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Case Report

Clinicopathological characterization of adenoid cystic carcinoma of the esophagus: a case report and literature review

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Abstract: Adenoid cystic carcinoma of the esophagus (EACC) is an infrequent malignancy prone to misdiagnosis because of it sharing similar histological patterns with other esophageal tumors. In this work, we comprehensively studied the pathological features of EACC based on a 53-year-old male patient. Histological examination revealed that the lesion presented three types of classical structures, including tubular, cribriform and solid patterns. Immunohistochemical analysis indicated that myoepithelial cell markers CD10 and P63-labelled cells locate in the outer layer of tubular and cribriform patterns, whereas glandular cell markers CK7 and CK8 positive cells accumulate in the inner layer of these patterns. As EACC develops from tubular and cribriform patterns to solid pattern, CK7 and CK8-labelled inner cells gradually disappeared, while P63-positive cells diffusely penetrated into entire tumor mass in the solid pattern. Additionally, it was found that enhanced staining of EMT (Epithelial to mesenchymal transition) marker vimentin in the course of the progression of EACC. These new identified immunohistochemical characters combined with classical histological patterns may not only facilitate precise diagnosis of EACC, but also help in developing targeted therapy for this malignancy.

Keywords: Adenoid cystic carcinoma, esophagus, P63, vimentin, EMT, diagnosis

Introduction

Adenoid cystic carcinoma (ACC) is a common malignant tumor of salivary gland, which is also often occurs in trachea, breast, skin, external auditory canal, the prostate gland, uterus, neck and other tissues. It is rarely found in the esophagus, accounting for just about 0.1% of the total incidence of esophageal malignancies [1]. Adenoid cystic carcinoma of the esophagus (EACC) is generally thought to be originated from esophageal submucosal glands [2]. Middle esophagus is the common place for EACC occurrence. EACC can be divided into three types in accordance with histological characteristics: tubular pattern, cribriform pattern, and solid pattern [3-5]. Compared to other malignant tumors of the esophagus, EACC is poor in prognosis, with stronger invasiveness, prone to distant metastases. Clinical data showed that the lesions were often surrounded with other types of adenocarcinoma or squamous cell carcinoma, making it easily misdiagnosed [2, 6-8]. This study reported a comprehensive examination on clinicopathological features of EACC, through combining classical histological analysis with specific immunohistochemical assays.

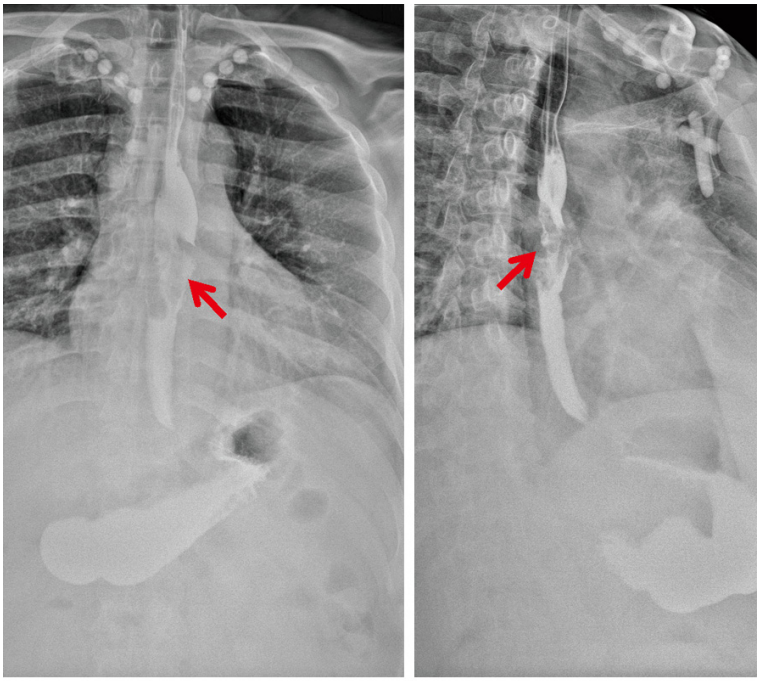

Figure 1. Esophagogram showing filling defect and mass shadow in the middle of the esophagus (red arrow indicated).

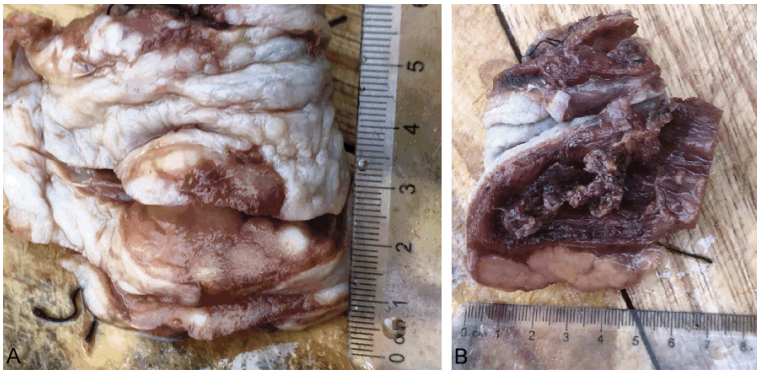

Figure 2. Gross appearance. Surgical specimen showing a protuberant lesion covered by apparently normal esophageal mucosa with slight depression in its vertex.

Case report

A 53-year-old male was under out-patient examination for one-month history of dysphagia in the outer court. Gastroscopy showed lesions located in the middle of the esophagus, diagnosed as poorly differentiated squamous cell carcinoma. Later transferring patient to our hospital (Cancer Hospital, Chinese Academy of Sciences, Hefei), barium radiography of upper gastrointestinal tract was performed. Barium swallow was blocked in the middle of the esophagus (trachea juga below). A 6.5 cm long of irregular filling defect and mass shadow were presented in the middle of the esophagus, accompanied with local mucosal disruption and lumen narrowing (**Figure 1**). The rest of esophagus didn't show apparent expansion and anomalies. Cardia of stomach opened freely. Stomach filled in high tension with a horn type. No retention was obviously found in the fasting stomach fluid. Sinus mucosa enlarged, but without shadow evidently and filling defect. Furthermore, no apparent anomalies existed in the duodenum.

Radical surgery of esophagectomy was performed with tracheal intubation under general anesthesia. The resected specimen was sent for pathological analysis to accurately diagnose the disease and assist in the prognosis. The surgical specimen consisted of 6 cm long segment of the esophagus. There was a protuberant lesion in the place which was 3.5 cm after the upper incisal end and 0.5 cm away from the lower incised edge. The tumor masses (2.5 cm × 2.5 cm × 1 cm) were covered by apparently normal esophageal mucosa with slight depression in its vertex (**Figure 2A**). It exposed visible hoar diseased tissue after incised the protuberant lesion (**Figure 2B**). The tumor slightly invaded the surrounding muscle layer.

Histological findings

Tumor specimen was fixed, sliced for HE (hematoxylin-eosin) staining and examined under microscope. Tumor mass was mainly localized in the submucosal layer which was covered with mild hyperplasia of esophageal epithelium. The boundary between tumor cell masses and epithelium is clear (**Figure 3A**). It was

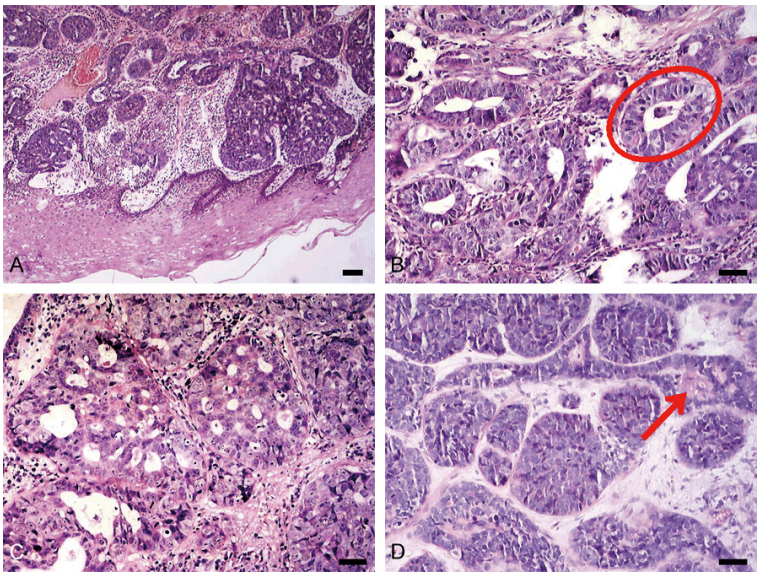

Figure 3. Histological findings. The tumor was covered by normal esophageal epithelium (A) and consists of three types of structures, including tubular pattern (B), cribriform pattern (C) and solid pattern (D). Tubular pattern was generally organized by two layers of cells as shown by red circle (B). Some of the solid pattern has acne necrosis in the center of tumor mass (D, red arrow indicated). Bar =100 μm.

observed three classical pathological structures of tumor cells of adenoid cystic carcinoma under high magnification, which includes tubular pattern (**Figure 3B**), cribriform pattern (**Figure 3C**), and solid pattern (**Figure 3D**). Tubular pattern was generally organized by two layers of cells (**Figure 3B**, red circle annotated), which was consistent with previous finding for EACC [4]. Some of the solid pattern has acne necrosis in the center of tumor mass (**Figure 3D**, red arrow indicated).

Immunohistochemical characteristics

Immunohistochemistry was further applied to determine the nature and malignant degree of the tumor. Routinely made slides were subjected to citrate-based antigen retrieval, thus were exposed to relevant antibodies. According to previous reports [4, 9], adenoid cystic carcinoma (ACC) contains 2 types of cells (myoepithelial cells and secretory type cells). Antibodies against CD10, P63 and CK5/6 were used to label myoepithelial cells. And antibodies against CK7 and CK8 were chosen to mark glandular epithelial cells. The results showed that CD10, P63 positive cells were distributed in the periphery of the tumor cell masses, but CK7, CK8 positive cells were distributed in the inner layer (**Figure 4A**), especially in cell masses with tubular pattern, implying that tumor tissues consists of two layer of cells with distinct properties. Another myoepithelial marker CK5/6 was not restricted to the periphery of cell masses but diffusedly distributed. In addition, cell surface marker CD117, a pro-oncogene whose overexpression could lead to cancer, was positive and evenly distributed in tumor cell masses (**Figure 4A**). Interestingly, we found that, in the tubular pattern, the cells of inner layer exhibited stronger staining for glandular epithelial cell markers CK7, CK8, but which gradually faded away in the cribriform and solid pattern. Meanwhile, myoepithelial cell marker P63 positive cells pervaded from the periphery to whole cell mass when EACC under conversion from tubular pattern to cribriform or solid pattern (**Figure 4B**), implying P63-positive cells obtain growth advantage during the development of EACC. Vimentin labeling was enhanced in the solid pattern compared to tubular and cribriform patterns, possibly indicating the occurrence of epithelial-to-mesenchymal transition (EMT) during tumor progression. It was shown more than 80% cells had P53 and Ki67 positive staining (**Figure 4C**). The higher rate of Ki67 positive cells indicated that tumor was in a state of active proliferation. The grading of the tumor was followed the criteria of WHO (2005), according to histological classification: predominant tubular pattern accompanies cribriform pattern without solid structure is classified as grade 1; pure cribriform pattern, or that mixed with solid pattern < 30%, are classified as grade 2; solid pattern > 30% are classified as grade 3 [10]. This case was mixed with three kinds of patterns, and solid structure > 30%, thus graded as level 3.

Discussion

Adenoid cystic carcinoma of the esophagus (EACC) is an occasional malignancy. Gregg and Stamler reported the first cases of EACC since

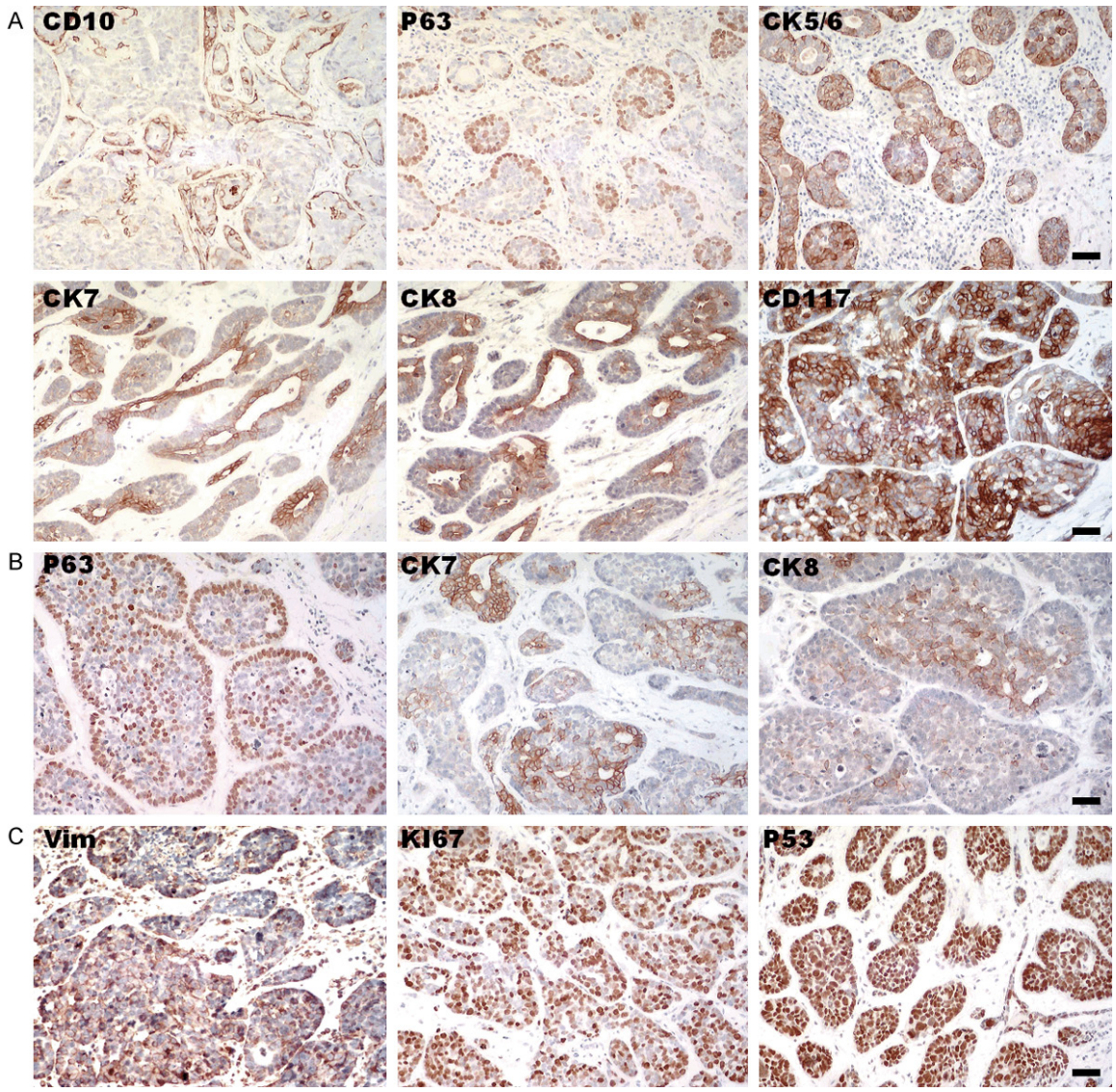

Figure 4. Immunohistochemical findings. A: In the tubular pattern, the periphery of tumor cell masses were labeled by myoepithelial cell markers CD10, P63 and the inner layer of cells were labeled by glandular epithelial cell markers CK7, CK8. CK5/6 and CD117 diffusely labeled whole cell mass. B: Not only the cells at the periphery, but also the cells inside of the cribriform or solid patterns were labeled by P63. By contrast, the intensities of CK7 and CK8 staining were gradually decreased in the cribriform or solid pattern. C: Enhanced staining of EMT marker vimentin (Vim) in solid pattern of EACC. In addition, large portion of cells were positive for P53 and Ki67 staining. Bar =100 μm.

1954 [11], and so far over one hundred cases of EACC were reported in literature by searching PUBMED database. As summarized in **Table 1**, from 1959 to 2015, nine articles reviewed the occurrence of EACC cases at various times in history, either based on publications from PUBMED database [12-14] or from specific regional literature, such as in Japanese [8, 15, 16] or Chinese [17]. Nelms et al., in 1972, reviewed theretofore total 9 reported EACC cases [12]. It was concluded this malignancy has a predilection for the middle of the esophagus, no sexual preference for occurrence and associates with poor prognosis. Subsequently, Jacobsohn reviewed another 21 cases and drew similar conclusions [13]. In 1986, Petursson compared 44 literature cases of EACC to adenoid cystic carcinoma of salivary gland origin, concluding EACC has distinct clinicopathologic characteristics from the salivary gland variant [14]. EACC has a higher tendency to metastasize and a much poorer prognosis

Table 1. Literature review of EACC cases reported in PUBMED or specific regional literatures

Year	Region	No. of Cases reviewed	Authors
2015	Japan	35	Sawada G., et al.
2012	China	17	Guo XF., et al.
1996	Japan	37	Morisaki Y., et al.
1986	Japan	24	Akamatsu T., et al.
1986	Worldwide	45	Petursson SR
1980	Worldwide	21	Jacobsohn WZ., et al.
1975	Worldwide	16	Pourzand A., et al.
1972	Worldwide	9	Nelms DC & Luna MA
1959	N.A	N.A	Rojas RA & Vallecillo LA

notes: N.A, not available.

with less than a quarter of 1-year survival rate. He proposed surgery combined with chemotherapy may effectively treat this tumor. Morisaki et al. reviewed clinical data on 37 cases of EACC reported in Japan in 1996 [15]. The age, sex ratio and most commonly affected region in EACC were seemly similar to squamous cell carcinoma. Although the poor prognosis of EACC has been reported due to frequent occurrence of organ metastasis, no detectable lymph node metastasis during surgery may indicate favorable prognosis. Sawada reviewed the reported cases of EACC from 1990-2014 in Japan again [16], drawing consistent conclusions with Morisaki that EACC has relatively better prognosis provided that the tumor is examined with no lymph node metastasis and the incidence of lymph node metastasis of EACC is less frequent as compared to that of SCC. He suggested less invasive thoracoscopic surgery should be applied for EACC at the early stage. Guo et al. reported two cases and review 15 cases reported in Chinese literature in 2012 [17]. They agreed this tumor was extremely rare and surgery should be the first choice for curing of disease. Through searching in the database of China National Knowledge Infrastructure (http://www.cnki.net/) for reported cases of EACC in Chinese from 1979 to 2017, we found a total of 25 cases reported in Chinese literature (**Table 2**). The first case was reported in 1989 in Zhejiang province of China. The majority of them were reported in Beijing city, followed by Jiangsu, Shanxi, Zhejiang, etc. The case described in this article was the first case reported in Anhui province. The age of disease onset for all these cases came on ranging from 42~79-year-old, which were mostly taken place in the middle or the lower part of the esophagus. The majority of tumor appearance was protruding. And the subsequent appearance was ulcerative. The tumor frequently invaded muscle layer, but occasionally developing lymph node metastasis. For the curing of EACC, surgery is currently the most effective means, whereas radiotherapy and chemotherapy as adjuvant therapy. Local large resection of diseased tissue can achieve the goal of eradicating the malignancy, especially effective for non-metastatic carcinoma. Principally, operation is performed in trying to excise surrounding tissues and adjacent nerve as much as possible, even sacrificing some visibly normal tissues. Postoperative radiotherapy is necessary to kill the remaining tumor cells, preventing from tumor recurrence and blood metastasis.

It is mainly believed that EACC is originated from esophageal submucosal glands, although some argued that EACC may be derived from esophageal epithelium. In the current case, the cancerous tissue was entirely localized in the mucosa and coated with normal esophageal epithelium with a distinct boundary to tumor cell masses, supporting that EACC is originated from esophageal submucosal glands. In pathology, ACC is featured with two different properties of cells, the inner layer of secretory glandular epithelial cells and the outer layer of myoepithelial cells, and forms three kinds of pathological structures: tubular, cribriform and solid patterns. There is evidence that the tubular, cribriform and solid patterns, respectively, represent different malignant degrees [18]. Patients with solid pattern have the worst performance on the overall prognosis, with a lower long-term survival rate and proneness to distant metastases. There is no difference between patients with tubular and cribriform patterns in cancer metastasis and overall survival, but the patients with cribriform pattern have a worse prognosis with a higher risk of recurrence. Therefore, from the perspective of positive correlation between malignant degree and cancer progression, EACC may develop from the tubular pattern to the cribriform pattern, and finally the solid pattern. Our results indicate, along with the conversion of patterns, CK7, CK8-labelled inner gland epithelial cells

Table 2. Clinical factors of the current case and 25 cases of EACC previously reported in China from 1977 to 2017

Year	Age/Sex	Area (Province)	Endoscopic appearance	Location in esophagus	Treatment	Depth of invasion	Lymph node metastasis	Lymphatic invasion	Vascular invasion	Observation period (month)
Present	53/M	Anhui	Protruding with ulcerative	Middle	Surgery	Muscle	-	-	-	1
2017	70/M	Jiangsu	Protruding	Lower	Surgery	Muscle	+	-	-	2
2016	79/M	Jiangsu	Protruding	Middle	Surgery	Muscle	-	-	-	0.5
2016	60/M	Jiangsu	Protruding	Middle	Surgery	Muscle	-	-	-	1
2015	64/F	Shanghai	Protruding	Upper	Surgery	Muscle	+	-	-	36
2013	57/F	Shanghai	Protruding	Middle	Surgery	Submucosa	-	-	-	~1
2012	59/M	Hubei	Protruding	Middle	Surgery	Submucosa	-	-	-	3
2008	N.A	Zhejiang	N.A	N.A	N.A	N.A	N.A	N.A	N.A	N.A
2007	49/M	Tianjin	Protruding	Lower	Surgery	Submucosa	-	-	-	N.A
2002	47/M	Beijing	Protruding	Lower	Surgery	Muscle	-	-	-	1
2002	60/M	Hebei	Protruding with ulcerative	Lower	Surgery	Muscle	-	-	-	1
2002	60/M	Siquan	Protruding	Middle	Surgery	Muscle	-	-	-	2
2002	68/M	Hebei	Protruding with ulcerative	Lower	Surgery	Muscle	N.A	N.A	N.A	3
2001	48/M	Guangdong	Protruding with ulcerative	Middle	Surgery	Submucosa	+	-	-	0.67
2000	54/F	Liaoning	Protruding	Middle	Surgery	Submucosa	N.A	N.A	N.A	1
1999	42~62/N.A	Beijing	Ulcerative	Upper	Surgery	Submucosa	N.A	N.A	N.A	N.A
1999	42~62/N.A	Beijing	Protruding with ulcerative	Lower	Surgery	Submucosa	N.A	N.A	N.A	N.A
1999	42~62/N.A	Beijing	Protruding	Middle	Surgery	Submucosa	N.A	N.A	N.A	N.A
1999	42~62/N.A	Beijing	Ulcerative	Middle	Surgery	Submucosa	N.A	N.A	N.A	N.A
1997	42~64/N.A	Shanxi	Protruding	Lower	Surgery	Muscle	-	-	-	2~12
1997	42~64/N.A	Shanxi	Ulcerative	Lower	Surgery	Muscle	-	-	-	2~12
1995	48/F	Shanxi	Protruding with ulcerative	Middle	Surgery	Muscle	+	-	-	12
1995	58/M	Beijing	Ulcerative	Middle	Surgery	Muscle	+	-	-	25
1995	60/M	Beijing	Ulcerative	Middle	Surgery	Muscle	+	-	-	6
1989	60/M	Zhejiang	Protruding	Upper	Surgery	Submucosa	-	-	-	>12

notes: N.A, not available; F, female; M, male.

gradually disappeared, concomitantly with P63-positive outer myoepithelial cells expanded to whole tumor cell mass. At the most advanced stage of solid pattern, the tumor cell mass was predominantly accompanied by P63-positive cells. The cells in solid pattern couldn't be labeled by other kinds of myoepithelial cell markers such as CD10 (**Figure 4A**), suggesting that the EACC development is not a simple process of myoepithelial cells to replace glandular epithelial cells. The enhanced vimentin-labelling indicates occurrence of the EMT process for cell transformation. We argue that above mentioned immunohistochemical characters could be applied for accurate diagnosis of EACC. For instance, one usage is to make a difference of ACC from BSCC (basaloid squamous cell carcinoma, BSCC), which is difficult in clinic. BSCC is composed of densely arranged cells with nuclei deep staining and high mitosis, showing a regularly organized solid mass. Some of tumor tissues also form in tubular and cribriform patterns [19]. Therefore, quite a few cases of BSCC or ACC may be previously misdiagnosed [20]. As an example, the reported case in this study was wrongly diagnosed as squamous cell carcinoma under endoscopic biopsy. This study develops an easy way to differ ACC from BSCC by distinguishable patterns of P60, CK7 and CK8 labelling. For BSCC in tubular pattern, myoepithelial cell markers P60 presents evenly labeling of whole cell mass with negative labeling of glandular cells markers such as CK7, CK8, but ACC shows only positive P60-labelling of peripheral cells combined with positive labeling of CK7 and CK8 in the inner layer of cells (as indicated in **Figure 4**).

The exact mechanism for the occurrence of EACC is still unknown. So far, there are no effective drugs to treat this kind of malignancy. Surgical resection is currently the main method for curing of EACC, but targeted therapy is also on the way. For instance, Jensen et al. applied radiotherapy combined with cetuximab to effectively mitigate the progression of ACC in

salivary [21]. Target drugs BRAF inhibitor vemurafenib showed good outcome for those ACC cases harboring BRAF kinase mutations [22]. The NF-κB inhibitor bortezomib obtained certain effectiveness for treatment of ACC in a clinical phase II trial [23]. Our work proposed EACC development was associated with upregulation of vimentin, indicating that epithelial-to-messenchymal transition occurs in the course of EACC progression. EMT increases the invasiveness of cancer and promotes cancer cells to escape from tumor suppressor pathways [24, 25]. Targeting EMT molecules may be effective for treatment of tumors accompanied with EMT process. Conclusively, immunophenotypic characteristics of EACC presented in this study would not only be helpful in precise diagnosis of EACC, but also shed light on targeted therapeutic strategy for this rare tumor.

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The patient provided written informed consent for the publication of the data and associated images.

Disclosure of conflict of interest

None.

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