Peer Review File

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Review Comments

Comment 1: I believe that discussion needs to be improved.

Reply 1: Thank you for your criticism. We have developed the discussion section. Specifically, we have discussed the diagnosis, treatment and recent progress in this disease more in detail in the revised manuscript (see Page 7, line21-Page 11, line1).

Changes in the text: Discussion

Tumors of the lacrimal sac are exceedingly rare with more than half being malignancies (9). The most common clinical symptom of lacrimal sac tumors is epiphora (10). As the tumor progresses, patients may experience new symptoms such as lumps, skin swelling and ulceration. However, due to poor specificity of these clinical symptoms and low incidence of lacrimal sac tumors, they could easily to be misdiagnosed, especially when in its early stage. Indeed, the present patient had a history of epiphora and nasal congestion for one year. He was diagnosed and treated as chronic dacryocystitis at the local hospital, but the symptoms were not improved. Therefore, we need to be alert to the possibility of malignant lacrimal sac tumors in patients with chronic dacryocystitis who had poor respond to standard treatments (11). ACC is an extremely rare form of malignant epithelial carcinoma of the lacrimal sac. ACC tends to have slower growth kinetics compared with other carcinomas but local recurrence and distant metastasis are frequently observed several years after resection(12). High capacity of perineural or perivascular invasion is thought to be critical in disease recurrence and metastasis (4,13). Lacrimal sac tumors tend to be

locally invasive into adjacent structures while lymph node metastasis of epithelial neoplasms of the lacrimal sac is not frequent, with less than one third of malignant cases reportedly spreading to the preauricular, submandibular, or cervical lymph nodes (9,14). On the contrast, hematogenous spreading of ACC is rather common, mainly involving the lungs, the liver, and the bones (4,12). In our case, the patient presented with tumor mass infiltrating into neighboring bones but without cervical lymphadenopathy. Histopathologically, ACC can be classified into three subtypes, namely the tubular (highly differentiated), the cribriform (moderately differentiated), and the solid ACC (poorly differentiated), in which the cribriform ACC is the most common subtype with the best prognosis while the solid ACC is rarest with poor prognosis (4,10,15). The present case demonstrated a cribriform subtype, indicating that the patient might have a relatively good prognosis.

Given the rarity of ACC of the lacrimal sac, there is currently no standard treatment. Most of the guidance for treatment of this tumor comes from the experience of ACC of the orbit. Complete excision of the tumor and lacrimal drainage system followed by radiotherapy with or without adjuvant chemotherapy was still the main treatment for ACC of the orbit (16-18). However, there are also argues that surgery in this area often involves orbital exenteration that would substantially impair the quality of life and raise psychological and psychiatric disorders in patients (11,19), while the prognosis might not necessary be improved (20). Therefore, extensive surgery should be carefully evaluated for patients with ACC of the lacrimal sac, especially in young patients such as that in the present case. Our observational study suggested that for those who are ineligible (for example old age or with comorbidities not allowing surgery) for surgical excision or unwilling to get surgery (such as that in this case),

radical concurrent chemoradiotherapy might be a choice in selected cases, given clear understandings of potential failure and side effects.

The patient in our case was relatively young with locally advanced disease (cT4aN0M0), who refused orbital exenteration surgery with concerns of vision damage and facial disfigurement but instead received concurrent chemoradiation combined with an anti-angiogenesis therapy with apatinib. The patient experienced moderate adverse effects that were manageable with symptomatic supportive treatment. The outcome was satisfactory until 22-month post-treatment, with no signs of local recurrence or distant metastasis. In addition, we consider that surgery might still be a salvage treatment if the disease recurs. Our study showed that the addition of apatinib seems to synergize with chemoradiotherapy to enforce the tumor response, although we could not tell the net effect of apatinib or chemoradiotherapy separately. Apatinib is a selective VEGFR2 tyrosine kinase inhibitor that act to inhibit endothelial cell proliferation and migration (21,22). In 2014, apatinib was firstly approved as a third-line treatment for advanced gastric cancer in China (23). Since then, more cases have reported active antitumor activity of apatinib in various advanced cancers. At present, a number of trials of apatinib in relapsed/metastatic ACC of head and neck are ongoing (NCT02775370, NCT02942693). Wang et al. reported anti-cancer effects of apatinib in a case with metastatic tracheal ACC (7). However, no data regarding the role of apatinib in locally advanced ACC was available. Our case study provided important clue that apatinib might be active and safe in the locally advanced ACC when combined with concurrent chemoradiotherapy.

In conclusion, potentially curative strategies such as combining local radical

radiotherapy and systemic therapies might provide alternative opportunity for patients with ACC of the lacrimal sac that are ineligible for or rejective to surgical treatment. Our case report is the first to demonstrate that apatinib combined with concurrent chemoradiotherapy might yield durable complete response in locally advanced ACC. Longer term efficacy remains to be determined.

Comment 2: more references in the discussion.

Reply 2: Thank you for your suggestion. We have extended the discussion and added new references in the revised manuscript (see Page 11, line17-Page 14, line12).

Comment 3: more photos presurgery and post treatment and endoscopic view.

Reply 3: Thank you for pointing out this important issue. We have considered to put the endoscopic data to better illustrate the clinical manifestation and the treatment outcome. However, the endoscopic view was not available since the patient did this exam in the local hospital and that he did not well keep these data. Nevertheless, we manage to obtain the facial skin morphology data before and after the treatment. With the consent of the patient, we added this information in the revised Figure 3. Noted that in this case, the patient only received biopsy but not surgical resection (see Page 7, line13).

Changes in the text: We have marked the Figure 3 following the sentence "The complete response of the tumor maintained until the latest follow-up by December 2020, 22 months post the combined therapy and the patient stay asymptomatic without significant side effects (Figure 3)."

Comment 4: in a current practice a postoperative pet-CT is necessary to see possible recurrence or persistence of the disease. Is not mentioned.

Reply 4: Thank you for your point of view. We agree that a PET-CT combined with orbital MRI should be better to evaluate the disease status in this case. However, since PET-CT is relatively expensive and could not be reimbursed at the moment, it is not a regular tool for patient follow-up evaluation. Instead, to rule out the possibilities, we ask the patient to undergo regular (every three month) head and neck MRI, orbital MRI, thoracic CT, liver MRI and yearly bone scintigraphy that evaluate main organs vulnerable to disease recurrence and metastasis. Until the last follow-up, no sign of disease recurrence and metastasis has been detected (see Page 7, line11-13).

Changes in the text: The complete response of the tumor maintained until the latest follow-up by December 2020, 22 months post the combined therapy and the patient stay asymptomatic without significant side effects.

Comment 5: after surgery the tear drainage was restored; test Jones 1 and 2 was permormed?

Reply 5: The patient went on regularly routine ophthalmological examination and reported no significant abnormalities regarding vision and tear drainage.

Changes in the text: None

Comment 6: frequently lacrimal sac tumors gives latero-cervical metastases was not mentioned.

Reply 6: Thank you for your comment. In this case, we did not detect any cervical

lymph node metastasis both on clinical physical examination and MRI exanimation. We mentioned this in the revised manuscript (see Page 5, line17-19 and Page 6, line 1-6).

Changes in the text: There were no ocular proptosis or eye movement abnormality, no significant sign of cutaneous involvement and cervical lymph node metastasis.

The patient completed a magnetic resonance imaging (MRI) of the orbit, nasal cavity, paranasal sinus and the neck area, which revealed a mass occupying the left lacrimal sac and the left naso-lacrymal duct area, invading into the left maxillary sinus, the left orbit, and the left ethmoid sinus (**Figure 1B**). No sign of distant metastasis was observed by the CT scan of the thorax, the MRI of the abdomen and the bone scintigraphy.