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Autoimmune pancreatitis not otherwise specified (NOS): Clinical features and outcomes of the forgotten type

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ABSTRACT

Background: Autoimmune pancreatitis (AIP) is a well-recognized fibroinflammatory disease of the pancreas. Despite the significant number of studies published on AIP type 1 and 2, no studies have been focused on AIP type not otherwise specified (NOS) and therefore very little is known about clinical features and long-term outcomes of these patients. The aim of this study was to investigate clinical and radiological features of AIP type NOS-patients.

Methods: Patients classified as AIP type NOS at clinical onset included in our database prospectively maintained since 1995 were evaluated. Epidemiological, clinical data were collected and analyzed.

Results: Forty-six patients were included in the study. The clinical onset was mainly characterized by weight loss, jaundice and acute pancreatitis. Eight patients (17.4%) were reclassified as AIP type 2 during follow-up because of the development of ulcerative colitis. Seven patients (15.2%) experienced relapse after steroid treatment but only one (2.2%) needed immunosuppressive drugs because of recurrent relapses.

Conclusions: AIP type NOS shares clinical features similar to AIP type 2 and a relevant proportion of patients was reclassified as AIP type 2 during follow-up because of the development of ulcerative colitis. The risk of relapse is low but not irrelevant.

Introduction

Autoimmune pancreatitis (AIP) is a fibroinflammatory disease of the pancreas characterized by a dramatic response to steroid therapy [1,2]. AIP is classified in type 1 and 2 on the basis of pancreatic specimens after surgery [3]. The presence of granulocytic epithelial lesions (GEL^+) or $IgG4^+$ plasma cells at immunochemistry are the main findings that allow the diagnosis of type 1 ($IgG4^+/GEL^-$) or type 2 ($IgG4^-/GEL^+$) AIP [3,4]. However, since these findings are difficult to evaluate in biopsies, the diagnosis of AIP subtype is difficult in clinical practice. Therefore, International Consensus Diagnostic Criteria (ICDC) was proposed [5]. Based on the ICDC, the diagnostic algorithm for AIP starts to confirm the diagnosis of AIP type 1 [5]. In the absence of conclusive criteria for the diagnosis of AIP type 1 (probable or definitive), the diagnosis of AIP type 2 following the specific algorithm needs to be investigated. Since the diagnosis of AIP type 2 is established only by a suggestive histology (definitive) or in the presence of concurrent inflammatory bowel disease (IBD) (probable), AIP type not otherwise specified (NOS) is diagnosed only in the absence of histological criteria and IBD.

Despite the significant number of studies published on AIP, very few papers have investigated not-type 1 AIP, probably because of the low prevalence of type 2 and type NOS, especially in Eastern countries [6,7]. However, AIP type 2 is recognized worldwide as an independent entity, which clearly differs from AIP type 1 in epidemiological, clinical and histological features [7–9]. On the other hand, AIP type NOS does not represent a real pathological entity but a category of patients suffering from AIP, not classifiable as type 1 or type 2. AIP type NOS represents 16% of AIP patients, as reported in a previous study [10], where clinical and epidemiological features at clinical onset of the disease have been described. However, no long-term data are currently available on this specific topic. The clinical management of patients suffering from AIP type NOS is still based on data obtained from patients with AIP type 1 and 2. Particularly, the acquisition of data on the evolution of the clinical features of the disease and on the risk of relapse during follow-up, are crucial in clinical practice and might improve the management of these patients.

The aim of the present study was to investigate clinical, epidemiological, and radiological features of AIP type NOS patients,

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Table 1
Main epidemiological, clinical and radiological features of patients who did not develop ulcerative colitis (Remain NOS) and patients who did develop ulcerative colitis (Switch type 2) during follow-up.

Variables	Total ($n=46$)	Remain NOS ($n=38$)	Switch type 2 ($n=8$)	P value
Age (yr)	41 (31–61)	44 (30–61)	38 (35–48)	0.56
Male	27 (58.7%)	23 (60.5%)	4 (50.0%)	0.70
Focal disease	29 (63.0%)	23 (60.5%)	6 (75.0%)	0.69
Symptoms at onset	27 (58.7%)	20 (52.6%)	7 (87.5%)	0.12
Pancreatitis	14 (30.4%)	11 (28.9%)	3 (37.5%)	0.68
Jaundice	16 (34.8%)	15 (39.5%)	1 (12.5%)	0.23
Weight loss	19 (41.3%)	13 (34.2%)	6 (75.0%)	0.51
Hyperamylasemia	6 (13.0%)	4 (10.5%)	2 (25.0%)	0.28
Abdominal pain	9 (19.6%)	6 (15.8%)	3 (37.5%)	0.18
Steatorrhea	0	0	0	>0.99
Diabetes	1 (2.2%)	0	1 (12.5%)	0.17
Relapse	7 (15.2%)	5 (13.2%)	2 (25.0%)	0.59
sIgG4 (mg/dL)	52.5 (29–73)	55 (22–71)	38 (34–89)	0.72

sIgG4: Serum immunoglobulin G type 4 level. NS: Not significant. NOS: Not otherwise specified.

focusing mainly on the risk to reclassify the disease into AIP type 1 or 2, and on long-term outcome, particularly on disease relapse rate.

Methods

Study population

All patients present in our database prospectively maintained since 1995 to 31th of December 2016 that were classified as AIP type NOS at clinical onset were evaluated. Patients classified as AIP type 1 (definitive or probable), type 2 (definitive or probable) or probable AIP were excluded [5]. Clinical, radiological and pathological data were re-evaluated and analyzed.

Diagnosis and definitions

Acute pancreatitis (AP) was diagnosed in the presence of two of the three following criteria: abdominal pain, serum amylase and/or lipase > 3 times the upper limit of normal, imaging suggestive of AP. The diagnosis of IBD was based on histological specimens.

The involvement of extra pancreatic organs was evaluated according to the ICDC for biliary tree, kidneys, salivary glands and retroperitoneum [5]. The IgG4 level was considered at the clinical onset before starting the first steroid therapy and was classified into negative (<140 mg/dL), level 1 (>280 mg/dL), and level 2 (140–280 mg/dL) based on the ICDC [5]. Relapses were defined as development of pancreatic and/or extra pancreatic alterations at CT or MRI, according to literature [11]. IgG4 elevation alone was not considered disease relapse.

Endocrine insufficiency was defined according to American Diabetes Association (ADA) criteria [12]. Exocrine insufficiency was defined as fecal-elastase <100 ug/g and/or clinical detectable steatorrhea.

Follow-up

Follow up was based on imaging (MRI-MRCP or CT), physical examination and serum IgG4 level every 6–12 months. Median follow-up was 24 months (12–156 months). All patients with less than 12 month of follow-up were excluded.

Statistical analysis

SPSS (version 22, IBM, Armonk, NY) was used for the statistical analysis. Chi-square test and Fisher's test were used for categorical variables. Kruskal–Wallis test and Mann–Whitney *U*-test were used for continuous variables. Statistical significance was considered as P value < 0.05.

Results

Main epidemiological, clinical and radiological features of the studied groups

Baseline characteristics of the population are reported in Table 1. Forty-six patients, including 27 males (58.7%) and 19 females (41.3%), fulfilled the inclusion criteria with a median age at clinical onset of 41 (interquartile range IQR: 31–61) years. There was no difference in the age of onset between males and females (46 vs. 40; $P=0.62$).

Clinically relevant symptoms were present at clinical onset in 27 patients (58.7%). In detail, weight loss (41.3%), obstructive jaundice (34.8%) and acute pancreatitis presentation (30.4%) were the most frequent symptoms. Furthermore, hyperamylasemia (13.0%), abdominal pain (13.0%) and pancreatic endocrine insufficiency (2.2%) were reported. None had pancreatic exocrine insufficiency. Nineteen patients (41.3%) were asymptomatic and were investigated for pancreatic diseases after a first imaging (US, CT, MRI) performed for non-pancreatic reasons such as follow-up of other diseases or screening. Radiologically, the disease appeared to be diffuse in 17 patients (37.0%) and focal in 29 (63.0%).

Two patients (4.3%) underwent biliary derivative non-resective surgery before the diagnosis of AIP type NOS because of suspicion of cancer. These two patients had a focal involvement of the pancreatic gland and underwent intraoperatory biopsy; moreover, the other 27 patients with focal disease underwent EUS-guided biopsy. All biopsies did not fulfill the criteria of level 1 or 2 based on the ICDC.

Median follow-up was 24 months (range 12–156). None of the 46 patients suffering from AIP type NOS developed pancreatic cancer or died. Moreover, none developed exocrine and/or endocrine insufficiency during the follow-up.

Other organs involvement and ulcerative colitis

Other organs involvement (OOI) was reported in 5 patients (10.9%) at clinical onset. These 5 patients had exclusively common bile duct involvement. None of the patients included in the present study had proximal biliary involvement, renal involvement, salivary glands involvement or retro-peritoneal fibrosis. Therefore, none may be classified as level 1 or 2 OOI by ICDC. Moreover, none developed level 1 or 2 OOI during the follow-up.

Furthermore, none of the AIP type NOS patients had a diagnosis of ulcerative colitis (UC) at the clinical onset of AIP. However, UC was diagnosed in 8 (17.4%) out of 46 patients during follow-up. The development of UC switches the diagnosis from AIP type NOS to AIP type 2, according to ICDC. The median follow-up before

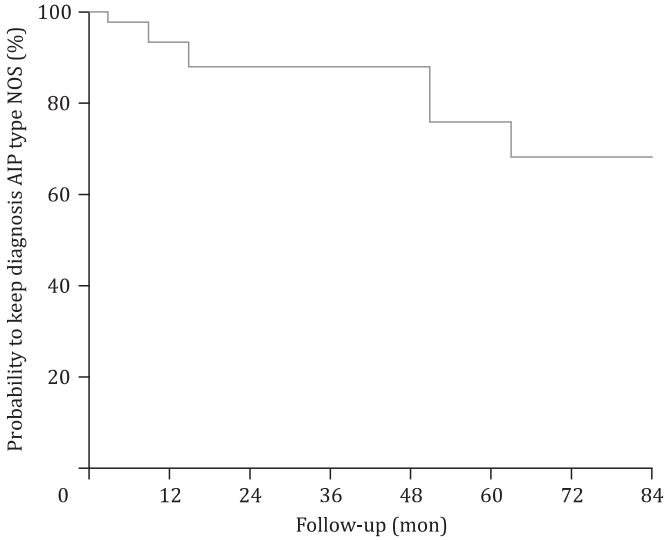

Fig. 1. Probability to keep diagnosis of AIP type not otherwise specified (NOS) during the follow-up.

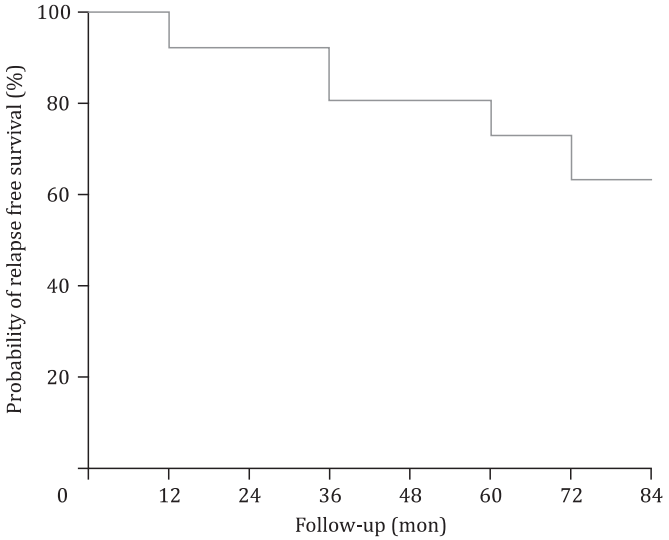

Fig. 2. Probability of relapse free survival in patients classified as AIP type NOS at clinical onset. NOS: not otherwise specified.

the onset of UC in these patients was 17 months (range 4–60). Fig. 1 reports the probability to reclassify the disease in AIP type 2 during the follow-up. The probability of reclassification was 7% at 1-year, 12% at 3-year and 25% at 5-year.

Serology

Serum IgG4 (sIgG4) were available in 40 (87.0%) out of 46 patients before steroids administration with a median sIgG4 level of 52.5 (IQR 29.5–73.0) mg/dL. In detail, none had IgG4 levels higher than 135 mg/dL. Therefore, 100% of these patients are considered IgG4 negative according to the ICDC. The median sIgG4 level was not different between males and females (55.0 mg/dL vs. 41.0 mg/dL; $P = 0.30$) and between patients who did and who did not develop UC (38.0 mg/dL vs. 55.0 mg/dL; $P = 0.72$). Moreover, none had elevated sIgG4 (>135 mg/dL) during the follow-up.

Risk of relapse

Seven patients (15.2%) experienced relapse after steroid therapy during follow-up (5 males and 2 females). Two had the first recurrence after development of UC and should therefore be considered as relapses into AIP type 2. All patients re-treated with steroids achieved new remission. Only one of them developed further relapses and was treated with azathioprine maintaining stable remission. Another single patient was treated with azathioprine after the first relapse, without further relapses. Therefore, the experience of immunosuppressive drugs in AIP type NOS is very limited. None was treated with rituximab. Fig. 2 reports the probability of relapse free survival in patients classified as AIP type NOS at clinical onset. The probability of relapse was 8% at 1-year, 20% at 3-year and 28% at 5-year.

Discussion

The present study is the first cohort study of patients suffering from AIP type NOS. We described the main epidemiological, clinical and instrumental findings at the clinical onset and during the follow-up. In a previous study by our group, we reported the clinical features of AIP type NOS in a limited number of patients, partially shared both with AIP type 1 and type 2 [10]. The conclusions of this first report were that AIP type NOS may be an IgG4-seronegative AIP type 1, an undiagnosed AIP type 2 or an overlap syndrome.

In the present study, we included a larger number of patients, described the clinical outcome, and particularly focused on the probability of disease relapse and of disease reclassification during the follow up.

About 25% of patients were reclassified during the first 5 years of follow-up (Fig. 1). All patients were reclassified in AIP type 2 because of the new histologically proven diagnosis of UC. The switch from AIP type NOS to AIP type 2 has never been described before, in our knowledge. These data confirm the hypothesis that AIP type 2 patients are sometimes classified as type NOS at clinical onset in the absence of conclusive criteria for probable/definitive AIP type 2. Therefore, AIP type NOS might be considered, in some patients, an AIP type 2 still not classifiable at clinical onset. However, the large part of patients remains classifiable as AIP type NOS during follow-up. These patients may be considered as seronegative AIP type 1 with low disease activity or not classifiable AIP type 2. Independently form these two theories; the low risk of recurrence seems to suggest avoiding an upfront maintenance therapy in these patients.

Unfortunately, we did not find in our population predictive factors for the onset of UC (Table 1), which was observed mainly within 2 years from the diagnosis of AIP. Fecal calprotectin might be considered a screening test at the clinical onset of the disease (before the steroid treatment), and in any case in a steroid-free period. Colonoscopy may consequently be performed in patients with high levels of fecal calprotectin. The clinical implication of this approach may be an early diagnosis of UC leading to a better control of colonic inflammation and to avoid further hospitalizations for colitis.

None of the patients were reclassified as type 1 during the follow-up. However, this reclassification is probably more challenging and can be reached by histology, OOI or elevations of sIgG4. Since histology is rarely required during follow-up of patients with a previous diagnosis of AIP treated with steroids, the only possibility is based on development of OOI (kidney, proximal biliary tree, retroperitoneum and salivary/lachrymal glands) and/or elevation of sIgG4. In our Institution, patients are routinely followed by abdominal MRI and sIgG4 level test yearly, and none of the patients developed OOI or had elevation of sIgG4, even in the case of disease relapse. Therefore, we believe that the probability

of reclassification as AIP type 1 is rare, even considering the retrospective design of this study.

The clinical onset was mainly characterized by jaundice and acute pancreatitis presentation, whereas the frequency of endocrine and exocrine insufficiency was negligible, probably related to the relative young age of these patients. The pancreas involvement at imaging was mainly focal (ICDC level 2), and only 2 patients underwent non-resective surgery in the suspicion of cancer. However, the low frequency of surgery in this setting of patients was related to the exclusion of patients treated with resective surgery that, based on pathology, were definitively classified into AIP type 1 or type 2.

The frequency of relapse after steroid treatment in 5 years was not irrelevant (28%). Interestingly, 2 out of 8 patients who switched diagnosis to AIP type 2 relapsed. This data is poorly understood, considering the low relapse rate of AIP type 2 reported in literature (less than 10%) [13,14]. Only one patient (2.2%) experienced more than 1 relapse, requiring immunosuppressive drugs with no further recurrences. However, the risk of relapse and the need of immunosuppressant appears clearly lower compared to the published data on AIP type 1 [14–17]. While an upfront maintenance therapy is proposed for AIP type 1 [18–20], our study suggest it should be avoid in AIP type NOS.

In conclusion, AIP type NOS may switch to AIP type 2 and the disease-behavior is different from AIP type 1. Despite the rarity of the disease, the sample size gives a good representation of the behavior of the disease, clinical outcome in terms of risk of recurrence and development of UC. Future prospective multicenter studies including a large number of patients are needed to better define disease's profile. However, our data imply that an upfront maintenance therapy should be avoided considering the low risk of recurrence. Moreover, patients should be informed that the diagnosis of AIP type NOS is associated with a significant risk of developing UC.

Contributors

PN proposed the study. VF, BA, BL and AA collected data. PN and FL analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. FL is the guarantor.

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Ethical approval

The study was approved by the ethics committee (393CESC).

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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