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Primary De novo ductal adenocarcinoma of the lacrimal gland☆

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ABSTRACT

Background: Primary ductal adenocarcinoma of the lacrimal gland is a rare and aggressive malignant epithelial lacrimal gland neoplasm, morphologically and phenotypically resembles salivary duct carcinoma, and both strongly resemble infiltrating ductal carcinoma of breast.
Method: Retrospective Chart review of cases of malignant lacrimal gland tumors from 2013 July to 2020 July. Authors describe the clinico radiological, morphological and immunohistochemical features of primary ductal adenocarcinoma (PDA) of lacrimal gland. Extensive review of literature of PDA of lacrimal gland and salivary gland ductal carcinoma has been performed.
Results: Retrospective chart review of the last 7 years yielded 22 malignant lacrimal gland neoplasms of which 4 cases demonstrated features of primary ductal adenocarcinoma of lacrimal gland, 2/4 cases showed an evidence of a pre existing pleomorphic adenoma and 2 were found to be de novo ductal adenocarcinomas. PDA of lacrimal gland showed expression of CK7, CK19, AR, HER2, cyclin D1 and were negative for CK5/14, CK 20, ER, PR, PSA, TTF-1, S-100 and SMA. Expression of GCDFP-15 was noted in one case. The presence of multiple events of loco-regional recurrences and/or distant metastasis necessitated a multidisciplinary approach.
Conclusions: Authors have expressed the need of clinical correlation; thorough tissue sampling and extensive immunohistochemical work up in identification of de novo PDA's and their molecular subtypes. A multi-institutional study might help in formulating the diagnostic criteria, identification of actionable targets, and thus study the role of targeted therapy in this rare and aggressive tumor which may result in better patient outcomes.

1. Introduction

Primary ductal adenocarcinoma (PDA) of the lacrimal gland is a rare aggressive lacrimal gland neoplasm [1,2], characterized by intraductal and infiltrating component of cords, trabeculae and tubules of pleomorphic malignant cells in a classically desmoplastic, hyalinised or paucicellular stroma with or without calcification. Tumor cells commonly express low molecular weight cytokeratins, HER2, androgen receptor, Gross cystic disease fluid protein and are negative for Estrogen and Progesterone receptors. To the best of authors' knowledge, only 34 cases of PDA have been described in English literature. Due to its rarity, surgical pathologists need to draw knowledge primarily from its salivary gland counterpart, and it is believed to be morphologically very similar to salivary duct carcinoma and both morphologically resemble infiltrating ductal carcinoma of the breast; genotypically resembling luminal AR; HER2 enriched sub type. Existing literature on PDA comprises of de novo cases and possibly also includes cases of high-grade transformation in a pre-existing pleomorphic adenoma. Due to its rarity and lack of uniform diagnostic criteria, the biological behaviour of PDA is poorly understood and treatment protocols are not well defined. Retrospective chart analysis of the authors' pathology laboratory data base and electronic medical records of the last 7 years (August 2013–July 2020)

☆ Key message: Limited knowledge of salivary and lacrimal gland primary ductal adenocarcinoma and its aggressive nature signifies an immediate need of a multi institutional study in unravelling the tumor pathogenesis, identification of possible tumor targets and formulation of targeted therapy.

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yielded 22 cases of malignant lacrimal gland tumors, of which 4 demonstrated features of primary lacrimal gland ductal adenocarcinoma. Two of these 4 cases had history of pre-existing pleomorphic adenoma, while 2/4 were confirmed as de novo lesions. Herein, the authors describe their clinical experience, extensive radiological, morphological and immunohistochemical evaluation, and long term follow up of their two cases of de novo PDA. Authors also present review of literature on the immunohistochemical results of PDA and the possible role of targeted therapy. Ethics approval was waived by our Institutional Ethics Committee, in view of the retrospective nature of the study. All the tests/procedures described here had been performed for routine patient management and care. The study was performed in accordance with the ethical standards as laid down in the 1975 Declaration of Helsinki and its later amendments in the year 2000 and informed consent was obtained from the patients.

2. Case 1

2.1. Clinical summary

A 66-year-old diabetic and hypertensive male patient presented to the authors' clinic with a chief complaint of a painless, slowly progressive swelling on the outer aspect of the right upper eyelid of four months' duration. A firm to hard non-tender soft tissue mass was palpated in the right lacrimal gland region and subtle fullness was noted in the temporal upper lid sulcus. There was minimal proptosis with inferior displacement of the globe (Fig. 1a). Ocular motility was restricted in abduction and elevation. There was no regional lymphadenopathy.

2.2. Radiological findings

CT orbits showed a heterogeneous mass of the right lacrimal gland with slightly irregular but well delineated borders, separate from the insertion of the lateral rectus muscle and without any evident bony changes (Fig. 1b, c). With a clinico-radiological diagnosis of a lacrimal gland tumor, possibly pleomorphic adenoma, the patient underwent an excision biopsy. Intra-operatively, a well circumscribed mass of the right lacrimal gland was noted and was removed en bloc.

2.3. Pathology

2.3.1. Morphological findings

Gross examination revealed a relatively circumscribed, non-encapsulated, greyish white solid mass measuring 29x24x14mm (Fig. 2a), with tiny specks of calcification in the centre. Microscopic examination revealed a partially circumscribed tumor with intraductal and infiltrating components. Periphery of the lesion showed lacrimal gland tissue. The tumor was more cellular towards its periphery, paucicellular at the centre, with dense hyalinization and sclerosis (Fig. 2b; square bracket marked field is further explained in Fig. 2g). Involvement of the acini with in lobules, ducts and its branches was clearly identifiable. The intraductal component was seen as a high-grade ductal carcinoma-in-situ with solid, comedo and cribriform patterns (Fig. 2c, d, e). Amorphous and granular calcification was noted within the necrotic debris. Prominent desmoplasia and chronic inflammation were seen surrounding the in-situ component. The infiltrating component was seen as tubules, cord, trabecular and nest-like arrangement of malignant cells. Cells were polygonal, arranged in syncytium or had identifiable cell membrane, abundant eosinophilic to pale/vacuolated cytoplasm, hyperchromatic pleomorphic nuclei with conspicuous to prominent

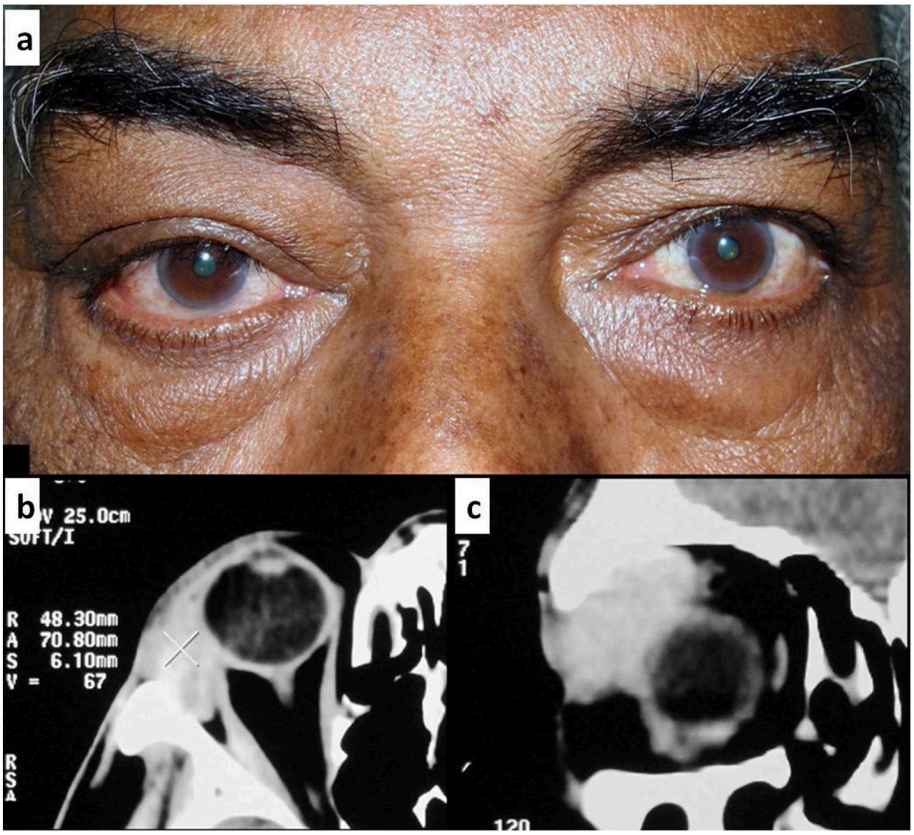

Fig. 1. Clinico radiological features of Case 1. Clinical examination revealed subtle right temporal upper eyelid fullness with minimal proptosis and slight inferior globe displacement (a). Imaging by CT showed a heterogeneous right lacrimal gland mass lesion with slightly irregular but well-defined borders (b, c). No changes were obvious in the adjacent bone.

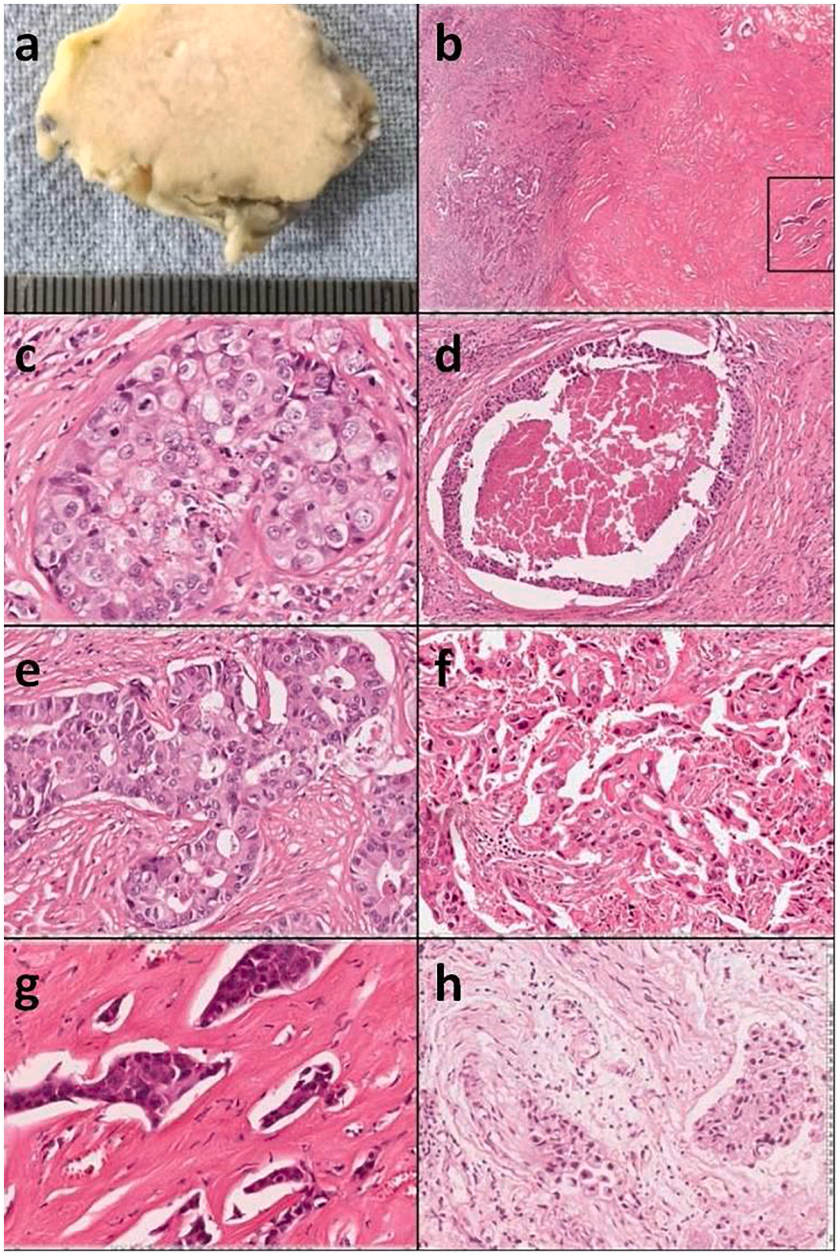

Fig. 2. Gross pathology of Case 1. Relatively circumscribed, non-encapsulated greyish white solid mass, with specks of calcification (a). Microscopy (Haematoxylin and Eosin stain) demonstrated a nodular lesion with peripheral cellularity and central hyalinization (a, original magnification X20; the square bracket marked field has been magnified in Fig. 2g). High grade intraductal component was seen as solid (c, X 400), comedo (d, X140) and cribriform patterns (e, X250). Lesional cells were polygonal with abundant eosinophilic to pale granular cytoplasm, pleomorphic nuclei with irregular nuclear membrane and conspicuous nucleoli (f, X200). Centre of the lesion was paucicellular, tumor cells were arranged in cords and trabecular pattern with dense intervening hyalinization (g: Inset in Fig. 2a; X300). Perineural and Intraneural invasion was noted (h, X200).

nucleoli (Fig. 2f). Bizarre cells were also noted. Brisk mitoses with atypical mitotic figures were observed. Mitotic count was 13/10hpf. Dense hyalinised, myxoid to cellular stroma was noted, predominant centrally, with interspersed cord-like arrangement of malignant cells. (Fig. 2g) Lymphovascular intra neural and perineural invasion was evident (Fig. 2h). Intra and periglandular lymph node involvement was also noted. Multiple sections and serial sections submitted did not show evidence of any component of pleomorphic adenoma.

2.3.2. *Immunohistochemistry*

Sections revealed expression of pancytokeratin, low molecular weight keratins-CK7 and CK19, (Fig. 3a, b) and Epithelial membrane antigen (EMA). There was no expression of high molecular weight keratin CK5/14 in the tumor cells. Tumor cells showed strong nuclear expression of Androgen receptor (AR; All red score of 8; Fig. 3c), cyclinD1, intense complete membrane staining of HER-2 (Fig. 3d) in 32% of cells and moderate complete membrane staining in rest of the cells (validated IHC scoring software-Aperio scanner).Ki-67 showed a proliferation index of 30–45% (Fig. 3e). Tumor cells did not express p53, ER, PR, PSA, GCDFP-15, and myoepithelial markers like SMA, p63 and p40. The hyalinised tissue also did not show expression of any of the myoepithelial markers. With a diagnosis of lacrimal gland ductal adenocarcinoma, systemic work up was requested.

2.4. *Systemic evaluation*

A detailed systemic oncology work up did not reveal any other primary malignant or metastatic foci (primary ductal adenocarcinoma; pT2a pN0 pM0 – AJCC 8th edition). Considering the aggressive nature of the tumor coupled with the presence of perineural and vascular invasion; the probability of local recurrence and systemic metastasis was deemed high and the patient was offered orbital exenteration with postoperative adjuvant radiotherapy. The patient declined orbital exenteration and received adjuvant radiotherapy.

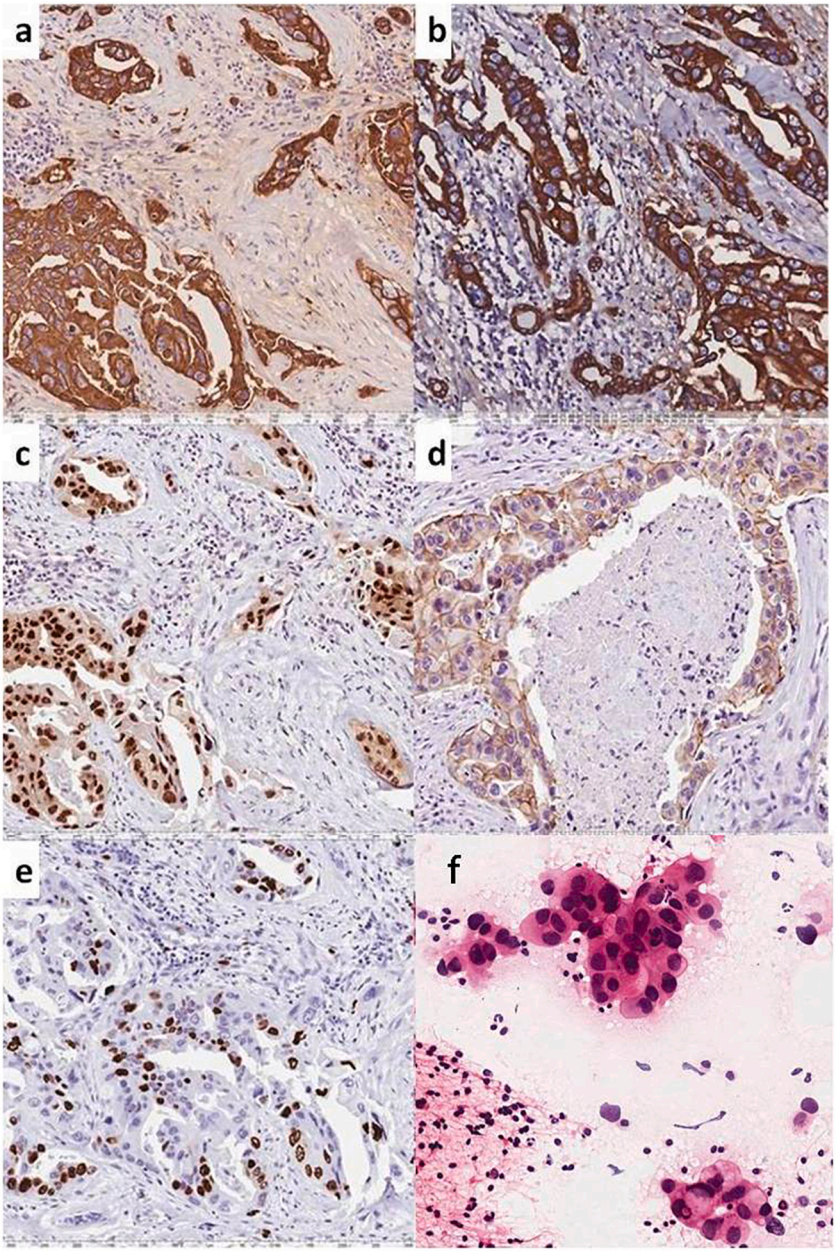

Fig. 3. Immunohistochemical evaluation. Demonstrated strong cytoplasmic expression of low molecular weight cytokeratin: CK7 (a, X150) and CK19 (b, X200).Strong nuclear expression of AR [Allred score of 8] (c, X150).Intense to moderate complete membrane staining of HER-2 in 32% and 68% of cells respectively (d, validated IHC scoring software; X200). Ki-67 showed a proliferation index of 30–45% (e, X150). Fine needle aspiration smear showed metastatic deposits (f, Haematoxylin &Eosin; X 260).

2.5. Follow up

At six months of follow up, he was doing well with no evidence of local recurrence or systemic disease.

At one year of follow up, he developed right pre-auricular lymphadenopathy. PET CT scan from skull to mid-thigh level revealed no activity in the entire body segment including the orbit except for the right cervical level 1(one) lymph nodes. Lymph node aspiration biopsy confirmed nodal involvement (Fig. 3f), following which neck dissection confirmed involvement of the right preauricular lymph node only. The patient received adjuvant chemotherapy (cisplatin with 5-fluorouracil) and was asymptomatic for 8 months.

At two years of follow up, he developed a nodal recurrence in the right pre-auricular region for which a radical neck dissection was performed followed by further adjuvant involved field radiation and chemotherapy.

He presented again to the authors' clinic after 30 months (2.6 years) of initial presentation with local recurrence of the disease. Examination revealed a firm, non-tender soft tissue mass, inferior to the right lateral canthus. Contrast enhanced CT scan revealed two space-occupying orbital lesions, one involving the right superior rectus and another involving the lateral rectus muscle. Bony erosion and extension into the right temporal fossa were observed. There was no evidence of intracranial extension. Incisional biopsy from both sites confirmed presence of tumor with morphology similar to the initial tumor except for the absence of any intraductal component. The patient was again counselled for exenteration. However, he refused and was referred for adjuvant radiotherapy. Intensity modulated radiation therapy was delivered over the next 6 weeks. The patient subsequently underwent an uneventful cataract extraction surgery in the right eye and recovered well.

The patient continued to be on regular periodic follow ups and was doing well without any further tumor recurrence. Recently, 6 years 3 months after the initial presentation, he reported with complete ptosis in the right eye that had progressively increased over the past 3 months. CT scan showed an extensive local recurrence with a poorly delineated soft tissue mass infiltrating the entire lateral half of the right orbit and the

optic nerve with bony erosion of the lateral wall and the roof of the orbit with intracranial and infratemporal fossa extensions. On consultation with the treating oncologist, he was advised for palliative chemotherapy.

3. Case 2

3.1. Clinical summary

A 58-year-old male patient reported to the authors' clinic with complaints of drooping of the right upper eyelid and painless protrusion of the right eyeball noted for the about a month. Hertel's exophthalmometry showed a proptosis of 7 mm on the right side and limitation of ductions in the right eye in all gaze directions.

3.2. Radiological findings

CT scan orbit showed a soft tissue mass lesion in the region of the right lacrimal gland with mild contrast enhancement and intralesional calcification. The mass was infiltrating the lateral rectus muscle. Bone changes were not evident. The patient underwent an incisional biopsy of the right orbital mass.

3.3. Pathology

3.3.1. Morphological findings

Incisional biopsy sections showed a relatively circumscribed non encapsulated mass comprising of a cellular tumor with central sclerosis and hyalinization (Fig. 4a). Periphery of the lesion showed lacrimal gland acini with atrophy, ductal hypertrophy and replacement of the glandular tissue by an infiltrating tumor arranged in tubules, cords, and nest-like arrangement of malignant cells (akin to that seen in case 1). There was perineural, intraneural and vascular invasion (Fig. 4b). Centre of the lesion showed extensive hyalinisation, necrosis with interspersed infiltrating tumor cells. Coarse linear-shaped calcification of the extensive necrosis was noted. (Fig. 4c) Spotty granular calcification of malignant cells was also noted.

3.3.2. Immunohistochemistry

The tumor cells expressed pan CK, CK7, CK19, and EMA. There was strong nuclear expression of p53, cyclin D1, AR(Allred score of 8), complete strong membranous expression of HER2 in more than 30% of cells (ASCO-CAP guidelines: validated IHC scoring software- Aperio scanner), and strong cytoplasmic expression of GCDFP-15.Ki-67 showed a proliferation index of 25%.Tumor cells did not express CK5/14, ER, PR, P40, P63, TTF-1 and PSA. The hyalinising stromal component did not show expression of SMA, S-100 or P63. Final histopathological diagnosis was ductal adenocarcinoma and systemic work up was advised.

3.4. Systemic evaluation

The clinical history was revisited to exclude a long standing pleomorphic adenoma or a recurrence/high grade transformation in a pleomorphic adenoma. The patient denied any previous history of mass lesion or surgery. A systemic work up failed to show any evidence of distant metastatic disease.

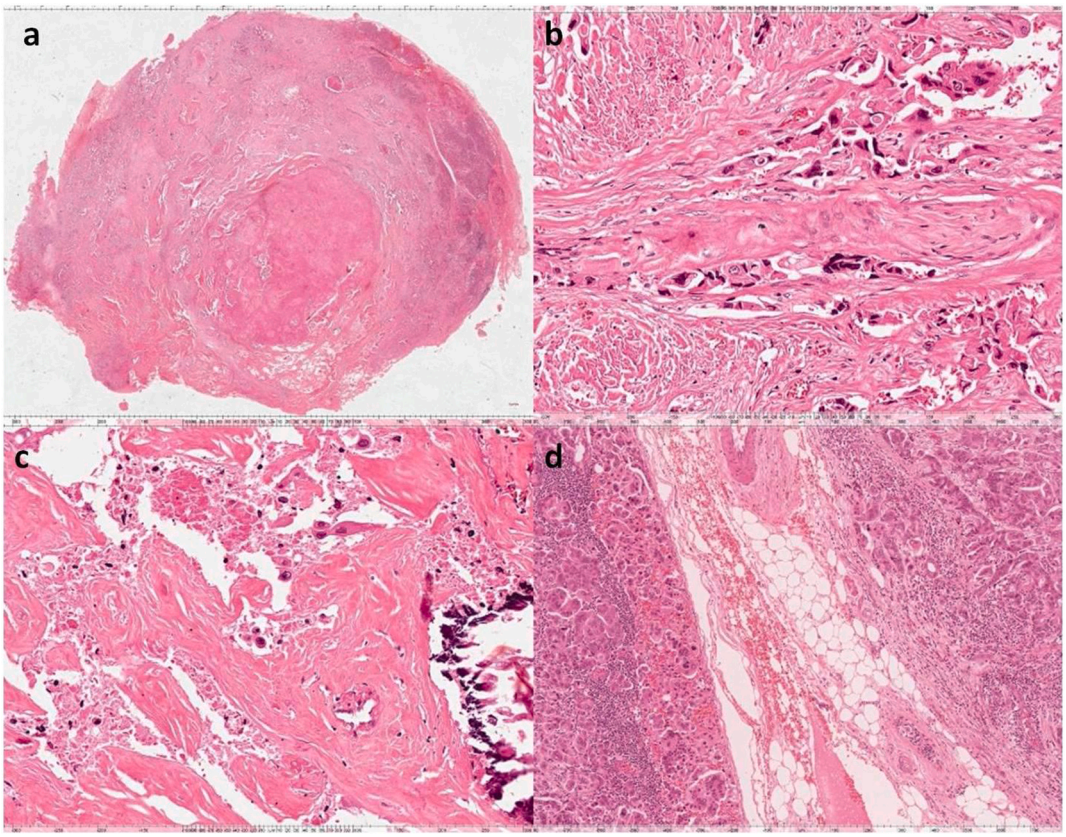

Fig. 4. Microscopic examination of Case 2. (Haematoxylin and Eosin stain) demonstrated a nodular lesion with partially retained lacrimal gland tissue in the periphery; lesion was more cellular in the periphery (a, original magnification X10). Hyalinized central, paucicellular lesion, neurovascular bundle noted with perineural and intravascular invasion (b, X200); necrosis and coarse linear calcification also noted (c, X200). Metatstatic tumor deposits were noted in the subcapsular sinus and cortex of lymph nodes with intervening perinodal connective tissue (d, X100).

3.5. Cytology findings

A week later after incisional biopsy, the patient was found to have enlarged right preauricular and submandibular lymph nodes. Fine needle aspiration biopsy of the enlarged lymph nodes confirmed an adenocarcinoma.

3.6. Subsequent surgical management and follow up

The patient underwent a lateral orbitotomy with debulking of the mass. Intraoperatively, the periosteum and the bony lateral orbital wall were infiltrated and the involved bone was removed by osteotomy. A modified neck dissection was also performed with the removal of pre-auricular, level 1a, 1b and level 2a, 2b cervical lymph nodes. Histopathology showed a predominantly infiltrating tumor (as explained above) with involvement of periosteum and Haversian canals of the bony lateral orbital wall. Level 2 B revealed 7 lymph nodes, largest node measured 21mmx18mm, all of which showed involvement by tumor (Fig. 4d) (pT3c pN1 pM0). There was perineural, intraneural and vascular invasion. The patient subsequently received adjuvant radiotherapy to the right lacrimal fossa and the involved field of the cervical lymph nodes along with chemotherapy.

He did well for almost a year when he was diagnosed to have metastasis in the urinary bladder for which he received chemotherapy.

Six months later, he developed CNS metastasis, and received further radiation and chemotherapy. Recently, three years after the initial presentation, the patient succumbed to his disease.

4. Discussion

Primary ductal adenocarcinoma of the lacrimal gland is a high grade aggressive tumor that arises from the ductal epithelium. It was first described by Katz et al. in 1996 [5].

The mean age at presentation is 58 years and it shows a striking male preponderance (3:1) [4]. Painless proptosis and an upper and outer eyelid swelling of short duration are the most common presenting symptoms [4]. One of our patients had a circumscribed mass and other had an infiltrative lesion with bone involvement. The incidence of bony involvement is reported to be 26%. Although the tumor usually does not initially present with locoregional or distant metastasis, local recurrence, nodal or distant metastasis may subsequently develop in 3%, 24% and 50% of cases respectively [4]. Our first case had episodes of extensive local recurrence that necessitated a repeat surgical intervention. Both of our cases developed loco-regional node metastasis and one patient developed distant metastasis within the follow up period. Treatment modalities have varied widely amongst the reported cases ranging from globe-sparing surgery to exenteration with or without adjuvant radiotherapy and chemotherapy. Follow up has ranged from 2 months to 17 years [3,4,6] and showed a 5-year survival rate of 40–66% [3,4]. Relatively short follow up, lack of definitive diagnostic criteria, lack or paucity of immunohistochemical correlation in several reported cases, pooling of cases of De novo presentation with possibly cases with high grade transformation in a pre-existing benign tumor and wide variations in treatment protocols has contributed to limited understanding of PDA. Recent literature, based on morphological, immunohistochemical and genetic evidences [7,8] suggests a role of targeted therapy. However, a review of published literature revealed only 2 cases that had received targeted targeted therapy, one of which succumbed to the disease and the other is currently on treatment with Transtuzumab having completed a follow-up period of 3 months only [4,9]. Literature describing tumor behaviour based upon morphology and immunohistochemical studies [3,10,11] have attempted to establish similarity between salivary duct carcinoma (SDC) and PDA of lacrimal duct and likeliness of their relationship with infiltrating ductal carcinoma of breast.

Estrogen receptor negative (ER-) breast cancers can be of basal (ER-; AR-) or molecular apocrine subtype (ER-; AR+), with the latter subtype having a higher frequency of HER2 overexpression. Immunohistochemical and gene expression studies have demonstrated that SDC resembles luminal AR; HER2 enriched type or basal type (CK5/6 and EGFR positive; AR negative) of breast cancer with clustering of SDC together with HER2 enriched or basal like breast tumors [12,13]. PDA, similarly to SDC is commonly reported to be ER- AR+, thus resembles luminal AR; HER2 enriched sub type of breast cancer. However, PDA has also been uncommonly reported to CK5/6 and EGFR with absence of AR expression, suggesting that it may also have basal subtypes.

Further adenocarcinoma of lacrimal gland may be a de novo lesion or a high-grade transformation in a pre-existing benign lacrimal gland neoplasm. Literature describes a case with history of a slowly progressive tumor of five years, with metastatic disease at presentation, expression of CK 5/6, and poor expression of AR (Allred score = 3) [7]. In addition, a recently published paper describes expression of CK 20 (3/13), CK 5(2/5) and S-100(1/14 cases) in PDA [4]. All these features as explained in the above published cases suggest that adenocarcinoma in these cases might have been a high-grade transformation in a pre-existing tumor. Literature on PDA is very similar to SDC and reports significant phenotypic and genotypic diversity, and inclusion of cases of adenocarcinoma ex pleomorphic adenoma [14] possibly has also contributed to the clinico morphological diversity in the literature of PDA. This may suggest a need to define purity in PDA, similar to existing concerns on defining purity in SDC. Authors in their work have excluded cases with high grade transformation in a pre-existing lacrimal gland tumor, by carefully revisiting the history, CT scans, submitting the tissue in entirety and performing extensive immunohistochemical examination to exclude myoepithelial component.

PDA of lacrimal gland and SDC perhaps closely resemble molecular apocrine subtype HER2 enriched breast cancer. Literature describes a cross talk between AR and HER2, and role of synergy in combined use of anti-androgen and anti HER2 therapy in reducing cell proliferation and increasing apoptosis in prostatic cancers and molecular apocrine subtypes of breast cancers [15], which might also hold promise in treatment of PDA with presence of actionable targets.

Authors are of an opinion that de novo primary ductal adenocarcinomas should be differentiated from cases that arise due to progression of a benign tumor, by a thorough clinical evaluation and extensive search for an identifiable low grade or a benign component, further complimented by immunohistochemical examination to exclude myoepithelial component in the cellular as well as the hyalinised paucicellular areas. PDA's should also be studied for presence of molecular apocrine or basal type differentiation. This will help in better understanding of tumor morphology, gene profile, and its behaviour and also help in identification of actionable targets and study the role of targeted therapy.

Authors have used the ASCO-CAP guidelines formulated for breast carcinoma for scoring of HER2 (using FDA approved antibodies) in PDA, due to lack of guidelines for scoring HER2 results for SDA and PDA of lacrimal gland.

In conclusion, despite a better understanding than in the past, PDA of the lacrimal gland continues to pose several diagnostic and management challenges. There is a need of strict diagnostic criteria, guidelines for scoring of AR and HER2 expression and a multi institutional study of whole genome sequencing of cases of de novo PDA versus adenocarcinoma in a pre-existing lacrimal gland tumor with high grade transformation. This will help in better identification of molecular targets and the role of targeted therapy and if needed in synergy. Currently, histopathology and immunohistochemistry remain the cornerstones of diagnosis as well as prognosis and plays a crucial role in the management of patients with this aggressive and often lethal tumor.

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