Clinical Case Report

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Primary poorly differentiated lacrimal gland adenocarcinoma in left ocular region

A rare case report

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Abstract

Rationale: Primary poorly differentiated lacrimal gland adenocarcinoma in the orbital region is an extremely rare type of neoplasm with only 1 related case in the literature. Its high grade of malignancy makes the timely data reported necessary. Hence, we present an extremely rare disease with biopsy results and recommendations on clinical treatment in an elderly male with Chinese descent.

Patient concerns: A 66-year-old Chinese man presented with swelling in the left ocular region and eyeball proptosis. On physical examination, the patient had redness, tenderness, and swelling of the left eye. A surgical incision was noted on the left orbital region. Left eye movements were restricted.

Diagnoses: Immunohistochemical examination revealed pan-cytokeratin (PCK, +), p63 (partial, +), cytokeratin 7 (CK7, +), cytokeratin 14 (CK14, +), epithelial membrane antigen (EMA, +), protein expressed by erythroblast transformation-specific related gene (ERG, −), S-100 (, −), Epstein–Barr virus-encoded small RNA (EBER, −), smooth muscle actin (SMA, −), and Ki-67 (with a proliferation index approximately 40%). After carefully reviewed the manifestations, imaging findings, and immunohistochemical evidences, a diagnosis of poorly differentiated adenocarcinoma of lacrimal gland was made.

Intervention: Based on the gene sequencing results, we started the patient with an intensive PF chemotherapy including a combination of cisplatine, fluorouracil, and epirubicin. Two months later, radiotherapy was introduced to the therapy regimen.

Outcomes: The patient responded well to the treatment without severe adverse events. MRI scan showed remarkable remission.

Lessons: This rare case report will help raise the awareness of high grade lacrimal gland cancer, and subsequently aid the diagnosis in future cases. Positive immunohistochemical markers of CK7, CK14, EMA, p63, and high proliferation index of Ki-67 can help establishing a diagnosis, and cisplatine–fluorouracil program is proved feasible. We share the difficulties we have encountered, hoping to improve patient care in the future.

Abbreviations: CEPA = carcinoma ex pleomorphic adenoma, CK7 = cytokeratin 7, CK14 = cytokeratin 14, EBER = Epstein–Barr virus-encoded small RNA, EMA = epithelial membrane antigen, ERG = protein expressed by erythroblast transformation-specific related gene, MRI = magnetic resonance imaging, PCK = pan-cytokeratin, PF program = cisplatine-fluorouracil program, SMA = smooth muscle actin.

Keywords: chemotherapy, immunohistology, lacrimal gland, primary poorly differentiated adenocarcinoma

1. Introduction

Primary poorly differentiated lacrimal gland adenocarcinoma in the ocular region is a type of malignant epithelial tumor mainly arising from the lacrimal gland.[1] To the best of our knowledge, only 1 case has been reported in the literature.[2] Most lacrimal gland tumors are glandular epithelial lesion. Approximately 10% of orbital tumors originates from lacrimal gland.[3] Adenoid cystic carcinoma is the most common epithelial orbital cancer, accounting for around 60% of malignant epithelial lacrimal gland tumors, followed by pleomorphic adenoma (20%), and other types making up 10% in proportion.[4–7] The diagnosis of a common orbital neoplasm is fairly simple, thanks to the great efforts of pathologists. However, diagnosing an atypical primary poorly differentiated adenocarcinoma is not as straightforward.[8] Due to the lack of population-based morphological and clinical behavior data, neither the diagnosis nor the treatment of this infrequent lesion is involved in any clinical guidelines. The high grade of malignancy and mortality urges the timely data being reported for further research.[2,9] Herein, we present a rare case report of primary poorly differentiated lacrimal gland adenocarcinoma in an elderly male with Chinese descent.

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Written informed consent was obtained from the parent for publication of this case report.

This case is not a clinical trial, so ethical approval was not necessary.

FX, WL, and JZ contributed equally to this work.

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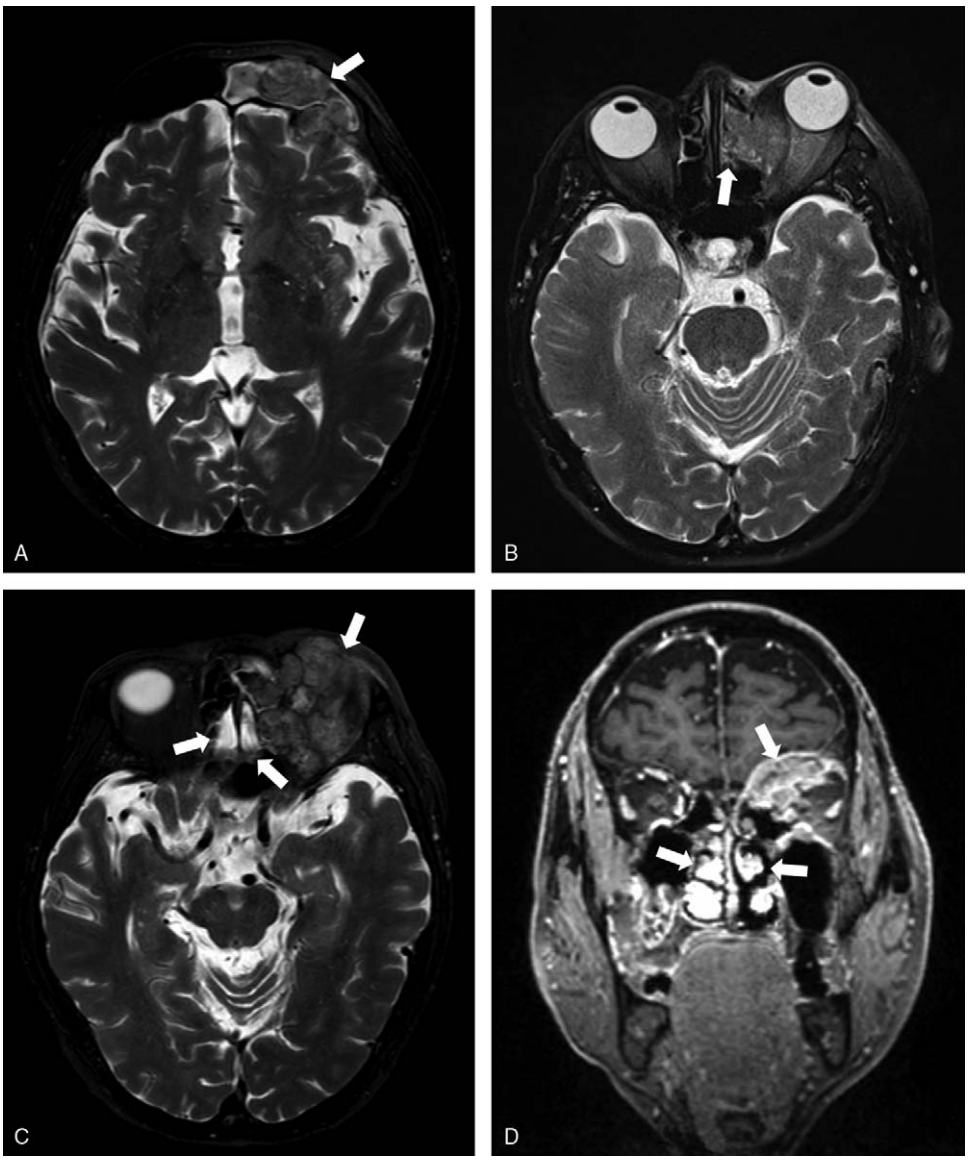

Figure 1. Magnetic resonance imaging of left ocular region. White arrows indicated the lesions. (A) Soft tissue mass in left frontal sinus, transverse section; (B) soft tissue mass in medial wall of left orbits and left ethmoid sinus, transverse section; (C) soft tissue mass in the bottom of left orbits and bilateral ethmoid sinus, transverse section; (D) soft tissue mass in bilateral ethmoid sinus, coronary section.

2. Case presentation

A 66-year-old Chinese man presented with a 5-week history of left eyeball proptosis and progressive periorbital swelling. On physical examination, the patient had redness, tenderness, and swelling of the left eye. A surgical incision was noted on the left orbital region. Left eye movements were restricted. There were no palpable superficial lymph nodes. Systemic examination did not reveal other abnormalities. The patient subsequently underwent a magnetic resonance imaging (MRI) examination of the left orbital region. MRI scan demonstrated a $5.5 \times 4.0 \times 6.2$ cm mass with a cloddy heterogeneous signal in the medial wall of left orbital region. The lesion presented masses with obvious heterogeneous enhancement after contrast enhancement. The boundaries of tumors with medial rectus and superior rectus were dim, while it was clear with optic nerve. The left nasal cavity, left frontal sinus, and adjacent meninges were involved. Long T2 signals could be detected on right maxillary sinus and bilateral ethmoidal sinus (Fig. 1). Imaging examinations strongly indicated malignancy, and the gold standard was still dependent on pathological results. The patient had undergone an eye-sparing orbitotomy for the left orbital fullness in local hospital. Intraoperative frozen section analysis suggested that invasive poorly differentiated adenocarcinomas in the left orbit derived from lacrimal gland epithelium. The specimen of mass was sent to our hospital for further pathological consultation. The immunohistochemical examination revealed pan-cytokeratin (PCK) (+), p63 (partial, +), cytokeratin 7 (CK7) (+),cytokeratin 14 (CK14) (+), epithelial membrane antigen (EMA) (+), protein expressed by erythroblast transformation-specific related gene (ERG) (−), S-100 (−),Epstein–Barr virus-encoded small RNA (EBER) (−), smooth muscle actin (SMA) (−), Ki-67 (with a proliferation index approximately 40%) (Fig. 2A–H), which confirms the neoplasms arose from the ductal epithelium.

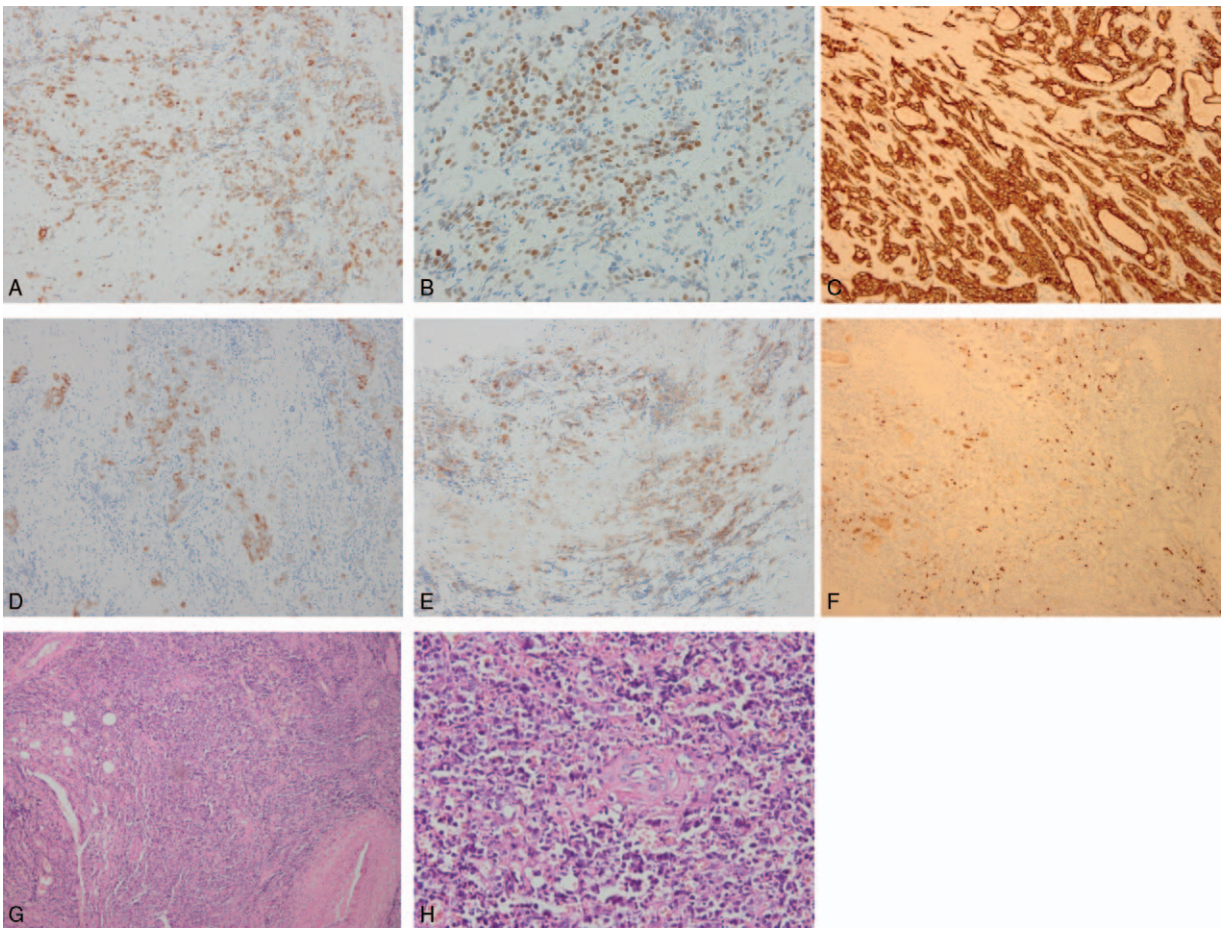

Figure 2. Histological findings of tumor samples from left ocular region. (A) PCK (×200). (B) p63 (×400), (C) CK7 (×200), (D) CK14 (×200), (E) EMA (×200), (F) Ki-67 (×100), (G) tissue sections on H&E stain (×100), (H) tissue sections on H&E stain (×400). EMA = epithelial membrane antigen, CK7 = cytokeratin 7, CK14 = cytokeratin 14, H&E = hematoxylin and eosin, PCK = pan-cytokeratin.

The clinical timeline of the patient is demonstrated in Fig. 3.

We started the patient on 2 cycles of standard PF chemotherapy (began on February 8, 2016 and February 16, 2016) (PF program: cisplatine–fluorouracil program, fluorouracil [day 1–5: 850 mg/m^2], cisplatine [day 1: 50 mg, day 2–5: 40 mg/m^2], calcium folinate [day 1–5: 200 mg/m^2]). After the first 2 courses of PF program, MRI scan of the left ocular region demonstrated that soft tissue mass next to the medial wall of left orbit was shrunk remarkably. However, after the 2 weeks of second chemotherapy course, the patient experienced a local recurrence. He came back with a left eye proptosis and swelling. Gene sequencing was performed for the purpose of optimizing the treatment regimen (on March 10, 2016). The result of gene sequencing indicated that the neoplasm is sensitive to all the 3 types of chemotherapy (Table 1). Based on the result of gene sequencing, we added epirubicin into his drug regimen. After another 2 courses of intensive chemotherapy (began at March 15, 2016 and April 17, 2016) (quaque 4 weeks): epirubicin (day 1: 65 mg/m^2), cisplatine (days 1–2: 500 mg/m^2), fluorouracil (days 1, 8, 15: 3000 mg/m^2), and calcium folinate (days 1, 8, 15: 0.5 g),

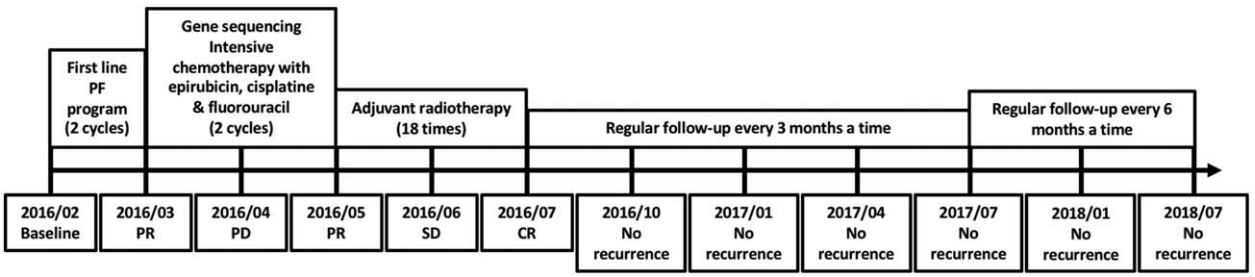

Figure 3. Treatment schema. CR = complete response, intensive program = cisplatine, fluorouracil, and epirubicin, PD = progressive disease, PF program = cisplatine and fluorouracil, PR = partial response.

Table 1

Gene sequencing results of the patient.

Project name	Gene name	Sequencing result	Gene status
Fluorouracil-related genes	DPYD*13 (1679T>G)	TT: wild type	Normal
	DPYD (2846T>A)	TT: wild type	Normal
	DPYD*2A (476002G>A)	GG: wild type	Normal
	GSTP1 (313A>G)	AG: heterozygous mutant	Normal
	MTHFR (677C>T)	CT: heterozygous mutant	Normal
	MTHFR (1298A>C)	AA: wild type	Normal
Doxorubicin-related genes	ABCB1 (3435T>C)	CC: homozygous mutant	Normal
Cisplatine-related genes	GSTP1 (313A>G)	AG: heterozygous mutant	Normal
	XPC (G>T)	GT: heterozygous mutant	Normal
	XRCC1 (1196T>C)	TC: heterozygous mutant	Normal
	ABCB1 (3435T>C)	CC: homozygous mutant	Normal
	MTHFR (677C>T)	CT: heterozygous mutant	Normal

ABCB1 = ATP-binding cassette subfamily B member 1, DPYD = dihydropyrimidine dehydrogenase, GSTP1 = glutathione S-transferase P1, MTHFR = methylene tetrahydrofolate reductase, XPC = xeroderma pigmentosum, complementation group C, XRCC1 = X-ray repair cross-complementing protein 1.

we started radiotherapy as an adjuvant therapy (from April 22, 2016 to June 30, 2016, SBRT [60 Gy], totally 18 times, with no obvious adverse events). MRI scan revealed remarkable remission (Fig. 4).

The regular follow-up is performed. We follow this patient up every 3 months in the first year after discharge, and then the follow-up frequency turns to be every 6 months a time. Based on the recent follow-up on July 2018, the condition of this patient is good, without tumor recurrence.

3. Discussion

Tumors of the lacrimal glands represent around 10% of all orbital masses. The epithelial malignant tumors of the lacrimal gland constitute 4% of all lacrimal gland tumors.[10] The less common epithelial carcinoma are carcinoma ex pleomorphic adenoma (CEPA), mucoepidermoid carcinoma, and adenocarcinoma.[11] These malignancies are usually presented with similar symptoms and imaging findings. Only pathology and histological characteristics could guide more accurate diagnosis.

This case presents a primary poorly differentiated lacrimal gland adenocarcinoma without any specific immunohistochemical markers in the orbital region. In the previous literature, diagnostic criteria for a high grade lacrimal gland adenocarcinoma included epithelial poor differentiation, increased mitotic activity in higher power field, Ki-67 > 10%, bone invasion, and necrosis. They are found to be indicators of an aggressive biology.[11] Relatively, high grade lacrimal gland adenocarcinoma presents with no specific characteristics in morphology. It could be associated with an intense immunoreactivity for gross cystic disease fluid protein 15 (GCDFP-15), which was mentioned in only 1 reported case.[2] Histopathological evaluation remains as the gold standard for diagnosis. On H and E stain, poorly differentiated tumor cells are in abnormal hyperplasia. Immunohistochemical methods could further determine the origin of the neoplasm. In this case, the tumor showed immunoreactivity for PCK, EMA, p63 (partial positive reaction), CK7, and CK14. Stains for ERG, S-100, EBER, and SMA were negative. The positive biomarkers revealed that the neoplasm arose from the epithelium of lacrimal gland. In addition, PCK,

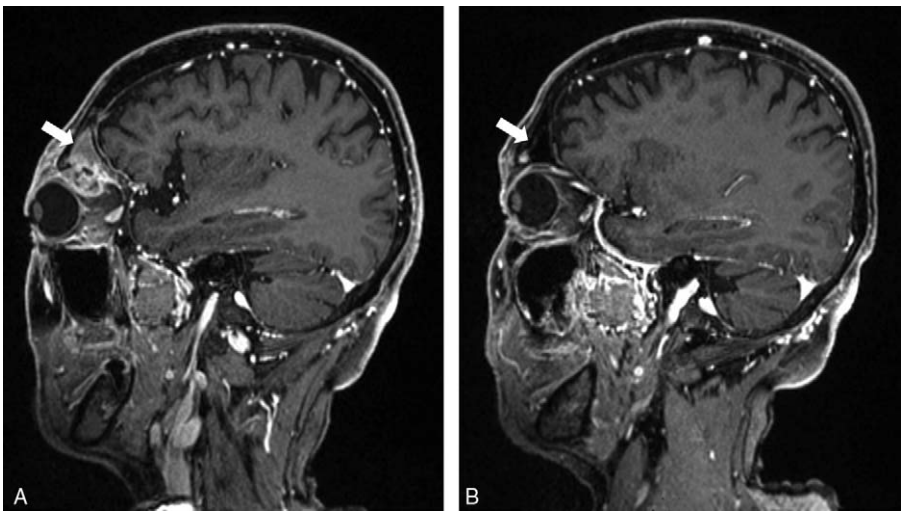

Figure 4. Magnetic resonance imaging of left ocular region before and after therapy. White arrows indicate the change of lesions. (A) Neoplasm and soft tissue mass in left frontal sinus before chemoradiotherapy, sagittal section; (B) lesions disappeared in left frontal sinus after chemoradiotherapy, sagittal section.

Table 2

Clinical characteristics of 3 less common epithelial carcinoma of lacrimal gland.

Tumor types	Clinical symptoms and signs	Pain[12]	Tumor characteristics	Immunohistochemical staining patterns
Carcinoma ex pleomorphic adenoma	Eyeball proptosis, redness and swelling of eyeball, retrobulbar resistance, restricted eye motility, diplopia[12]	+	Malignant component coexisted in or arised from benign component, with no specific characteristics.[3]	p53, HER2, AR[14]
Adenocarcinoma		+	No specific histological characteristics	No evaluated specific biomarkers. CK7, CK14, EMA, p63, GCDFP-15 may have potential diagnostic value[2]
Mucoepidermoid carcinoma		–	A mixture of mucin columnar produce cells, polygonal intermediate cells, epidermoid (squamous) cells[8]	p63, CK5, CK6, CK7, HER2, EGFR[13]

AR = androgen receptor, CK5 = cytokeratin 5, CK6 = cytokeratin 6, CK7 = cytokeratin 7, CK14 = cytokeratin 14, EGFR = epidermal growth factor receptor, EMA = epithelial membrane antigen, GCDFP-15 = gross cystic disease fluid protein 15, HER2 = human epidermal growth factor receptor 2.

EMA, CK7, CK14, and p63 are common indicators for epithelial malignancies. The tumor showed negative immunoreactivity for SMA, which is overexpressed in myoepithelium, suggesting that the tumor did not derive from myoepithelium. Moreover, the positive reactivity of CK7, CK14, and EMA could reveal that the tumor derived from glandular epithelium. The diagnosis of a primary poorly differentiated lacrimal gland adenocarcinoma can be established based on the high proliferation index of Ki-67 (>10%), hematoxylin and eosin stain, and immunohistologic evaluation.

When it comes to primary poorly differentiated lacrimal gland adenocarcinoma, differential diagnosis is a challenge. Compared to CEPA and mucoepidermoid carcinoma, primary poorly differentiated lacrimal gland adenocarcinoma has a similar age of onset and clinical symptoms such as proptosis, displacement of the globe, retrobulbar resistance, restricted eye motility, and diplopia. However, periorbital pain is a relatively common complaint in patients with adenocarcinoma while the other 2 neoplasms are usually painless. Patients with CEPA and mucoepidermoid carcinoma almost never complaint of periorbital pain.[12] Comparing the duration of symptoms, both adenocarcinoma and CEPA occurs in a year while the mean duration of mucoepidermoid carcinoma lasts from 1 to 2 years.[11] A previous publication demonstrated that mucoepidermoid carcinoma of lacrimal gland could be strongly stained with p63.[13] Based on the morphology of tumor tissue and clinical signs of patients, mucoepidermoid could be ruled out. CEPA is considered to be a type of carcinoma that exhibits histological features of benign pleomorphic adenoma.[14] Residual benign pleomorphic adenoma with transition zones between benign and malignant components could be seen on biopsy specimen. The malignant components of CEPA are usually adenocarcinomas while other types could be seen occasionally.[12] Ideally, with the help of histopathologic evaluation, CEPA could be excluded (Table 2).

Primary poorly differentiated lacrimal gland adenocarcinoma is a disease of diagnostic challenge and no available guidelines. Due to the complexity of orbital anatomy, a complete surgical resection is limited. Concurrent chemoradiotherapy could be beneficial to achieve partial remission. However, this rare clinical disease is barely related to standard management guidelines in the existing documents. In this case, PF program was firstly used and then epirubicin was added into the drug regimen based on the results of gene sequencing. The patient underwent intensive chemotherapy followed by radiation therapy. The outcome proved the effectiveness of this therapy. The role of adjuvant radiation therapy to improve recurrence-free rates in malignant epithelial neoplasms of the lacrimal gland is also emphasized by Skinner et al.[15] It was investigated that patients who did not receive adjuvant radiation therapy developed local recurrence earlier than those who did, especially malignant tumors.[11]

In the literature, a related clinical prospectively research mentioned that PF program could be used in lacrimal gland carcinoma. However, no published data can support the statement.[16] Hence, this case study would be the first case using PF program in the treatment of lacrimal gland carcinoma in the literature.

In conclusion, we describe a rare case of primary poorly differentiated lacrimal gland adenocarcinoma in the orbital region through manifestations, imaging findings, and immunohistochemical evidences. Positive pathological markers of CK7, CK14, EMA, p63, and high proliferation index of Ki-67 could help establish a correct diagnosis. Additionally, it is proved that PF program shows therapeutic valuable in treating lacrimal gland carcinoma, especially in atypical high grade lacrimal gland tumors. Gene sequencing could guide drug choices and help find a better treatment regimen. It is quite a diversity in the features of epithelial neoplasm of the carcinoma in lacrimal gland with nonspecific makers, where more research should be carried on to optimize clinical diagnosis and treatment.

Author contributions

Data curation: Fan Xia, Wenwu Ling, Yifan Zhang.
Funding acquisition: Wenwu Ling.
Investigation: Jing Zhang.
Project administration: Xuelei Ma.
Resources: Fan Xia.
Validation: Jing Zhang.
Writing – original draft: Fan Xia.
Writing – review & editing: Fan Xia, Yifan Zhang.

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