

DIAGNOSING VON HIPPEL LINDAU DISEASE BY RETINAL CAPILLARY HAEMANGIOBLASTOMAS

Yurike Mandrasari¹, Wino Vrieda Vierlia¹, Andhika Yudhistira², Nadia Artha Dewi¹

¹Department of Ophthalmology, Faculty of Medicine, Universitas Brawijaya

²Department of Orthopaedics, Faculty of Medicine, Universitas Brawijaya
Dr. Saiful Anwar General Hospital, Indonesia

Abstract

Introduction: Von Hippel-Lindau (VHL) syndrome is a disease characterized by the formation of tumors or cysts in many different parts of the body caused by germline. The prevalence of this autosomal dominant condition is very rare. Understanding of clinical manifestation and diagnostic criteria is needed.

Case Report: Female, 22-year-old was referred from orthopaedic department suffered from blurred and misalignment of the left eye since 3 months ago. Based on indirect funduscopy examination, we found disc swelling with exudative retinal detachment on her left eye and orange-reddish retinal mass concluded as Retinal Capillary Hemangioblastoma (RCH) with tortuosity and dilatation of blood vessel on her right eye. The MRI showed multiple masses in cervical to lumbar vertebrae and multiple cyst on pancreatic gland.

Discussion: This patient had 1 ocular RCH, multiple spinal tumor and multiple pancreatic cysts with no confirmed family history, therefore almost fulfilling the diagnostic criteria of VHL. To further confirm the diagnosis, it was necessary to find other common comorbidities of VHL such as gene testing of VHL heterozygous germline mutation. Interdisciplinary approach consists of not only diagnostic and treatment plans from one speciality department, but also the ones from other related divisions and departments.

Conclusion: Screening and interdisciplinary approach in managing Von Hippel-Lindau syndrome are required to be performed promptly.

Keywords: Von Hippel-Lindau syndrome, retinal capillary hemangioma, multiple spinal masses, multiple cyst on pancreas gland

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Correspondence to:

Yurike Mandrasari,
Department of Ophthalmology,
Faculty of Medicine, Universitas
Brawijaya
yurike2010@gmail.com

INTRODUCTION

Von Hippel-Lindau (VHL) disease is a predisposing syndrome of tumor that is passed

down through autosomal dominant inheritance. Gene mutation in VHL occurs in 3p26-25 chromosome. People who suffered from VHL usually developed benign or malignant tumors in organ systems such as

retinal capillary haemangioblastoma (RCH), hemangioblastoma of central nervous system (CNS HB), endolymphatic sac tumor, neuroendocrine tumor, pancreatic cyst, renal cyst or tumor, pheochromocytoma, testicular cyst or tumor, and ovarian cyst or tumor.¹⁻³ Retinal capillary haemangioma (RCH) is a rare kind of tumor that can be threatening to vision. The prevalence of retinal tumor in VHL is about 60%. Approximately 50% of patients had single lesion, and almost all of the patients with multiple lesions had VHL. The incidence of VHL is about 1:36.000 in newborn, with estimated prevalence in Europe is about 1-9/100.000. The diagnosed patients had pretty young age average, 26 years old.^{2,3}

The diagnosis of VHL can be established clinically when a patient has typical clinical history and manifestations. Clinical diagnosis can be established when following conditions are met there is one tumor index (haemangioblastoma, pheochromocytoma, or clear cell renal carcinoma) accompanied by one positive family history of VHL, or there are 2 or more CNS haemangioblastoma accompanied by one visceral manifestation without positive family history of VHL. Genetic testing of VHL heterozygous germline mutation may be used to confirm diagnosis.^{3,4}

Patients that came to seek treatment had varying degree of disease severity. A delay in diagnostic process due to failure of recognition could result in various unexpected effects. Mortality in VHL usually happened due to metastatic process of renal carcinoma and CNS HB.^{3,4} The aim of this case report is to increase the readers knowledge and understanding of VHL and how to make good interdisciplinary diagnostic and treatment approach to the patients suffering from it.

CASE REPORT

A 22 years old female patient was referred from orthopaedic outpatient clinic of RSUD dr. Saiful Anwar Malang to ophthalmology department to consult about outward rotation of her left eye that had started about 3 months before admission. No other ocular symptoms were reported. She initially came to seek treatment for weakness in her left leg accompanied by walking difficulties for about 2 years. This condition worsened since about a month before admission. Other systemic complaints such as weight loss, headache, coughing, shortness of breath, nausea, vomiting, and urination/defecation problems were denied.

The patient presented with decreased motor function of left leg. Patient had normal level of consciousness and vital signs. From anterior eye segment examination, the visual acuity of her right eye was found to be 6/6, while her left eye had LP (+) with good projection centrally and 6/6 temporally. The Hirschberg test result was 15 degrees XT on *up gaze, primary gaze* and *down gaze OD leading eye*. RAPD was positive on left eye. Other anterior segment examinations, intraocular pressure, eye movement examinations, eyelids, and other cranial nerve II functions (Amsler grid, Ishihara, confrontation test) were all within normal limits.



Figure 1. **Anterior segment.** 15 degrees XT on *up gaze, primary gaze* and *down gaze OD leading eye*.

Fundoscopy of right eye showed tortuosity, vasodilation, and round retinal mass with size of 1,5 DD (disk diameter), well-defined margins, smooth surface, and orange-reddish color in superonasal quadrant of cranial nerve II head. There were also tortuosity and dilation of nearby blood vessels.

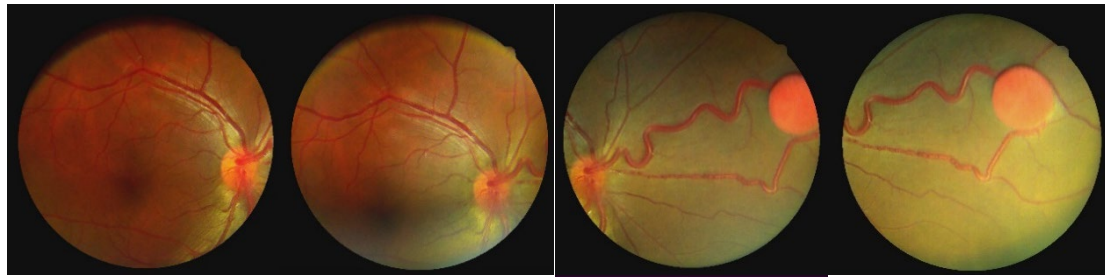


Figure 2. **Fundoscopy of right eye.** On funduscopy examination there were tortuosity, vasodilation, and retinal capillary haemangioblastoma (RCH)

Fundoscopy of left eye revealed blurred margins in all of optic nerve head quadrants, tortuosity, vasodilation, exudate, and almost fully detached retinal surface.

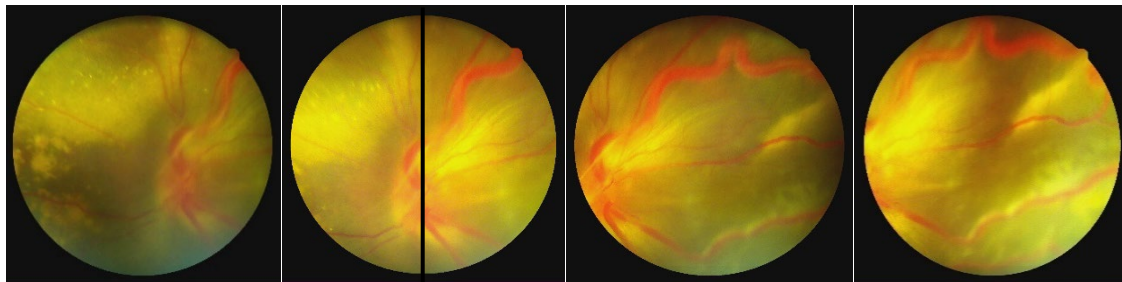


Figure 3. **Fundoscopy of left eye.** On funduscopy examination there were tortuosity, vasodilation, exudate, and retinal detachment.

Angiography analysis of the lesion in 8x8mm scan revealed a superficial layer mass in right eye. OCT of cranial nerve II head of right eye showed thickenings in superior, nasal, and inferior quadrants. There were thickening of superior quadrant and thinning of inferior and temporal quadrants in left eye.

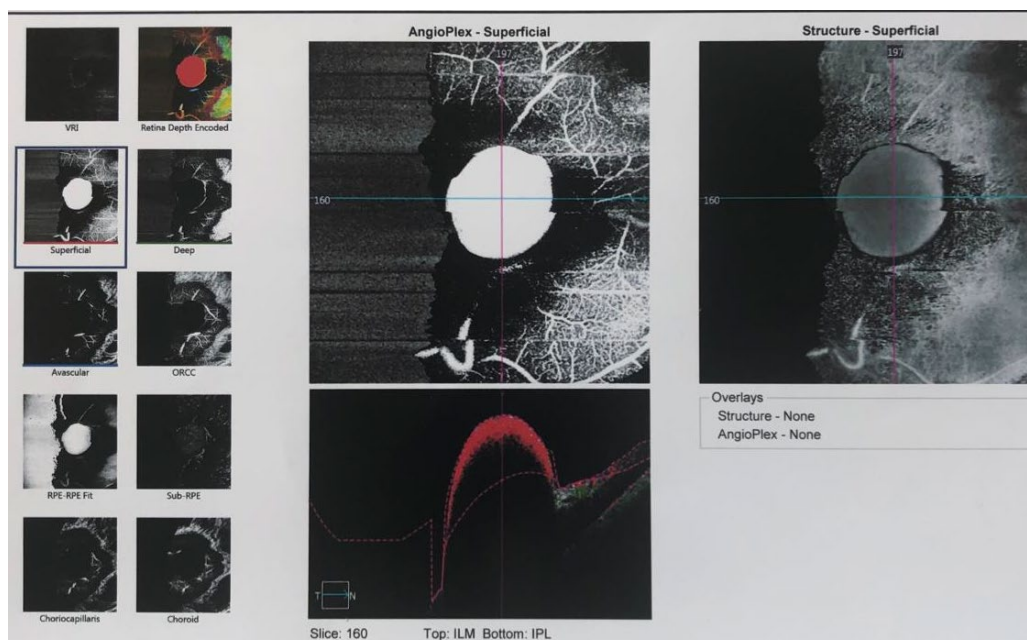


Figure 4. **Angiography analysis of right eye.** Round mass in superficial layer, retinal capillary haemangioblastoma (RCH)

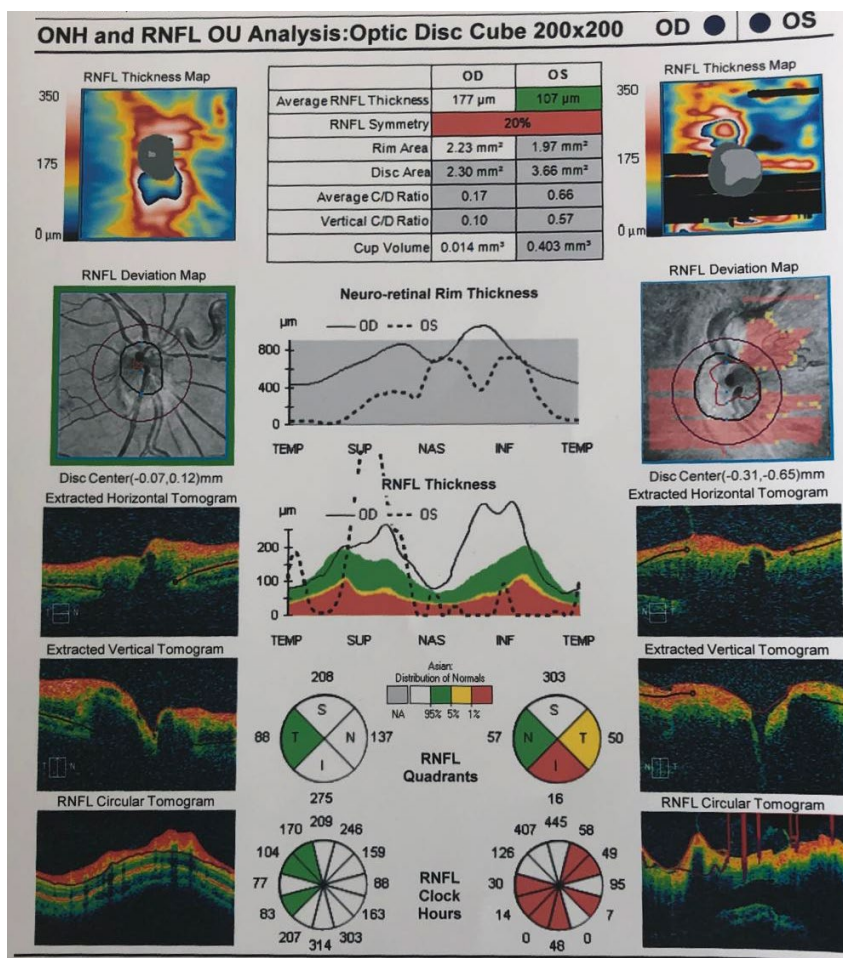


Figure 5. OCT of Cranial Nerve II head. Thickening of superior, nasal, and inferior quadrants of right eye and superior quadrant of left eye. Thinning of inferior and temporal quadrants of left eye.

The patient had been experiencing left lower extremity weakness for 2 years. Whole spine MRI revealed the existence of multiple site syringomyelia and IDIM (Intradural Intramedullary) tumor along cervical and lumbar vertebrae. No other systemic problems were reported, although multiloculated cystic lesions all over pancreatic parenchyma of variable size were found in lumbal vertebrae MRI examination.

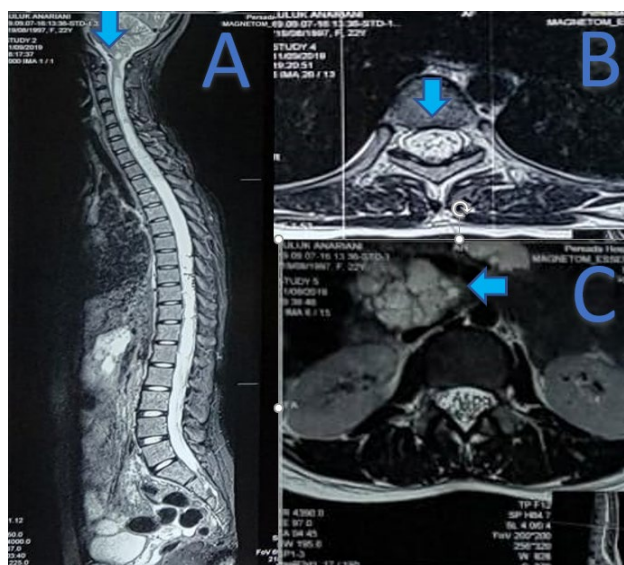


Figure 6. A and B. Whole Spine MRI, sagittal and axial view. Multiple masses along cervical and lumbar vertebrae C. Lumbar MRI. Multiple pancreatic gland cysts in axial view

Patient was therefore diagnosed with multiple site syringomyelia and IDIM tumor of cervical-lumbar vertebrae, multiloculated cystic lesions of pancreatic parenchymal tissue with various size that were found in lumbar vertebrae MRI, ODS papilledema and compressive optic neuropathy, OD retinal capillary hemangioblastoma (RCH), OS exudative retinal detachment + XT sensory, suspected to be Von Hippel Lindau Syndrome. Interdisciplinary approach to this patient was made between orthopaedics, ophthalmology and radiology departments. Then we consult to internal medicine department due to lumbar MRI finding of multiple pancreatic gland cysts.

The ophthalmology team planned to do head and orbital MRI with and without contrast. Orthopaedics team, specifically the spine subdivision team, planned to do shunting and decompression. Further screening of other organ systems such as kidneys, ENT, abdomen, etc. was also planned.

DISCUSSION

The diagnosis of VHL can be established by clinical criteria when there were typical clinical history and manifestations. Clinical diagnosis can be established when there is one tumor index (haemangioblastoma, pheochromocytoma, or clear cell renal carcinoma) accompanied by one positive family history of VHL. It can also be established when there are 2 or more CNS haemangioblastoma accompanied by one visceral manifestation without positive family history of VHL. This patient had 1 RCH of the eye, multiple spinal tumors, multiple pancreatic cysts with no confirmed family history, so the diagnostic criteria of VHL was suspected.³ Genetic testing of VHL heterozygous germline mutation may be used to confirm diagnosis.^{4,9}

People who suffered from VHL usually developed benign or malignant tumors in organ systems such as retinal capillary haemangioblastoma (RCH), hemangioblastoma of central nervous system (CNS HB), endolymphatic sac tumor, neuroendocrine tumor, pancreatic cyst, renal cyst or tumor, pheochromocytoma, testicular cyst or tumor, and ovarian cyst or tumor. Physical examinations of this patient showed that there were decreased motor function and pathological reflex of left lower extremity indicated an upper motor neuron lesions

in spine.²⁻⁶ Examination results of this patient established the diagnosis of VHL.^{2,11}

Fundoscopy of left eye revealed the existence of papilledema, which was established by the findings of blurred margins in all of optic nerve head quadrants, tortuosity, vasodilation, exudate, and almost fully detached retinal surface. Exudative retinal detachment might happen in RCH, but it could be suppressed by administering intraocular anti-VEGF and peribulbar corticosteroid.⁸ Papilledema in VHL is most commonly caused by cerebellar hemangioblastoma. Typical findings in cerebellar hemangioblastoma are headache, dysmetria, tremor, and ataxia. Papilledema can be found in large cerebellar hemangioblastoma as a result of increased intracranial pressure. Therefore, head MRI is needed.^{7,9,10}

Retinal capillary haemangioma (RCH) is a rare kind of tumor that can be threatening to vision. The prevalence of retinal tumor in VHL is about 60%. Approximately 50% of patients had single lesion, and almost all of the patients with multiple lesions had VHL.² Based on its histological and clinical characteristics, there are 2 types of retinal hemangioma: cavernous hemangioma and capillary hemangioma. Cavernous hemangioma is darker due to the presence of intraretinal aneurysm blots, while capillary hemangioma resembles a light bulb due to the presence of large capillary vessels with normal endothelium that are separated by polygonal interstitial stromal cells.¹¹

The prevalence of retinal tumor or RCH in VHL is about 60%. RCH caused blindness in 6% of all cases.² Typical histological findings of RCH are fenestrated endothelial cells, pericytes, and lipid-rich foamy stromal cells. This tumor, which appears peripherally in 85% of cases, is usually asymptomatic for years, but it may cause visual problems if there are retinal edema, lipid deposits, tractional and exudative retinal detachment, and in the presence of macular lesions. Eye examinations such as funduscopy, retinal angiography, and OCT (if needed) can be done.^{3,4}

The patient complained of blurred vision on the left eye since 3 months before the initial visit. Decreased visual acuity in the patient's left eye could be explained by exudate, and retinal detachment around the macular area.

Asymptomatic RCH which is progressively getting bigger over time may cause leakage and may lead to retinal detachment and may affect the macula. Severe visual reduction in one eye could also be the cause of the sensory strabismus in this patient's left eye.⁴

RCH treatment plans range from watchful observation, laser photocoagulation, PDT (Photodynamic Therapy), cryotherapy, intravitreal anti VEGF injection, to vitrectomy. In smaller lesions (up to 500 μm) with no exudate or subretinal fluid, watchful observation is recommended, especially for stable juxtapapillary lesions that pose higher risk of optic nerve damage with destructive laser treatment. For peripheral tumors, pharmacological treatments must be considered as they have less local side effects, and there is possibility of lesion enlargement that will be harder to treat with laser or cryotherapy. For hemangioma with the size of up to 4,5 mm, several sessions of laser therapy may be effective, but this therapy is most effective for tumors sized 1,5 mm or smaller. Photocoagulation can be applied to tumor or to arteries, or both. For juxtapapillary or exophytic lesions, laser burns must be strong enough to coagulate all retinal layers, although it can be dangerous for optic nerve and major retinal vessels. Photodynamic therapy can be a preferred alternative due to its less risk of damaging the optic nerve. Laser and cryotherapy have little effects to hemangioma larger than 4 mm. In this case, aggressive approach using plaque radiotherapy or external beam radiation can be considered. Intravitreal anti VEGF injection is also a viable option for stabilization and exudation prevention in RCH. Anti VEGF reportedly could decrease vascular permeability by altering the balance of vasoactive cytokines such as nitric oxide and endothelin-1, or by directly altering endothelial tight junction. Those processes lead to production of other angiogenic factors that promote the growth of primary hemangioma. This therapy is considered as an alternative choice for progressive RCH, especially in patients with normal eyesight. In large capillary retinal hemangioma that is predicted to develop into tractional or rhegmatogenous retinal ablation, pars plana vitrectomy may be needed.^{2 11 12 13 14}

This patient was diagnosed with VHL due to the findings of ocular RCH, multiple intradural tumor

lesion in spine, and multiple pancreatic cysts. To further confirm the diagnosis, it was necessary to find other common comorbidities of VHL. Interdisciplinary approach consists of not only diagnostic and treatment plans from one speciality department, but also the ones from other related divisions and departments. Later manifestations of VHL can be detected and treated sooner if "prophylactic" screening tests are done to patients and their relatives who are at risk to increase their survival rate. Ideally, screening tests are also needed for the patients' family members. Patients should also undergo routine screening tests by ENT, internal medicine, radiology, and neurology specialists besides routine ophthalmology tests.^{1 2}

CONCLUSION

Von Hippel-Lindau disease is an autosomal dominant disorder that most commonly manifests as multiple organ tumors. Symptoms may vary widely, from walking disorders to vision problems. Ophthalmologists play an important role in diagnosing and treating the disease due to its ability to manifest as visual symptoms such as changes in vision due to exudation, hemorrhage, and retinal detachment. RCH is likely to be an early manifestation and is the most frequent finding in VHL disease. Therefore, interdisciplinary approach is required in diagnosing and treating this disease.

REFERENCES

1. Aufforth RD, Ramakant P, Sadowski SM, Mehta A, Trebska-McGowan K, Nilubol N, et al. Pheochromocytoma screening initiation and frequency in von Hippel-Lindau syndrome. *The Journal of Clinical Endocrinology & Metabolism*. 2015;100(12):4498-504.
2. Kanski JJ, Bowling B. *Clinical ophthalmology: a systematic approach*: Elsevier Health Sciences; 2011.
3. Ganeshan D, Menias CO, Pickhardt PJ, Sandrasegaran K, Lubner MG, Ramalingam P, et al. Tumors in von Hippel-Lindau Syndrome: From head to toe—comprehensive state-of-the-art review. *RadioGraphics*. 2018;38(3):849-66.

4. Schmid S, Gillessen S, Binet I, Brändle M, Engeler D, Greiner J, et al. Management of von hippel-lindau disease: an interdisciplinary review. *Oncology research and treatment*. 2014;37(12):761-71.
5. Chittiboina P, Lonser RR. von Hippel–Lindau disease. *Handbook of clinical neurology*: Elsevier; 2015. p. 139-56.
6. Loo SF, Justin NK, Lee RA, Hew YC, Lim KS, Tan CT. Differentiating extensor plantar response in pathological and normal population. *Annals of Indian Academy of Neurology*. 2018;21(2):144.
7. Gaudric A, Krivosic V, Duguid G, Massin P, Giraud S, Richard S. Vitreoretinal surgery for severe retinal capillary hemangiomas in von Hippel–Lindau disease. *Ophthalmology*. 2011;118(1):142-9.
8. Chen Y, Liu H, Zhang K, Gao L. Massive exudative retinal detachment following photodynamic therapy for retinal hemangioma in von Hippel–Lindau Syndrome. *Photodiagnosis and photodynamic therapy*. 2014;11(2):250-3.
9. Yunus Amran M, Hasmawaty B, Kurnia Bintang A, Akbar M. A robust allegation of von Hippel-Lindau (VHL) associated haemangioblastoma in the central nervous system (CNS): A case report. 2014.
10. Hasan N, Chawla R, Kumar A. Optic Disc Hemangioblastoma with Papilledema in a Case of Von Hippel-Lindau Disease. *Ophthalmology Retina*. 2019;3(9):733.
11. Jorge R. Retinal Hemangiomas. 2017; *Neuro-Ophthalmology, Vitreoretinal*:1.
12. Chelala E, Dirani A, Fadlallah A. Intravitreal anti-VEGF injection for the treatment of progressive juxtapapillary retinal capillary hemangioma: a case report and mini review of the literature. *Clinical ophthalmology (Auckland, NZ)*. 2013;7:2143.
13. Gunduz GU, Gelisken O, Yalcinbayir O, Guler K. Laser photocoagulation, intravitreal anti-VEGF, and vitreous surgery for the treatment of juxtapapillary retinal capillary hemangioma. *Indian journal of ophthalmology*. 2019;67(12):2104.
14. Francis JH, Slakter JS, Abramson DH, Odrich SA, Gobin YP. Treatment of juxtapapillary hemangioblastoma by intra-arterial (ophthalmic artery) chemotherapy with bevacizumab. *American journal of ophthalmology case reports*. 2018;11:49-51.



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