Autoimmunity Reviews 16 (2017) 875–882

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Comparative clinical characteristics and natural history of three variants of sclerosing cholangitis: IgG4-related SC, PSC/AIH and PSC alone

Min Lian [a,1], Bo Li [a,1], Xiao Xiao [a,1], Yue Yang [a], Pan Jiang [a], Li Yan [a], Chunyan Sun [a], Jun Zhang [a], Yiran Wei [a], Yanmei Li [a], Weihua Chen [a], Xiang Jiang [a], Qi Miao [a], Xiaoyu Chen [a], Dekai Qiu [a], Li Sheng [a], Jing Hua [a], Ruqi Tang [a], Qixia Wang [a,*], M. Eric Gershwin [b,*], Xiong Ma [a,*]

[a] Division of Gastroenterology and Hepatology, Key Laboratory of Gastroenterology and Hepatology, Ministry of Health, State Key Laboratory for Oncogenes and Related Genes, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai Institute of Digestive Disease, 145 Middle Shandong Road, Shanghai 200001, China
[b] Division of Rheumatology, Department of Medicine, Allergy and Clinical Immunology, University of California at Davis, Davis, CA, USA

ARTICLE INFO

Article history:
Received 2 May 2017
Accepted 8 May 2017
Available online 28 May 2017

Keywords:
IgG4-SC
PSC/AIH overlap
IgG4
Prognosis

ABSTRACT

There is increased interest and recognition of the clinical variants of Sclerosing Cholangitis (SC) namely IgG4-SC, PSC/AIH overlap and PSC. For most Centers, the characteristic of IgG4-SC has not been thoroughly clinically compared with other sclerosing cholangitis variants. Further there are relatively few PSC/AIH overlap patients and the clinical outcome is not well characterized, especially for the PSC/AIH overlap syndrome. Our objective herein is to clarify the differences and similarities of the natural history of IgG4-SC, the PSC/AIH overlap and PSC alone. We also place in perspective the diagnostic value of serum IgG4 for IgG4-SC and investigate biomarkers for predicting the prognosis of sclerosing cholangitis. In this study, we took advantage of our large and well-defined patient cohort to perform a retrospective cohort study including 57 IgG4-SC, 36 PSC/AIH overlap patients, and 55 PSC patients. Firstly, as expected, we noted significant differences among immunoglobulin profiles and all patients exhibited similar cholestatic profiles at presentation. Cirrhotic events were found in 20 of total 57 IgG4-SC, 15 of 36 PSC/AIH overlap, and 18 of 55 PSC patients. Serum IgG4 was elevated in 92.65% of IgG4-SC patients with an 86% sensitivity and 98% specificity for diagnosis. IgG4-SC patients had a better treatment response at 6-month and 1-year than PSC/AIH patients, while the latter responded better with steroids than PSC patients. Importantly the adverse outcome-free survival of IgG4-SC patients was reduced, unlike earlier reports, and therefore similar to the PSC/AIH overlap syndrome. Serum IgG and total bilirubin were useful to predict long-term survival of IgG4-SC and PSC/AIH, respectively. In conclusion, serum IgG4 ≧ 1.25 ULN shows an excellent predictability to distinguish IgG4-SC among SC patients. IgG4-SC appears to be immune-mediated inflammatory process, while PSC/AIH overlap more tends to be cholestatic disease.

1. Introduction

Sclerosing cholangitis is an idiopathic cholestatic liver disease, affecting the intra- and/or extra-hepatic bile ducts, usually medium and large-size ducts. There are three clinical variants including IgG4-related sclerosing cholangitis (IgG4-SC), PSC/AIH overlap and Primary Sclerosing Cholangitis (PSC). There have been extensive efforts to define their pathogenesis, genetics, clinical and immunologic characteristics [1–6]. Several large cohorts of IgG4-related diseases have been published [7–9], but there is considerably less data on the PSC/AIH overlap syndrome [10,11]. The role of IgG4 continues to be of broad interest in autoimmunity [12,13]. Superfically IgG4-SC and PSC/AIH overlap syndrome resemble each other in terms of pathology and clinical symptoms, including cholestasis, elevated serum immunoglobulin levels, cholangiographic changes in bile ducts, lymphoplasmacytic infiltration and steroids treatment responses. The aim of the study herein was to evaluate the clinical course and outcome of IgG4-SC and PSC/AIH overlap syndrome in comparison with a group of "classical" cases of PSC using our large database.

2. Clinical characteristics of patients

2.1. Patient variants

We collected and analyzed data of all patients with IgG4 related sclerosing cholangitis with or without autoimmune pancreatitis, all patients with primary sclerosing cholangitis with or without autoimmune

* Corresponding authors.
E-mail addresses: wqx0221155@126.com (Q. Wang), megershwin@ucdavis.edu (M. Eric Gershwin), maxiongmd@hotmail.com (X. Ma).
[1] These authors contributed equally to this paper.

http://dx.doi.org/10.1016/j.autrev.2017.05.018
1568-9972/

hepatitis and all patients with PSC alone between January 2004 and January 2017 at our teaching Unit at Renji Hospital. 67 Patients were diagnosed with probable or definite IgG4-related disease in the hepatobiliary-pancreatic system initially using the Japan Pancreas Society criteria [14]and confirmed using HISORt criteria [15]. International Consensus Diagnostic Criteria were applied in 2011 [16] and were retrospectively analyzed on all patients going back to study entry in 2004. PSC patients were diagnosed according to the 2009 European Association for the Study of the Liver Clinical Practice Guidelines "Management of cholestatic liver diseases", based on serological findings (cholestatic serum liver test profile; supportive: atypical perinuclear anti-neutrophil cytoplasmic antibody), combined with typical findings of multifocal strictures and dilatations on magnetic resonance cholangiopancreaticography and by exclusion of known causes for Secondary Sclerosing Cholangitis [17,18]. The diagnosis of PSC/AIH overlap syndrome [19] was established when patients met both the criteria of PSC and the simplified criteria of AIH [20,21]. We recruited a total of 158 patients in our study, including 91 patients diagnosed with PSC (36 of which were diagnosed with PSC/AIH overlap syndrome). A total of 67 patients were diagnosed with IgG4 related disease in the hepatobiliary-pancreatic system. Patients with solitary AIP (10/67, 14.9%) responded with steroids, with follow-up records indicating no evidence of sclerosing cholangitis and therefore were excluded from our study. Therefore, a total of 57 patients were included in the final IgG4-SC cohort.

2.2. Histologic analysis

Biopsy specimens were assessed by two "blinded" pathologists independently (QM and XYC). Histological features of IgG4 sclerosing cholangitis included lymphoplasmacytic infiltration rich in IgG4 plasma cells, obliterative phlebitis, storiform fibrosis and mild to moderate tissue eosinophilia. Histological features of PSC included periductal fibrosis with inflammation, bile duct proliferation, ductopenia and "onion-skinning" periductal fibrosis. Histological features of AIH included interface hepatitis or piecemeal necrosis, lymphoplasmacytic cell infiltrates, and rosettes of liver cells.

2.3. Treatment regimen and response evaluation

Sclerosing cholangitis patients were treated with ursodeoxycholic acid (UDCA) 12–15 mg/kg per day. Patients with IgG4-SC [8] or PSC/AIH [22] also received steroid treatment after exclusion of any contraindication according to empiric therapy. The steroid treatment protocol was 0.5 mg/kg of prednisolone for 2–4 weeks and then a reduction of the dose by 5 mg per 1–2 weeks, gradually tapered over 2 to 3 months, with regular monitoring of biochemistry and repeated imaging after week 4 and then every 1–3 months. When patients had an inadequate response or relapse as steroids being tapered, combined steroid and one or more drugs (e.g. Azathioprine, Mycophenolate, Bezafibrate, Fenofibrate) were added.

Treatment response was defined [8] as a reduction in absolute values in liver function tests, reduction in serum IgG4 or IgG levels, reduction in size or resolution of mass/stricture/inflammatory change on imaging, reduction or resolution of stricture, and stent removal at endoscopic retrograde cholangiopancreatography.

2.4. Observation endpoints

The endpoints of follow-up were defined using a composite of new occurrence of decompensated liver related events (including gastroesophageal variceal bleeding, ascites, splenomegaly, or hepatic encephalopathy), malignancies, liver transplantation and liver-related death (death from end-stage liver disease, death from liver surgery, death from cholangiosepsis). For those with more than one event, the data were recorded at the time of the first adverse outcome.

2.5. Statistical analysis

Patient characteristics and laboratory values were expressed as mean ± standard deviation. Continuous statistics were compared using Mann-Whitney tests, and categorical data by the Fisher's exact test. Receiver operating characteristic (ROC) analysis was performed to determine the cutoffs of continuous data and to estimate the sensitivity and specificity associated with cutoffs. Survival rate was analyzed using the Kaplan-Meier curve and log-rank test. Statistical analysis was performed using the statistical package of SPSS 19.0 (SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

3. Clinical features

3.1. Demographic and clinical features at presentation

A total of 148 patients (51.4% male, 44.6 years old on average) with well-documented data were included in this retrospective study, comprising 57 IgG4-SC, 36 PSC/AIH overlap and 55 PSC patients. Patients with PSC/AIH overlap syndrome and PSC alone were diagnosed younger (mean ± SD, 41.6 ± 12.3 in PSC/AIH, 42.3 ± 14.7 in PSC), in contrast to IgG4-SC patients (mean ± SD, 49.4 ± 16.7) (Table 1). There was a mean follow-up from diagnosis until reaching an endpoint or date of our last follow-up, of 23.1 months (range 3–60 months) in IgG4-SC patients, 23.7 months (range 2–84 months) and 19.5 months (range 1–66 months) in PSC/AIH overlap and PSC alone patients respectively. We observed no gender difference among three groups, while IgG4-SC and PSC were slightly male predominance (57.9% and 50.9% respectively, compared with 41.7% of PSC/AIH overlap patients).

In our 57 patients with IgG4-SC, the majority 50 (87.7%) patients were diagnosed with IgG4-related sclerosing cholangitis solitary or with AIP (59.6% and 28.1%, respectively), 3(5.3%) IgG4-SC with IgG4-related hepatopathy [23], and 4 (7.0%) patients had IgG4-SC/AIH overlap syndrome. All patients concomitant with AIP in our study had Type 1 AIP.

Among the total 91 PSC/AIH overlap and PSC patients, 52 (57.8%) patients were diagnosed with large duct PSC, 3 (3.3%) small duct PSC, and 36 (39.6%) patients with PSC/AIH overlap syndrome. Concomitant inflammatory bowel disease (IBD) was present in 18 (19.8%) patients, the majority (16/91 (17.6%)) suffered from ulcerative colitis. Ulcerative colitis was diagnosed before PSC in 55.6% of PSC patients and 62.5% of PSC/AIH patients. Two patients were diagnosed with Crohn disease, one was diagnosed at 2004 and 10 years later diagnosed with PSC, the other one's diagnosis was confirmed at 2013 and after 2 years with PSC/AIH overlap.

20 (35.1%) out of 57 IgG4-SC patients had cirrhosis related events at study entrance, including 12 patients with abdominal imaging proven cirrhosis, 15 patients with ascites, 6 patients with portal hypertension, 13 with splenomegaly and moreover, 13 patients had more than one events. Among the PSC/AIH overlap patients, 15 (41.7%) patients were diagnosed concomitant with liver related events at presentation and all 9 patients with splenomegaly had other events. The numbers of overlap patients presented with imaging proven cirrhosis, ascites, and portal hypertension were 7, 11, 3, respectively. 50% (9/18) of PSC patients, in contrast, had more than one adverse events among the ones who presented with ascites. The numbers of PSC patients with imaging proven cirrhosis, portal hypertension and splenomegaly were 10, 6 and 12, respectively.

When we retrospectively analyzed the clinical data of patients at study entrance, there were no significant differences between PSC/AIH and PSC alone in terms of gender ratio, age, concomitant inflammatory bowel disease (25% vs. 18.2%), splenomegaly, portal hypertension, cirrhosis at diagnosis. However, more PSC/AIH patients had ascites at onset than PSC patients (30.6% vs. 12.7%, $p = 0.037$).

Table 1 summarizes the patient demographic and biochemical characteristics. Overall, all three group manifested typical cholestatic parameters, while AST levels in PSC/AIH overlap patients were higher than