IgG4-related Disease and the Liver

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KEYWORDS

• IgG4-related disease • IgG4 • IgG4-related sclerosing cholangitis
• Primary sclerosing cholangitis • Autoimmune pancreatitis

KEY POINTS

- IgG4-related disease (IgG4-RD) can present in the liver as cholangitis with or without tumefactive lesions. IgG4-RD affects a wide range of ages and both genders, but most commonly middle-aged to elderly men.
- Although imperfect, histology currently represents the single best gold standard for diagnosis of IgG4-RD. Classic histologic appearance is storiform fibrosis, obliterative phlebitis, and an IgG4-enriched lymphoplasmacytic infiltrate.
- An enriched $IgG4^+$ lymphoplasmacytic infiltrate (IgG4:IgG ratio >0.4) supports, but is not sufficient for, a diagnosis. An interdisciplinary approach integrating pathologic features, imaging, and clinical history is necessary for diagnosis.
- IgG4-related sclerosing cholangitis (IgG4-SC) is an uncommon disease and a wide differential diagnosis should be considered, one that includes primary sclerosing cholangitis (PSC), bile duct carcinoma, intrahepatic cholangiocarcinoma, inflammatory myofibroblastic tumor (IMT), and lymphoproliferative disorders.
- Recent evidence suggests that IgG4-RD is associated with unique T-cell and B-cell oligoclonal populations that may help with diagnosis of IgG4-RD and uncover unique therapeutic targets.

INTRODUCTION

IgG4-RD is a recently described entity that generally presents with multifocal mass-forming lesions that are frequently concerning for cancer.[1,2] Like sarcoidosis and granulomatosis with polyangiitis (GPA) (formerly Wegener granulomatosis), this protean disease can affect 1 or more organs, synchronously or metachronously, and may present differently from patient to patient. Previously, the manifestations in each organ system were classified as unrelated diseases (eg, type 1 autoimmune

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pancreatitis, Riedel thyroiditis, Küttner tumor [submandibular gland], and Mikulicz disease [salivary and lacrimal glands]).

The realization that patients often had lesions in multiple organs and expressed high levels of IgG4,[3] however, led to unification of these diseases under the IgG4-RD umbrella.[4,5] Currently, IgG4-RD is primarily diagnosed based on its characteristic histologic appearance notable for storiform fibrosis, obliterative phlebitis, and a lymphoplasmacytic infiltrate.[6] This lymphocytic infiltrate contains predominantly $CD4^+$ T cells but is especially remarkable for an increased number of plasma cells class-switched to express the IgG4 antibody isotype, with a high ratio of $IgG4^+$ to IgG^+ plasma cells. Most patients respond to steroids or rituximab in the short term.[7,8] Relapse is common, however, and better therapies are needed.

This review focuses on the diagnosis of IgG4-RD in the hepatobiliary system — commonly termed, *IgG4-SC*.[9–11] Diagnosing IgG4-SC can be especially challenging for the practicing pathologist because its lesions can mimic bile duct carcinoma, PSC, and other entities. Prior to the recognition of IgG4-SC, a majority of these cases were labeled as PSC. For example, retrospective review of a case published as PSC in the "Case Records of the Massachusetts General Hospital" series in *The New England Journal of Medicine* in 1982 reveals that the overall findings are more in keeping with IgG4-SC (**Fig. 1**).[12]

Further adding to the diagnostic difficulty is that bile duct biopsies are often small and may contain crush artifact, and needle biopsies from the liver may not show classic histologic features. Because biopsies may miss areas with neoplastic cells, the absence of malignant cells on a slide does not rule out cancer in a fibrotic specimen. Additionally, demographic features of age and gender provide little assistance in diagnosis. IgG4-RD generally presents in middle-aged to elderly men, which is a common presentation for bile duct carcinoma. Importantly, although IgG4-RD isolated to the hepatobiliary system occurs, it usually presents with other organ manifestations. A history of IgG4-RD, pancreatitis, sialadenitis, tubulointerstitial nephritis, dacryoadenitis, or retroperitoneal fibrosis should raise the possibility of IgG4-RD. Given that it generally portends a good prognosis with immunosuppressive therapy and can spare

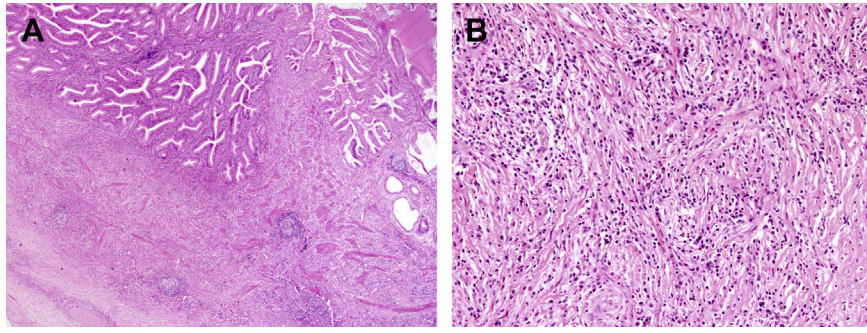

Fig. 1. The gallbladder (*A*, hematoxylin-eosin, original magnification ×40) shows an extramural fibroinflammatory infiltrate with storiform pattern of fibrosis (*B*, hematoxylin-eosin, original magnification ×100). Obliterative phlebitis was observed (not shown). An immunohistochemical stain for IgG4 performed retrospectively showed greater than 100 $IgG4^+$ plasma cells per HPF and an IgG4:IgG ratio greater than 40%. Collectively, the evidence supports a diagnosis of IgG4-SC. In the past, most examples of IgG4-SC were diagnosed PSC, as in this example.