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Case Report

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Gullo's Syndrome. Thinking Outside the Box in A Difficult Scenario - A Case Report and Review of Literature

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1. Abstract

Benign pancreatic hyperenzymemia, often known as Gullo's syndrome, is an illness characterized by a gradual rise in pancreatic enzymes over the course of a year, without any physical or functional harm to the pancreas. To our knowledge, there have been no reports of this diagnosis in Romania to date. An 18-year-old female patient was referred to our Gastroenterology department for epigastric pain, nausea, and abdominal discomfort. The biochemistry panel revealed an elevated level of amylase and lipase, and amylasuria. The patient underwent a comprehensive assessment at the Paediatric Gastroenterology Department for a duration of 16 months. The abdominal ultrasonography showed no evident lesion of the pancreatic parenchyma. A computed tomography scan was performed, and any acute or a chronic pancreatic injury was ruled out. Additionally, an abdominal magnetic resonance cholangiopancreatography also excluded the bile obstruction, the ampullary masses or sludge in the main biliary duct. Further, an extensive work-up was performed, and the diagnosis of Gullo's syndrome was formulated. The patient was conservatively treated, consisting of a combination of a proton pump inhibitors and a prokinetic. One-month follow-up, the patient was in clinical remission. However, a persistent elevated value of serum amylase was documented during the follow-up, confirming the chronic and the benign nature of the disease.

2. Introduction

The condition known as benign pancreatic hyperenzymemia (BPH) or Gullo's syndrome (GS) was initially documented by Professor Lucio Gullo, an Italian gastroenterologist, in a cohort of 18 adults who exhibited no symptoms [1]. Since its initial publication in 1996, the number of documented cases has been limited, resulting in an uncertain global prevalence rate based on available data [2]. Amylase activity is present in various organs and body secretions, with the pancreas and salivary glands containing amylase concentrations significantly higher than other organs. Electrophoresis reveals two main types of serum amylase: P-type amylase from the pancreas and S-type amylase from the salivary glands [3]. Other sources of amylase include the fallopian tubes, cyst fluid, testes, lungs, thyroid, tonsils, breast milk, sweat, tears, and certain malignant tumours. Amylase from the fallopian tubes, tears, breast milk, and sweat has an electrophoretic mobility like salivary isoamylase, but the salivary glands are the primary source of S-type isoamylase [4]. The exact metabolic pathways of serum amylase are not completely understood. Individuals who have undergone a nephrectomy or have renal insufficiency exhibit serum amylase levels that are approximately 50% higher than those of healthy individuals, indicating that the kidneys play a significant role in amylase metabolism. However, the kidneys are not the only organs responsible for amylase clearance in humans, and

the extrarenal mechanisms for amylase clearance are not well defined [5]. Elevated serum amylase levels in cases of hepatic necrosis and cirrhosis suggest that the liver also plays a role in amylase metabolism [6]. The etiology of BPH remains incompletely established [6,7]. A structural change in the basolateral surface of the acinar cells is responsible for the increased release of pancreatic enzymes into the bloodstream or the impact of secretin in the Wirsung pancreatic duct [8]. The potential issue in the transportation of pancreatic enzymes from the trans-Golgi network to the cell membrane was reported by Cook et al, [9]. Several researchers have provided evidence suggesting that an elevated release of amylase in the bloodstream may be attributed to a cellular dysfunction [10]. The patient has pleomorphic clinical appearance, without of any evocative symptoms. As previously stated, the diagnosis involves the exclusion of both pancreatic and non-pancreatic conditions [11]. The utilization of computer tomography (CT) scan and magnetic resonance imaging (MRCP) techniques demonstrates a notable degree of specificity and sensitivity when assessing the pancreas. In our case, we excluded through MRCP and CT scans the presence of any associated pancreatic congenital anomalies, as these alterations have been described in some cases [12]. GS is distinguished by a sustained increase in pancreatic enzymes for a duration exceeding one year, without any indication of pancreatic damage [13]. Pancreatic enzymes (amylase and lipase) are elevated in 95% of cases. Hence, the diagnosis is established by ruling out alternative pathologies, including macroamylasemia, celiac disease, inflammatory bowel disease, neoplastic illnesses, acute or chronic pancreatitis. This determination is made through a comprehensive evaluation of clinical and paraclinical assessments [1,7,14]. The literature cites it as a potential risk factor for the development of pancreatic cancer [15,16]. An unequivocal diagnosis defines the therapeutic strategy and reduces the expenses associated with medical treatment [17]. In this article, we present the first case of Gullo's syndrome in Romania and a literature review.

3. Case Report

An 18-year-old female patient presented to our Gastroenterology Department for nausea and recurrent epigastric pain. On physical examination, the patient exhibited normal vital signs, with stature-weight growth delays of -2.5 standard deviations. Additionally, the abdomen was found to be soft, and normal bowel sounds were detected. The rectal examination yielded typical results, and the oral examination provided no abnormalities. The consistency of the faeces was within the expected range and the urine was normochromic. She denied smoking or occupational exposure to toxins. The patient has no significant family medical history. Laboratory tests revealed elevated levels of amylase and lipase (423 U/L and 270 U/L, respectively). The complete blood count, liver and renal function, clotting profile, albumin, serum electrolytes and lipid levels were within the normal range. Amylasuria was indicated by the urine results. Table 1 presents a comprehensive panel of tests conducted to facilitate the differential diagnosis of hyperamylasemia.

HLA= human leucocyte antigen; CFTR= cystic fibrosis transmembrane conductance regulator; LE= lupus erythematosus. Abdominal ultrasound revealed a normal pancreatic parenchyma, without any observable abnormalities such as nodules or cysts (Figure 1). To exclude the presence of congenital malformations such as pancreas divisum and enhance visualization of the pancreatic parenchyma, a CT scan was done, revealing no anomalies. Further, a MRCP was performed. Biliary obstruction, including strictures, neoplastic alterations, dilatations, as well as the presence of thin walls and the absence of biliary sludge within the gallbladder were excluded (Figure 2). The patient received symptomatic treatment consisting of proton pump inhibitors and antiemetics, with a favourable outcome. The medication doses were gradually reduced and discontinued after one month. During monthly follow-ups, the patient did not require the initiation of any new treatment. Based on the established definition, Gullo's syndrome was diagnosed, emphasizing on the benign characteristics of this illness.

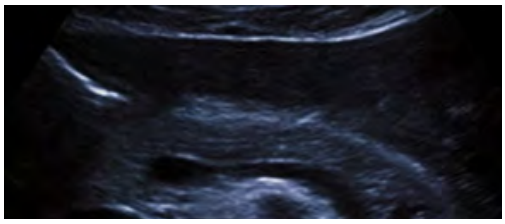

Figure 1: Ultrasound aspects of the pancreatic gland.

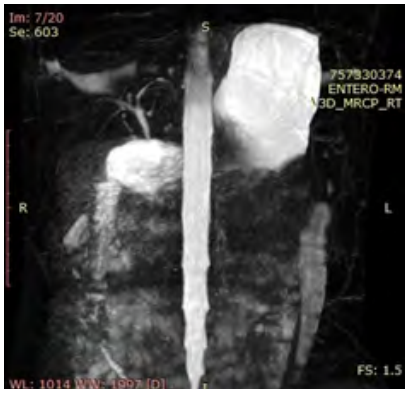

Figure 2: MRCP aspects of the pancreatic gland.

Table 1. Summary table of laboratory tests.

Laboratory tests	Patient result	Reference level
ImunoglobulineG4	0.6350 g/dl	0.0300-2.0100 g/dl
Amylase alpha in saliva	95.1 U/ml	3.1-423.1 U/ml
Pancreatic elastase	1190 µg/g	>200 µg/g
CFTR gene (cystic fibrosis)	Negative	Negative
Alpha 1 antitrypsin	142.16 mg/dl	110-180 mg/dl

HLA= human leucocyte antigen; CFTR= cystic fibrosis transmembrane conductance regulator; LE= lupus erythematosus.

4. Discussions

BPH is an unusual diagnostic finding [1,2,6,7,17,18]. The prevalence of BPH among subjects who underwent blood tests for pancreatic serum enzymes was found to be 2% in a retrospective cross-sectional observational study involving a substantial sample of the general Italian population [1]. In contrast, there is a lack of reports from other countries. The prevalence of BPH is 1.5 times higher in men compared to women, and it can occur at any stage of life [19]. In our case, we had to make an extensive differential diagnosis using a well-defined algorithm based on anamnesis, clinical exam, laboratory findings and literature data. The most common causes of hyperamylasaemia and hyperamylasuria were systematically assessed. The clinical examination was normal. Laboratory analyses revealed a constantly elevated value of serum amylase, and hyperamylasuria. Pancreatic ultrasound did not show any structural anomaly, so we continued to investigate the etiology of the disease with complex imaging techniques. The CT scan was within normal parameters, without any suspicion of organic damage. Further, MRCP excluded any alteration in hepatic biliary tree. No radiographic abnormalities were identified in our case. The patient did not have any pre-existing condition with a possible implication in triggering the disease. The association with other diseases is not very common [16-18]. In 2006, Antonio Carroccio et al. conducted a study [17] which found that approximately 25% of patients, both adults and children, diagnosed with celiac disease had elevated pancreatic enzyme values. This included subjects without gastrointestinal symptoms and those who appeared to be asymptomatic. A case report by Glencross et al. [18] described acute porphyria as potential mistaken diagnostic in the presence of hyperamylasaemia. Liverany et al. [19] reported a case of GS associated with ulcerative colitis while on azathioprine treatment. A study by Gullo et al. [1] did not identify any relationship between a genetic disorder related to specific genes as serine protease-inhibitor Kazal-type 1 (SPINK 1) and serine protease 1 (PRSS1) and GS. Regarding the follow-up protocol, there are not certain studies to define the most correct approach from a radiological point of view. There are several diseases related to an increased level of pancreatic enzymes, but the association is rare, so a careful interpretation is advised [3,7,10,13,14]. Gullo et al. [20] investigated if GS may be linked to celiac disease. However, in patients with GS, pancreati enzyme levels did not normalize after changing to a gluten-free diet. GS is thought to result from a defect in the basolateral surface of acinar cells, leading to increased enzyme passage into the blood, or from the effect of secretin on the pancreatic duct of Wirsung. The diagnosis of macroamylasemia was the most significant challenge in our case. Macroamylasemia is a medical disease that is distinguished by an elevation in serum amylase activity resulting from the presence of complex macromolecules that are too large to be excreted through urine. The phenomenon in question lacks a consistent correlation with any specific pathological condition and should be considered as a benign chemical derangement [21]. The urine sample of our patient indicated amylasuria, a condition that does not suggest the presence of macroamylasemia. Moreover, the electrophoresis findings were within the normal range. Special consideration should be given to neoplastic conditions, such as pulmonary, ovarian, pheochromocytoma, thymoma, multiple myeloma, and breast cancers, which are documented in the literature as potential causes of ectopic amylase secretion. Additionally, given the patient's female gender, a thorough and cautious evaluation should be directed towards gynaecological conditions, including ruptured ectopic pregnancy, fallopian tube and ovarian cysts, as well as infectious diseases, such as salpingitis. Despite their rare incidence, these conditions should not be overlooked in the differential diagnosis [22]. As part of the differential diagnosis, attention should also be given to the salivary glands, which may underlie elevated amylase levels. Ericson et al. [6] and Gokel et al. [23] have identified that the primary conditions responsible include trauma to the salivary glands, radiation exposure affecting the parotid glands, and pathologies involving calculus formation. Furthermore, transient increases in amylase levels can be observed in 30-60% of patients following cardiac surgery [24]. Differential diagnosis for potential pancreatic impairment leading to hyperamylasemia includes acute pancreatitis and chronic pancreatitis encompassing various etiologies, spanning classical causes to drug-induced factors like Methotrexate and genetic predisposition. Additionally, considerations extend to complications of acute pancreatitis such as pseudocysts, walled-off necrosis, and pancreatic ascites, as well as post-traumatic factors including recent abdominal surgery, blunt trauma, and endoscopic retrograde cholangiopancreatography. Furthermore, benign and malignant neoplastic conditions are also addressed in the differential diagnosis. Treatment will be tailored to each individual case [25-27]. Considering that GS is a benign disease, the primary focus will be on symptomatology. The literature provides detailed guidance on the therapeutic management of the underlying causal conditions [27]. Prior to defining pancreatic hyperenzymemia as benign, it is necessary to monitor patients for at least one year [1,2,5,7-9,10,15]. This is because in 1-2% of pancreatic cancer cases, asymptomatic BPH can serve as an early laboratory abnormality, particularly in older individuals [12]. A curative treatment was not possible in our case, considering the lack of data in the literature that would indicate a targeted drug in this condition [25]. The patient received symptomatic treatment with a favourable clinical outcome, and she was informed of the chronic nature of this condition, however with the necessity of period medical follow-up. Follow-up should be encouraged, as a very small percentage of patients have a higher risk of developing pancreatic cancer, however the data is scarce.

5. Conclusions

Gullo's syndrome poses numerous diagnostic challenges for health care specialists as the increased levels of amylase may be found in numerous other medical conditions. Therefore, careful assessment of these abnormalities is advised. The interpretation of amylase and lipase values must be individualized for each case. Investigations

should be tailored specifically to the proposed diagnosis, and the diagnosis of Gullo's syndrome can only be made after all other possibilities have been thoroughly excluded. This necessitates a multidisciplinary approach, involving collaboration among gastroenterologists, internists, radiologists, and other relevant medical specialists, to ensure comprehensive evaluation and management of the patient.

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