CASE REPORT

A Rare Case of Multiorgan Solid Cystic Lesion: Von Hippel Lindau Syndrome - An Institutional Experience

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Abstract

Von Hippel-Lindau syndrome is a rare hereditary multisystemic tumour predisposition disorder, caused by a mutation in the VHL gene. The incidence is 1 in 39,000 individuals. Here we report a case of a 20-year-old male patient who presented with complaints of dull aching abdominal pain for 2 months. CT-abdomen shows a mixed solid cystic lesion in the right kidneys and right supra renal gland & benign serous cyst adenomatous in the pancreas. Right total adrenalectomy with enucleation of the right kidney was done. Histopathology and immunohistochemistry showed pheochromocytoma with clear cell renal carcinoma of the kidney.

Keywords

Von Hippel Lindau Syndrome, Clear cell Renal carcinoma, Pheochromocytoma, VHL gene, Tumour suppressor gene, hemangioblastoma

Introduction

Von Hippel Lindau syndrome is a rare disorder, which is autosomal dominant in inheritance, this occurs due to a mutation in the VHL gene located in chromosome 3p. It is seen in 1 in 39,000 individuals and more than 80% are affected at age of 60 years. [1] This germline mutation leads to the formation of cystic tumours in multiple organs like pancreatic cysts, cerebellar and retinal hemangioblastoma, pheochromocytoma, ovarian cysts, clear cell renal carcinoma, and endolymphatic tumour.

The Diagnosis of VHL can be done, when the patient has a positive family history and any one of the following (cerebellar or retinal hemangioblastoma, pheochromocytoma, clear cell renal cell carcinoma, pancreatic cyst), or two of the tumours should be present without a family history of VHL.[2]

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Because of multisystem involvement, several management and screening, and follow-ups are needed. The common cause of mortality due to complications related to renal cell carcinoma and central nervous system (CNS) tumours.[3]

Case Report

A 20-year-old male patient presented with complaints of dull aching abdominal pain for 2 months. The patient also complained of loss of appetite and loss of weight. The patient is a known case of diabetes mellitus and hypertension for the past year and is on regular medication.

Upon physical examination, vitals were stable. Abdominal examination revealed mild distension. Upon palpation,

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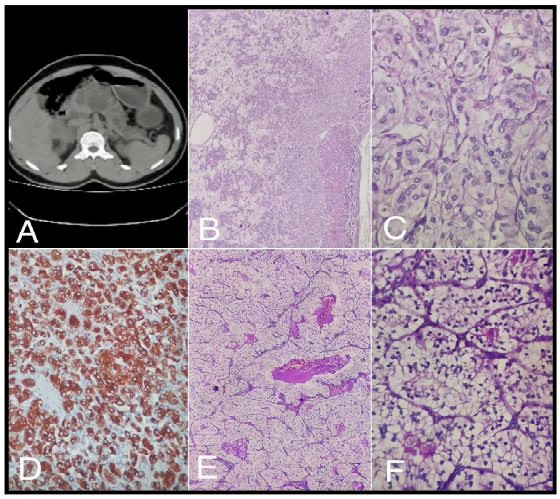

Fig. 1A* CT abdomen showing benign serous cyst adenomatous in the pancreas. I B: right adrenal H&E* stained 100x shows tumor cells were aranged in a zellballen pattern. IC 400Xshows tumor cells are polygonal with granular eosinophilic cytoplasam and pleomorphic Nucli. ID: IHC** of synaptophysin shows strong cytoplasmic postivity. IE: Kidney H&E* 100x shows tumor cells were aranged on nests seprated by fibrous septate. IF 400X shows tumor cells were polygonal with clear cytoplasam with inconspicuous Nucleoli. * Hematoxin and Esosin ** Immunohistochemistry

tenderness is present over the right lower quadrant. On radiological investigation, CT-abdomen shows a mixed solid cystic lesion in the right kidneys and an intense heterogenous lesion in the right supra renal gland & benign serous cyst adenomatous in the pancreas (***Fig 1A***). Right total adrenalectomy with enucleation of the right kidney was done and sent for histopathological examination. Histopathological examination showed tumour cells were arranged in a zellballen pattern (*Fig 1B*). Individual cells are polygonal with granular eosinophilic cytoplasm and pleomorphic nuclei (*Fig 1C*). Immunohistochemistry (IHC) of synaptophysin showed strong cytoplasmic positivity (*Fig 1D*). All these features were suggestive of pheochromocytoma. Histopathological examination of kidney showed tumour cells were arranged on nests separated by fibrous septate (*Fig1E*). Individual tumour cells were polygonal with clear cytoplasm with inconspicuous nucleoli (*Fig 1F*). Suggestive of clear cell renal cell carcinoma. As the radiological and histopathological findings fit the criteria of VHL, a final diagnosis of VHL was made.

Discussion

Von Hippel Lindau syndrome (VHL) is a rare autosomal dominant multiorgan predisposition due to a germline mutation of the VHL gene located in chromosome 3p. This mutation predisposes and leads to the formation of various benign and malignant neoplasms in various organs. This includes hemangioblastoma of the cerebellum and retina, cysts of (the pancreas, liver, and kidney), pheochromocytoma, clear renal cell carcinoma, and papillary cystadenoma of epididymis or ovary.[4]

The VHL is the component of the ubiquitin ligase complex. Hypoxia-inducing factor -1 alpha (HLF-1A) is the main substrate for VHL ubiquitin ligase. In hypoxic conditions, the HIF-1A is not hydroxylated, so escapes from recognition of VHL. HIF-1A is not ubiquitinated and is not degraded. This results in the accumulation of HIF-1A in the nuclei of the hypoxic cell turns on the genes encoding angiogenic factors and alter cell metabolism favour's growth. Loss of function of the VHL gene prevents ubiquitination and degradation HIFA. This leads to an increase in angiogenic growth factor VEGF, PDGF, and alteration in cell metabolism, which favour's the growth of tumour cells. [5]

Criteria for diagnosis of VHL :

When there is a positive family history of VHL has anyone one or more of the following tumours listed below. If the individual has no family history of VHL syndrome, VHL can be diagnosed when two or more of the tumours are present. [6]

The tumours that can be seen in VHL syndrome are - Clear renal cell carcinoma, Pheochromocytoma, Pancreatic cyst, Hemangioblastoma retina, or cerebellum. Pheochromocytoma also known as intra-adrenal paraganglioma is the neoplasm of the adrenal medulla composed of the chromaffin cell (special neuroendocrine cells) and supporting cells (sustentacular cells). The major source of catecholamine in our body is epinephrine and norepinephrine. The familial syndrome associated are Multiple endocrine neoplasm (MEN) 2A and 2B, VHL,

Hereditary paraganglioma [1,3,4] and Polycythaemia paraganglioma syndrome.[4]

Pheochromocytoma, tumour cells are polygonal, and surrounded by a capillary-rich framework is a Zellballen appearance. PAS-positive for glycogen-rich eosinophilic granules. The potassium dichromate, turns the tumour dark brown, because of the oxidation of stored catecholamines. Immunohistochemistry such as S 100 positive for sustentacular cells, OCT-4 (germ cell tumour marker) is a sensitive marker of pheochromocytoma, and Synaptophysin shows cytoplasmic positivity.[7]

Clear Renal Cell Carcinoma is the most common type, most are sporadic, but familial cancers are 4% and occur in younger individuals. The tumour arises at any part of the kidney but mostly in the poles. Clear renal cell carcinoma arises from proximal convoluted tubules. Microscopically, tumour cells are round to oval in shape with clear or granular cytoplasm (made up of glycogen or lipid). IHC for Carbonic anhydrase IX shows diffuse, membrane positivity.[8]

Hemangioblastoma is most common in the cerebellum and retina. It is a benign tumour of the blood vessel. The VEGF induces excess vascular proliferation which results in hemangioblastoma. The erythropoietin causes polycythaemia in 10% of hemangioblastoma cases. The lesion is made up of a capillary network with neoplastic cells known as a stromal cell, with foamy or vacuolated cytoplasm rich in lipids.

The stromal cells are often positive for S-100, NSE, and CD56/NCAM helps in the distinction of hemangioblastoma from haemangiomas. 9

Non-mucinous neoplasms of pancreas, serous cyst adenoma, solid pseudopapillary neoplasm, cystic neuroendocrine tumour. The serous cystic neoplasms have lesion commonly seen in body and tail of pancreas. This has dense capillary network which is positive for vascular marker CD 31. The serous cystic neoplasm has germline VHL association or sporadic VHL mutation observed in these neoplasms. [10]

References

1. Jonasch E, Donskov F, Iliopoulos O, Rathmell WK, Narayan VK, Maughan BL, et al. Belzutifan for Renal Cell Carcinoma in von Hippel-Lindau Disease. N Engl J Med 2021 ;385(22):2036-46.
2. van Leeuwaarde RS, Ahmad S, Links TP, et al.Von Hippel-Lindau Syndrome. 2000 May 17 [Updated 2018 Sep 6]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1463/
3. Arnon L, Halperin R, Tirosh A. Impact of Pancreatic Neuroendocrine Tumor on Mortality in Patients With von Hippel-Lindau Disease. Endocr Pract 2021 ;27(10) :1040-5.
4. Robbins & Cotran Pathologic Basis of Disease - 10th Edition [Internet]. [cited 2022 Oct 14]. Available from: https://www.elsevier.com/books/robbins-and-cotran-pathologic-basis-of-disease/kumar/978-0-323-53113-9
5. Kim E, Zschiedrich S. Renal Cell Carcinoma in von Hippel-Lindau Disease-From Tumor Genetics to Novel Therapeutic Strategies. Front Pediatr [Internet]. 2018 Feb 9 [cited 2022 Oct 20];6:16. Available from: http://journal.frontiersin.org/article/10.3389/fped.2018.00016/full
6. Von Hippel-Lindau Disease (VHL) By M. Cristina Victorio , MD, Akron Children's Hospital. Available from: https://www.msdmanuals.com/en-in/professional/pediatrics/neurocutaneous-syndromes/von-hippel%E2%80%93lindau-disease-vhl
7. Mills SE, Greenson JK, Hornick JL, Longacre TA, Reuter VE, editors. Sternberg's diagnostic surgical pathology. Vol. 2. Sixth edition. Vol. 2. Philadelphia: Wolters Kluwer; 2015. .pp.1375 .
8. Albiñana V, Gallardo-Vara E, de Rojas-P I, Recio-Poveda L, Aguado T, Canto-Cano A, et al. Targeting 2-Adrenergic Receptors Shows Therapeutical Benefits in Clear Cell Renal Cell Carcinoma from Von Hippel-Lindau Disease. J Clin Med [Internet] 2020 Aug 25 [cited 2022 Oct 20];9(9):2740. Available from: https://www.mdpi.com/2077-0383/9/9/2740
9. Klingler JH, Gläsker S, Bausch B, Urbach H, Krauss T, Jilg CA, et al. Hemangioblastoma and von Hippel-Lindau disease: genetic background, spectrum of disease, and neurosurgical treatment. Childs Nerv Syst [Internet]. 2020 Oct [cited 2022 Oct 20];36(10):2537-52. Available from: https://link.springer.com/10.1007/s00381-020-04712-5
10. Esposito I, Haeberle L. Nonmucinous Cystic Lesions of the Pancreas. Arch Pathol Lab Med [Internet]. 2022 Mar 1 [cited 2022 Oct 20];146(3):312-21. Available from: https://meridian.allenpress.com/aplm/article/146/3/312/451671/Nonmucinous-Cystic-Lesions-of-the-Pancreas