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Review Article

Neuropathology of von Hippel-Lindau Disease

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Abstract

VHL patients develop tumors in brain, spinal cord, nerve roots, kidney, adrenal gland and extra-adrenal ganglia, pancreas, epididymis and broad ligament. VHL disease produces highly characteristic neuropathologic changes which are presented in this review. Highly vascularized tumors, hemangioblastomas, involve cerebellum and spinal cord of the majority of patients. A smaller number of patients may develop endolymphatic sac tumors that originate in the petrous bone, but may extend into the brain. Lastly, neuropathology may be produced by metastasis of renal clear cell carcinoma or other VHL disease-associated neoplasms.

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INTRODUCTION

von Hippel-Lindau (VHL) disease is an autosomal dominantly inherited tumor syndrome, characterized by the frequent development of specific tumors in selective topographic sites. Affected patients develop central nervous system (CNS) hemangioblastomas, renal clear cell carcinomas, pheochromocytomas and extra-adrenal paragangliomas, endolymphatic sac tumors, pancreatic microcystic adenomas and pancreatic neuroendocrine tumors [1]. Male patients frequently develop epididymal cystadenoma, while female patients occasionally develop clear cell tumors of the broad ligament. The incidence of VHL disease is about one in 36,000 live births [2,3] and the disease has over 90 % of penetrance by age 65 [4].

Patients with VHL disease carry a germline mutation of the VHL tumor suppressor gene (*VHL*) [5]. The "second hit", inactivation of the wild-type *VHL* copy, appears to be a prerequisite for tumorigenesis [6]. VHL inactivation causes activation of hypoxia-inducible factors HIF1 and HIF2 as well as HIF target proteins including VEGF, erythropoiesis factor Epo, nitric oxide synthase (NOS), and glucose transporter 1 (GLUT1) which are abundantly expressed in VHL disease-associated tumors. This article reviews VHL disease-associated tumors that involve or potentially affect the central nervous system: hemangioblastoma, endolymphatic sac tumor, and tumor metastasis.

Hemangioblastoma

Hemangioblastomas are the most vascular of nervous system tumors. While sporadic hemangioblastomas constitute 1 to 2 % of intracranial neoplasms, they are observed in 80% of von Hippel-Lindau (VHL) patients and are a defining feature of VHL disease [4,7-9]. Hemangioblastomas occur equally in women and men and show a consistent pattern of topographic distribution.

Retina, cerebellum, brainstem and the dorsal spinal cord are the most frequent localizations. Multiple hemangioblastomas occur frequently in patients with VHL disease.

Although hemangioblastomas are benign tumors, they may cause significant neurological deficits [10,11]. Hemangioblastomas in the cerebellum and brainstem are associated with a high mortality rate if they are not treated before producing acute hydrocephalus, tonsillar herniation, and brainstem compression [4,12,13]. Symptoms are usually not caused by the tumor itself but rather by an associated pseudocyst or syrinx, which is caused by the tumor [14] and which is usually much larger than the tumor itself [15].

Usually the diagnosis can be established by MRI because of the typical appearance of a densely contrast-enhancing tumor with smooth margins, often as a "cystic lesion" with a contrast enhancing solid tumor at the margins of a pseudocyst in the cerebellum or a syrinx in the spinal cord [16,17].

Pathology: Grossly, the tumor nodule appears soft with bright or dark red color. Recorded tumor sizes vary between less than 2mm^3 and 36cm^3 [18]. Histologically, surrounding brain or pseudocyst wall tissue reveals chronic astrocytosis with abundant Rosenthal fibers; pseudocystic spaces are a result of secretory tumoral activity, as they disappear weeks or months after successful surgical removal of the hemangioblastoma nodule [19].

The histology of hemangioblastomas varies remarkably (Figure 1). Cytologically, hemangioblastomas are composed of two main constituents. The first cytologic component is characterized by conspicuous neoplastic clear cells carrying VHL gene deletion [20] – a near-consistent feature of any tumor arising in the context of VHL disease. Conventionally, neoplastic clear cells in hemangioblastomas are called "stromal" cells. "Stromal" cells do not exist in normal nervous system tissue, and their origin has been controversial. They appear as lipid- and glycogen-rich cells with abundant clear cytoplasm and small to intermediate-sized nuclei the outline of which is frequently scalloped by lipidized bubbles. Nuclei may be round, enlarged, or bizarre-shaped, mitotic figures are rare. The other, second cytologic component of hemangioblastomas is represented by abundant mature vascular structures. Most, if not all of these vascular structures represent reactive angiogenesis [20,21].

Hemangioblastomas show not only marked cytological, but also marked architectural variation (Figure 1). Tumor cells may be rather inconspicuous and nearly obscured by abundant reactive angiogenesis which gives the appearance of an "angiomatotic" process that was originally described by von Hippel. This pattern is frequently referred to as "reticular" [22] or "mesenchymal" [18]. Other tumors may reveal prominent epitheloid clusters of tumor cells and are referred to as "cellular" [22] or "epitheloid" [18]. A recent study on 156 tumors concluded that the architectural pattern correlates with tumor size [18]; small tumors of less than 8 mm^3 in size consistently showed mesenchymal architecture, while larger tumors additionally revealed epitheloid patterns [18]. The clustering of "stromal" cells has been interpreted as differentiation of hemangioblast precursor cells into blood islands, and a subset of these tumors reveals downstream differentiation into red blood cell precursors [23,24]. In remarkable contrast to small, intensely vascularized tumors, larger hemangioblastomas

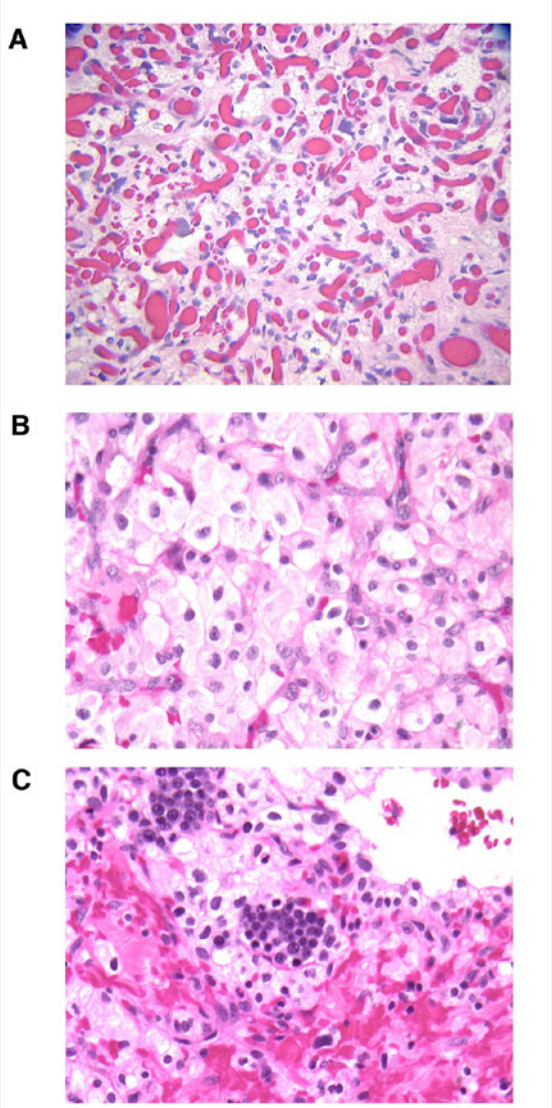

Figure 1 Hemangioblastoma; A, Tumors with exclusively mesenchymal (reticular) architecture show abundant delicate vascularization; B, Epitheloid hemangioblastoma reveals clustering of cells with abundant pink or clear cytoplasm; C, Two foci of hematopoiesis in an hemangioblastoma.

with prominent epitheloid cell ("cellular") clusters may resemble cancerous growth and need to be differentiated from metastatic renal clear cell carcinoma.

Selective genetic analysis of the "stromal" cells in CNS and retinal tumors revealed them to be VHL-deficient [20, 21,25] and thus to represent neoplastic cells. Secondary to VHL deficiency, hypoxia inducible factors (HIF) activation and vascular endothelial growth factor (VEGF) expression, hemangioblastomas show intense reactive vascularization.

"Stromal" cell differentiation into red blood cells has been noted [23,26] and demonstrated [24,27] confirming Cushing's original concept of a hemangioblastic origin of hemangioblastomas [28]. The hemangioblastic nature of hemangioblastomas has been further confirmed by their positive immunoreactivity with antibodies against Scl, brachyury, Csf-1R, Gata-1, Flk-1 and Tie-

2 [29]. While hemangioblastic differentiation occurs during embryonic and early fetal CNS development, hemangioblasts are not constituents of mature nervous system. The possible persistence of hemangioblastic activity in the nervous system of VHL patients has revived Lindau's original concept that VHL tumorigenesis is initiated by disturbed embryonal development [30]. Anatomic studies on spinal cord and cerebellum of VHL patients revealed numerous developmentally arrested structural elements [31] that serve as potential precursor material for hemangioblastic tumors [32].

Endolymphatic sac tumors (ELSTs)

The endolymphatic sac and duct are part of the nonsensory membranous labyrinth of the inner ear. Putative functions include maintenance of homeostasis [33,34] and pressure [35] of the inner ear, phagocytosis of debris [36] and immunologic functions [37,38]. In 1989, Heffner reported papillary-cystic tumors of the temporal bone and identified the endolymphatic sac as most likely site of origin [39]. In 1997, ELSTs were identified as component tumors of VHL disease by clinical observation [40], subsequently confirmed by genetic and molecular studies [20, 41-43]. As further confirmation of VHL deficiency, neoplastic cells were found to show activation of both HIF1 and HIF2 [42]. In addition, ELSTs express CAIX and GLUT-1, downstream targets of HIF [42]. ELSTs also co-express erythropoietin (EPO) and his receptor (EPOR), which has been implicated in promotion of their growth [44].

Early diagnosis and early management are important prognostic factors [45-47]. Numerous studies report that surgical resection is the best treatment [39,45-59]. When hearing loss has occurred, it is irreversible. However, in most cases further hearing loss is prevent by surgery [46-49,53,55,58,60,61] and symptoms like vertigo and tinnitus disappear [47-49,53,60]. Complications and recurrence are more prone to happen in patients with large tumors and after subtotal resection [39,46,50,53,57,59]. Stereotactic radiosurgery may be considered when surgery is not possible and in cases of focal recurrence [49,58,62].

Pathology: Grossly, ELSTs present as bright or dark red soft tissue masses [49]. Reported sizes vary between $3mm^3$ [42] and $54cm^3$ [59]. Histologically, three types of architecture have been identified - papillary, cystic and epitheloid clear cell patterns [39,42] (Figure 2). Extensively vascularized papillary structures are consistently observed. Papillary proliferations are lined by a single row of cuboidal epithelial cells. Mitotic figures are rare. Areas of cystic growth can be observed in a subset of tumors. The cysts have a single epithelial lining and frequently contain proteinaceous material. Epitheloid clear cell clusters, reminiscent of renal clear cell carcinoma, can be occasionally observed. Extensive hemosiderin deposits are common and associated with degenerative features including fibrosis, inflammation and cholesterol cleft formation. A feature of all tumors is extensive vascularization. Immunoreactivity with anti-AE1/AE3 [39,42,59,60,63], anti-MAK-6 [42,60] and anti-NSE [42,64] appear consistently positive in the tumoral cells. A subset of cases reveals positive reactivity for EMA [42,59,60,63,64], S100 [39,42,59,64] vimentin [60] and synaptophysin [64].

Structural and molecular analysis of surgical and autopsy material derived from VHL patients identified endolymphatic sac/duct epithelium as primary site of origin [42]. In the extraosseous portion of the endolymphatic sac as well as along the entire intraosseous endolymphatic sac/duct multifocal

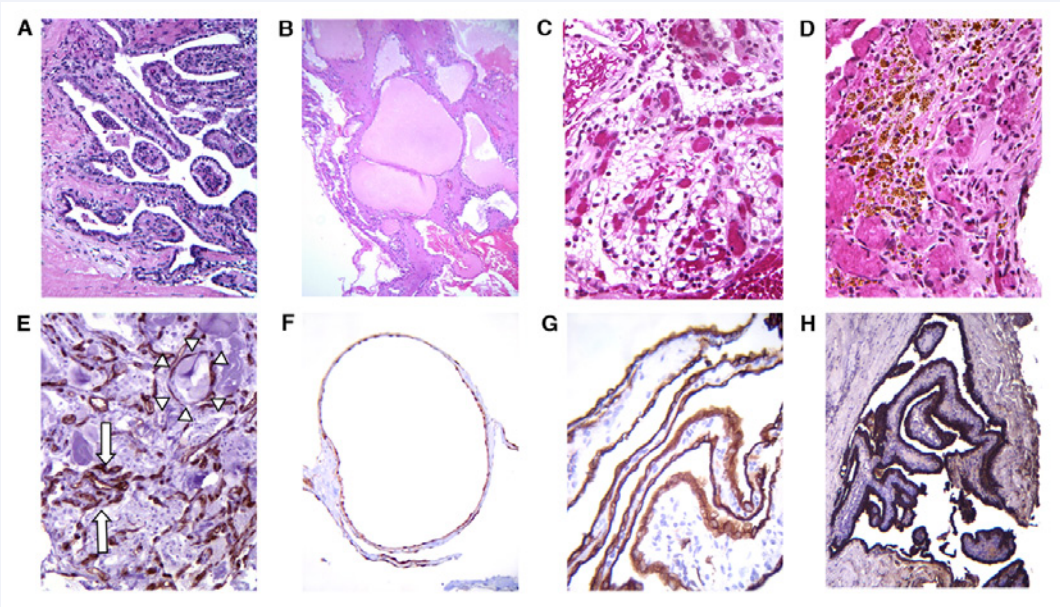

Figure 2 Endolymphatic sac tumors (ELSTs) consistently reveal papillary architecture (A), frequently associated with cystic areas (B), and occasionally clear cell areas (C) resembling metastatic RCCC; D, Extensive hemosiderin deposits are common; E, ELSTs are intensely vascularized (immunohistochemistry with an anti-CD 34 antibody for vascular structures) with abundant vessels in papillary stroma (arrows) and immediate contact of numerous small vessels with the cystic epithelium (arrowheads); immunohistochemistry for NSE (F), MAK6 (G), and AE1/AE3 (H) is frequently positive (modified from Glasker and al.[42]).

Table 1: Immunohistochemical differentiation between Hemangioblastoma and Metastatic RCCC.

	Metastatic RCCC		Hemangioblastoma			Metastatic RCCC		Hemangioblastoma	
	reactivity	cases	reactivity	cases		reactivity	cases	reactivity	cases
EMA					***Aquaporin 1***				
Andrew 1986	100%	5	0%	5	Chen 2006	**-**	**-**	100%	17
Gouldesbrough 1988	100%	10	55%	9	Longatti 2006	-	-	100%	10
Frank 1989	100%	4	-	-	Weinbreck 2008	38%	34	100%	67
Hufnagel 1989	100%	12	0%	9	**Total**	**38%**	**34**	**100%**	**94**
Lach 1999	-	-	0%	14	***NSE***				
Hoang 2003	-	-	0%	6	Gouldesbrough 1988	70%	9	100%	9
Ishizawa 2005	-	-	0%	17	Grant 1988	-	-	100%	10
Jung 2005	-	-	0%	7	Becker 1989	-	-	100%	15
Weinbreck 2008	97%	34	36%	67	Lach 1999	**-**	**-**	86%	**14**
Total	**98%**	**65**	***20%***	***149***	**Total**	**70%**	**9**	**96%**	**48**
CD10					***Inhibin A***				
Jung 2005	100%	5	0%	22	Hoang 2003	0%	19	100%	25
Weinbreck 2008	79%	34	0%	67	Jung 2005	12%	16	91%	22
Ingold 2008	85%	54	0%	71	Rivera 2010	12%	17	87%	15
Riviera 2010	82%	17	12%	15	Carney 2011	0%	16	100%	20
Total	**83%**	**110**	**1%**	**175**	**Total**	**6%**	**68**	**95%**	**82**
GLUT-1					***Vimentin***				
North 2000	**100%**	**9**	**8%**	**12**	Frank 1989	-	-	86%	22
PAX 8					Mizuno 1993	-	-	100%	7
Carney 2011	**94%**	**16**	**0%**	**20**	Lach 1999	-	-	100%	42
PAX 2					Ding 2007	-	-	85%	40
Rivera 2010	88%	17	0%	15	Lee 2013	83%	29	-	-
Carney 2011	88%	16	5%	19	**Total**	**83%**	**29**	**92%**	**111**
Total	***88%***	***33***	**2%**	**34**	***Brachyury***				
AE1/AE3					Barresi 2012	**0%**	**8**	**100%**	**22**
Lach 1999	-	-	64%	14	***NCAM***				
Weinbreck 2008	88%	34	0%	67	Bohling 1996	**8%**	**12**	**96%**	**24**
Total	**88%**	**34**	**11%**	**81**	***D2-40***				
RCC Marker(antibody)					Roy 2005	0%	8	100%	23
Ingold 2008	**51%**	**149**	**0%**	**71**	Weinbreck 2008	19%	67	35%	34
CAM 5.2					**Total**	**17%**	**75**	**61%**	**57**
Gouldesbrough 1988	**50%**	**10**	**0%**	**9**	***Leu-7***				
					Hufnagel 1989	0%	9	41%	12
					Lach 1996	-	-	0%	12
					Total	**0%**	**9**	**21%**	**24**

microscopic papillary projections were identified as potential precursor structures as molecular analysis of these structures revealed loss of heterozygosity of VHL, positive nuclear signal for HIF1 and HIF2 as well as expression of target proteins CAIX and GLUT-1 [42]. Although precursor structures were also identified in extraosseous endolymphatic sac, tumorigenesis appears to occur exclusively from intraosseous portions of the endolymphatic sac/duct system as temporal bone location and bony erosion appears to be a frequent, if not consistent feature of these tumors [39,42]. It remains therefore unclear, whether bone erosion occurs due to aggressive biology or due to intraosseous location.

Metastasis

Metastasis into the nervous system can occur from three different types of VHL disease-associated tumors. Most frequently, metastasis is caused by renal carcinoma the clear cell morphology of which may strikingly resemble primary hemangioblastoma or ELST. Far less frequently observed is metastatic pheochromocytoma/paraganglioma or metastatic neuroendocrine tumors.

Renal clear cell carcinoma (RCCC) is the most frequent malignant neoplasm occurring in the context of VHL disease and occurs in 24 to 45% of VHL patients [1,4,8]. Mean age at presentation is 39 years [1]. Prognosis of VHL disease mainly depends on the occurrence of RCCC and postoperative complications after neurosurgery. Before introduction of modern imaging methods like CT and MRI, 13 to 42% of VHL patients died of metastatic renal cell carcinoma [65]. As RCCCs often remain asymptomatic for long intervals, monitoring of VHL patients with contrast-enhanced abdominal CT is essential for early diagnosis [1]. Early detection of RCCCs in VHL patients has significantly reduced morbidity and mortality of VHL disease [1].

Pathology: Metastasis of RCCC can occur anywhere within the nervous system. If metastasis occurs into cerebellum, brainstem, or spinal cord, differentiation from primary hemangioblastoma may be difficult because of significant overlap of morphologic features. Both hemangioblastoma and metastatic RCCC are composed of tumor cells with clear or vacuolated cytoplasm, are extensively vascularized and may reveal similar clustering of epitheloid cells. Both types of tumors share VHL gene deficiency as well as expression of VEGF, HIF, CAIX and other *VHL* target proteins.

Helpful histologic features are more distinct cytoplasmic membranes of renal carcinoma cells. Also, mitotic figures are frequently found in RCCC, but are rare in hemangioblastoma. Also, necrosis is virtually never seen in hemangioblastoma, unless tumors had been pretreated with radiation or embolization. Immunohistochemistry is a valuable tool to distinguish hemangioblastoma from metastatic renal clear cell carcinoma. Initially, EMA has been identified as a marker for metastatic RCCC [66-73], while hemangioblastomas are near consistently positive for NSE [67,70,74,75]. Additional useful markers have been subsequently described including brachyury [76], NCAM [77], aquaporin 1 [73,78,79], AE1/AE3 [70,73], GLUT 1, vimentine [70,80-84], D2-40 [73,85] and RCC marker (antibody) [86] (Table 1). Combined immunohistochemistry for PAX2, PAX8 and inhibin A [87] has been suggested to be most useful to resolve the differential diagnosis. In a particularly challenging tumor with focal expression of EMA the diagnosis of hemangioblastoma was ascertained after proteome comparison of microdissected tumor areas on 2D gels [88].

Immunohistochemistry is particularly useful for identifying tumor heterogeneity that is caused by tumor metastasis into hemangioblastoma as a recent study found 8% of hemangioblastomas to be involved by metastatic tumor [89].

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