CMI Clinical Management Issues

Case Report

Familial Gullo's Syndrome: A Clinical Case Report

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Abstract

This case report describes a male patient born in 1953 presenting an occasional increase in serum amylase and lipase forty years ago. The monitoring of enzymes was accompanied by radiological investigations, which did not reveal pancreatic pathology. In his family, including 10 siblings, half were carriers of this isolated anomaly; multiple cysts in pancreas, kidneys, and liver were present in some family members, in addition to a pancreatic neoplasia in a sister who did not carry the enzymatic abnormality. Our patient developed colon adenocarcinoma at the age of 67. Here we examine the characteristics of non-pathological chronic pancreatic hyperenzymemia defined as such by the main Italian pioneer Professor Gullo.

Keywords: Hyperamylasemia; Hyperlipasemia; Familial Pancreatic Hyperenzimemia; Gullo's Syndrome; Magnetic Resonance Cholangiopancreatography Imaging
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INTRODUCTION

Chronic asymptomatic pancreatic hyperenzymemia (CAPH) is a persistent abnormal increase in the serum concentrations of pancreatic enzymes without pancreatic symptoms and imaging findings of pancreatic diseases. The elevation of serum enzymes is fluctuating, with frequent and temporary findings of levels within the normal range. In 1996, Professor Lucio Gullo for the first time used the expression chronic non pathological hyperamylasemia (CNPH) of pancreatic origin and named it "Gullo's syndrome" [1,2]. CAPH has been considered a benign condition [3] that can occur sporadically or in familial forms.

CASE DESCRIPTION

In a Caucasian subject born in 1953, an increase in amylase and lipase was found during a routine blood test check carried out in 1980. The maximum values achieved were:

- for total amylases 228 U/L (normal values [nv] 10-120 U/ L);
- for pancreatic amylase 151 U/L (nv <53 U/L);
- for lipase 766 U/L (nv <67 U/L).

Why Do we Describe This Case

The finding of isolated hyperamylasemia and/or hyperlipasemia not associated with abdominal symptoms involves a series of investigations aimed at ruling out or confirming a pancreatic pathology. The periodic oscillations of these enzymes, with intermittent return to normal values, can configure a benign chronic pancreatic hyperenzymemia, especially if associated with the finding of familiarity

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Box 1. Drugs associated with pancreatic hyperenzimemia (modified from [6])

- *Paracetamol*
- *Steroids*
- *Azathioprine*
- *Ephedrine*
- *Ritodrine*
- *Chemotherapy*
- *Roxithromycin*
- *Cyclosporine*
- *Clozapine*
- *Pentamidine*
- *Didanosine*

Box 2. Drugs involved in the onset of acute pancreatitis (modified from [7])

- *Didanosine*
- *Azathioprine/6-mercaptopurine*
- *Pentamidine*
- *Stibogluconate*
- *Tetracyclines: doxycycline, tigecycline*
- *Amoxicillin/clavulanic acid*
- *Metronidazole*
- *Methimazole*
- *Antihypertensives: furosemide, thiazide, α-methyldopa*
- *Angiotensin-converting enzyme (ACE)-inhibitors: captopril, benazepril, enalapril, lisinopril, ramipril, quinapril*
- *Angiotensin receptor blockers: irbesartan, valsartan, and losartan*
- *Amiodarone*
- *Sulfasalazine*
- *5-Aminosalicylic acid (mesalazine)*
- *Statins: simvastatin, pravastatin, rosuvastatin*
- *Dipeptidyl peptidase-4 inhibitors: sitagliptin, saxagliptin, alogliptin, and vildagliptin*
- *Glucagon-like-peptide–1 receptors agonists: albiglutide, exenatide, and liraglutide*
- *Sodium-glucose cotransporter 2 inhibitors: canagliflozin*
- *L-asparaginase*
- *Valproic acid*
- *Sulindac*
- *Salicylates*
- *Calcium*
- *Estrogen*
- *Trenbolone (anabolic steroid)*
- *Tamoxifen*
- *Antipsychotics: olanzapine, clozapine, quetiapine, and mirtazapine*
- *Paracetamol*

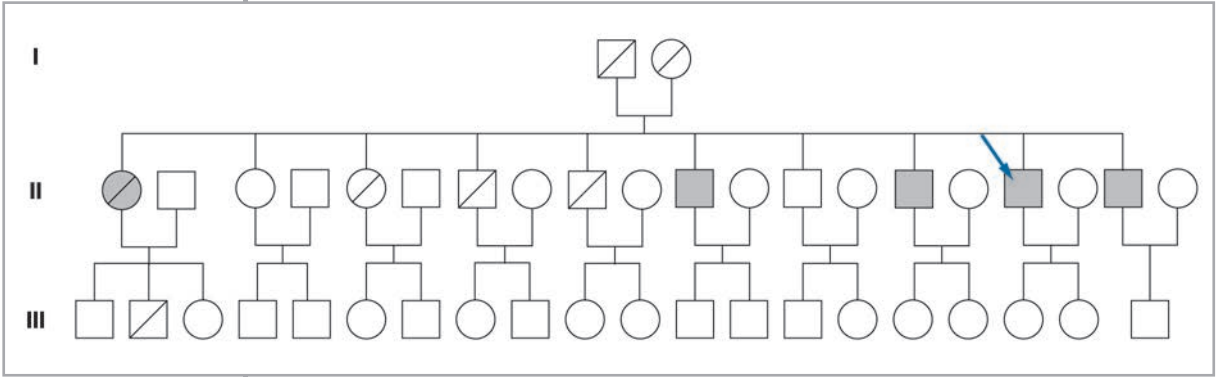

Figure 1. *Genealogical tree study.*

I, II, III = first, second, and third generation

These findings were never associated with abdominal pains or acute back pain. During the 40-year observation period, the increased values alternated with normal values: no pancreatic disease has been recorded so far. A first ultrasound of the complete abdomen, performed 8 years after the first finding of hyperenzymemia, showed: moderate hepatic steatosis, a small incision at the right kidney, a prostate with adenoma aspect in the central site. The patient was affected by: sleep apnea syndrome, esophageal hiatus hernia, chronic gastritis, diffuse colon diverticulosis, hyperplastic descending colon polyp, arterial hypertension, nasal obstruction, coxarthrosis (arthroplasty), chronic obstructive pulmonary disease, type 2 diabetes mellitus (in diet therapy only), thyroid node, fusiform aneurysm on the right iliac artery, and prostatic hypertrophy. A new diagnosis of renal insufficiency, viral hepatitis, Sjögren syndrome [4], celiac disease, and inflammatory bowel diseas [5] was not made. Alcohol intake was occasional and moderate.

Affected		Year first answer	Total amylase (nv 10-120 U/L): maximum value achieved	Lipase (nv <67 U/L): maximum value achieved	Observation period (number of years)	Cause of death (year)	Comorbidities										
							Pancreas cancer	Pancreatic cysts	Hepatic and renal cysts	Type 2 diabetes	Arterial aneurisms	Colon diverticulosis	Colon cancer	Hypertension	Prostatic hypertrophy	Prostate cancer	Hip osteoarthritis
Affected																	
1936	F	1980	1900	1200	38	Myelofibrosis (2018)				X		X					X
1945	M	1980	900	1100	40			X				X		X		X	
1950	M	1980	610	1622	40			X						X	X		X
1953*	M	1980	228	766	40				X	X	X	X	X	X	X		X
1956	M	1989	209	656	31							X					
Not affected																	
1938	F							X	X								X
1939	F					Breast cancer metastasis (2018)	X (2008)										
1941	M					Undifferentiated cancer metastasis (2008)						X	X		X		X
1943	M					Trauma (2003)											
1947	M							X	X	X	X	X		X	X		

Table I. *Clinical features of the patient in analysis (*) and his 9 siblings, 5 of whom were carriers of chronic pancreatic hyperenzymemia.*
nv = normal values

Date	Total amylase (nv 10-120 U/L)	Pancreatic amylasis (nv <53 U/L)	Lipase (nv 2- 67 U/L)	CA 19.9 (nv <31 KU/L)	CEA (in non-smokers nv <4 µg/L)
2005	93		150	8.04	
2008, March	115		151	2.44	
2008, December	160		387	2.04	
2009, February	181		489		
2009, December	66		22	3.55	
2010	90		76		
2011, May	134		309		
2011, November	**228**		670	9.02	
2012, February	65		32		
2012, June	87		59	7.89	
2012, September	156		411	8.07	
2013, January		21	39	8.90	
2016		129	**766**		
2017		86	504		
2018		22			
2019, February	**151**		364		
2019, September	117	75.8	219	**80**	1.8
2019, October: colon adenocarcinoma, right hemicolectomy					
2019, December				4.2	1.5
2020, February				10.8	3
2020, June	65		27	9.2 (nv <35.4)*	3.3
2020, October				10.6	2
2020, November	141 (nv: <100)*		402 (nv <60)*		

Table II. *Summary table of pancreatic enzyme (and oncologic markers) values in our patient relating to 19 consecutive blood tests, found over a 15-year period. Maximum values reached are in bold. Lipase and total amylase were measured with kinetic colorimetric method, pancreatic amylasis using enzymatic kinetic method, and CA 19.9 and CEA employing chemiluminescence.*
nv = normal values
*change in normal values in 2020

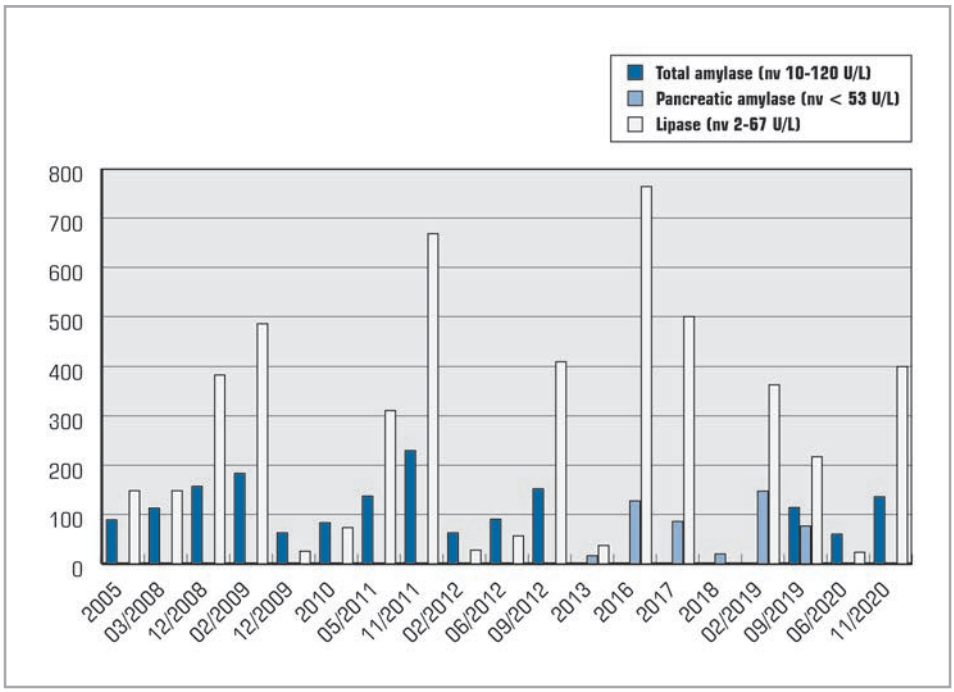

Figure 2. *Graphic representation of maximum serum values of pancreatic enzymes (38 determinations) over 15 years in our patient. Enzymes were abnormally elevated, albeit with fluctuations and transient normalization. In the period 2013-2019 only pancreatic amylases were measured in our laboratory.*

nv = normal values

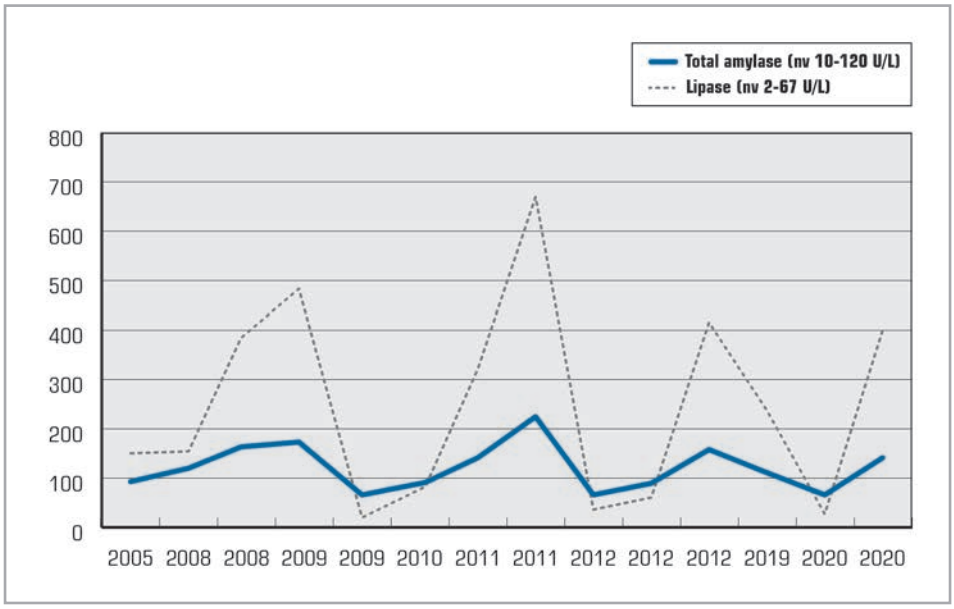

Figure 3. *Fluctuating values of total amylase and lipase from 2005 to November 2020. In the period 2013-2019 only pancreatic amylases were measured in our laboratory.*

nv = normal values

He did not use any drug that could induce hyperamylasemia or hyperlipasemia (Box 1 [6]) or acute pancreatitis (Box 2 [7]).

His family history revealed:

- a mother who died at the age of 63 years after cholecystectomy for multiple cholelithiasis;
- out of 10 siblings, half were carriers of hyperamylasemia (with a maximum value of 1900 U/L) and/or hyperlipasemia (with a maximum value of 1622 U/L), found after the age of 27-44 years;
- a sister, born in 1936, suffering from Hashimoto's thyroiditis and myelofibrosis, died at 82 years from aplastic anemia;
- a brother, born in 1945, is a carrier of prostate cancer and has pancreatic cysts on abdomen CT scan;
- a 69-year-old brother is a carrier of cystic pancreatic lesions detected by CT scan;
- a brother, born in 1956, is a carrier of isolated hyperenzymemia;
- it should also be noted that out of two sisters without hyperenzymemia, one died at

Parameter	Detected level												Normal range
	2018		2019			2020							
	March	May	May	October (pre-surgery)	December (pre-chemoterapy started by 12/2019)	January	February	March	June	July	October	November	
Glucose (mmol/L)	7.6		5.2	7.5						7.5	7.7		3.35-5.55
Glycated hemoglobin (%)		6.2	5.8	4.7							6.3		4-6
Aspartate aminotransferase (U/L)	17			23	19	18	20	17	37	26	29		<35
Alanine aminotransferase (U/L)	14	23		29	23	15	20	14	34	22	39		<45
Total bilirubin (µmol/L)					10.5	8.9	11.3	9.8	16.3	16.9	13		1.7-17
Conjugated bilirubin (µmol/L)					4.3	4.0	4.9	3.8	6.4	2.85			<5.1
γ-glutamyltransferase				35	34					51	70	60	3-55
Sodium (mmol/L)				139	138	138	142	140	138	146	136		136-145
Potassium (mmol/L)				3.8	3.8	3.9	3.8	3.8	3.8	4.7	3.8		
Total creatine kinase (U/L)	117												<171
C-reactive protein (mg/L)	30.46									3.27			<5
Creatinine (µmol/L)		83	87	99	103	103	95	102	116	104	93		64-104
Total cholesterol (mmol/L)			5.11	5.05						4.9			<4.92
HDL cholesterol (mmol/L)			1.21	1.18						1.06			<1.40
Triglycerides (mmol/L)			1.10	1.61						1.36			<1.70
Prostate specific antigen (PSA) (µg/L)		1.69		1.73	1.42					1.23	1.51		<4
Red blood cells ($\times 10^{12}$/L)		5.39		5.24	4.86	4.9	4.42	4.37	4.05	4.55	5.53		4.50-5.50
Hemoglobin (g/L)		161		155	142	141	128	136	136	147	163		135-160
Platelets ($\times 10^9$/L)		165		144	161	160	142	180	130	170	156		150-400
White blood cells ($\times 10^9$/L)		7.19		1.88	5.85	4.15	3.6	4.46	3.02	4.34	4.80		4-10
Neutrophils ($\times 10^9$/L)		4.23		1.31	3.42	1.92	1.97	2.36	1.39	2.45	2.32		1.9-8
Total protein (g/dL)			6.8	6.7						6.9			6.6-8.7
Albumin (%)			66.4	66.1									55.8-66.1
α-1-globulins (%)			2.8	3.1									2.9-4.9
α-2-globulins (%)			8.1	7.8									7.1-11.8
ß-1-globulins (%)			6.3	6.3									4.7-7.2
ß-2-globulins (%)			4.3	4.5									3.2-6.5
γ-globulins (%)			12.1	11.8									11.1-18.8

Table III. *Summary table of laboratory tests performed during the last two years (2018-2020), before and after surgery (hemicolectomy) with subsequent chemotherapy.*

79 years for cancer of the breast and pancreas, while the other, 81-year-old, carries multiple cysts of pancreas, kidney, and liver.

The genealogic tree is shown in Figure 1, whilst Table I details the clinical features of the family members.

In our subject the presence of macroamylasemia and macrolipasemia was excluded (as well as macro-creatine phosphokinase—macro-CPK). The periodic control of oncological markers (CA19-9) was negative.

The evolution over time of total amylase, pancreatic amylase, and lipase values is shown in Table II and Figures 2 and 3. Additional laboratory tests are shown in Table III.

In 2018, after 38 years from the first finding of hyperenzymemia, the magnetic resonance imaging (MRI) findings of the upper abdo-

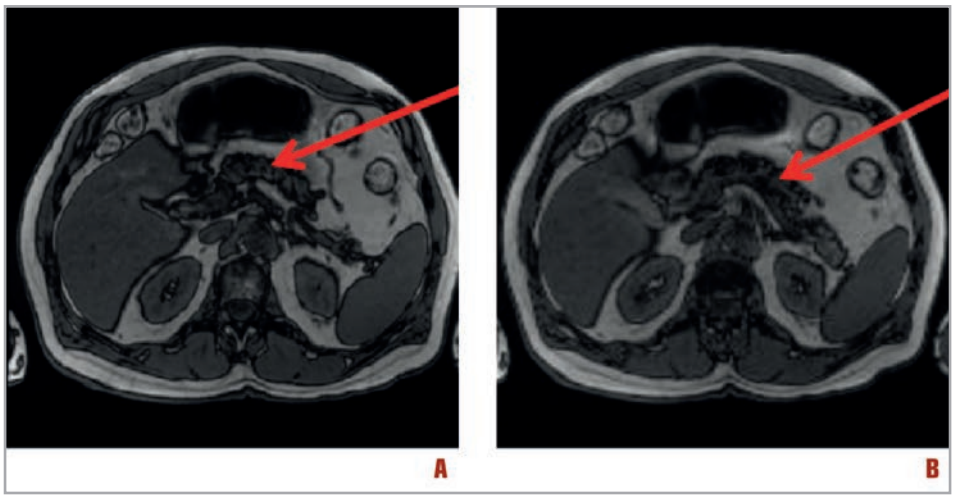

Figure 4. *Findings from magnetic resonance cholangio-pancreatography (MRCP) performed in 2018. The arrows indicate normal pancreas (A and B).*

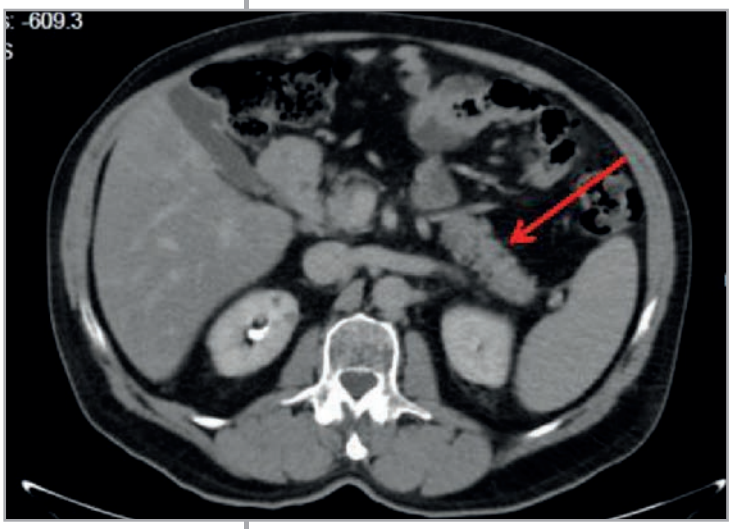

Figure 5. *Contrast-enhanced abdominal CT scan in October 2020 showed normal pancreas (red arrow).*

men revealed: liver containing some small cystic formations scattered in both lobes, the greatest being 10 mm large; pancreas within limits; some bilateral renal cystic cortical formation, greater than 17 mm; no areas of pathological enhancement after paramagnetic contrast medium infusion (gadoteridol) of the upper abdomen organs. The magnetic resonance cholangio-pancreatography (MRCP) [2] showed no biliary lithiasis, no dilatation of the intrahepatic biliary tree, hepato-choledochus with a maximum caliber of 7 mm, regular Wirsung duct (Figure 4).

The laboratory tests performed in February 2019 (Table II) demonstrated: total amylase = 151 U/L (nv 10-120 U/L), lipase = 364 U/L (nv 2-67 U/L), γGT = 53 U/L (nv <55 U/L), blood glucose = 107 mg/dL, total cholesterol = 197 mg/dL, triglicerides = 153 mg/dl. The laboratory tests in September 2019 have found: lipase = 219 U/L (nv 13-60 U/L), α-amylase = 117 U/L (nv 28-100 U/L), pancreatic iso-amylase = 75.8 U/L (nv 13-53 U/L), faecal calprotectin = 81 μg/g faeces (nv <50 μg/g) [8], CA 19-9 = 80 KU/L (nv <31 KU/L), positive occult blood in the faeces.

In October 2019, colonoscopy showed an ulcer in the right flessure and the biopsy revealed an adenocarcinoma. The patient underwent right hemicolectomy (October 2019) and subsequent 8 cycles of chemotherapy (oxaliplatin + capecitabine). He was negative for the nasopharyngeal swab

What should the clinician ask him/herself or the patient?

- *Are changes in pancreatic enzymes associated with abdominal disorders?*
- *Was the finding of hyperamylasemia and/or hyperlipasemia occasional?*
- *Is periodic control of pancreatic enzymes recommended?*
- *What first level investigations should be performed?*
- *Which second level investigations are to be considered optional?*
- *How long should pancreatic enzymes be monitored?*
- *Is there familiarity?*
- *When can we reassure the patient about the benignity of the anomaly?*
- *Could there be dietary suggestions or drug treatments capable of reducing the pancreatic abnormality?*

for COVID-19. Laboratory tests in June 2020, after the last course of chemotherapy, showed: amylase = 65 U/L (nv 10-120 U/L), lipase = 27 U/L (nv 2-67 U/L), CA 19-9 = 9.2 KU/L (nv <35.4 KU/L), CEA = 3.3 µg/L (nv <4.0 µg/L). The contrast-enhanced abdominal CT scan revealed normal pancreas, minute hypodensity of cystic appearance in the liver, bilateral renal cysts, the largest 24 mm on the left.

The most recent laboratory tests, performed in November 2020 (Tables II), detected serum amylase = 141 U/L (nv <100 U/L) and serum lipase = 402 U/L (nv <60 U/L). The contrast-enhanced abdominal CT showed normal pancreas, unchanged liver, and kidney cysts (Figure 5).

DISCUSSION

Our clinical case meets the criteria for the definition of chronic asymptomatic pancreatic hyperenzymemia. In fact, the diagnostic criteria are [9,10]:

- an increase by >10% of the upper normal limits of serum amylase and/or lipase found on >3 occasions, lasting more than 6 months;
- absence of upper abdominal or back pain;
- idiopathic presentation.

We excluded through the MRCP the presence of any associated congenital anomalies (pancreas divisum, annular pancreas, Wirsungocele, cystic lesions at the pancreatic tail, Santorinicele, diffuse dilation of the main pancreatic duct) and intraductal papillary mucinous tumor of the pancreas, as these alterations have been described in some cases [11-14]. We did not perform a MRCP with secretin stimulation, currently considered as the method of choice in the study of CAPH subjects [9,15] for the search for sphincter of Oddi dysfunction or even early (mild) chronic pancreatitis: this investigation would not have added significant data to the always stable clinical picture. Similar considerations apply to the use of endoscopic ultrasonography [16-18].

In the family group in analysis, two brothers with hyperenzymemia had pancreatic cysts, while a third brother had only hepatic and renal cysts. Of two siblings without hyperenzymemia, one had multiple cysts in the pancreas, kidney, and liver, while the second died due to pancreas (and breast) cancer at the age of 79 years. The significance of these associations, as well as the appearance of colon adenocarcinoma in our patient, at the present time is not clear.

The patients must be followed for a period of at least one year before labeling their pancreatic hyperenzymemia as benign, because in 1-2% of cases of pancreatic cancer, asymptomatic pancreatic hyperenzymemia can be an early witnessed laboratory abnormality, especially in elderly age group [19,20].

In adulthood, the prevalence of incidentally found pancreatic cystic lesions is high (between 2.6% and 19.6%) [21-24]. They are heterogeneous and include malignant, benign, and pre-malignant lesions, capable of evolving into invasive carcinoma over time. The differential diagnosis between intraductal papillary mucinous neoplasm, mucinous cystoadenoma and serous cystoadenoma could be made by endoscopic ultrasonography fine needle aspiration or even better with endoscopic ultrasonography through-the-needle microforceps biopsy [25], with the determination of intracystic glucose concentration, having been found to be more sensitive than the concentration of carcinoembryonic antigen [24]; however, this investigation is not carried out in our hospital.

It should be considered that a long-lasting CAPH, defined as benign, should be studied in depth at least with MRCP for the possibility, among others, of finding intraductal papillary mucinous neoplasm in small pancreatic cystic formations [12,14,26].

Also for this reason, the follow-up of hyperenzymemia must be continued for at least two years [27].

In our patient, after the end of chemotherapy for the colon adenocarcinoma, the fluctuations of lipase and amylase remained unchanged.

The ethiology of Gullo's syndrome remains unknown. It is known that there is a defect in the basolateral surface of the acinar cells that causes the increased secretion of pancreatic enzymes into the blood or the effect of secretin in the pancreatic duct of Wirsung [2].

Regarding the study of cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations and serine peptidase inhibitor, Kazal type 1 (SPINK1) and serine protease 1 (PSSR1) genes, no significant differences compared to the general population have been described in benign familial hyperenzymemia [28-30].

The prevalence of CAPH among subjects who underwent blood tests for multiple pancreatic serum enzymes was 2% in

a retrospective cross-sectional observational study in a large sample of the general Italian population [31].

In another Italian case series relating to 125,483 total accesses registered in a University Emergency Department [32], a prevalence of benign pancreatic hyperenzymemia equal to 0.09% cases for every 100,000 accesses was found.

Unlike the very extensive Italian cases, reports in other countries are limited. In literature, few cases are reported in Japan [4,11], Belgium [14], USA [17,33], India [34], Taiwan [35], Brazil [36], Austria [37], Poland [38], Ukraine [39], Australia [40], Spain [41,42], Venezuela [43], Morocco [44], and Germany [45].

The most recent Italian case series was published in December 2019 [46].

Pancreatic hyperenzymemia can appear at almost every age: the ratio of affected men and women is 1.5:1. It is a rare finding in children: only a few sporadic cases have been described in the literature [41,47-49].

The coexistence of hyperenzymemia in siblings is diagnostic for familial form of CAPH, which has an incidence between 4% and 39% in the series described in the literature [3,8,10,12,39,43,50].

CONCLUSION

In the family group here described, the long follow-up between 31 and 40 years confirms the benignity of the enzymatic anomaly regarding pancreatic diseases. This familial association supports the concept of a genetic basis underlying pancreatic enzyme abnormalities, despite the fact that so far no correlations have been found with the genetic mutations studied.

CONSENT TO PUBLICATION

The consent to publication was obtained from the patient here described.

Key points

- *The increase in serum amylase and/or lipase affects the extension of first-level laboratory and instrumental investigations aimed at confirming the presence of a pancreatic pathology.*
- *Pancreatic hyperenzymemia may be secondary to extra-pancreatic diseases.*
- *The periodic, but persistent over time, fluctuations of these enzymes with frequent return to normalization can result in chronic pancreatic hyperenzymemia (Gullo's Syndrome), which is considered in most cases to be a benign enzymatic anomaly.*
- *Gullo's Syndrome remains a diagnosis by exclusion: from the first finding of hyperenzymemia it is necessary to wait two years before confirming it.*
- *In order to reach the diagnosis of CAPH, "second level" radiological investigations (MRCP, endoscopic ultrasonography) are necessary to rule out pancreatic anomalies (especially) of an anatomical type.*
- *The presence of this anomaly in relatives is an indicative element to confirm the diagnosis and its benignity.*

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