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CASE STUDY

IMAGING IN VON HIPPEL-LINDAU SYNDROME: A CASE REPORT

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ABSTRACT

Von Hippel-Lindau (VHL) syndrome is a multisystem disease caused by mutations of the VHL gene. In patients with family history of this syndrome, the diagnosis is usually easy to establish and these patients require screening for various lesions. However, diagnosis of this syndrome, in the absence of family history, is challenging. We present a case of VHL syndrome in a young female, with no family history. The case highlights the significance of high degree of clinical suspicion and close follow up, for lesions of VHL syndrome, in patients with cerebellar hemangioblastoma.

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INTRODUCTION

von Hippel-Lindau disease is a rare autosomal dominant familial tumor syndrome associated with a variety of lesions including brain, retinal, and spinal cord hemangioblastomas; renal cysts and renal cell carcinoma; pheochromocytomas; pancreatic cysts, pancreatic serous cystadenomas and pancreatic neuroendocrine tumors. We present a case of von Hippel-Lindau Syndrome with CNS, ocular and abdominal manifestations.

CASE REPORT

An 19 year old female presented to the hospital with sudden onset of painless loss of vision in left eye and history of abdominal pain since 1 month. She had a history of surgery for posterior fossa brain tumor 3 years back. MRI done prior to the surgery showed a predominantly cystic lesion with strongly enhancing mural nodule in posterior fossa. Attendant hydrocephalus was also noted due to pressure over the fourth ventricle (Figures 1, 2).

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Post operative histopathological examination showed proliferation of haphazardly oriented capillaries of variable size, thin walled vessels and large neoplastic stromal cells having vacuolated cytoplasm and hyperchromatic nuclei. Histopathological findings were consistent with the diagnosis of cerebellar hemangioblastoma. In view of young age of the patient, ultrasound (USG) abdomen and MRI spine were done to screen for other lesions. However, at that time USG abdomen was normal and MRI spine didn't reveal any lesion in the spine. There was no family history of VHL syndrome or cerebellar hemangioblastoma. Presently, the patient was referred to the radiology department for B Scan and USG abdomen. B-Scan of left eye showed evidence of retinal detachment with echogenic contents in posterior segment. Further, an echogenic lesion was noted on lateral aspect of left eyeball with vascularity on colour Doppler (Figure 3). Right eye was normal. On USG abdomen, multiple anechoic lesions were noted within the pancreas (Figure 5). Main pancreatic duct couldn't be definitively visualized. Liver, bilateral kidneys, spleen and gall bladder were normal. The patient was advised MRI orbit and MRI abdomen for further evaluation. MRI orbit revealed an enhancing lesion on superolateral aspect of left eyeball in the region of ora serrata.

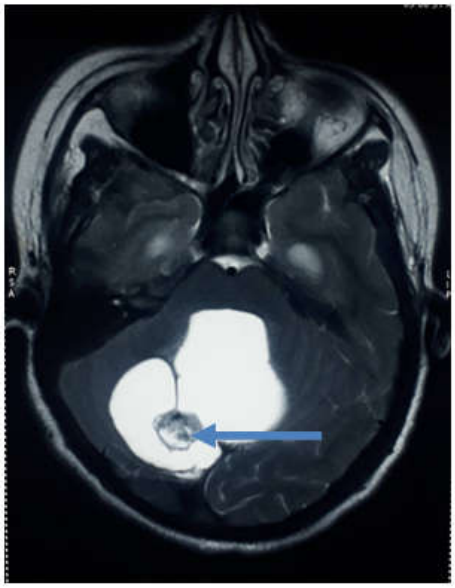

Figure 1. Axial T2 MRI image showing hyperintense lesion in posterior fossa with heterogenous intensity mural nodule (arrow)

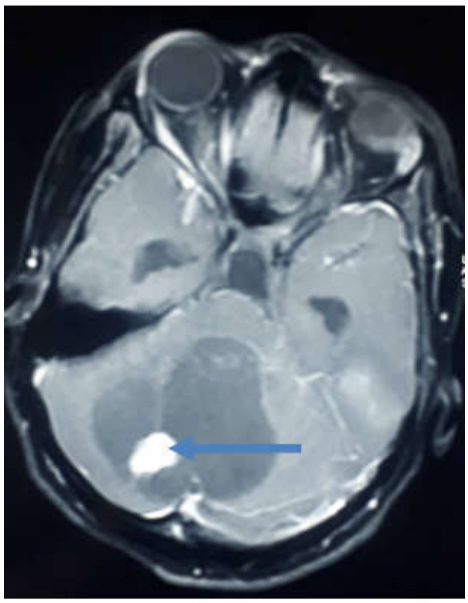

Figure 2. Axial post contrast T1 MRI image showing intensely enhancing mural nodule (arrow)

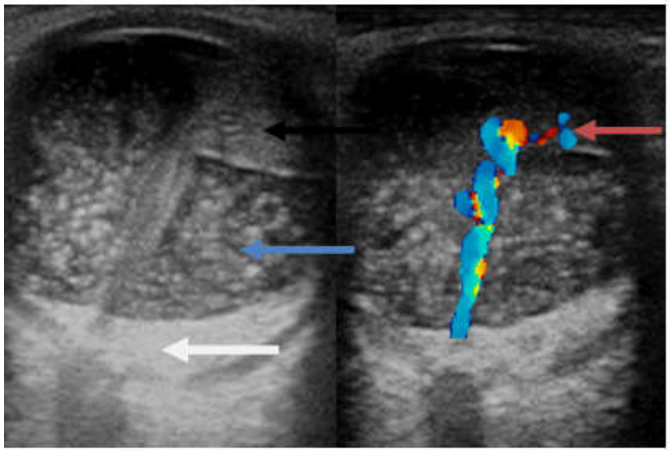

Figure 3. B Scan image showing retinal detachment (white arrow), echoes in posterior segment (blue arrow), echogenic lesion at ora serrata (black arrow) with prominent vessel supplying the lesion (red arrow)

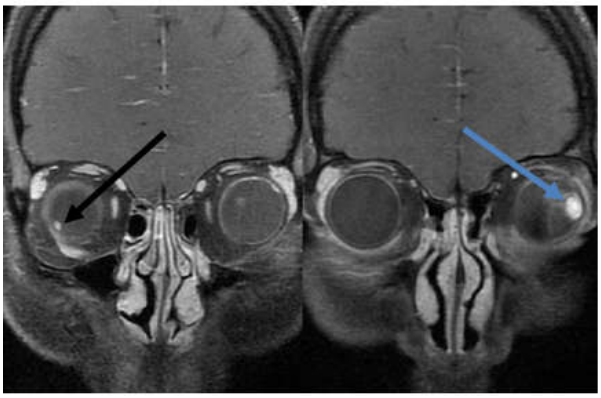

Figure 4. Coronal post contrast T1 weighted images showing intensly enhancing lesions at lateral aspect of left eyeball (blue arrow) and at lateral aspect of right eyeball (black arrow)

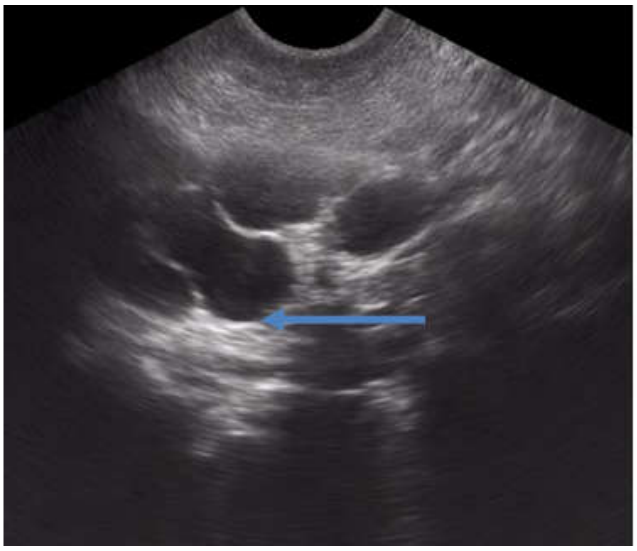

Figure 5. USG abdomen image showing multiple anechoic cysts in pancreatic body region (arrow)

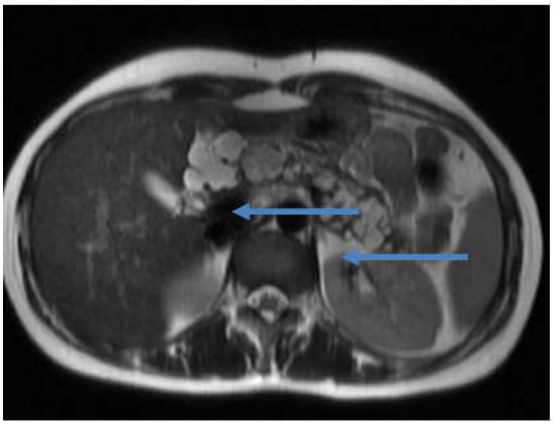

Figure 6. Axial T2 MRI image showing extensive hyperintense cysts replacing pancreatic parenchyma (arrows)

There was associated total retinal detachment and subretinal hemorrhage. Similar smaller punctate enhancing lesion was also seen on inferolateral aspect of left eye (Figure 4). Imaging findings were suggestive of retinal hemangioblastomas. MRI Abdomen revealed extensive T2 hyperintense cystic lesions replacing pancreatic parenchyma (Figure 6). No evidence of solid component was noted within these lesions.

Based on imaging findings and previous surgical history, a diagnosis of von-Hippel Lindau syndrome was established, as per the diagnostic criteria for this entity (Shuin *et al*., 2006).

DISCUSSION

Von Hippel-Lindau syndrome is a familial tumor syndrome characterised by the development of numerous benign and malignant tumors in different organs due to mutations in the VHL tumor suppressor gene on chromosome 3. The disease carries an autosomal dominant inheritance with high expression and variable penetrance. It classically results from an inactivation of VHL, a tumor suppressor gene located on chromosome 3p25.5. However, no mutation is identified in up to 30% of cases (Leung *et al*., 2008). The VHL protein normally plays an important role in the oxygen-sensing pathway. During hypoxia, series of events due to the presence of an inactive VHL gene results in upregulation of multiple growth factors, including vascular endothelial growth factors, which results in cell proliferation and unregulated cell growth leading to development of tumors in multiple organs (Haase, 2006). The commonly involved organs are the pancreas, central nervous system, kidneys, eyes, adrenal gland, epididymis, and inner ear (Lonser *et al*., 2003). Among all, the most common tumors include retinal angiomas, cerebellar and spinal cord hemangioblastomas, endolymphatic sac tumors, renal cysts, renal cell carcinomas, pheochromocytomas, epididymal cysts and cystadenomas, simple cysts, serous cystadenomas, and neuroendocrine tumors of the pancreas (Leung, 2008).

Age at the time of diagnosis varies. Patients often present in childhood or as young adults. Patients usually present with one of the tumors. Painless loss of vision is a common presenting symptom in patients with retinal hemangioblastomas due to retinal detachment and hemorrhage. The diagnostic criteria for VHL disease include: (a) More than one central nervous system (CNS) hemangioblastoma, (b) One CNS hemangioblastoma and one visceral tumor, and (c) CNS hemangioblastoma/ pheochromocytoma/ clear cell renal carcinoma along with a known family history (Shuin *et al*., 2006). It is very important to screen individuals who carry the VHL gene and are as yet asymptomatic, as the lesions in VHL disease are treatable if identified early. Various modalities like Ultrasound, CT and MRI help in delineating various pathologies. Ultrasonography is useful to find out pancreatic, renal and sometimes adrenal pathologies. Screening for renal cell carcinoma is one of the major goals due to its high mortality. MRI is the modality of choice for CNS lesions in VHL patients. It is also useful in the evaluation of renal, pancreatic, and adrenal lesions. Hemangioblastomas involving spine and brain are one of the most common manifestations of VHL disease. Cerebellum is the commonest site in brain, pituitary stalk being the commonest supratentorial site. VHL patients develop cerebellar hemangioblastomas in 44-72% and spinal cord hemangioblastomas in 13-50% cases. These tumors usually develop at a younger age and have worse prognosis (Katabathina, 2014). On CT/MRI, hemangioblastomas commonly appear as cystic lesions with mural nodule. Approximately two-third of these tumors are predominantly cystic, while the remaining are solid or solid-cystic lesions. On MRI, the tumors appear as low to medium signal intensity lesions on T1- weighted images and hyperintense lesions on T2- weighted images.

On gadolinium administration, marked enhancement of the solid portions is identified due to rich capillary network (Filling-Katz, 1989). Retinal hemangioblastomas (commonly referred to as 'angiomas') are among the most frequent manifestation of VHL disease and can develop in up to 60 % patients; they are bilateral and multifocal with a mean age of presentation around 25 years, although 5 % cases may present before the age of 10 years (Butman, 2008; Choyke *et al*., 1995). Tumors can develop in both at the macula and in periphery of the retina. Smaller tumors are asymptomatic and visual symptoms including partial or complete vision loss may occur as tumors grow and cause retinal detachment. On MRI, retinal angiomas appear hyperintense on non-enhanced T1 weighted sequences and isointense on T2 weighted images and enhance intensely after contrast administration. The frequency of pancreatic involvement in von Hippel-Lindau disease is 15–77% (Neumann *et al*., 1991; Hammel *et al*., 2000). Lesions include simple pancreatic cysts, serous cystadenomas, neuroendocrine tumors, and combined lesions (Marcos *et al*., 2002).

Pancreatic cystic lesions are benign, whereas neuroendocrine tumors can be malignant. Pancreatic adenocarcinoma and hemangioblastoma have also been described in von Hippel-Lindau disease. In most patients, pancreatic cysts are asymptomatic. However, in some instances they can cause local compression of adjacent organs, vessels, and the common bile duct. CT and MRI show multiple pancreatic cysts with no enhancement after contrast injection (Taouli *et al*., 2003). The patient in the present case initially didn't satisfy the criteria for the diagnosis of VHL syndrome. However, there was a high index of suspicion. On follow up, she developed retinal angiomas and pancreatic cysts, and was diagnosed as having VHL syndrome. This outlines the significance of close follow up in patients with suspected VHL syndrome. Screening for hemangioblastomas, renal cell carcinoma and pheochromocytoma at regular (annual) intervals is recommended as these are the major causes of death in these patients.

Conclusion

Imaging has a key role in establishing the diagnosis of, and in surveillance thereafter, in von Hippel-Lindau syndrome. USG is an excellent imaging modality for screening pathologies of various abdominal viscera. CT and MRI with contrast can delineate various CNS and ocular abnormalities. A high degree of clinical suspicion is required in young patients with brain or spinal hemangioblastomas and screening for associated lesions must be done regularly. Appropriate clinical history and prompt investigations lead to an early diagnosis and hence, guides timely management.

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