Type 1 Diabetes Mellitus and Von Hipple Lindau Syndrome- Sweet Presentation of a Bitter Disease- A Case Report

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ABSTRACT

Von Hipple-Lindau (vHL) is an autosomal dominant disorder that predisposes individuals to an increased risk of developing multi-organ neoplasms. Pancreatic involvement with subsequent development of type II diabetes mellitus is a well-documented complication of this disorder. In this case report, we present a case of a young man who presented with primary symptoms of polyuria and polydipsia. Patient was later found to be in diabetic ketoacidosis and upon further investigation, was diagnosed with diabetes mellitus type I. Patient's history of persistent abdominal pain prompted further imaging studies, which demonstrated a left sided pheochromocytoma and right sided renal cell carcinoma. Genetic studies confirmed presence of 384delT frame-shift mutation in exon 2 of the tumor suppressor, E3 ubiquitin protein ligase, vHL gene. This case report represents the only one in literature with a rare association of vHL and islet cell autoantibody positive, type I diabetes mellitus.

Keywords: Von Hippel Lindau; Renal Cell Carcinoma; Pheochromocytoma; Diabetes Mellitus

INTRODUCTION

Von Hipple-Lindau (vHL) disease is an autosomal dominant disorder where the affected individuals are predisposed to develop a variety of multi-organ neoplasms involving the central nervous system, renal, pancreatic, adrenal and ependidymal tissues [1-3]. Its incidence is approximately 1 in 36000 live births with 90% of disease penetrance by the age of 65 years [3].

Pancreatic involvement in vHL disease is common and includes the development of pancreatic cysts, dilatation of main pancreatic ducts, pancreatic neuro-endocrine tumors, and pancreatic cystadenomas [4]. Type II diabetes mellitus is a well-documented complication of vHL disease [5]. However, type I diabetes mellitus has never been associated with this syndrome. In this case report, we present a rare association of type 1 diabetes mellitus, with positive islet cell autoantibodies in a male patient with vHL disease. Upon a thorough database literature review, we did not find a similar case and hence believe that this is the first case report demonstrating such an association.

CASE REPORT

A 19-year-old Saudi male presented to the emergency department with one-week history of polyuria and polydipsia. Physical examination findings were unremarkable. His father had died as a complication of metastatic renal carcinoma. Initial workup demonstrated random blood glucose of 16.3 mmol/L and HbA1C of 9.1%. Urinalysis was positive for ketone bodies, and blood analysis was positive for traces of ketone bodies. Patient was acidotic with pH of 7.3 and bicarbonate levels of 19 mmol/L. A presumptive diagnosis of diabetic ketoacidosis (DKA) was made; immune markers including glutamic acid decarboxylase (GAD) autoantibodies and islet cell autoantibodies were sent to exclude type I diabetes mellitus and maturity onset diabetes of the young. Intravenous insulin infusion and other appropriate management were initiated to control

blood sugars and to correct the associated DKA. Later, the diagnosis of type I diabetes mellitus was confirmed with the presence of islet cell autoantibodies and that C-peptide level were within normal range.

Ultra-sound abdomen was performed as the patient complained of persistent abdominal pain even after correction of DKA. Ultrasound abdomen demonstrated an incidental finding of a well-defined hypo-echoic soft tissue mass measuring 3.7 x 4.7 cm in the left supra-renal region. Computerized tomography (CT) scan was performed for further evaluation. It demonstrated a 3.7 x 4.0 cm rounded lesion in the left adrenal gland with intense enhancement, suggestive of pheochromocytoma. A small hypo-dense lesion was also noted in the left renal upper pole, measuring 2.3 cm, with heterogeneous enhancement suggestive of a solid mass. The CT scan also demonstrated multiple rounded cystic lesions in the head, body, neck and tail of the pancreas representing pancreatic cysts. The above findings collectively were suggestive of phakomatosis disorders, in particular, vHL disease. Chromosomal studies were sent for detection of genetic mutations and confirmation of the diagnosis.

MRI abdomen was highly suggestive of a left sided pheochromocytoma (Figure 1). It also demonstrated multiple cystic lesions in the pancreas (Figure 2) and bilateral cortical lesions in the kidneys, which demonstrated internal septal enhancement in the post gadolinium injection phase, highly indicative of renal cell carcinoma. Nuclear medicine scan demonstrated increased tracer uptake in the left suprarenal gland.

Meanwhile, laboratory studies demonstrated increased serum normetanephrine level of 11.80 nmol/l, urine metanephrine level of 400nmol/24hrs, and urine normetanephrine level of 1210 nmol/24hrs. Serum cortisol, aldosterone and renin levels were within normal limits. A diagnosis of pheochromocytoma was confirmed and patient was started on anti-hypertensive medications and scheduled for surgical removal of the pheochromocytoma and the suspicious renal masses.

Patient underwent robot assisted laparoscopic left adrenalectomy and left renal mass excision. Two renal nodules were removed. The post-operative course was unremarkable and patient was discharged home in stable condition. Histopathologic evaluation confirmed the diagnosis of pheochromocytoma; the renal masses were determined as renal clear cell carcinoma Furham grade I. Chromosomal analysis confirmed the presence of 384delT of frame-shift mutation in exon 2 of the tumor suppressor, E3 ubiquitin protein ligase, vHL gene. Screening was done for the family. Three of his eight siblings tested positive for the 384delT mutation.

DISCUSSION

vHL syndrome is an autosomal dominant syndrome with an approximate incidence of 1 in 36000 live births [3]. In vHL, individuals are predisposed to developing a magnitude of malignant cellular proliferations involving the central nervous system (e.g CNS hemangioblastomas), renal tumors (e.g renal cell carcinomas), pancreatic cysts, adrenal tumors (pheochromocytoma) and ependidymal tissue tumors [1-3].

The overall prevalence of pheochromocytoma is around 1:6500 to 1:2500 affected individuals in the United States [6], while vHL gene is rarely the underlying pathology in majority of these cases unless the age of presentation is less than 20 years or the tumor is located bilaterally [7]. Renal cell carcinoma accounts for up-to 4% of the total adult cancer population, and is present in 70% of individuals with vHL syndrome [7, 8].

Patients with an underlying pheochromocytoma can present in a variety of clinical scenarios, with signs and symptoms of hypertension being the commonest modes of presentation [9]. Gross painless hematuria remains the commonest presentations of renal cell carcinoma [10].

Loss of vHL gene in pancreatic beta cells has been demonstrated to lead to a defect in glucose homeostasis [11], resulting in defective insulin secretion in response to high blood glucose levels in experimental mouse models. vHL protein has been demonstrated to regulate hypoxia-inducible factor (HIF), a vital transcription factor that allows various cell types to adapt to hypoxia for un-interrupted oxidative phosphorylation and to ensure normal beta cell function [12]. In addition, loss of HIF impairs GLUT 4 translocation and glucose uptake by skeletal muscle cells [13]. Therefore, the hypoxia response pathway theory, presents as a strong basis for the association of type II diabetes mellitus in patients with vHL disease.

However, our patient developed type 1 diabetes mellitus with the presence of islet cell autoantibodies. Type 1 diabetes mellitus represents an autoimmune destruction of pancreatic beta cells hampering the production of

Figure 1: MRI image demonstrating a 3.7 x 4.0 cm mass situated in the left supra-renal gland (black long arrow); also appreciated is a right sided renal cortical lesion (white short arrow) which demonstrated internal septal enhancement in the post gadolinium injection phase

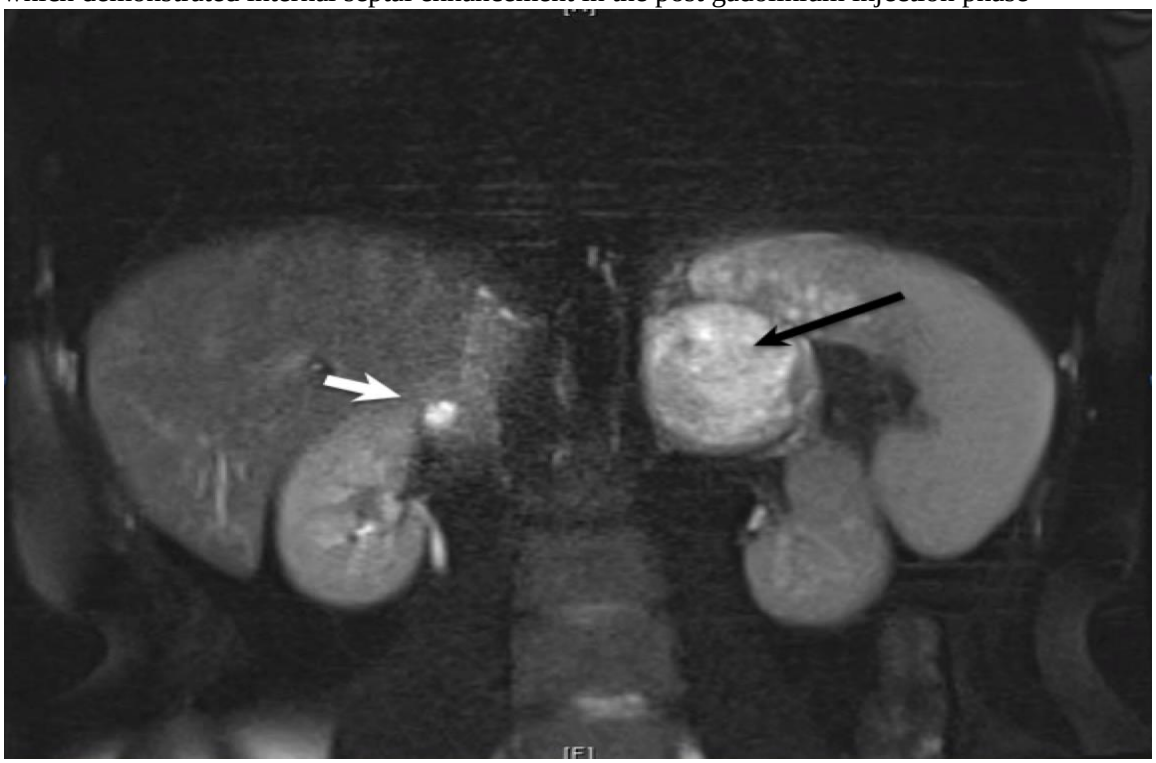
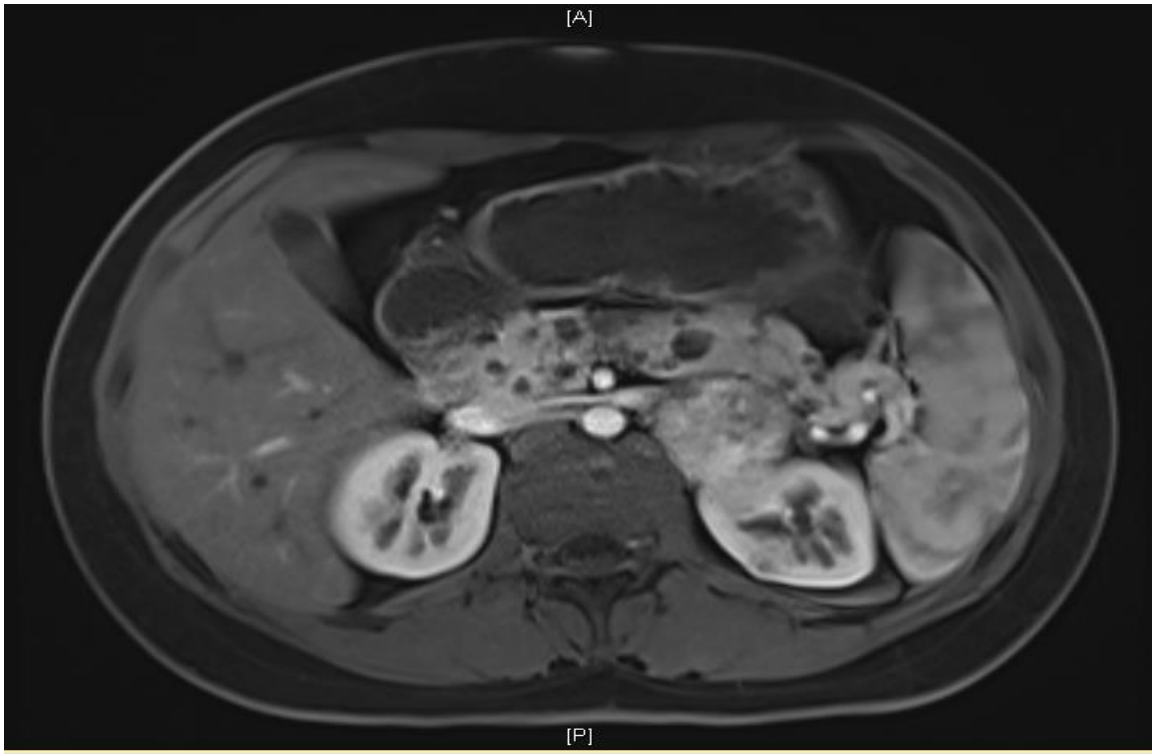


Figure 2: MRI image demonstrating multiple cysts within the pancreas



insulin and therefore leading to hyperglycemia. Several genes have been implicated in the development of diabetes including HLA, insulin, PTPN22, IL2Ra, and CTLA4 genes [14].

The pathogenesis in this scenario cannot be explained by the hypoxia response pathway theory, as islet cell destruction in type 1 diabetes mellitus follows an immunologic process. vHL has been associated with presence of other immunologic disorders. Sheth [15] and colleagues described a case of vHL disease associated with antibody positive myasthenia gravis and thymoma. However, they were unable to conclude if this association was coincidental or had an underling genetic basis for the presentation. Tenner et al. [16] described a case of vHL complicated by acute pancreatitis and Evan's syndrome. Evan syndrome is characterized by autoimmune thrombocytopenia and autoimmune hemolytic anemia [16]. These associations may suggest underlying immunologic dysfunctions that may be associated with vHL gene mutation and shared amongst these disorders.

In conclusion, several autoimmune disorders have been associated with vHL syndrome. In this case report, the authors describe the first ever association of type I diabetes mellitus with vHL syndrome suggesting an underlying autoimmune pathologic pathway subsequently leading to hyperglycemia and the presenting symptoms of polyuria and polydipsia in a young Arab male patient. Further studies are warranted to establish whether this association follows a cause and effect pathway, and to investigate the underlying molecular changes contributing to the pathophysiology.

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