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Hemangioblastoma

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Hemangioblastomas are slow-growing, but highly vascular tumors that arise in specific regions of the central nervous system (CNS) and retina. They constitute about 0.9 % of total brain tumors [1]. Hemangioblastomas may occur sporadically, or as tumors associated with von Hippel–Lindau syndrome (vHL) in about 35–40 % of patients [1–3]. In some series, as much as 80 % of hemangioblastomas are associated with vHL.

Genetics

vHL syndrome is associated with a germline mutation in the *VHL* gene on chromosome 3p25. However, according to the genetic "two-hit hypothesis" proposed by Knudson, tumorigenesis requires a second somatic inactivation of the other *VHL* allele.

Other than mutations in *VHL*, there is a paucity of data regarding other genetic hits in hemangioblastomas that might contribute to tumorigenesis. Sprenger et al. performed comparative genomic hybridization (CGH) of ten sporadic hemangioblastomas and found that the most common genetic aberrations in sporadic tumors are loss of chromosome 3 (70 %), loss of chromosome 6 (50 %), loss of chromosome 9 (30 %), loss of 18q (30 %), and gain of chromosome 19 (30 %). Based on the frequencies and co-occurrence of these genetic changes, they hypothesized that the loss of chromosome 3 is an early event in oncogenesis in sporadic hemangioblastomas, followed by loss of chromosome 6 and subsequently chromosomes 9 and 18q, and lastly by the gain of chromosome 19 [4]. In another study, CGH results of 7 vHL-associated and 16 sporadic hemangioblastomas were compared. Mutations in the *VHL* gene on 3p25-56 were found in 100 % of hereditary hemangioblastomas, but only in 30 % of sporadic tumors. Conversely, complete loss of chromosome 3 occurred more commonly in sporadic hemangioblastomas (69 %) than in vHL-associated hemangioblastomas (14 %). Thus, it can be concluded that sporadic mutation in the *VHL* gene is not the primary oncogenic event in sporadic hemangioblastomas [5].

Epigenetic and other means of somatic inactivation of *VHL* are also being investigated. It has been proposed that inactivation of promoter CpG islands, due to hypermethylation, leads to transcriptional silencing of *VHL* [6].

Prowse et al. examined 53 vHL-related tumors, including 30 renal cell carcinomas (RCCs), 15 hemangioblastomas, 5 pheochromocytomas and 3 pancreatic tumors, for genetic changes such as LOH (loss of heterozygosity), intragenic somatic mutations as well as DNA hypermethylation. In this series, hypermethylation of the vHL gene was detected in 33 % of tumors (6 out of 18 tumors; 2 RCCs and 4 hemangioblastomas). Two tumors, both hemangioblastomas, showed intragenic somatic mutations in a wild-type gene [6].

In a subsequent study, Rickert et al. performed CGH of 20 hemangioblastomas (one vHL and the remainder sporadic), which revealed that the most common cytogenetic changes associated with hemangioblastomas include the loss of chromosomes 19, 6, and 22q, which are seen in 35 %, 30 %, and 15 % of patients, respectively, and the loss of chromosome 6 being significantly associated with the cellular variant. Loss of chromosome 3 was uncommon in this series of sporadic hemangioblastomas, in contrast to the earlier studies by Sprenger et al. [7].

Lemeta et al. suggested that LOH at 6q is common and concurrent with 3p loss in sporadic hemangioblastomas [8]. This finding was subsequently confirmed by other studies [4, 7, 9]. The same authors subsequently demonstrated high prevalence of LOH at the ZAC-1 tumor suppressor gene region located on 6q24-25. Moreover, they also demonstrated that promoter methylation of ZAC-1 leads to epigenetic silencing of the gene in 90 % of tumors [10].

CGH has demonstrated that the reticular and cellular variants of hemangioblastoma have different cytogenetic profiles, with the loss of chromosome 6 significantly associated with the cellular variants [7].

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Pathogenesis

vHL tumorigenesis can be mediated by both hypoxia-induced factor (HIF) and non-HIF-mediated mechanisms. HIF-1 is a heterodimeric transcriptional factor that regulates genes which respond to changes in oxygen levels in tissues [11, 12]. It is composed of HIF-1α and HIF-1β subunits [13]. Levels of HIF-1α are upregulated under hypoxic conditions and, by translocation into the nucleus and dimerization with HIF-1β, activate genes that promote angiogenesis (VEGF), erythropoiesis (EPO), nitric oxide synthesis (NOS), and glucose transport (GLUT-1). However, under normoxic conditions, HIF-1α undergoes ubiquitin-mediated degradation in the proteosomes, which are mediated by vHL protein [14–19]. The vHL protein binds to HIF-1α only after it undergoes oxygen-dependent hydroxylation of the proline residues 402 or 564 or both by members of the Elongin family (EG1N) [15, 18–21]. EG1N1 is the primary HIF-1 hydroxylase while EG1N2 and EG1N3 play compensatory roles under certain conditions [22]. However, when vHL is mutated, HIF-1α will not undergo degradation and remains constitutionally active [23]. This promotes tumorigenesis by increased transcriptional activation of genes that promote angiogenesis and other growth factors.

It has also been demonstrated that vHL is critical for cellular [24] differentiation during development and its inactivation causes developmental arrest [25] and protracted cellular differentiation [26]. The cell of origin in hemangioblastoma is an embryologically arrested hemangioblast derived from the mesoderm, which retains its multipotent properties and ability to differentiate into both red blood cells and blood vessel endothelium [27, 28]. Accordingly, foci of extramedullary hematopoeisis have been detected in hemangioblastomas. Vortmeyer et al. have detected the presence of fetal hemoglobin in these areas of extramedullary hematopoeisis, suggesting that the vHL deletion leads to primitive hematopoeisis [25, 26]. Moreover, co-expression of Epo and Epo receptor on these hemangioblasts represents a key event in vHL deficiency and further promotes tumor growth via autocrine and paracrine stimulation [25]. Developmentally arrested structural elements composed of hemangioblast progenitor cells have been demonstrated in the cerebella of *VHL*-mutated patients [29]. Hemangioblastic activity in the nervous system occurs in the embryonic stage [30] and hence its presence in adult brain depicts persistence of developmentally arrested hemangioblastic cells. vHL disease produces developmental aberrations giving rise to angiomesenchymal tumorlets resembling hemangioblastomas in the human CNS [31]. More recently, the pleuripotent vHL deficient cells in hemangioblastomas have been demonstrated to give rise to mast cells via the c-Kit signaling pathway. Accordingly, mast cells from tumor samples of patients exhibited LOH in the VHL alleles when compared with the peripheral blood lymphocytes [32].

Pathology

Macroscopically, hemangioblastoma is a well-circumscribed tumor, with both solid and cystic components. The tumor appears yellow in color due to its high lipid content.

Microscopically, the tumor has two components: a network of capillaries lined by hyperplastic endothelial cells with intervening vacuolated stromal cells, which have pale cytoplasms, pleomorphic nuclei and high lipid content. Mitoses are conspicuously absent [33]. A recent study of 156 tumors reports that tumor architecture relates to the size of the tumor; with smaller tumors (<8 mm^3) composed of mesenchymal architecture comprising of a network of capillaries, while the larger tumors composed of enlarged stromal cells clustered in groups (Fig. 14.1) [26]. The stromal cell, which is the tumor cell in hemangioblastoma, is an embryologically arrested hemangioblast derived from the mesoderm that retains its multipotent properties as well as the ability to differentiate into both red blood cells and blood vessel endothelium. The stromal cells are immunoreactive for cytokeratin, S-100, NSE (neuron specific enolase), actin, GFAP (glial fibrillary acid protein), vimentin, and EMA (epithelial membrane antigen). The stromal and capillary endothelial cells express different surface adhesion molecules suggesting different cells of origin. The capillary endothelial cells express endothelium associated adhesion molecules such as ICAM-1, ICAM-2, PECAM, ELAM, and VCAM-1. The stromal cells express neuronal cell adhesion molecule (NCAM), which further supports its mesenchymal origin. Since NCAM is also expressed by metastatic renal cell cancer to the CNS, its expression by hemangioblastoma can present as a diagnostic challenge [34, 35]. The stromal cells also stain negatively for von Willebrand factor, a marker of endothelial origin [36]. Brachyury, a protein transcription product of the T box gene, which regulates the formation of mesoderm, is expressed in the cytoplasm of stromal cells and is highly specific for hemangioblastoma, distinguishing it from morphologically similar lesions such as metastatic clear cell renal cell cancer and angiomatous meningioma [37, 38].

Histologically, hemangioblastomas are classified into two variants: the more common reticular variant (composed of proliferating vascular elements) and the rare cellular variant (composed of epitheloid clusters of stromal cells), which are associated with greater GFAP positivity, higher proliferation index, and probability of recurrence [39].

Receptors for cellular growth factors including pro-angiogenic factors, such as epidermal growth factor receptor (EGFR), platelet derived growth factor receptor (PDGFR), placental growth factor receptor (PFG-1), and vascular endothelial growth factor receptor (VEGF), are expressed on tumor cells in hemangioblastomas [40]. However, unlike malignant gliomas, the VEGF expression does not correlate with the vascular density as indicated by the expression of

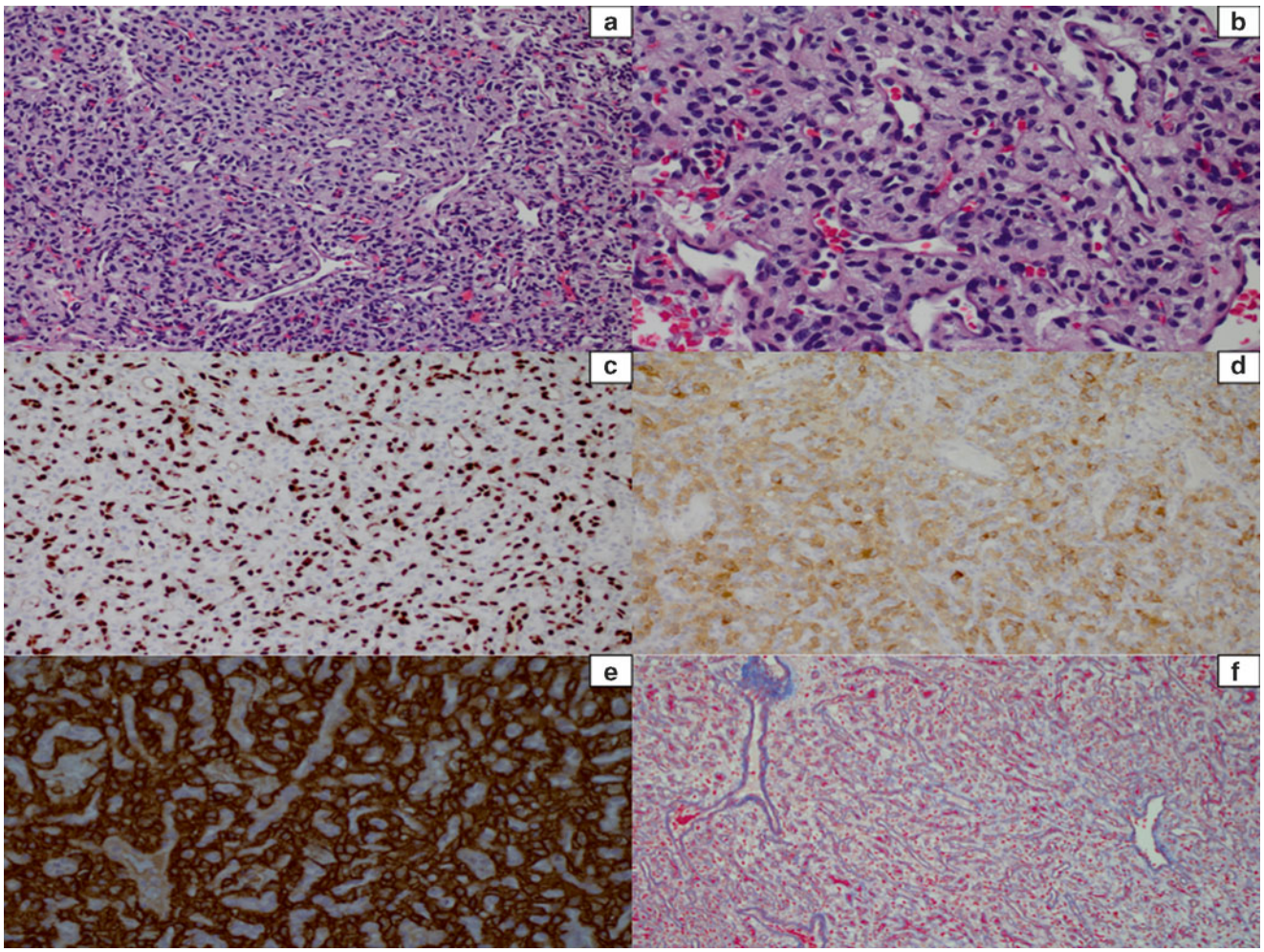

Fig. 14.1. (**a**, **b**) H&E, (**c**) ERG, (**d**) Inhibin, (**e**) Carbomic anhydrase and (**f**) Azocarmine. (**a**) H&E stain shows a highly vascular neoplasm. The tumor is composed of vascular cells and cells with round nuclei designated as "stromal" cells. (**b**) Higher power reveals numerous vascular channels (v) and interspersed stromal cells are seen. Note the nuclear pseudoinclusion in a stromal cell (*arrowhead*). (**c**): ERG immunohistochemistry. Note the intense nuclear staining in vascular cells; (**d**, **e**) Inhibin and carbonic anhydrase immunohistochemistry. Note the intense staining in stromal cells (**f**) Azocarmine stain highlights vascular channels (**a**, **f**, ×50; **b–d**, and **e**, ×100).

CD34-positive endothelial cells. This suggests that pro-angiogenic factors other than VEGF probably contribute to the intense tumor vascularity [41].

Clinical Features

Hemangioblastomas most commonly arise in the CNS especially, but not exclusively, in the posterior fossa. The frequent sites of occurrence in the order of commonality are cerebellum, dorsal part of the spinal cord, brainstem, and retina (Figs. 14.2 and 14.3) [42–44]. The most common site of occurrence of hemangioblastomas in the spinal cord is the thoracic region, followed by cervical and lumbar (48 %, 36 % and 16 %, respectively) [45]. Spinal cord and brainstem hemangioblastomas are frequently associated with tumors at other sites and especially cerebellar hemangioblastomas; in turn, however, cerebellar hemangioblastomas are less frequently associated with tumors at the other sites, suggesting that the spinal cord/brainstem hemangioblastomas are the accompanying manifestation of the latter [46, 47]. Supratentorial (cerebral, sellar/suprasellar, intraventricular) hemangioblastomas are rare [48–50]. It is sometimes difficult to differentiate supratentorial hemangioblastoma from meningioma [38, 51]. Occasionally, hemangioblastomas may arise in extraneural sites such as bone, soft tissue, skin, liver, pancreas, and kidney [52–55].

One-third of hemangioblastomas are associated with the vHL syndrome. The spectrum of tumors [56] associated with vHL is broad and includes hemangioblastomas, renal cell

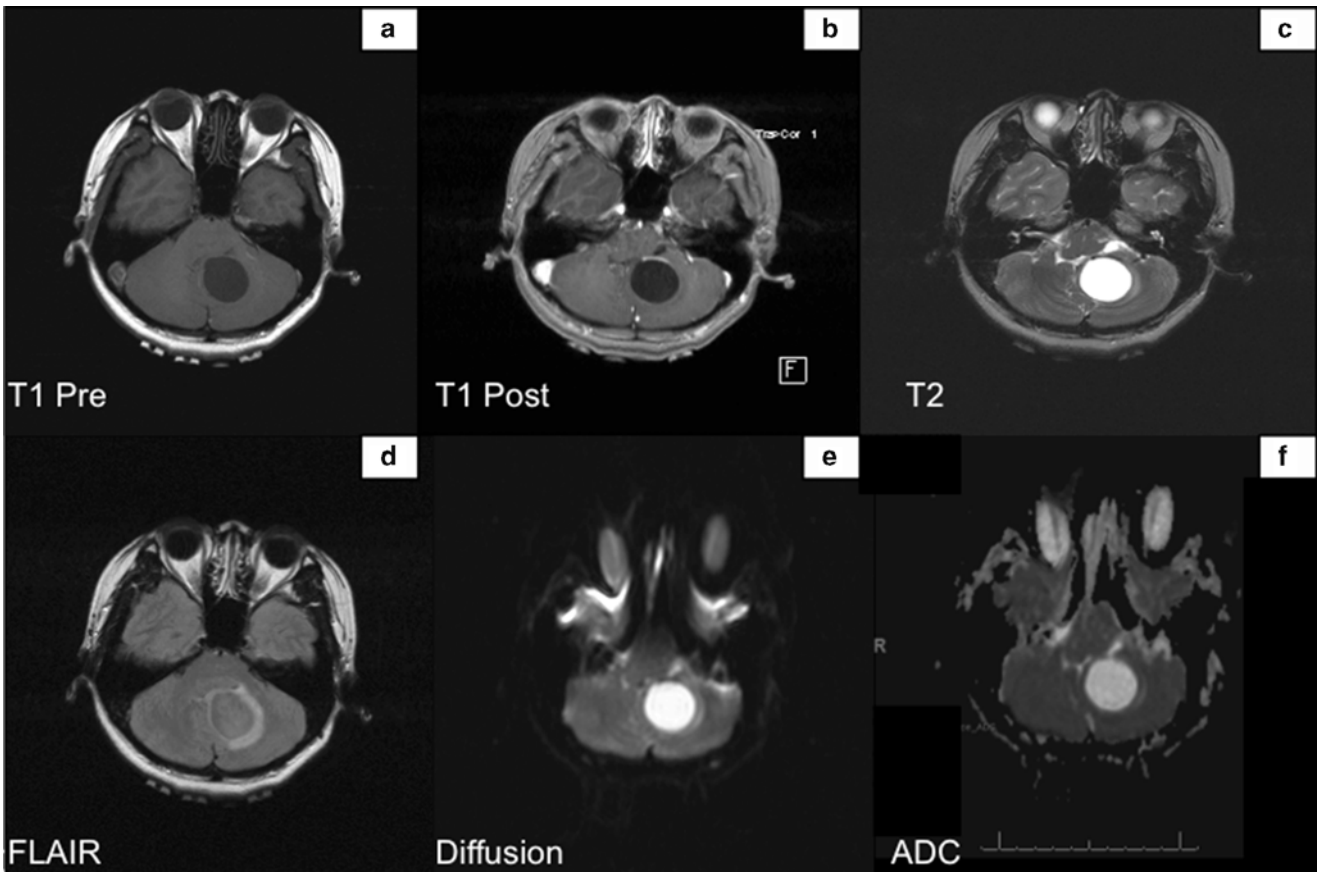

FIG. 14.2 MRI shows the tumor within the inferior medial left cerebellum. Lesion in isointense with the adjacent brain parenchyma on the T1 weighted sequences (Panel **a**), hyperintense on T2 weighted sequence (Panel **c**), and avidly enhances gadolinium (Panel **b**). Diffusion weighted sequence does not demonstrate hyperintense signal within the mass (Panels **e** and **f**)

carcinomas [57, 58], pheochromocytomas [59], extra-adrenal paragangliomas [60, 61], retinal angiomas [62–64], neuroendocrine pancreatic tumors [65–69], papillary cystadenomas of the epididymis [70] and broad uterine ligament [71], as well as endolymphatic sac tumors (ELSTs) of the middle ear [72–74]. vHL-mutated patients with hemangioblastomas are generally younger and present with multiple tumors, while the non-vHL-associated tumors are seen in older patients and are usually solitary.

Based on clinical manifestations, vHL is classified into type 1 and type 2. Type 1 vHL is not associated with pheochromocytoma while type 2 is. Type 2 is further divided into type 2A, 2B, and 2C. vHL-type 2b is associated with high incidence of hemangioblastoma and pheochromocytoma [44, 75–77].

Since patients with vHL syndrome are predisposed to developing multiple hemangioblastomas and require specialized surveillance and treatment, it is imperative to correctly diagnose vHL as early as possible. Genetic testing for vHL in addition to a comprehensive family history should be considered standard practice for all patients with CNS hemangioblastomas, especially those diagnosed under 30 years of age. Clinical screening of vHL-associated tumors consists of complete neuraxis imaging with magnetic resonance imaging (MRI) of the brain and entire spine, MRI of the abdomen, retinoscopy, and measurement of urine catecholamines. Some authors have suggested ophthalmologic screening for family members of vHL disease for early detection of retinal hemangioblastomas [78].

Hemangioblastomas are considered benign tumors, but can cause significant neurological deficits depending on their size and location. Headache, vomiting, cerebellar symptoms, and cranial nerve involvement may be the presenting features. Posterior fossa tumors can also cause cerebrospinal fluid (CSF) flow obstruction leading to hydrocephalus [79, 80]. Patients with spinal cord tumors may present with progressive scoliosis and radicular symptoms until the tumor is large enough to cause weakness. Onset of retinal hemangioblastomas can start prior to 10 years of age until 30 years, after which the risk gradually decreases. It usually presents with unilateral involvement [77]. Hemangioblastomas exhibit a stuttering growth pattern, i.e., there are periods of growth followed by periods of quiescence, which may be as long as 2 years. Indications for treatment relate to the

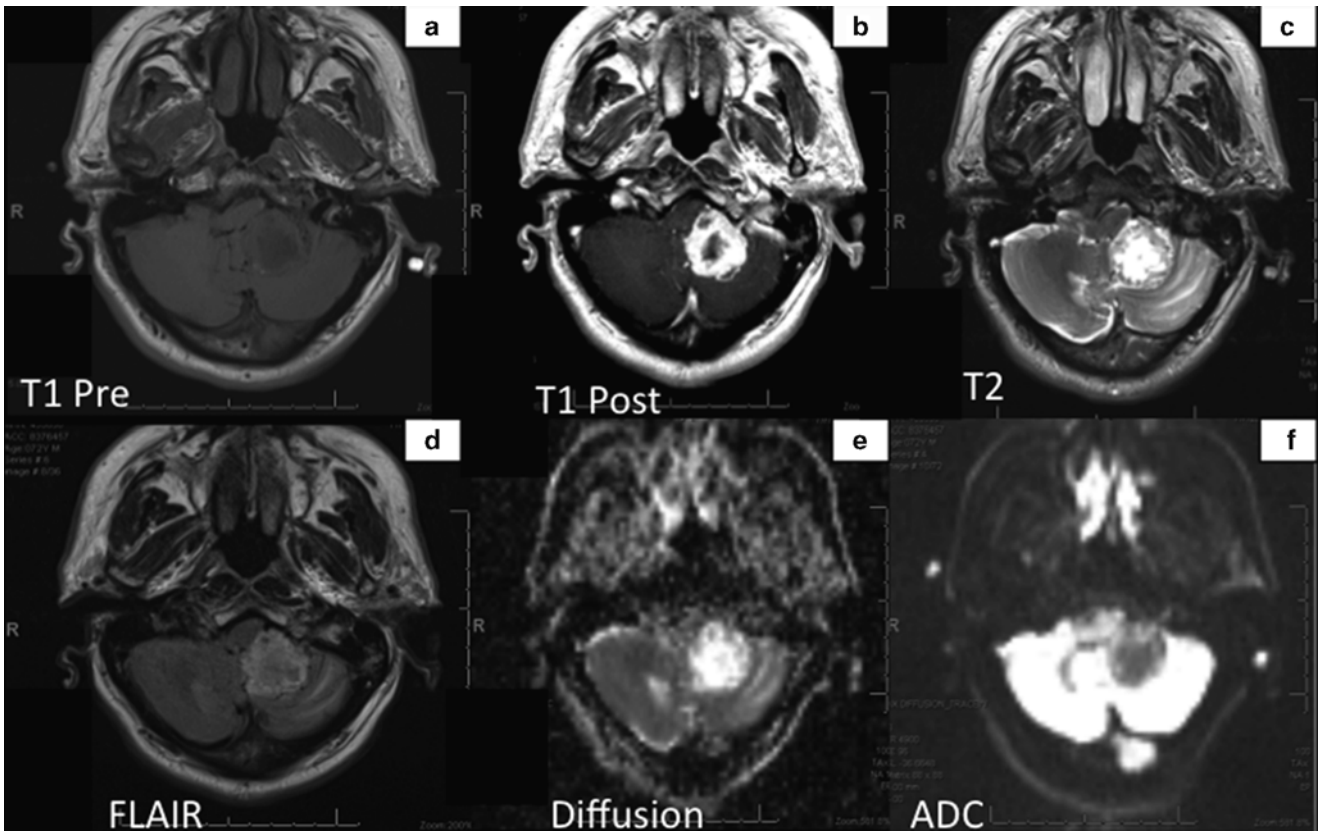

FIG. 14.3. MRI shows the tumor that appears as an irregular thick-walled mass in the region of the left cerebellar tonsil, which enhances intensely with gadolinium (Panel **b**). Mass in predominantly T1 hypointense (panel **a**) but contains several areas of T2 hyperintensity indicating hemorrhagic component (Panel **c**). Diffusion studies show hyperintensity relative to the contralateral white matter (Panels **e** and **f**).

patient's symptoms and tumor size, location, and rate of progression [81]. It is quite common for spinal cord hemangioblastomas to present with syrinx formation [82]. Occurrence of erythrocytosis with male predominance is common in hemangioblastomas due to production of erythropoietin [83, 84]. Due to their arteriovenous malformation-like vascularization, solid hemangioblastomas present a unique neurosurgical challenge [85].

There have been numerous clinical reports of worsening of vHL-associated hemangioblastomas in pregnancy, leading to progressive neurological deficits and obstructive hydrocephalus [86–90]. However, in the first prospective study comparing the rate of tumor growth in pregnant versus the nonpregnant cohorts with vHL-associated hemangioblastomas, Ye et al. observed that there were no differences in tumor growth rate, peritumoral cyst growth and the need for surgery. However, this was a small study with only 27 patients in the pregnancy cohort and it is possible that patients who chose to become pregnant were already in a better state of health leading to selection bias [91].

Imaging

Hemangioblastomas show post-contrast enhancement on computed tomogram (CT) scans and T1-weighed MRI. Imaging studies show the typical appearance of a cyst with mural nodule in approximately 60 % of cases. The nodular portion shows flow voids in the T1 and T2-weighted sequences. Generally, the cysts are slightly hyperintense compared to CSF in T1-weighted images. Both the nodule and the cyst appear bright on T2 and fluid attenuated inversion recovery (FLAIR) sequences [92].

Treatment

While most neurosurgeons agree that surgical intervention of symptomatic hemangioblastomas is required, controversy arises in dealing with asymptomatic hemangioblastomas, which commonly occur in patients with vHL syndrome. Unlike other benign intracranial tumors that exhibit a slow,

progressive growth pattern, hemangioblastomas often have prolonged periods of growth arrest, thus making their natural course difficult to predict [81]. For asymptomatic, radiographically stable tumors, no treatment may be recommended. When asymptomatic tumors show progression on imaging only, the best time for intervention may be difficult to determine [93–96]. Similar to patients with other tumor predisposition syndromes, the optimal clinical management of vHL requires a specialist who oversees and coordinates a multidisciplinary plan of care, including appropriate screening tests.

From a therapeutic perspective, surgical removal remains the treatment of choice for hemangioblastomas and has been successfully employed for cerebellar [97], spinal [98, 99], and brainstem [94, 100] hemangioblastomas. Preoperative cerebral angiography helps surgeons determine the nature of the tumor vascular supply. Following diagnostic imaging, pretreatment with dexamethasone for several days is generally recommended. Intraoperative bleeding increases with tumor size, making en bloc resection of larger tumors difficult. However, modern microsurgical techniques are used to identify feeding vessels and thus help minimize intraoperative bleeding. Dissection should be carried out along the external surface of the tumor in the gliotic brain-tumor interface, to avoid entering the tumor, thus preventing brisk hemorrhage from the hemangioblastoma. The tumor-associated cysts are non-neoplastic and consist of compressed glial tissue, which collapses on its own once the associated tumor is removed. Postoperative complications include temporary worsening of neurological deficits, new neurological deficits, which may or may not resolve during follow-up, cranial postoperative infection, hydrocephalus and aseptic meningitis [101]. A postoperative contrast-enhanced MRI is routinely obtained to verify extent of resection. If no residual is noted, tumor recurrence is rare.

More recently, stereotactic radiosurgery is also being employed with encouraging results especially in spinal hemangioblastomas [102–105]. One advantage of radiosurgery is the ability to treat multiple lesions in a single treatment setting. In a series of 9 patients with 20 spinal hemangioblastomas, 4-year tumor overall and solid tumor control rates with stereotactic radiosurgery were as high as 90 % and 95 %, respectively [106]. In other studies, however, patients with multiple hemangioblastomas associated with vHL syndrome were found to less likely exhibit tumor control after treatment with radiation therapy compared to single sporadic hemangioblastomas [107, 108]. In general, smaller tumor volumes and higher doses of radiation (median 16 Gy) confer a better tumor control [109].

In contrast to surgery and radiation therapy, there is a paucity of data on systemic treatment of hemangioblastomas. Since hemangioblastomas are highly vascular, systemic anti-angiogenic therapies are being investigated as an alternative to surgery, particularly in vHL patients with multiple tumors. Several vHL patients have been treated with semaxanib, a multi-tyrosine kinase inhibitor predominantly active against VEGFR-2. Although disease stabilization outside the CNS was observed in some patients, most of the treatment responses were limited to retinal hemangioblastomas [110]. In a clinical trial for vHL patients with sunitinib, which predominantly targets VEGFR and PDGFR, antitumor activity was seen against renal cell carcinoma, but not hemangioblastomas [111]. EGFR, which is overexpressed and activated in hemangioblastomas, represents an additional attractive target for therapeutic intervention and study in future clinical trials [112]. There have been case reports on the use of anti-angiogenic agents such as bevacizumab [113], pazopanib [114], sunitinib [115], thalidomide [116], and interferon [117] with limited success. However, no prospective clinical trials using these agents have been conducted to date.

Prognosis

Gross total tumor resection was a predictor of prolonged progression-free survival (PFS) in one series [118]. Poor prognostic factors include poor performance status [101], multiple hemangioblastomas, retinal hemangioblastomas, and presence of solid rather than cystic tumors. The risk of recurrence in the future is higher if the age of diagnosis is younger than 40 years with primary sites being the brainstem and spinal cord [119].

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