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Case Report

Endolymphatic sac tumor with von Hippel-Lindau disease: report of a case with atypical pathology of endolymphatic sac tumor

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Abstract: The authors described a case of a patient with co-existing endolymphatic sac tumor (ELST) and hemangioblastoma in the posterior cranial fossa, which belonged to a subtype of Von Hippel-Lindau (VHL) disease confirmed by the test of VHL-gene. The signs in this 42-year-old female included intermittent headache and dizziness. Imaging revealed a giant mass in the right cerebellopontine angle (CPA) region and another lesion in the left cerebellar hemisphere. The results of biopsy after two operations confirmed the diagnosis respectively. Both of the tumors were resected totally. Nevertheless, we had to confess the misdiagnosis as vascular tumor instead of ELST at the initial diagnosis because of the rarity of ELST associated with atypical histological characteristics. The purposes we reported this case were to describe the atypical pathological feature of ELST and the mutation of germline VHL not mentioned in previously literature, furthermore, to foster understanding of ELSTs with the avoidance of the similar misdiagnosis as far as possible in future.

Keywords: Endolymphatic sac tumor (ELST), hemangioblastoma, cerebellopontine angle (CPA), cerebellar hemisphere, von Hippel-Lindau disease (VHL)

Introduction

Endolymphatic sac tumors (ELSTs) are extremely rare and locally aggressive neoplasm that were first reported by Hassard et al [1] in 1984. And clinically destructive behavior invade the skull base including the posterior petrous bone, cerebellopontine angle structures and cranial nerve [2]. In 1989, Heffner's 20 cases of an identical tumor entity showed a distinct pathologic entity and proposed the origin of endolymphatic sac [3]. Endolymphatic sac tumors were recommended for these aggressive papillary tumors of the petrous bone by Li et al [4] in 1993. Of course, these tumors can arise sporadically or coexisting with von Hippel-Lindau (VHL) disease [5]. It can easily be confused with other tumors due to the rarity and very heterogeneous histology. Here we presented a 42-year-old female patient co-existing endolymphatic sac tumor, who was initially misdiagnosed as vascular tumor, and hemangioblastoma in the posterior cranial fossa with the following aims: 1) to get better understanding of the variable and heterogeneous pathology of ELSTs, 2) to firstly report the mutation of germline VHL with 10-nucleotide insertion within exon 1 and 3) to review the features of ELSTs to avoid the homologous misdiagnosis in future.

Case report

History and imaging examination

A 42-year-old female was admitted with complaints of a 15-day history of intermittent headaches and dizziness, without nausea and vomiting. Computed tomography (CT) revealed a giant mass lesion with mixed density in the right CPA region along with the destroyed petrous bone (**Figure 1A**), and a low density space-occupying lesion in the left cerebellar hemisphere. No abnormal physical and laboratory examination including abdominal CT, were found except for a past history of appendicitis excision and cesarean section and the impair-

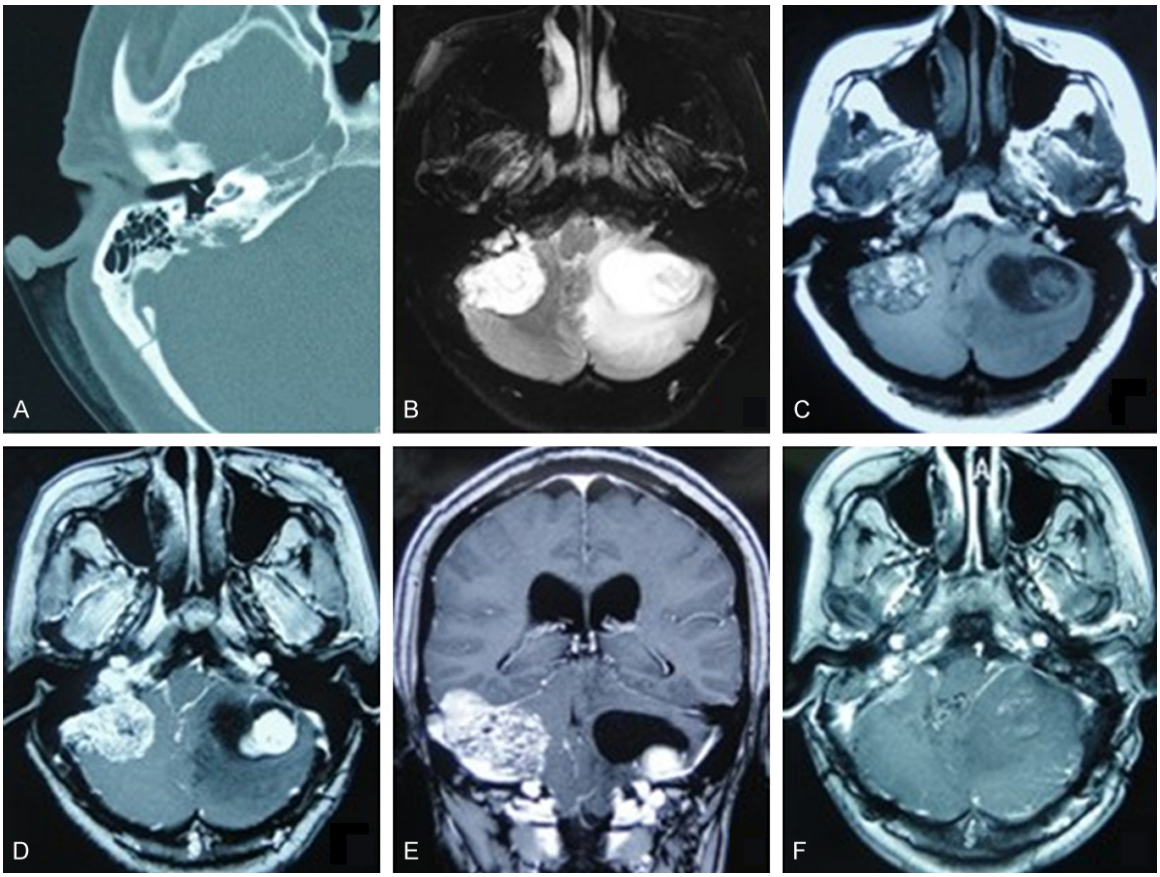

Figure 1. Radiologic characterization of endolymphatic sac tumor and hemangioblastoma. A: CT imaging demonstrated a destroyed petrous bone involving the right mastoid and the middle ear. B-E: MR scan showed two giant masses co-existing in the posterior cranial fossa. The right one in the CPA was irregular, heterogeneous on T1/T2-weighted images as well as heterogeneous contrast enhancement, the left lesion was shown with solid and cyst change in cerebellar hemisphere. F: MRI scan after the second operation showed totally resection of both lesions.

ment of right hearing resulting from otitis media in childhood. Cranial magnetic resonance imaging (MRI) described two tumors that were 4 × 3 × 3 cm in size in the right CPA region with mixed-signal intensity on T1, T2-weighted images and heterogeneous contrast enhancement; and 4.1 × 2.5 × 3.0 cm in size in the left cerebellar hemisphere with being obviously cystic change (**Figure 1B-E**). The boundary of two lesions were relatively clear from surrounding parenchyma.

Operation and pathological findings

Both tumors were completely removed via right and left retrosigmoid sinus craniotomy respectively within 25 days. During the first operation, lesion with demarcating from normal cerebellar tissue and invading part of petrous bone were found. The origin of the tumor from petrous bone could be apparently observed. In the second operation, the brown cyst fluid associated with old hemorrhage and soft solid nodule were seen. Under a microscope observation after the first surgery, intense vascularization of the tumor and the obviously primarily cystic architecture were observed. The cystic architecture filled with colloid-like material. Most of them were lined by a single layer of flattened epithelial cells, few covered by a single layer of cuboidal to columnar cells (**Figure 2A-D**). Immunohistochemical staining demonstrated vascular cells positive reactivity for CD31 (**Figure 3A**) and CD34 (**Figure 3C**), which were mistaken for the tumor cells at the initial diagnosis. Subsequently, further immunohistochemical staining showed positive reactivity for PAS (**Figure 3B**), epithelial membrane antigen (EMA) (**Figure 3D**), NSE and cytokeratin (CK) but negative for D2-40 and S-100. As to another speci-

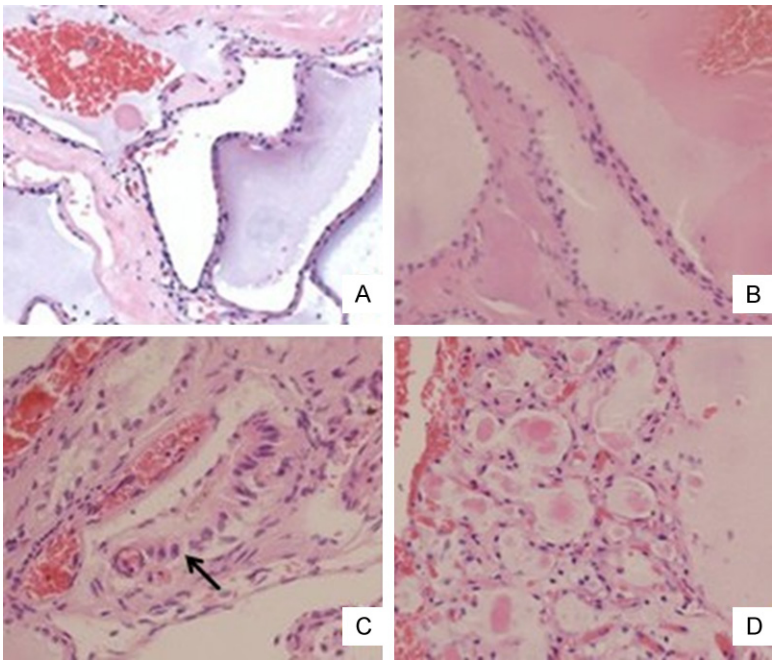

Figure 2. Histopathologic characterization of endolymphatic sac tumor. A, B: Histologic sections showed cystic structures which were lined by a single layer of flattened epithelial cells, these cells were misdiagnosed as endothelial at the initial diagnosis, the content of eosinophilic colloid-like material was characteristic of ELST but remarkably similar to lymph fluid (H&E, 100×). C: Few observed cuboidal-to-columnar cells appeared to be a papillary component (black arrow) (H&E, 200×). D: There were richly blood vessels which could misguide to diagnosis of vascular tumor (H&E, 100×).

men, histological examination shown round-to-oval nuclei and abundant clear cytoplasms in most of cells (**Figure 4**). Immunohistochemical staining confirmed hemangioblastoma.

The result of VHL-gene test

We extracted VHL-006 specimens from Peripheral blood DNA and did a test of VHL-gene by PCR amplification, gel electrophoresis and sequencing analysis.

The measured sequences of exon 2 and exon 3 showed 100% agreement with the VHL sequence of homology comparison. 291st site of Exon 1 was insertion of 10 nucleotides (GCCGCAGCCC), via the homology comparison and coded amino acid analysis, the insertion sequence led to serious changes in gene coding protein (**Figure 5**). "MPRRAENWDEAEVGAEEAGVEEYGPEEDGGEESGAEESGPEESGPEELGAEEEMEAGRPRPVLRSVNSREPSQVIFCNRSPRVVLPVWLNFDGEPQPYPTLPPGTGRRIHSYRGHLWLFRDAGTHDGLLVNQTELFVPSLNVDGQPIFANITLPVYTLKERCLQVVRSLVKPENYRRLDIVRSLYEDLEDHPNVQKDLERLTQERIAHQRMGD" changed into "MPRRAENWDEAEVGAEEAGVEEYGPEEDGGEESGAEESGPEESGPEELGAEEEMEAGRPRPVLRSVNSREPSQVIFCNRSPRVVLPVWLNFDGEPQPAAALPNAAAWHGPPHPQLPRSPLALQRCRDTRWASG", which led to a decrease of 80 amino acids and changes of 36 amino acids. (YPTLPPGTGRRIHSYRGHLWLFRDAGTHDGLLVNQT change into AAALPNAAAWHGPPHPQLPRSPLALQRCRDTRWASG).

Postoperative course

The patient recovered well after operations. The preoperative symptoms gradually disappeared. Repeated MRI scans showed the totally resection of both neoplasms after the second surgery and no recurrence during the follow-up period (**Figure 1F**).

Discussion

ELSTs are rare neoplasm involving the temporal bone, which occurred in patients with age from 4 to 85 years old [2]. The tumors can arise sporadically or coexisting with von Hippel-Lindau (VHL) disease. The mean age with VHL disease is 31.3 years according to the statistics of limited cases [2]. Patients with VHL disease are apt to be female in some individual studies [6], however, VHL disease is autosomally dominant and affects males and females equally in theory. To our knowledge, there are three cases of metastases reported in the literature although ELSTs are known to be locally aggressive [7-9]. It can be misdiagnosed as Meniere disease at earlier stage because of the abnormal of hearing and equilibrium function [10]. Slowly progressive hearing loss, tinnitus, vertigo, and facial nerve paresis are the common complaints [11]. Interestingly, the chief complaint of our case was not hearing loss or tinnitus because of the past history of the right hearing loss resulted from otitis media in childhood. Therefore, we can't track the previous medical history of the ELST definitely.

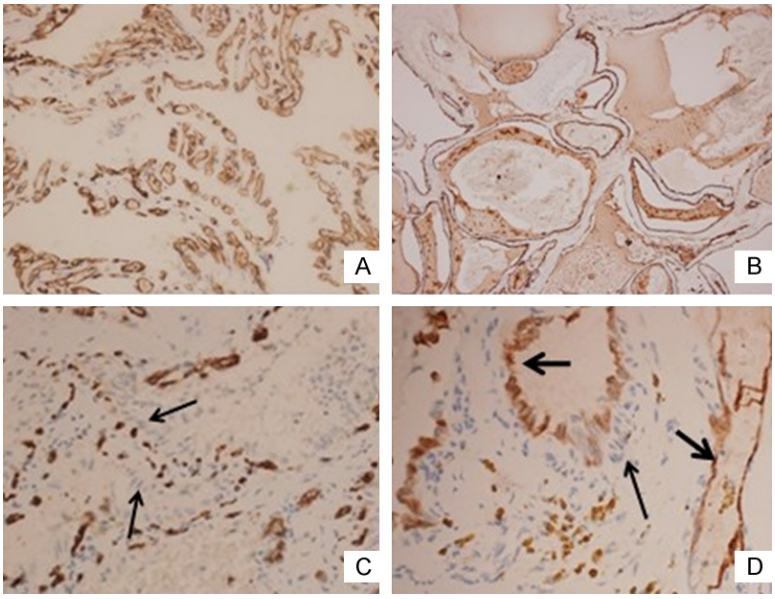

Figure 3. Immunophenotype of endolymphatic sac tumor. A: The CD31+ vascular cells were mistaken for the tumor cells at the initial diagnosis (immunostaining, 400×). B: The tumor cells showed positive reactivity with PAS which confirmed the eosinophilic colloid-like material (immunostaining, 100×). C: The vascular cells showed positive reactivity with CD34, but the cuboidal-to-columnar cells, namely tumor cells, showed negative (black arrow), which indicated the difference between vascular cells and tumor cells (immunostaining, 200×). D: The tumor cells shown positive reactivity with EMA determining the correct diagnosis of ELST. Interestingly, positive for flattened epithelial cells (thick arrows) but negative for some cuboidal-to-columnar cells (thin arrow) shown atypical pathology characteristics (immunostaining, 200×).

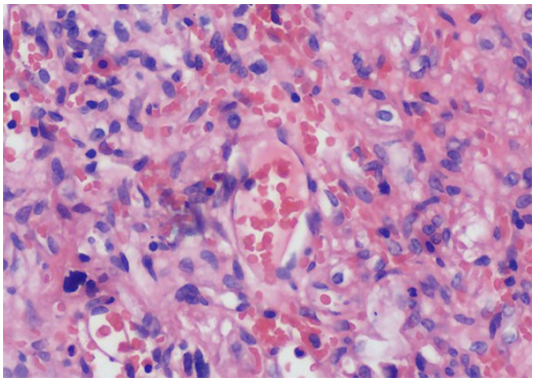

Figure 4. Histopathologic characterization of hemangioblastoma. Photomicrograph of the left lesion demonstrated sporadic vessels by a single layer of flattened endothelial cells and clusters of polygonal tumor cells with round-to-oval nuclei and abundant clear cytoplasms, part of tumor nuclei were weird (H&E, 400×).

Imaging findings in ELSTs are usually revealed the erosion of temporal bone including the endolymphatic sac, retrolabyrinthine, and presigmoid region on computed tomography (CT). On MRI scan, lesion often shows heterogeneous foci of low and high signal intensity on both T1-weighted image and T2-weighted image with heterogeneous enhancement [12, 13]. Our case demonstrated the destroyed bone extended to the right posterior fossa as well as the right middle ear. And showed heterogeneous foci on T1- and T2-weighted images association with heterogeneous enhancing mass in the right CPA region. A classic radiological feature of hemangioblastoma was observed in the left cerebellar hemisphere which was supported by postoperative biopsy. In order to enhance understanding of our case, the test of VHL-gene from peripheral blood DNA was completed to draw a conclusion that the change of 291st site within Exon 1 induced protein change mutation. The mutation of germline VHL with 10-nucleotide insertion within exon 1 has not been previously reported in ELSTs [14]. Then, the relationship between the two tumors could be interpreted by VHL disease in our case.

But even so, we are still difficult to avoid the trend to misdiagnosis during the initial diagnosis because of the rarity and the atypical pathological feature of the ELST. Misdiagnosis of these lesions would be made usually on the basis of both the radiologic and histopathologic characteristics. ELSTs may be preoperatively misdiagnosed as paraganglioma, glomus tumor, angioblastic meningioma, and other temporal tumors because of the lesion with hypervascular in radiology [15]. Histopathologically, these tumors are often composed of papillary structures and cystic structures containing eosinophilic colloid-like material, which are lined by a single layer of flattened cuboidal-to-columnar cells. The nuclei of the epithelial layer show slight variability in size and shape. The stroma is richly fibrovascular where hemorrhage, hemosiderin deposits, cholesterol clefts, and chronic inflammatory cells are frequently

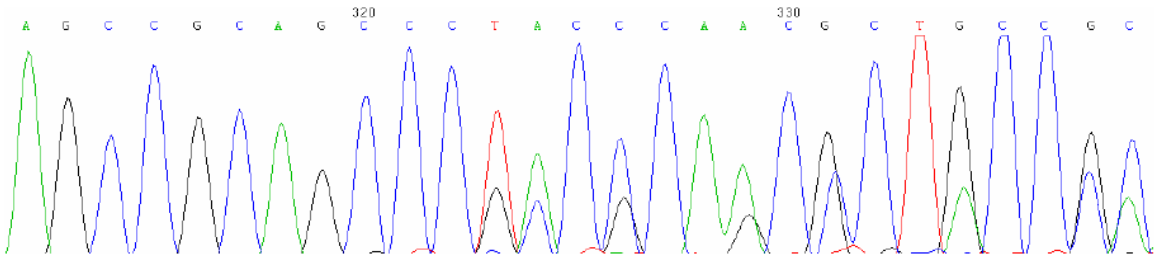

Figure 5. The sequence diagram of exon 1. The change of 291st site within Exon 1 with 10-nucleotide insertion induced protein change mutation.

observed. The histopathologic differential diagnosis of ELSTs involve other papillary lesions such as middle ear adenoma, paraganglioma, chorioid plexus papilloma, papillary ependymoma, and metastatic carcinoma of the thyroid, kidney, prostate and lung [2, 16, 17]. However, the representation of the pathology in our case was weird and ambiguous without typical papillary structure. Hardly can epithelial cells such as cuboidal-to-columnar cells be observed. The cells lining the cysts were interpreted incorrectly as endothelial instead of flattened epithelial at first time. Cystic structures containing eosinophilic colloid-like material were thought as the change of lymph vessels filled with lymph fluid. Combined abundant blood vessels and positive reactions to CD31 and CD34, the designation of hemangiolymphangioma was wrongly made at the initial diagnosis [18], which was regarded with suspicion by others. Subsequently, further immunohistochemical staining helped to distinguish the essence of this neoplasm. Eosinophilic colloid-like material showed positive reactions for PAS staining denied the possible of lymph fluid. The tumor cells shown positive reactivity with EMA determining the correct diagnosis of ELST. Carefully observation, those EMA+ tumor cells were different from the CD31+ vascular cells. The misdiagnosis occurred because an intense network of reactive CD31+ and CD34+ vascular cells was misinterpreted as vascular tumor and because epithelial tumor cells were unusually inconspicuous–not forming typical papillary structure, but presenting as few cuboidal-to-columnar cells or even flat cystic structures. The tumor cells with NSE and CK expression backed up the diagnosis of ELST. By the aid of VHL gene test, the diagnosis of ELST could be consolidated without doubtfully.

Actually speaking, it was very difficult for us to make correctly diagnosis to ELSTs, eapecially when we did not encounter these tumors previously. The comprehensive methods including radiologic and histopathologic characteristics as well as VHL gene examination would be helpful for diagnosing ELSTs.

The treatment for ELSTs and hemangioblastomas is surgical resection. Conservative management of ELSTs is conducted for not amenable to a hearing preserving surgery on the basis of the radiological stability or the same stuttering growth pattern as hemangioblastomas [19]. In our case, two operations were completed with totally resection respectively disregarding the previously right hearing loss. A gamma-knife radiosurgery for residual tumor may be advised. A long-term follow-up should be taken in order to monitor the progression of the diseases because of the potential of recurrence and growth from other positions. The children of this patient should also be observed in case of genetic inheritance.

Conclusions

In conclusion, we reported a case of a patient with co-existing ELST and hemangioblastoma in the posterior cranial fossa, who was misdiagnosed with vascular tumor in place of ELST due to the rare and very heterogeneous histology of ELSTs. It is hoped that the study would contribute to a better understanding of ELSTs and help to make correctly diagnosis for ELSTs in future.

Disclosure of conflict of interest

None.

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