BMJ Open Gastroenterology

Pancreaticobiliary versus head and neck presentation of immunoglobulin G4-related disease: different sides of the same coin?

Bidour Awadelkarim ,[1] Josephine Vila,[2] Manu K Nayar ,[1] John S Leeds ,[1,3] Bridget Griffiths,[4] Kofi W Oppong [1,5]

To cite: Awadelkarim B, Vila J, Nayar MK, *et al*. Pancreaticobiliary versus head and neck presentation of immunoglobulin G4-related disease: different sides of the same coin?. *BMJ Open Gastro* 2023;**10**:e000961. doi:10.1136/bmjgast-2022-000961

Received 26 September 2022
Accepted 7 December 2022

[1]HPB Medicine, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[2]Rheumatology Department, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[3]Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK
[4]Rheumatology Department, Newcastle Upon Tyne Hospitals NHS Trust, Newcastle upon Tyne, UK
[5]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK

Correspondence to
Professor Kofi W Oppong; kofi.oppong@nhs.net

ABSTRACT

Background and study aim Immunoglobulin G4-related disease (IgG4-RD) is a rare immune mediated fibroinflammatory condition. Pancreaticobiliary (PB) and head and neck (HN) are two of the most commonly involved anatomical sites. It has been postulated that PB IgG4-RD and HN IgG4-RD have distinct clinical phenotypes. Whether the optimum treatment regimen or response to therapy differs between them is unknown. We aimed to assess differences between PB and HN IgG4-RD in a cohort of IgG4 disease managed by an IgG4-RD multispecialty team.

Methods We performed a retrospective study of a prospectively maintained multidisciplinary IgG4-RD database to identify patients diagnosed with PB and HN IgG4-RD (based on initial presentation) between 2005 and 2019. The electronic patient records were reviewed. Use of immunosuppressive agents and clinical course was analysed.

Results 60 patients with PB IgG4-RD and 14 with HN IgG4-RD were included in the study. PB IgG4-RD was associated with older age at diagnosis 64 versus 51 years (p<0.001), higher serum IgG4 level as a multiple of upper limit of normal median (IQR) 2 (1–3.75) vs 1 (1–2), (p=0.04) and greater proportion with more than one organ involved 68% vs 33% (p=0.03). HN IgG4-RD was more likely to receive second-line therapy 71% versus 36% (p=0.03). Persistent elevation of serum IgG4 after therapy was more common in PB IgG4-RD 84% versus 43% (p=0.03).

Conclusion These findings support the contention that PB IgG4-RD and HN IgG4-RD have different clinical profiles and represent distinct subtypes of IgG4-RD.

WHAT IS ALREADY KNOWN ABOUT THE TOPIC

⇒ Immunoglobulin G4-related disease (IgG4-RD) is a rare disease that can affect any organ, but the head and neck (HN) region and the pancreas are among the most affected organs. Recent studies postulated that pancreatobiliary (PB) IgG4-RD and head and neck IgG4-RD have distinct clinical phenotypes but have not explored the difference in response to therapy.

WHAT THIS STUDY ADDS

⇒ This study highlights the significant difference between the PB and HN IgG4-RD in clinical profiles including the response to therapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Recognising the difference in clinical profiles between the PB IgG4-RD and the HN group, leading to further studies, which might shape future clinical practice and guidelines.

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a systemic fibroinflammatory condition characterised by focal or diffuse organ infiltration by IgG4-positive plasma cells with or without elevated plasma levels of IgG4. It has characteristic histological features with dense lymphoplasmacytic infiltration, storiform fibrosis and obliterative phlebitis[1] . The disease is rare and has a prevalence of fewer than 1 per 100 000[2] in the general population and was only identified as a distinct disease in 2003.[3]

Although IgG4-RD can affect virtually any organ, it has strong predilections for certain organs, including the major salivary glands, orbits and lacrimal glands, the pancreas and biliary tree and the aorta and retroperitoneum[4] . The pathogenesis of the disease remains largely unknown, but data support the role of T-helper type 2 cells and regulatory T cells (T reg cells) in the initiation of the inflammatory and fibrotic process[5] .

The clinical presentation of IgG4-RD is variable depending on the organs involved and can manifest synchronously or metachronously in one or more organs.[4] . About 10%–20% of patients have single organ involvement[6] . The disease process is often subacute or chronic and the patient may be

entirely asymptomatic or present with significant tissue damage and organ failure[7].

Early recognition and treatment are essential to prevent complications and irreversible organ damage. Corticosteroids are the first-line therapy for most patients.[8] Disease-modifying agents perform poorly in induction of remission but have a role in maintenance treatment for some patients or as steroid sparing agents.[8 9] Rituximab was approved by National Health Service (NHS) England for treatment of refractory IgG4-RD in 2016.[10]

In recent years, several studies have described the different frequencies of manifestations of the disease, but the pattern of organ involvement still remains rather unclear.[4 9] Defining typical patterns of organ involvement might identify homogenous groups of IgG4-RD patients, facilitating earlier recognition of the condition.

An analysis of two international cross-sectional cohorts published in 2018 has identified four distinctive IgG4-RD phenotypes according to organ involvement and being Asian or female may predispose individuals to head and neck (HN)-limited disease.[11] A further study published in 2019 has suggested that pancreaticobiliary (PB) and HN IgG4-RD have distinct clinical profiles with earlier age of onset and more even sex distribution in HN compared with PB.[12] Whether response to therapy or need to escalate differs is unknown.

We aimed to assess the clinical presentations and response to therapy based on initial presentation between PB and HN IgG4-RD in a UK cohort of IgG4 RD managed by a tertiary IgG4-RD multispecialty team in the North East of England.

METHODS

The Newcastle upon Tyne NHS Foundation trust serves as the tertiary referral centre for IgG4-RD. Patients are referred from across the north east of England and North Yorkshire. The diagnosis of IgG4-RD was made according to the clinical history, laboratory investigations, imaging and histopathological features and in accordance with the international consensus diagnostic criteria (ICDC) for autoimmune pancreatitis[13] and the 2019 American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) classification criteria for IgG4-related disease.[14]

We performed a retrospective study using the IgG4-RD database. These included cases diagnosed from 2005 until the conduction of this study in 2019. The electronic records of all the patients in the database were screened. Patients were classified to the PB or HN IgG4-RD group based on which organ system involvement led to the initial presentation. Patients presenting with other organ system involvement which are not PB or HN involvement on their initial presentation were excluded from the study.

The medical records were reviewed, and data were collected on demography, age at the time of presentation, symptoms, clinical signs, history of atopy and laboratory investigations including serum IgG4 levels and eosinophil count. Organ involvement was also recorded based on the clinical signs and the review of imaging results, including CT, MRI, fluorodeoxyglucose positron emission tomography-CT, endoscopic ultrasound as well as histological features. The medical therapy was reviewed and recorded, including first-line therapy (corticosteroids), the second-line agent used (azathioprine/mycophenolate mofetil (MMF) and/or methotrexate) and when treatment escalation was needed.

Rituximab was authorised for use in IgG4-RD by National Health Service England in 2016 for refractory or organ threatening disease.[10] The clinical commissioning policy recommended case discussion and oversight of Rutuximab therapy by a multidisciplinary team (MDT) typically including rheumatologists, radiologists, gastroenterologists and hepatologists. Following this guidance, we formalised our multispeciality IgG4-RD MDT. Complex cases were discussed in the MDT for decisions regarding diagnosis, treatment options and ratification of the use of Rituximab since the inception of the MDT was recorded.

PB IgG4-RD was defined as patients with established diagnosis of IgG4-related pancreatitis (type 1 auto immune pancreatitis (AIP)) and/or IgG4-related sclerosing cholangitis as per ICDC.[13] Patients classified as HN IgG4-RD were those with established diagnosis of nasopharyngeal IgG4-RD, IgG4-related ophthalmic disease and IgG4-related sialadenitis.

For the laboratory investigations, serum IgG4 and peripheral blood eosinophil count were recorded. As the cut-off value of serum IgG4 differs depending on the assay used and different assays were used during the course of the study serum, IgG4 was reported in relationship to the upper limit of normal (ULN) of the assay used.

For IgG4-RD organ involvement, each organ involved in the different systems was recorded. The bile duct was considered as a separate organ regardless of the position of the stricture in those with pancreatic involvement. All the salivary glands were regarded as one organ regardless of the number or group. Lymph nodes were regarded as a single-organ entity when involved regardless of number or location.

Statistical analysis

Continuous variables were reported as mean and SD if normally distributed and the median and IQR otherwise. The data were compared between the two groups (PB and HN IgG4-RD) using χ^2 test or Fisher's exact test to analyse categorical variables and student t-test for continuous variables. For all analyses, a p value <0.05 was considered statistically significant. Institutional authorisation to hold a prospective patient database for use for quality improvement was obtained.

RESULTS

60 patients were diagnosed with PB-IgG4-RD between 2005 and 2019 while 14 patients were diagnosed with

Table 1 Summary of the differences between the two IgG4-RD groups

Variable	PB group (n=60)	HN group (n=14)	P
Sex (male)	81.7% (n=49)	57.1% (n=8)	0.023
Age, mean (SD)	64.4 (12.5)	51.1 (15.5)	0.001
History of atopy	36.6% (n=22)	28.5% (n=4)	0.76
Eosinophil count>upper limit of normal (ULN)	21.7% (n=13)	35.7% (n=5)	
Serum IgG4 as (ULN)	74.5% (n=44/59)	50% (n=7)	0.10
Serum IgG4 level, median (IQR) multiples of ULN	2 [1–3.75)	1(1-2)	
Elevated serum IgG4 after therapy	84.1% (n=37/44)	42.8% (n=3/7)	0.031
Number of organs involved>1	68.3% (n=41)	33.3% (n=5)	0.033
Number of organs involved (median)	2	1	

HN, head and neck; PB, pancreatobiliary; ULN, upper limit of normal.

HN-IgG4-RD between 2013 and 2019. Table 1 summarises differences in demographics and clinical parameters between the two groups. Compared with HN-IgG4-RD, patients with PB-IgG4-RD were significantly older at presentation (median age 64.4 years vs 51.1 years p=0.001) and had a higher proportion of men (81.7% vs 57.1%, p=0.023) and an older age at presentation (mean age (SD), 64.4 years (12.5) vs 51.1 years (15.5)) (p=0.001). 22/60 (36.6%) in the PB group had a history of atopy compared with 4/14 (28.5%) in the HN group (with no significant differences between the two groups (p=0.76)). In 2/6 (33.3%) patients with confirmed nasopharyngeal IgG4-RD, cocaine use (snorting) was reported.

Serum IgG4 levels at the time of diagnosis were elevated in 44/59 (74.5 %) PB patients and 7/14 (50%) HN patients (p=0.10). However, those in the PB group had more cases with IgG4 levels elevated as higher multiples of the ULN compared with the HN group (2 (1.0–3.75) vs 1 (1–2), p=0.036). Persistent elevation of IgG4 following successful therapy was significantly more common in the PB group than the HN group (37/44 (84%) vs 3/7 (42.8%), p=0.0310). There was no significant difference in elevation of eosinophil count at the time of presentation between the two groups (13/60 (21.6%) in the PB group vs 5/14 (35.7%) in the HN group, p=0.31).

Of the 74 patients included in the study, 20 had PET CT. All patients in the HN group and the PB group had some form of cross-sectional imaging. Table 2 details the organ involvement at presentation and any other organ involvement that was subsequently identified.

Patients in the PB group had a greater number of organs involved compared with the HN group (41/60 (68.3%) vs 5/14 (33.3%), p=0.033). The median number of additional organs involved was one in the HN group and two in the PB group.

In the HN group, 6/14 (42.8%) patients presented with orbital symptoms, of these, only 1/6 (16.6%) patient had other organ involvement (pterygopalatine fossa and retroperitoneum) in addition to the orbit. In the HN group 6/14 (42.8%) presented with nasopharyngeal symptoms, only 2/6 (33.3%) patients had other organs involved (lungs and salivary grands) in addition to the nasopharynx. One patient presented with salivary gland disease had pancreas and retroperitoneum involvement

Table 2 Organ involvement according to the initial presentation

Group	Organ involved at initial presentation	Number of patients with subsequent organ involvement identified following presentation	Organs involved
Head and neck group (n=14)	Orbit (n=6/14)	1/6	Pterygopalatine fossa and retroperitoneum
	Nasopharynx (n=6/14)	1/6	Lungs
		1/6	Salivary glands
	Salivary gland (n=1/14)	1/1	Pancreas and retroperitoneal
	Cervical lymph node (n=1/4)	1/1	Biliary tree
Pancreatobiliary group (n=60)	Pancreas (n=56)	30/56	Biliary tree
		2/56	Retroperitoneum
		1/56	Gallbladder
		1/56	Biliary tree and kidneys
		1/56	Biliary tree and mediastinal lymph nodes
		1/56	Retroperitoneum and biliary tree
		1/56	Retroperitoneum, lungs and kidneys
		1/56	Biliary tree, lungs and kidneys
		1/56	Biliary tree, parotid, liver and mediastinum
	Biliary tree (n=4)	1/4	Liver, duodenum lungs and

while another patient presenting with cervical lymph node disease had biliary involvement.

In the PB group (n=60), the pancreas was involved in 56/60 (93.3%). In addition to the pancreas, 30/56 (53.5%) patients had biliary tree involvement, 2/56 (3.5%) patients had retroperitoneum involvement and 1/56 (1.8%) patients had gallbladder involvement, while 17/56 (30.3%) patients had only pancreas involvement. The remaining 5/56 (8.9%) patients had other organs involved in addition to the biliary tree (multisystem IgG4-RD) with lungs, kidneys, parotid gland, retroperitoneum, mediastinum and liver involvement while 1/56 (1.8%) patient had retroperitoneum, lungs and kidney involvement. 3/60 (5%) patients had only biliary involvement and 1/60 (1.6%) patients had biliary with liver, duodenum lungs and retroperitoneum involvement.

Regarding therapy, all 14 patients in the HN group received first-line therapy (corticosteroids) compared with 44/60 (73.3%) in the PB group (p=0.031). In the PB group, 2/60 (3.3%) patients received surgical resection and 14/60 (23.3%) did not receive any treatment. There was a significant difference between the two groups in escalation of therapy with only 16/60 (26.7%) of the PB group received at least one second-line therapy compared with the HN group (10/14 vs 16/60, p=0.036).

In the PB group, the most common second-line agent was azathioprine 13/60 (21.6%) followed by methotrexate 4/60 (6.6%), then MMF 2/60 (3.3%). In the HN group, MMF was used in 6/14 (42.8%), methotrexate in 5/14 (35.7%) and azathioprine in 3/14 (21.4%) as second-line therapy. There was a significant difference between the two groups regarding rituximab therapy as only 1/29 (3.4%) in the PB group received rituximab compared with 6/12 (50%) in the HN group (p=0.001). Table 3 summarises the treatment differences between the two groups.

DISCUSSION

The diagnosis of IgG4-RD can be challenging and often involves taking into consideration the clinical presentation, laboratory findings, imaging and histopathological features. Elevated serum IgG4 levels are neither essential nor sufficient for the diagnosis of IgG4-RD but might have a role in disease monitoring.[13 14] The immunohistochemical demonstration of tissue infiltration by IgG4-bearing plasma cells and the morphological evidence of lymphoplasmacytic infiltrates, storiform fibrosis and obliterative phlebitis remain key in the diagnosis.[1 13 14] In 2019, the ACR and the EULAR developed and validated classification criteria for IgG4-RD. The criterion is a three-step process with organ involvement, exclusion and inclusion criteria.[14]

The ICDC were developed in 2011 to aid in the accurate diagnosis of AIP. The ICDC used five cardinal features of AIP, namely, imaging of pancreatic parenchyma and duct, serology, other organ involvement, pancreatic histology and an optional criterion of response to corticosteroid therapy.[13]

PB IgG4-RD is the most frequently observed presentation followed by HN.[4 8] The present study compared the two groups and showed a distinct difference in regards to demographic and clinical profiles similar to some previous studies.[11 12]

In the PB group, the patients were older, predominantly above 60 years of age at the time of presentation, and men in keeping with various previous studies.[11 12] In the HN group, patients were mostly below 60 at the time of presentation, with the female predominance been reported in some previous studies not replicated here.[11 12] The significance of the difference in age and sex between the two groups remains uncertain.

Some studies suggested a possible role of different genetic and environmental factors in the pathogenesis of the disease including smoking.[15] It was difficult to assess all the different environmental factors in this retrospective study. There does not seem to be a clear association with smoking as half of the patients in both the PB and HN group had no smoking history. Lazillotta *et al*[16] looking at a series of destructive and tumefactive lesions of the sinonasal and oral cavity suggested that histological examination was needed to differentiate IgG4 from granulomatosis with polyangiitis and cocaine-induced midline destructive lesions. In our study group, the two patients with nasopharyngeal IgG4-RD who reported cocaine use had histological features consistent with IgG4 disease, hence the association between the two remains unclear.

Although a study[17] reported an association between atopic phenotypes and HN manifestation of IgG4 -RD, our study did not show any differences in the prevalence of a history of atopy. Nevertheless, the eosinophil count was elevated in 21.7% of the PB group and 35.7% of the HN group. In both groups, more than half of those with elevated eosinophil counts did not have a clear history of atopy similar to a previous study,[18] suggesting peripheral blood eosinophilia might reflect processes inherent to the disease itself rather than an association with atopy.

Serum IgG4 levels can be a helpful marker and have been included in many IgG4 RD diagnostic criteria[14]

Table 3 Differences in treatment between the two IgG4-RD groups

Variable	PB group (x)	HN group (Y)	P
Initial steroid therapy	73.3% (n=44)	100% (n=14)	0.031
Second line therapy, at least one agent* Azathioprine MMF Methotrexate	26.7% (n=16) 22% (n=13) 3.3% (n=2) 6.7% (n=4)	71.4% (n=10) 21.4% (n=3) 42.9% (n=6) 35.7% (n=5)	0.031
RTX therapy (in cases diagnosed since 2016)	3.4% (n=1/29)	50% (n=6/12)	0.001

*n=the number of times a second line agent was prescribed—some individuals had more than one second line agent.
HN, head and neck; PB, pancreatobiliary; RTX, Rituximab.

although it is not specific in the diagnosis of IgG4-RD.[19] Previous studies[11] reported higher concentrations of serum IgG4 in the HN presentations compared with other presentations although this has not been the case in the present study as higher serum levels of IgG4 were seen in the PB group compared with the HN group. This was seen when comparing the degree of IgG4 elevation as multiples of the ULN. Mohapatra *et al* reported similar results although it was not statistically significant in their study group.[12] The higher levels of serum IgG4 might be related to the number of organs involved with the disease.[20] and this is supported by the fact that 68% of the patients in the PB group had more than one organ involvement compared with only 33% in the HN group. An analysis of two cross-sectional studies[11] suggested that there might be an association between higher IgG4 concentrations and more extensive disease and in those advanced imaging should be considered.

The pattern of organ involvement also differed between the two groups with only limited organ involvement outside the HN region in this group (lung and retroperitoneum outside the HN region) and with no PB involvement. Meanwhile, a diffuse pattern of organ involvement was seen in the PB group and in only 1/60 had HN manifestation of the disease, in the context of multisystem IgG4-RD. These results might be related to our sample size, but several studies[12 20] showed that HN involvement is not commonly seen in those with PB involvement. Similarly, pancreatobiliary manifestations were uncommon in those with HN IgG4-RD.[12 21 22]

Corticosteroids remain the first line of treatment in IgG4-RD.[4 23] The response to therapy differs depending on the organ involved and the degree of fibrosis[7] and although corticosteroids are initially effective, disease can relapse once they are tapered, and they are associated with possible side effects.[23] Immunosuppressant agents are commonly used with multiple reports of clinical improvement.[8] In the present study, PB group 73.3% of patients had their initial therapy with corticosteroid compared with 100% in the HN group, this is due to a number of patients in the PB group undergoing other interventions in the form of endoscopic/surgical resection. AIP generally responds well to corticosteroid therapy[24] with only 36.3% of the PB group requiring escalation of therapy following initial oral corticosteroids compared with 71.4% in the HN group.

Rituximab (RTX), an anti-CD20 monoclonal antibody, was shown to be a safe and effective treatment in IgG4-RD for the induction and maintenance of remission[25] by inducing B cell depletion, resulting in a decrease in IgG4 plasma cells.[26] It was approved in 2016 by NHS England as a third-line agent in patients with active disease refractory to corticosteroids and other immunosuppression or in patients with contraindications or who experienced adverse reaction to conventional therapies.[10] Half of the patients in the HN group diagnosed since 2016 received RTX therapy compared with a much smaller percentage in the PB group, where only 1/29 received rituximab therapy.

One might argue that this difference might reflect the approach of the different teams in managing these patients. However, since 2016, MDT discussion was mandatory for all cases of IgG4-RD with organ threatening or refractory disease in whom Rituximab therapy was under consideration. This difference in treatment may reflect true differences in the aggressiveness of disease activity between the two groups. A more rapid escalation of therapy in HN disease due to concerns about organ threatening disease is also a possibility.

There are several limitations to this study; as a retrospective study of a well-maintained cohort over a 14-year period, data collection was limited to the information available on the medical records for these patients. Although all cases had confirmed IgG4-RD, investigations have not been standardised across the cohort such as the use of advanced imaging, which might have underestimated the degree of other organ involvement. The establishment of the multidisciplinary team to discuss treatment escalation did not occur until 2016. Sample size is small reflecting the rarity of the condition. Due to the low incidence of the other organ presentations in our centre, including breast and retroperitoneum, these were excluded from our study.

In conclusion, the present study has identified significant differences between PB and HN IgG4-RD cohorts. PB IgG4-RD appears to be associated with an older age at diagnosis, higher serum IgG4 levels and greater risk of multiorgan involvement. A patient with HN IgG4-RD was more likely to receive second and third-line therapy and for treatment response to lead to a reduction in serum IgG4. The findings of this study provide support to the contention that PB IgG4-RD and HN IgG4-RD have distinct clinical profiles and represent distinct subtypes of IgG4-RD. The reasons for this are unclear and further prospective studies are required.

Contributors BA: study concept and design; data collection, analysis and interpretation of data, drafting of the article. KWO: study concept and design; data analysis, and interpretation of data, drafting of the article; critical revision of the article; final approval and guarantor of the article. JV, MKN, JSL, BG: critical revision of the article; final approval of the article.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval As per the United Kingdom National Health Service research, ethics guidance ethical approval from an institutional review body was not required for this study.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement No data are available.

ORCID iDs
Bidour Awadelkarim http://orcid.org/0000-0002-0869-1788

Manu K Nayar http://orcid.org/0000-0002-1196-3406
John S Leeds http://orcid.org/0000-0002-5140-6225
Kofi W Oppong http://orcid.org/0000-0002-7381-7412

REFERENCES

1 Deshpande V, Zen Y, Chan JK, *et al*. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012;25:1181–92.
2 Uchida K, Masamune A, Shimosegawa T, *et al*. Prevalence of IgG4-related disease in Japan based on nationwide survey in 2009. *Int J Rheumatol* 2012;2012:1–5.
3 Kamisawa T, Funata N, Hayashi Y, *et al*. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003;38:982–4.
4 Yamada K, Yamamoto M, Saeki T, *et al*. New clues to the nature of immunoglobulin G4-related disease: a retrospective Japanese multicenter study of baseline clinical features of 334 cases. *Arthritis Res Ther* 2017;19.
5 Chen LYC, Mattman A, Seidman MA, *et al*. Igg4-Related disease: what a hematologist needs to know. *Haematologica* 2019;104:444–55.
6 Chen Y, Zhao J-Z, Feng R-E, *et al*. Types of organ involvement in patients with immunoglobulin G4-related disease. *Chin Med J* 2016;129:1525–32.
7 Wallace ZS, Deshpande V, Mattoo H, *et al*. Igg4-Related disease: clinical and laboratory features in one hundred twenty-five patients. *Arthritis Rheumatol* 2015;67:2466–75.
8 Haldar D, Cockwell P, Richter AG, *et al*. An overview of the diagnosis and management of immunoglobulin G4-related disease. *CMAJ* 2016;188:953–61.
9 Campochiaro C, Ramirez GA, Bozzolo EP, *et al*. Igg4-Related disease in Italy: clinical features and outcomes of a large cohort of patients. *Scand J Rheumatol* 2016;45:135–45.
10 England NHS. *Clinical Commissioning Policy Rituximab for immunoglobulin G4- related disease (IgG4-RD) : 16057/P*, in press.
11 Wallace ZS, Zhang Y, Perugino CA, *et al*. Clinical phenotypes of IgG4-related disease: an analysis of two international cross-sectional cohorts. *Ann Rheum Dis* 2019;78:406–12.
12 Mohapatra S, Sharma A, Chari ST. Pancreatobiliary versus head and neck manifestations in immunoglobulin G4-related disease: distinct subsets of the same disease? *Pancreas* 2019;48:799–804.
13 Shimosegawa T, Chari ST, Frulloni L, *et al*. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International association of Pancreatology. *Pancreas* 2011;40:352–8.
14 Wallace ZS, Naden RP, Chari S, *et al*. The 2019 American College of Rheumatology/European League against rheumatism classification criteria for IgG4-related disease. *Ann Rheum Dis* 2020;79:77–87.
15 Maire F, Rebours V, Vullierme MP, *et al*. Does tobacco influence the natural history of autoimmune pancreatitis? *Pancreatology* 2014;14:284–8.
16 Lanzillotta M, Campochiaro C, Trimarchi M, *et al*. Deconstructing IgG4-related disease involvement of midline structures: comparison to common mimickers. *Mod Rheumatol* 2017;27:638–45.
17 Sanders S, Della Torre E, Perugino CA. Salivary Gland Disease in IgG4-Related Disease Is Associated with Allergic Histories [abstract].. *Arthritis Rheumatol.* 2018;70.
18 Della Torre E, Mattoo H, Mahajan VS, *et al*. Prevalence of atopy, eosinophilia, and IgE elevation in IgG4-related disease. *Allergy* 2014;69:269–72.
19 Ngwa TN, Law R, Murray D, *et al*. Serum immunoglobulin G4 level is a poor predictor of immunoglobulin G4-related disease. *Pancreas* 2014;43:704–7.
20 Kanno A, Nishimori I, Masamune A, *et al*. Nationwide epidemiological survey of autoimmune pancreatitis in Japan. *Pancreas* 2012;41:835–9.
21 Ryu JH, Horie R, Sekiguchi H, *et al*. Spectrum of disorders associated with elevated serum IgG4 levels encountered in clinical practice. *Int J Rheumatol* 2012;2012:1–6.
22 Koizumi S, Kamisawa T, Kuruma S, *et al*. Organ correlation in IgG4-related diseases. *J Korean Med Sci* 2015;30:743–8.
23 Khosroshahi A, Wallace ZS, Crowe JL, *et al*. International consensus guidance statement on the management and treatment of IgG4-related disease. *Arthritis Rheumatol* 2015;67:1688–99.
24 Majumder S, Takahashi N, Chari ST. Autoimmune pancreatitis. *Dig Dis Sci* 2017;62:1762–9.
25 Campochiaro C, Della TE, Lanzillotta M. FRI0584 efficacy and safety of rituximab for induction of remission and maintenance of IgG4-related disease: experience from an Italian national referral centre. in: Annals of the rheumatic diseases. *Vol 78. BMJ* 2019;987:2–988.
26 Khosroshahi A, Bloch DB, Deshpande V, *et al*. Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. *Arthritis Rheum* 2010;62:1755–62.