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Management, Outcomes and Survival of an Australian IgG4-SC Cohort: The MOSAIC study.

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Abbreviations

AIP-1	Type 1 autoimmune pancreatitis
ALA-CRN	Australian Liver Association Clinical Trials Network

ERCP	Endoscopic retrograde cholangiopancreatography
GESA	Gastroenterological Society of Australia
HCC	Hepatocellular Carcinoma
IAC	IgG4-associated cholangitis IAC
IgG4-RD	IgG4-related disease
IRC	gG4-related cholangitis
IgG4-SC	IgG4 Sclerosing Cholangitis
MMF	mycophenolate mofetil
MTX	methotrexate
NASH	non-alcoholic steatohepatitis
PSC	primary sclerosing cholangitis
SLE	Systemic Lupus Erythematosis
UDCA	ursodeoxycholic acid
ULN	Upper limit of normal

Lay Summary

IgG4-SC is a rare disorder of the bile ducts. Best management and the outcomes of treatment are poorly defined. Our study shows excellent response to steroid treatment but high relapse. Overall there are low rates of cancer development or other complications.

ABSTRACT

Background and Aims: IgG4 sclerosing cholangitis (IgG4-SC) is the biliary component of the multisystem IgG4-related disease. We aimed to investigate the clinical features, demographics, treatment response and outcomes of IgG4-SC in a large Australian cohort.

Methods: We conducted Nationwide retrospective cohort via the Australian Liver Association Clinical Trials Network (ALA-CRN). 39 sites were invited to participate. IgG4-SC was defined by the clinical diagnostic criteria established by the Japanese Biliary Association in 2012. Data was collected on

patient demographic, clinical and laboratory information, presenting features, response to therapy and clinical outcomes.

Results: 67 patients meet inclusion criteria from 22 sites. 76% were male with mean age of 63.3 ± 14.5 years and a median IgG4 level of 3.6 g/L [0.09-67.1]. The most frequent presenting symptom was jaundice (62%) and abdominal pain (42%) and Type 1 biliary stricturing (52%) at the distal common bile duct was the most frequent biliary tract finding. Prednisolone was used as a primary treatment in 61 (91%) and partial or complete response occurred in 95% of subjects. Relapse was common (42%) in those who ceased medical therapy. After a median follow up 3.9 years there was one hepatocellular carcinoma and no cholangiocarcinomas.

Conclusions: Our study confirms the preponderance of IgG4-SC in males and highlights the steroid response nature of this condition although relapse is common after steroid cessation. Progression to malignancy was uncommon

Keywords: Cholangitis; autoimmune; biliary disease; cancer

IgG4-related disease (IgG4-RD) is an uncommon, but increasingly recognised condition that includes a spectrum of multiorgan involvement characterised by a fibro-inflammatory process with infiltration of IgG4 positive plasma cells[1]. The typical histopathological finding consists of lymphoplasmacytic infiltration, obliterative phlebitis, and storiform fibrosis[2]. Serum IgG4 levels are often but not universally elevated[3].

IgG4-sclerosing cholangitis (IgG4-SC, also referred to as IgG4-associated cholangitis (IAC), or the recently proposed IgG4-related cholangitis[4] (IRC)) is the biliary manifestation of IgG4-RD[5]. Although the radiological manifestations of IgG4-SC can resemble the appearance of primary sclerosing cholangitis (PSC), clinical diagnostic criteria for IgG4-SC have been established[6] and have recently been updated[7]. IgG4-SC is frequently accompanied by type 1 autoimmune pancreatitis (AIP) but may also be associated with other organ involvement of IgG4-RD. Untreated, IgG4-SC can result in progressive biliary duct stenosis and destruction, and although data suggest the response to corticosteroids is excellent[8] this has not been evaluated in randomised controlled trials.

There are limited data describing the natural history, management and outcomes of IgG4-SC. The three largest population-based cohort studies of IgG4-SC from Japan[9], UK[10] and USA[11] have included 527, 68 and 53 patients respectively. Significant variations in the initiation of corticosteroids (56%-88%), relapse rates (19%-54%) and cancer development were seen across the cohorts highlighting the need for additional data. Furthermore, there are limited data on the use of second line

immunosuppression in the treatment of IgG4-SC. The prevalence of IgG4-SC is also unknown, however studies from Japan have estimated the prevalence of AIP at 4.6 per 100,000 Japanese population with less than 40% of cases having evidence of IgG4-SC[12].

The uncommon nature of the condition means that controlled trials of treatment in IgG4-SC are not practical and a pragmatic approach to therapy informed by cohort studies is necessary. This study aims to describe for the first time the management and outcomes of an Australian IgG4-SC cohort with particular emphasis on the response to initial therapy and use of second line or alternative immunosuppressive agents, medium-term disease progression and cancer development.

PATIENTS AND METHODS

Study design and population

This was a multicentre, Australia-wide retrospective study with data collection via a comprehensive questionnaire that was sent to interested liver clinic sites following an expression of interest campaign from the Gastroenterological Society of Australia (GESA) – Australian Liver Association Clinical Trials Network (ALA-CRN) that encompassed all mainland states and territories in Australia. Patients were eligible for inclusion if they fulfilled the clinical diagnostic definition for either probable or definite IgG4-SC proposed by Ohara et al[6] and had a minimum of one month follow up. The cholangiographic findings were subtyped according to the classification proposed by Nakazawa[13]. Patients were excluded if (i) there was another cause of chronic liver disease including but not limited to hepatitis C, hepatitis B, alcohol, non-alcoholic steatohepatitis (NASH), metabolic liver disease (haemochromatosis, Wilson's disease, alpha1-antitrypsin deficiency), and coeliac disease, (ii) there was a diagnosis of PSC or other form of secondary sclerosing cholangitis, or (iii) the presence of a concomitant immune-mediated disorder requiring treatment with systemic corticosteroids or other immunosuppressive or immunomodulatory therapy (eg. SLE, ulcerative colitis, rheumatoid arthritis). Immunosuppression for IgG4-RD was not an exclusion. The study protocol was approved by the relevant institution's Human Research and Ethics committee at all sites.

Data collection

Individual patient data were collected from the electronic/paper medical record and/or from existing hospital / department databases. Data were transcribed into the study specific questionnaire that encompassed the following domains: patient demographics, clinical presentation, biochemistry, treatment and treatment response, and outcomes of patients. Data collection forms

were sent to a central site for entry into a password-protected electronic database. Case finding included a search of hospital or clinic medical record, radiology database search for hepato-biliary changes consistent with IgG4-SC or IgG4-RD, anatomical pathology database search for histological features of IgG4-SC, biochemistry results consistent with IgG4-SC and/or elevated IgG4 levels, ERCP reports consistent with IgG4-SC.

Treatment response definitions

Response to therapy was defined as: (i) Remission: complete resolution of strictures and/or normalization of liver test results (ALT, ALP and bilirubin); (ii) Incomplete response (ie. partial response): improvement in ALT, ALP and/or bilirubin >25% and/or improvement in biliary tract abnormalities but not fulfilling the definition of remission; (iii) Relapse: progression of disease on imaging after prior improvement or deterioration in liver biochemistry tests (but not related to stent dysfunction); (iv) Non-response (or treatment failure): failure to improve liver function by >25% from baseline (ALT, ALP and/or bilirubin) and/or an absence of improvement in biliary tract abnormalities on imaging. Deterioration in liver function tests was defined as abnormal ALT, ALP and/or bilirubin when previously normal or a worsening of >25% from the best achieved.

Statistical Analyses

Descriptive statistics of the cohort were performed with continuous variables presented as mean ± standard deviation if normally distributed, or median (interquartile range) if not. Categorical variables were summarized by using frequencies or proportions. Survival rate was assessed using the Kaplan-Meier curve and log-rank test. All reported P values are two-tailed, and $P < .05$ indicated statistical significance. All statistical analyses were performed using SPSS Statistics version 24. All authors had access to the study data if requested and reviewed and approved the final manuscript.

RESULTS

Demographics and clinical features at presentation

A total of 39 sites were invited to participate and data was received from 22 of these. The other 17 sites declined to participate or had no patients to contribute. In total 67 subjects met the inclusion/exclusion criteria. The baseline demographic and clinical characteristics of the cohort at presentation are shown in Table 1. The majority were male (n=51, 76%) with the mean age at diagnosis being 63.3 ± 14.5 years. One child was included in the cohort who was aged 14.5 years at

diagnosis and had classic cholangiographic findings and histological evidence of IgG4-SC. 61% were Caucasian while 34% were of Asian background. The median follow-up of subjects was 3.9 years (1.7 – 7.4 years).

The most frequent presenting symptom was jaundice (62%) followed by abdominal pain (42%), pruritus (19%) and weight loss (13%). Cirrhosis was identified at diagnosis in 4 patients (6%) and 2 patients had evidence of portal hypertension but no prior history of decompensation.

At diagnosis, bilirubin was elevated in 48 patients (median 50 µmol/L [4-420]) as were serum ALT (150 U/L [6-1503]) and ALP (340 U/L [47-1429] (Table 1). IgG4 levels were recorded at diagnosis in 58 patients and were greater than the ULN in 52 patients with a median of 3.6 g/L [0.09-67.1]. 49 subjects (84%) had an IgG4 level > 1.35 g/L.

Diagnosis details

Biliary histology from bile duct biopsy or surgical specimen was used as a criterion to establish a diagnosis of IgG4-SC in 31% of cases. The remaining cases relied on imaging and clinical criteria to fulfil case definition (Figure 1). Using the Nakazawa classification based upon the cholangiographic appearance of biliary tract lesions[14], the most frequent biliary tract lesions was Type 1 (52%) characterised by stricturing located only in the lower part of the common bile duct followed by Type 4 (17%) with strictures detected only in the hilar hepatic region. Type 2A, 2B and Type 3 biliary tract lesions were detected in 12%, 1.5% and 12% respectively. In 5% the type was not classified on cholangiogram (Figure 2).

IgG4-Related diseases

The co-existence of other IgG4-RD were identified in 81% of cases with the most frequent being; auto-immune pancreatitis (52%), pancreatic pseudotumour (16%), sialadenitis/dacryoadenitis (12%) and lymphadenopathy (9%). Furthermore, the presence of diabetes mellitus was seen in 30% of subjects (Figure 3).

Initial treatments

Prednisolone was used as the primary treatment in 61 (91%) patients with the median starting dose being 40mg/d (range 15mg-60mg) and median duration of treatment being 153 days (range 8 to

1402). Of the other 6 patients not treated with prednisolone initially, four underwent biliary tract surgery (excluding cholecystectomy) as primary therapy that included biliary resection and reconstructive surgery or bypass. Two of these subsequently developed other manifestations of IgG4-RD and one demonstrated progression of IgG4-SC requiring biliary stenting. In addition, one patient received biliary stenting only, and one was treated with ursodeoxycholic acid (UDCA) alone. The latter patient was maintained on UDCA long term with an incomplete response but no evidence of progressive disease (Figure 4).

Initial treatment response

Overall, 56 (92%) of the 61 patients treated with prednisolone had their response to therapy known and documented. Among these patients, 70% (n=39) achieved remission, 25% (n=14) had an incomplete response and 5% (n=3) had non-response. Of those who achieved remission on prednisolone (median time 81 days), 19 (49%) patients ceased steroid therapy completely of which 8 (42%) relapsed during follow up requiring retreatment with prednisolone and/or azathioprine. Of the 20 patients who were continued on maintenance prednisolone therapy (median dose of 5mg/d, range 2.5-10mg/d), 11 did so on prednisolone alone with the remainder managed with prednisolone in combination with an alternative agent (azathioprine (n=6), mycophenolate mofetil (MMF) (n=1), 6-mercaptopurine (n=1) and methotrexate (MTX) (n=1)). 73% of the prednisolone treated patients had a reduction of ALP by greater than 50% of their baseline and a documented improvement in biliary stricturing in 57%. However, 5 patients discontinued steroids due to toxicity.

Second-line treatment(s)

Of the 14 patients who achieved an incomplete response to prednisolone alone, 11 received azathioprine ± prednisolone as a second line agent and 3 (27%) of these subsequently achieved remission. A further two subjects achieved remission with the addition of a third line agent (UDCA n=1 and MMF n=1). Thus, an additional 5 patients were able to achieve remission with the use of combination of second or third line. Despite the frequent use of steroids, additional biliary tract intervention was common with 55% requiring biliary tract stent insertion and 21% undergoing biliary tract dilation.

Overall an alternative or second line agent was used in the management of IgG4-SC in 34/67 (51%) of subjects. The most common agent was azathioprine (30/34) however 2 patients were treated with

UDCA and MMF, while 6-mercaptopurine and MTX were each used in 1 patient. These agents were mostly used as steroid sparing agents being used in combination with prednisolone in 65%. However, 4 subjects received a second line agent due to relapse and 1 due to an incomplete response. There were 4 subjects who achieved a complete remission on Azathioprine alone.

Clinical outcomes during follow up

After a median follow up 3.9 years (1.7 – 7.4 years) 1 patient progressed to cirrhosis and the development of portal hypertension and 8 patients had progression or development of other IgG4-RD. One of these patients had biopsy proven IgG4-SC type 1 at baseline and despite treatment with prednisolone and azathioprine progressed to type 2 IgG4-SC. A second patient developed chronic pancreatitis and pancreatic insufficiency. Development of additional IgG4-RD included retroperitoneal involvement, submandibular glandular and pulmonary involvement.

Two patients developed solid organ malignancy during a total of 328 patient years of follow up which included one diagnosis of prostate cancer and one hepatocellular carcinoma (HCC). An additional patient developed multiple myeloma. The HCC developed in a 64 year old man, 12.5 years after the diagnosis of IgG4-SC. This patient already had features of cirrhosis at the time of IgG4-SC diagnosis. There were no cases of cholangiocarcinoma. At the end of follow up 2 patients (3%) had died, including the patient with HCC (Figure 5). No patients underwent liver transplantation.

DISCUSSION

Despite recognition of IgG4-SC as the biliary manifestation of IgG4-RD, current management principles are primarily informed by case reports, case series, cohort studies and extrapolation from the management of AIP and IgG4-RD more generally. Recent consensus guidelines[4, 15] highlight the uncertainty regarding the management of IgG4-SC steroid-refractory disease, long term outcomes and the risk of future malignancy. In this study we included 67 patients with IgG4-SC recruited from 22 sites around Australia. This cohort represents the third largest cohort of IgG4-SC and the second largest to be reported from a Western country. The data not only consolidates the experience of previous cohort studies in the management of IgG4-SC but moreover, expands upon the understanding of the long-term outcomes of this disease.

The clinical presentation of our cohort is consistent with that of published cohorts from Japan[9], UK[10] and USA[11]. A comparison of the key findings of these studies is shown in Table 2. There is a male

preponderance greater than 2:1 and the median age at presentation was 63 years. When interpreted in conjunction with previous studies, these demographic features appear to be consistent across all cohorts and ethnicities. Obstructive jaundice was the most frequent presenting symptom (62%) and is in line with data from the USA (77%) and UK (74%) although the latter included a cohort of AIP/IgG4-SC. Of note, jaundice was a presenting symptom in only 35% of the Japanese cohort although evidence of cholestasis with an elevated ALP was found in 79%.

There are limited epidemiological data regarding the occurrence of IgG4-SC. The retrospective nature of our study prevents an analysis of the incidence and prevalence of IgG4 in the Australian community. It is recognised that IgG4-SC can occur in isolation, however it is often associated with other IgG4-RD[7] and in particular may be the most frequent extra-pancreatic manifestation of AIP. In our cohort, evidence of AIP was documented in approximately half of the IgG4-SC cases. This is comparatively low compared to the cohorts of Ghazale et al[11] and Tanaka et al[9] who had an incidence of AIP of 92% and 87% respectively. Similarly, IgG4-SC is a frequent finding amongst patients with AIP with Huggett et al[10] detected IgG4-SC in 56% of their AIP cohort, and of those with IgG4-SC, 85% had involvement of the intrapancreatic portion of the common bile duct or the pancreatic parenchyma. A 2011 epidemiological survey from Japan[12] suggested the overall prevalence rate of AIP was 4.6 per 100,000 population and estimated annual incidence rate of 1.4 per 100,000 population. Extrapolating data from the Japanese 2015 nationwide survey[9], the total prevalence of IgG4-SC was estimated as 2.0 per 100,000 population, and the number of patients with IgG4-SC in Japan was thus estimated at 2,500[15]. If the prevalence of this condition was similar in the Australian population, this would translate to approximately 500 patients with IgG4-SC.

The diagnosis of IgG4-SC can be challenging. Various definitions for the diagnosis of IgG4-SC have been proposed including the initial HISORt (histology, imaging, serology, other organ involvement, and response to steroid therapy) criteria originally developed for AIP[16] and adapted for IgG4-SC[11]. However, recognising the potential difficulty in obtaining histology in IgG4-SC and the potential to misdiagnose IgG4-SC due to similar cholangiographic findings of primary sclerosing cholangitis or biliary tract or pancreatic head malignancy, the Japanese Biliary Association developed clinical diagnostic criteria of IgG4-SC[6] based on the following criteria: (i) characteristic biliary imaging findings; (ii) elevation of serum IgG4 levels; (iii) coexistence of IgG4-related diseases, except those of the biliary tract; and (iv) characteristic histopathologic features. Evaluation of the effectiveness of steroid therapy represents an optional additional diagnostic criterion in the 2012 criteria in recognition of the potential challenges in obtaining sufficient biopsy specimens from the bile duct from patients suffering from IgG4-SC. A recent revision of the clinical diagnostic criteria of IgG4-SC now regard the effectiveness of steroid therapy as one the diagnostic criteria[7]. While 21 subjects in

our study had histological confirmation of IgG4 disease, this was not a prerequisite for inclusion in our study. Consistent with previous studies[9] and due to the timing of subject recruitment into our study, we used the Clinical Diagnostic Criteria for the diagnosis of IgG4-SC 2012 and included only patients with a definite or probable diagnosis. Application of the revised 2021 diagnostic criteria would not have excluded any of subjects. We found the most frequent cholangiographic finding was a common bile duct stricture isolated to the lower bile duct (Type 1) which was present in 50% of our cohort. In this context differentiating IgG4-SC from cholangiocarcinoma or pancreatic head malignancy is imperative but can be difficult[17, 18]. The remaining patients had approximately equal distribution of Type 2, 3 and 4 cholangiographic findings. This pattern of bile duct involvement also appears similar across international cohorts.

IgG4-SC is considered a steroid responsive disease[4, 15] and glucocorticoid therapy is recommended as first-line therapy unless there are contraindications for its use[19]. European guidelines on IgG4-SC indicate a rate of steroid response from 62 to 100% with a relapse of approximately 30% during glucocorticoid tapering or after withdrawal of glucocorticoids[4]. Over 90% of patients in our cohort receive oral prednisolone as first line therapy and in-line with previous cohorts, the response to steroids was excellent with 95% experiencing a response and 70% achieving complete remission. The duration of treatment before an attempt at withdrawal remains uncertain. Treatment guidelines established by the Japanese Society of Hepato-Biliary-Pancreatic Surgery suggest continuation of steroid for at least 3 years[15] consistent with the regime used in AIP[20] in which relapse-free survival was significantly longer in the 3 year maintenance therapy group compared to the group who ceased therapy at 26 weeks (p=0.007). The limited data on relapse rates of IgG4-SC following withdrawal of steroids suggest approximately half of patients will relapse[10, 11]. The median time to cessation of steroids in our cohort of patients who entered remission was 170 days (Range 56-1402 days) and while 9/19 (47%) relapsed, remission could be re-induced in all patients following recommencement of prednisolone alone or in combination with azathioprine.

Critical to the long-term management of patients with IgG4-SC is an understanding of the risk of future disease progression and malignancy. Our study includes a median follow-up of over 46 months and overall the outcomes were excellent. Progression to cirrhosis was uncommon with only one patient progressing to cirrhosis over a 13 year period, and, no patients required liver transplant. There are reports that IgG4-SC patients are at increased risk of developing cancer[21] and that differentiating IgG4-SC from cholangiocarcinoma can be challenging both radiologically and clinically[18, 22]. In our study the development of hepatobiliary malignancy was very uncommon. There were only 2 solid organ malignancies in over a median follow up of 3.9 years accounting for 328 patient years of follow up. There were no cholangiocarcinomas detected and only one patient

developed an HCC who was an older male with pre-existing cirrhosis who developed HCC after 12.5 years of follow up. The low rate of hepatobiliary malignancy in our cohort is consistent with the findings of Tanaka et al[9] who detected 2 cases of cholangiocarcinoma during follow up of 527 subjects (and an additional 2 cases at the time of IG4-SC diagnosis). Taken together these findings support the assertion that IgG4-SC is associated with a relatively low risk for developing cholangiocarcinoma. However these findings have not been observed across all cohorts. Huggett et al[10] reporting 3 pancreaticobiliary cancers in a cohort 115 patient with AIP and/or IgG4-SC and a large international multicentre retrospective study[23] found malignancy developed in 56 of the 978 patients with type 1 AIP. These cancers included 5 with pancreatic cancer and 3 with cholangiocarcinoma although the malignancy rate specifically in the subgroup with IgG4-SC in unclear. Hence, cholangiocarcinoma and pancreatic cancer remain important differentials in the diagnosis of IgG4-SC and must be strongly considered in patients not responding to treatment. The utility, modality and frequency of screening patients with an established diagnosis of IgG4-SC remains unknown.

Our study represents a large multicentre national cohort of IgG4-SC and the third largest series internationally of this increasingly appreciated but uncommon condition. These data serve to highlight firstly the steroid responsive nature of this condition including the ability to recapture response in those that relapse, and secondly the relatively low risk of pancreatico-biliary malignancy during medium-term follow up. However, the retrospective nature of this study means there may be ascertainment bias and incomplete data collection, particularly regarding treatment response. Thus, caution should be exercised in the interpretation of treatment efficacy of the risk of disease progression and cancer development. Despite these limitations, this study provides further evidence for the use of prednisolone as first-line therapy in the management of IgG4-SC as well as additional information on the outcomes of second-line therapies on incomplete treatment responders. Moreover, our study provides some reassurance for the absence of pancreatico-biliary malignancy during follow up although clearly IgG4-SC cohorts should be followed for longer to help inform clinicians on the long-term prognosis and outcomes of this condition

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Jacob George, Amany Zekry, Abhimati Ravikulan

	Tanaka et al[9]	Huggett et al[10]	Ghazale et al[11]	Kemp et al
Region	Japan	UK	USA	Australia
Cases (n)	527	68	53	67
Follow up (mths)	49.2	32.5	29.5	46.8
Gender Male %	83	74*	85	76
Age (yrs)	66	61	62	63
AIP present (%)	449 (87)[c]	59 (87)	49 (92)	35 (52)

Table 1. Baseline patient demographics and characteristics of IgG4-SC cohort

	Data available (N)	**Value**
Gender Male:Female	67	51:16 (76%:24%)
Age (years)	67	65.4 (54.1-74.1)
Racial group	67	
Caucasian		41
Asian		23
Other		3
Total Protein (g/L)	50	72.5 (69.0-76.5)
Albumin (g/L)	61	34 (30.5-39.0)
Bilirubin (µmol/L)	62	50 (19.8-116.3)
ALT (U/L)	62	150 (64.8-427)
ALP (U/L)	62	340 (232.8-571.0)
GgT (U/L)	62	639 (249.5-1040.5)
IgG (g/L)	54	15.2 (12.0-19.4)
IgG4 (g/L)	58	3.6 (1.95-7.0)
Ca19-9 (kU/L)	45	34 (17.1-182)

Values expressed as Median (IQR25%-75%) unless otherwise specified. ALT; Alanine Transferase. ALP; Alkaline phosphatase. GgT; Gamma-glutamyl transpeptidase.

Dominant symptom (%)	Jaundice (35)	Jaundice (74)[b]	Jaundice (77)	Jaundice (62)
Cholangiographic pattern (%)		NA		
Type 1	64		51	52
Type 2a	5		36[e]	12
Type 2b	8		-	2
Type 3	10		4	12
Type 4	10		9	17
Not specified	4			5
Primary treatment with steroids (%)	458 (88)	98 (85)[b]	30 (57)	61 (91)
Steroid response (%)	90	97 [b]	97	95
Relapse after steroid cessation (%)	NA	59 [b]	53	42
Progression to cirrhosis (%)	NA	6 (5.2)	4 (7.5)	1 (1.5)
Cholangiocarcinoma	4[d]	2	0	0
Hepatocellular carcinoma	0	0	0	1

Table 2: Comparison of the clinical, treatment and outcome data of patients with IgG4-SC

AIP; Autoimmune pancreatitis. *The proportion of 115 patients with AIP/IgG4-SC, including those without IgG4-SC. [a]Median age of 115 patients with autoimmune pancreatitis (AIP)/IgG4-SC. [b]The proportion of 115 patients with autoimmune pancreatitis, including those without IgG4-SC. [C]From 519 subjects assessed for AIP. [d]2 cases diagnosed approximately at the same time as IgG4-SC and 2 cases diagnosed at 4 months and 4 years. [e]Data extrapolated from text and differentiation of type 2a and 2b is not available.

Figure 1. Diagnostic features of the MOSAIC IgG4-SC cohort (n=67)

[*]Diagnostic criteria as per Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. Ohara et al[6]. Criteria consist of the following parameters: (1) Biliary tract imaging of diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with the thickening of bile duct wall. (2) Histopathological features: a. Marked lymphocytic and plasmacyte infiltration and fibrosis b. Infiltration of IgG4-positive plasma cells > 10 IgG4-positive plasma

cells/HPF c. Storiform fibrosis d. Obliterative phlebitis. (3) A coexisting IgG4 disease of autoimmune pancreatitis, IgG4-related dacryoadenitis/sialadenitis, or IgG4-related retroperitoneal fibrosis (4) Elevated serum IgG4 concentrations (≥ 135 mg/dl). (5) Optional criteria of effectiveness of steroid therapy can be used in conjunction with compatible imaging and elevated IgG4 level for a probable diagnosis of IgG4-SC

Figure 2. Distribution of cholangiographic findings in patients with IgG4-SC according to the classification proposed by Nakazawa et al[13]. Type 1; Stenosis is located only in the lower part of the common bile duct. Type 2a; Stenosis is diffusely distributed in the intra-and extra-hepatic bile ducts with narrowing of the intrahepatic bile ducts with prestenotic dilation being widely distributed. Type 2b; Stenosis is diffusely distributed in the intra-and extra-hepatic bile ducts with narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches are widely distributed. Type 3; Stenosis is detected in both the hilar hepatic lesions and the lower part of the common bile ducts. Type 4; Strictures of the bile duct are detected only in the hilar hepatic lesions.

Figure 3: Prevalence of other organ involvement in IgG4-related disease and associated autoimmune conditions

Figure 4: Flow-diagram of treatment allocation and treatment response of the study patients (n=67).

[1]Other includes treatment with Ursodeoxycholic acid (n=1) and biliary stenting (n=1). [2]Combination includes Azathioprine (n=6), MMF (n=1), 6-MP (n=1) and Methotrexate (n=1). [3]Includes treatment with 6-MP (n=1), and cessation of all therapy (n=1).

Figure 5: Cumulative cancer free survival of patients with IgG4-SC

1. Umehara H, Okazaki K, Masaki Y, et al. A novel clinical entity, IgG4-relateddisease (IgG4RD): General concept and details. Modern Rheumatology. 2012;22(1):1-14.

2. Kamisawa T, Zen Y, Pillai S, et al. IgG4-related disease. The Lancet. 2015;385(9976):1460-1471.

3. Umehara H, Okazaki K, Nakamura T, et al. Current approach to the diagnosis of IgG4-related disease-Combination of comprehensive diagnostic and organ-specific criteria. Modern Rheumatology. 2017;27(3):381-391.

4. Lohr JM, Beuers U, Vujasinovic M, et al. European Guideline on IgG4-related digestive disease - UEG and SGF evidence-based recommendations. United European Gastroenterol J. 2020;8(6):637-666.

5. Miyabe K, Zen Y, Cornell LD, et al. Gastrointestinal and Extra-Intestinal Manifestations of IgG4-Related Disease. Gastroenterology. 2018;155(4):990-1003 e1001.

6. Ohara H, Okazaki K, Tsubouchi H, et al. Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. Journal of Hepato-Biliary-Pancreatic Sciences. 2012;19(5):536-542.

7. Nakazawa T, Kamisawa T, Okazaki K, et al. Clinical diagnostic criteria for IgG4-related sclerosing cholangitis 2020: (Revision of the clinical diagnostic criteria for IgG4-related sclerosing cholangitis 2012). J Hepatobiliary Pancreat Sci. 2021;28(3):235-242.

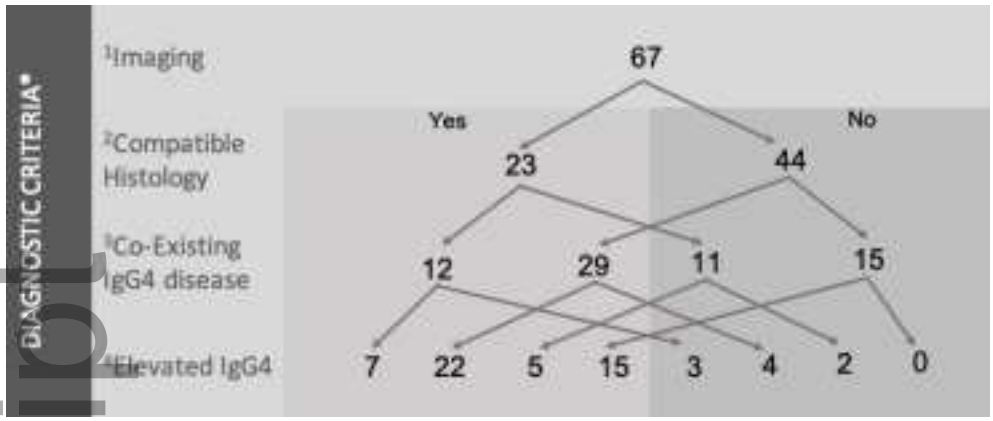
8. Tanaka A. Immunoglobulin G4-related sclerosing cholangitis. J Dig Dis. 2019;20(7):357-362.

9. Tanaka A, Tazuma S, Okazaki K, et al. Clinical Features, Response to Treatment, and Outcomes of IgG4-Related Sclerosing Cholangitis. Clinical Gastroenterology and Hepatology. 2017;15(6):920-926 e923.

10. Huggett MT, Culver EL, Kumar M, et al. Type 1 autoimmune pancreatitis and IgG4-related sclerosing cholangitis is associated with extrapancreatic organ failure, malignancy, and mortality in a prospective UK cohort. Am J Gastroenterol. 2014;109(10):1675-1683.

11. Ghazale A, Chari ST, Zhang L, et al. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. Gastroenterology. 2008;134(3):706-715.

12. Kanno A, Masamune A, Okazaki K, et al. Nationwide epidemiological survey of autoimmune pancreatitis in Japan in 2011. Pancreas. 2015;44(4):535-539.
13. Nakazawa T, Ohara H, Sano H, et al. Schematic classification of sclerosing cholangitis with autoimmune pancreatitis by cholangiography. Pancreas. 2006;32(2):229.
14. Nakazawa T, Naitoh I, Hayashi K, et al. Diagnosis of IgG4-related sclerosing cholangitis. World Journal of Gastroenterology. 2013;19(43):7661-7670.
15. Kamisawa T, Nakazawa T, Tazuma S, et al. Clinical practice guidelines for IgG4-related sclerosing cholangitis. J Hepatobiliary Pancreat Sci. 2019;26(1):9-42.
16. Chari ST, Smyrk TC, Levy MJ, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. Clin Gastroenterol Hepatol. 2006;4(8):1010-1016; quiz 1934.
17. Du S, Liu G, Cheng X, et al. Differential Diagnosis of Immunoglobulin G4-associated Cholangitis From Cholangiocarcinoma. J Clin Gastroenterol. 2016;50(6):501-505.
18. Swensson J, Tirkes T, Tann M, et al. Differentiating IgG4-related sclerosing cholangiopathy from cholangiocarcinoma using CT and MRI: experience from a tertiary referring center. Abdom Radiol (NY). 2019;44(6):2111-2115.
19. Iaccarino L, R T, C S, et al. IgG4-related diseases: State of the art on clinical practice guidelines. RMD Open. 2019;4(Supplement 1):no pagination.
20. Masamune A, Nishimori I, Kikuta K, et al. Randomised controlled trial of long-term maintenance corticosteroid therapy in patients with autoimmune pancreatitis. Gut. 2017;66(3):487-494.
21. Nishino T, M K, M T, et al. Incidence of cancer and risk factors for complication by cacer in IgG4-related sclerosing cholangitis. Gastrointestinal Endoscopy. 2017;85(5 Supplement 1):AB618.
22. Roos E, Hubers LM, Coelen RJS, et al. IgG4-Associated Cholangitis in Patients Resected for Presumed Perihilar Cholangiocarcinoma: a 30-Year Tertiary Care Experience. Am J Gastroenterol. 2018;113(5):765-772.
23. Hart PA, Kamisawa T, Brugge WR, et al. Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis. Gut. 2013;62(12):1771-1776.



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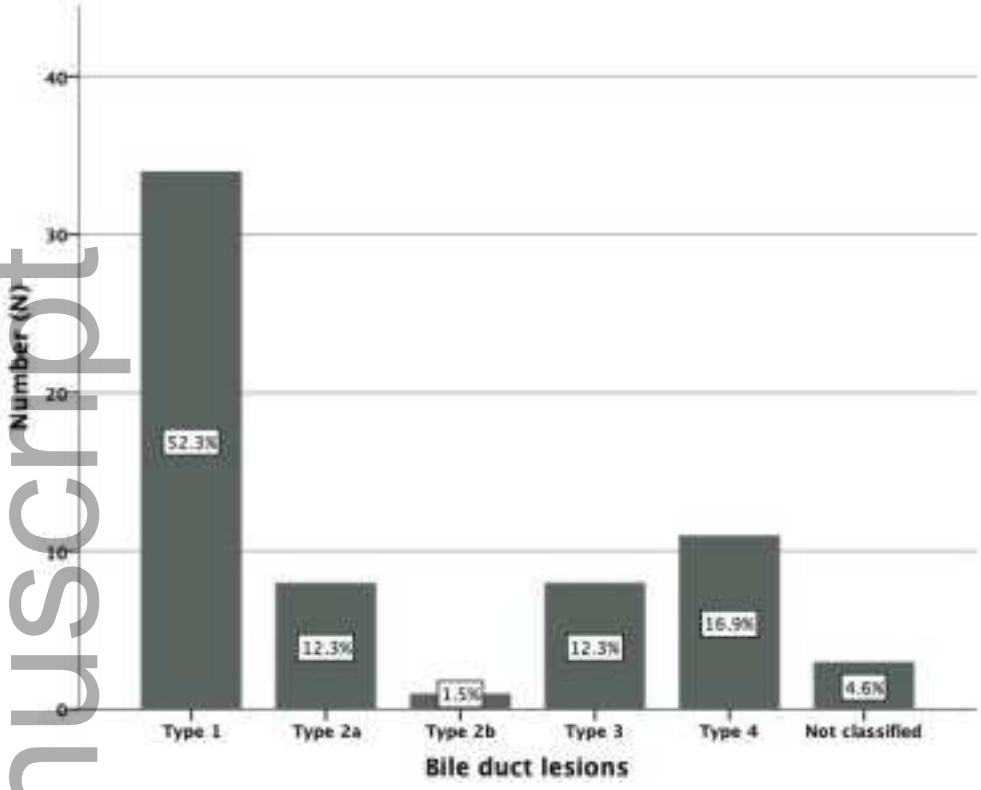

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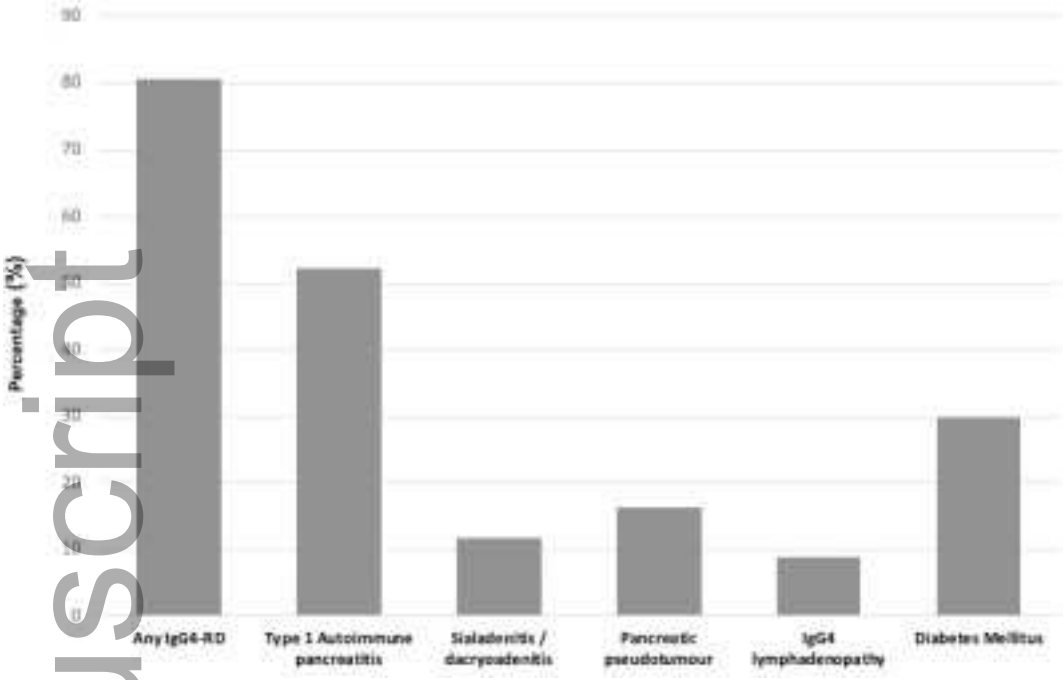

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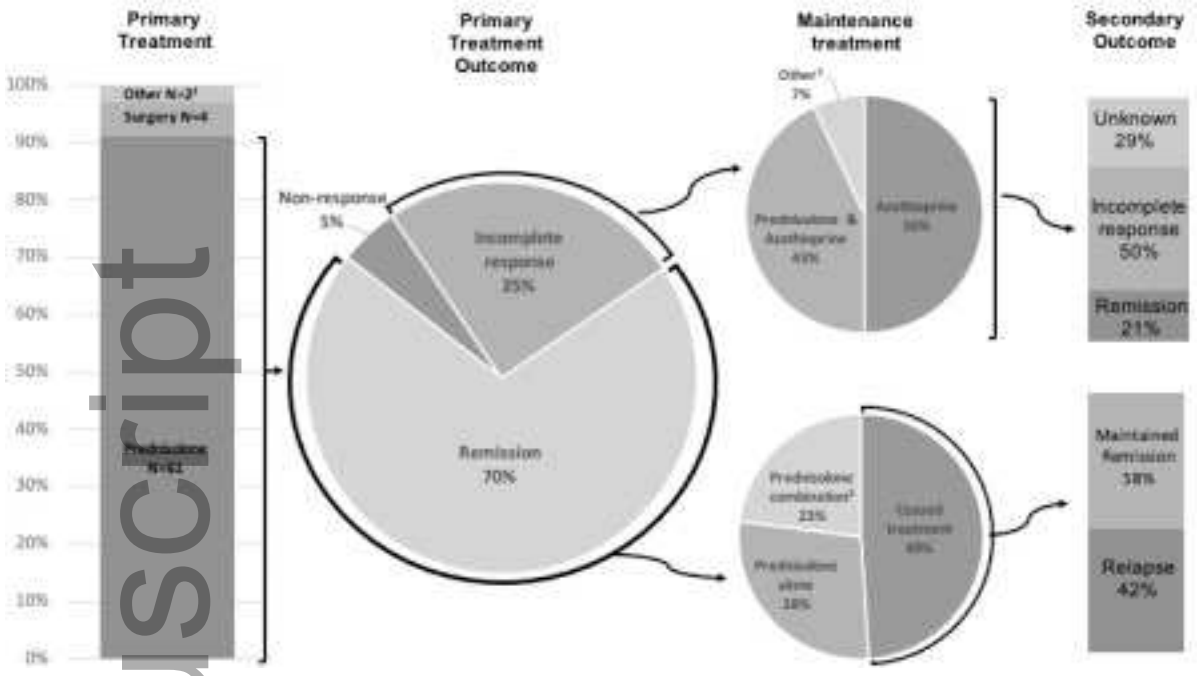

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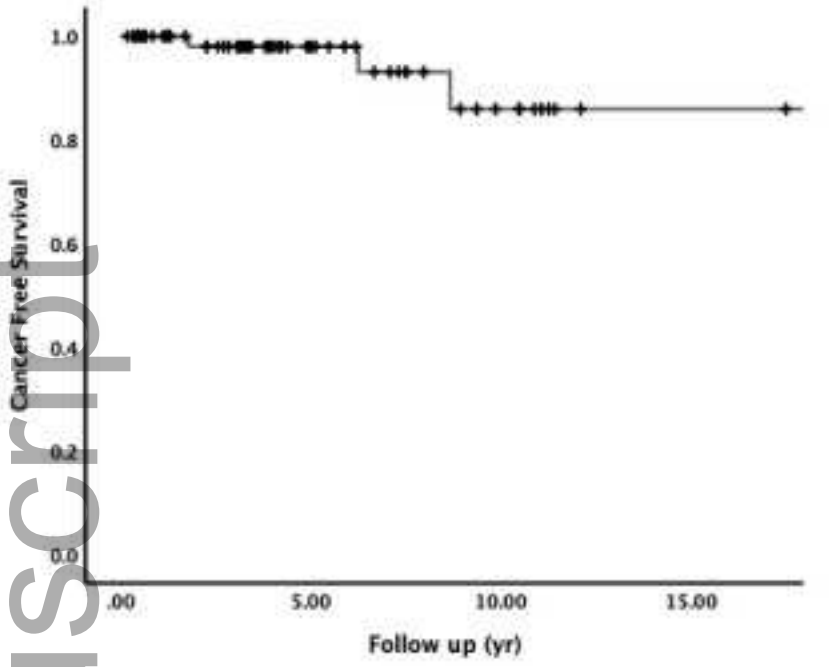

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