Sclerosing Cholangitis With Granulocytic Epithelial Lesion

A Benign Form of Sclerosing Cholangiopathy

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Abstract: The association between autoimmune pancreatitis and sclerosing cholangitis has attracted considerable attention. In contrast to type 1 (IgG4-related) autoimmune pancreatitis, bile duct involvement is uncommon in type 2 autoimmune pancreatitis, a more benign condition characterized histologically by granulocytic epithelial lesions (GELs). Following our recent report on a child with GEL-positive sclerosing cholangitis and excellent response to steroids, we retrospectively reviewed the liver histology of a large number of patients with sclerosing cholangitis to investigate the possible role of type 2 autoimmune pancreatitis in this pathology. Liver biopsies of 103 children with autoimmune sclerosing cholangitis and 142 adults with primary sclerosing cholangitis were reviewed for the presence of neutrophilic bile duct injury. Histologic findings were correlated with clinical features, response to treatment, and outcome. Neutrophilic bile duct lesions similar to GEL were identified in 5 cases (4 children and 1 adult; 4% of autoimmune sclerosing cholangitis and 0.7% of primary sclerosing cholangitis). GEL was more commonly seen in wedge biopsy specimens. One patient had concomitant pancreatitis. Cholangiograms showed diffuse stricturing of bile ducts in all cases. The number of liver tissue $IgG4^+$ plasma cells did not increase, and serum IgG4 levels were normal in 3 patients tested. All patients went into remission with prednisolone and/or ursodeoxycholic acid, and their liver function tests remained completely normal without relapses over a follow-up period of 6 to 16 years. Although rare, the diagnosis of sclerosing cholangitis with GEL is important in view of its excellent and apparently sustained response to immunosuppressive treatment.

Key Words: primary sclerosing cholangitis, autoimmune sclerosing cholangitis, autoimmune pancreatitis, IgG4, steroid

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Sclerosing cholangiopathy can be caused by several etiological factors including immunodeficiency, ischemia, or bile duct stones.[1,2] The idiopathic form called primary sclerosing cholangitis (PSC) is characterized by multifocal stricturing and dilatation, generally involving both the intrahepatic and extrahepatic biliary system.[3] PSC responds poorly to treatment and usually progresses to end-stage liver damage requiring liver transplantation. Sclerosing cholangitis in children is more commonly associated with autoimmune features including elevated titers of autoantibodies, in particular antinuclear antibodies and anti-smooth muscle antibodies, elevated immunoglobulin G (IgG), and histologic evidence of interface hepatitis.[4] Given the overlap with autoimmune hepatitis, juvenile sclerosing cholangitis is called autoimmune sclerosing cholangitis (ASC).[4,5] Children with ASC initially respond to immunosuppressive treatment, but the bile duct disease progresses in almost 50% of them in the long term.[6]

During the last decade, IgG4-related sclerosing cholangitis has been recognized as a distinct entity in the context of systemic IgG4-related disease, which is characterized by elevated levels of serum IgG4, tissue infiltration by $IgG4^+$ plasma cells, and marked response to steroid therapy.[7,8] IgG4-related cholangitis is often associated with type 1 autoimmune pancreatitis (IgG4-related pancreatitis)[8,9]; in the absence of concomitant pancreatitis, it is difficult to differentiate from PSC on the basis of cholangiographic findings alone.[10] Another, less common, form of autoimmune pancreatitis, in which the pancreatic duct epithelium is heavily infiltrated by neutrophils [granulocytic epithelial lesion (GEL)],[11,12] is defined as type 2 autoimmune pancreatitis (Fig. 1).[13] As this condition has no serological markers (IgG4 levels are normal), histologic evidence of GEL is a prerequisite for diagnosis.[11,14,15]

Patients with type 1 autoimmune pancreatitis are typically adults and frequently have extrapancreatic IgG4-related disease.[16,17] In contrast, type 2 autoimmune pancreatitis can affect both children and adults and is not associated with systemic symptoms, except possibly for inflammatory bowel disease (IBD).[16,17] Steroid therapy is highly effective in both types of pancreatitis, and spontaneous remission can occur without steroids in some patients. The relapse rate is higher in type 1 than in type 2.[17] Concomitant bile duct involvement is commonly

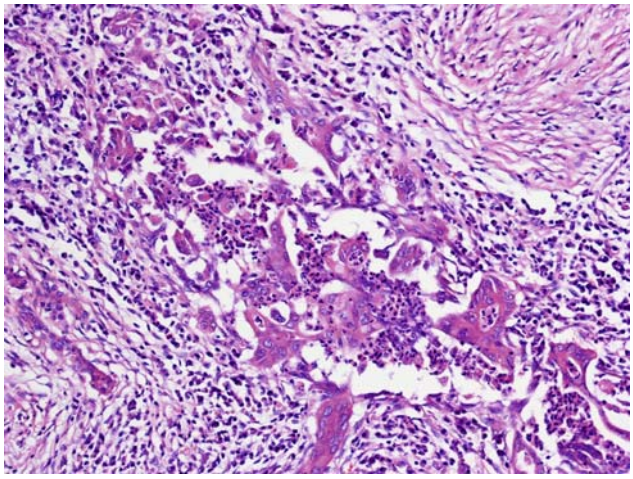

FIGURE 1. GEL in type 2 autoimmune pancreatitis. A Whipple's specimen shows a pancreatic duct infiltrated by many neutrophils, in which the lining epithelium is disrupted (hematoxylin and eosin). full color online

present in type 1 but is not a feature of type 2 autoimmune pancreatitis. Recently, we reported a case of steroid-responsive ASC with excellent outcome, in which the liver biopsy at disease onset showed neutrophilic bile duct damage reminiscent of GEL, leading to the hypothesis that GEL may characterize a form of steroid-responsive sclerosing cholangitis.[18]

In this study, we have retrospectively examined the liver biopsy specimens of a large cohort of patients with ASC and PSC to investigate whether GEL-positive cholangitis represents a distinct entity.

PATIENTS AND METHODS

Patients

Consecutive cases of ASC and PSC were selected from the histopathology files of the Institute of Liver Studies, King's College Hospital, London, during the period 1985 to 2011 for ASC and from 1999 to 2011 for PSC. Inclusion criteria were availability of liver biopsy slides at diagnosis and the patients being treated at our institution. An additional child diagnosed elsewhere with ASC in 1989, whose histology slides were sent to us for a second opinion in 1991, was also included in the study. A total of 103 patients with ASC and 142 patients with PSC were enrolled. Median age and male/female ratio were: ASC, 12 years (range, 2 to 16 y), 63 male patients/40 female patients; PSC, 41 years (range, 17 to 75 y), 91 male patients/51 female patients. The diagnosis of sclerosing cholangitis was based on diffuse bile duct abnormalities including stricturing and dilatation on endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography. Other potential causes of sclerosing cholangitis such as ischemia, sickle cell disease, and immunodeficiency were excluded.

Histologic Examination and Definition of GEL

Archived histology slides of liver biopsies were reviewed. Original slides were stained with hematoxylin and eosin, periodic acid-Schiff after diastase digestion, reticulin, orcein, or Perls. The following 11 histologic features were assessed: (1) GEL (−, absent; +, present); (2) stage of fibrosis (0, no fibrosis; 1, periportal fibrosis with or without early septum formation; 2, bridging fibrosis; 3, parenchymal distortion with focal nodular change; 4, cirrhosis); (3) portal inflammation (0, absent; 1, mild; 2, moderate; 3 severe); (4) interface hepatitis (0, absent; 1, focal; 2, extensive); (5) lobular hepatitis (−, 0 to 2 foci of focal necrosis/$\times$10 objective field; +, $\geq$3 foci of focal necrosis/$\times$10 objective field); (6) plasma cell infiltration [−, 0 to 9 cells/hpf ($\times$40 objective field); +, $\geq$10 cells/hpf]; (7) eosinophilic infiltration (−, 0 to 4 cells/hpf in portal area; +, $\geq$5 cells/hpf); (8) neutrophilic infiltration (−, 0 to 10 cells/hpf in portal area; +, $\geq$10 cells/hpf); (9) periductal "onion-skin" concentric fibrosis (−, absent; +, present); (10) bile duct loss (−, absent; +, present); (11) orcein-positive granules (0, absent; 1, focal; 2, extensive).

GEL was defined as an extensive neutrophilic infiltration into the biliary epithelial layer, associated with an irregular duct outline and/or disruption of the lining epithelium. Features of suppurative cholangitis—namely, dilated bile ducts with aggregated neutrophils within their lumen and epithelial attenuation—were not counted as GEL. Only native bile ducts were assessed for the presence or absence of GEL. Reactive bile ductules at the portal periphery that are commonly associated with sparse neutrophils were not considered as GEL.

Immunostaining for IgG4 was performed in all cases of GEL-positive cholangitis using an autostainer (BOND MAX; Leica Microsystems, Wetzlar, Germany) as per the manufacturer's instructions. The most recent 30 cases of GEL-negative ASC were stained for IgG4 for comparison. Sections were pretreated with proteinase and incubated with a mouse monoclonal antibody for human IgG4 (Zymed Laboratory Inc., San Francisco, CA). Specimens of tonsil were used as positive controls. $IgG4^+$ plasma cells were counted in 3 different hpf ($\times$10 eyepiece and $\times$40 objective lens, 0.237 mm^2) of areas with intense inflammation and averaged.

Clinical Features

Clinical data of patients with GEL-positive cholangitis were reviewed in terms of presentation, history of pancreatitis or IBD, laboratory findings, radiologic features, treatment, and follow-up clinical course. Serum IgG4 concentrations were tested retrospectively when frozen serum samples at the time of diagnosis were available.

Statistical Analysis

A statistical analysis was performed using the χ^2 test or Mann-Whitney U test to analyze variables. A probability of $P < 0.05$ was considered to be statistically significant.

RESULTS

Histologic Examination

ASC: Liver specimens of ASC cases consisted of 3 wedge and 100 needle biopsies. Neutrophilic bile duct damage consistent with GEL was identified in 4 of 103 biopsies (4%), including that of the one child referred from outside. All 3 wedge biopsy specimens (patients 1, 2, and 3), but only 1 needle specimen (patient 4), showed GEL. Patient 1 had a wedge biopsy taken during an exploratory laparotomy for lymphadenopathy, which turned out to be reactive. Patient 2 had a wedge liver biopsy performed at the time of subtotal colectomy for ulcerative colitis. Patient 3, who had both pancreatitis and sclerosing cholangitis, underwent laparotomy to obtain surgical biopsy specimens from both the pancreas and liver.

GELs were patchily distributed, affecting only 7% to 10% of portal tracts. Neutrophilic infiltration was seen in 50% of ASC cases, particularly around reactive bile ductules (cholangiolitis), which was easily distinguishable from GEL. Bile ducts involved in GEL were more centrally located in the portal tracts and well demarcated, features in keeping with native bile ducts (Fig. 2). The affected ducts showed irregular configuration or disruption of the lining epithelium (Fig. 2). One wedge specimen contained a medium-sized portal vein branch, which showed a fibrous obliteration with a mild lymphoplasmacytic infiltration. Except for the presence or absence of GEL, there was no significant difference between GEL-positive and GEL-negative cases with regard to the other 10 histologic features described in the Patients and Methods section (Table 1). All cases of GEL-positive cholangitis were at a relatively early disease stage, but 2 showed established bridging fibrosis. Periductal concentric fibrosis and copper-associated protein deposition were seen in 2 cases each. Numbers of $IgG4^+$ plasma cells did not increase in the 4 GEL-positive patients and the 30 GEL-negative controls (all cases, ≤ 5/hpf).

PSC: Of the 142 PSC patients, 136 underwent needle, and 6 underwent wedge liver biopsies. Only 1/136 needle biopsies was positive for GEL (0.7% in total) (patient 5). His biopsy showed a slightly distorted lobular architecture with periportal fibrosis (stage 1). Portal tracts were enlarged because of dense, predominantly lymphocytic infiltrates, including a fair number of eosinophils and neutrophils, associated with interface hepatitis in places. A minute granuloma was present in the parenchyma. Only 1 of 8 portal tracts sampled was positive for GEL. The affected duct was obscured by infiltrating neutrophils and disruption of the lining epithelium and was surrounded by concentric fibrosis (Fig. 3). Neither copper-associated protein deposition nor $IgG4^+$ cell infiltration was identified. The degree of portal inflammation was higher than that expected in typical PSC (Fig. 3).

GEL was not identified in any of the 6 PSC patients who underwent wedge biopsies at the time of protocolectomy for ulcerative colitis (n = 3), cholecystectomy for chronic cholecystitis (n = 1), the Whipple procedure for pancreatic head carcinoma (n = 1), and laparotomy for a dominant stricture of the common hepatic duct (n = 1).

Clinical Characteristics of Sclerosing Cholangitis With GEL

Clinical information has been summarized in Table 2. Patient 1 was described in a previous report.[18] Patients 1, 3, and 4 were diagnosed with liver disease at the time of first presentation, whereas patients 2 and 5 were found to have liver dysfunction during follow-up for ulcerative colitis. Patients 1, 2, 3, and 5 had a history of IBD. All patients had abnormal liver enzymes, in particular elevated levels of alkaline phosphatase and γ-glutamyl transpeptidase. Autoimmune features were present in all 4 pediatric cases: 3 had elevated IgG concentration, 3 were positive for antinuclear antibodies, and 2 for antineutrophil cytoplasmic antibody. Serum IgG4 concentrations were within the normal range in the 3 children tested. The adult patient was not tested for autoantibody and total IgG levels. Cholangiography showed diffuse biliary abnormalities, predominantly involving intrahepatic bile ducts in patients 1, 2, 3, and 4, and were associated with severe hilar stenosis, which required insertion of a stent in patient 5.

For patient 3, whose histology slides were sent to our center for a second opinion, the only clinical information available was that contained in the referral letter. He presented with fever, abdominal pain, and jaundice. The diagnosis of ASC was made on the basis of serological autoimmune abnormalities, endoscopic retrograde cholangiopancreatography findings, and liver biopsy. He was also suspected to have pancreatitis on the basis of the radiologic appearance of the pancreas, which showed diffuse enlargement. Open pancreatic biopsy, which was not sent to us for review, was reported as pancreatitis without further specification. Treatment with prednisolone (50 mg/d) was followed by improvement of all clinical and laboratory abnormalities. Ten months later, the patient noticed rectal bleeding, and a rectal biopsy confirmed the diagnosis of ulcerative colitis. Further follow-up data are not available.

Patients 1, 2, and 4 were treated with prednisolone (initial dose, 40 to 60 mg/d), with improvement in liver function test results. Patient 1 is currently off prednisolone, and patients 2 and 4 are being maintained on low-dose prednisolone (2.5 to 5.0 mg/d). In all 3 patients, liver enzymes were entirely normal for >3 years without radiologic evidence of disease progression. The adult patient with PSC had been diagnosed in a different center with ulcerative colitis at the age of 12 years and underwent a subtotal colectomy at the age of 14 years. No information about his liver function and medical treatment in childhood is available, although it is likely that he was treated with steroids for IBD. He was referred to King's at the age of 41 years and diagnosed as having PSC with a dominant stricture, which was initially treated with a biliary stent, which was removed 3 months later. His liver function tests returned to normal after a 2-year treatment with ursodeoxycholic acid (UDCA, 1000 mg/day) and with mesalazine (suppositories plus 900 mg/d orally) and prednisolone suppositories

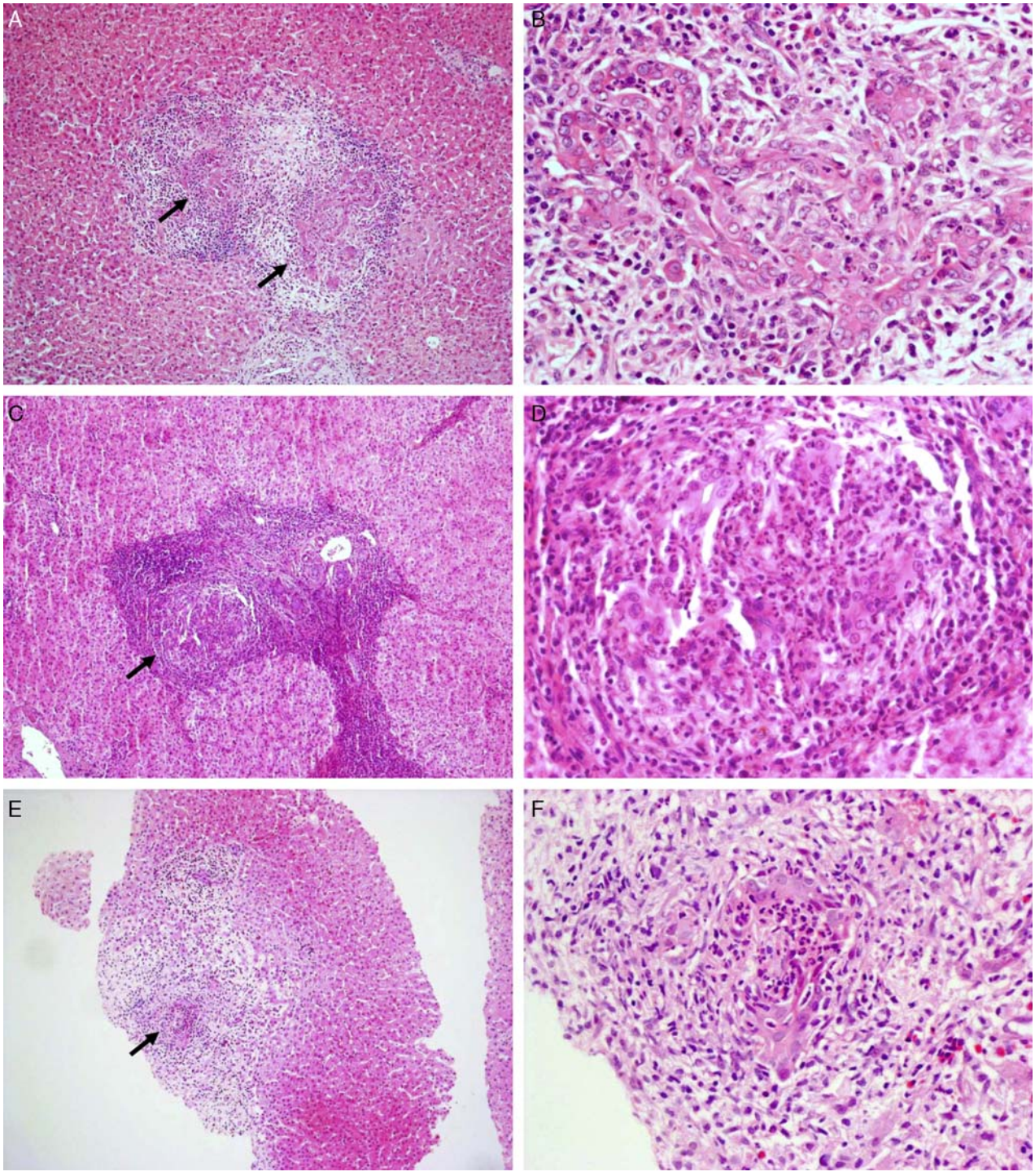

FIGURE 2. Histologic features of GEL-positive cholangitis in children. Portal tracts are enlarged with mild to moderate inflammatory cell infiltration and GELs [arrows in (A), (C), and (E)]. The affected bile ducts show infiltration by many neutrophils associated with irregular configuration or disruption of the lining epithelium (B, D, and F). F, The central part of the ductal structure, which contains many neutrophils, is not a ductal lumen but protruded periductal connective tissue. (A to F, hematoxylin and eosin; A and B, patient 1; C and D, patient 3; E and F, patient 4).

for persistent proctitis. At present he remains well on UDCA alone (300 mg/d). The liver is radiologically unremarkable except for a slight atrophy of the right posterior segment. No symptomatic relapse occurred in any of these patients (follow-up periods: 6 to 16 y, median 10.5 y).

TABLE 1. Liver Biopsy Findings of Sclerosing Cholangitis With GEL

	GEL-positive Sclerosing Cholangitis						
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	GEL-negative ASC (n = 99)	P*
Age (y)	13	14	11	14	41	2-16	0.387
Sex (male/female)	M	M	M	M	M	59/40	0.270
Type of biopsy	Wedge	Wedge	Wedge	Needle	Needle	All needle	< 0.001
% of diagnostic portal tracts	6/60 (10%)	1/12 (8%)	8/88 (9%)	1/15 (7%)	1/8 (13%)	Not applicable	—
Stage of fibrosis (1; 2; 3; 4)	Stage 1	Stage 1	Stage 2	Stage 2	Stage 1	32; 28; 24; 15	0.189
Portal inflammation (mild; moderate; severe)	Moderate	Mild	Moderate	Moderate	Severe	61; 31; 7	0.220
Interface hepatitis (absent; focal; extensive)	Focal	Absent	Extensive	Focal	Extensive	56; 31; 12	0.201
Coppe-associated protein deposition (absent; focal; extensive)	Absent	Focal	Focal	Absent	Absent	42; 35; 22	0.497
Lobular hepatitis	–	–	+	–	+	27 (27%)	0.636
Plasma cells (≥ 10 cells/hpf)	+	–	+	+	–	35 (35%)	0.279
Eosinophils (≥ 5 cells/hpf)	+	–	+	+	+	30 (30%)	0.183
Neutrophils (≥ 5 cells/hpf)	+	+	+	+	+	50 (50%)	0.152
Periductal concentric fibrosis	+	–	+	–	+	29 (29%)	0.741
Bile duct loss	–	–	–	–	–	33 (33%)	0.393
GEL	+	+	+	+	+	0	< 0.001
$IgG4^+$ plasma cells (number/hpf)	0	2	2	0.6	0	0.3 (0-5)	0.152

*Comparison between GEL-positive ASC (patients 1, 2, 3, and 4) and GEL-negative ASC.

DISCUSSION

This study describes a peculiar form of cholangitis characterized by the presence of GEL. The clinicopathologic features of GEL-positive cholangitis overlap with those of type 2 autoimmune pancreatitis, in particular the presence of neutrophilic duct injury, association with IBD, a good response to steroid therapy, and a low risk for relapse.[16,17] These features raise the possibility that the 2 entities may belong to the same disease spectrum.

GEL-positive cholangitis accounted for 2% of the sclerosing cholangitis cases, including both ASC and PSC, referred to our center over the study period. This figure may be an underestimate, as GELs are patchily distributed and likely to escape sampling by biopsy needles. Most of the positive biopsies in our series were wedge and interestingly from children with ASC. GEL may preferentially involve intrahepatic large-sized/medium-sized bile ducts, leading to sampling error.

If GEL-positive cholangitis is truly a biliary counterpart of type 2 autoimmune pancreatitis, children and adults should be affected with a similar frequency.[11,16,17] The fact that GEL was not detected in the wedge biopsies from adult PSC patients may be because of a larger order of ducts being affected. Another explanation could be that GEL represents an early change that is burnt out in longer-standing disease. A similar explanation has been put forward to account for autoimmune features being prevalent in ASC and being rare in adult PSC. Thus GEL-positive cholangitis falling mainly in the spectrum of ASC, that is sclerosing cholangitis with florid

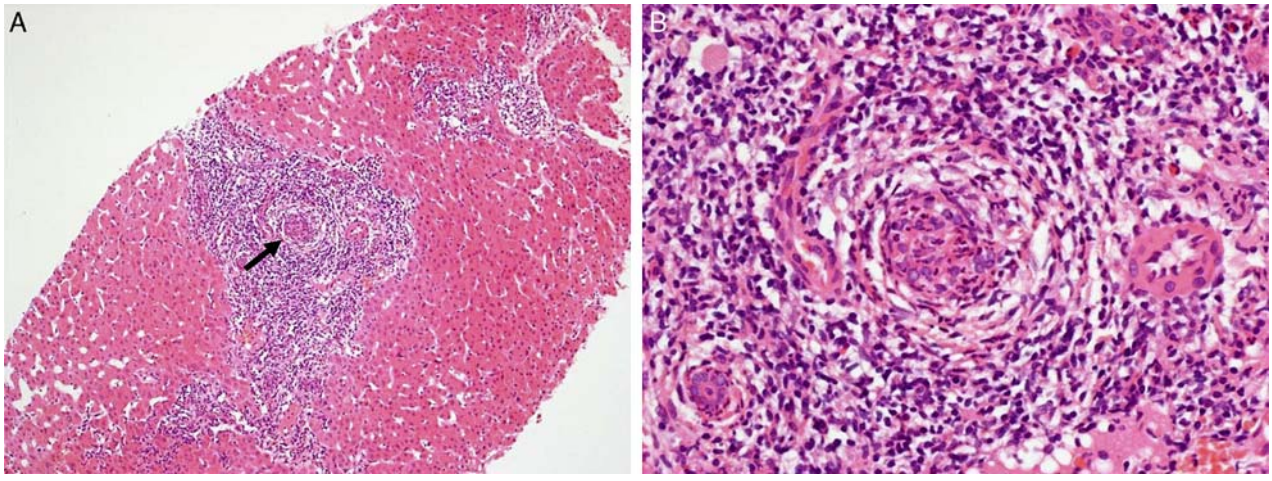

FIGURE 3. Histologic features of GEL-positive cholangitis in an adult (patient 4). A portal tract is enlarged with dense lymphocytic infiltration and interface activity (A). The arrow indicates GEL. The affected bile duct is infiltrated by many neutrophils and surrounded by loose connective tissue (B) (A and B, hematoxylin and eosin). full color online

TABLE 2. Clinical Summary of Patients With Sclerosing Cholangitis and GEL

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (y)	13	14	11	14	41
Sex	M	M	M	M	M
Presentation	Abdominal pain, bloody diarrhea, weight loss	Found to have liver dysfunction during follow-up for ulcerative colitis	Fever, abdominal pain, jaundice	Abdominal pain	Jaundice
Medical history	Crohn disease (13 y old) ASC (13 y old)	Ulcerative colitis (11 y old) Subtotal colectomy (14 y old) ASC (14 y old)	ASC (11 y old) Pancreatitis (11 y old) Ulcerative colitis (12 y old)	Gastric worms (14 y old) ASC (14 y old)	Ulcerative colitis (12 y old) Subtotal colectomy (14 y old) PSC (41 y old) Rectal cancer (41 y old)
Laboratory data					
AST (10-50 IU/L)	180	72	232	123	76
ALP (30-130 IU/L)	160	480	374	859	289
GGT (1-55 IU/L)	87	178	345	541	501
IgG (7-18.6 g/L)	20.9	33.6	37.1	17.3	Not examined
IgG4 (< 135 mg/dL)	64	6.7	Not examined	27	Not examined
ANA	+ (1/640)	–	+ (1/1250)	+ (1/20)	Not examined
SMA	–	–	–	–	Not examined
ANCA	–	+ (PR3)	–	+ (not further clarified)	–
Cholangiogram	Diffuse abnormalities predominantly involving intrahepatic bile ducts. Normal pancreatic ducts	Diffuse abnormalities predominantly involving intrahepatic bile ducts. Normal pancreatic ducts	Diffuse abnormalities predominantly involving intrahepatic bile ducts. Diffusely enlarged pancreas	Diffuse abnormalities in intrahepatic bile ducts. Extrahepatic bile duct and pancreatic duct are unremarkable	Multiple strictures involving both intrahepatic and extrahepatic bile ducts with severe hilar duct stenosis, which was stented. Normal pancreatic ducts
Treatment	Good response to PSL (40 mg/d). Maintained on PSL 5 mg/alternate days for 20 y. Currently off steroids	Good response to PSL (40 mg/d). Maintained on PSL 2.5 mg/d. No recurrence	Good response to PSL (50 mg/d): normalization of liver function tests. No follow-up	Good response to PSL (60 mg/d). One episode of AST elevation, controlled by PSL (30 mg/d). Currently on PSL maintenance (5 mg/d)	Biliary stenting; UDCA (1000 mg/d); mesalazine and PSL suppositories plus oral mesalazine (900 mg/d) for persistent proctitis
Current state	Normal LFTs and US	Normal LFTs and US	Not available	Normal LFTs and US. ANA weakly positive (1/10)	Normal LFTs. Mild atrophy of the right posterior segment of liver, otherwise normal CT
Time to normal liver function tests	6 mo	3 y	Not specified	6 y	8 mo
Total follow-up period	16 y	6 y	No follow-up data	12 y	9 y

ALP indicates alkaline phosphatase; ANA, antinuclear antibody; ANCA, anti-neutrophilic cytoplasmic antibody; AST, aspartate aminotransferase; CT, computed tomography; GGT, γ-glutamyl transpeptidase; LFTs, liver function tests; PSL, prednisolone; SMA, anti-smooth muscle antibody; US, ultrasonography.

autoimmune features, could reflect the fact that the time of appearance of the histologic change is limited to an early stage of the disease. A serum diagnostic biomarker for type 2 autoimmune pancreatitis, currently unavailable, would help clarify whether GEL-positive cholangitis is a feature of type 2 autoimmune pancreatitis and which proportion of patients with ASC or PSC are affected by this distinct form of cholangitis.

Interestingly, patient 3 presented with sclerosing cholangitis and concomitant pancreatitis. Although radiologic images of the pancreas were not available for review, his pancreas was described as being diffusely enlarged, and both liver and pancreatic diseases responded well to steroid treatment. Although we do not have IgG4 levels for this patient, the fact that he is a child and has IBD supports a diagnosis of autoimmune pancreatitis type 2. The tissue IgG4 level in the liver biopsy was also not elevated.

Until recently, biliary involvement was believed not to occur in type 2 autoimmune pancreatitis.[16,17] Our previously reported patient 1 and an international study reporting that 23% of patients with type 2 autoimmune

pancreatitis have some form of proximal bile duct involvement challenge this view.[18,19] These findings, however, require confirmation in larger studies. One potential confounding factor is that type 2 autoimmune pancreatitis with sclerosing cholangitis in the absence of histology might be misclassified as type 1 autoimmune pancreatitis, because the presence of proximal bile duct involvement may be regarded as part of other organ involvement, suggestive of type 1 autoimmune pancreatitis.[20] In addition, a mild rise in serum IgG4 levels can rarely be detected in type 2 autoimmune pancreatitis.[17]

Whether GEL-positive cholangitis is a distinct entity or represents a very early stage of ASC or PSC is uncertain. Besides the histologic finding of GEL, clinical features, serological abnormalities, and cholangiographic findings are in keeping with ASC and PSC. Interestingly, the adult patient with GEL-positive cholangitis described here might be a missed ASC. He was diagnosed and treated for severe IBD in childhood, and the histologic picture at the time of presentation to our center was more compatible with ASC than with PSC. His autoimmune markers were not assessed at presentation, but the marked response of his liver disease to immunosuppression for IBD and to UDCA is also more in keeping with ASC than with PSC. Larger studies with a better definition of adult and pediatric patients from the immunologic point of view and longer follow-up are necessary to clarify whether the presence of GEL heralds a satisfactory response to steroid therapy and a good long-term prognosis in patients with ASC and PSC.

The excellent and sustained response to treatment of GEL-positive cholangitis is remarkable. Although the time to remission of the pediatric patients with GEL in our series is not shorter than that of classical ASC, the long-term remission on low-dose steroids or without treatment is exceptional.[5,6] Response to immunosuppressive/UDCA treatment and the clinical course of patients with ASC were examined in our previous studies. Approximately 90% of patients initially responded to immunosuppression; aspartate aminotransferase normalized in 83% in 0.2 to 107 months after starting the treatment, γ-glutamyl transpeptidase in 89% in 1 to 96 months, and alkaline phosphatase in 92% in 1 to 40 months.[5] However, during a 13-year follow-up the bile duct disease progressed in approximately 50%,[6] one third of the patients had one or more episodes of biochemical relapse,[5] and 22% required liver transplantation.[6]

From the pathologic point of view, GEL needs to be distinguished from suppurative/ascending cholangitis, in which many neutrophils are seen in the duct lumen and in the epithelial layer.[21] In addition, GEL has to be distinguished from the common bile ductular reaction associated with neutrophilic infiltration. The location and overall architecture of the affected ducts help in the differential diagnosis.

In conclusion, this study identifies a potentially distinct form of cholangitis with GEL. This form of cholangitis appears to be rare, but it is important to recognize given the apparent satisfactory response to steroid therapy.

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