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CLINICAL

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

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**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.

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## CASE 1

A 67-year-old man presented with a progressive decline in kidney function; serum creatinine rose from 73 µmol to 346 µmol (n=60–120 µmol) 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).[1] 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 µmol to 251 µmol 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=0–15). The serum creatinine was 716 µmol (estimated glomerular filtration rate [eGFR]=7 mL/min/1.73m$^2$). C-reactive protein was elevated at 22 g/L (n=0–5) and he was anaemic with a haemoglobin (Hb) of 106 g/L (n=130–180); haematinics, LFTs, calcium, phosphate and albumin were all normal and neither serum paraproteins nor

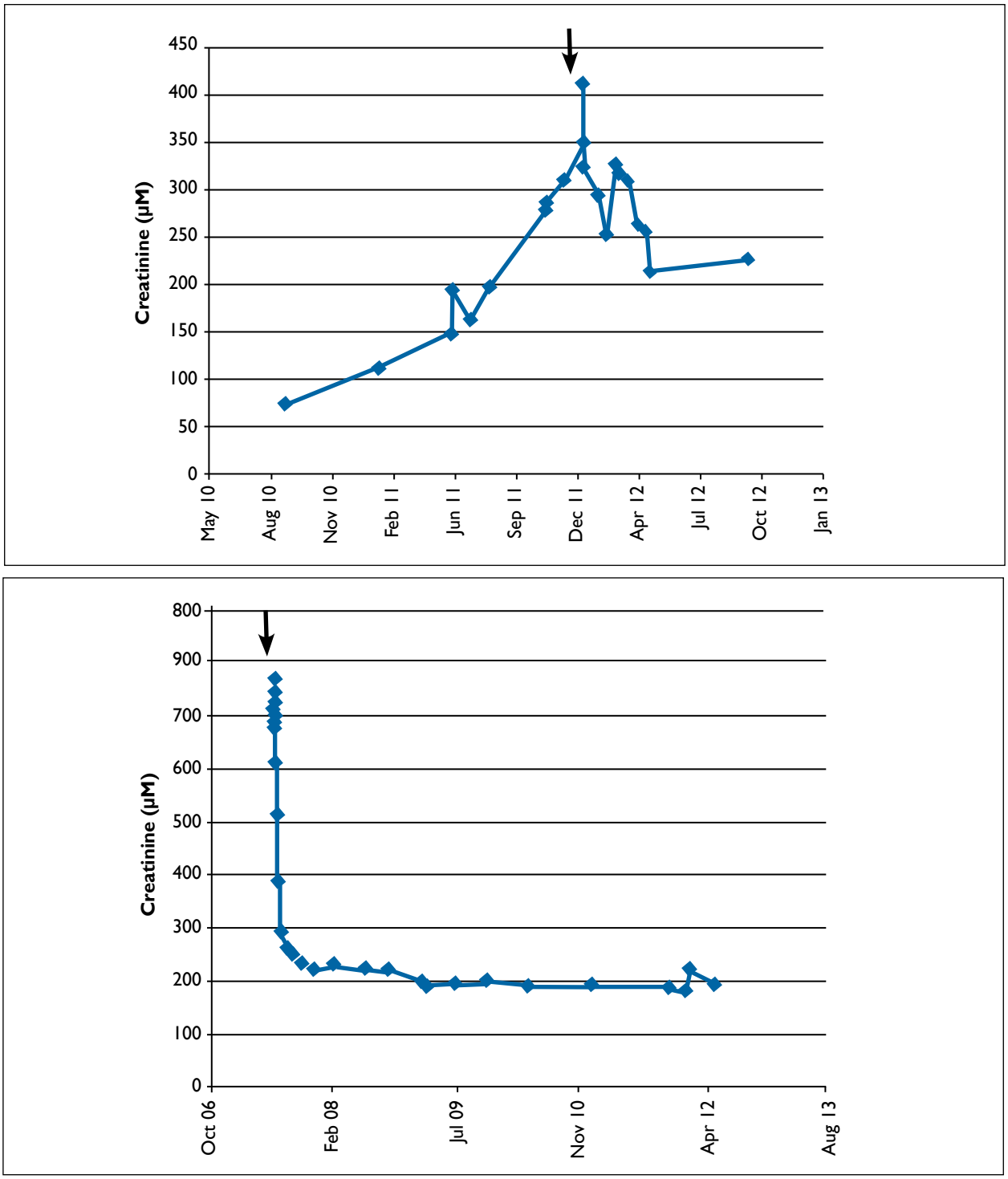
**TABLE 1A** Summary of the clinical features seen in three cases presented

| | 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 1B** 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 dexoxyribonucleic 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 1B. 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 1A/1B). 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.

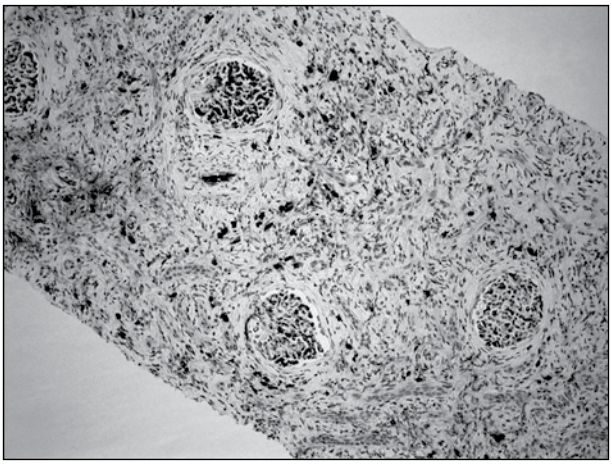


**FIGURE 1C** Representative image of the renal biopsy from Case 1 demonstrating severe chronic tubulointerstitial nephritis, tubular atrophy, interstitial scarring, dense fibroblastic sclerosis and loss of peritubular capillaries. Numerous IgG4 positive plasma cells (dark staining) are seen in glomeruli 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.

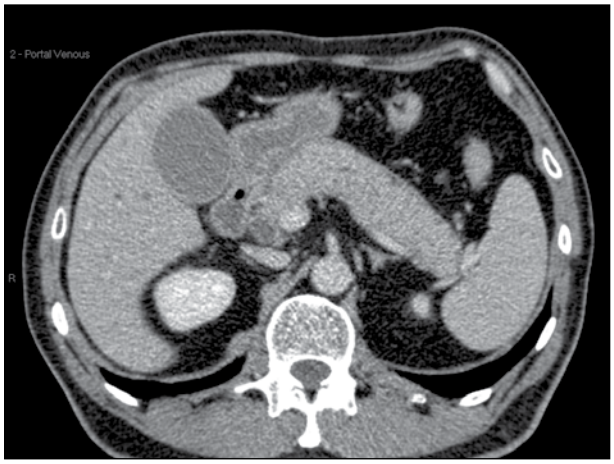



**FIGURE 2A** Representative imaging in IgG4-RD pancreatic/biliary disease. Computed tomography scan of the abdomen demonstrating a 'sausage' pancreas with surrounding hypoechoic rim, classical features of IgG4-RD/autoimmune pancreatitis.

## 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

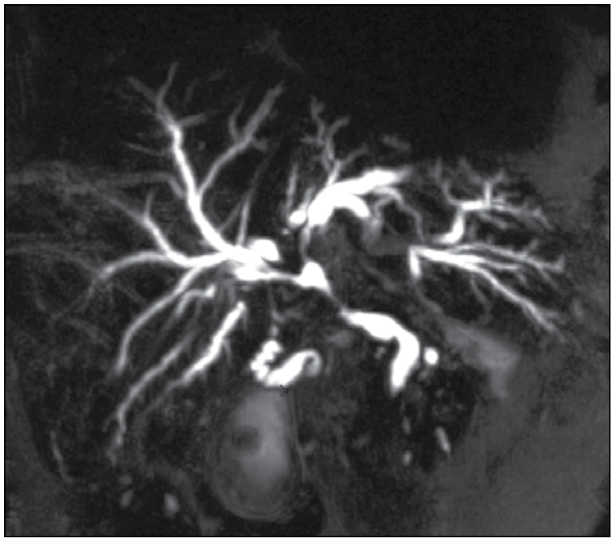


**FIGURE 2B** Magnetic resonance cholangio-pancreatography (MRCP) cholangiogram demonstrating multiple strictures throughout the biliary tree.

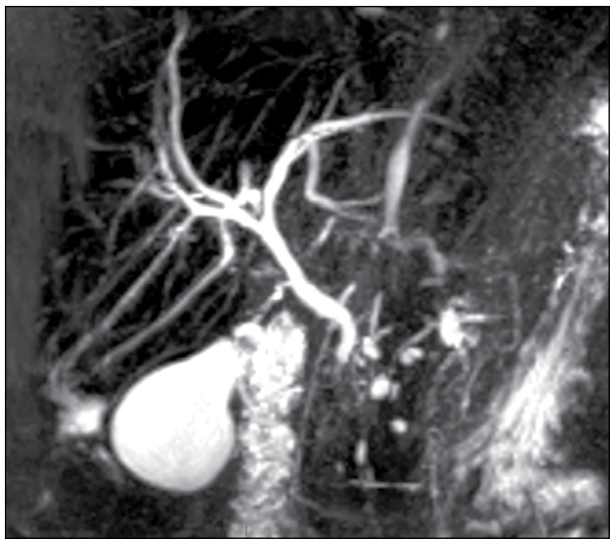


**FIGURE 2C** Resolution of the changes seen in previous Figure after four weeks of corticosteroid therapy.

asthma, gastroesophageal reflux disease and impaired glucose tolerance. Blood tests showed bilirubin 10 µmol (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 µmol (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 µg/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 cholangio-pancreatography (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[15] 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,[1] sialadenitis (Mikulicz's disease),[2] parenchymal kidney disease[3,4] and retroperitonal fibrosis.[5,6] 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.[7–9] There are several detailed reviews of this condition covering many clinical and biological aspects of IgG4-RD.[10–17]

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.[18] The identification

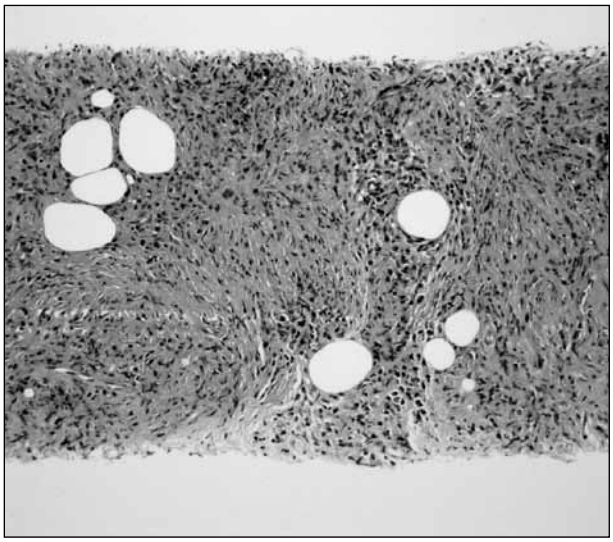


**FIGURE 3A** Haematoxylin and eosin stain (H&E): Case 3 pancreatic trucut biopsy: representative image showing lymphoplasmacytic inflammation, fibrosis and virtually no recognisable pancreatic tissue.

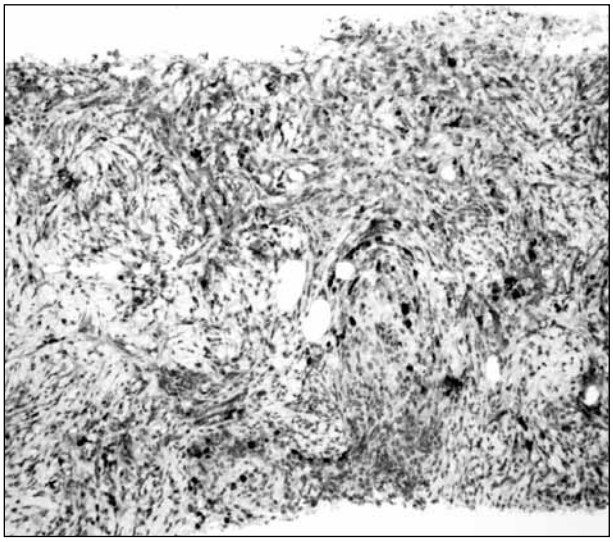


**FIGURE 3B** IgG4 stain: Case 3 pancreatic trucut biopsy: representative image showing increased numbers of IgG4 positive plasma cells (dark staining).

of serum IgG4 as a discriminating factor for IgG4-RD has aided diagnosis, though raised IgG4 alone should not be relied upon;[9,18–21] 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.[22] However, it has become clear that IgG4-RD is neither confined to Japan nor patients of Japanese origin but affects patients around the world.[3,23–29] 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.[30] There is no

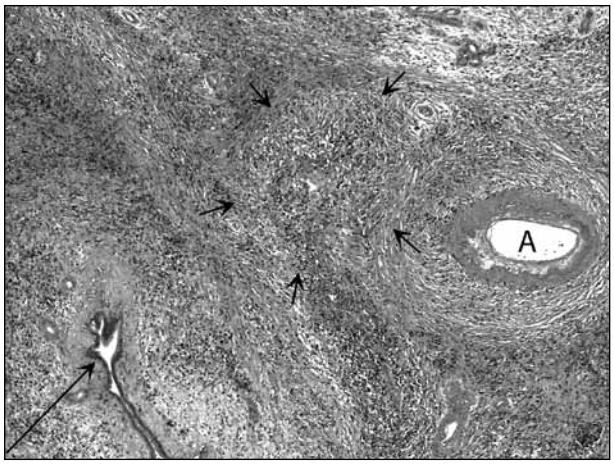



**FIGURE 3C** Haematoxylin and eosin stain (H&E). A typical example of IgG4-related autoimmune pancreatitis in a Whipple's resection (from another patient). Virtually all of the normal pancreatic tissue has been replaced by a lymphoplasmacytic infiltrate and storiform fibrosis. A residual pancreatic 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.

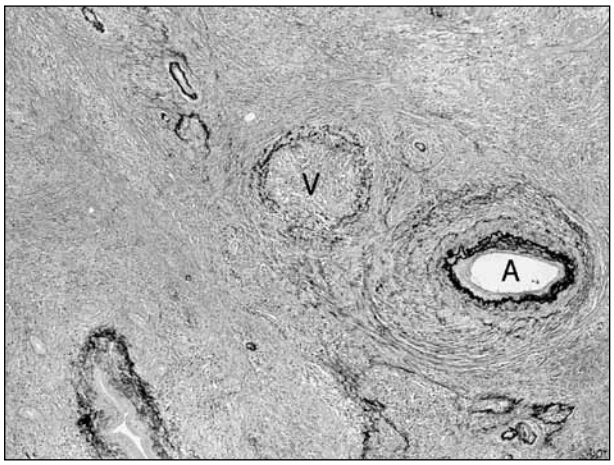



**FIGURE 3D** Same area as Figure 2C: this elastic van Gieson (EVG) stain highlights the occlusive venulitis. The venule (V) is now easily detectable.

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).[31,32]

The disease is a direct cause of significant damage to affected tissues[3,33–36] but it is usually highly responsive to steroid therapy.[37] 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.[38] 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.[3,4,27,39–43] Second-line immunosuppression using

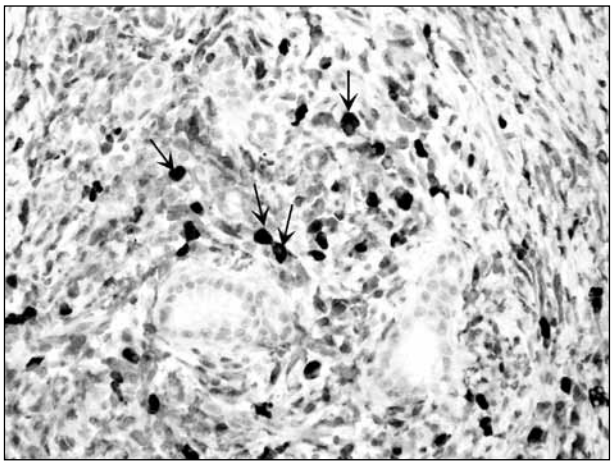


**FIGURE 3E** IgG4 stain. Same case as Figures 2C/2D: IgG4-related autoimmune pancreatitis. Representative image showing 25 IgG4 positive plasma cells per high power field.

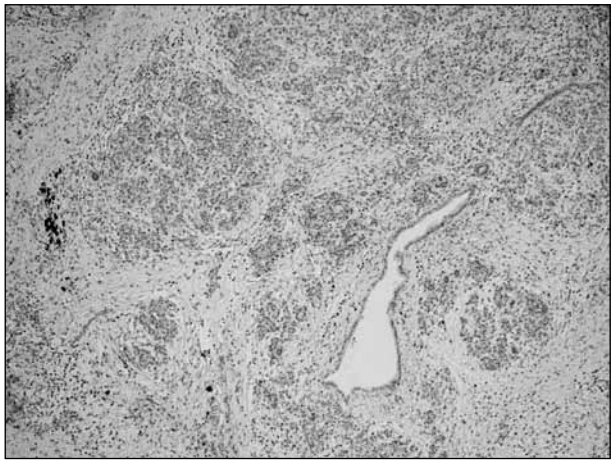


**FIGURE 3F** For comparison. Usual type chronic pancreatitis (not IgG4-related) stained with IgG4 – this representative low power view shows that in most areas there are no IgG4 positive plasma cells per high power field. A rare cluster of positive cells is seen on the left. The average count is less 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,[44] mycophenolate mofetil,[45] bortezomib (a proteasome inhibitor with cytotoxic effect against plasma cells)[46] and rituximab (a monoclonal antibody against the CD20 protein)[47,48] have been described.

We believe that clinicians in a wide variety of specialities 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.

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## 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

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.