Endolymphatic Sac Tumors in von Hippel-Lindau Disease: Report of Three Cases

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Objectives: To illustrate the diagnostic and pathophysiological issues of endolymphatic sac tumors (ELSTs) and its clinical association with von Hippel-Lindau (VHL) disease and to demonstrate the interest of genetic testing in such cases.

Study Design: Retrospective analysis of 3 cases of ELST with VHL in 3 different clinical and prognostic situations.

Main Outcomes: The first case was diagnosed on the concomitant finding of a central nervous system lesion. The familial genetic testing revealed the presence of the VHL mutation in an asymptomatic daughter, which justified regular follow-up. In the second case of known VHL syndromic disease, the pathophysiological role of the endolymphatic sac was questioned, with vertigo as the initial, unique symptom of ELST. In the third case, a giant hypervascularized ELST, initially diagnosed as jugular parangangioma, was the unique manifestation of VHL disease.

The young age of the patient could explain the absence of other tumors.

Conclusion: Diagnosis of ELSTs may be difficult especially when the original site of the lesion cannot be clearly identified. Such tumors may be revealed or may develop with VHL disease. On presentation of a lytic, vascularized tumor of the posterior face of the petrous bone, clinicians should systematically search for other manifestations of VHL disease involving a VHL genetic testing for patients, and relatives in case of a positive test, to detect early asymptomatic other tumors. The type of VHL mutation might predict the aggressiveness.

Key Words: Endolymphatic sac tumors—Genetic testing—Low-grade adenocarcinoma—Vertigo—von Hippel-Lindau.


Endolymphatic sac tumors (ELSTs) are rare, low-grade adenocarcinomas of the temporal bone associated with substantial audiovestibular morbidity (1). They can be sporadic, but in most cases, they are associated with von Hippel-Lindau (VHL) disease, a dominantly inherited familial cancer syndrome linked to a germline mutation of the VHL gene (2).

We report 3 cases of ELST associated with VHL disease that illustrate 3 different presentation and evolution aspects.

CASE REPORTS

Case 1

A 33-year-old woman with no unusual medical history, presented in November 1999 with an 8-month history of right-sided otalgia and progressive hearing loss. Otoscopy examination revealed a reddish, raspberry-like hypotympanic mass behind a normal tympanic membrane. Audiometry revealed complete hearing loss of the right ear.
Computed tomographic (CT) scan and magnetic resonance imaging (MRI) revealed lysis of the posterior face of the petrous pyramid by a voluminous heterogenous mass invading the infralabyrinthine and retrolabyrinthine regions (Fig. 1, A and B) and the posterior cranial fossa (Fig. 1, C and D) and an infracentimetric hypervascular lesion in the right cerebellum highly suggestive of a hemangioblastoma. These findings evoked the diagnosis of ELST associated with VHL disease.

The tumor was resected by translabyrinthine and translabyrinthine approaches 2 days after embolization. Histopathology showed a low-grade papillary adenocarcinoma of the endolymphatic sac, with strong immunoreactivity for cytokeratin (KL1), vimentin, and neuron-specific enolase and variable immunoreactivity for epithelial membrane antigen.

A missense germline mutation in exon 1 of the VHL gene was identified in the patient (p. Asp92Gly). The patient’s family members (parents and 2 daughters aged 10 and 5 yr) then underwent genetic testing. The mutation was found in the youngest daughter. Full evaluation of the positive carrier did not reveal any tumor localization.

Abdominal ultrasonography and MRI of the patient showed multiple pancreatic cysts but no renal or adrenal gland abnormalities. Spinal MRI and ophthalmoscopy gave normal results.

Regular medical follow-up 4 years after the discovery of the disease showed a right renal cyst and centimetric tumor of the left kidney. At 10 years, imaging revealed stable disease, with no recurrence of the ELST nor evolution of the pancreatic and kidney lesions.

**Case 2**

A 46-year-old woman had a VHL disease diagnosed for 16 years. She had undergone 5 surgical procedures for cerebellar hemangioblastomas and renal cystic tumors and several photocoagulations for retinal hemangioblastomas. Genetic testing revealed a missense germline mutation in exon 3 of the VHL gene (p.Leu158Pro). No mutation was found in the family. In August 2008, the patient presented acute vertigo crisis lasting for a few hours, with no tinnitus or hearing loss. Computed tomographic scan and MRI revealed a small lytic, hypervascularized lesion in the area of the right endolymphatic sac (Fig. 2, A and B). Vestibular and audiometric testing gave normal results.

Complete surgical removal was achieved in June 2009 using translabyrinthine approach. Histopathology and immunohistochemistry examination of the surgical specimen showed low-grade papillary adenocarcinoma of the endolymphatic sac and strong immunoreactivity for...
cytokeratin (KL1). Follow-up was uneventful. Audiometry at 6 months gave normal results.

Case 3

A 16-year-old woman from Tunisia presented in November 2006 with a 6-year history of right-sided progressive hearing loss accompanied by otalgia and intermittent otorrhea. Otoscopy revealed a granulomatous, polypoïd mass in the right external auditory canal. The rest of the clinical examination showed no abnormalities. However, audiography revealed a right-sided anacusis.

Computed tomography revealed a massive lytic lesion of the right petrous pyramid extending to the middle ear cavities (Fig. 3A). T1-Weighted MRI revealed a voluminous heterogenous tumor centered on the posterior face of the right petrous pyramid and protruding into the posterior cranial fossa (Fig. 3B).

The patient was referred to our department with the initial diagnosis of giant right tympanojugular paraganglioma. Somatostatin receptor scintigraphy revealed a tumor tracer uptake, but the mild intensity was unusual for a paraganglioma.

In February 2007, embolization followed by an infratemporal approach with anterior rerouting of the facial nerve was performed. A highly vascularized tumor originating from the endolymphatic sac area was found invading the retrolabyrinthine bony cells and reaching the posterior dura. Resection of the tumor was macroscopically complete. The postoperative follow-up was uneventful, with no facial paralysis.

Histopathology examination revealed a low-grade papillary adenocarcinoma of the endolymphatic sac (Fig. 4). Immunohistochemistry showed a strong immunoreactivity for cytokeratin (KL1) and vimentin.

The direct sequencing of VHL gene showed an 11-nucleotide deletion within exon 1 of the gene causing a frameshift mutation (p.Val62GlyfsX66). To our knowledge, that mutation was not previously described. Family history, as assessed by questioning the young patient, did not reveal any other symptomatic cases, but familial genetic testing could not be done.

Abdominal ultrasonography and CT revealed no signs of pancreatic, renal, or adrenal lesion. Findings were normal on spinal MRI and ophthalmoscopy.

FIG. 3. Axial CT scan (A) of Case 3 showing a large heterogenous destruction of the right petrous bone with dispersed residual bony fragments occupying also the middle ear cavities. Axial T1-weighted MRI (B) without gadolinium enhancement showing a voluminous, heterogenous mass of the right petrous bone invading the posterior cranial fossa.
The patient was 10 years old, that is, 6 years before diagnosis, and ELST was the unique manifestation of VHL disease. This situation could be explained by the absence of a full picture of the disease in this young patient.

All three cases had unilateral ELST even if bilateral tumors were found in almost one third of patients with VHL disease (3).

Genetic Aspects

Here, the 3 described cases of ELST were associated with VHL disease. This autosomal-dominant inherited disease is known to be related to a germline mutation in the tumor suppressor gene VHL that has been mapped to chromosome 3p25. The VHL gene encodes a protein (pVHL) that plays an important role in tumor angiogenesis, accounting for the hypervascular pattern of the VHL-related tumors (4).

Analysis of our series of cases underlines the interest of a VHL genetic testing, which allows 1) to identify VHL disease in the absence of family history in front of an isolated lesion; 2) in the case of a positive test, to complete imaging and ophthalmologic evaluation and to manage regular and prolonged follow-up to detect early asymptomatic tumors; 3) to propose a familial presymptomatic genetic testing in first relatives and a specific follow-up only for the positive mutation carriers; and 4) conversely, to reassure negative mutation carriers.

Management Considerations

A remarkable feature of our series is the striking difference in aggressiveness of the disease. Case 3, who carried a frameshift mutation of VHL causing a truncated protein, presented a voluminous ELST that recurred massively twice rapidly after surgery, whereas Case 1 did not show any recurrence 12 years postoperation, and Case 2 presented a centimetric ELST 15 years after diagnosis of VHL. The latter 2 presented a missense mutation of VHL gene.

Thus, the type of VHL mutation might predict the aggressiveness and/or the development of ELST during the growth in childhood might be a risk factor of aggressiveness and thus influence the management. Treatment of choice is supposed to be surgical resection of this locally aggressive tumor before it affects auditory, vestibular, or facial function. However, the early massive recurrence observed in Case 3 suggests the interest of alternative treatment. Radiotherapy has been proposed but needs to be evaluated in a large series (5). Antiangiogenic agents that have been shown to be effective in renal localizations of VHL (6) deserve to be evaluated in ELST.

CONCLUSION

Endolymphatic sac tumors are rare tumors with increased local destructive potential and are, in many cases, revealed by neurosensory hearing loss, tinnitus, and vertigo. The hypothesis of a VHL disease should always be raised, and VHL genetic testing should be proposed even
when the ELST seems isolated. The association of ELST and VHL disease requires regular follow-up in the patient and relatives to detect other asymptomatic syndromic lesions.

REFERENCES


