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IgG4 Associated Cholangitis

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Abstract

IgG4-related disease (IgG4-RD) is a systemic inflammatory disease characterized by an infiltration of lymphoplasmacytic enriched IgG4-positive plasma cells, variable degrees of fibrosis and mass forming lesions. Previously, this disorder was known as IgG4 multi-organ lymphoproliferative syndrome (IgG4 MOSLP), IgG4 sclerosing disease, or IgG4-related systemic plasmocytic syndrome (SIPS). The most common clinical manifestations are parotid inflammation, lymphadenopathy and autoimmune pancreatitis.

Keywords: IgG4; Autoimmune; Allergic reaction

Abbreviations

AIP: Autoimmune Pancreatitis; IgG4: Immunoglobulin G4

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a systemic inflammatory disease characterized by an infiltration of lymphoplasmacytic-enriched IgG4-positive plasma cells, variable degrees of fibrosis, and mass forming lesions. Formerly, this condition was known as IgG4 multi-organ lymphoproliferative syndrome (IgG4 MOSLP), IgG4 sclerosing disease, or IgG4-related systemic plasmocytic syndrome (SIPS) [1]. The most common clinical manifestations are lymphadenopathy, and autoimmune pancreatitis and parotid inflammation.

Autoimmune pancreatitis is the entity from the IgG4-RD spectrum that has been most studied. In 1984, Montefusco et al. [2] described a series of patients with pancreatitis with extrapancreatic involvement, with predominantly primary sclerosing cholangitis (PSC)-like features. These patients met criteria for PSC, but had a better prognosis, responding to corticosteroids. In 1999, Erkelens et al. [3] demonstrated a good response to corticosteroid therapy in patients with sclerosing cholangitis, and an autoimmune basis was considered in this type of biliary disease. When a new entity is described, several names are proposed, depending on the reporting author. Some of these names include inflammatory pseudotumor from sclerosing cholangitis, lymphoplasmacytic-sclerosing pancreatitis with cholangitis, and IgG4-related lymphoplasmacytic-sclerosing cholangitis [4,5]. It wasn't until 2007, however, when Bjornsoon et al. [6] suggested this condition be named IgG4-associated cholangitis (IAC), began being studied as a single disease. IAC is a recently defined disease that frequently involves extrahepatic ducts that usually respond to corticosteroids. It is characterized by IgG4-positive lymphoplasmacytic infiltration of the biliary tract, which shares clinical, biochemical, and radiologic features with PSC [7].

IAC forms part of sclerosing cholangitis group of diseases. Sclerosing cholangitis of unknown etiology is called PSC. PSC is typically diagnosed between the ages of 30 and 40 years and is frequently associated with inflammatory bowel disease [7]. In contrast to PSC, IAC is not usually associated with inflammatory bowel disease, affects elderly men above the age of 60, and responds to immunosuppressive treatment. There are no data on prevalence in the general population for IAC. Takikawa et al. [8] analyzed 388 patients with PSC in Japan and concluded that 28 (7%) patients had PSC associated with autoimmune pancreatitis (AIP). Mendes et al. [9] reported on the prevalence of IAC among patients presenting PSC and found that approximately 7% to 9% of patients presenting with PSC had features of IAC.

Pathogenesis

Pathophysiologic mechanisms underlying IAC are poorly understood. Clinical features such as hypergammaglobulinemia, increased levels of IgG4, and response to corticosteroids suggest an autoimmune mechanism plays a part in the disease. Potentially initiating mechanisms include bacterial infection and molecular mimicry in a genetically predisposed individual. Antibodies against carbonic anhydrase II and lactoferrin have been frequently detected in AIP [10]. Immune complex deposition has also been found in pancreas, kidneys, and other organs with IgG4-RD [11]. Molecular mimicry between Helicobacter pylori (H pylori) and constituents of pancreatic and biliary cells have been described, suggesting that gastric H pylori infection may trigger AIP through antibody cross-reactivity in predisposed persons [12]. Predisposed individuals in Japanese populations include persons with HLA serotypes DRB1 0405 and DQB1

0401 who have an increased susceptibility to IgG4-related disease [13].

Unlike autoimmune diseases presenting primarily in young women, the majority of patients with IAC are men over the age of 60. In patients with AIP, high levels of IgE have been demonstrated, and excellent responses to corticosteroids have also been observed in allergic disorders, suggesting a possible alternative mechanism for IgG4-RD [14]. Allergic disorders are characterized by T helper 2 (Th2) lymphocyte responses mediated by interleukin (IL)-4, IL-5, and IL-13.

Studies have shown elevated levels of IL-4, IL-5, IL-13, and IL-10 in patients with IAC compared to samples from disease-control patients with PSC or primary biliary cirrhosis with normal levels of IFN-gamma [15]. This suggests a possible allergic reaction, wherein interleukins may direct B lymphocytes to produce IgG4 [16]. However, no specific antigen has been convincingly identified in these patients.

Typically, IgG4 is the least frequently found subclass from the total pool of IgG levels, accounting for less than 5% [17]. IgG4 varies greatly among healthy individuals, generally ranging from 10 µg/mL to 1.4 mg/mL [18]. Elevated IgG4 titers are found in both allergic (asthma and eczema) and autoimmune diseases. Elevated serum IgG4 is a typical diagnostic feature of IAC. It is uncertain if IgG4 is primarily expressed in IgG4-RD or if it is overexpressed secondarily in response to an unknown primary inflammatory event. IgG4 clones are found in tissue, peripheral blood, and active disease, with a decrease in levels after corticosteroids. IgG4 is primarily controlled by Th2 that releases IL-10. In IgG4-related diseases, there is an upregulation of Th2, leading to excessive production of anti-inflammatory cytokines such as IL-10, generating an expansion of IgG4-producing plasma cells [19].

Clinical Presentation

With the advancement of better radiological imaging, IgG4-RD is usually found incidentally after imaging is done. IAC is the most common extra-pancreatic manifestation of type 1 AIP and may affect over 70 % of these patients [20]. Patients with pancreatic disease may present with steatorrhea and new-onset diabetes mellitus.

IAC presents primarily in men over the age of 60, and obstructive jaundice is the most common presenting symptom [21]. In a cohort of 53 patients with IAC, the mean patient age was 62 years (range, 14-85 y) and 44 (83%) were older than age 50. The majority of patients were men (45, 85%). Clinical features on presentation included obstructive jaundice in 41 (77%), weight loss in 27 (51%), steatorrhea in 8 (15%), new-onset diabetes mellitus in 4 (8%), and abdominal pain in 14 patients (26%) [22]. Nakazawa et al. [23] directly compared clinical presentation between PSC and IAC and found that obstructive jaundice occurred more abruptly in IAC patients (75%) than in classic PSC patients (4%).

Diagnosis

Imaging

Unlike AIP, in which typical pancreatic imaging features are described, biliary strictures in IAC do not have any highly specific diagnostic features. However, clinical clues to the diagnosis of IAC include proximal bile duct or intrahepatic strictures in a patient with a pancreatic mass and multifocal biliary strictures [22] Nishino et al. [24] identified more segmental strictures and strictures of distal bile ducts in IAC than in PSC patients in whom band-like strictures with a beaded appearance are predominant. Naitoh et al. [25] retrospectively evaluated ultrasonographic findings in [23] patients with IAC and found that a bile duct wall thickness exceeding 0.8 mm in non-strictured regions was highly suggestive of IAC. Imaging features of patients with AIP described extra-pancreatic bile duct changes in 14 of 16 (88%) patients, with intrahepatic strictures in 2 (13%), distal bile duct strictures in 9 (56%), and proximal bile duct strictures in 2 (13%), suggesting that strictures can be seen throughout the entire biliary tree [26]. One characteristic feature that strictures respond to is corticosteroids.

Immunoserology

Increased serum IgG4 is characteristic of IAC; however it is not diagnostic of the disease. Ghazale et al. [22] reported a sensitivity of serum IgG4 for IAC of 74%, which is comparable to AIP. Mendes et al. [9] found that 9% of PSC patients had an increased IgG4 level. Moreover, Hirano et al. [26] showed that patients with IAC did not have increased IgG4 levels at time of diagnosis but developed high levels on follow up. Thus, elevated serum IgG4 levels are considered characteristic, but should not be used alone for the diagnosis of IAC.

Histopathology

Endoscopic biopsies and brush cytology are usually performed before giving corticosteroids. Consensus for histology highly suggestive of IgG4-RD is made when 3 histologic features are seen: 1) dense lymphoplasmacytic infiltrates with a IgG4 +/ IgG+plasma cell ratio >40%, 2) focal fibrosis in a storiform pattern, and 3) obliterative phlebitis [27]. The sensitivity and specificity of IgG4 immunostaining in bile duct biopsies have not been established. In IgG4-related autoimmune pancreatitis, the finding of more than 30 IgG4 plasma cells per high-power field (hpf) has been reported to have acceptable specificity [28]. However, the appropriate normal values may vary from organ to organ. The consensus statement on the pathology of IgG4-related disease suggests that more than 50 IgG4+plasma cells/hpf in a bile duct from a surgical specimen are highly suggestive of IgG4-RD [29]. On the other hand, more than 10 IgG4+plasma cells/hpf in a bile duct biopsy specimen represents probable histologic features of IgG4-RD [22,30].

Typical histologic findings include dense lymphoplasmacytic infiltration of the bile duct wall with transmural fibrosis and

phlebitis in the periportal areas. While lymphocytes and plasma cells predominate, eosinophils can be numerous and are occasionally numerically dominant [31]. In contrast to PSC, where mucosal erosions and neutrophilic inflammation are usually present, the biliary epithelium is usually intact without neutrophilic inflammation [21,27].

Bile IgG4

Other diagnostic methods are under evaluation. Bile IgG4 levels have been shown to be markedly elevated in patients with IAC compared with patients with other biliary disorders. This study included 67 patients with biliary disease who had bile collected during cholangiography. Further studies are needed to validate this approach [32].

Diagnostic Criteria

HISORt criteria for AIP have been proposed to facilitate diagnosis. They involve findings in histology, imaging, serology, other organ involvement, and response to therapy [33].

Parallel to HISORt for AIP, HISORt criteria for IAC have also been proposed [22]. This is a valuable tool in clinical practice, as it allows a practical approach for diagnosis and management; however, it cannot completely exclude other biliary disorders. The criteria are summarized in Table 1. The diagnosis is established when there is a typical histology or when classic images are found in conjunction with increased serum levels of IgG4 [34].

Table 1: HISORt Criteria for IAC [22].

Characteristic	Criteria
Histology of the biliary duct	Lymphoplasmacytic infiltrate with >10 IgG4-positive cells/hpf within and around bile ducts with associated obliterative phlebitis and storiform fibrosis
Imaging	One or more strictures involving intrahepatic, proximal extrahepatic, or intrapancreatic bile ducts Fleeting/migrating biliary strictures
Serology	Increased levels of serum IgG4
Other organ involvement	Other organ involvement Pancreas: classic features of AIP: focal pancreatic mass or enlargement, focal pancreatic duct stricture, pancreatic atrophy Mediastinal lymphadenopathy Parotid/lacrimal gland involvement Retroperitoneal fibrosis
Response to corticosteroids	Normalization of liver enzyme levels or resolution of stricture

Treatment

There are no randomized trials comparing different approaches of therapy for IAC; however, responsiveness to corticosteroids makes them first-line therapy. The initial goal of treatment is to control the symptoms (usually obstructive jaundice). In general, steroid treatment offers a quick resolution of symptoms; however, biliary stenting is also performed in some patients. There are no randomized trials comparing both approaches. If stents are placed at presentation, endoscopic retrograde cholangiopancreatography should be repeated 6 to 8 weeks after initiating treatment in order to evaluate the status of the strictures. If the strictures are improved, the stents should be removed.

There are no data on what the duration of treatment of IAC should be. Recommendations for the corticosteroid regimen and duration of use are highly variable.

Prednisolone at a dose of 0.6 mg/kg of body weight per day for 2 to 4 weeks, with a tapering over a period of 3 to 6 months to 5 mg/day, and continuing at a maintenance dose between 2.5 and 5.0 mg/day for up to 3 years is recommended by a consensus statement from Japan [35,36]. The Mayo Clinic Rochester, MN protocol is to treat with 40 mg/day of prednisone for 4 weeks, followed by a 5 mg/wk taper, for a total of 11 weeks of treatment [22]. Discontinuing glucocorticoids within 3 months is another approach considered, as complete long-term remission after 3 months of treatment has been reported, especially in disease with primarily distal involvement. However, the extent of disease may affect the long-term response.

The measurement of IgG4 serum concentration as an indicator of disease activity is controversial, and it may not indicate relapse of the disease [36]. A disease responder index was proposed by the Organizing Committee of the International IgG4-related Disease Symposium to detect changes in disease activity and to quantify objectively the treatment response by providing standardized outcome measures. It evaluates the activity within a specific organ system by the physician who gives a score for symptomatic patient, urgent disease, or permanent damage [37].

Azathioprine, mycophenolate mofetil, methotrexate, and rituximab are used as glucocorticoid-sparing agents or remission-maintenance drugs [6].

Biliary stents can be placed to relieve symptoms from obstructive jaundice. Pretreatment biliary stenting leads to quicker resolution of symptoms; however, resolution of jaundice solely with corticosteroid treatment is seen.

Prognosis

IAC prognosis seems to be more favorable than classic PSC; however, since it is a relatively new entity limited data exists on the its clinical course and prognosis , and further long-term follow-up studies are needed [6].

Cholangiocarcinoma is a complication of PSC that develops in up to 10% to 30% of patients. But development of cholangiocarcinoma has not been reported to occur in patients with IAC, suggesting a different pathophysiologic mechanism [38].

Conclusion

IAC is a recently described disease with a largely unknown pathogenesis. It presents more in elderly men, with jaundice as the initial symptom. In the majority of cases, pancreatic involvement is present, and the diagnosis is supported by high levels of IgG4 in serum and lymphoplasmacytic infiltration on histology of the affected bile ducts. HISORt criteria are useful for prompt diagnosis. Accurate and early diagnosis is important, as patients usually respond to steroids. Unrevealing the pathophysiologic background of IAC remains key for developing novel diagnostic tests and therapy.

References

1. Nizar AH, Toubi E (2015) IgG4-related disease: case report and literature review. Auto- immunity highlights 6: 7-15.
2. Montefusco PP, Geiss AC, Bronzo RL, Randall S, Kahn E, et al. (1948) Sclerosing cholangitis, chronic pancreatitis, and Sjogren's syndrome: a syndrome complex. American journal of surgery 147: 822-826.
3. Erkelens GW, Vleggaar FP, Lesterhuis W, van Buuren HR, van der Werf SD (1999) Sclerosing pancreato-cholangitis responsive to steroid therapy. Lancet 354: 43-44.
4. Jafri SZ, Bree RL, Agha FP, Schwab RE (1983) Inflammatory pseudotumor from sclerosing cholangitis. Journal of computer assisted tomography 7: 902-904.
5. Kawaguchi K, Koike M, Tsuruta K, Okamoto A, Tabata I, et al. (1991) Lymphoplasmacytic sclerosing pancreatitis with cholangitis: a variant of primary sclerosing cholangitis extensively involving pancreas. Human pathology 22: 387-395.
6. Bjornsson E, Chari ST, Smyrk TC, Lindor K (2007) Immunoglobulin G4 associated cholangitis: description of an emerging clinical entity based on review of the literature. Hepatology 45: 1547-1554.
7. Alderlieste YA, van den Elzen BD, Rauws EA, Beuers U (2009) Immunoglobulin G4-associated cholangitis: one variant of immunoglobulin G4-related systemic disease. Digestion 79: 220-228.
8. Takikawa H, Takamori Y, Tanaka A, Kurihara H, Nakanuma Y (2004) Analysis of 388 cases of primary sclerosing cholangitis in Japan; Presence of a subgroup without pancreatic involvement in older patients. Hep res 29: 153-159.
9. Mendes FD, Jorgensen R, Keach J, Katzmann JA, Smyrk T, et al. (2006) Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis. Am j gastroenterol 101: 2070-2075.
10. Frulloni L, Lunardi C, Simone R, Dolcino M, Scattolini C, et al. (2009) Identification of a novel antibody associated with autoimmune pancreatitis. The New England journal of medicine 361: 2135-2142.
11. Zen Y, Nakanuma Y (2011) Pathogenesis of IgG4-related disease. Curr Opin Rheumatol 23: 114-118.
12. Guarneri F, Guarneri C, Benvenga S (2005) Helicobacter pylori and autoimmune pancreatitis: role of carbonic anhydrase via molecular mimicry? J Cell Mol Med 9: 741-744.
13. Kawa S, Ota M, Yoshizawa K, Horiuchi A, Hamano H, et al. (2002) HLA DRB10405-DQB10401 haplotype is associated with autoimmune pancreatitis in the Japanese population. Gastroenterology 122: 1264-1269.
14. Umemura T, Zen Y, Hamano H, Kawa S, Nakanuma Y, et al. (2007) Immunoglobin G4-hepatopathy: association of immunoglobin G4-bearing plasma cells in liver with autoimmune pancreatitis. Hepatology 46: 463-471.
15. Kamisawa T, Okamoto A (2008) IgG4-related sclerosing disease. World J Gastroenterol 14: 3948-3955.
16. Zen Y, Fujii T, Harada K, Kawano M, Yamada K, et al. (2007) Th2 and regulatory immune reactions are increased in immunoglobin G4-related sclerosing pancreatitis and cholangitis. Hepatology 45: 1538-1546.
17. Engelmann R, Brandt J, Eggert M, Karberg K, Krause A, et al. (2008) IgG1 and IgG4 are the predominant subclasses among auto-antibodies against two citrullinated antigens in RA. Rheumatology 47: 1489-1492.
18. Chen G, Cheuk W, Chan JK (2010) [IgG4-related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity]. Adv Anat Pathol 39: 851-868.
19. Okazaki K, Uchida K, Koyabu M, Miyoshi H, Takaoka M (2011) Recent advances in the concept and diagnosis of autoimmune pancreatitis and IgG4-related disease. J Gastroenterol 46: 277-288.
20. Khosroshahi A, Stone JH (2011) A clinical overview of IgG4-related systemic disease. Curr Opin Rheumatol 23: 57-66.
21. Novotny I, Dite P, Trna J, Lata J, Husova L, et al. (2012) Immunoglobulin G4-related cholangitis: a variant of IgG4-related systemic disease. Dig Dis 30: 216-219.
22. Ghazale A, Chari ST, Zhang L, Smyrk TC, Takahashi N, et al. (2008) Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. Gastroenterology 134: 706-715.
23. Nakazawa T, Ohara H, Sano H, Ando T, Aoki S, et al. (2005) Clinical differences between primary sclerosing cholangitis and sclerosing cholangitis with autoimmune pancreatitis. Pancreas 30: 20-25.
24. Nishino T, Oyama H, Hashimoto E, Toki F, Oi I, et al. (2007) Clinicopathological differentiation between sclerosing cholangitis with autoimmune pancreatitis and primary sclerosing cholangitis. Journal Gastroenterol 42: 550-559.
25. Naitoh I, Nakazawa T, Ohara H, Ando T, Hayashi K, et al. (2009) Endoscopic transpapillary intraductal ultrasonography and biopsy in the diagnosis of IgG4-related sclerosing cholangitis. Journal of gastroenterology 44: 1147-1155.
26. Hirano K, Shiratori Y, Komatsu Y, Yamamoto N, Sasahira N, et al. (2003) Involvement of the biliary system in autoimmune

pancreatitis: a follow-up study. Clin Gastroenterol Hepatol 1:453-464.

27. Oh HC, Kim JG, Kim JW, Lee KS, Kim MK, et al. (2008) Early bile duct cancer in a background of sclerosing cholangitis and autoimmune pancreatitis. Internal medicine 47: 2025-2028.
28. Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, et al. (2003) A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol 38: 982-984.
29. Deshpande V, Zen Y, Chan JK, et al. (2012) Consensus statement on the pathology of IgG4-related disease. Mod Pathol 25: 1181-1192.
30. Zen Y, Fujii T, Sato Y, Masuda S, Nakanuma Y (2007) Pathological classification of hepatic inflammatory pseudotumor with respect to IgG4-related disease. Mod pathol 20: 884-894.
31. Zen Y, Harada K, Sasaki M, Sato Y, Tsuneyama K, et al. (2004) IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? Am J surg pathol 28: 1193-1203.
32. Vosskuhl K, Negm AA, Framke T, Weismüller T, Manns MP, et al. (2012) Measurement of IgG4 in bile: a new approach for the diagnosis of IgG4-associated cholangiopathy. Endoscopy 44: 48-52.
33. Chari ST, Smyrk TC, Levy MJ, Topazian, Takahashi N, et al. (2006) Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. Clin Gastroenterol Hepatol 4 :1010-1016.
34. Silveira MG (2013) IgG4-associated cholangitis. Clin Liver Dis 17: 255-268.
35. Kamisawa T, Shimosegawa T, Okazaki K, Nishino T, Watanabe H, et al. (2009) Standard steroid treatment for autoimmune pancreatitis. Gut 58: 1504-1507.
36. Kamisawa T, Okazaki K, Kawa S, Shimosegawa T, Tanaka M (2010) Japanese consensus guidelines for management of autoimmune pancreatitis: III. Treatment and prognosis of AIP. J Gastroenterol 45: 471-477.
37. Carruthers MN, Stone JH, Deshpande V, Khosroshahi A (2012) Development of an IgG4-RD Responder Index. International journal of rheumatology : 259408.
38. Bjornsson E, Kilander A, Olsson R (1999) CA 19-9 and CEA are unreliable markers for cholangiocarcinoma in patients with primary sclerosing cholangitis. Liver 19: 501-508.