [20] in one case and of a sarcomatoid spindle cell population with myoepithelial immunophenotype [14] in the other.

All reported dedifferentiated AdCC have shown a much higher proliferative rate in the high-grade areas than in the low-grade areas, with proportional increases in the Ki67 positivity rate. About half of reported cases have shown p53 staining of a large percentage of tumor cells in the high-grade areas but not in the low grade areas, suggesting that genomic instability associated with p53 abnormalities play a major role in the high-grade transformation [12, 15].

Recent studies have indicated that the presence of MYB-NFIB fusion resulting from the (6;9)(q22–23;p23–24) translocation is a crucial oncogenic step in the development of AdCC [25–28], leading to loss of apoptosis and cell cycle control, independent cell growth, tumor angiogenesis, and loss of cell adhesion [25–28].

The differential diagnosis of lacrimal gland AdCCs with high grade transformation mainly includes the solid variant of AdCC, carcinoma ex-pleomorphic adenoma, and ductal carcinoma. Similar to AdCC-HGT, the solid variant of AdCC has a poorer prognosis, and shows a predominantly solid growth pattern, in addition to focal areas showing tubular or cribriform patterns, shows increased pleomorphism, increased number of mitotic figures, and may show necrosis. However, the neoplastic cells in the solid variant of AdCC maintain their basaloid phenotype with small hyperchromatic angular nuclei without prominent nucleoli and scant indistinct cytoplasm, as opposed to the malignant cells of the high-grade transformation of AdCC which

Table 3 Clinicopathologic features of lacrimal gland AdCCs with high grade transformation

Case	Author	Year	Age	Sex	Tumor site	Size (cm)	Histology	
							AdCC-LG	HG
1	Terasaki et al.	2000	49	F	Orbit and middle fossa (R)	NP	Cribriform	Solid with necrosis
2	Panarelli et al.	2011	52	M	Extraconal comp. (R)	3.2 × 3.2 × 2.9	Cribriform	Myoepithelial sarcomatoid
3	Present case	2012	39	F	Extraconal comp. (L)	2 × 3 × 2.2	Cribriform	Myoepithelial comedo-carcinomatous

AdCC-LG adenoid cystic carcinoma low grade, HG high grade, F female, M male, Comp. compartment, R right, L left, NP not provided

show moderate amounts of eosinophilic cytoplasm and larger, more pleomorphic nuclei with open chromatin and visible to prominent nucleoli. The presence of areas of typical pleomorphic adenoma can be helpful in differentiating high grade AdCC from carcinoma ex-pleomorphic adenoma [18]. Basal cell adenocarcinoma is characterized by the monotonous proliferation of basaloid cells forming primarily solid nests that invade adjacent normal tissues, but typically lack necrosis, prominent cellular atypia and pleomorphism [12]. The high grade areas of AdCC-HGT appear histologically similar to ductal carcinomas [12]; however, the latter lack areas of low-grade AdCC.

The treatment of choice for lacrimal AdCC is the complete en block resection of the primary tumor with adequate surgical margins, followed by radiation therapy when the resection is incomplete or there is intracranial invasion [19]. Chemotherapy may also be used as it has shown promising results in the treatment of high grade AdCC [25].

In conclusion, awareness of the potential for high grade transformation of AdCC of the lacrimal gland is helpful in overcoming the difficulties that may be encountered in the diagnosis of such unusual tumors.

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