IgG4-Related Sclerosing Cholangitis: A Medical Disease That Should Be Recognized by Hepatopancreatobiliary Surgeons - Postprint

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Abstract

IgG4-related disease (IRD) is an autoimmune disease involving multiple organ systems that has emerged as a recognized entity only within the past decade, characterized by elevated serum IgG4, storiform fibrosis, and dense infiltration of IgG4-positive plasma cells. The biliary tract represents one of the frequently involved organs in IRD. IgG4-related sclerosing cholangitis (IRSC) constitutes the clinical manifestation of IRD in the biliary system. IRSC frequently exhibits clinical presentations analogous to pancreatobiliary malignancies, including focal thickening of the bile duct wall, bile duct dilation, and obstructive jaundice. IRSC is steroid-responsive with a favorable prognosis; concomitant malignant tumors are exceedingly rare, and surgical intervention is unnecessary in the vast majority of cases. Nevertheless, in recent years, the author has continued to encounter cases in clinical practice where surgical treatment was undertaken for "bile duct stricture and obstructive jaundice," with postoperative pathological confirmation of IRSC. Retrospective review of the diagnostic and therapeutic course in these cases reveals that IRSC was seldom considered in the preoperative differential diagnosis. Conversely, clinical scenarios are also encountered where preoperative elevation of serum IgG4 leads to initial misdiagnosis of IRSC, resulting in missed optimal surgical windows, with postoperative pathology ultimately confirming cholangiocarcinoma. Therefore, enhancing awareness and understanding of IRSC, particularly among hepatopancreatobiliary surgeons, is of paramount clinical importance.

Full Text

IgG4-Related Sclerosing Cholangitis: An Internal Medicine Disease That Hepatobiliary-Pancreatic Surgeons Should Take Seriously

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Abstract

IgG4-related disease (IRD) is a newly defined multi-organ autoimmune disease recognized only within the past decade, characterized by elevated serum IgG4, storiform fibrosis, and massive infiltration of IgG4-positive plasma cells. The biliary tract is one of the most commonly involved organs, and IgG4-related sclerosing cholangitis (IRSC) represents the clinical manifestation of IRD in the biliary system. IRSC often presents with localized bile duct wall thickening, ductal dilation, and obstructive jaundice—clinical features that closely mimic hepatobiliary-pancreatic malignancies. While IRSC is highly responsive to steroids with favorable prognosis and rarely requires surgical intervention, the authors continue to encounter cases in clinical practice where patients undergo surgery for "bile duct stricture and obstructive jaundice," only to have postoperative pathology confirm IRSC. Review of these cases reveals that IRSC was seldom considered preoperatively. Conversely, some patients with elevated serum IgG4 are initially misdiagnosed with IRSC, missing the optimal window for surgical treatment, only to have postoperative pathology reveal cholangiocarcinoma. Therefore, strengthening education about IRSC, particularly deepening hepatobiliary-pancreatic surgeons' understanding of this condition, holds significant clinical importance.

Keywords: IgG4-related disease; IgG4-related sclerosing cholangitis; Biliary-pancreatic malignancy; Obstructive jaundice

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IgG4-related disease (IRD) is a systemic autoimmune condition recognized in this century, characterized by elevated serum IgG4, storiform fibrosis in affected tissues, and massive infiltration of IgG4-positive cells that can involve multiple organ systems [1]. Historically known by various names, this disease category was formally designated as IRD in 2011 [2]. The biliary tract represents a frequently involved organ system, and IgG4-related sclerosing cholangitis (IRSC) constitutes the clinical manifestation of IRD in the bile ducts. IRSC is a

medical condition highly responsive to steroid therapy with favorable outcomes that rarely necessitates surgical intervention. However, because IRSC predominantly affects elderly men—unlike most autoimmune diseases—and presents with bile duct wall thickening, ductal dilation, and obstructive jaundice mimicking biliary-pancreatic malignancies, misdiagnosis and inappropriate surgical treatment occur clinically. Furthermore, since elevated serum IgG4 is not specific to IRSC (5–22% of biliary-pancreatic malignancies also show elevated IgG4), some malignancies are misdiagnosed as IRSC, resulting in missed surgical opportunities. Although IRSC is fundamentally a medical disease, its frequent need for differentiation from biliary-pancreatic malignancies makes enhanced education and particularly deeper understanding among hepatobiliary-pancreatic surgeons crucial for appropriate management. This article reviews the history of IRD and IRSC, clinical manifestations, diagnostic criteria and classification, imaging features distinguishing IRSC from cholangiocarcinoma, and the relationship between IgG4 and biliary-pancreatic malignancies.

Historical Development

In 1995, Japanese scholar Yoshida et al. described a case of pancreatitis associated with hypergammaglobulinemia that responded to steroid therapy, proposing the concept of autoimmune pancreatitis (AIP) [3]. In 2001, Hamano et al. analyzed serum IgG and its subclasses in 20 such patients and found significantly elevated IgG4, establishing a close relationship between this pancreatitis subtype and IgG4 [4]. Kamisawa et al. subsequently examined pancreaticoduodenectomy specimens from 8 AIP patients in 2003, revealing massive IgG4-positive plasma cell infiltration not only in the pancreas but also in peripancreatic tissues, gallbladder, bile ducts, gastric mucosa, and lymph nodes. They proposed that AIP represented merely one clinical manifestation of a broader IgG4-related autoimmune disease affecting multiple organ systems [5]. These investigators also observed that AIP patients frequently developed sclerosing cholangitis that improved with steroid therapy, with pathology confirming abundant IgG4-positive plasma cell infiltration in the bile ducts. They termed this condition autoimmune pancreatitis-related sclerosing cholangitis (AIP-SC) [6]. In 2007, Björnsson et al. formally proposed the term "IgG4-related cholangitis" through literature review, recognizing it as a novel sclerosing cholangitis entity distinct from primary sclerosing cholangitis [7]. As increasing numbers of previously unclassifiable fibroinflammatory conditions with steroid responsiveness were linked to IgG4, a surge of new disease names prefixed with "IgG4" emerged [8]. Takahashi et al. formally introduced the concept of IgG4-related disease in 2010 [9], and the 2011 International Symposium on IgG4-Related Disease unified the nomenclature as "IgG4-related disease," acknowledging its potential to affect virtually any organ system. IRD rapidly became a major focus of academic research and discussion. In 2012, Deshpande et al. proposed pathological diagnostic consensus criteria for IRD [10], while Ohara et al. established clinical consensus guidelines for IRSC [11]. An international multidisciplinary expert panel published consensus guidance on IRD management in 2015 [12], and *The*

New England Journal of Medicine and *The Lancet* featured comprehensive reviews on IRD in 2012 and 2015, respectively [1, 8].

2.1 Clinical Manifestations

IRSC predominantly affects men over 60 years of age, with a male-to-female ratio of 4–6:1, distinguishing it from most autoimmune diseases. A 2017 nationwide Japanese survey of 527 IRSC patients represents the largest case series reported internationally [13]. The median age was 66.2 years with a male-to-female ratio of 4.9:1. Common symptoms included jaundice (35%), pruritus (13%), abdominal pain (11%), and cholangitis (10%); notably, 28% of patients were asymptomatic. Serum IgG4 was elevated in 84.4% of cases. Malignancies were identified in 25 patients (4.7%), including 4 cases of cholangiocarcinoma (0.8%) and 21 other cancers (5 lung, 3 gastric, 3 duodenal), indicating that IRSC patients carry a significantly higher malignancy risk than the general elderly population. IRSC frequently coexists with AIP, while isolated IRSC is relatively uncommon, with 87% of patients in this series having concurrent AIP.

In 2014, British investigators reported 115 IRSC patients with AIP, documenting an 11% malignancy rate [14]. Atsushi et al. described 43 cases of isolated IRSC in the same year [15]. This isolated IRSC cohort had a median age of 69.3 years and male-to-female ratio of 3.3:1, with 54% asymptomatic, 22% presenting with jaundice, 20% with pruritus, and 17% with cholangitis; 89.5% had elevated IgG4. Nakazawa et al. reported that 21 of 40 IRSC patients (52.2%) had elevated CA19-9 [16]. The authors also reported clinical data from 72 IRSC patients treated at Peking Union Medical College Hospital between 2004 and 2014 [17]. This cohort had a mean age of 59.8 years and male-to-female ratio of 5.5:1, with 68.1% experiencing abdominal pain and 81.9% jaundice; all patients had concurrent AIP, and no malignancies were identified in this group.

2.2 Diagnostic Criteria and Classification

The Japanese Biliary Association proposed clinical diagnostic criteria for IRSC in 2012 [11, 16]. Diagnosis requires comprehensive evaluation of five aspects: (1) typical imaging showing segmental or diffuse bile duct strictures with wall thickening; (2) serum IgG4 >135 mg/dl; (3) involvement of other organ systems such as AIP, IgG4-related dacryoadenitis, or IgG4-related retroperitoneal fibrosis; (4) characteristic pathological features; and (5) response to diagnostic steroid therapy. Pathological hallmarks include: (a) dense lymphoplasmacytic infiltration; (b) >10 IgG4-positive plasma cells per high-power field (HPF); (c) storiform fibrosis; and (d) obliterative phlebitis. Integration of these factors yields diagnostic categories of definite, probable, and possible. Definite diagnosis requires: (1)+(3); (1)+(2)+(4)a,b; (4)a,b,c; or (4)a,b,d. Probable diagnosis requires: (1)+(2)+(5). Possible diagnosis requires: (1)+(2).

Based on anatomical location, IRSC is classified as: Type 1 (distal bile duct), Type 2a (distal + segmental intrahepatic ducts), Type 2b (distal + diffuse in-

trahepatic ducts), Type 3 (hilar + distal ducts), and Type 4 (hilar ducts). Type 1 is most common (~60%), Type 2 accounts for ~15%, and Types 3 and 4 each represent ~10%. Type 1 IRSC must be distinguished from cholangiocarcinoma, pancreatic cancer, and chronic pancreatitis; Type 2a from primary sclerosing cholangitis; and Types 3 and 4 from hilar cholangiocarcinoma and gallbladder cancer. In 2013, Takahiro et al. proposed a diagnostic algorithm noting that distinguishing Types 3 and 4 IRSC from hilar cholangiocarcinoma is particularly challenging, though ERCP-guided brush cytology, intraductal ultrasonography (IDUS), and higher IgG4 levels facilitate diagnosis [18].

Some investigators have questioned the definition of Type 1 IRSC, suggesting it may represent extrinsic compression of the intrapancreatic bile duct by AIP rather than a distinct IRSC subtype. In 43 isolated IRSC cases, Type 1 comprised only 10% while Types 3 and 4 accounted for 60%—a distribution markedly different from IRSC with concurrent AIP, warranting deeper exploration of the relationship between Type 1 IRSC and AIP [15]. The 2012 diagnostic criteria were established before reports of IRSC coexisting with cholangiocarcinoma emerged. Recent case reports of IRSC with concurrent malignancy necessitate reevaluation of whether (1)+(3) alone constitutes a definite diagnosis, particularly whether AIP with distal bile duct thickening definitively excludes biliary-pancreatic malignancy.

2.3 Treatment and Prognosis

Unlike primary sclerosing cholangitis, IRSC exhibits steroid responsiveness with approximately 90% response rate, though relapse occurs in some patients. Among 438 IRSC patients receiving steroids, 386 (87%) achieved >50% reduction or normalization of alkaline phosphatase, and 377 (90%) showed significant biliary stricture improvement. With a median follow-up of 4.1 years, overall relapse rate was 19%, with 1-, 3-, and 5-year relapse rates of 1.6%, 7.6%, and 16.5%, respectively [13]. In the Peking Union cohort of 72 patients, 57 received steroid therapy with a 2-year relapse rate of 37.2%. Relapse risk correlates with the number of involved bile duct segments and organ systems, and some studies have linked pretreatment IgG4 levels to post-treatment relapse risk [15].

IRSC generally carries a favorable prognosis. In the Japanese cohort of 527 patients, 5- and 10-year survival rates were 94.5% and 81%, respectively [13]. For 43 isolated IRSC cases in Japan, 3-year survival was approximately 90% [15]. However, a prospective UK study of 115 AIP and IRSC patients with median follow-up of 33 months reported initial steroid response rate of 90% but relapse rate of 50%, overall mortality of 10%, malignancy rate of 11% (including 3 biliary-pancreatic tumors), and significantly higher rates of hepatic, pancreatic, pulmonary, and renal dysfunction compared to age-matched controls [14].

2.4 Imaging Features Distinguishing IRSC from Extrahepatic Cholangiocarcinoma

Dimitrios et al. analyzed 152 patients with biliary lesions and found that serum IgG4 and bile duct brush cytology demonstrated poor sensitivity (60%) and specificity (56%) for IRSC, whereas typical CT features showed 75% sensitivity, 89% specificity, and 83% accuracy [19]. Multidetector CT revealing solitary strictures, intraductal masses, and normal pancreas favors cholangiocarcinoma. Arikawa et al. compared multidetector contrast-enhanced CT features between extrahepatic cholangiocarcinoma (16 cases) and IRSC (13 cases) [20]. IRSC involved longer ductal segments, exhibited concentric uniform wall thickening (mostly <3 mm) with patent lumen, while cholangiocarcinoma showed eccentric thickening; IRSC frequently coexisted with pancreatic lesions absent in cholangiocarcinoma. Wall thickness <3 mm and concentric enhancement yielded 76.9% sensitivity, 93.8% specificity, and 86.2% accuracy for distinguishing IRSC from cholangiocarcinoma, while 100% sensitivity, 87.5% specificity, and 93.1% accuracy were achieved for concentric uniform thickening.

In 2016, Yata et al. compared larger cohorts of IRSC (33 cases) and extrahepatic cholangiocarcinoma (39 cases) using multidetector contrast-enhanced CT [21]. No significant difference in wall thickness was observed (P=0.263), though cholangiocarcinoma showed more pronounced proximal ductal dilation (P<0.001). IRSC demonstrated skip lesions absent in cholangiocarcinoma. Multiphasic CT revealed that IRSC predominantly exhibited single-layered contrast enhancement with uniform enhancement and washout, whereas cholangiocarcinoma typically showed double-layered enhancement with heterogeneous patterns, likely reflecting tumor invasion of periductal tissues.

IDUS offers superior evaluation by enabling close-range direct assessment of biliary lesions [22]. IDUS demonstrates that IRSC typically shows concentric symmetric wall thickening with smooth, uniform internal and external echo patterns. Non-strictured bile duct walls are significantly thicker in IRSC than in cholangiocarcinoma. Non-strictured wall thickness >0.8 mm yields 95% sensitivity, 90.9% specificity, and 93.5% accuracy for IRSC diagnosis. However, bile duct biopsy shows dense lymphocytic infiltration in 100% of cases, fibrosis in 82%, abundant IgG4-positive plasma cells in only 18%, and obliterative phlebitis in 0%, indicating poor diagnostic sensitivity and specificity for IRSC, though biopsy remains important for excluding cholangiocarcinoma. PET-CT holds value for systemic assessment of IRD but lacks specific data for distinguishing IRSC from cholangiocarcinoma [23].

3. Relationship Between IgG4 and Biliary-Pancreatic Malignancies

Despite the "IgG4" prefix in IRD and IRSC nomenclature, elevated serum IgG4 and IgG4-positive plasma cell infiltration are not disease-specific. Approximately 5% of pancreatic cancers and 22% of cholangiocarcinomas exhibit elevated serum IgG4 [16], while 17% of pancreatic cancers and 32% of cholangio-

carcinomas show >20 IgG4-positive plasma cells/HPF in tissue [24]. Since IgG4 is induced by T-helper 2 (Th2) cell-related cytokines that promote immune tolerance and suppress anti-tumor immunity, IgG4 may paradoxically correlate with malignancy development and progression. Although the relationship between serum IgG4 and biliary-pancreatic malignancies remains unclear, analysis of 95 postoperative pancreatic cancer specimens revealed significantly more IgG4-positive cells in tumor tissue than in adjacent tissue, with intratumoral IgG4 cell density inversely correlating with prognosis [25]. Miyatani et al. reported similar findings in gastric cancer [26]. Karagiannis et al. demonstrated that melanoma cells secrete Th2 cytokines inducing IgG4-positive plasma cell differentiation, which subsequently suppresses anti-melanoma immune responses, with serum IgG4 levels inversely correlating with melanoma patient prognosis [27, 28].

4. Conclusion

IRD represents a disease category newly defined in this century, with IRSC as its biliary manifestation. Although IRSC clinically mimics biliary-pancreatic malignancies, its steroid responsiveness, rarity of concurrent cholangiocarcinoma, and favorable prognosis render surgical intervention inappropriate. For hepatobiliary-pancreatic surgeons, enhanced awareness of IRSC is crucial to avoid unnecessary operations. The authors recommend the following clinical approaches: (1) Consider IRSC in the differential diagnosis of bile duct strictures and obstructive jaundice; (2) Maintain high suspicion for IRSC when AIP coexists; (3) Recognize that elevated serum IgG4 does not confirm IRSC (false positive rate 10–20%) and normal IgG4 does not exclude it (false negative rate 20–40%); (4) Utilize ERCP, EUS, or IDUS to improve diagnostic accuracy in challenging cases, acknowledging that biopsy has limited sensitivity and specificity for IRSC; (5) Avoid diagnosing IRSC based solely on abundant IgG4-positive plasma cells without other characteristic pathological features; and (6) Remember that IRSC and AIP carry higher malignancy risk than the general population, necessitating vigilant screening to avoid missed diagnoses.

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Note: Figure translations are in progress. See original paper for figures.