CASE REPORT

IgG4-related disease: long-term natural history and management of a relapsing multisystem disease entity

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SUMMARY

Although awareness of IgG4-related disease has grown over the past decade, with earlier diagnosis and treatment, understanding of its natural history over the long term and the optimal management remains unclear. We report the case of a 48-year-old man who presented with a pancreatic pseudotumour causing bile duct obstruction with coexisting autoimmune hepatitis and multisystem involvement. His symptoms settled on steroids and maintenance with azathioprine was commenced, however periodic relapses occurred involving multiple organs. A timeline-relating IgG4 levels, clinical features and immunosuppressive therapy are presented. The protean and relapsing–remitting nature of this condition is emphasised, and a brief review of long-term therapeutic options is provided.

BACKGROUND

IgG4-related disease (IgG4-RD) is a poorly understood and potentially underappreciated disease entity which requires a high index of suspicion for diagnosis. Data and reports concerning long-term natural history and follow-up are lacking. This case emphasises initial diagnostic and management challenges and goes on to describe clinical fluctuations over a 6-year period.

CASE PRESENTATION

Initial presentation

A previously well 48-year-old Caucasian man presented to the surgical team with a 1-week history of jaundice preceded by 2 weeks of central abdominal discomfort. Examination revealed no other signs. Initial blood tests included bilirubin 240 $\mu\text{mol/L}$, alanine aminotransferase (ALT) 599 U/L, alkaline phosphatase 251 U/L and gamma-glutamyltransferase 1077 U/L. Cancer antigen 19–9 was 79 kU/L. CT confirmed biliary obstruction with intrahepatic and extrahepatic bile duct dilatation. The common bile duct (CBD) was 16 mm in diameter, with a 2.1 $\times$ 1.8 cm enhancing mass in the head of the pancreas and enlarged left para-aortic nodes, the largest measuring 13 mm (figure 1). MRI revealed an ill-defined bulky mass involving the pancreatic head and uncinate process. The pancreas was noted to have lost its normal 'feathery' outline. The distal CBD had a tight stricture with shouldering of the CBD as it entered the pancreatic head (figure 2).

Appearances were reported to be in keeping with malignancy, and the patient was informed that pancreatic cancer was the most likely diagnosis. Initial discussions concerning risks and benefits of Whipple's procedure for curative resection of pancreatic cancer were undertaken with the patient.

At this stage, a further medical review was requested. Serum immunoglobulin levels (total and subclasses) were tested. Total IgG was 17.5 g/L (normal range 6–16); IgG4 was 4.39 g/L (normal range 0.23–1.11). These results were suggestive of IgG4-mediated autoimmune pancreatitis (AIP, type 1) mimicking pancreatic cancer. The concurrent elevation in ALT indicated active hepatitis. Plans for pancreatic surgery were cancelled, and steroid therapy (prednisolone 40 mg once a day) was commenced.

At oesophagogastroduodenoscopy, performed 1 week later, grade 1 to 2 oesophageal varices and a duodenal ulcer were detected. Immunostaining of the biopsy material from the ulcer revealed occasional IgG4-positive plasma cells (1 cell/high-powered field (hpf), figure 3). A liver biopsy was performed, and it demonstrated a mild lymphocytic infiltrate with interface activity, in keeping with an autoimmune aetiology. There was stage 1 fibrosis only.

Following the introduction of prednisolone, bilirubin level fell rapidly reaching 37 $\mu\text{mol/L}$ within 2 weeks, with ALT level falling to 114 U/L. Due to high serum IgG4 levels with coexisting hepatitis and rapid improvement in biochemical and radiological appearance following steroid therapy, further investigations like endoscopic ultrasound were not pursued. Azathioprine was commenced after normal thiopurine methyltransferase levels had been confirmed.

Progress from 2010 to 2016

The prednisolone dose was weaned after therapeutic azathioprine dose had been reached. However, relapses occurred in 2012 and 2016 (figure 4), causing abdominal pain similar to the initial presentation, deranged liver function and abnormal pancreatic radiology (figure 5A–C). These responded well to short-term increments in steroid dose. In 2010, he developed lacrimal gland swelling which resolved with an increase in steroid dose. Three years after the first presentation, he developed symptoms of prostate hypertrophy

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Figure 1 CT scan demonstrating a mass in the head of the pancreas (arrow).

during a relapse of the IgG4 condition. A prostate biopsy was planned but prostate symptoms improved dramatically with the increase in steroid dose for the IgG4 relapse. Hence, a biopsy was thought to be unnecessary as the symptoms could be attributed to IgG4-mediated prostatitis. During this episode, he also developed sinusitis and a CT scan of the sinuses showed thickening of the mucosa in all the sinuses. These symptoms resolved with the increase in steroids. Due to some non-specific side effects (light headedness) attributed to azathioprine, the patient's preference was to reduce the azathioprine dose after recovery from a relapse, thus immunosuppressant doses fluctuated during the clinical course.

DISCUSSION

Studies have reported that 60%–90% of patients with IgG4-RD have multiple organ involvement¹ and this is demonstrated in our case. AIP is the most recognised manifestation, typically

Figure 2 MRI scan (detail) demonstrating uniformly enlarged pancreas (black arrow) and biliary dilatation (white arrow) to the level of the pancreatic head.

Figure 3 Duodenal biopsy (magnification ×40) with a single plasma cell staining positively (dark brown) for IgG4.

presenting with diffuse pancreatic inflammation, pancreatic or biliary strictures, and raised serum IgG4 levels.² Inflammatory tumours in the head of the pancreas with associated biliary obstruction, mimicking the presentation of pancreatic head carcinoma, are well described, and the possibility of IgG4 disease must always be considered before embarking on invasive investigations or treatment of presumed pancreatic malignancy. Extra-pancreatic manifestations are also common and include autoimmune sclerosing cholangitis (with similar clinical and radiological features to primary sclerosing cholangitis),³ sclerosing cholecystitis and retroperitoneal fibrosis. Further still from the pancreas, autoimmune sialadenitis, nephritis, prostatitis and cerebritis have been observed as part of a systemic autoimmune IgG4-mediated disease. Due to the involvement of multiple systems and characteristic lymphoplasmacytic inflammation with IgG4-positive cells on histology the condition has also been called 'hyper-IgG4 disease'.⁴

Autoimmune hepatitis (AIH) presenting in association with AIP is reported rarely. An analysis of liver sections from 17 patients with AIP found definite features of coexisting hepatitis

Pred (mg/d)	40	20	7.5	1.5	2.5	0	0	20	5	1	0	0	40	2.5
Aza (mg/d)	0	50	100	100	100	50	50	150	150	25	100	150	150	0

Figure 4 Graph showing ALT values (green) and IgG4 titre (red) over time, with corresponding prednisolone and azathioprine doses beneath.

ALT, alanine aminotransferase.

5 a

5 b

5 c

Figure 5 (A-C) Fluctuating bile duct diameter on CT and MRI scans (2009—presentation, 2015—in remission and 2016—flare).

in 11 (65%) of them.⁵ A study of liver sections from 26 patients with an established diagnosis of AIH found IgG4-positive cells in 9 of them, indicating that AIH can certainly be attributed to IgG4 disease in some cases, however these patients did not have AIP.⁶ There are no existing reports of chronic liver disease with portal hypertension secondary to AIH coexisting with an acute presentation of AIP.

IgG4-related lacrimal, salivary gland and sinus disease have been reported and case reports indicate a good response to steroid or rituximab therapy.⁷

IgG4-related prostatitis is an under-recognised association and can cause raised PSA levels mimicking prostate cancer which leads to multiple surgical resections. However, if the right diagnosis is made, literature indicates steroids and rituximab have been used for successful treatment of this disease.⁷ It is important to make this association to avoid unnecessary surgeries leading to potential loss of exocrine function.

Diagnosis remains challenging as there is no specific laboratory, imaging or histopathological finding pathognomonic to IgG4-RD. Serum IgG4 levels can be misleading and should not be used as the sole criterion. Number of other diseases, such as cancer, infections and autoimmune diseases, including vasculitis, are associated with increased IgG4 levels.⁸ Histology is still considered the gold standard, however AIP is the only organ manifestation where a definitive diagnosis can be made without histology as the imaging features highly specific to this condition are known.⁹ The major histological findings are dense lymphoplasmacytic infiltrate, fibrosis and obliterative phlebitis.¹⁰ Absolute IgG4 cell count and IgG4/IgG ratio are not very accurate for diagnosis.¹⁰ New modalities like FDG PET (fluorodeoxyglucose positron emission tomography) and plasmablast levels need further investigation but may be used in the future. FDG PET provides a non-invasive tool to get metabolic information about the whole body and can guide the selection of site for biopsy.¹¹ Circulating IgG4 + plasmablasts can be a potentially useful biomarker for diagnosis and assessing the response to treatment.¹²

Timely treatment of IgG4-RD in vital organs is important as irreversible damage may occur very quickly. Steroids have been the mainstay of treatment since the description of the disease a decade ago. Treatment of AIP and IgG4-mediated cholangitis is steroid based, although high relapse rates have been described, and the use of azathioprine is to be anticipated in many cases.¹³ By extension, a similar approach is probably required in IgG4-associated AIH or other organ involvement.

There is no consensus regarding the duration of maintenance therapy though the Japanese guidelines for AIP recommend low-dose steroids for up to 3 years.¹⁴ Evidence certainly suggests that maintenance therapy reduces relapses in AIP and this probably applies to multisystem diseases. Steroid-sparing agents like azathioprine, mycophenolate mofetil and methotrexate can be used for induction and maintenance and their use varies greatly depending on the specialty managing the condition. Rituximab (anti-CD20) appears to have potential in treating the patients' refractory to steroids.⁷ It works by depleting B lymphocytes and reducing IgG4 levels. However, there is a lack of randomised controlled trials regarding use of rituximab or steroid-sparing medications.

In conclusion, the long-term monitoring and treatment of this entity remains challenging. Steroids are accepted as the mainstay of treatment; however, there is no consensus about the long-term maintenance therapy with either steroid-sparing agents or rituximab due to lack of randomised trials. The burden of immunosuppression is significant for patients,

who may feel well between relapses (as in our patient's case). Additionally, where progressive or irreversible disease has not been demonstrated, the argument for long-term maintenance is less strong. We acknowledge that our patient was treated on the basis of clinical and biochemical markers, rather than strong histological evidence, but the pattern of clinical symptoms occurring with raised IgG4 and rapid response to treatment on each occasion makes the diagnosis firm. Pending large-scale, long-term cohort studies, a case-by-case approach with consideration of patient preference and ongoing monitoring are advisable.

Learning points

- ▶ IgG4-related disease is a rare disease entity with protean manifestations, and should be considered in appropriate cases before diagnosing pancreatic malignancy.
- ▶ The mainstay of treatment is corticosteroid, and data are relatively lacking regarding long-term immunosuppression.
- ▶ A case by case approach is required, with consideration given to a patient's preference, the pattern of relapses/remissions and the burden of ongoing monitoring.

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Contributors All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, writing or revision of the manuscript. Furthermore, each author certifies that this material has not been submitted to or published in any other publication. PB: conception and revising the manuscript critically for important intellectual content. SK and PB: writing. All authors: revision; clinical management of the case and approval of the version of the manuscript to be published.

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