Primary epithelioid angiomatous nodule of the vocal cord: A case report and literature review

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Abstract. A primary epithelioid angiomatous nodule (EAN) of the vocal cord is a rare vascular endothelial cell-derived lesion. The present study describes the clinical, histopathological and immunohistochemical characteristics of a 31-year-old male patient with EAN of the vocal cord and reviews the relevant literature. The patient complained of recurrent hoarseness for over a month. A fiber laryngoscopy revealed a red polypoid mass on the left vocal cord. Post-surgical resection, the microscopic examination revealed clear tumor boundaries, a solid arrangement of epithelioid tumor cells, obvious nucleoli, vacuolated nuclei, eosinophilic or clear cytoplasm, no mitotic figures and scant inflammatory cell infiltration. The immunohistochemical results also showed positivity for CD34 and CD31 in the tumor cells. Fluorescence *in situ* hybridization excluded calmodulin-binding transcription activator 1 rearrangement. The patient was followed up for 6 months and no recurrence was found. However, close follow-up is necessary in this case due to a positive surgical margin.

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Introduction

As rare benign lesions derived from vascular endothelial cells, epithelioid angiomatous nodules (EANs), were first reported in the English literature in 2004 (1). EAN occurs in the head and neck (including the face, nasal cavity, scalp, oral cavity and outer ear), trunk (including the breast and penis) and limbs (2,3). However, to the best of our knowledge, no case of EAN of the vocal cord has been documented internationally to date. Moreover, single lesions are more common than multifocal lesions. Microscopically, the tumor has clear boundaries and comprises proliferating epithelioid vascular endothelial cells, with no obvious atypia (or mild to moderate atypia in some cases), large nucleoli, vacuolated nuclei, eosinophilic or clear cytoplasm, and no or few mitotic figures, but with 9/10 high-powered fields (HPF) reported in individual cases (4). The tumor cells form primitive blood vessels, and the lumen contains red blood cells. The interstitium has minimal inflammatory cell infiltration and no obvious chondromyxoid matrix. Moreover, immunohistochemical results show positive expression of CD31 and CD34, and an almost complete absence of cytokeratin (CK) and epithelial membrane antigen (EMA) expression (5). Since a small number of biopsies have resulted in a diagnosis of epithelioid hemangioendothelioma (EHE) (3), differentiation from angiosarcoma is required to avoid overtreatment. EAN is typically treated by tumor resection to ensure negative margins and no recurrence; however, hormones or immunosuppressants are other treatment options (6-8). The present study reports a case of an EAN in the vocal cords to provide some reference value for clinical and pathological doctors.

Case report

In February 2025, a 31-year-old man was admitted to the Department of Ear, Nose and Throat of The First People's Hospital of Xiaoshan District (Hangzhou, China) due to

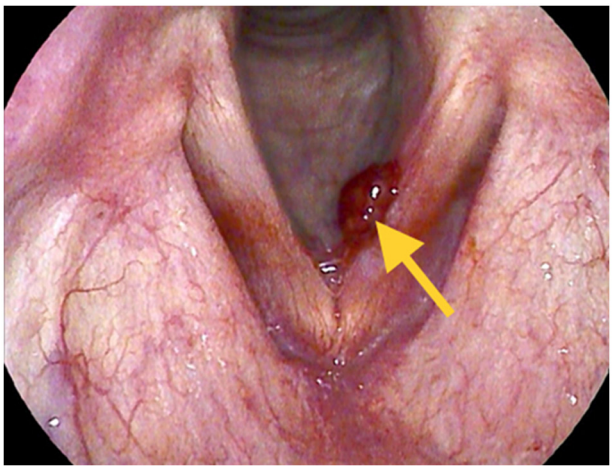

Figure 1. Red polypoid mass on the left vocal cord.

repeated hoarseness for over a month, accompanied by a small amount of coughing and sputum, and occasional hemoptysis with bright red blood streaks, but no fever. Initial screening was negative for human immunodeficiency virus antibodies. However, a fiber laryngoscopy showed a red polypoid mass with a diameter of 1 cm on the left vocal cord (Fig. 1). Although no abnormalities were observed on the right vocal cord, blood oozing was observed during the vocal cord movement. The clinical diagnosis was of a left vocal cord polyp. Dye to the concern that a biopsy would cause significant bleeding and due to the consideration of a benign lesion, the surgeon directly ordered a surgical resection without biopsy to achieve a curative effect.

The patient underwent endoscopically-assisted laryngeal microsurgery of the vocal cord lesion. The mucosa was incised along the base of the neoplasm, and the neoplasms were removed with forceps in stages. The vocal cord wound was flattened until the vocal cord's edge was flat, and the tissue was sent for pathological examination.

The tissue was fixed with 10% neutral formalin (24 h at 25˚C), embedded in paraffin, and serially sectioned at 3 μm, before being subjected to hematoxylin and eosin staining (3 h at 25˚C) (all Shanghai Regal Biological Technology Development Co., Ltd.; Sinopharm Chemical Reagent Co., Ltd.). Observations were performed under a Leica DM2000 light microscope (Leica Microsystems GmbH). Macroexamination revealed a pile of soft gray-red tissue with a volume of 0.6x0.5x0.2 cm. Microscopically (Figs. 2-4), the tissue was fragmented. Furthermore, proliferative squamous subepithelial epithelioid tumor cells showed solid lamellar hyperplasia with clear boundaries, round or elliptic tumor cells, unequal nuclear sizes, round or elliptic shapes, visible nucleoli, vacuolated nuclei, eosinophilic or clear cytoplasm, partial vacuolation, formation of primitive vascular lumina and no mitotic signs. However, there was no cartilaginous mucoid matrix or suppurative inflammatory cell infiltration on the surface. Diseased tissues were identified at the surgical margins.

Immunohistochemical staining was conducted with the EnVision Systems method using antibodies purchased from Beijing Zhongshan Jinqiao Biotechnology Co., Ltd., and Fuzhou Maixin Biotechnology Development Co., Ltd.

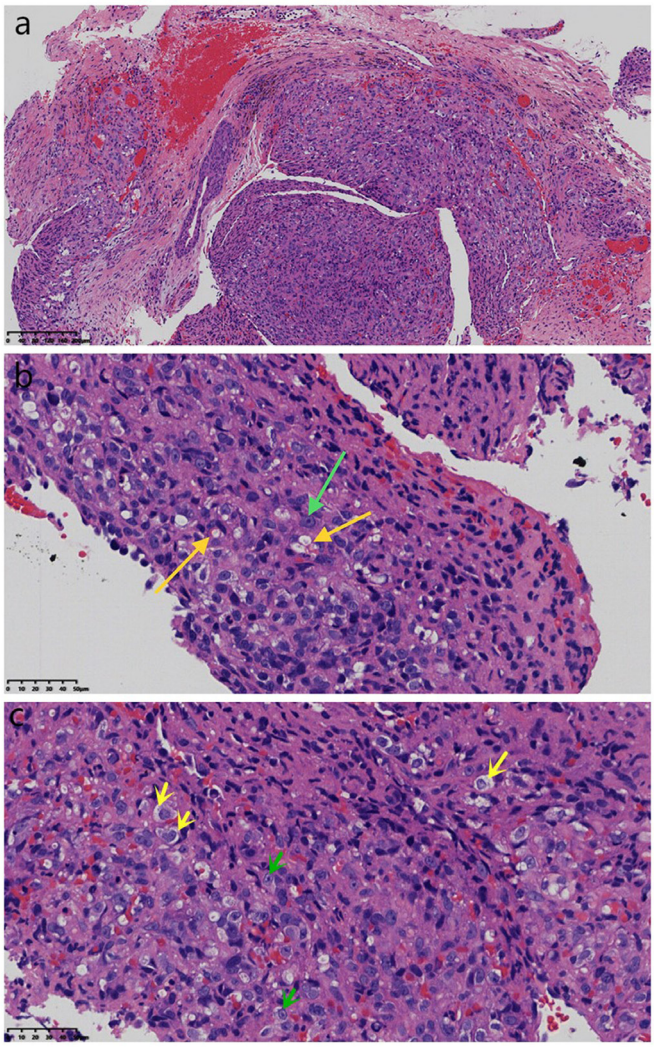

Figure 2. Pathological analysis of the tumor showing (A) solid flaky hyperplasia with a clear boundary (magnification, x100; scale bar, 200 μm; hematoxylin and eosin staining), (B) clearly visible tumor cell nucleoli (green arrow) and initial vascular lumina (yellow arrow) established in the region (magnification, x400; scale bar, 50 μm; hematoxylin and eosin staining), and (C) vacuolated tumor cell nuclei (green arrow) with partially clear cytoplasm (yellow arrow) (magnification, x400; scale bar, 50 μm; hematoxylin and eosin staining).

Blocking was performed with 5% goat serum for 1 h at 25˚C. Incubation with primary antibodies was for 1-2 h at 37˚C, while secondary antibody incubation was for 1 h at 37˚C. The tumor cells were positive for CD31 (1:100; cat. no. 20073115), CD34 (1:100; cat. no. 21016826) (Fig. 3A and B) and negative for cytokeratin (1:100; cat. no. 21061509), EMA (1:100; cat. no 21020730), desmin (1:200; cat. no. 21011686), transcription factor E3 (TFE3; working fluid; cat. no 2205110663c) and S-100 protein (1:100; cat. no. 2012240585C8) (Fig. 4A-E). Moreover, the Ki-67 proliferative index was 25% (1:200; cat. no. 21030436) (digital slice scanner; Ningbo Jiangfeng Biological Information Technology Co. Ltd.). Additionally, a fluorescence *in situ* hybridization molecular assay revealed no rearrangement of the calmodulin-binding transcription activator 1 (CAMTA1) fusion gene (as performed by the Department of Pathology, Shanghai Cancer Hospital, Shanghai, China). The pathological diagnosis was an EAN of the left vocal cord.

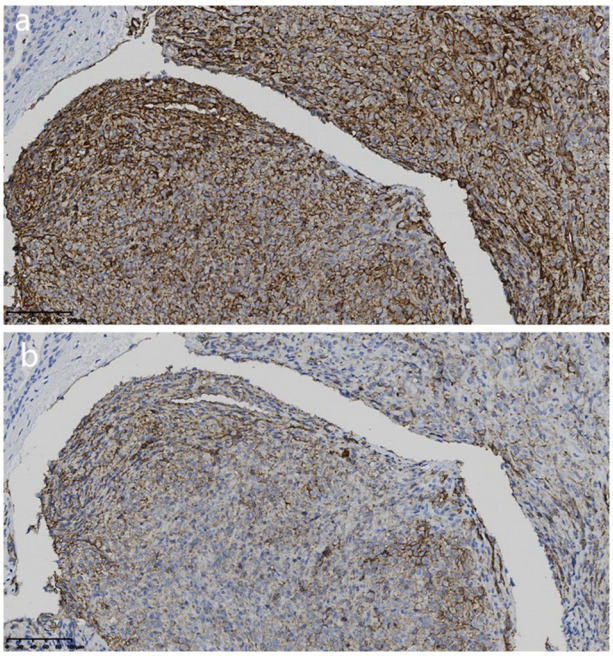

Figure 3. Immunohistochemical analysis showing tumor cells expressing (A) CD31 positivity (magnification, x200; scale bar, 100 μm) and (B) CD34 positivity (magnification, x200; scale bar, 100 μm).

The postoperative management included a single dose of prophylactic intravenous methylprednisolone (80 mg) to mitigate airway edema, and budesonide nebulization (2 mg twice a day for 3 days) for localized anti-inflammatory effects. However, there was no hoarseness at the 3-month follow-up. At the 6-month follow-up, a fiber laryngoscopy was performed, and no recurrence of vocal cord lesions was observed. However, it was recommended that the patient undergo regular fiber laryngoscopic examinations every 3 months due to the diseased tissue at the surgical margin.

Discussion

EAN was first reported in 2004 by Brenn and Fletcher (1). A total of 67 EAN cases have been reported in the international literature between 2004 and 2024 (2,3) according to a search of the PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Scopus (https://www.elsevier.com/products/scopus/) databases using the following key words: 'Epithelioid', 'angiomatous', 'nodule', 'vocal cords', 'angiosarcoma' and 'hemangioendothelioma'. Inclusion criteria for this search were as follows: Research related to one or more of these key words, covering the clinical features, pathological diagnosis, differential diagnosis, treatment methods and other aspects of these lesions. The exclusion criteria were as follows: Studies unrelated to the key words, low quality of literature and duplicate publications. Among the vascular neoplasms of the larynx, hemangiomas are the most common tumors in infants and are less common in adults; however, angiosarcomas are rarely reported (9). To the best of our knowledge, the present case report is the first in the international literature to describe an EAN in a laryngeal location. An extensive literature review may provide an evidence-based framework of diagnosis and treatment for this variant of EAN on the vocal cord.

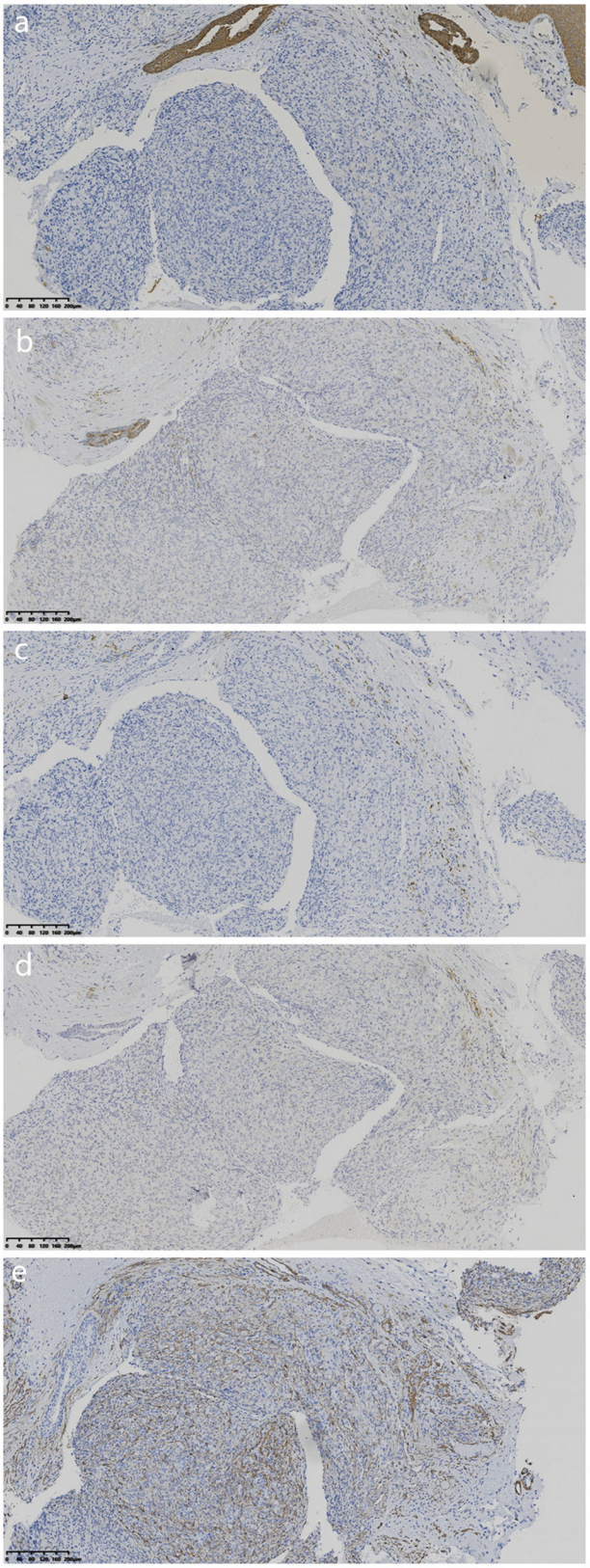

Figure 4. (A-E) Immunohistochemical analysis showing tumor cells with a lack of expression for cytokeratin, epithelial membrane antigen, desmin, transcription factor E3 and smooth muscle actin (magnification, x100; scale bar, 200 μm).

EAN occurs in the head and neck (including the face, nasal cavity, scalp, oral cavity and outer ear), the trunk (including the breast and penis) and the limbs (2,3). Based on

the reviewed cases, the age range of such cases is 13-84 years. The mean age is 42 years, and the male-to-female ratio is 1.31:1 (38:29). The asymptomatic clinical symptoms vary by site; some studies have also reported pain, bleeding and itching (25%; 17/67). Most cases are present on the body surface, with bluish-red papules or nodules (mostly single and some multifocal) visible to the naked eye, ranging from 0.2 to 2.5 cm; however, those in the nasal cavity require an endoscopy to detect the lesions (10,11). Microscopically, EAN exhibits consistent histomorphological patterns across various anatomical sites. The tumor is well-circumscribed and consists of proliferating epithelioid vascular endothelial cells. Epithelioid cells are round, oval or polygonal, without atypia, and in individual cases with immunosuppression, cells show mild to moderate atypia (4). These endothelial cells exhibit large nuclei, distinct nucleoli, vacuolated nuclei and few or no mitotic images, but with 9/10 HPF reported in individual cases (4). The cytoplasm is abundant, eosinophilic or clear. Cytoplasmic vacuoles are observed, original blood vessels have been formed and the lumen contains red blood cells. The interstitium shows reduced inflammatory cell infiltration (including eosinophils) and no chondromyxoid matrix. Immunohistochemical expression of CD31, CD34 and coagulation factor VIII is often positive, while that of CK and S-100 is negative (1,2). Among the literature cases, 1 patient showed positive EMA and estrogen receptor expression (5). Ki-67 was expressed by <30% of tumor cells in 7 reported cases (2,3). To the best of our knowledge, the present case reports the occurrence of EAN on the vocal cord for the first time. The clinical manifestations included repeated hoarseness for over a month, and the symptoms were similar to those of vocal cord polyps. A fiber laryngoscopy revealed a red polypoid mass on the left vocal cord. The polypoid tumor displayed clear boundaries, and epithelioid cells showed a solid pattern with the original blood vessels and vacuolated structures. Immunohistochemically, the tumor cells expressed CD31 and CD34. Ki-67 was expressed in 25% of the tumor cells, indicating some proliferative capacity, but is within the range reported in the literature (2,3). The CAMTA1 fusion gene was not rearranged, and the pathological diagnosis was consistent with EAN.

EAN has also been midiagnosed as EHE (3) and should be distinguished from other tumors as follows: i) In EHE, epithelioid endothelial cells grow in cords/nests in chondromyxoid tissue, with mildly eosinophilic cytoplasm. Genetic testing often shows WW domain containing transcription regulator 1-CAMTA1 or Yes-associated protein 1-transcription factor E3-TFE3 rearrangements. ii) In epithelioid angiosarcoma, irregular vascular lumina are present, with invasive/destructive growth, obvious cell atypia and prominent mitotic figures. iii) Epithelioid hemangiomas (benign) are composed of hyperplastic small vessels (few with dilated lumina), while epithelioid endothelial cells (large, abundant cytoplasm) exhibit round/oval nuclei and prominent nucleoli, and mild nuclear atypia is present in some cases. iv) Epithelioid sarcoma mostly occurs in the distal extremities, and its microscopic features include obvious central tumor necrosis, significant pleomorphism of epithelioid cells, numerous mitotic figures and no obvious primitive blood vessels or cytoplasmic vacuolation. Molecular detection of SWI/SNF related matrix associated actin-dependent regulator of chromatin subfamily B1 deletion helps in the diagnosis. v) Malignant melanomas may exhibit visible pigment, marked cell atypia, discoverable mitotic figures and necrosis. S-100 protein and human melanoma black-45 are positively expressed. vi) Pyogenic granulomas contain lobulated proliferating capillaries with mildly hyperplastic endothelial cells on microscopy. The stroma shows fibromyxoid degeneration with edema. Additionally, surface mucosal erosion is visible, as well as acute and chronic inflammatory cell infiltration (12).

The primary treatment for EAN is surgical excision; however, a few studies have reported regression after using topical corticosteroids and cryotherapy (6,7). In another patient with multiple-skin EAN, the lesions gradually disappeared 16 months after discontinuing cyclosporine (8). However, 2 cases showed recurrence after an incomplete resection (4), and another case with multiple sites reported recurrence in a new location post-resection (13). A total of 67 non-metastatic cases have been reported in the literature (100% benign), with follow-up periods ranging between 1 month and 7 years. In the present case, the patient underwent an endoscopic resection, anti-inflammatory detumescence and symptomatic treatment. Although the surgical margins showed the presence of diseased tissue, the pathological results suggested that the EAN was a benign lesion. If the lesion reoccurred on the vocal cords, this might cause complications, such as hoarseness, if treated again. Hence, a regular fiber laryngoscopy every 3 months was recommended. The patient was followed up for 3 months without hoarseness, and there was no recurrence at 6 months. Therefore, regular postoperative follow-up may be used as a valuable reference.

In conclusion, EAN of the vocal cord is a rare benign lesion. Since its diagnosis relies on pathological analysis, the differentiation between malignant epithelioid vascular tumors is essential. Although surgical resection is the conventional treatment, regular postoperative follow-ups should be conducted due to the risk of recurrence. Owing to the limited literature on such lesions, this case report may have positive effects on the diagnosis and treatment of vocal cord tumors.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KL and BH drafted the manuscript and conceived the study. LC and JS were responsible for the collection and analysis of the case data and literature. BH, YG and KL revised the

manuscript and interpreted the data. MJ and MH obtained medical images. NQ carried out the immunohistochemical analysis. LC and JS confirmed the authenticity of the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Ethical approval was provided by the Ethics Committee of Xiaoshan District First People's Hospital (Hangzhou, China; approval no. 2024-07).

Patient consent for publication

The patient provided written informed consent for the publication of the case report and images.

Competing interests

The authors declare that they have no competing interests.

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