

# IgG4-related disease: a novel, important but easily missed condition

<sup>1</sup>JS Lees, <sup>2</sup>N Church, <sup>3</sup>B Langdale-Brown, <sup>3</sup>C Bellamy, <sup>4</sup>P Gibson, <sup>4</sup>S Watson

<sup>1</sup>Core Medical Trainee, Department of Renal Medicine; <sup>2</sup>Consultant Gastroenterologist, Department of Gastroenterology; <sup>3</sup>Consultant Histopathologist, Department of Histopathology; <sup>4</sup>Consultant Nephrologist, Department of Renal Medicine; Royal Infirmary of Edinburgh, UK

**ABSTRACT** Immunoglobulin G4-related disease (IgG4-RD) is a multisystem, fibroinflammatory condition unrecognised in medical science until the last decade. It is characterised by progressive scarring and dysfunction of affected organs and tissues including the pancreas, hepatobiliary tree, kidneys, salivary glands, retroperitoneum and lungs. The diagnosis is made with the presence of numerous IgG4 positive plasma cells within a histologically-distinct chronic inflammatory process; most patients also have elevated serum IgG4. Though early cases were all identified in Japan, subsequent reports clearly demonstrate that IgG4-RD exists worldwide. There are no data confirming the prevalence of IgG4-RD in the West but it is thought to be very rare. Limited awareness of the condition and its heterogeneous presentation frequently results in misdiagnosis. Prompt and correct diagnosis is critical, as a rapid reversal of even advanced disease is often seen with corticosteroid therapy. We present three cases that illustrate some of the typical features of this condition.

**KEYWORDS** IgG4, IgG4-RD, interstitial nephritis, autoimmune pancreatitis, corticosteroids, retroperitoneal fibrosis

**DECLARATION OF INTERESTS** No conflicts of interest declared.

**Correspondence to S Watson**  
Department of Renal Medicine  
Royal Infirmary of Edinburgh  
51 Little France Crescent  
Edinburgh EH16 4SA, UK

tel. +44 (0)131 242 1246  
e-mail [simon.watson@nhs.net](mailto:simon.watson@nhs.net)

## CASE 1

A 67-year-old man presented with a progressive decline in kidney function; serum creatinine rose from 73  $\mu\text{mol}$  to 346  $\mu\text{mol}$  ( $n=60\text{--}120$   $\mu\text{mol}$ ) between 2010 and 2012 (Figure 1A). Previous medical history included recent onset type 2 diabetes mellitus (HbA1c  $<7\%$  – diet controlled), kidney stones and colorectal adenocarcinoma, treated with an anterior resection complicated by pseudomembranous colitis. Physical examination demonstrated evidence of previous colorectal surgery but no other medical condition of note. The clinical features are summarised in Table 1A.

A urine dipstick test showed protein++ and blood+++ . The urinary albumin:creatinine ratio was 3.7 mg/mmol (n=0–2.5). Urinary Bence Jones protein, plasma electrophoresis, serum calcium and liver function test (LFTs) results were normal. Immunological investigations are summarised in Table 1B.

An abdominal ultrasound scan (USS) showed a non-obstructive left renal calculus. A biopsy of the left kidney was performed; the histological findings were consistent with IgG4-RD associated nephropathy, with coincidental clinically-insignificant mesangial immunoglobulin A (IgA) disease (Figure 1A).<sup>1</sup> This diagnosis was supported by significantly elevated serum IgG4 with otherwise normal

IgG4 subclasses (Table 1B). Given normal LFTs and no significant pancreatic symptoms, the diagnosis of diabetes was felt to be unrelated to IgG4-RD.

Prednisolone 40 mg once daily (0.5 mg/kg/day) was commenced and the serum creatinine fell from 408  $\mu\text{mol}$  to 251  $\mu\text{mol}$  within four weeks (Figure 1A). Gradual steroid reduction in 5 mg increments per fortnight began after eight weeks; dialysis was not required.

## CASE 2

A 55-year-old man presented with malaise, dyspepsia, weight loss (7 kg), dry eyes, intermittent cramps and pruritus. Previous medical history included chronic sialadenitis of the right submandibular gland and two pulmonary emboli (the patient was on life-long warfarin). He took no other long-term medications. His blood pressure was 131/83 mm Hg. A full physical examination was unremarkable. Urinalysis showed traces of blood and protein; the urinary protein:creatinine ratio was 122 mg/mmol ( $n=0\text{--}15$ ). The serum creatinine was 716  $\mu\text{mol}$  (estimated glomerular filtration rate [eGFR]=7 mL/min/1.73m<sup>2</sup>). C-reactive protein was elevated at 22 g/L ( $n=0\text{--}5$ ) and he was anaemic with a haemoglobin (Hb) of 106 g/L ( $n=130\text{--}180$ ); haematinics, LFTs, calcium, phosphate and albumin were all normal and neither serum paraproteins nor

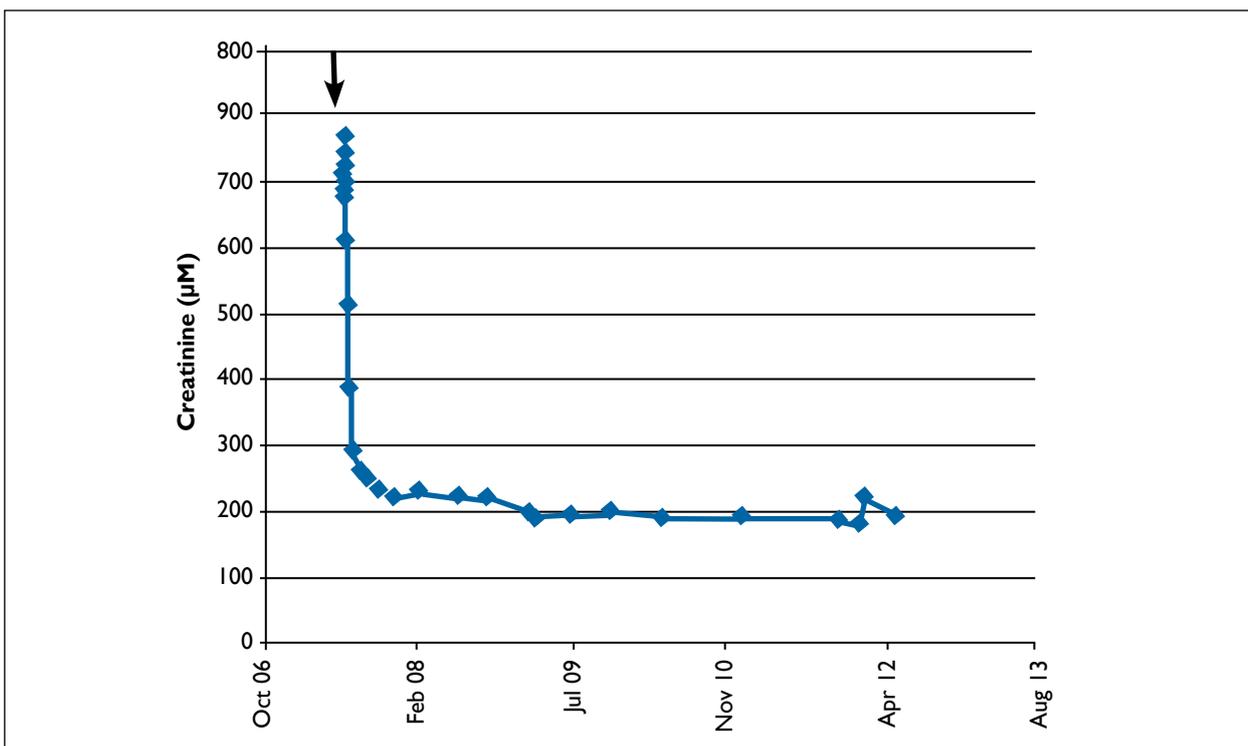
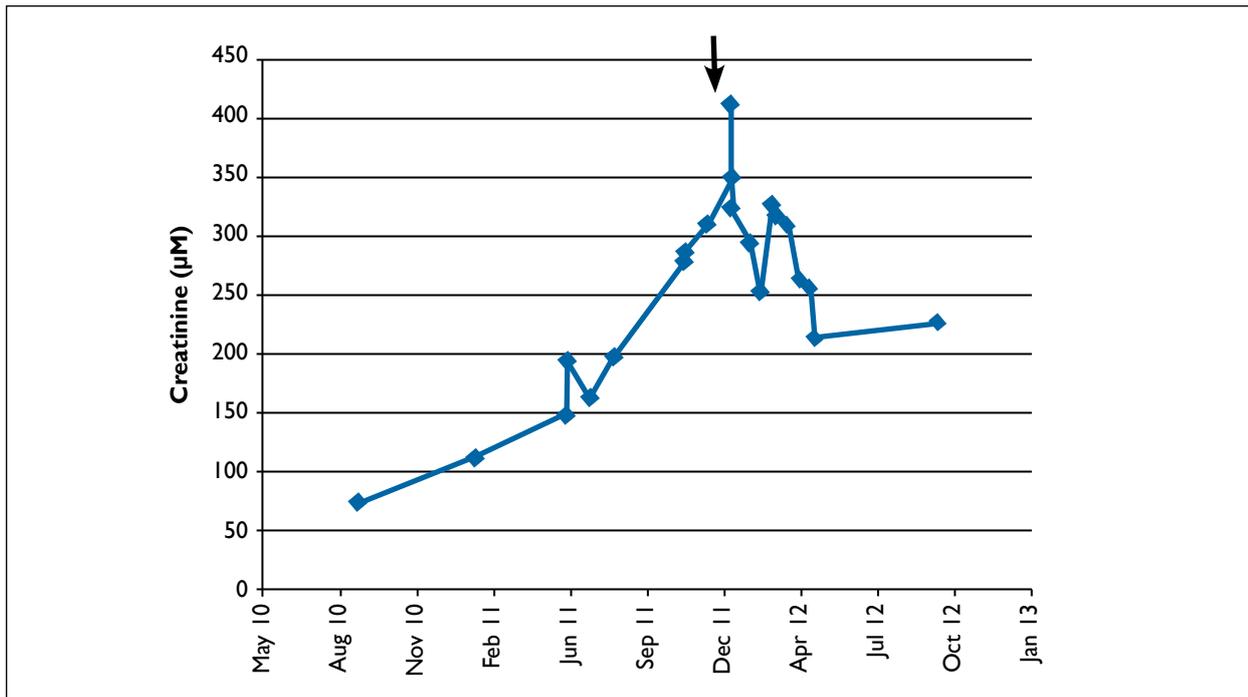
**TABLE IA** Summary of the clinical features seen in three cases presented

	Case 1	Case 2	Case 3
Age	67	55	70
Gender	M	M	F
Clinical presentation	Incidental abnormal renal function	Malaise, dyspepsia, weight loss, dry eyes, intermittent cramps and pruritus	Steatorrhoea, dark urine and pruritis
Organ involvement	Kidney	Kidney, salivary gland	Pancreas, retro-peritoneum
Serum levels of IgG4 (0.039–0.86 g/L)	3.78	>1.56	8.85
Treatment	Prednisolone	Prednisolone, azathioprine	Prednisolone
Length of follow-up	10 months	6 years	17 months

**TABLE IB** Summary of the immunological tests performed in each of the three cases presented

Immunological test		Case 1	Case 2	Case 3
Serum level of IgG4	Total (6.0–16.0 g/L)	13.5	23.6	23.6
	IgG1 (3.82–9.28 g/L)	7.58	13.4	10
	IgG2 (2.41–7.00 g/L)	4.27	6.43	2.49
	IgG3 (0.22–1.76 g/L)	1.43	>1.99	1.41
	IgG4 (0.039–0.86 g/L)	3.78	>1.56	8.85
ANCA by EIA	MPO	Negative	Negative	Not tested
	PR3	Negative	Negative	Not tested
ANA		Negative	Positive (1/40 homogeneous)	Positive (1/160 homogeneous)
Anti-dsDNA (0–15 IU/mL)		Not tested	39	27.1
ENA screen	Ro	Negative	Not tested	Not tested
	La	Negative	Not tested	Not tested
	Sm	Negative	Not tested	Not tested
	RNP	Negative	Not tested	Not tested
	SC170	Negative	Not tested	Not tested
	Jo1	Negative	Not tested	Not tested
Anti-GBM (0–20 U/mL)		Not tested	4.5	Not tested
C3 (0.73–1.4 g/L)		0.88	0.43	Not tested
C4 (0.12–0.3 g/L)		0.1	0.02	Not tested
Classical complement pathway (47.6–130.4 % activity)		0.6	Not tested	Not tested
Total haemolytic complement		Not tested	No lysis	Not tested
Anti thyroid peroxidase (0–50 U/mL)		Not tested	Not tested	17.0
Intrinsic factor (0–6.0 IU/mL)		0.4	Not tested	Not tested
Smooth muscle antibody		Not tested	Not tested	Not tested
Gastric parietal cell		Not tested	Not tested	Positive
Mitochondrial antibody		Not tested	Not tested	Negative
Cyclic citrullinated peptide (0–4.8 U/mL)		1.8	Not tested	Not tested
Rheumatoid factor (0–20 IU/mL)		Not tested	2	Not tested

**ANCA by EIA**= anti-neutrophil cytoplasmic antibody by enzyme immunoassay; **ANA**= anti-nuclear antibody; **Anti-dsDNA**= anti-double stranded dextoxyribonucleic acid antibody; **ENA**= extractable nuclear antigen; **MPO**= myeloperoxidase; **PR3**= proteinase 3; **RNP**= ribonuclear protein; **C3**= complement component 3; **C4**= complement component 4

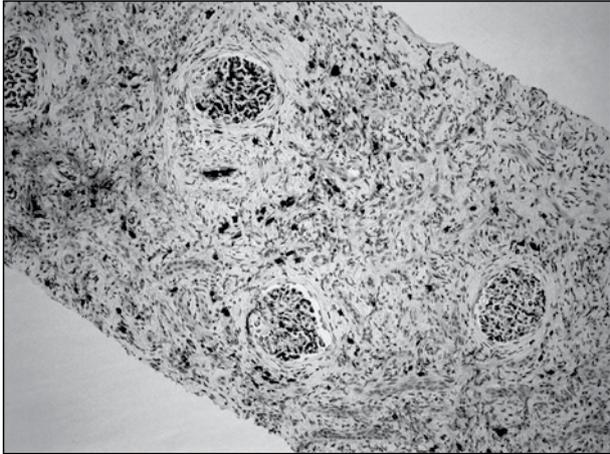


**FIGURES 1A AND 1B** Graphs showing serial serum creatinine measurements (µmol Y-axis) over time (year, X-axis) for case 1 (upper graph) and case 2 (lower graph). In each graph arrows indicate the time that corticosteroid therapy was commenced.

urinary Bence Jones protein were identified. Immunology is summarised in Table IB. Chest radiograph and a renal tract USS were unremarkable.

A renal biopsy showed significant fibrosis, plasma cell and eosinophil-rich interstitial nephritis consistent with IgG4-RD nephritis, supported by a raised serum IgG4 (Tables IA/IB). A retrospective analysis of previously-

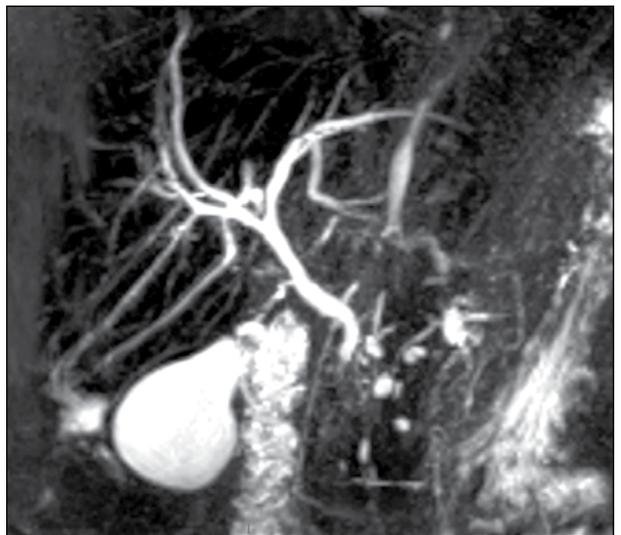
resected submandibular gland tissue also demonstrated IgG4-related disease. The patient's serum creatinine fell rapidly following the commencement of prednisolone 60 mg/day (716 to 386 µmol within two weeks. Figure 1B). Steroids were subsequently withdrawn and stable, moderate chronic kidney disease (CKD) was treated with 100 mg/day of azathioprine.



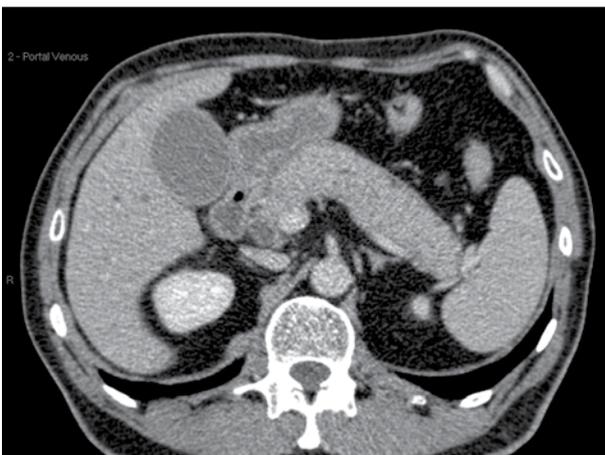
**FIGURE 1C** Representative image of the renal biopsy from Case 1 demonstrating severe chronic tubulointerstitial nephritis, tubular atrophy, interstitial scarring, dense fibroblastic sclerosis and loss of peritubular capillaries. Numerous IgG4 positive plasma cells (dark staining) are seen in glomeruli and tubulointerstitial compartments. With immunofluorescence, glomeruli showed mild to moderate (++) mesangial granular immunopositivity for IgA and weak positivity for complement C3, but were immunonegative for other immunoglobulin heavy chains, complement C1q and light chains. On light microscopy there was no mesangial, endocapillary or extra capillary proliferation, no significant mesangial matrix increase and no evidence of segmental sclerosis or other attributable lesion. Electron microscopy showed mild expansion of mesangial matrix with some wrinkling of capillary walls but no electron dense deposits in the planes of section. It was concluded that the mesangial IgA identified was incidental to the clinical presentation, and not associated with metrics of significant glomerulonephritic activity or attributable lesions of chronic glomerulonephritis. Similar features (except IgA nephropathy) seen in the biopsy from Case 2.



**FIGURE 2B** Magnetic resonance cholangio-pancreatography (MRCP) cholangiogram demonstrating multiple strictures throughout the biliary tree.



**FIGURE 2C** Resolution of the changes seen in previous Figure after four weeks of corticosteroid therapy.



**FIGURE 2A** Representative imaging in IgG4-RD pancreatic/biliary disease. Computed tomography scan of the abdomen demonstrating a 'sausage' pancreas with surrounding hypoechoic rim, classical features of IgG4-RD/autoimmune pancreatitis.

### CASE 3

A 70-year-old woman presented with steatorrhoea, dark urine and pruritis. She maintained a good appetite and denied weight loss. Her past medical history included

asthma, gastroesophageal reflux disease and impaired glucose tolerance. Blood tests showed bilirubin 10  $\mu\text{mol}$  ( $n=3-16$ ), alanine-transferase (ALT) 63 U/L ( $n=10-50$ ), alkaline phosphatase 1,215 U/L ( $n=40-125$ ), gamma glutamyltranspeptidase (GGT) 158 U/L ( $n=5-35$ ) and evidence of renal impairment – serum creatinine 130  $\mu\text{mol}$  ( $n=60-120$ ), eGFR 35 with normal electrolytes. She had normocytic anaemia (Hb 99 g/L [ $n=115-160$  g/L]) with normal haematinics. Albumin was low at 33 g/L ( $n=35-50$ ) and faecal elastase very low ( $<50$   $\mu\text{g/g}$  [ $n=200-1,000$ ]) suggesting pancreatic insufficiency. A coagulation screen, amylase, ferritin and serum calcium levels were normal. An abdominal USS revealed a distended gallbladder with calculi and debris, dilated intra- and extra-hepatic bile ducts and a possible mass at the pancreatic head. Computerised tomography (CT) scanning of the abdomen identified a bulky pancreatic

head and uncinate process, gallstones and biliary dilatation with retroperitoneal fibrosis and cortical enhancement of two unobstructed kidneys. On endoscopic USS, appearances were strongly suggestive of an autoimmune pancreatitis (AIP) and magnetic resonance cholangiopancreatography (MRCP) demonstrated an atrophied pancreas with an irregular pancreatic duct and a common bile duct stricture (Figures 2A–C). A percutaneous pancreatic biopsy showed features consistent with AIP (Figures 3A and B). Serum IgG4 was markedly elevated with normal or only mildly elevated IgG1-3 subtypes (Table 1B). Prednisolone 40 mg/day was commenced and LFTs rapidly improved (bilirubin 4 µmol/L, ALT 27 U/L, alkaline phosphatase 228 U/L and GGT 74 U/L), together with radiological and clinical resolution of features of obstruction and pancreatic insufficiency.

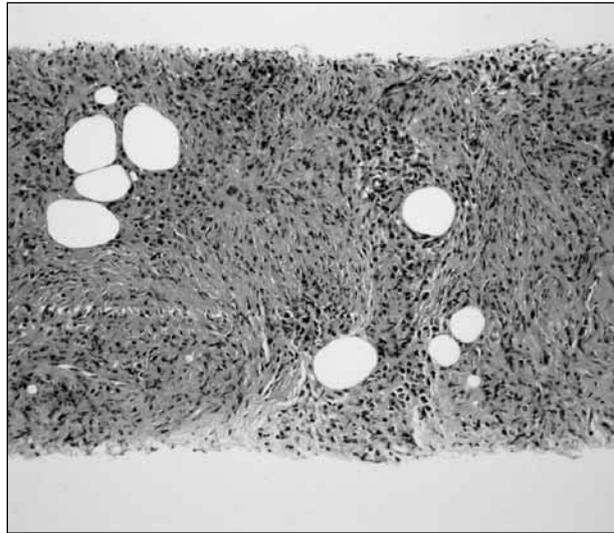
**TABLE 2** Common organs affected by IgG4-RD. A review by Zen and Nakanuma<sup>15</sup> of 114 cases of IgG4-RD identified 206 separate histologically confirmed lesions. The distribution of these lesions and the frequency (expressed as a percentage of the total number of lesions) is summarised below.

Anatomical site	Frequency (% of total)
Liver and biliary tree	26
Salivary and lacrimal glands	26
Lungs and pleura	15
Pancreas	14
Aortitis and retroperitoneal fibrosis	11
Kidney	5
Other (lymph nodes, prostate, breast and peripheral nerves)	4

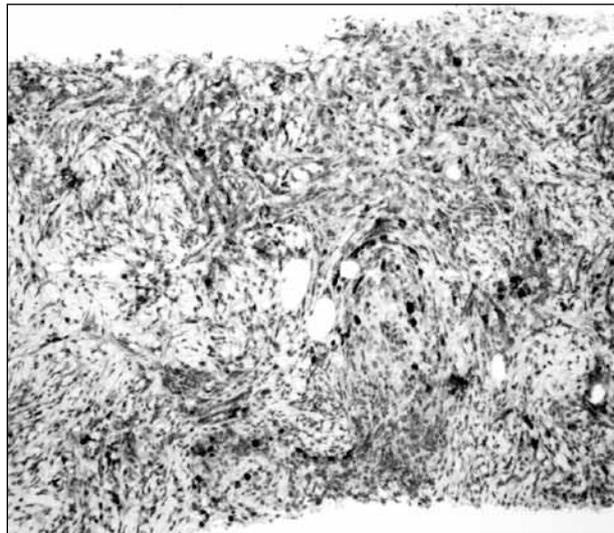
**DISCUSSION**

The cases we have presented demonstrate many typical clinical manifestations of IgG4-RD including AIP,<sup>1</sup> sialadenitis (Mikulicz’s disease),<sup>2</sup> parenchymal kidney disease<sup>3,4</sup> and retroperitoneal fibrosis.<sup>5,6</sup> A comprehensive list of frequently affected organs is listed in Table 2. The diagnosis is based upon end-organ dysfunction due to a distinct form of chronic inflammation and elevation of serum IgG4 (>1.35 g/L). The characteristic histopathological features are a marked lymphoplasmacytic infiltration, storiform fibrosis, occlusive venulitis and increased IgG4+ plasma cells (Figures 3C, D, E and F). In recent years, consensus diagnostic and management guidelines have been developed.<sup>7-9</sup> There are several detailed reviews of this condition covering many clinical and biological aspects of IgG4-RD.<sup>10-17</sup>

Immunoglobulin G4-related disease causes significant morbidity due to direct organ damage and indirectly by misidentification as malignancy. The AIP mimicry of pancreatic cancer is particularly problematic and, historically, accounted for approximately a quarter of the cases of non-malignant pancreatic mass lesions removed using Whipple’s procedure.<sup>18</sup> The identification



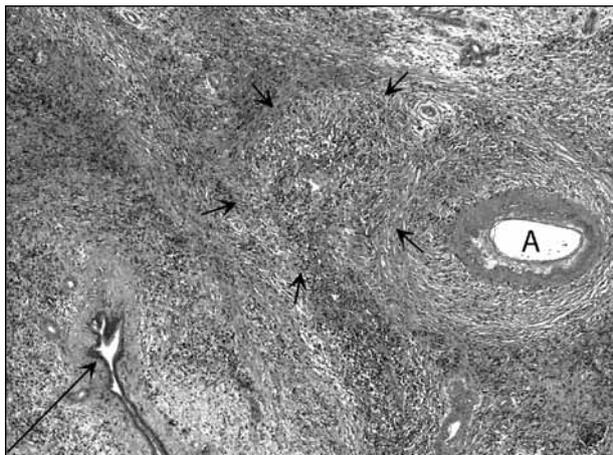
**FIGURE 3A** Haematoxylin and eosin stain (H&E): Case 3 pancreatic trucut biopsy: representative image showing lymphoplasmacytic inflammation, fibrosis and virtually no recognisable pancreatic tissue.



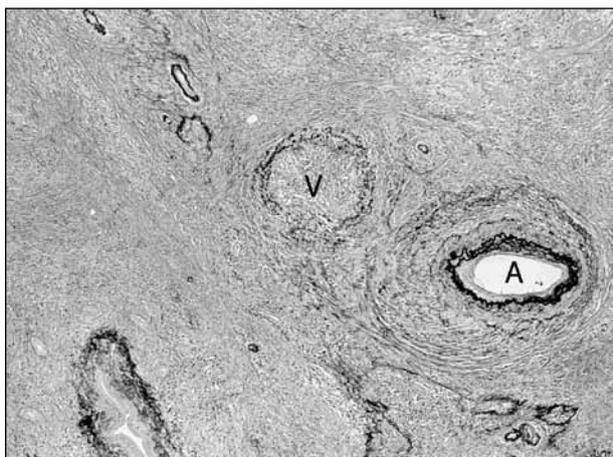
**FIGURE 3B** IgG4 stain: Case 3 pancreatic trucut biopsy: representative image showing increased numbers of IgG4 positive plasma cells (dark staining).

of serum IgG4 as a discriminating factor for IgG4-RD has aided diagnosis, though raised IgG4 alone should not be relied upon;<sup>9,18-21</sup> confirmatory tissue diagnosis is usually required.

The majority of reported cases of IgG4-RD are in Japanese patients, though it is unclear whether this reflects greater prevalence or better recognition of the condition in Japan.<sup>22</sup> However, it has become clear that IgG4-RD is neither confined to Japan nor patients of Japanese origin but affects patients around the world.<sup>3,23-29</sup> Epidemiological data come largely from a single Japanese study of AIP which described a male:female ratio of 2.85:1, peak age of onset of 61–65 years old and an estimated prevalence of 0.82 per 100,000 adults.<sup>30</sup> There is no



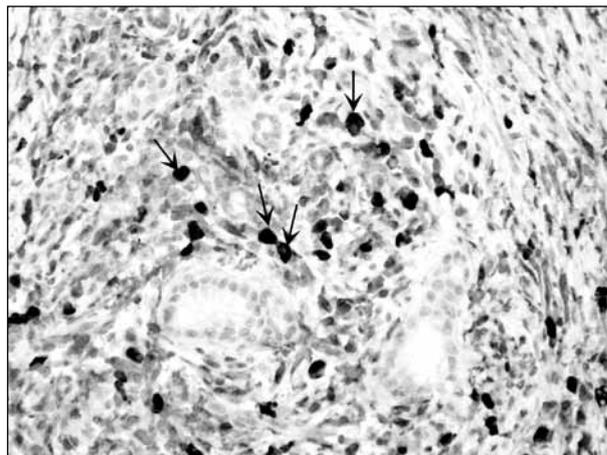
**FIGURE 3C** Haematoxylin and eosin stain (H&E). A typical example of IgG4-related autoimmune pancreatitis in a Whipple's resection (from another patient). Virtually all of the normal pancreatic tissue has been replaced by a lymphoplasmacytic infiltrate and storiform fibrosis. A residual pancreatic duct is seen bottom left (long arrow). An arteriole, (A), is seen on the right, but its accompanying venule (short arrows), is almost undetectable on H&E due to the occlusive venulitis which is characteristic of IgG4-RD.



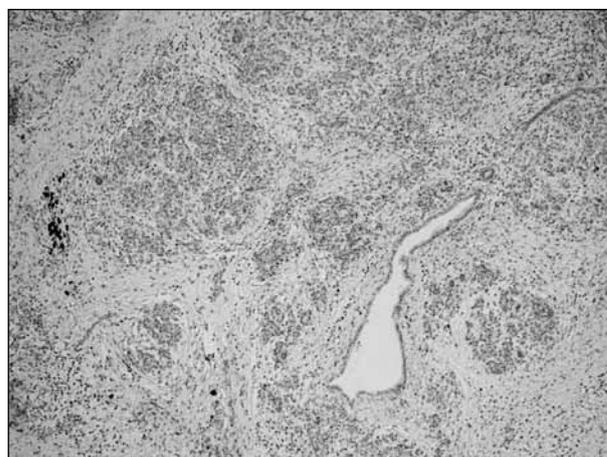
**FIGURE 3D** Same area as Figure 2C: this elastic van Gieson (EVG) stain highlights the occlusive venulitis. The venule (V) is now easily detectable.

reliable estimate of prevalence in the West, however it can be seen in comparison with other better known conditions (the prevalence of Hodgkin's lymphoma and amyloid A [AA] amyloidosis in Western Europe for example are 0.5 and 1.0 per 100,000 respectively).<sup>31,32</sup>

The disease is a direct cause of significant damage to affected tissues<sup>3,33-36</sup> but it is usually highly responsive to steroid therapy.<sup>37</sup> Standard therapy is prednisolone 0.6 mg/kg induction treatment for two to four weeks, reducing by 5 mg increments every one to two weeks.<sup>38</sup> The efficacy of corticosteroids in even advanced cases of IgG4-RD kidney disease is well-established and rapid response to steroid therapy can help to establish the diagnosis.<sup>3,4,27,39-43</sup> Second-line immunosuppression using



**FIGURE 3E** IgG4 stain. Same case as Figures 2C/2D: IgG4-related autoimmune pancreatitis. Representative image showing 25 IgG4 positive plasma cells per high power field.



**FIGURE 3F** For comparison. Usual type chronic pancreatitis (not IgG4-related) stained with IgG4 – this representative low power view shows that in most areas there are no IgG4 positive plasma cells per high power field. A rare cluster of positive cells is seen on the left. The average count is less than one per high power field, range 0-13.

## SUMMARY

1. IgG4-RD is a multisystem disorder affecting many organs but with a preponderance for glandular tissues.
2. Older males are most often affected.
3. Serum IgG4 is a useful diagnostic marker but tissue or radiological evidence is usually required before treatment begins.
4. Corticosteroids are almost always the first-line therapy.
5. Even very advanced cases are frequently responsive to corticosteroid therapy.

azathioprine,<sup>44</sup> mycophenolate mofetil,<sup>45</sup> bortezomib (a proteasome inhibitor with cytotoxic effect against plasma cells)<sup>46</sup> and rituximab (a monoclonal antibody against the CD20 protein)<sup>47,48</sup> have been described.

We believe that clinicians in a wide variety of specialties are probably encountering, but perhaps not always identifying, cases of IgG4-RD. We acknowledge the

inconsistencies in immunological testing in our own cases, and believe that this highlights the need for a more uniform diagnostic approach across specialties. We hope this report will help to raise awareness of an under-recognised, serious but treatable condition.

## REFERENCES

- Sarles H, Sarles JC, Muratore R et al. Chronic inflammatory sclerosis of the pancreas – an autonomous pancreatic disease? *Am J Dig Dis* 1961; 6:688–98. <http://dx.doi.org/10.1007/BF02232341>
- Mikulicz J. Über eine eigenartige symmetrische Erkrankung der Tränen und Mundspeicheldrüsen. *Beitr Chir Fortsch Gewidmet Theodor Billroth* 1892;6:10–30. German.
- Watson SJ, Jenkins DA, Bellamy CO. Nephropathy in IgG4-related systemic disease. *Am J Surg Pathol* 2006; 30:1472–7. <http://dx.doi.org/10.1097/01.pas.0000213308.43929.97>
- Takeda S, Haratake J, Kasai T et al. IgG4-associated idiopathic tubulointerstitial nephritis complicating autoimmune pancreatitis. *Nephrol Dial Transplant* 2004; 19:474–6. <http://dx.doi.org/10.1093/ndt/gfg477>
- Fukukura Y, Fujiyoshi F, Nakamura F et al. Autoimmune pancreatitis associated with idiopathic retroperitoneal fibrosis. *AJR Am J Roentgenol* 2003; 181:993–5.
- Sevenet F, Capron-Chivrac D, Dalcenserie R et al. Idiopathic retroperitoneal fibrosis and primary biliary cirrhosis. A new association? *Arch Intern Med* 1985; 145:2124–5. <http://dx.doi.org/10.1001/archinte.1985.00360110200042>
- Massachusetts General Hospital. *IgG4-related disease responder index (IgG4-RD RI)* [Internet]. Boston: MGH [cited 2013 Jan 24]. Available from: <http://www2.massgeneral.org/pathology/symposium/pdf/PDF1-ResponderIndexinstructionguide.pdf>.
- Umehara H, Okazaki K, Masaki Y et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 2012; 22:21–30. <http://dx.doi.org/10.1007/s10165-011-0571-z>
- 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. <http://dx.doi.org/10.1097/MPA.0b013e3182142fd2>
- Stone JH, Zen Y, Deshpande V. IgG4-related disease. *New Engl J Med* 2012; 366:539–51. <http://dx.doi.org/10.1056/NEJMra1104650>
- Khosroshahi A, Stone JH. A clinical overview of IgG-4 related systemic disease. *Curr Opin Rheumatol* 2011; 23:57–66. <http://dx.doi.org/10.1097/BOR.0b013e3283418057>
- Khosroshahi A, Stone JH. Treatment approaches to IgG-4 related systemic disease. *Curr Opin Rheumatol* 2011; 23:67–71. <http://dx.doi.org/10.1097/BOR.0b013e328341a240>
- Khosroshahi A, Stone JH. IgG4-related systemic disease: the age of discovery. *Curr Opin Rheumatol* 2011; 23:72–3. <http://dx.doi.org/10.1097/BOR.0b013e328341a229>
- Geyer JT, Deshpande V. IgG4-associated sialadenitis. *Curr Opin Rheumatol* 2011; 23:95–101. <http://dx.doi.org/10.1097/BOR.0b013e3283413011>
- Zen Y, Nakanuma Y. Pathogenesis of IgG4-related disease. *Curr Opin Rheumatol* 2011; 23:114–8. <http://dx.doi.org/10.1097/BOR.0b013e3283412f4a>
- Carruthers MN, Stone JH, Khosroshahi A. The latest on IgG4-RD: a rapidly emerging disease. *Curr Opin Rheumatol* 2012; 24:60–9. <http://dx.doi.org/10.1097/BOR.0b013e32834ddb4a>
- Stone JH, Khosroshahi A, Deshpande V et al. Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. *Arthritis Rheum* 2012; 64:3061–7. <http://dx.doi.org/10.1002/art.34593>
- Hamano H, Kawa S, Horiuchi A et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *New Engl J Med* 2001; 344:732–8. <http://dx.doi.org/10.1056/NEJM200103083441005>
- Chen RY, Adams DB. IgG4 levels in non-Japanese patients with autoimmune sclerosing pancreatitis. *New Engl J Med* 2002; 346:1919. <http://dx.doi.org/10.1056/NEJM200206133462420>
- Hughes DB, Grobmyer SR, Brennan MF. Preventing pancreaticoduodenectomy for lymphoplasmacytic sclerosing pancreatitis: cost effectiveness of IgG4. *Pancreas* 2004; 29:167. <http://dx.doi.org/10.1097/00006676-200408000-00013>
- Kawano M, Saeki T, Nakashima H et al. Proposal for diagnostic criteria for IgG4-related kidney disease. *Clin Exp Nephrol* 2011; 15:615–26. <http://dx.doi.org/10.1007/s10157-011-0521-2>
- Umehara H, Okazaki K, Masaki Y et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. *Mod Rheumatol* 2011; 22:1–14. <http://dx.doi.org/10.1007/s10165-011-0508-6>
- Neild GH, Rodriguez-Justo M, Wall C et al. Hyper-IgG4 disease: report and characterisation of a new disease. *BMC Med* 2006; 4:23. <http://dx.doi.org/10.1186/1741-7015-4-23>
- Cravedi P, Abbate M, Gagliardini E et al. Membranous nephropathy associated with IgG4-related disease. *Am J Kidney Dis* 2011; 58:272–5. <http://dx.doi.org/10.1053/j.ajkd.2011.05.002>
- Van Moerkercke V, Verhamme M, Meeus G et al. A case of IgG4-related sclerosing disease with retroperitoneal fibrosis, autoimmune pancreatitis and bilateral focal nephritis. *Pancreas* 2009; 38:825–32. <http://dx.doi.org/10.1097/MPA.0b013e318ac522f>
- Dhobale S, Bedetti C, Killian P et al. IgG4 related sclerosing disease with multiple organ involvements and response to corticosteroid treatment. *J Clin Rheumatol* 2009; 15:354–7. <http://dx.doi.org/10.1097/RHU.0b013e3181b5d631>
- Cornell LD, Chicano SL, Deshpande V et al. Pseudotumors due to IgG4 immune-complex tubulointerstitial nephritis associated with autoimmune pancreatocentric disease. *Am J Surg Pathol* 2007; 31:1586–97. <http://dx.doi.org/10.1097/PAS.0b013e318059b87c>
- Kim KP, Kim MH, Song MH et al. Autoimmune chronic pancreatitis. *Am J Gastroenterol* 2004; 99:1605–16. <http://dx.doi.org/10.1111/j.1572-0241.2004.30336.x>
- Pearson RK, Longnecker DS, Chari ST et al. Controversies in clinical pancreatology: autoimmune pancreatitis: does it exist? *Pancreas* 2003; 27:1–13. <http://dx.doi.org/10.1097/00006676-200307000-00001>
- Nishimori I, Tamakoshi A, Otsuki M. Prevalence of autoimmune pancreatitis in Japan from a nationwide survey in 2002. *J Gastroenterol* 2007; 42 Suppl 18:6–8. <http://dx.doi.org/10.1007/s00535-007-2043-y>
- World Health Organization. *GLOBOCAN 2008. Cancer incidence and mortality worldwide*. [Internet] France: International Agency for Research on Cancer; 2010 [cited 2013 Jan 24]. Available from: <http://globocan.iarc.fr>.
- Simms RV, Prout MN, Cohen AS. The epidemiology of AL and AA amyloidosis. *Baillieres Clin Rheumatol* 1994; 8:627–34. [http://dx.doi.org/10.1016/S0950-3579\(05\)80119-0](http://dx.doi.org/10.1016/S0950-3579(05)80119-0)
- Stone JH, Khosroshahi A, Deshpande V et al. IgG4-related systemic disease accounts for a significant proportion of thoracic lymphoplasmacytic aortitis cases. *Arthritis Care Res (Hoboken)* 2010; 62:316–22. <http://dx.doi.org/10.1002/acr.20095>

- 34 Dahlgren M, Khosroshahi A, Nielsen GP, et al. Riedel's thyroiditis and multifocal fibrosclerosis are part of the IgG4-related systemic disease spectrum. *Arthritis Care Res (Hoboken)* 2010; 62:1312–8. <http://dx.doi.org/10.1002/acr.20215>
- 35 Zen Y, Onodera M, Inoue D et al. Retroperitoneal fibrosis: a clinicopathologic study with respect to immunoglobulin G4. *Am J Surg Pathol* 2009; 33:1833–9. <http://dx.doi.org/10.1097/PAS.0b013e3181b72882>
- 36 Stone JH, Khosroshahi A, Hilgenberg A et al. IgG4-related systemic disease and lymphoplasmacytic aortitis. *Arthritis Rheum* 2009; 60:3139–45. <http://dx.doi.org/10.1002/art.24798>
- 37 Khosroshahi A, Stone JH. Treatment approaches to IgG4-related systemic disease. *Curr Opin Rheumatol* 2011; 23:67–71. <http://dx.doi.org/10.1097/BOR.0b013e328341a240>
- 38 Kamisawa T, Okazaki K, Kawa S et al. Japanese consensus guidelines for management of autoimmune pancreatitis: III. Treatment and prognosis of AIP. *J Gastroenterol* 2010; 45:471–7. <http://dx.doi.org/10.1007/s00535-010-0221-9>
- 39 Umehara H, Okazaki K, Masaki Y et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. *Mod Rheumatol* 2012; 22:1–14. <http://dx.doi.org/10.1007/s10165-011-0508-6>
- 40 Cornell LD. IgG4-related tubulointerstitial nephritis. *Kidney Int* 2010; 78:951–3. <http://dx.doi.org/10.1038/ki.2010.342>
- 41 Yoneda K, Murata K, Katayama K et al. Tubulointerstitial nephritis associated with IgG4-related autoimmune disease. *Am J Kid Dis* 2007; 50:455–62. <http://dx.doi.org/10.1053/j.ajkd.2007.05.018>
- 42 Saeki T, Nishi S, Ito T et al. Renal lesions in IgG4-related systemic disease. *Intern Med* 2007; 46:1365–71. <http://dx.doi.org/10.2169/internalmedicine.46.0183>
- 43 Nakamura H, Wada H, Origuchi T et al. A case of IgG4-related autoimmune disease with multiple organ involvement. *Scand J Rheumatol* 2006; 35:69–71. <http://dx.doi.org/10.1080/03009740500499484>
- 44 Naitoh I, Nakazawa T, Ohara H et al. Autoimmune pancreatitis associated with various extrapancreatic lesions during a long-term clinical course successfully treated with azathioprine and corticosteroid maintenance therapy. *Intern Med* 2009; 48:2003–7. <http://dx.doi.org/10.2169/internalmedicine.48.2695>
- 45 Mannion M, Cron RQ. Successful treatment of pediatric IgG4 related systemic disease with mycophenolate mofetil: case report and a review of the pediatric autoimmune pancreatitis literature. *Pediatr Rheumatol Online J* 2011; 9:1. <http://dx.doi.org/10.1186/1546-0096-9-1>
- 46 Khan ML, Colby TV, Viggiano RW et al. Treatment with bortezomib of a patient having hyper IgG4 disease. *Clin Lymphoma Myeloma Leuk* 2010; 10:217–9. <http://dx.doi.org/10.3816/CLML.2010.n.034>
- 47 Khosroshahi A, Carruthers MN, Deshpande V et al. Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. *Medicine (Baltimore)* 2012; 91:57–66. <http://dx.doi.org/10.1097/MD.0b013e3182431ef6>
- 48 Massachusetts General Hospital. *Rheumatology Research Laboratory* [Internet]. Boston: MGH [cited 2013 Jan 24]. Available from: <http://www.massgeneral.org/rheumatology/research/researchlab.aspx?id=1430>.

## SENIOR FELLOWS' CLUB PRIZE

The Senior Fellow's Club Prize for 2012 has been won by GE Walker and colleagues for their paper on 'Intravenous fluid use in the acutely unwell adult medical inpatient: improving practice through a clinical audit process'. This can be read in issue 3 2012 at [http://www.rcpe.ac.uk/journal/issue/journal\\_42\\_3/wood.pdf](http://www.rcpe.ac.uk/journal/issue/journal_42_3/wood.pdf)

A prize of £250 will be awarded to the first-named (or corresponding) author of an original research paper on a clinical topic, deemed by a panel of judges to be the best paper by a doctor-in-training (i.e. pre-consultant level) published in *The Journal of the Royal College of Physicians of Edinburgh* in 2013. The best paper will be selected by a panel of judges, including a senior Fellow, an active clinician and a member of the editorial team.

Further details may be obtained from the Editorial Office, RCPE, 9 Queen Street, Edinburgh, EH2 1JQ, tel 0131 247 3652 or email [editorial@rcpe.ac.uk](mailto:editorial@rcpe.ac.uk).