RESEARCH ARTICLE

Update on Epidemiology of IgG4-related Disease Involving the Liver and Pancreas

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ABSTRACT

IgG4-related disease (IgG4-RD) is a rare condition characterized by an immune-mediated fibro-inflammation affecting various organs (liver, pancreas, heart, kidney, brain among others) with peculiar histopathologic feature. Few epidemiological data have been published so far, although a dramatic increase in the number of patients diagnosed with IgG4-RD has been recorded in the last years. The clinical manifestations of IgG4-RD involve frequently liver and pancreas. Specifically, a crucial challenge in differential diagnosis is IgG4-related sclerosing cholangitis which is frequently accompanied by pancreatic involvement. Inflammatory alterations of liver parenchyma have also been described, with a new nosology of IgG4-autoimmune hepatitis. Type 1 autoimmune pancreatitis is the pancreatic manifestation of the IgG4-RD. The first-ever epidemiological study to estimate the point prevalence of IgG4-related sclerosing cholangitis has been recently conducted in Japan. Moreover, several demographic studies on IgG4-RD involving liver and pancreas have been published in other countries, although the majority of them are cohort studies and data on incidence/prevalence are lacking. This review aims to update the recent epidemiological and clinical knowledge of IgG4-RD involving liver and pancreas, focusing also on the risk of malignancy.
Introduction

Immunoglobulin G4–related disease (IgG4-RD) represents a wide spectrum of pathologies affecting multiple organs and sharing some common immune-mediated conditions. They lead to fibro-inflammatory lesions, such as cholangitis and pancreatitis, and retroperitoneal fibrosis. There is an increasing interest in IgG4-RD among the scientific community. The research on pubmed.gov (30/September/2022) has sorted in 4,489 results with a peak of 599 results in 2021. In fact, IgG4-RD is a rare multiorgan condition that has been under-recognized for many years and was firstly described in 2003 in 7 patients with an initial diagnosis of autoimmune pancreatitis (AIP) in whom an extensive organ involvement with IgG4-positive plasma cell infiltrate was described (Kamisawa et al., 2003). Although the first cases were reported in Japan and other Asian countries, IgG4-RD can affect all racial and ethnic groups even with a low reported prevalence. The mean onset age is 59 years, but some cases were described also in the paediatric population (Carballo et al., 2021). Most of the studies reported a slight male prevalence (around 56%), not always confirmed in most recent studies. In general, the IgG4-RD manifestations affected internal organs in male patients, leading to an increased frequency of autoimmune pancreatitis, sclerosing cholangitis and retroperitoneal fibrosis with respect to female ones (Wang et al., 2019). The onset in women is earlier in age than in males. Despite the increasing interest in IgG4-RD, its epidemiology and the clinical outcome are mostly undiscovered. A recent retrospective observational study analysing for the first time a large number of US patients observed that this condition has long been underestimated, according to the diagnostic criteria which were recently updated (Z. Wallace et al., 2022). In the 524 IgG4-RD patients analysed in this study, a mean age of 56.5 years was observed, as well as a slight female prevalence (57.6%), and the observed incidence was 1.41/100,000 person per year. In this cohort of patients, hepatobiliary disease was the most observed IgG4-RD manifestation and glucocorticoid-based therapies the most prescribed treatment. Recently, the diagnostic criteria for IgG4-RD have been updated by the Japanese IgG4 team organized by the Ministry of Health, Labor and Welfare (Umehara et al., 2021). The diagnostic criteria consist of 3 domains: 1) clinical and radiological features; 2) serological diagnosis; 3) pathological diagnosis. Patients generally present with simultaneous or metachronous lesions in multiple organs (more frequently salivary glands and pancreas). Involvement of a single lymph node was not included as a criterion for IgG4-RD, due to a frequent involvement of lymph nodes in benign and malignant diseases. Elevated serum levels of IgG4 above 135 mg/dl was confirmed in the recent diagnostic criteria, according to the previous guidelines, previously established in the International Symposium held in Boston in 2011, and subsequently in 2014 and 2017. Tissue biopsies are important hallmarks of IgG4-RD and indispensable for its diagnosis (Stone et al., 2012). First of all, tissue samples from each involved organ must rule out malignant tumours and similar benign conditions (i.e. Sjogren’s Syndrome, primary sclerosing cholangitis (PSC), multicentric Castleman’s disease, etc.). The typical histopathological changes include: i) dense lymphocyte and plasma cell infiltration with fibrosis; ii) ratio of IgG4-positive plasma cells/IgG-positive cells greater than 10 per high powered field; iii) typical tissue fibrosis, particularly storiform fibrosis, or obliterative phlebitis. The storiform fibrosis is a swirling pattern of fibrosis which may have a patchy distribution, and therefore can be missed with small biopsies. It is constituted by fibrotic collagen deposition containing fibroblasts and myofibroblasts, in a similar way as fibrotic-histiocytic malignancies. Obliterative phlebitis can be identified in veins with inflammatory infiltrate filling both the walls and lumina (Deshpande et al., 2012). Up to now there are still insufficient data on incidence/prevalence of IgG4-RD. Due to enormous number of manuscripts describing the involvement of all dozy organs, herein we furnish an update on the IgG4-RD involving the liver and pancreas.

Epidemiology of IgG4-RD and the risk of malignancy

Most data regarding the epidemiology of IgG4-RD come from Japan, but it is not known whether Asian patients are more susceptible to IgG4-RD than others. In a Nationwide survey conducted in 2009 in the Ishikawa Prefecture in Japan, the incidence of IgG4-RD was 0.28–1.08/100,000 population with 336-1300 patients newly diagnosed per year from 2003 to 2009 (Uchida et al., 2012). The estimated prevalence was 62 per million subjects. However, the available epidemiological data should be interpreted according to organ involvement, unless multiple organ involvement is very common. Moreover, in the recent years it has been shown that IgG4-RD should not be considered as a benign disease, because several cases of malignancy have been described in patients with IgG4-RD (Hirano et al., 2014; Yamamoto et al., 2012). One of the most important target organs for malignancy is the pancreas (Ikeura et al., 2014; Kamisawa et al., 2009; Shiokawa et al., 2013). In a Nationwide
epidemiological survey conducted in Japan, the overall prevalence of malignant disease in IgG4-RD cases was estimated to be 10,900 per 100,000 cases, which was significantly higher than that of malignant disease (Sumimoto et al., 2022). The prevalence of malignant lymphoma in IgG4-RD was the highest and was estimated to be 1985 per 100,000 inhabitants. The most important clinical features of IgG4-RSC include jaundice, weight loss, abdominal pain, biliary strictures and pancreatic or liver masses that mimic malignant disease (Löhr et al., 2022). Table 1 summarizes the main clinical features of different cohorts of IgG4-RSC (Ghazale et al., 2008; Huggett et al., 2014; Kemp et al., 2021; Tanaka et al., 2017; Xiao et al., 2018). The median age at diagnosis ranges between 61 and 67 years and male sex is ≥ 74% of cases.

Table 1. Clinical features of different cohorts of IgG4-RSC

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>N. of patients</th>
<th>Males</th>
<th>Median age at diagnosis (yrs)</th>
<th>Symptoms at diagnosis</th>
<th>Association with AIP</th>
<th>Median follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>2008</td>
<td>53</td>
<td>85%</td>
<td>62</td>
<td>Jaundice (77%)</td>
<td>92%</td>
<td>29.5 months</td>
</tr>
<tr>
<td>UK</td>
<td>2014</td>
<td>68</td>
<td>74%</td>
<td>61</td>
<td>Jaundice (74%)</td>
<td>88%</td>
<td>33 months</td>
</tr>
<tr>
<td>Japan</td>
<td>2017</td>
<td>527</td>
<td>83%</td>
<td>66.2</td>
<td>NA</td>
<td>32%</td>
<td>4.1 yrs</td>
</tr>
<tr>
<td>China</td>
<td>2018</td>
<td>39</td>
<td>82%</td>
<td>NA</td>
<td>Jaundice (67%)</td>
<td>52%</td>
<td>9-36 months</td>
</tr>
<tr>
<td>Australia</td>
<td>2021</td>
<td>67</td>
<td>76%</td>
<td>63.3</td>
<td>Jaundice (62%)</td>
<td>52%</td>
<td>3.9 yrs</td>
</tr>
<tr>
<td>Japan</td>
<td>2021</td>
<td>873</td>
<td>78.4%</td>
<td>66.8</td>
<td>Jaundice (NA)</td>
<td>83.7%</td>
<td>5.1 yrs</td>
</tr>
</tbody>
</table>

Abbreviations: NA=not available

No patient developed IgG4-RSC in childhood or adolescence. Interestingly, in the Japanese cohort (Tanaka et al., 2020) 410 patients (37%) were diagnosed as having IgG4-RSC without any symptom. This finding is probably due to the high chances of having blood test for health check-ups in Japan. The association with AIP is very high with a peak of 92% in USA (Ghazale et al., 2008) and with the lowest rate (32%) in China (Xiao et al., 2018). Based on the strict association with AIP the diagnostic criteria of IgG4-RSC have been recently revised (Nakazawa et al., 2021). Specifically, 6 criteria have been included: i) narrowing of the intrahepatic and/or extrahepatic bile duct; ii) thickening of the bile duct wall; iii) serologic findings; iv) pathologic findings; v) other organ involvement; vi) effectiveness of steroid therapy. According to the new diagnostic criteria the patient with IgG4-RSC is classified as “with” or “without” AIP. Both subtypes, however, have been shown to have a similar rate of association with other organs (Naitoh & Nakazawa, 2022). Both IgG4-RSC with and without AIP are rarely associated with IBD (Tanaka et al., 2017). In the large cohort including 872 patients from Japan, the proportion of females was significantly higher in IgG4-RSC without AIP (28.9% vs 20.1%, p=0.025) (Naitoh et al., 2021). Table 2 summarizes the outcomes for the US, UK, Japanese, Chinese and Australian cohorts.
Most patients have been treated with steroids. Progression to cirrhosis ranged between 1.4 and 7.5%. Mortality ranged between 5 and 13%. The number of liver transplant was negligible. Mortality due to liver of bile duct complications was observed in only one case in the US cohort, in 3 cases in the UK cohort (2 end-stage liver disease and one cholangiocarcinoma). In the Japanese cohort only 4 patients died from liver or bile duct-related pathological conditions.

Although corticosteroids are the first line treatment for IgG4-RSC, it is not known whether the treatment should be prolonged for ever. In fact, relapse of IgG4-RSC is commonly observed, particularly in patients for whom corticosteroids have been stopped. In the Japanese cohort, relapse of IgG4-RSC was noted in 104 patients (19%) (Tanaka et al., 2017). The cumulative rate of restenosis was 1.6%, 7.6% and 16.5% at 1, 3 and 5 years after diagnosis, respectively. In the multivariate analysis, the presence of any symptoms at presentation and discontinuation of corticosteroid treatment were identified as factors independently associated with relapse (Tanaka et al., 2017). A total of 70 patients with IgG4-RD (88% of whom with bile duct or pancreas involvement) were randomized to receive glucocorticoid monotherapy or glucocorticoid plus mycophenolate mofetil (Yunyun et al., 2019). The remission rate after 1 year was higher in the group treated with combination therapy (76.4% vs 51.42%). Finally, a meta-analysis analysed the efficacy and safety of rituximab for IgG4-related pancreato-biliary disease (Lanzillotta et al., 2021). One hundred and one patients from seven cohort studies were included with a median follow-up time of 19 months. The pooled rate of complete response at 6 months was 88.9%, and the relapse rate 21%

**IgG4-autoimmune hepatitis (IgG4-AIH)**

The concept of IgG4-AIH was firstly reported by Umemura et al in 2007 (Umemura et al., 2007) who described a clinical case of a 54-year-old lady with altered liver function tests and chronic cholecystitis. The liver biopsy taken during cholecystectomy found severe lobular hepatitis with mild portal inflammation. IgG4-bearing plasma cell infiltration was found both in the liver and gall bladder wall. Subsequently, five studies have been reported in the literature, four with adult and one with paediatric cases (Amarapurkar & Amarapurkar, 2015; Aydemir et al., 2019; Canivet et al., 2016; Chung et al., 2010; Umemura et al., 2011). Minaga et al. (Minaga et al., 2019) revised these published five studies and pinpointed that only 3 studies met the diagnostic criteria proposed by Nakanuma (Nakanuma et al., 2016), namely the presence of elevated concentration of serum IgG4 and infiltration of IgG4-expressing plasma cells in the liver ≥10/high-power field. Moreover, the authors stressed that ALT normalization time after the steroid treatment might be shorter in IgG4-AIH than in IgG4-non associated AIH.

IgG4-AIH has been described in association with idiopathic hyper-eosinophilia syndrome (HES) in a 46-year-old woman treated successfully with a combination therapy of prednisone and azathioprine (Kastin et al., 2021). Moreover, IgG4-AIH has been reported in a 73-year-old female simultaneously concomitant with autoimmune pancreatitis (AIP) (Yokoyama et al., 2021). Although several cases of IgG4-AIH have been described, no consensus regarding the histological features of IgG4-AIH has been established so far, and clinical implications remain obscure (Tanaka & Notohara, 2021). Indeed, there is a grey zone characterized by AIH with lacking of elevated serum IgG4 levels, and without the strict criteria for diagnosis of IgG4-AIH. This group of patients has been suggested to be considered as classical AIH (Chung et al., 2010). Compared to classical AIH, IgG4-AIH has a relapse rate significantly low during a median follow-up period of 139 months (Arase et al., 2021).

**IgG4-RD involving the pancreas**

Among the most common organs affected by IgG-4-RD, pancreas and hepatobiliary tree share similar pathological findings, such as abundant infiltration of IgG4-positive cells, storiform fibrosis and obliterative phlebitis.

### Table 2. Treatment and outcomes of patients with IgG4-RSC

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>N. of patients</th>
<th>Corticosteroids (%)</th>
<th>Progression to cirrhosis (%)</th>
<th>All-cause mortality</th>
<th>Liver transplant</th>
<th>Mortality for liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>2008</td>
<td>53</td>
<td>30 (57%)</td>
<td>4 (7.5%)</td>
<td>7 (13%)</td>
<td>0</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>UK</td>
<td>2014</td>
<td>68</td>
<td>98 (85%)</td>
<td>6 (5.2%)</td>
<td>11 (9.6%)</td>
<td>1</td>
<td>3 (2.6%)</td>
</tr>
<tr>
<td>Japan</td>
<td>2017</td>
<td>527</td>
<td>458 (88%)</td>
<td>NA</td>
<td>26 (5%)</td>
<td>0</td>
<td>4 (0.8%)</td>
</tr>
<tr>
<td>China</td>
<td>2018</td>
<td>39</td>
<td>29 (74.3%)</td>
<td>NA</td>
<td>NA</td>
<td>NO</td>
<td>NA</td>
</tr>
<tr>
<td>Australia</td>
<td>2021</td>
<td>67</td>
<td>61 (91%)</td>
<td>1 (1.4%)</td>
<td>NA</td>
<td>NO</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: NA=not available
**IgG4-related pancreatitis**

IgG4-related pancreatitis, also known as type 1 autoimmune pancreatitis (AIP), is the pancreatic manifestation of IgG4-RD predominantly affecting males. In the mid of 1990s, this pathology was generally defined as autoimmune pancreatitis (AIP), term used till 2011, when a consensus in the definition of “type 1” AIP was obtained at the International Meeting of Pancreatolog (Shimosegawa et al., 2011). According to the new definition, type 1 AIP is a pancreatitis frequently associated with obstructive jaundice with or without a pancreatic mass responding to steroid therapy, and histologically characterized by a lymphoplasmacytic infiltrate and fibrosis, and abundant IgG4-positive cells in biopsies (>10 cells/high power field) as well as more than 135 mg/dL of serum IgG4 level. For diagnosis, a marked elevation of serum IgG4 (more than 2 times the upper normal limit) is strongly suggestive of IgG4-related autoimmune pancreatitis in the setting of obstructive jaundice/pancreatic mass. Various diagnostic criteria have been proposed along years in many countries, e.g. Japan (Okazaki et al., 2006) and Korea (Kim et al., 2006), the countries with the great number of reported cases, and the United States (Chari et al., 2006). As stated by Okazaki, type 1 AIP clinical manifestations include: i) mild abdominal symptoms, in general without acute events of pancreatitis, ii) occasional obstructive jaundice, iii) increased levels of plasma γ-globulin, IgG, and/or IgG4, iv) presence of autoantibodies, v) pancreas enlargement accompanied to diffuse/segmental/focal narrowing of the main pancreatic duct (Okazaki, 2019; Otsubo et al., 2008). Type 1 AIP affected patients have a dramatic response to corticosteroid therapy, even though a consensus on the duration and therapy regimen is still debated (Vlachou et al., 2011). Generally, patients were treated with a starting dose of 30-40 mg of prednisone or similar medications, and then with a lower maintenance dose for 3-4 weeks. Unfortunately, despite its efficacy in reducing symptoms, this regimen doesn’t guarantee the absence of disease recurrence, that is experienced by 20-40% of patients (Ghazale & Chari, 2007). A retrospective study analysing 57 patients with autoimmune pancreatitis between 2000-2009, showed that 44% had a diffuse disease, 49% focal disease and 7% multifocal disease, and in all patients the narrowing of pancreatic duct was observed (Vlachou et al., 2011). Moreover, 88% of patients with autoimmune pancreatitis have also an IgG4-4-related sclerosing cholangitis. Among patients with IgG4-4-RD, more than 50% display pancreatitis and about 30% show an involvement of biliary tract (Rebours & Lévy, 2020). To exclude adenocarcinoma, it is strongly suggested to include the evaluation of IgG4 to IgG ratio, that has to exceed 40% to confirm the diagnosis of type 1 AIP (Deshpande et al., 2012). This is of primary importance to exclude possible confounding factors, since adenocarcinoma could display a dense peritumoral IgG-4 plasma cell infiltrate and a wrong diagnosis could delay and narrow the window for surgical tumour resection (Deshpande, 2015). For this reasons, the histological analysis of IgG-4 immunostaining needs to be carefully interpreted to avoid overdiagnosis of type 1 AIP (Zen, 2016). Typically, a plasma IgG4/IgG ratio higher that 40% is found in more that 70% of IgG-4-RD.

Another study evaluating 235 patients with IgG-4-RD observed that 60% of them developed pancreatitis and 13% have hepatobiliary manifestations without intrapancreatic bile duct involvement (Zen, 2016). Among patients with pancreatobiliary abnormalities, 98% suffer from pancreatitis irrespective to the presence of cholangiopathy. The study of Mayo clinic on 53 patients cited above, observed that the 92% of patients with IgG-4 related cholangiopathy concomitantly developed pancreatitis (Ghazale et al., 2008), demonstrating that is uncommon that patients have real isolated cholangiopathy without type 1 AIP.

A recent study analysed the long term outcome in a cohort of 46 IgG4-RD/type 1 AIP patients from a German tertiary referral centre, some of which treated with rituximab, an anti-CD20 B-cell-depleting monoclonal antibody (Backhus et al., 2021). The 67% of patients (n= 34) were males and the mean age was 54 years. The 74% of them started with an initial treatment with a steroid pulse, followed by an immunomodulatory maintenance therapy with azathioprine or rituximab in a subgroup of patients. This study concluded that even though steroid-based therapy remains the first-line treatment with up to 99% of response (but also with high relapse rate), rituximab, due to its considerable safety and efficacy, should be considered as a maintenance therapeutic option in difficult-to-treat cases.

In patients diagnosed with type 1 AIP, the incidence of cancer was higher than in general population with the same age, sex and observation period, as reported in different cohorts of patients with IgG-4 related pancreatitis (Okamoto et al., 2019). Yamamoto reported that among 106 patients with IgG-4-RD, 11 developed cancer during the follow-
up period (Yamamoto et al., 2012). Similarly, another study observed an increase of standardized cancer ratio (SIR) in IgG-4 RD patients of 2.7, significantly higher than in the general population with the same age and gender (Shiokawa et al., 2013). Wallace and collaborators suggested that the relation between IgG-4 RD/type 1 AIP and cancer development could be mutual, thus the development of one of the two pathological conditions could favour the development of the other (Z. S. Wallace et al., 2016). Notably, other two studies failed to observe the same relation (Hart et al., 2014; Hirano et al., 2014), but the reason of this discrepancy is far to be elucidated, and may reside in unknown molecular mechanisms underlying the relation between type 1 AIP and cancer (Okamoto et al., 2019).

**Conclusions**

IgG4-RD is a new clinical entity potentially involving all organs, but is more frequent in the liver and pancreas. From the epidemiology point of view there are insufficient data on incidence/prevalence of this entity. The majority of data come from Japan, but it is not known whether Asian patients are more susceptible to IgG4-RD than others; hence the available epidemiologic data should be interpreted carefully. As a new concept, it should be stressed that there is a risk for malignancy, unless not relevant, for IgG4-RD. Moreover, a number of uncertainties still remain, including aetiology, natural history, treatment and long-term outcomes.
References


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