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Case Report

A Von Hippel-Lindau Masked by an Acute Pancreatitis

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We describe the case-report of a 45 years-old man suffering from chronic pancreatic disease with strong acute mesogastric pain, nausea and vomiting result of acute abdomen suspicious for acute pancreatitis. A thorough diagnostic investigation led us to diagnose a rare disease.

A 45 years-old man was admitted to the Emergency Department for exacerbation of chronic mesogastric pain, started approximately one year before and actually worsened. An abdominal MRI revealed a pancreas with a lot of several cystic lesions with a maximum diameter of 2.5 mm (Figures 1-3). On clinical examination the arterial pressure was 140/80 mmHg at both arms, arterial pulse 85 beats per minute; the weight around 80 Kg. The abdomen was soft, with strong pain on palpation in the mesogastric region without irradiation; instead the rest of the clinical examination was normal. The haematocrit level was 41% (reference range, 41.0 to 53.0 in men), the platelet count 356,000 per cubic millimeter (reference range, 150,000 to 400,000), the lipase level 2.1 U/dL (reference range, 1.3 to 6.0), and the amylase level 57 U/L (reference range, 3 to 100), mild hyperglycaemia (6.5 mmol/L), hypercholesterolemia (total cholesterol 5.3 mmol/L, LDL cholesterol 3.9 mmol/L), increased levels of ALAT (58 U/L) and mild hypocalcaemia (2.17 mmol/L). Others laboratory-test results (including the white-cell count and the differential count, serum levels of electrolytes, total protein, albumin, globulin, bilirubin, creatine kinase, creatine kinase isoenzymes and troponin I and tests of coagulation and renal function) were normal. A previous Esophago-Gastro-Duodenal Scopy (EGDS) showed pangastritis with large amount of bile.

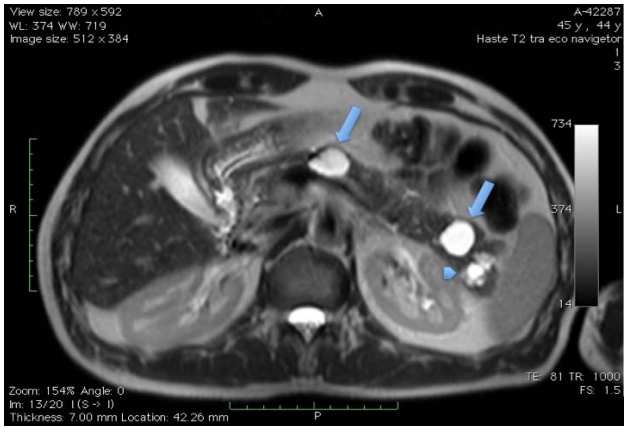

Figure 1: Axial abdominal-MRI with multiple simple pancreatic cystic lesions of little dimensions (arrowhead) and big, complex cysts (arrows).

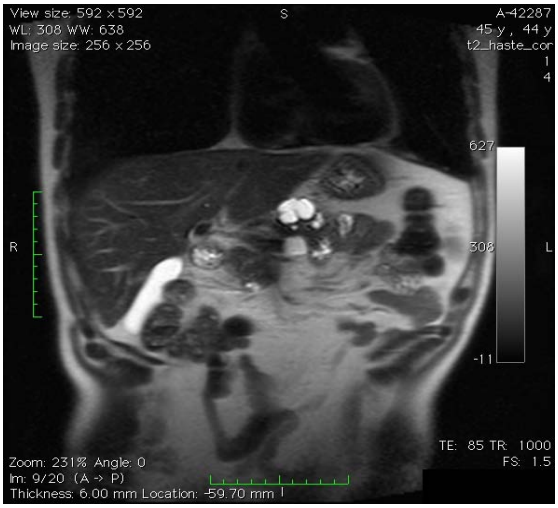

Figure 2: Coronal abdominal-MRI showing the same cystic lesions of the axial plan in another view.

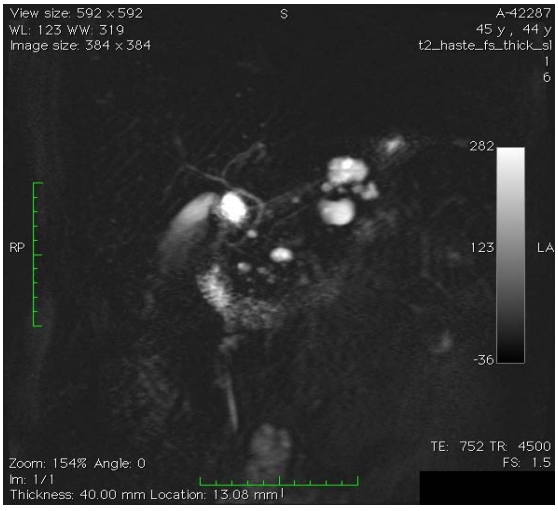

Figure 3: Coronal abdominal-MRI with static-fluid representation; note all various cystic lesions distributed along the entire pancreas, especially in the tail.

The patient has been followed for years with the diagnosis of chronic pancreatitis as long as the pain did not become so strong suspicion of acute pancreatitis and to be admitted to the Intensive Care Unit. The patient's history included four years ago a previous left superior pulmonary lobectomy for recurrent spontaneous pneumothorax due to multiple bilateral blebs with severe anaemia

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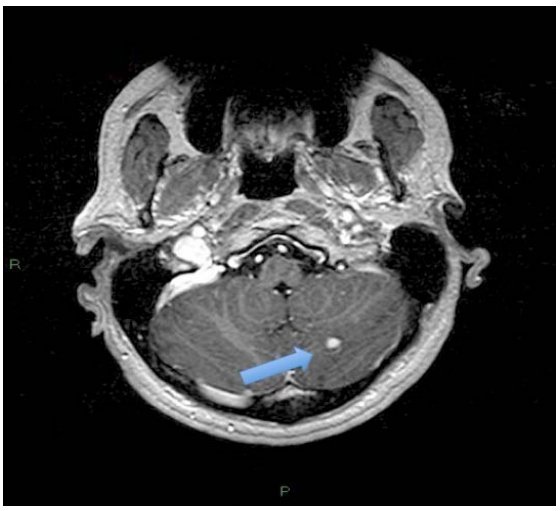

Figure 4: Cerebellar MRI (T1-weight) with a left cerebellar lesion (hyperintensive, oval shape with an own capillary vessel) diagnostic for hemangioma.

and bleeding due to rupture of one of these, and two years ago a concomitant resection of a source of asymptomatic adrenal pheochromocytoma.

Previous laboratory tests and ultrasound study of the thyroid and parathyroid glands allowed us to exclude the presence of a multiple endocrine neoplasia (MEN) type 2 and 3. Considering the history of multiple cysts in pancreas and lung, and the presence with pheochromocytoma, we suspected a Von Hippel-Lindau syndrome. We therefore looked forward for other cystic lesions as part of this syndrome so we performed a cerebral MRI which indicated the presence of a cerebellar haemangioma of 3-4 mm (Figure 4).

Amplification by Polimerase Chain Reaction and gene sequencing revealed a previously unknown and non-described heterozygous point mutation on chromosome 3p on the VHL gene at codon 162 (c.502_504delAGC), with a type deletion of Serine amino-acid, confirming our clinical suspect: Von Hippel-Lindau Syndrome Type 2C.

Von Hippel-Lindau syndrome is a rare genetic disorder first described by a German ophthalmologist (Dr. Von Hippel) and a Swedish pathologist (Dr. Lindau) in the first years of 20th Century; it is characterized by formation of multiple cystic lesions in different parenchymatous organs (CNS, retina, kidney, etc…) [1]. Clinically there are two different VHL diseases: patients with VHL type 1never present any pheochromocytoma, while in case of VHL type 2 there is a low (2a), medium (2b) or high risk (2c) to develop this neoplasia [2]. The cystic lesions may occur in all parenchymatous organs (usually CNS/retina, kidney, pancreas, among others), generally before 40th-50th year, with various pattern of localization [1]. The only organ spared by this condition, for unknown reasons, appears to be the lung [3]; only the group of Klein J. described lung lesions in this syndrome without the identification of a constituent genetic mutation as in our case [4].

Von-Hippel-Lindau syndrome is an autosomal dominant disease, with a prevalence around 1:35.000 people, mapping on a gene called VHL-gene on chromosome 3p. VHL-gene's mRNA produces two protein isoforms, one of 30 kDa (VHL30) with a cytosolic localization, and one of 19 kDa (VHL19) with a nuclear localization, derived from alternative splicing; although every isoform has specific functions, these two proteins present some common functions. The main is the Ubiquitin-ligase function: VHL-gene can bind other proteins, attaching some Ubiquitins to every Proline residual, creating therefore a poly-ubiquitinated product ready to be destroyed by the cell [1-3].

The main target of VHL-protein is the Hypoxia-Induced Factor (HIF) that represents the most important product in the control of cellular survival during hypoxic state. There are two different protein products of this gene: HIF-alfa, which is unstable and is constantly removed from the cell by VHL-protein, and HIF-beta, a stable protein that is constitutively present in the cellular nucleus [5,6]. VHL is a oxygen-sensitive protein and at low partial tension of oxygen it become inactivated, with a subsequent stabilization of HIF-alfa (no anymore destroyed by VHL), which can migrate to the nucleus and dimerizes with HIF-beta, and subsequently activate many growth proliferating factors [2,3]. With VHL-dysfunction (i.e. secondary to mutation, as in our case) there is a constitutive activation of HIF's pathway, with a subsequent incremental risk of neoplasia [1-3].

After this diagnosis, we proposed a genetic counselling at the patient's family, particularly at two sons of 14 and 12 years old. Only the first one resulted positive for the disease, without clinical symptoms or lesions at MRI/CT- scan. Regarding our patient, the treatment was only symptomatic using analgesics and serial screening with MRI; intervention was reserved only for symptomatic lesions or if they displayed accelerated growth. Surveillance has focused primarily on hemangioblastomas (including retinal capillary hemangioblastomas), renal cell carcinomas, and pheochromocytomas, the three manifestations most often resulting in severe disability or death. There is not any evidence about this program of screening; according to general practice we performed annually a screening with physical examination by clinician well informed about VHL disease, eye/retinal examination with indirect ophthalmoscopy, abdominal contrast MRI-scan to assess kidneys, pancreas and adrenals and laboratory test for plasma and urinary metanephrines using 24-hour collecting urine test. Every 2 years we prescribed brain contrast-MRI and cervical spine and audiology assessment by an audiologist. In this special case, in order to monitor the thorax lesions, a chest CT-scan every 2 years was also performed.

The life expectancy of those affected by this syndrome has been less than 50 years. The prognosis can be affected by mutation analysis results, especially regarding the risk of developing pheochromocytoma. Relatives may benefit from presymptomatic detection of increased tumor susceptibility, followed by regular surveillance for tumor development [8].

This picture illustrates the importance of keeping in mind the differential diagnostic clues in all clinical scenarios, especially in Emergency Medicine. In this case a complex manifestation of VHL-disease simulated an acute pancreatitis. This diagnosis was confirmed by PCR and gene-sequencing, revealing a previously unknown and non-described heterozygous point mutation of this VHL-gene and a new clinical presentation involving the lungs.