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Hemangioblastoma: A Window into the diagnosis of Von Hippel Lindau syndrome.

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ABSTRACT

von Hippel-Lindau disease is a autosomal dominant multisystem disease due to defective gene on 3p25-26. The earliest manifestations of the disease is predisposition to develop hemangioblastomas of the neuraxial system (most common). Other manifestations are pheochromocytoma, renal cell carcinoma, endolymphatic sac tumors and cysts in pancreas, kidney and epididymis. We recently encountered a case of a 55 year old lady, presenting with a complaint of lower back pain; radiating to the anterior trunk for the past 6 months. On radiologic examination, two brilliantly enhancing lesions at the C2 level and D7-D8 levels were noted, suggestive of a hemangioblastoma. Also noted were multiple hypodense pancreatic and renal cortical cysts, suggestive of multiple serous cystadenomas were evidenced. The histopathology of the spine lesion was consistent with a hemangioblastoma. The clinico-radiologic data along with the pathology of the lesion supported a diagnosis of *VHL* disease. A diagnosis of *VHL* disease requires a high degree of suspicion. When hemangioblastomas of the neuraxial system are documented, it should alert towards a possibility of an underlying *VHL* disease. A detailed family history and genetic analysis of the patient is also necessary for a confident diagnosis of this rare entity.

Keywords: Hemangioblastoma, *VHL*, Multisystem cancer

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INTRODUCTION

von Hippel-Lindau disease is an autosomal dominant multisystem disease due to a defective gene on 3p25-26. [1] The manifestations of the disease include a predisposition to hemangioblastomas of the neuraxial system (most common), pheochromocytoma, renal cell carcinoma, endolymphatic sac tumors and cysts in pancreas, kidney and epididymis. [1,2] It occurs in people of all ethnicities and there is no male or female preponderance of the disease. By 65 years of age, the disease is said to have 80-90% penetrance. The disease has highly variable expression [3]

CASE REPORT

A 55-year-old female presented with a complaint of lower back pain radiating to the anterior trunk for the past 6 months. The pain was continuous, nonrelenting and partially relieved by pain killers. There was no history of trauma. She also complained of weakness of both lower limbs (Right > Left) and she was able to walk with support for only a small distance. Pain had become debilitating since 15 days and she was forced to stay in bed. On radiologic examination, two brilliantly enhancing lesions at the C2 level and T7-T8 levels were noted, suggestive of a hemangioblastoma. Also noted were multiple hypodense pancreatic and renal cortical cysts, suggestive of multiple serous cystadenomas. The histopathology of the spine lesion was consistent with a hemangioblastoma. (Fig 1 and 2) The clinico-radiologic data along with the pathology of the lesion supported a diagnosis of VHL disease. No hydrocephalus was present. She also had a history of H. pylori induced chronic active gastritis. She underwent a T7-T8 laminectomy followed by C1-C3 laminectomy two months later for removal of the subpial hemangioblastomas. The patient on discharge was healthy and spasticity was considerably reduced along with improvement in lower limb power 3/5 to 4/5.

DISCUSSION

Von Hippel-Lindau disease (VHL) is an autosomal dominant disease which results from a mutation in the von Hippel-Lindau tumor suppressor gene on chromosome 3p25.3. [2] The manifestations of the disease include a predisposition to hemangioblastomas of the neuraxial system (most common), pheochromocytoma, renal cell carcinoma, endolymphatic sac tumors and cysts in pancreas, kidney and epididymis. [1,2] HIF (Hypoxia Inducible factor) transcriptional complex promotes expression of growth factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and erythropoietin, during hypoxia. [4] Loss of function mutation in VHL gene leads to uncontrolled HIF activity resulting in overexpression of growth factors. This is responsible for manifestations of VHL disease - hemangioblastomas in CNS and retina, pheochromocytoma, renal cell carcinoma, and cystic lesions in other organs. [4]

The disease has many characteristic features but not a single pathognomonic finding, that is unique. Due to multisystem involvement, multidisciplinary diagnosis and management of the disease is vital.

In our case, the patient had a cerebellar hemangioblastoma along with two other hemangioblastomas in the spinal cord at C2 and T7-T8 levels. Central nervous system involvement is reported in 21% to 72% of VHL patients. 21-72% of VHL patients have some form of CNS involvement, most commonly in the cerebellum. [5] The medulla, spinal cord, and spinal nerve roots can also be involved. Supratentorial hemangioblastomas can occur, although they are rare. It has been seen that VHL patients with cerebellar hemangioblastomas are in a younger age group compared to patients who have hemangioblastomas at sporadic sites. Usually multiple tumors. VHL shows benign hemangioblastomas (Fig 1 and 2), but they can produce symptoms or be asymptomatic. It depends on the site, size and number of hemangioblastomas. They can cause an increase in intracranial tension or compress nerve roots leading to impaired neurologic function. [3,4] Syringomyelia can occur due to spinal cord lesions. CNS hemangioblastomas can be surgically resected, with excellent results. Patient morbidity and mortality in VHL is strongly linked to multiple CNS lesions and CNS involvement in VHL. [8,9] CNS lesions in VHL can cause nausea, headache, broad-based gait and vertigo. Clinical signs like slurred speech, ataxia, papilledema and nystagmus may be seen. [3] Screening guidelines for VHL have helped detect asymptomatic or presymptomatic tumors. Use of modern imaging techniques has made it easier to identify CNS tumors. Gadolinium-enhanced magnetic resonance imaging (MRI) is currently the most preferred method to detect CNS lesions in VHL disease. [6]

Although our patient did not have any renal lesions, they are present in more than 50% cases of VHL.^[11] Approximately 20% of all pheochromocytomas ^[3]are reported to be due to VHL .Pancreatic involvement is frequent in VHL disease but in most cases is limited to multiple cysts that are rarely of functional significance,like in our patient. Rarely,pancreatic tumors can occur (commonly non secretory islet cell tumors^[8]).10% - 60% of male patients with VHL develop epididymal lesions.^[3] It has been estimated that 10% of VHL patients develop endolymphatic sac tumors.^[13]Patients presenting with otologic complaints should be screened for the same.

The diagnosis of the disease is established by the following criteria:^[4]

- More than one hemangioblastoma in the CNS or retina or
- One CNS hemangioblastoma and visceral manifestations of VHL or
- One manifestation and a known family history

It has been suggested to classify patients having VHL type 1 as those having phaeochromocytoma (plus other manifestations) and VHL type 2 as those with manifestations of VHL but free of phaeochromocytoma ^[5]

Mutations in the genome have been identified in majority of the VHL patients. Once an index VHL patient is identified, we can identify other carriers in his/her family who have as of yet shown any disease manifestations

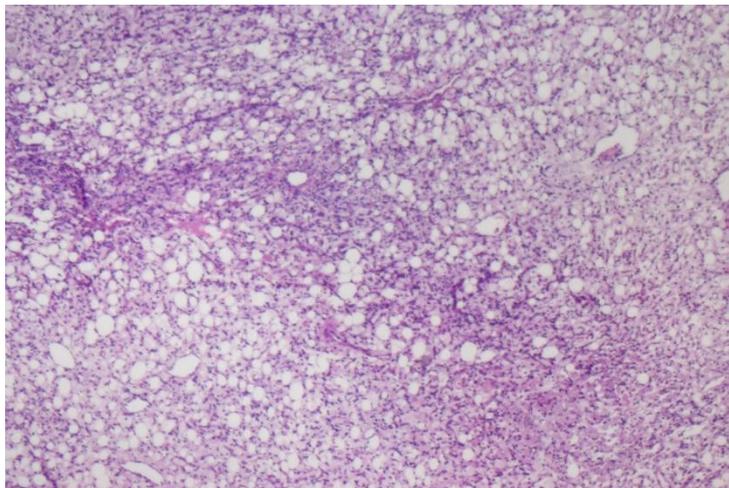


Figure 1:Shows an ill circumscribed vascular neoplasm with retinal meshwork of capillary-sized feeder vessels and polygonal stromal neoplastic cells (H and E ;50 x).

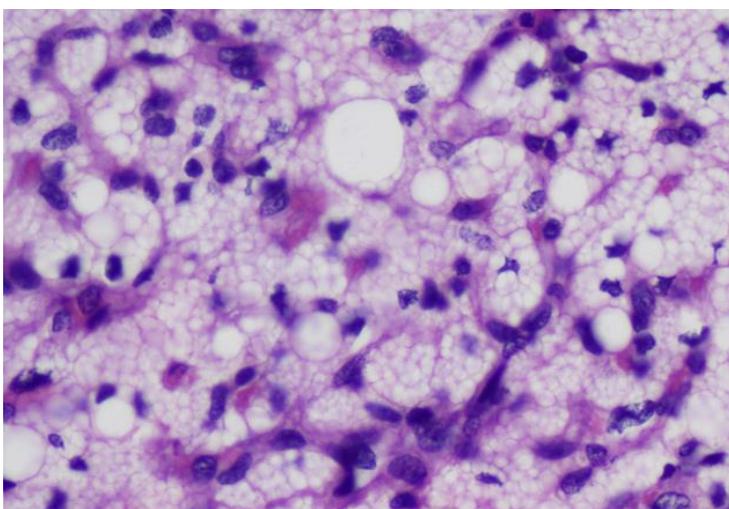


Figure 2: Neoplastic cells with pale eosinophilic to lipidized cytoplasm and centrally placed nucleus(H and E ; 400x)

Screening of family members should be done^[8]. Since infancy they should undergo physical and ophthalmologic examination every year. Urinary catecholamines should be evaluated every 1-2 years, from age 2 onwards. It has been recommended to have ultrasound examination of abdomen every year, along with MRI of brain and spine, after the child is 11 years old. In case any cyst or tumors are reported in USG, then CT scan should be done every 6 months. However, if no evidence of the disease is seen till 60 years of age, for screening he/she can undergo MRI (brain and spine) every 3-5 years and CT scan (abdomen) every alternate year.^[9]

Patients with VHL syndrome rarely live beyond the age of 50 years.^[10] The prognosis may be improved because of earlier diagnosis and intervention. If diagnosed early, prognosis is improved due to intervention at early stage. Genotype-phenotype correlation studies have been useful in prognostic counseling (especially as regards to pheochromocytoma).^[11] Prognosis of VHL patients have improved, largely due to development of surveillance protocols that help to monitor predictable complications.

CONCLUSION

A diagnosis of *VHL* disease requires a high degree of suspicion. When hemangioblastomas of the neuraxial system are documented, it should alert towards a possibility of an underlying *VHL* disease. A detailed family history and genetic analysis of the patient is also necessary for a confident diagnosis of this rare entity

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