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Idiopathic Duct-Centric Pancreatitis: Disease Description and Endoscopic Ultrasonography-Guided Trucut Biopsy Diagnosis

Michael J. Levy[a] Thomas C. Smyrk[b] Naoki Takahashi[c] Lizhi Zhang[b]
Suresh T. Chari[a]

[a]Division of Gastroenterology and Hepatology, Departments of [b]Pathology and [c]Radiology, Mayo Clinic, Rochester, Minn., USA

Key Words
Autoimmune pancreatitis · Endoscopic ultrasonography · Trucut biopsy

Abstract
Background/Aims: Recent data demonstrate the presence of two autoimmune pancreatitis (AIP) subtypes. All existing endoscopic ultrasonography-guided trucut biopsy (EUS-TCB) data pertain to type 1 disease. Our aim is to determine if EUS-TCB samples are sufficient for diagnosing type 2 AIP. ***Methods:*** This is a retrospective case series conducted in an academic tertiary care center. Patients included those with type 2 AIP (n = 5), retrospectively identified from a database of all patients with AIP, diagnosed by HISORt criteria (n = 125). The primary outcome measure was the diagnostic capability of EUS-TCB for type 2 AIP. ***Results:*** 5 patients (4 male, 1 female; mean age 39.6 years) who underwent EUS-TCB were diagnosed with type 2 AIP. The serum IgG_4 level was elevated in 1 of the 4 patients tested. CT/MRI revealed diffuse pancreas enlargement (n = 3), a pancreas head mass (n = 1), and a normal pancreas (n = 1). Prior to EUS, AIP was not specifically suspected, but part of a broad differential (n = 3) or not suspected at all (n = 2). Fine-needle aspiration was negative for neoplasia and AIP. The TCB histology was definitive (n = 4) or suggestive (n = 1) for type 2 AIP. No complications developed. ***Conclusions:*** EUS-TCB may be safe and may provide sufficient material to definitively diagnose type 2 AIP.

Introduction

Autoimmune pancreatitis (AIP) is a fibroinflammatory disease that readily responds to steroid therapy. Following the first description by Sarles et al. [1] in 1961, subsequent reports included only patients with florid disease manifestations [2–4]. Over time, there has been a greater understanding of the diverse clinical, laboratory, and histological manifestations, leading to a more comprehensive set of diagnostic criteria that now allow us to diagnose AIP in a broader spectrum of patients while maintaining diagnostic specificity. Worldwide experience led to differing sets of diagnostic criteria [5–9]. The most comprehensive is the Mayo HISORt system that considers histology, imaging, serology, other organ (nonpancreatic) involvement, and steroid response [7, 10–15]. The Japanese, Korean and HISORt criteria are designed to diagnose type 1

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Michael J. Levy, MD
Mayo Clinic
Division of Gastroenterology and Hepatology
200 First Street SW, Rochester, MN 55905 (USA)
Tel. +1 507 266 6931, E-Mail levy.michael@mayo.edu

Table 1. Distinguishing features of the 2 AIP subtypes

Features	Type 1 AIP	Type 2 AIP
Age (at diagnosis)	6th decade	4th decade
Gender	male predominance	equal
IgG_4 (serum)	typically elevated	seldom elevated
Histological pattern	lymphoplasmacytic sclerosing pancreatitis	idiopathic duct-centric pancreatitis
Histological hallmarks	periductal lymphoplasmacytic infiltrate, swirling fibrosis, obliterative venulitis (phlebitis), preservation of arterioles	lymphoplasmacytic infiltrate, granulocyte epithelial lesion (with partial/complete duct obstruction)
IgG_4 immunostain[1]	moderate-to-severe (98%)	none-to-mild (60%), moderate (40%)
Associated diseases	sclerosing sialadenitis, autoimmune cholangiopathy, retroperitoneal fibrosis, tubulointerstitial nephritis	inflammatory bowel disease

[1] Mild = 1–10 positive cells/hpf; moderate = 11–30 positive cells/hpf; severe = >30 IgG_4-positive cells/hpf.

but not type 2 AIP. The HISORt criteria were developed based on features of histologically confirmed lymphoplasmacytic sclerosing pancreatitis (LPSP), the histological pattern seen in type 1 AIP. The disease subtypes are most reliably distinguished by histological features [11, 16]. However, differences in age at presentation, gender, results of IgG_4 staining, and the presence of associated disorders often provide additional clues (table 1). Given the paucity of diagnostic clues and the need for the histological review of large-core pancreatic biopsies, until recently, the definitive diagnosis of type 2 AIP was only possible following surgical pancreatic biopsy or resection. While our initial experience using endoscopic ultrasonography-guided trucut biopsy (EUS-TCB) offered the promise of enhanced diagnosis for patients with type 1 disease [22], we questioned the potential utility and role of EUS-TCB diagnosis of type 2 disease.

Methods

We retrospectively reviewed an ongoing database of all patients with AIP diagnosed by HISORt criteria (n = 125) to identify patients with type 2 AIP who had undergone pancreatic EUS-TCB. The Institutional Review Board granted study approval and informed consent was obtained for all procedures. The diagnostic criteria were based on established norms [4, 8, 21, 23]. A dedicated GI pathologist blinded to the clinical data reviewed the EUS-FNA (fine-needle aspiration) samples on the day of the EUS. Due to the time required for the processing of histological samples, a second dedicated GI pathologist, blinded to the clinical data and the EUS-FNA interpretation of the first pathologist, examined the histological sample 1 day after EUS. Final diagnosis was determined by a combination of clinical, outcome, laboratory, and imaging data [4, 8, 23]. All complications were prospectively tracked and logged in the database.

Results

We identified 5 patients (4 male; mean age 39.6 years, range 25–71) with type 2 AIP who underwent pancreatic EUS-TCB. Clinical, laboratory, imaging, histology and therapeutic response and course are detailed in online supplementary table 1 (available at: www.karger.com/doi/10.1159/000324189). Patients presented with obstructive jaundice (n = 2), abdominal pain (n = 2), and recurrent acute pancreatitis (n = 1). The serum IgG_4 level was marginally elevated in 1 of the 4 patients in whom it was measured. The serum CA 19-9 was normal in each of the 3 patients measured. Pre-EUS CT (n = 4) and MRI (n = 1) revealed diffuse pancreatic enlargement (n = 3), a focal pancreatic head mass (n = 1), and a normal pancreas (n = 1). One patient had ulcerative colitis. Based on all pre-EUS data, the diagnosis of AIP (of either subtype) was not specifically suspected in any of the 5 patients, considered as part of a broad differential in 3 patients, and not suspected at all in 2 patients. In these last 2 patients, the finding of a diffusely hypoechoic gland on EUS led to the initial suspicion and decision of TCB.

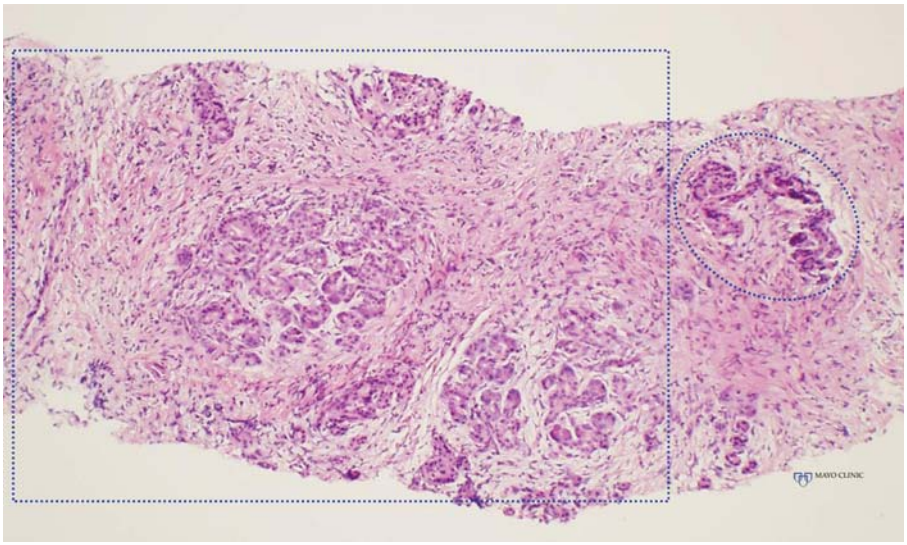

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Fig. 1. EUS-TCN reveals GEL among a background of dense fibrosis. The rectangle demonstrates storiform fibrosis with inflamed stroma, mild lobular inflammation and atrophy. The oval demonstrates GEL lesions in pancreatic ducts. GEL = Granulocyte epithelial lesions. HE. ×10.

EUS revealed a diffusely hypoechoic pancreas in each patient and 1 patient also presented with a focal pancreatic head mass. Four patients underwent a mean of 2.25 FNA (range 2–3) (Echotip; Wilson-Cook, Winston-Salem, N.C., USA) that demonstrated pancreatic acinar cells, without evidence of neoplasia or AIP of either subtype. A mean of 3.6 TCB (range 2–7) (QuikCore, Wilson-Cook) was obtained. No complications developed. The histological features, when considered in isolation, were deemed definitively diagnostic in 4 patients and suggestive of type 2 AIP in 1 patient. For the final 2 patients, the clinical and imaging response to steroids helped enable the diagnosis. No patient required surgical intervention for diagnosis or management.

Patients underwent a course of steroids at an initial prednisone dose of 40 mg/day that was tapered over 3–4 months (n = 4). One patient was initiated on 20 mg that was rapidly tapered over 2 weeks. All 5 patients experienced rapid and complete resolution of symptoms and the CT findings were abnormal for the 2 patients in whom post-EUS imaging was performed. Over a mean follow-up of 19.8 months (range 12–31), 4 patients experienced no evidence of disease recurrence. The remaining patient, who has now been followed for 20 months, experienced a migratory arthralgia and 10-pound weight loss with no associated gastrointestinal or extraintestinal symptoms. These symptoms spontaneously resolved without a specific diagnosis and he has been asymptomatic over the past 3 months with no firm evidence of AIP-related manifestations.

Discussion

Two subtypes of AIP have been recently recognized, including type 1 that demonstrates the histological features termed LPSP [11, 20, 24] and type 2 that is referred to as idiopathic duct-centric chronic pancreatitis (IDCP) [11]. Histological evaluation reliably differentiates the 2 subtypes and accurately distinguishes usual (nonautoimmune) chronic pancreatitis and tumor-related postobstructive pancreatitis (fig. 1) [11, 16, 21, 25, 26]. We now realize that most existing AIP data in fact pertain only to type 1 AIP, seen to be true because initial descriptions of AIP originated from Japan where type 2 disease is rarely reported. In a retrospective review of resected AIP from the Mayo Clinic, 33% had type 2 AIP [11]. Nearly 40% of resected AIP patients from Europe have type 2 AIP [16]. The reasons for this higher percentage were unclear until reports emerged from England and Italy revealing that we have been dealing with 2 disease variants. The diagnosis of type 2 disease is difficult and it is likely that many affected patients are never correctly diagnosed. This problem arises from the need for histological evaluation of large biopsy specimens for definitive diagnosis, which, until recently, mandated surgical biopsy or resection. Diagnosis of type 2 AIP is further hampered by the paucity of clinical, serologic, and imaging clues when compared to patients with type 1 disease.

Distinction of AIP from usual chronic pancreatitis and pancreas cancer requires histological examination of tissue samples containing preserved architecture. Cytology review of FNA samples, while sufficient to diagnose

cancer, is unsuitable for AIP [27]. Expert panel deliberations at the AIP International 2009 Honolulu Meeting reached consensus that FNA is incapable of diagnosing either form of AIP. Pancreatic-core biopsies obtained via surgical, percutaneous or endoscopic routes offer the potential for histological diagnosis [7, 13, 16, 22]. However, pancreatic core biopsy risks complications, small sample size and sampling error. Most centers do not perform EUS-TCB and instead opt for a diagnostic and therapeutic steroid trial. We refrain from diagnostic steroid trials where possible and pursue definitive diagnosis, restricting steroid use to a therapeutic trial. This approach mandates EUS-TCB when other nonhistological features are nondiagnostic. We restrict the use of a diagnostic steroid trial to patients who refuse or have failed TCB diagnosis after all efforts have been made to exclude malignancy.

While EUS-TCB findings and/or the response to a steroid trial may be necessary to diagnose AIP, this information is not available at the time of the initial evaluation. Instead, pancreatic imaging and serology are performed, which permit diagnosis in many patients with type 1 AIP. In this patient cohort, we pursue EUS-TCB diagnosis when imaging and serology produce diagnostic uncertainty. This approach allows for safe and accurate diagnosis in nearly all patients with type 1 disease, as demonstrated by the fact that only 4 of 76 type 1 AIP patients have required surgical intervention since the introduction of EUS-TCB in our center in 2003. The results have not been as favorable for patients with type 2 disease, in whom fewer diagnostic clinical, laboratory, and imaging clues exist. Among the 6 patients with a final diagnosis of type 2 AIP seen in our center since 2003, only 1 has undergone surgical intervention due to failure to consider AIP prior to surgery. This patient had not undergone EUS.

Our report is limited by the small patient cohort, but may nevertheless be of value to clinicians evaluating patients for possible type 2 AIP. The retrospective nature of the report also only allows us to describe those patients with a final diagnosis of type 2 AIP who underwent EUS-TCB so it is not possible to determine performance characteristics, in particular the specificity of TCB, in this cohort. It is likely that other patients have been evaluated at our center that had type 2 AIP, but for whom the diagnosis was never established given the general need for a histological diagnosis. As such, our findings may suggest a greater diagnostic sensitivity than truly exists.

The findings support the notion that patients with type 2 AIP present with a paucity of supporting features to suggest the diagnosis and indicate that TCB is required to allow definitive diagnosis. If these tissue specimens had not been available, then none of our patients would have satisfied currently available diagnostic algorithms for AIP. Our preliminary data suggest that EUS-TCB may safely establish the diagnosis of type 2 AIP. Doing so helps guide management, may help avoid unnecessary surgery or diagnostic steroid trials, and provide prognostic information in terms of disease recurrence.

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