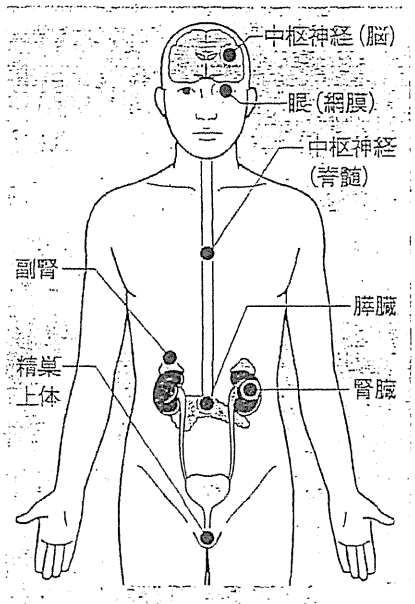
図 VHL 病の病態と診断基準

A. 腫瘍を発症する臓器



● の部分は各臓器における腫瘍を示す

B. 診断基準

1. VHL 病の家族歴がある場合
- 以下の病変がある
  中枢神経系血管芽腫，網膜血管腫，腎細胞癌，褐色細胞腫，膵嚢胞，膵神経内分泌腫瘍，精巣上体嚢胞腺腫

2. VHL 病の家族歴がない場合
- 中枢神経系血管芽腫と網膜血管腫が過去または現在ある
- 上記のどちらか 1 つと，以下の疾患がある
  腎細胞癌，褐色細胞腫，膵嚢胞，膵神経内分泌腫瘍，精巣上体嚢胞腺腫

低酸素誘導因子）を含む蛋白群の分解を制御している．VHL 蛋白は Elongin C，Elongin B，CUL2，RBX1 と結合し，E3 ubiquitin ligase 複合体を形成する（Lindau，1927[4]；Melmon ら，1964[5]；Lamiell ら，1989[6]）．E3 ubiquitin ligase 複合体は分解される標的蛋白と結合するが，このユビキチン化される標的蛋白の一つが，プロリン残基の水酸化という翻訳後修飾を受けた HIF1α，HIF2α である．HIF は HIFα と HIFβ の複合体を形成し，転写因子としての機能をもつ．HIFα は正常酸素圧状態では HIF prolyl hydroxylase（HPH）によりそのプロリン基が水酸化される．HPH により水酸化された HIF 蛋白は E3 ubiquitin ligase 複合体でユビキチン化され，その後 proteasome で分解される．しかし，低酸素状態では HIFα のユビキチン化と分解が抑制され，HIFα は核内に移行して HIFβ と結合し，遺伝子 promoter 内の hypoxia response element（HIF 結合領域）に結合し，さまざまな遺伝子の転写を促進する（遺伝医学関連学会，2003[9]）．

- HIF により転写される遺伝子は 100 以上があり，血管新生，グルコースの取り込み・嫌気的解糖系の促進，好気的解糖系（TCA cycle）の抑制，細胞接着性の低下，運動性・転移能の促進，マトリックスの再構成など，さまざまな機能に関与している（遺伝医学関連学会，2003[9]；Lonser ら，2003[10]；Chen ら，1995[11]；Walther ら，1999[12]）．
- VHL 病の病因として生体内で *VHL* 遺伝子が胚細胞の段階で遺伝子変異により全細胞で 1 コピーが不活性化しており，two-hit 説によりもう 1 つの *VHL* 遺伝子も成長の過程で欠失やメチル化を起こし，2 コピーの

遺伝子機能が消失して正常酸素圧状態でもHIFの分解ができず，HIFは先の遺伝子群を過剰に発現し，種々の臓器細胞の腫瘍化に結びついている．

- 血管新生に関連する遺伝子としては，VEGF，PDGFβが知られており，血管内皮細胞の増殖を促進し，血管の新生・成熟・維持などの作用をもつ．VHL病で発症する中枢神経系血管芽腫や淡明細胞型腎細胞癌ではVEGFが高発現して腫瘍血管の増生が著しく，腫瘍発症の原因となる．

臨床症状・合併症と臨床分類

- 中枢神経系血管芽腫，網膜血管(芽)腫，内耳リンパ嚢腫，膵嚢胞，膵神経内分泌腫瘍，腎嚢胞，腎細胞癌，褐色細胞腫，精巣上体嚢胞腺腫が発症する．
- 2に国内の腫瘍の発症年齢と症状と頻度を示す．発症する腫瘍は多くが多発性，再発性，若年発症である．その典型の中枢神経系血管芽腫は多発性，再発性で神経症状を示し，神経機能低下によるQOLの著しい低下を起こす．腎細胞癌と膵神経内分泌腫瘍は，多発性，再発性で，肺や肝臓，リンパ節などに転移を示す悪性腫瘍である．これらの腫瘍摘出で臓器機能の低下が起こり，腎不全や，膵機能低下（糖尿病など）を引き起こす．まれに副腎褐色細胞腫が悪性像を示す．1に腫瘍を発症する各臓器とVHL病の診断基準を示す．
- 臨床分類として，褐色細胞腫を発症しないか，発症するかでVHL病1型（褐色細胞腫発症なし），VHL病2型（褐色細胞腫発症あり）と分類する．2型のなかでも腎細胞癌発症の有無でさらに2型A（腎細胞癌なし），2型B（腎細胞癌あり）に分類し，さらに褐色細胞腫のみが発症するものを2型Cと分類する（3）．

検査，診断と鑑別診断

- 母斑症に分類されているが皮膚の母斑を示す症例は非常に少ない．
- 1の診断基準に従い，家族歴で複数の腫瘍を発症している家系内の患者がいる場合はVHL病を疑い，下記の方法により各科専門医によって診断される．診断が確定している場合は，各腫瘍の有無を定期的に調べる．

臨床的診断法

中枢神経系血管芽腫

- 頭部と脊髄について，造影MRIによる特徴的な濃染像と嚢胞様の所見で，脳神経外科医，放射線科医により診断される．

2 VHL 病で発症する腫瘍

病変	症状	発症年齢（歳）	頻度（%）
網膜血管腫	視野障害～視力障害	1～67	30
中枢神経系血管芽腫		9～78	約 70
小脳	頭痛		44～72
脳幹	自覚症状なし		10～25
脊髄	項部痛，腫瘍部のある脊椎付近の刺激症状		13～50
内耳リンパ嚢腫	めまい	12～50	11～16
膵嚢胞	時に圧迫による痛み	13～80	17～61
膵神経内分泌腫瘍	症状なし	16～68	8～17
腎嚢胞	無症状	?	60～80
腎細胞癌	初期は無症状，晩期には血尿	20～60	25～50
副腎，パラガングリオンの褐色細胞腫	高血圧など褐色細胞腫に関係する症状	3～60	10～20
精巣上体嚢胞腺腫（男性）		思春期以降	25～60
子宮広間膜嚢腫（女性）		16～46	不明

3 VHL 病の分類

臨床分類	腎細胞癌	褐色細胞腫	網膜血管腫	中枢神経系血管芽腫
VHL 病 1 型	±	−	+	+
VHL 病 2 型 A	−	+	+	+
VHL 病 2 型 B	+	+	+	+
VHL 病 2 型 C	−	+	−	−

臨床分類として，褐色細胞腫を発症しないか，発症するかで VHL 病 1 型（褐色細胞腫発症なし），VHL 病 2 型（褐色細胞腫発症あり）と分類する．2 型のなかでも腎細胞癌発症の有無でさらに 2 型 A（腎細胞癌なし），2 型 B（腎細胞癌あり）に分類し，さらに褐色細胞腫のみが発症するものを 2 型 C と分類する．

内耳リンパ嚢腫

- 造影 MRI（場合により造影 CT 追加）にて診断する．頭部の中枢神経系血管芽腫の診断の際に同時に行える．脳神経外科医，放射線科医により診断される．

網膜血管腫

- 散瞳下眼底検査，細隙灯顕微鏡検査にて特徴的な血管腫像を示す．眼科医により診断される．

褐色細胞腫

- ホルモン産生に関するスクリーニング検査：内分泌内科医によって行われる．
  ① 24 時間酸性蓄尿による，アドレナリン・ノルアドレナリン検査，メタネフリン・ノルメタネフリン検査（基準値上限の 3 倍以上を陽性）．
  ② 血中カテコールアミン検査（基準値上限の 2 倍以上を陽性）．

生化学検査では，①が②より精度が高く，勧められる．

- 画像検査：dynamic CT（造影 CT の早期相），単純 MRI で多発性の特徴的な腫瘍所見を示す．放射線科医，内分泌内科医によって診断される．

腎細胞癌

- dynamic CT（造影 CT の早期相），単純 MRI で多発性の特徴的な腫瘍所見を示す．多くで腎嚢胞の所見を合併する．同じ CT で膵嚢胞，膵神経内分泌腫瘍を同時に診断することが望ましい．泌尿器科医により診断される．

膵嚢胞

- 腎細胞癌を診断する際の造影 CT 早期相で，特徴的な多発性嚢胞の所見を示す．消化器内科医により診断される．

膵神経内分泌腫瘍

- dynamic CT（造影 CT の早期相）で濃染する腫瘍像を示す．腎細胞癌の診断の際の造影 CT で同時に診断することが望ましい．消化器内科医により診断される．

遺伝子診断

- 遺伝学的検査に関するガイドラインなどによれば，発病率が 100 %の疾患であって，予防法と治療法が確立しており，治療によって QOL が保たれる疾患は遺伝子診断を行うことができる疾患とされる．これより VHL 病は遺伝子診断で予後が改善する疾患であると考えられる（遺伝医学関連学会，2003[9]）．
- 遺伝子診断は遺伝カウンセリングと対になっている検査であり，詳細は高知大学医学部泌尿器科学教室のホームページ内の「フォン・ヒッペル・リンドウ（VHL）病診療ガイドライン（http://www.kochi-ms.ac.jp/~hs_urol/htm/topics/vhl-guide/vhl-guide.htm）」を参照されたい．

治療法，経過観察法と予後について

- **4** に従って，幼児期から画像やその他の検査で経過観察を行う．腫瘍の性質が明らかになって生命予後は改善されているが，頻回の手術などの治療により中枢神経機能，視野，視力，腎機能，副腎機能，膵機能などの低下をきたし，QOL は著しく低下する．

中枢神経系血管芽腫

- 脳神経外科医により腫瘍が発見された場合，症状が出るまで適宜に経過観察を行い，症状が出た場合は摘出手術を行う．

網膜血管腫

- **4** による定期的な経過観察で網膜血管腫が発見されれば，視野や視力に問題なければ光凝固を行う．視野や視力に問題をきたす部位では，治

4 各疾患の経過観察について

疾患名	検査開始時期		
	0～9歳	10～19歳	20歳以上
網膜血管腫	0歳～ 眼底検査 ・病変なし：3年に1回 ・病変あり：1年に1回		
褐色細胞腫	2歳～ 問診・生化学検査	腹部超音波 1年に1回 腹部MRI 2～3年に1回	腹部CT 1～2年に1回
中枢神経系血管芽腫 (含む内耳リンパ嚢腫)		11歳～ 脳脊髄MRI 2年に1回	
腎細胞癌		15歳～ 腹部CT* ・病変なし：3年に1回 ・病変あり：1年に1～2回	
膵神経内分泌腫瘍(膵嚢胞)		15歳～ 腹部CT ・病変なし：3年に1回 ・病変あり：1年に1～2回	

*腎機能障害がある場合は腹部MRI.
腎臓，副腎，膵臓の画像検査は，各診療科の協力によりできる限り少ない回数で行う.

療は専門家の判断による.

褐色細胞腫

- 褐色細胞腫が合併する2型家系では，内分泌内科医により**4**に従って経過観察を行う．VHL病における褐色細胞腫は一般例よりホルモン活性，臨床症状が比較的軽いものが多く，経過観察も可能とされる場合もある(Walther ら，1999[12]；Gimenez-Roqueplo ら，2006[13]；Eisenhofer ら，1999[14]，2001[15]，2008[16])．
- 褐色細胞腫が合併する2型家系では，2歳時から24時間酸性蓄尿による，アドレナリン・ノルアドレナリン検査，メタネフリン・ノルメタネフリン検査を行う．①生化学検査が陽性化，あるいは，②腫瘍が3.5 cm以上に増大，あるいは，③腎臓などの他の手術を予定する時点で，褐色細胞腫の手術を行う(Maranchie ら，2001[17])．腹腔鏡などの低侵襲手技が勧められる(Maranchie ら，2001[17]；Yip ら，2004[18])．VHL病では対側副腎に発症の可能性があるので，できるだけ部分切除により副腎機能の温存を図る.

腎細胞癌

- **4**に従い，小児期から経過観察して腫瘍が確認された場合，腫瘍の直径が2 cmになった段階で治療を行う．小腫瘍ではラジオ波焼灼術などを行う.
- 外科的な治療としてはできる限り腎温存手術（腎部分切除術または腫瘍核出術）を行う．開腹手術を行う際は同時に発見される小腫瘍も部分切除や核出術を行う．中心部発生の腫瘍など腫瘍の部位で部分切除が不可能な場合，発見時の腫瘍が大きい場合，多数の腫瘍である場合に腎

摘除術が行われる.

●遠隔転移を有する症例に対しては，一般的な腎細胞癌の有転移例と同様に「腎癌診療ガイドライン」に従い治療する.

膵神経内分泌腫瘍

●消化器内科医により[4]に従い造影 CT にて定期的な経過観察を行うが，腫瘍が発見され，最大腫瘍サイズ≧2 cm，腫瘍の倍増速度≦500 日の場合は，腫瘍核出を基本とした手術を行う.

おわりに

●VHL 病の歴史的な概略，臨床的診断法，遺伝子診断法，泌尿器系治療法と経過観察法についてなるべく簡潔に述べた．中枢神経系血管芽腫，網膜血管腫，膵腫瘍の治療と経過観察の要点については，高知大学医学部泌尿器科学教室のホームページ内「フォン・ヒッペル・リンドウ（VHL）病について必要な知識（http://www.kochi-ms.ac.jp/~fm_urol/japanese/vhl.html）」を参考にしていただきたい.

（執印太郎，田村賢司，井上啓史，山崎一郎）

▶文献は巻末に収載

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Review Article

Retinal Capillary Hemangioma in von Hippel-Lindau Disease: Current Concept, Diagnosis and Managements

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- Management

Abstract

von Hippel-Lindau (VHL) disease is caused by a mutation in the VHL gene, resulting in the functional disorder in VHL-encoded protein (pVHL). Recent advances in experimental and clinical studies on VHL gene/protein and VHL disease have provided novel concepts in molecular pathology and clinical managements. pVHL plays a critical role in the regulation of hypoxia inducible factor (HIF)-dependent as well as HIF-independent signaling pathways. These mechanisms should underlie the pathogenesis of VHL-related retinal vascular tumors. It is still controversial whether the histological term "hemangioma" vs "hemangioblastoma" should be appropriate in calling retinal vascular tumors of VHL disease. Recent clinical studies have proved efficacy of various therapeutic options depending on the location of retinal tumors between peripheral and optic disc/juxtapapillary hemangioma. Long-term follow-up observation can be achieved in VHL disease patients, showing favorable outcomes of conventional standard treatments. However, there still exists a population suffering from irreversible severe visual disturbance even though the conventional treatments had been performed enough. Further challenging of molecular targeting therapy as well as development of vitreoretinal surgeries and gene/protein transfer technique may contribute to preservation of the patients' vision in the future.

INTRODUCTION

von Hippel-Lindau (VHL) disease is a rare hereditary (1/36,000 live births) autosomal dominant syndrome [1]. VHL disease is manifested by a range of different benign and malignant tumors, including hemangioma/hemangioblastoma of the retina and central nervous system, renal cell carcinoma, pheochromocytomas, pancreatic carcinoma, and cysts in the kidneys, liver, and pancreas [2]. There are two different clinical patterns for diagnosis of the disease: 1) patients with a positive

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history of developing retinal hemangioma as well as systemic tumors such as renal cell carcinoma, pheochromocytoma, pancreatic tumors or cysts, epididymal cystadenoma associated with VHL, and 2) patients without a family history of VHL who present with retinal hemangioma in combination with other various tumors [3]. VHL is an age-dependent and highly penetrant disease with the more common manifestations being retinal hemangiomas. VHL-associated retinal hemangioma occurs in over 60% of the patients [4], and is the first manifestation of the disease in 43% of patients [5]. On the other hand, about half of retinal hemangiomas are related to VHL [6]. However, it remains unclear whether retinal capillary hemangioma that occurs without a family history is most commonly sporadic or most commonly represents an initial manifestation of VHL [7,8].

It is indisputable that biotechnology and molecular science have developed dramatically during a couple of decades. Indeed, long-term follow-up cases have been accumulated according to recent literatures. These backgrounds certainly provide an opportunity to reconsider the previous concept and clinical aspects of the disease. In this review, the current development of molecular pathological studies, clinical characteristics, histopathology, differential diagnosis and managements are included and discussed.

Recent advances in molecular pathology of VHL

VHL disease is caused by a mutation in the *VHL* gene [2], resulting in the functional disorder in VHL-encoded protein (pVHL). Originally identified as a tumor suppressor, the pVHL is now known to repress expression of mRNAs that are normally induced under hypoxic conditions [9]. The hypoxia-inducible factor (HIF) is a key transcription factor responsible for up-regulation of various hypoxia-inducible genes' expression. When mutated, the *VHL* gene produces a protein that is unable to regulate HIF, permitting accumulation of HIF and subsequent activation of vascular endothelial growth factor (VEGF) and other hypoxia-inducible genes [10]. This can result in growth of retinal hemangiomas and other tumors associated with VHL disease. pVHL is a substrate recognition component of an E3-ubiquitin ligase that rapidly destabilizes HIF-alpha under normoxic, but not hypoxic, conditions. Thus, pVHL is known to be regulating angiogenic factors through HIF-alpha depending on tissue oxygen concentration. Chemokines are a group of structurally related secretory and transmembrane proteins whose major tasks are to coordinately recruit various leukocyte populations into target tissue sites via specific receptors. Chemokine receptor CXCR4 is reported to be down-regulated by the pVHL and upregulated by HIF [11].

Apart from HIF dysregulation, further conditions that favor tumorigenesis may be related to both non-functional or absent pVHL in the cell. VHL-deficient cells lose the ability to exit the cell cycle, making it the initial step in VHL tumorigenesis. Ultimately, cells lacking pVHL are deficient in assembly of an extracellular fibronectin matrix or in regulating growth arrest mediated by cell-extracellular matrix signaling [12,13]. To clarify how the HIF-independent mechanisms by pVHL underlie pathogenesis of retinal hemangioma is a future issue.

Recent *in vivo* studies have shown that VHL gene is essential for normal development of the retinal tissue and vitreoretinal vasculature. Kurihara et al. generated retina-specific conditional-knockout mice for VHL (Vhl(alpha)(-CreKO) mice. These mice exhibit arrested transition from the fetal to the adult circulatory system, persistence of hyaloid vessels and poorly formed retinal vessels. These defects are suppressed by intraocular injection of FLT1-Fc protein [a VEGF receptor-1 (FLT1)/Fc chimeric protein that can bind VEGF and inhibit its activity], or by inactivating the HIF-1alpha gene. These suggest that not only macrophages mediating programmed cell death, but also tissue oxygen-sensing mechanisms regulate the transition from the fetal to the adult circulatory system in the retina [14]. VHL also plays a crucial role in the tissue maintenance of the neural retina as well as retinal pigment epithelium (RPE). Lange et al. demonstrated that VHL-dependent regulation of HIF-1alpha in the RPE is essential for normal RPE and iris development, ocular growth and vascular development in the anterior chamber, whereas VHL-dependent regulation of other downstream pathways is crucial for normal development and maintenance of the retinal vasculature [15].

Clinical features of retinal capillary hemangioma

Ocular VHL disease typically occurs as retinal capillary hemangioma found either in the peripheral retina and/or the optic disc/juxtapapillary region (Figure 1). Retinal hemangioma originates from the inner, midperipheral retina and usually grow, causing visual impairment due to leakage leading to various secondary changes in the eye [16]. Approximately one-third of patients have multiple retinal capillary hemangiomas, while two-third have isolated tumor [4]. The most common clinical finding of these retinal hemangiomas is a highly vascularized tumor in the superotemporal region of the retina [17]. The coloration of the vascularized tumors is commonly found as reddish, while orange-yellow tumors can be seen [18]. These tumors are often endophytic and peripheral spherical masses classically associated with a dilated tortuous feeding artery and a draining vein. Usually, two or three tortuous feeding vessels with dilatation are accompanied with the peripheral tumors. Even in case of peripheral retinal hemangiomas, coloration of the optic disc can be reddish, and the optic disc margin may be unclear (Figure 1) in the same eye. Alternatively, retinal hemangioma may

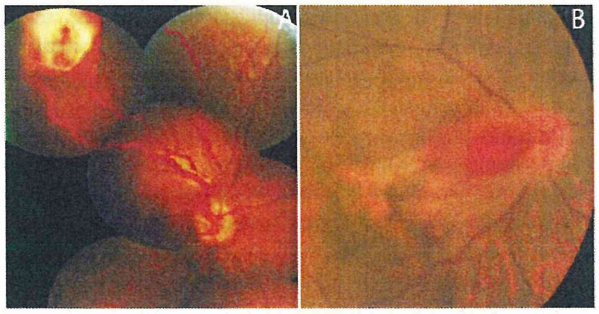

Figure 1 Fundus photograph of two von Hippel Lindau Disease patients with retinal capillary hemangioma in the temporal periphery (A), and juxtapapillary hemangioma (B) of the right eye. Two dilated vessels emanate from the tumor (A). In contrast, no dilated feeder vessels are noted in juxtapapillary hemangioma (B). (B: Case courtesy of Dr Hiroshi Yoshikawa).

be exophytic, and arise from the outer retinal layers. Exophytic tumors are not usually associated with arteriovenous shunting. They tend to develop in the juxtapapillary region (Figure 1), and are frequently misdiagnosed as papilledema, choroidal neovascularization or tumors of RPE or choroid.

Approximately one quarter (22%) of eyes demonstrated de novo ocular involvement, with 18% demonstrating new retinal hemangiomas in a peripheral retinal location only, 2% demonstrating new tumors in a juxtapapillary location only, and 2% demonstrating new tumors in both juxtapapillary and peripheral locations [19]. These anatomical features between peripheral and optic disc/juxtapapillary tumors may reflect on different clinical course and therapeutic approach. In a recent cross sectional study, vision loss in 335 patients with VHL-associated retinal hemangiomas more likely occurred when the lesions were in the juxtapapillary region [20]. Severe vision loss in the affected eyes was also related to the patients' age, the number and size of tumors located in the periphery [20]. The study also showed that although bilateral involvements are common, the rate of bilateral visual impairment is less common due to the asymmetric disease burden. However, the tumor can still lead to blindness and the rate of significant morbidity in one eye remains high. Among eyes with ocular VHL disease at baseline, 88% did not demonstrate retinal hemangiomas in a new retinal location, 70% remained stable in the number of retinal hemangioma, and 79% remained stable in the extent of the tumor involvement. Mean visual acuity for all study eyes decreased by 5.1 ± 0.6 letters across follow-up, with 16.1% of the eyes decreasing by more than 10 letters in visual acuity. Among eyes affected at baseline, greater vision loss was associated with the presence of juxtapapillary hemangioma, development of retinal hemangioma in a new location, and increase in peripheral hemangioma number and extent [19].

Secondary changes of the disease usually entail exudative or tractional effects surrounding the tumor [21]. Exudation occurs in 25% of cases, of which 10% is intraretinal exudation and a further 16% can cause retina detachment. Fibrovascular proliferation secondary to peritumoral ischemia in the 9% of cases produces tractional retinal detachment, macular ectopia, epimacular proliferation and traction leading to rhegmatogenous retinal detachment [22].

Of all the ancillary tests available to detect retinal capillary hemangioma, fluorescein angiography (FA) is the most informative diagnostic tool because of the vascular nature of the tumor. The retinal tumor has fine capillary filling, which rapidly becomes homogeneous. The draining vein becomes prominent in the venous phase, while the tumor demonstrates progressive hyperfluorescence with late leakage of dye into the surrounding structures [4]. Optical coherence tomography (OCT) is useful in diagnosis of the exophytic retinal hemangioma [23] despite the presence of the juxtapapillary or peripheral region [24], in detecting subretinal fluid, and in monitoring the response to treatments [25].

Histopathology of surgically excised retinal tissues

Whether we should use terms "hemangioma" or "hemangioblastoma" in calling retinal vascular tumors has yet to be determined. Hemangioblasts are the multipotent precursor cells that can differentiate into both hemopoietic and endothelial cells [26]. Principally, the term "hemangioblastoma" should be used in tumorigenesis of the hemangioblasts. Recently, isolated erythropoietin-positive cells, indicative of developmentally arrested hemangioblasts, were detected in retinal vascular tumor associated with VHL [27,28], suggesting that the retinal tumor may be closely associated with the term "hemangioblastoma". On the other hand, when the term "hemangioblastoma" is used, the tumor cells morphologically should have nuclear atypia and dense cell proliferation with some undifferentiated changes, malignancy and/or malignant potential rather than "hemangioma". For example, these tendencies are clearly seen in histology of retinoblastoma, which is totally different from that of retinoma [29]. As described below, the tumor cells do not present with nuclear atypia, mitotic figure, or high cellularity in case of retinal vascular tumor in VHL disease. These findings are marginally different from cerebellar hemangioblastoma in VHL. In order to prove this, comparative studies on histopathology will be needed between the retinal and cerebellar vascular tumors of VHL disease. Although traditionally the vascular tumor in VHL disease has been recognized as hemangioblastoma, various authors have recommended that capillary hemangioma rather than hemangioblastoma be used to describe vascular tumors in VHL disease [4], based on histological findings. Therefore, in this review, the term "hemangioma" has been used in retinal vascular tumor observed in VHL disease.

Histologically, the basic lesion is a capillary hemangioma, but not cavernous hemangioma, in vascular tumors of the retina in patients with VHL. The tumor, a capillary hemangioma, is composed of endothelial cells, pericytes, and stromal cells. It is likely that the hemangioma replaces full-thickness of the retina. Retinal hemangioma reveals a variety of vacuolated "foamy" stromal cells reside among the thin capillary-like channels [30]. Morphologically, the stromal cells can present with characteristic pale, polygonal cells (Figure 2). The stromal cells appear foamy due to the presence of phagocytosed lipids produced by leaking capillary endothelium. The lipid is plasma-derived cholesterol stearate [31]. In addition to these typical histological findings, Chan and associates have identified sporadic tumorlet-like cells characterized by small cellular clusters, which form angiomesenchymal islands in optic disc hemangioma of VHL disease [28,32]. Immunohistochemical studies show that the

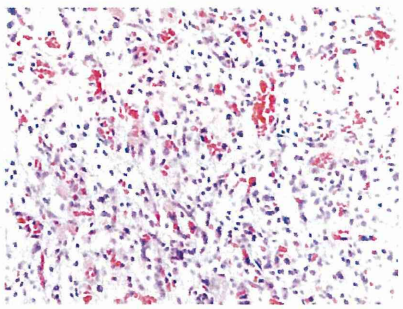

Figure 2 Histological finding of retinal hemangioma in a patient with von Hippel Lindau Disease (Case courtesy of Professor Akito Hirakata). Note collection of marked microvessels without nuclear atypia admixed with foamy stromal cells.

foamy stromal cells reveal positive reaction for glial fibrillary acidic protein, which appear to be of glial origin. However, the stromal cells also showed positive for neuron-specific enolase (NSE), indicating that the stromal cells are not originated from glial cells only. Some of the stromal cells stained positively for inhibin alpha [27]. These results suggest that stromal cells in retinal hemangiomas are neuroectodermal in origin with immunohistochemical features. Miyazawa et al. recently demonstrated that the NSE-positive stromal cells expressed VEGF protein in retinal hemangioma. Chan CC et al. showed expression of VEGF, and HIF, as well as several stem cell markers including erythropoietin, erythropoietin receptor, and CD133, in human retinal and juxtapapillary hemangioma in VHL disease [28,33,34]. In contrast, CD117, the stem cell factor receptor, was not expressed in retinal tumor cells of VHL disease, suggesting that the tumor may not have myeloid/neural crest lineage [28]. Recently, Liang et al. demonstrated CXCR4 immunoreactivity in the cytoplasm and nuclei of the stromal and vascular cells in retinal hemangiomas of VHL cases, whilst CXCL12 was negative in the retina [35]. They also showed that gene expression of VEGF and CXCR4 was highly detected in retinal hemangioma tissues. The VHL gene deletion may be restricted to the stromal cells, suggesting that the stromal cells are the neoplastic component in retinal hemangiomas, and induce the associated neovascularization [36]. Further pathological examinations will definitely characterize the morphology and biological features in hemangioma/hemangioblastoma.

Differential diagnosis

Primitive retinal vascular abnormalities are benign conditions of the retinal circulation that comprise vascular tumors and telangiectasias. Retinal vascular tumors include not only retinal capillary hemangioma, but also vasoproliferative retinal tumors (VPRTs), cavernous hemangioma of the retina, and racemose hemangiomatosis of the retina or Wyburn-Mason syndrome [25]. Of particular importance, many of the vascular tumors of the retina have significant associations with systemic disease. As ocular symptoms are often the most common presenting disease manifestation, the ophthalmologist plays an important role in accurate and early diagnosis [37]. Especially, recent several researchers have conducted pathological and immunohistological analyses in patients with VPRT. Therefore, clinical and molecular differences in VPRT from retinal hemangioma are discussed in this review; otherwise, please refer to recent and previous review articles regarding differential diagnosis of other important retinal vascular tumors [4,25].

VPRTs are benign glial and vascularized tumors of the sensory retina (Figure 3), located at the temporal periphery. VPRT causes retinal neovascularization or exudative retinal changes. The tumors are associated with no large retinal feeder vessels, as observed in retinal hemangiomas associated with VHL disease. Approximately 75% of cases are idiopathic and the rest is secondary to retinitis pigmentosa, chronic retinal detachment, and Coats disease. Patients with VPRTs have no systemic tumors such as VHL disease Laser photocoagulation or cryotherapy is commonly performed for these tumors [38]. Plaque radiotherapy, photodynamic therapy (PDT), or pals plana vitrectomy might be performed when the tumors do not respond to these procedures [39]. The histology of the tumor

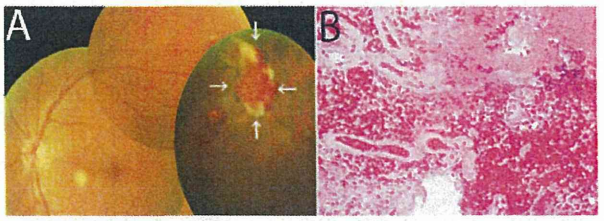

Figure 3 Fundus photographs (A), and histological findings (B) of the surgically excised vasoproliferative retinal tumor tissue.

Fundus photograph shows elevated reddish retinal tumor at the temporal mid-periphery (arrow), involving neovascularization on the surface (A). Light micrograph demonstrates a correction of small vessels with thickened vessel walls and marked hyalinization. Spindle-shaped stromal cells are intermingled in the tumor. (hematoxylin-eosin, original magnification x200).

demonstrated a correlation between small vessels with a thickened vessel wall and marked hyalinization, where glial cells are intermingled (Figure 3). The pathological findings in the abnormal vessels are different from those in retinal hemangioma of VHL disease. Liang et al. demonstrated that there was no immunoreactivity against VEGF or CXCR4 in VPRT [35], whereas we have shown immunoreactivity for VEGF in tumor tissues of VPRT [40]. Although the immunohistochemical results are still controversial, anti-VEGF antibody therapy is basically effective for patients with VPRT [40]. Loss of heterozygosity of VHL genes is detected with microsatellite marker D3S1110 in retinal tumor tissues coming from VHL disease but not in VRPT [35].

Managements of peripheral retinal hemangioma

The universal goal in the treatment of retinal hemangioma is preservation of visual acuity and the visual field without destruction of the function of the retina around the tumor. In order to achieve the therapeutic goal, it may be a significant process to reduce tumor volume via sclerosis of dilated feeder vessels. A study showed that patients with smaller lesions (less than 1.5 mm) were more likely to remain stable. Those that progressed in this group were well controlled with standard therapies including cryotherapy and/or photocoagulation [41]. Hence, retinal hemangiomas are generally treated with cryotherapy or laser photocoagulation, and patients receive a 72% and 74% success rate, respectively [41]. Laser treatment is sufficient in small peripheral tumors and cryotherapy could be carried out in patients with large retinal tumors. We herein demonstrate a VHL case of peripheral retinal hemangioma treated with laser photocoagulation (Figure 4). A twenty-year-old female complained of blurred vision in both eyes. She had a medical history of cerebellar and spinal cord hemangioblastomas. Her father had been diagnosed with VHL disease. At the age of 23, visual acuity became no light perception in her right eye due to retinal detachment although she received several times of laser photocoagulation. In contrast, she also received laser photocoagulation to the small retinal tumors for 21 times in total, which has been keeping favorable vision over 20 years (Figure 4). In addition to those therapies, Kreusel et al. conducted retrospective study including 25 retinal capillary hemangiomas of 24 patients treated with brachytherapy using 106-ruthenium/106-rhodium plaques. Of 25 tumors, 23