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Review

Hypercalcemia, hyperlipidemia and rheumatic diseases: uncommon causes inducing acute pancreatitis

S. Delakidis[1], A. Elezoglou[2]

INTRODUCTION

Acute pancreatitis is a common disorder with numerous causes, obscure pathogenesis and often, unpredictable outcome. Gallstones and alcohol abuse are still the major etiological causes corresponding to 80% of all cases.[1] Less common but significant agents are drugs, infections, trauma, ischemia, genetic factors, hormonal disturbances (gestational pancreatitis), endoscopic examinations of the bile and pancreatic ducts (ERCP), upper abdominal operations, protein deficiency, metabolic disorders and rheumatic diseases. Finally approximately 10% of all cases are idiopathic. Recently, prospective studies have shown that in most of these idiopathic cases, microlithiasis of the gallbladder is present. Relatively new forms of pancreatitis are that induced by lithotripsy and pancreatitis in patients with AIDS.

Despite the causes of acute pancreatitis the disease presents a similar clinical pattern. Thus, it is proposed that the varied causes of acute pancreatitis converge in a common point that initiates a cascade of events that causes pancreatitis.

Although the etiology and pathogenesis of pancreatitis has not been completely identified, it can be maintained that the autodigestion occurring to pancreatic tissue, by activation of proenzymes before they reach the intestinal lumen, is of vital importance.

[1]Department of Gastroenterology, Sismanoglion General Hospital, Athens, [2]Rheumatology Department, Asklepeion General Hospital, Voula, Athens

Author for correspondence: Stergios Delakidis, 12 Archelaou str., 116 35 Athens, Greece, Tel.: (+301) 7216654

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Several authors have noted that the incidence of acute pancreatitis has increased by a factor of 10 during the last two decades. The reasons for this increase are unclear, but they may be related to an increase in alcohol abuse and an improved ability to diagnose the disease.

Evaluating of the existing data on metabolic disorders causing pancreatitis, hypertriglyceridemia and hypercalcemia are considered as the most common causes. Hyperlipaemia is the etiological factor for acute pancreatitis in 1.3-3.8% of cases and is more common than hypercalcemia. Clinical recognition of hyperlipaemia and its association with acute pancreatitis is extremely important because it constitutes a treatable type of pancreatitis with recurrent acute episodes that can prevent and diminish the danger of further pancreatic damage. In the modern medical era hypercalcemia can be recognized sooner and so it may not be severe enough to cause pancreatitis.

Literature review on pancreatitis complicating rheumatic diseases revealed that is a rather infrequent and sometimes subclinical condition. Autoimmune phenomena, vasculitis and drug toxicity is the main complex of the etiology of the pancreatic inflammation in rheumatic diseases.

A. HYPERCALCEMIA AND ACUTE PANCREATITIS

Calcium Homeostasis and Exocrine Pancreas

Calcium homeostasis and exocrine pancreas interact on several levels under both physiologic and pathophysiologic conditions:[2] 1) Calcium is essential for the intracellular processes associated with pancreatic secretion. In the acinar cells, it acts as an intracellular messenger of secretagogues, including cholecystokinin, acetylcho-

line and bombesin. Attachment of secretagogue to its receptor on the surface of the cell causes a sudden increase in the intracellular calcium concentration. 2) Disturbed calcium secretion in pancreatic juice can be observed even following slight pancreatic alteration; conversely disturbed calcium secretion may be of importance in the pathogenesis of chronic calcifying pancreatitis. 3) Calcium plays an important role in the conversion of the trypsinogen to active trypsin. It is also known that enterokinase can activate pancreatic juice much more rapidly in the presence of calcium. 4) Pancreatitis complicates chronic and acute hypercalcemic syndromes though the pathogenic mechanism is uncertain. 5) Hypocalcemia is an important symptom of acute pancreatitis whose pathogenesis has not been fully elucidated.

Several experimental protocols are been developed to study the effect of hypercalcemia on pancreatic morphology and physiology. The rat is the most frequently used animal for the study of experimental pancreatitis. Hypercalcemia is induced in the rat by per oral application of dihydrotachysterol followed by an intra peritoneal injection of ferric dextran. Edematous pancreatitis is found in 47% of the animals. In a different model, experimental hyperparathyroidism is induced in rats by parathyroid transplantation. Acute hemorrhagic pancreatitis and hyperamylasemia are found in the presence of hypercalcemia. Because these models used indirect methods to induce hypercalcemia, the question of whether or not calcium itself is responsible for acute pancreatitis could not be elucidated conclusively. In cats calcium infusion locally into the splenic artery, under experimental conditions, induces necrotizing pancreatitis.[3] The mechanism by which hypercalcemia leads to the development of acute pancreatitis is unclear and some investigators have not confirmed this association and the assumed causal relationship between these two clinical entities is been questioned.

Hypercalcemia was shown to increase pancreatic enzyme output and conversion to active forms.[4] It is well established that calcium is an essential co-factor in trypsinogen autoactivation. The conversion of trypsinogen to active trypsin occurs by cleavage of a small peptide (TAP, trypsinogen activation peptide) which is easily assayed and provides a quantitative index of active trypsin generation and a good marker for the severity of pancreatitis.[5] Removal of TAP allows the inactive trypsinogen molecule to undergo a conformational change resulting in active trypsin.[6] Calcium increases the stability and activity of trypsin, possibly by binding to the N-terminal aspartyl residues of TAPs, thereby eliminating their inhibitory effect on autocatalytic activation. Increased calcium concentrations would promote this effect, resulting in an increased activation of trypsinogen. As shown in vitro, increased calcium concentrations increase trypsinogen autoactivation. In addition, hypercalcemia induces release of cholecystokinin through a cholinergic pathway. This may by relevant because cholecystokinin stimulation of pancreatic acinar cells has been shown to cause intracellular activation of pancreatic proteases.

Other studies assumed that acute hypercalcemia enhances the permeability of pancreatic ducts, thereby producing leakage of enzymes that can damage pancreatic cells.[7] The relationship between an increase in ductal permeability and the development of pancreatitis deserves mention. In animal models the main pancreatic duct can be made abnormally permeable so those molecules normally contained in the lumen can leak out. When such a permeable duct is perfused with activated pancreatic enzymes acute pancreatitis is produced. If the duct has not first made permeable or if the enzymes have not been activated, pancreatitis does not develop. Agents already known to increase duct permeability include bile salts and ethanol applied locally, and ethanol consumed orally. Acute elevation of serum calcium produces a similar result in experimental models of acute pancreatitis. Some investigators have pointed out that short-term elevations of calcium concentrations are more likely to be associated with acute pancreatitis than chronic hypercalcemic conditions.

Hypercalcemic conditions associated with acute pancreatitis

Hypercalcemia is a known etiological factor for acute pancreatitis. In the modern medical era, hypercalcemia can be recognized sooner and so it may not be severe enough to cause pancreatitis. Erdheim in 1903 described first, an association between these two conditions in a patient with hyperparathyroidism.

In addition to hyperparathyroidism, numerous other causes of hypercalcemia have been associated with pancreatitis. In several case reports authors have described pancreatitis in association with malignancy-related hypercalcemia. Examples of this include multiple myeloma,[8,9] adult T-cell leukemia,[10-12] breast carcinoma, and metastatic islet carcinoma of the pancreas. Pancreatitis occurred with the humoral hypercalcemia of malignancy, secondary to leiomyosarcoma.[13] Calcium infusion with total parental nutrition and calcium gluconate administration in renal failure has been associated with pancre-

atitis. Improper hemodialisis causing hypercalcemia was also associated with pancreatitis. Other causes of hypercalcemia including vitamin D intoxication,[14] sarcoidosis, milk-alkali syndrom[15] and familial hypocalciuric hypercalcemia,[16,17] a hereditary disease compatible with autosomal dominant inheritance, also, have been associated with pancreatitis. Table 1 shows the hypercalcemic causes that are associated in literature with pancreatitis.

As previously mentioned the first reported case of an association between hyperparathyroidism and acute pancreatitis was documented in 1903. In 1962 Mixter et al reviewed the literature and found 62 cases of this association. In 50% of these, pancreatitis was the event that preceded the investigation of hypercalcemia and hyperparathyroidism. The authors went on to state that the high frequency of this association "establishes an etiologic relation between pancreatitis and hyperparathyroidsm". Many case reports and reviews supporting or refuting this association have been published since then.[18-20] Some of the reviews reporting the occurrence of pancreatitis in hyperparathyroidism patients are shown in Table 2. The prevalence ranges from 0.9 to 34%, earlier series tend to have higher prevalence rates compared to later series. There are over one hundred cases of pancreatitis associated with hyperparathyroidsm in the literature. And all forms of pancreatitis have been observed including severe, acute, necrotizing often ending fatal, as well as, relapsing and chronic pancreatitis with marked exocrine and endocrine insufficiency. Contributing to earlier diagnosis and operative treatment the frequency of acute or chronic pancreatitis in primary hyperparathyroidism has decreased from a percentage of 5-10% to 1-2%. Twenty-five to 45% of the patients with pancreatitis associated with hyperparathyroidsm develop pancretic parenchymal calcinosis or ductal stones. Pancreatic dysfunction has been demonstrated in patients with hyperparathyroidism, even in the absence of an overt history of pancreatitis. In such cases, secretory precipitates have been described histologically within the pancreatic ducts. In patients with pancreatitis and hyperparathyroidism it is important to exclude other possible etiological factors that are found in 64% of the patients with these two diseases.

Acute pancreatitis is a well-recognized complication after cardiopulmonary bypass[21] (CPB), underestimated in occurrence and with a great importance because of the frequency of CPB procedures and the unfavorable clinical course and mortality that tends to 86%. Many authors have suggested pancreatic ischemia resulting from temporary hypotension during CPB as a possible factor for this complication. Drugs such as phenylephrine, norepinephrine, narcotics and steroids contribute to this complication but the exact cause is still not known. Administration of a large dose of calcium during separation from CPB, as shown in recent clinical studies, is an

Table 1. Hypercalcemic conditions associated with pancreatitis in the literature

Hyperparathyroidism
Multiple myeloma
Familial hypocalciuric hypercalcemia
Adult T-cell leukemia
Metastatic breast carcinoma
Metastatic islet carcinoma of the pancreas
Non-small cell bronchial carcinoma
Leiomyosarcoma
Vitamin D-poisoning
Sarcoidosis
Renal transplant
Metolazone - induced hypercalcemia
Thyrotoxicosis
Milk-alkali syndrom
Calcium infusion
Calcium gluconate in dialysis
Calcium chloride in cardiopulmonary bypass
Total parentral nutrition

Table 2. Incidence of pancreatitis in patients with Hyperparathyroidism (HPT)

Author	Pancreatitis (n)	HPT (n)	%
Fink 1961	19	56	34.0
Mixter 1962	11	155	7.0
Kyle 1962	5	40	12.0
Anglem 1966	8	69	11.5
Herskovic 1967	15	450	3.3
Kelly 1968	23	87	26.0
Schmidt 1970	24	370	6.5
Lejeune 1972	2	38	5.0
Rosin 1976	9	1000	0.9
Bess 1980	17	1153	1.5
Paloyan 1982	6	176	3.4
Wang 1984	4	28	14.0
Sitges-Serra 1988	7	86	8.0
Carnaille 1998	40	1435	3.2

equally significant risk factor. Large calcium doses are routinely administered because serum calcium may decrease during CPB, and postoperative cardiovascular function can benefit from its inotropic and vasopressor effects. Other studies, however, oppose to the use of calcium as not being beneficial and propose other available drugs to be used in a need for vasoconstriction to minimize the risk for pancreatitis. Hyperamylasaemia is common after cardiac surgery but a diagnosis of acute pancreatitis must only be made when a clinical syndrome or pathological evidence of the disease accompanies it.[22]

Adult T-cell leukemia is a human T-cell virus type I-associated leukemia, endemic in southern Japan and the Caribbean basin. Although there is a high frequency of hypercalcemia associated with adult T-cell leukemia, 40% in male patients and 16% in females, acute pancreatitis has rarely reported as complication.[10-12] The etiology of hypercalcemia in adult T-cell leukemia is not known. Parathyroid hormone and prostaglandin E are found to be within normal ranges. Humoral factors that activate the osteoclasts and are produced by adult T-cell leukemic cells have been reported recently as a possible agent for hypercalcemia. Moreover pancreatic infiltration of adult T-cell leukemia cells was found in 31.3% of autopsy subjects.

Sarcoidosis is a chronic granulomatous disorder of unknown cause that is characterized by activation of T-lymphocytes and macrophages. For many years, sarcoidosis was presumed to be an atypical manifestation of tuberculosis because of the similarity between the inflammatory responses of the two diseases. However, as culture techniques became more widely employed to diagnose tuberculosis and tuberculosis became less common, it became clear that sarcoidosis was not simply a variation of tuberculosis but a different disease. The definitive diagnosis of sarcoidosis requires tissue confirmation of granuloma, with no evidence of mycobacterial or fungal infection. Gastric and duodenal localization are the most frequent sites of gastrointestinal involvement in sarcoidosis. Sarcoidosis of the pancreas has rarely been described in reported series of necropsies, with a prevalence of 1% in postmortem examination.[23,24] The clinical features may vary from acute pancreatitis or pancreatic insufficiency, to even a pseudotumoral syndrome with granulomas in pancreas and peripancreatic lymph nodes. Prompt resolution of the sarcoidosis-induced pancreatitis may occur after treatment with steroids, which are contraindicated for the most usual forms of pancreatitis.

Familial hypocalciuric hypercalcemia is a hereditary disease compatible with autosomal dominant inheritance that usually is not associated with any symptoms. Pancreatitis is an unusual complication.[16,17] The disease differs from typical primary hyperparathyroidism in that the renal calcium excretion is reduced, parathyroid hormone is normal or slightly elevated and has a familial history. Differentiation is important in order to avoid unnecessary parathyroidectomy. The disease usually has a benign course. It has been reported that familial hypocalciuric hypercalcemia with recurred pancreatitis is associated with calcium-sensing receptor mutations, and thus this variant has the same genetic etiology as typical familial hypocalciuric hypercalcemia.

The milk-alkali syndrome was recognized first in association with antacid therapy for peptic ulcer disease in 1915. The classic triad of symptoms in the milk-alkali syndrome includes hypercalcemia, alkalosis, and renal insufficiency. There are two case reports with milk-alkali syndrome and associated pancreatitis in the literature.

B. HYPERLIPIDEMIC PANCREATITIS

Acute pancreatitis is one of the complications associated with severe primary and secondary hypertriglyceridemia. Compared with the main etiological factors like alcohol abuse and gallstones, hyperlipaemia is of minor incidence in the development of acute pancreatitis. Recognition of hyperlipaemia as etiologic factor of acute pancreatitis is extremely important, because it constitutes a type of treatable pancreatitis in which recurrences of the episodes of acute pancreatitis and presumably of further pancreatic damage can be prevented.[25] This etiology may be overlooked if the triglyceride level is not measured shortly after admission because fasting, discontinuation of medications and administration of insulin may lower its concentrations. Hyperlipaemia is thought to be the etiology in 1.3-3.8% of patients with acute pancreatitis and is a more common cause of pancreatitis than is hypercalcemia.[26] Nevertheless several authors have reported that acute pancreatitis and hyperlipaemia coincide in 4%-38% of patients. This wide range of hyperlipaemia in acute pancreatitis seems to result from the patient populations, because patients with alcoholic pancreatitis are more frequently hyperlipidemic than the patients with biliary pancreatitis.[27]

The mechanisms by which hyperlipaemia leads to acute pancreatitis are not known. One concept is that the damage of the acinar cells is caused by the effect of free fatty acids. These fatty acids are broken down products of triglycerides and were generated within the pancreas by the hydrolytic action from pancreatic lipase on triglycerides. This process may be potentiated by the pres-

ence of high concentration of lipoprotein phospholipids and pancreatic phospholipase with the appearance of cytotoxic lysolecithins. There are two other hypotheses that could explain the mechanism by which hyperlipemia causes parenchymal necrosis during acute pancreatitis. Trypsinogen could be activated by acidosis due to the presence of fatty acids, or the free fatty acids may disturb the microcirculation of the pancreas by damaging the vessel endothelium. In 1989, Nagai et al postulated that interstitial fission of triglycerides by the pancreatic lipase might lead to a detergent-like destruction of the cell membrane. Several investigators have demonstrated that the pancreas preferentially uses lipids as a metabolic substrate. This preference may account for the high level of lipoprotein lipase in the pancreas, which may predispose the pancreas during hyperlipidemia.

Triglyceride levels in excess of 1000 mg per deciliter increase the likelihood of pancreatitis. Hypertriglyceridemia of less than 500 mg/dL should not be incriminated as a factor in the etiology of pancreatitis. Marked elevation of of triglyceride levels appears to be causally linked to acute pancreatitis and is found in 4%-38% of patients presenting with acute pancreatitis.

The clinical course of hyperlipidemic pancreatitis may be as mild, moderate, or severe as any other case of pancreatitis but it is usually mild to moderate in severity. Sometimes pancreatic secretory insufficiency develops after multiple attacks over a period of years.

In patients suffering from familial hyperlipoproteinemia (types I, IV and V according to the classification of Frederickson), acute pancreatitis occurs with an incidence of up to 21%. In those cases, patients have increased serum concentrations of chylomicrons and triglycerides. The classic (type I) hyperlipidemic phenotype includes the onset of attacks of recurrent pancreatitis in childhood and may also include hepatosplenomegaly, hyperhylomicronemia, lipemia retinalis and eruptive xanthomas. These individuals often have no lipoprotein lipase activity and normal apoprotein C-II levels, or normal lipoprotein lipase activity and low or absent apo C-II levels, depending on the genotype. Fully functional apo C-II is necessary for optimal lipoprotein lipase activity. Inheritance is autosomal dominant and the disorder is rare. Type V hyperlipoproteinaemia is more common (elevation of both chylomicrons and VLDL containing high concentrations of triglycerides). Patients with type V are often diabetic, obese and hyperuricemic. Clearance of triglyceride carrying lipoproteins is reduced, lipoprotein lipase activity may be normal, and hepatic VLDL production may be higher. Patients may develop attacks of pancreatitis in adulthood, but they have triglyceride levels that are not severely elevated as type I patients.

Recently it has been identified a group of normotriglyceridemic patients with a previous attack of acute pancreatitis, at least 6 months earlier, who had an impaired clearance of serum triglycerides after an oral fat tolerance test.[28] The clearance of ingested triglycerides was significantly impaired as compared to a control group, irrespective of the presence of diabetes, alcohol consumption or biliary lithiasis. It is suggested that a triglyceride tolerance test is the only way to detect the patients in whom future attacks of pancreatitis may be precipitated by a diet rich in fat or alcoholic debauch. In another study the authors suggested that the abnormal oral fat tolerance test in patients with previous acute pancreatitis and normotriglyceridemia is secondary to an impaired chylomicron remnants clearance. These findings strongly suggest a relatively common and preexisting defect in lipid metabolism, which may be important in the pathogenesis of the disease. This abnormality may represent a preexistent genetic condition expressed in either the apoprotein composition of chylomicrons or in the hepatic apolipoprotein E-receptor activity. The presence of this metabolic abnormality might explain the fact that only a minor proportion of patients with gallstone or alcohol ingestion does develop acute pancreatitis.

Three syndromes characterize the clinical spectrum of pancreatitis secondary to hyperlipidemia. The most common presentation is that of a patient with poorly controlled diabetes, a history of hypertriglyceridemia and obesity. The second presentation is that of an alcoholic who is found to have hypertriglyceridemia or lactescent serum on admission. The third clinical presentation is that of a non-diabetic, non-alcoholic, non-obese patient with drug or diet-induced hypertriglyceridemia causing pancreatitis.

Severe hypertriglyceridemia causing pancreatitis is a rare but serious complication of pregnancy carrying a high risk of death for both mother and fetus, usually occurring in the second and third trimesters.[29] Although gallstones are the most common cause for pancreatitis in pregnancy, the possibility of existing hypertriglyceridemia, which is readily treatable, must not be overlooked. During pregnancy, the plasma cholesterol rises on average about 50% with the major increase occurring during the second trimester. Triglycerides rise threefold, reaching a peak during the third trimester. Several factors contribute to hyperlipoproteinemia during pregnancy. They include enhanced adipose tissue lipolysis, facilitating the

availability to the liver of substrates for the synthesis of triglycerides and thus including a high flux of VLDLs into the circulation, and a reduction in lipoprotein lipase activity, causing inadequate triglyceride removal. Plasma exchange can rapidly and safely resolve extreme hyperlipemia and be associated with prompt resolution of pancreatitis in women with severe gestational hyperlipidemic pancreatitis.

Iatrogenic hypertriglyceridemia can be caused by several drugs including synthetic oestrogens, especially the oestrogen-progesterone contraceptives, and to a lesser extent natural oestrogens taken orally as a replacement treatment during menopause, certain hypotensive drugs (non-cardioselective b-blockers and thiazidic diuretics), corticosteroids, retinoids, cyclosporine, enzyme inductors, iodine produces and tamoxifen.[30] All these drugs should be kept in mind when high lipid levels are observed.

Tamoxifen, a non-steroid estrogen antagonist, has been widely used in a hormonal treatment for breast cancer. The side effects of tamoxifen are generally recognized to be mild but severe hyperlipaemia associated with pancreatitis has been reported. It is shown that the activity of lipoprotein lipase and hepatic triglyceride lipase, the key enzymes of triglyceride metabolism decreased significantly as a result of tamoxifen treatment.

Isotretinoin is a retinoid derivative, in wide use as a treatment for severe acne and other dermatological conditions. Its effects on serum lipids, most notably the induction of hypertriglyceridemia, have been well documented. The lipid changes seen reverse promptly with cessation of therapy.

In many women, use of oral contraceptives is associated with modest elevation of serum triglyceride levels. In some women marked elevation and pancreatitis occur. It is the estrogen component of the contraceptives, which induces hypertriglyceridemia. Oral contraceptives users have depressed postheparin lipolytic activity and increased insulin levels. In those with underlying primary triglyceride disorder, the addition of estrogens can lead to acute pancreatitis. Estrogen-induced pancreatitis is now much less common, perhaps because the newer oral contraceptive agents have smaller doses of estrogen.

C. PANCREATITIS IN RHEUMATIC DISEASES

All forms of pancreatitis from acute, hemorrhagic to chronic, calcifying or idiopathic have been reported in patients with rheumatic diseases and at all ages.[31,32] Most of these reports associate pancreatitis with Sjogren's syndrome or systemic lupus erythematosus. Still the pathogenesis remains obscure but the autoimmune phenomena that are present, the co-existing vasculitis and drug toxicity contribute to the complex of the pancreatic inflammation etiology in rheumatic diseases.

Autoimmune epithelitis[33] (or autoimmune exocrinopathy[34] or dry gland syndrome[35]) a disease complex that refers to Sjogren's syndrome, primary sclerosing cholangitis, renal tubular acidosis and primary biliary cirrhosis seems to be the main etiologic factor for idiopathic chronic pancreatitis that frequently complicates these diseases.[36] Although the exact mechanisms remain poorly understood, it has been reported that patients with Sjogren's syndrome, systemic lupus erythematosus and idiopathic chronic pancreatitis have serum antibodies that react with duct cells in salivary glands and in pancreas.[37]

Systemic vasculitis with involvement of the pancreatic vessels, stands as the main cause for acute pancreatitis in polyartiritis nodosa,[38] Wegener's granulomatosis,[39] Henoch-Shonlein purpura,[40,41] Churg-Strauss syndrome,[38] Kawasaki's disease,[42] Adamantiades-Behcet's disease[43] and others.

Drug toxicity, can be an additional etiology agent for acute pancreatitis. The long-term use of corticosteroids and immunosuppresives has been well associated with pancreatitis.[44-47] Indomethacin, ketoprofen, mefenamic acid and piroxicam have been reported to be associated with pancreatitis.[48] Sulindac is definitely associated with pancreatitis, in a number of case reports.[49]

Systemic Lupus Erythematosus

Acute or chronic pancreatitis is an unusual complication of systemic lupus erythematosus (SLE) occurring in 4 to 8% of the patients,[50-52] however it can be the initial presentation of the disease and may appear even in childhood.[44,53]

First reported in 1953 by Dubois,[54] it presents with severe epigastric pain, nausea, vomiting, dehydration and an elevated serum amylase level. Although corticosteroid treatment may blur the clinical diagnosis in these patients and may aggravate the pancreatic dysfunction, its administration does not appear to be the major cause of the condition.[55,56] Multiple mechanisms have been shown to be present.[57] Reynolds et al[58] combined a literature survey with a review of 20 patients. Eight of them had recurrent attacks of pancreatitis with a mean duration of 15.5 days for each episode. The amylase levels

did not correlate with renal dysfunction that characterizes SLE activity, or steroid doses. The chief clue to the cause (i.e., SLE vs. drug-induced) was that most of the patients with SLE-induced pancreatitis had multisystem involvement, with an average of 6.2 organs involved, and also responded well to increased steroid administration. Other researchers also support this view.[53,59] Controversial reports, however, shown that corticosteroids, azathioprine and thiazide diuretics used in the treatment of SLE may induce attacks of pancreatitis that are independent of the disease.[46,47] The role of cyclosporine A in pancreatic dysfunction is not well documented in the literature.[48,90]

Several cases of panniculitis and subcutaneous fat necrosis have been reported as being associated with SLE and pancreatitis.[60] Type I hyperlipidemia with increased levels of chylomicrons and thrombi in pancreatic vessels causing pancreatitis, is due to antiphospholipid antibodies (lupus anticoagulant, aCL) that often are circulating in the sera of SLE patients.[61,62]

Cases of pancreatic vasculitis have been documented since 1939, although systemic vasculitis complicated SLE with acute pancreatitis is quite rare. In 25 lupus necropsies, 8 cases of pancreatitis were found, 50% had pancreatic vasculitis and the rest 50% were though to have steroid-induced disease as reported.[63] Twenty-seven necropsy reports on SLE patients with pancreatic involvement have been reviewed later in 1991.[64]

Mild elevations of serum amylase levels may be noted in patients with SLE in the absence of pancreatitis. Hasselbacher et al65 found a statistically significant difference in the mean amylase level, between SLE patients without pancreatitis and non-SLE controls. Macroamylasemia was only present in the SLE group (24%) and resulted from decreased renal clearance of an immunoglobulin-amylase complex. The presence of an autoantibody to amylase was proposed.[65] Active SLE has been associated with elevated amylase levels, and also with the pancreatic component, in patients without abdominal pain, as an indication of subclinical pancreatic dysfunction.[66,67] Pancreatic vessel involvement as it has been proved in post mortal autopsies together with corticosteroid and immunosuppressive treatment are the main etiological factors for acute pancreatitis in SLE.

Treatment in SLE pancreatic involvement includes immediate discontinuation of non-essential drugs that can induce pancreatitis, azathioprine and diuretics. The decision on whether to use corticosteroids is difficult if the patient has evidence of active SLE and is on high-dose steroid therapy already. Careful observation is essential.

Sjogren's syndrome

Deranged pancreatic secretion is reported as a frequent feature in patients with Sjogren's syndrome (SjS) by several workers, however acute pancreatitis is rather infrequent.[68,69] Gobelet et al[69] investigated the exocrine pancreatic function using the NBT PABA (N-benzoyl-L-tyrosyl-p-amino-benzoic acid) test and RIA trypsinemia and found pathological levels in one third of SjS patients. No one had any clinical manifestations of pancreatic disease, but the findings suggest the presence of subclinical pancreatic insufficiency. Antibodies to pancreatic duct epithelial cells found in the sera of 33.3% of SjS patients. In addition to the pathologic findings in pancreas (mononuclear infiltration) this points to an autoimmune mechanism for the pancreatic involvement.[70]

It has been well documented that chronic pancreatitis is occasionally observed as a complication in patients with SjS, primary sclerosing cholangitis (PSC) and primary biliary cirrhosis.[71,72] Based on clinical findings, the concept of a disease complex, autoimmune epithelitis[33] or autoimmune exocrinopathy[34] or dry gland syndrome,[35] has been found to describe patients with the above mentioned diseases. It is hypothesized that they may be manifestations in district organs of an autoimmune reaction against an antigen that is expressed by the ductal epithelial cells (salivary, esophageal and pancreatic glands, biliary duct, distal renal tubule) of these organs, causing altered immunologic response and resulting in chronic inflammation and eventual fibrosis of these tissues.[73,74] The molecular nature of this antigen has not been yet determined. Recently as reported by several investigators, patients with SjS, SLE and PSC have serum autoantibodies to human carbonic anhydrase II (CAII).[75-77] The same autoantibody was found in sera, in a significant percentage (33.3%), of patients with idiopathic chronic pancreatitis (ICP) whereas a great percentage (46.2%) of these patients were positive for antinuclear antibody (ANA).[78,79] These facts imply an association between ICP and autoimmune conditions and may explain the chronic pancreatic involvement with eventual fibrosis of the glands in these autoimmune diseases. This autoimmune pancreatitis appears to be characterized by a diffusely swollen pancreas on imaging studies, thumb-printing in the duct by infiltration of mononuclear cells and responds well to steroid treatment.

Moreover, serum hyperamylasemia was reported in

24% of primary SjS patient, by Tsianos et al66, corresponding to P-type and S-type isoamylases. None of the patients had suffered any symptoms of pancreatitis or gallbladder disease or had received prednisolone at least 2 months prior to study. None was known to abuse alcohol. This hyperamylasemia may probably reflect a slow subclinical inflammatory process of exocrine pancreas. As the salivary glands often rise the titers of serum total amylase, pancreatic isoamylase is often necessary to be measured.

In a recent case report, multiple pancreatic masses were detected in a 59-year-old woman with positive ANA and high titer of serum gama-globulin. She developed SjS in the course of one year and the pancreatic masses spread diffusely and compressed the main pancreatic duct. Biopsies showed duct and acinar infiltration by CD4+ T-lymphocytes and HLA-DR antigens expression in the sites. This was suggestive of autoimmune-related pancreatitis. Oral prednisolone was administrated and a marked improvement of the abdominal findings followed.[80]

Primary Systemic Vasculitis Syndromes

Vasculitis syndromes are characterized by inflammation, with or without deposition of fibrinoid, proliferation, narrowing, fibrosis, and eventual necrosis of blood vessels. These progressive damages result in occlusions and ischemia of tissues supplied by the involved vessels. Vessels can be affected from focal lesions to larger segments with associated aneurysms or rarely thrombosis. Classification of vasculitis is difficult and many attempts based on pathogenesis, size of the vessels involved and treatment are made, but no single classification system is adequate. These syndromes are usually multi-systematic and most of them are autoimmune-mediated, (immune complex and granuloma formation, anti-endothelial cell antibodies, anti-lysosomal enzyme antibodies) although vascular damage also can occur secondary to tumor cell or infectious agent-mediated injury. Acute pancreatitis is seldom reported, although pancreatic vasculitis has been demonstrated in a great number of autopsies in patients with rheumatic diseases.

Patients with polyarteritis nodosa (PAN), microscopic polyangiitis and Churg-Strauss syndrome may present in 32-62% of the cases with abdominal pain as a manifestation of gastrointestinal vasculitis.[38,81,82] Vasculitis mainly affect the small bowel but pancreatitis and malabsorption with a high probability of death have been described.[82,83] Pancreatic pseudocyst formation is also reported as a complication of necrotizing PAN.[84]

Abdominal pain, diarrhea and bleeding are frequent in Wegener's granulomatosis[85] whereas also recurrent acute pancreatitis with formation of granuloma[39] in pancreas and pancreatic mass with extrahepatic obstruction have been reported.[86]

The IgA complex deposition in vessels is the initial event that results in allergic necrotising or leukocytoclastic vasculitis that characterized the Henoch-Shonlein purpura, with gastrointestinal involvement up to 60% of cases. Pancreatitis is although rare; four cases have been reported to date.[40,41,87]

Adult Kawasaki's disease complicated with pancreatitis has been reported.[42] Acute pancreatitis in Adamantiades-Behcet's disease is extremely rare, although the gastrointestinal manifestations of the disease are common.[43] In autopsy reports Behcet's vasculitis of the pancreas involving veins, veinules and capillaries with perivascular infiltration of inflammatory cells is present.[88]

In patients with systemic vasculitis, already receiving corticosteroids, the lack of physical signs on abdominal examination may provide the physician with a false sense of non- existing pancreatic involvement but autopsies often come to prove him wrong. The indicating treatment for vasculitis, like high dose corticosteroids, cyclophosphamide or azathioprine, although it can induce drug-mediated pancreatitis, in these cases however seems the only therapy that alters the course of the disease and settles the pancreatic involvement.

Rheumatoid Arthritis, Rheumatoid Vasculitis and Other Rheumatic Diseases

Pancreatic involvement in rheumatoid arthritis (RA) may occur as a manifestation of treatment complications (gold salts,[45,89] cyclosporine A,[90] azathioprine,[46,47,91] corticosteroids[55]) or of the co-existence of secondary Sjogren's syndrome[32,69,92] or also of the concurrent vascular inflammation in internal organs called systemic rheumatoid vasculitis (SRV).[93,94] Significant abdominal pain, often presenting as acute abdominal, occurred in nearly 50% of patients with overlap between SRV and PAN complicating RA, in contrast with only 10% in SRV patients.[93] Autopsy revealed SRV in pancreas and other organs in a case malignant RA which was difficult to distinguish from PAN.[94]

Reversible pancreatitis associated with either intramuscular or oral gold therapy in RA patients has been reported in three cases. Gold-induced toxicity is likely due to a hypersensitivity reaction mediated by gold's interaction with membranes.[45,89]

The exocrine response of the pancreas to standard stimulation is depressed in one third of the patients with progressive systemic scleroderma (PSS).[95] Idiopathic calcific pancreatitis has been also reported in these patients.[96] In addition arteritis leading to pancreatic necrosis has been described in PSS.[97] One case of acute pancreatitis has been reported in mixed connective tissue disease.[98]

Rheumatic Diseases in Childhood Complicated with Pancreatitis

Acute pancreatitis in children may be associated with significant morbidity and mortality (59%) and the diagnosis is often delayed. Presenting signs and symptoms, like abdominal pain and vomiting, are often non-localizing and in up to 35% of cases is caused by multi-system diseases like Henoch-Schonlein purpura[87] and Kawasaki disease. Medium-sized artery vasculitis of the pancreas has been noted in autopsy studies of children died of Kawasaki disease without clinically apparent pancreatitis.[42,99,100]

In childhood, SLE-pancreatitis is related to either primary disease or therapy and rarely is fatal.[101] A 16-year-old who died of acute hemorrhagic pancreatitis, possibly caused by combination therapy with methotrexate, steroids and azathioprine, has been described.[44]

Additionally, acute or chronic pancreatitis or trauma leading to pseudocyst formation, in children may result in disseminated fat necrosis with accompanying subcutaneous nodules, fever and systemic illness. A juvenile rheumatoid arthritis-like polyarthritis may result, usually 2 to 4 weeks following the initial illness. The disease is often self-limited but corticosteroids, supportive measures and intravenous administration of octreotide may be helpful. Rarely surgery may be necessary.[101,102]

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