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Acute recurrent pancreatitis: An autoimmune disease?

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Abstract

In this review article, we will briefly describe the main characteristics of autoimmune pancreatitis and then we will concentrate on our aim, namely, evaluating the clinical characteristics of patients having recurrence of pain from the disease. In fact, the open question is to evaluate the possible presence of autoimmune pancreatitis in patients with an undefined etiology of acute pancreatitis and for this reason we carried out a search in the literature in order to explore this issue. In cases of recurrent attacks of pain in patients with "idiopathic" pancreatitis, we need to keep in mind the possibility that our patients may have autoimmune pancreatitis. Even though the frequency of this disease seems to be quite low, we believe that in the future, by increasing our knowledge on the subject, we will be able to diagnose an ever-increasing number of patients having acute recurrence of pain from autoimmune pancreatitis.

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Key words: Pancreatitis; Autoimmune pancreatitis; Diagnosis; Therapy; Outcome

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INTRODUCTION

In 1961, Sarles *et al*^[1] reported the case of a non drinker patient suffering from pancreatitis associated with hypergammaglobulinemia. The authors hypothesized that the disease in this patient was an autonomous pancreatic disease of autoimmune origin. After this report, other authors around the world reported similar cases and they named the disease in several manners: chronic

pancreatitis with diffuse narrowing of the pancreatic duct, primary inflammatory pancreatitis, non-alcoholic duct destructive chronic pancreatitis, lymphoplasmacytic sclerosing pancreatitis, granulomatous pancreatitis, idiopathic tumefactive chronic pancreatitis, and sclerosing pancreatocholangitis^[2,3]. In 1995, Yoshida^[4] suggested the term "autoimmune pancreatitis" for this disease and, therefore, this term has become largely accepted for pancreatic disease of an autoimmune origin. In the last 10 years, there have been an increasing number of cases reported in Japan and Europe^[5]. In this review article, we will briefly describe the main characteristics of autoimmune pancreatitis and then we will concentrate on our aim, namely, evaluating the clinical characteristics of patients having recurrence of pain from the disease.

Incidence

At present, the exact incidence of the disease is not known. The only available data are those reported in Japan and in Italy. In these two countries, the estimated incidence of autoimmune pancreatitis is quite similar, 4.6% and 6.0% in Japan and in Italy, respectively^[5] and we are awaiting data from the United States as well as from other countries in order to define the real incidence of the disease around the world. Autoimmune pancreatitis seems to have a preference for the male gender; in fact, about 80% of the cases described are males^[5]. However, a geographic variation may be observed because, in Italy, the male: female ratio is 1:1. At diagnosis, the patients were more than 55 years of age^[5]. Diabetes mellitus is present in about half of the patients^[5].

Pathogenesis

From a pathological point of view, the disease is characterized by diffuse or focal pancreatic swelling with a narrowing of the pancreatic duct and/or common bile duct and the histological hallmark of this type of pancreatitis is lymphoplasmacytic infiltration, especially concentrated on the pancreatic ducts^[6-8]. Some authors have defined autoimmune pancreatitis^[9] as the simultaneous involvement of the pancreas, the salivary glands and the liver (primary biliary cirrhosis) by means of an immune-mediated inflammatory process. Thus, the still open question is the differentiation of autoimmune pancreatitis as a primary or a secondary disease based on the absence or presence of other autoimmune diseases.

Clinical aspects

From a clinical point of view, patients with autoimmune

pancreatitis rarely complain about the typical severe abdominal pain of pancreatitis and are usually hospitalized for painless jaundice^[10]; other symptoms of autoimmune pancreatitis include non-specific mild abdominal pain and weight loss. The diagnosis is sometimes quite intriguing because the disease may be mistaken for pancreatic cancer^[11].

Laboratory data

Laboratory analysis is undergoing continuous evolution. Serum amylase and lipase may often be normal or a mild elevation of the serum pancreatic enzymes may be observed, and in only a few cases is there a marked elevation of these pancreatic damage markers^[12]. Hypergammaglobulinemia and IgG serum increase have been reported in percentages ranging from 37% to 76%^[13,14]. Japanese authors have claimed that elevated serum levels of IgG4, a subtype of IgG, are a biochemical hallmark of autoimmune pancreatitis^[15]; however, other authors have recently questioned the specificity of the IgG4 because elevated IgG4 levels are present in patients suffering from pancreatic carcinoma and other types of chronic pancreatitis^[5].

Non-specific autoantibodies, such as antinuclear antibodies, antimicrosomal antibodies and so on have a low sensitivity in diagnosing autoimmune pancreatitis; the detection rate of specific antibodies such as antilactoferrin antibodies and anticarbonic anhydrase II antibodies have not been widely assessed in clinical setting because they require a special laboratory for their measurement which is available to only a low number of clinicians. A number of groups have tried to find other laboratory indicators of autoimmune pancreatitis and evaluation of the alleles of major histocompatibility complex genes seems to be a promising tool for identifying patients susceptible to autoimmune pancreatitis. One report mentioned that DRB1*0405 and DQB1*0401 are significantly more frequent in patients with autoimmune pancreatitis when compared to chronic calcifying pancreatitis^[16]. At the present time, however, further studies are required to evaluate the value of each laboratory indicator and to find a more reliable one.

Imaging evaluation

Imaging evaluation is essential in the diagnosis of autoimmune pancreatitis^[17]. Ultrasound is often the first imaging technique to be utilized in a patient with obstructive jaundice or with upper abdominal pain and a hypoechoic diffuse swelling in the pancreas (sausage-like appearance), or a focal swelling of the pancreas simulating a neoplastic lesion can be observed as well as a dilation of the extrapancreatic bile duct, secondary to an involvement of its intrapancreatic portion. Contrast-enhanced ultrasonography can successfully visualize fine vessels in pancreatic lesions and may play a pivotal role in the depiction and differential diagnosis of pancreatic tumors. In particular, some Authors have analyzed the enhancement of focal pancreatic lesions and it has been shown that, while most of the inflammatory pancreatic masses show a pattern of enhancement similar to

the normal pancreatic gland ("isovascular"), a focal pancreatic tumor is hypovascular to the surrounding normal parenchyma. At both computed tomography and magnetic resonance imaging, a focal or diffuse swelling of the pancreatic gland can be observed. Dynamic imaging at computed tomography or magnetic resonance imaging shows a delayed enhancement of the segments of the gland, which are involved. In some cases, minimal peripancreatic stranding suggesting inflammation can be seen. Moreover, a capsule-like smooth rim can be observed which is hypodense on computed tomography and hypointense on T2 weighted images, showing delayed enhancement on dynamic imaging. This is thought to correspond to an inflammatory process involving peripancreatic tissues and appears to be a characteristic finding of autoimmune pancreatitis. Pancreatic calcifications are rarely seen in autoimmune pancreatitis. Involvement of the main pancreatic duct and the biliary duct is well-described in the literature. Endoscopic retrograde cholangiopancreatographic criteria for the diagnosis of autoimmune pancreatitis include diffuse irregular narrowing of the main pancreatic duct and abnormalities which normalized after steroid therapy. The same alterations can be observed at MR cholangiopancreatography. The invasion of vessels, vascular encasement, mass effect and fluid collections are absent in autoimmune pancreatitis.

Diagnostic criteria

The diagnostic criteria currently used for autoimmune pancreatitis are those proposed by the Japan Pancreas Society^[18] and are reported in Table 1; interestingly, the criteria do not include symptoms or common laboratory findings as they are not specific to autoimmune pancreatitis^[12,19]. Italian criteria include some differences with respect to the Japanese diagnostic criteria (Table 2)^[5] such as the association with other autoimmune diseases and the response of the disease to steroid treatment. Korean researchers utilize a third classification which takes into account the Japanese and the Italian diagnostic criteria (Table 3)^[20]. Furthermore, a fourth classification system has been proposed from the same Korean researchers (Table 4)^[20]. It seems that there is a need for a classification system for such a rare disease; therefore, an international consensus statement releasing widely accepted guidelines for autoimmune pancreatitis would be welcome.

Open questions

The open question is to evaluate the possible presence of autoimmune pancreatitis in patients with an undefined etiology; in fact, a recent study has reported that clinical or biochemical autoimmune stigmata are present in 40% of patients with idiopathic chronic pancreatitis and, therefore, autoimmune mechanisms may be frequent in idiopathic pancreatitis^[21]. We also need to know the possible cause of failure of steroid therapy in some patients; finally, we need to evaluate the reason why some patients experience more attacks of pain in a disease characterized by a painless course. We carried out a search in the literature in order to explore this latter issue.

Table 1 Diagnostic criteria for autoimmune pancreatitis released by the Japan Pancreas Society

Criteria	Definition
I Imaging criterion	Diffuse narrowing of the main pancreatic duct with an irregular wall (more than 1/3 length of the entire pancreas) and enlargement of the pancreas
II Laboratory criterion	Abnormally elevated levels of serum gammaglobulin and/or IgG, or the presence of autoantibodies
III Histopathologic criterion	Marked lymphoplasmacytic infiltration and dense fibrosis

For diagnosis, criterion I must be present, together with criterion II and/or III.

Table 2 Italian diagnostic criteria for autoimmune pancreatitis

Criteria	Definition
Criterion I	Histology and cytology
Criterion II	Association with other postulated autoimmune disease
Criterion III	Response to steroid therapy

One or more criteria must be present in order to diagnose autoimmune pancreatitis.

DEFINITION OF RECURRENT PANCREATITIS

For the aim of this study, we defined acute recurrent pancreatitis as the presence of an attack of pancreatic pain in patients with proven autoimmune pancreatitis.

SEARCH LITERATURE PROCEDURE

On August 1st 2006, we performed a search using three different data bases (MEDLINE, Web of Science and Scopus) in order to find the data existing in the literature on the presence of recurrent pancreatitis in patients with autoimmune pancreatitis. The terms “recurrent pancreatitis” and “autoimmune pancreatitis” were searched as topics for MEDLINE, as Topic terms (TS) for Web of Science (WoS) and as article titles, abstracts and keywords containing the two terms for Scopus. One-hundred and twenty-six papers on MEDLINE, 15 on WoS, and 14 on Scopus were found. Only papers regarding studies carried out on humans, in English and in full text were considered. Fourteen duplicate papers were found among the various databases; 10 of these were present simultaneously in MEDLINE, WoS and Scopus, three were present in both Scopus and WoS while the remaining one was present in both MEDLINE and Scopus. One-hundred and thirty-one papers were found. Of these, 24 papers were excluded because they were review articles^[4,12,22-43] and one was an editorial letter to the editor not reporting original data^[3]. The remaining 106 original papers were considered for the purpose of this study. Of these 106 original papers, 18 were excluded because they reported data not useful for the aim of this study^[44-61]. Therefore, 88 studies satisfied the aim of our

Table 3 Korean diagnostic criteria for autoimmune pancreatitis released by the Asian Medical Center

Criteria	Definition
Criterion I	Pancreatic imaging (essential): (1) CT: Diffuse enlargement (swelling) of pancreas and (2) ERCP: Diffuse or segmental irregular narrowing of main pancreatic duct
Criterion II	Laboratory findings: (1) elevated levels of IgG and/or IgG4 or (2) detected autoantibodies
Criterion III	Histopathologic findings: Fibrosis and lymphoplasmacytic infiltration
Criterion IV	Response to steroids

Definite diagnosis: Criterion I and any of criteria II-IV.

Table 4 A proposal of revised Korean diagnostic criteria for autoimmune pancreatitis

Criteria	Definition
Criterion I	Pancreatic imaging (essential): (1) CT: Diffuse enlargement (swelling) of pancreas and (2) ERCP: Diffuse or segmental irregular narrowing of main pancreatic duct
Criterion II	Laboratory findings: (1) elevated levels of IgG and/or IgG4 or (2) detected autoantibodies
Criterion III	Histopathologic findings Fibrosis and lymphoplasmocytic infiltration
Criterion IV	Association with other postulated autoimmune disease

Definite diagnosis: I + II + III + IV or I + II + III or I + II or I + III; Probable diagnosis: I + IV (Rediagnosed as “definite” if “response to steroids” is present); Possible diagnosis: I (Rediagnosed as “definite” if “response to steroids” is present).

study; however, 79 of these papers do not report data on the recurrence of acute pancreatitis in the follow-up of patients with autoimmune pancreatitis^[6,14,62-138]. Therefore, 9 papers were evaluated for the purpose of this study^[13,139-146].

RESULTS

A total of 15 patients with recurrent episodes of acute pancreatitis during the course of autoimmune pancreatitis are reported with a clinical follow-up ranging from 5 to 276 mo and their data are shown in Tables 5 and 6.

Taking into consideration only the studies of Hardacre^[142], Weber^[145] and Zamboni^[146] which reported a high number of patients, the frequency of autoimmune pancreatitis patients with recurrent abdominal pain was 2.7% (1/37), 3.2% (1/31) and 4.5% (1/22) in the three above-mentioned studies with a mean frequency of 3.3%.

Considering all the cases reported with recurrence of pain, most of the patients were under 50 years of age and the ratio male: female was near to one. The major part of the patients (5/8, 62.5%) had more than one recurrence; some experienced more than 4 recurrences of pain in the follow-up period and most of them were operated on. In the study of Wayne *et al*^[144], two of the five patients with recurrent pancreatitis underwent pancreatic surgery 2 and

Table 5 Clinical and morphological data of autoimmune pancreatitis patients with recurrent pancreatitis

Study	Type of study	Patients studied	Associated disease	Median FU (mo)	FU range (mo)	Criteria adopted	Imaging alterations	IgG elevation	IgG4 elevation	Antibodies present
Borum ^[140]	CR	2	SLE		132-253	Histology	Yes	NR	NR	Yes
Wakabayashi ^[13]	R	7	5 U		28-75	JPS	Yes	5/7	NR	1/8
Hardacre ^[142]	R	37	1 SS, 2 UC	33	NR	Histology	NR	NR	NR	NR
Weber ^[145]	P	31	1 BP + LD + F, 1 IN, 1 Pa, 1 RA, 1 SS+GD+AI, 1 UC+GS+G	38	0-72	Histology	Yes	NR	NR	NR
Fernandez-del Castillo ^[141]	CR	1	None	5		Histology	Yes	NR	NR	NR
Zamboni ^[146]	R	53	2 SS, 1 SS + T, 1 SS + RF, 2 CD, 1 CD + RA, 3 UC, 4 U	36 ¹	6-276 ¹	Histology	NR	NR	NR	NR
Tanvetyanon ^[143]	CR	1	MS	14		JPS	Yes	NR	No	No
Wayne ^[144]	R	6	None	60	48-240	Histology	3/6	NR	NR	1/7
Abisi ^[139]	CR	1	IN, SS, LA	NR	NR	Histology	Yes	Yes	NR	Yes

FU: Follow-up; CR: Case report; R: Retrospective; P: Prospective; JPS: Japanese Pancreatic Society criteria for autoimmune pancreatitis; NR: Not reported; SLE: Systemic lupus erythematosus; SS: Sjogren syndrome; UC: Ulcerative colitis; BP: Bell's palsy; LD: Lyme disease; F: Fibromyalgia; IN: Interstitial nephritis; Pa: Parotiditis; RA: Rheumatoid arthritis; GA: Grave's disease; AI: Adrenal insufficiency; GS: Granulomatous sialadenitis; G: Goiter; T: Thyroiditis; RF: retroperitoneal fibrosis; CD: Crohn's disease; LA: Lupus anticoagulant; MS: Myelodysplastic syndrome; U: Unspecified. ¹The follow-up period has been reported for only 22 patients.

Table 6 Clinical characteristic, medical/surgical treatment and complications of autoimmune pancreatitis patients with recurrent pancreatitis

Study	No. patients with acute recurrent pancreatitis	Age at diagnosis (yr)	Sex	Localization	No. of recurrences	Surgery	No. of operation	Type of surgery	Steroid therapy	Improvement with steroids	Pancreatic complication
Borum ^[140]	1	34	Female	Tail	2	Yes	1	DP	Yes	No	Calcifications Pseudocyst
Wakabayashi ^[13]	3	NR	NR	NR	1	No			NR		NR
Hardacre ^[142]	1	NR	NR	NR	NR	Yes	1	NR	No		NR
Weber ^[145]	1	NR	NR	NR	1	No			No		NR
Fernandez-del Castillo ^[141]	1	36	Male	Head	> 2	Yes	1	PD	NR		NR
Zamboni ^[146]	1	49	Male	Head	1	Yes	1	PD	No		No
Tanvetyanon ^[143]	1	44	Male	Diffuse	> 10	No			Yes	Yes	Pseudocysts
Wayne ^[144]	5	30 (25-39) ¹	5 females	3 tail, 2 diffuse	2-> 10	Yes	1 (1-3)*	4 DP, 2 PD, 1 PP, 1 TP	1/5	No	1 pseudocyst, 1 calcifications
Abisi ^[139]	1	78	Male	Diffuse	4	Yes	2	1 DP, 1 CJ+G	Yes	Yes	Calcifications Pseudocyst

DP: Distal pancreatectomy; PD: Pancreaticoduodenectomy; PP: Puestow procedure; TP: Total pancreatectomy; CJ: Choledochojunostomy; G: Gastroenterostomy; NR: Not reported. ¹median and (range).

3 times. Information about the presence of pancreatic complications was reported in nine patients; pseudocysts and pancreatic calcifications developed in more than 50% of the cases. It is worth noting that, in most of the patients studied, the diagnosis was only histologically proven and the Japanese criteria for diagnosis acute pancreatitis were carried out in only two studies^[13,143]. Therefore, imaging techniques in patients having autoimmune pancreatitis with a recurrent attack of pain seem to have a limited role in preoperatively diagnosing the disease; furthermore, the serological indices of autoimmunity were carried out in only a limited number of patients. Regarding medical therapy, steroids had no beneficial effects on 2 of the 4 patients on whom the treatment was carried out.

PRACTICAL CONSIDERATIONS

The frequency of recurrent pancreatitis in patients with autoimmune pancreatitis seems to be very low. In fact, if we considered that the frequency of autoimmune pancreatitis is of about 5%, in these patients, the frequency of recurrent attacks of pain is of about 3%. Furthermore, in these patients, steroids seem to be effective only in an half of them and the number of pancreatic operations is quite high in. We probably need to utilize more extensively the information given by imaging techniques and serological indices compatible with the disease in order to decrease a false diagnosis in autoimmune pancreatitis patients with recurrent attacks of pain. However, in this regard we need to remember that, in recent years, the accuracy of IgG4 in diagnosing the autoimmune forms

of pancreatitis seems to be lower than that reported in the past^[5]. Furthermore, we need a world consensus on the diagnostic work-up of autoimmune pancreatitis because the criteria utilized until now seem to be inadequate^[5,91]. We also need a well-executed international study in order to obtain more information regarding the recurrent pain in patients with autoimmune pancreatitis in order to increase our knowledge of the risk factors of recurrence, diagnosis, and therapy.

CONCLUSION

In cases of recurrent attacks of pain in patients with “idiopathic” chronic pancreatitis, we need to keep in mind the possibility that our patients may have autoimmune pancreatitis. Even though the frequency of this disease seems to be quite low, we believe that in the future, by increasing our knowledge on the subject, we will be able to diagnose an ever-increasing number of patients having acute recurrence of pain from autoimmune pancreatitis. The possibility of finding these diagnostic possibilities and treatment for this disease is still a challenge.

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