Case Report

# Successful management of adenoid cystic carcinoma of the lacrimal sac with apatinib combined with concurrent chemoradiotherapy: a case report

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**Abstract:** Adenoid cystic carcinoma (ACC) of the lacrimal sac is an extremely rare disease with a poor prognosis. There is currently no standard treatment for this malignancy. Radical surgical excision followed by radiotherapy and chemotherapy is the preferred treatment for localized ACC of the lacrimal sac. Apatinib has shown efficacy in recurrent/metastatic ACC. The role of apatinib in combination with concurrent chemoradiotherapy in patients with non-operated localized advanced ACC is not clear. Here, we report a 30-year-old man with a 1-year history of epiphora of the left eye and nasal congestion who was diagnosed as ACC of the lacrimal sac. The computed tomography (CT) scan showed the tumor invading the left orbit and left maxillary sinus. He refused surgical resection and instead received combined apatinib and nedaplatin-based concurrent chemoradiotherapy. He experienced moderate adverse effects such as nausea, hypertension, myelosuppression that were well controlled after symptomatic supportive care. Complete response was observed 3 weeks following the treatment. The patient remained free of disease until the last follow up by December 2020, 22 months after the treatment. This case suggested that combined apatinib and concurrent chemoradiotherapy might be an option for locally advanced ACC patients who are ineligible for or rejective to surgical resection.

**Keywords:** Adenoid cystic carcinoma; lacrimal sac tumor; apatinib; concurrent chemoradiotherapy; case report

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## Introduction

ACC of the lacrimal sac is an extremely rare malignant tumor, most patients present with non-specific clinical manifestations such as epiphora and lacrimal sac mass, which is often misdiagnosed as chronic dacryocystitis or lacrimal duct obstruction (1). Consequently, diagnosis is often delayed and the prognosis is poor (2). There is currently no standard treatment for ACC of the lacrimal sac. Radical surgical excision followed by radiotherapy and chemotherapy is the preferred treatment to prevent disease recurrence and metastasis (3). Moreover, multiple new agents targeting specific genetic alterations or neo-angiogenesis in ACC are under investigations (4). Among them, apatinib, a highly selective VEGFR2 inhibitor against tumor angiogenesis as well as VEGF-mediated cell proliferation, tumor invasion and migration, has shown potential anti-cancer effect in recurrent/metastatic ACC (5-7). However, its role in localized ACC is not clear. Whether apatinib combined with chemoradiotherapy might be an alternative treatment for patient ineligible or rejective to surgical resection has not been investigated.

Here, we report a durable complete response in a case

of apatinib combined with concurrent chemoradiotherapy for locally advanced ACC of the lacrimal sac who refused to surgical resection. The treatment has achieved positive effect and the patient is still under scheduled follow-up without signs of disease recurrence of metastasis.

We present the following article in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1934).

## Case presentation

A 30-year-old man with a 1-year history of epiphora of the left eye and nasal congestion was admitted to our department on December 13, 2018. Before admission, a nasopharyngoscope performed in another hospital had shown a pink irregular neoplasm with purulent secretions in the right middle turbinate and left nasal tract. In addition, a computed tomography (CT) scan of the nasal cavity and paranasal sinus indicated a soft tissue mass in the left nasal cavity with bone destruction of the medial wall of the left maxillary sinus, the medial wall of the left orbit, the inferior wall of frontal sinus, and the left ethmoid sinus. Consecutively, the patient had received a nasal cavity mass biopsy on December 5th, 2018 that revealed an adenoid cystic carcinoma (cribriform) of the lacrimal sac origin. The immunohistochemical (IHC) staining showed that CD117 (focal positive), CK7 (focal positive), EMA (focal positive), CAM5.2 (focal+), CK5/6 (focal positive), P63 (focal positive), SOX-10 (positive), Vimentin (positive), p53 (positive), and the Ki-67Li was about 20% (*Figure 1*).

On admission, a solid, immobile soft-tissue mass with a diameter of 2 cm was palpable anterior to the left lacrimal sac of the patient. There were no ocular proptosis or eye movement abnormality, no significant sign of cutaneous involvement and cervical lymph node metastasis. The pathologist in our institute confirmed a cribriform ACC of the lacrimal sac (*Figure 1A*). For medical history, he had no other medical history and denied any smoking or drinking history. No family history of cancer was reported. 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. The patient was diagnosed with ACC of the lacrimal sac, stage IVA (cT4aN0M0, based on the AJCC cancer staging system, 8th edition, 2017) (8). We recommended an extended excision of the tumor followed by radiotherapy. However, considering the impact of facial disfigurement and the possibility that the surgery could not obtain negative margin, the young patient refused the operation and asked for conservative treatment instead. After weighing carefully about the pros and contras of radiotherapy-based treatment, the patient decided to receive concurrent chemoradiotherapy in combination with apatinib, a novel selective anti-VEGFR2 agent. He initiated oral apatinib (0.5 g, daily) since December 17, 2018, while waiting for radiotherapy. He received radiotherapy from December 24, 2018 to February 3, 2019 by means of TomoTherapy HD with prescribed doses as follows: PTV-GTVp of 70 Gy in 31fractions, PTV-CTVp of 60 Gy in 31fractions; PTV-CTV2 of 54 Gy in 31fractions (*Figure 1C*) and with targeted volume shown in *Figure 1D*. In addition, the patient received concurrent chemotherapy with nedaplatin (50 mg, weekly) and continued to take apatinib orally (0.5 g, daily).

The main treatment-associated adverse reactions included a temporarily elevated blood pressure (160/110 mmHg), grade II nausea, grade II leukopenia, grade III radiation dermatitis, all of which were improved after symptomatic supportive treatments. However, after three weeks of the combination therapy, the patient developed intermittent epistaxis, so the dose of apatinib was reduced to 0.25 g per day from January 14, 2019. In the fifth week of the combined therapy, the patient developed wet exfoliation in the radiotherapy area, with increased risk of skin necrosis and rupture. Therefore, the use of apatinib was discontinued on January 30, 2019 (*Figure 1C*). A review of the head and neck MRI three weeks post the combined therapy showed that the lesions almost completely disappeared. The subsequent scheduled follow-up every three months showed no obvious signs of recurrence and metastasis (*Figure 2*). 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*).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

## Discussion

Tumors of the lacrimal sac are exceedingly rare with more

 

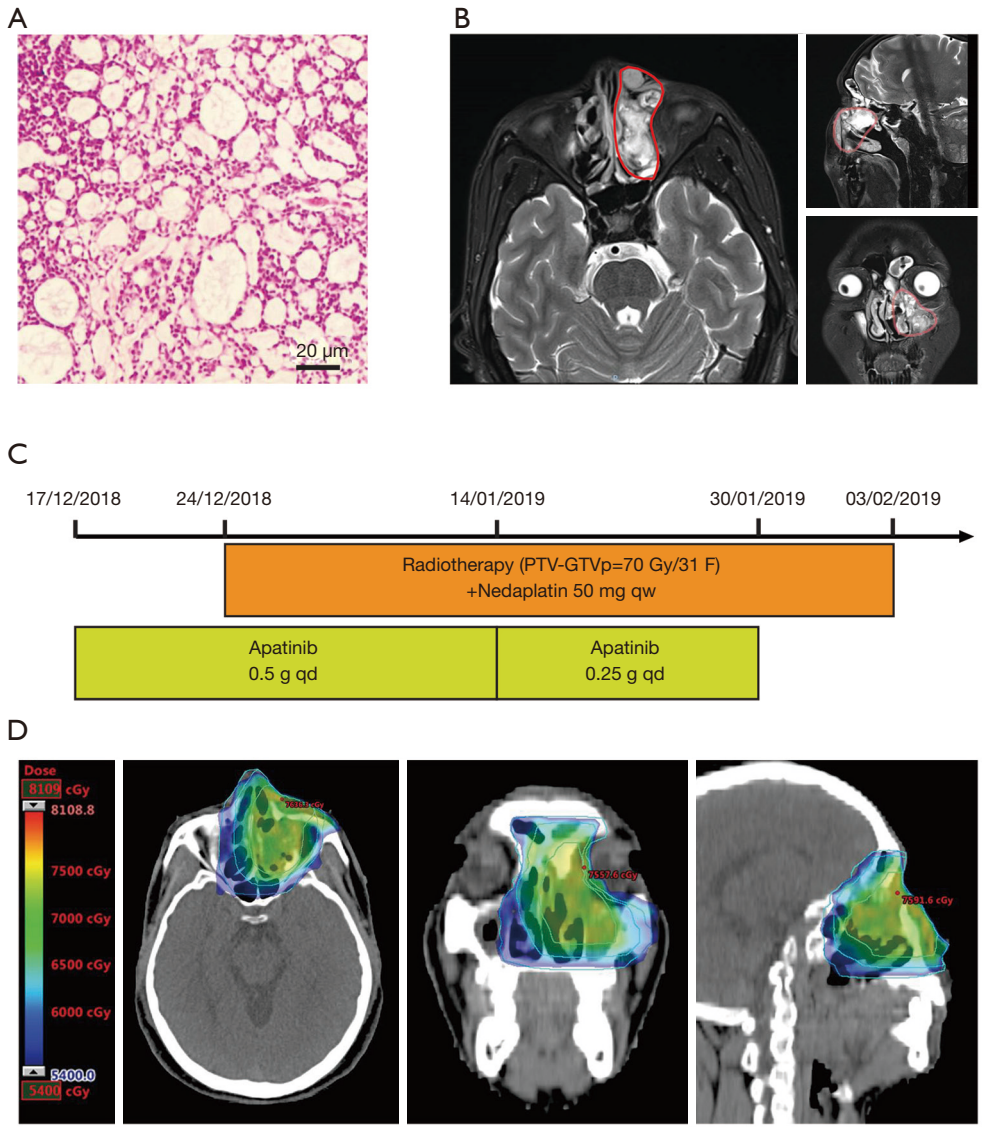


**Figure 1** HE staining (A), MRI manifestations (B), treatments (C) and radiotherapy protocol of the case (D). The red circles in Figure 1B indicated the extent of the lesion displayed in the transverse (left), sagittal (upper right), and coronal (lower right) planes, respectively.

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

 

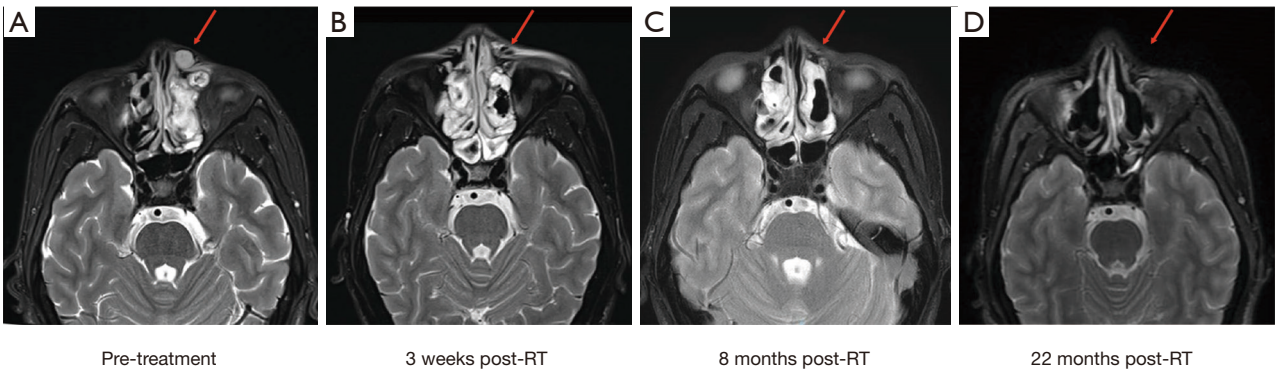


**Figure 2** Follow-up and treatment efficacy of the case. Red arrow indicates the area of previous tumor.

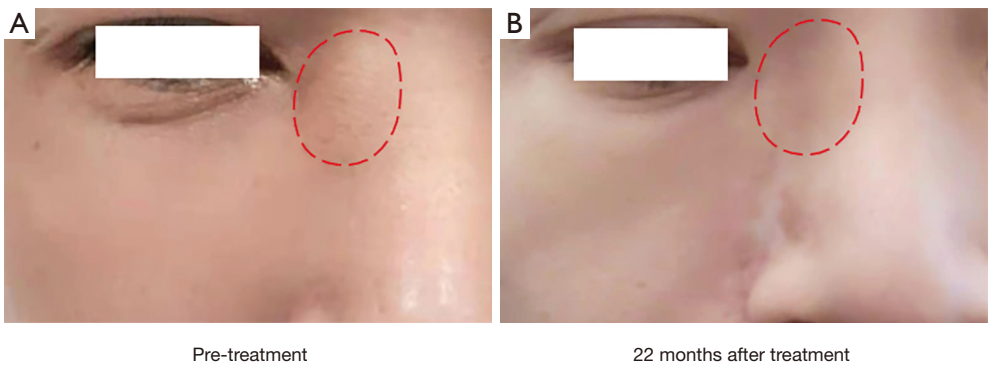


**Figure 3** Facial skin morphology recovery after the treatment.

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.

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## Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-1934

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this study and any accompanying images.



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