IgG4-related pulmonary disease: the protean impersonator?

D Slim[1], H Gunawardena[2], JM Calvert[3], RS Daly[4], MJ Plummeridge[5], AR Medford[6]

Abstract

IgG4-related disease is an immune-mediated fibro-inflammatory disease, characterised by distinct pathological features. An increasing number of clinical phenotypes are described, from single-organ disease to a multisystem disorder, which can present to a variety of different specialities. Recognition is key; its protean manifestations can mimic other inflammatory diseases, infection and malignancy. Here, we present three cases to highlight the importance of being familiar with this condition in its various forms

Keywords: aortitis, autoimmune, IgG4-related disease, MOLPS, pulmonary disease

Declaration of interests: No conflict of interests declared

Correspondence to:
ARL Medford
North Bristol Lung Centre &
University of Bristol
Brunel Building
Southmead Hospital
Westbury-on-Trym
Bristol BS10 5NB
UK

Email:
andrew.medford@nbt.nhs.uk

Case 1 – Cough

A 74-year-old male presented with refractory cough despite inhaled corticosteroids and bronchodilators. Clinical assessment was non-contributory. Lung function tests showed reduced small airway function (50% predicted), a positive mannitol challenge test and an elevated fractional exhaled nitric oxide (FeNO) of 120 parts per billion (ppb) (normal range < 25 ppb in adults). A bronchoscopy showed mild lymphocytic inflammation on endobronchial biopsy with a neutrophilic lavage but no eosinophilia. Nebulised corticosteroids were trialled with mild clinical improvement but FeNO remained elevated (270 ppb).

The patient had reported improvement in cough with oral prednisolone, with worsening on dose reduction. A trial of azathioprine had no effect. Positron emission tomography (PET) showed fludeoxyglucose avidity consistent with thoracic aortitis and major branches of aorta upper arms. Anti-nuclear, anti-cyclic citrullinated peptide and anti-neutrophil cytoplasmic antibodies were negative. Despite a normal total immunoglobulin G (IgG), immunoglobulin G4 (IgG4) subclass was elevated at 3.08 g/L (<1.32) (peaking at 4.30 g/L). There was a slight eosinophilia (0.5–1.0) (normal <0.41 10^9/L). CT thorax showed mild bronchial wall thickening but no pulmonary infiltrates. Because of urological symptoms, magnetic resonance imaging was undertaken; this demonstrated prostatic inflammation. A clinical diagnosis of IgG4-related systemic disease (IgG4-RD) was made, based on respiratory manifestations, aortic and prostatic inflammation. Tissue diagnosis was not possible. Pulsed methylprednisolone was initiated followed by oral steroids and methotrexate. There was initial symptomatic improvement in respiratory symptoms and follow-up PET showed resolution of fludeoxyglucose avidity. Symptoms increased on steroid reduction with complications on higher doses. Higher dose methotrexate was not tolerated and interval PET-CT showed recurrence with thoracic aorta uptake. Rituximab was initiated with PET-CT scan 8 months later demonstrating response. FeNO has acted as a biomarker of disease activity with the most recent measurement 70 ppb.

Case 2 – Weight loss with narrowed bronchus

An 80-year-old male presented with unexplained 13 kg weight loss over 6 months on a background of autoimmune pancreatitis. Serum electrophoresis showed a raised total IgG with elevated IgG subclasses; notably IgG4 was 16 g/L (< 1.32). CT thorax, abdomen and pelvis revealed narrowing of the right upper lobe bronchus. Bronchoscopy revealed no obstruction but endobronchial biopsy showed eosinophilia and a plasmacytic infiltrate negative for IgG4 staining (Figure 1). The patient declined to attend the Autoimmune Connective Tissue Disease Clinic to consider IgG4-RD systemic treatment options (for both his autoimmune pancreatitis and endobronchial disease).

Case 3 – Incidental pulmonary nodules

A 62-year-old female presented with palpitations. CT coronary angiogram revealed cavitating lung nodules (Figure 2). She had no respiratory or constitutional symptoms. CT pulmonary angiography and abdominopelvic CT revealed no pulmonary emboli or malignancy. Both vasculitic screen and broncho-alveolar lavage were unremarkable. She was treated empirically for atypical infection. The nodules

[1]Respiratory Specialty Trainee Year 6; [2]Consultant in Rheumatology, Autoimmune Connective Tissue Disease & Vasculitis; [3,5,6]Consultants in Respiratory Medicine; [4]Consultant in Cellular Pathology, North Bristol Lung Centre, Southmead Hospital, Bristol, UK

Figure 1 Haematoxylin & eosin stained section from wedge biopsy lower lobe right lung, x 400 magnification. Illustrating a high proportion of plasma cells among the inflammatory cell infiltrate, with intervening capillary and lymphatic channels. Plasma cells (white arrow) are recognised by their eccentrically placed nucleus, harbouring condensed chromatin in a 'clock face' pattern, and their basophilic cytoplasm

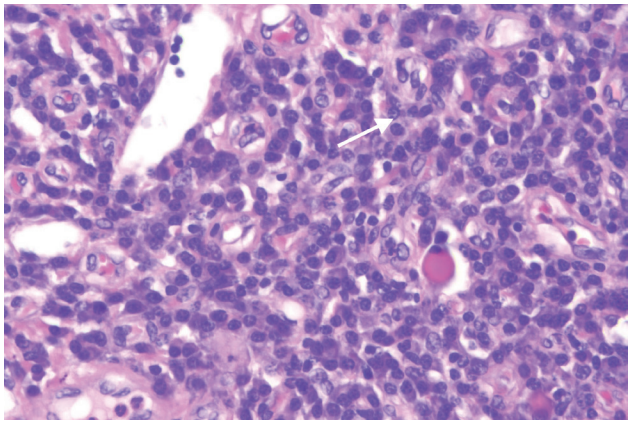


Figure 2 Cavitating pulmonary nodule (white arrow) in the right lower lobe

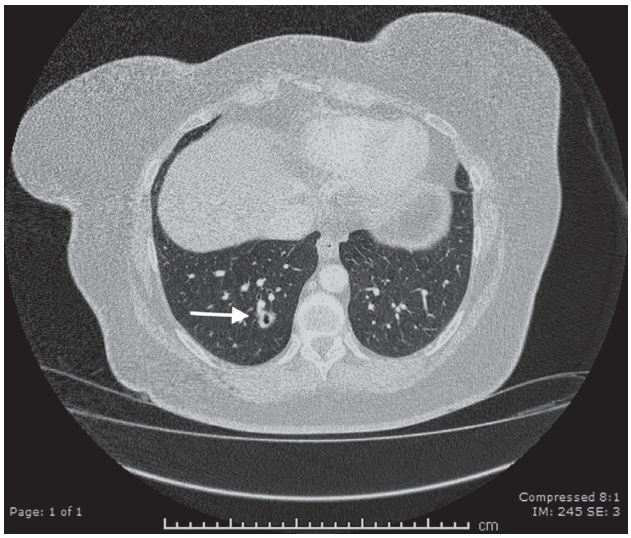
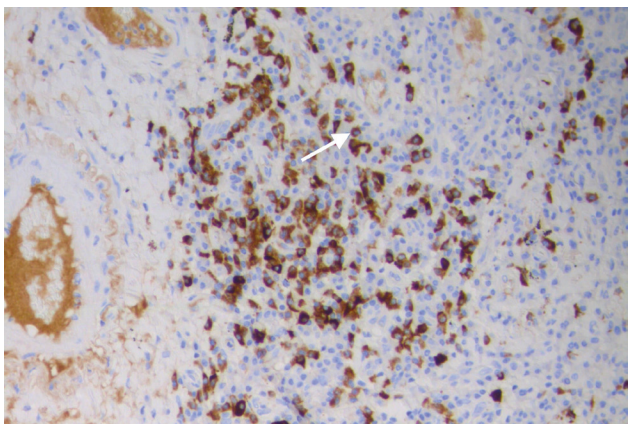


Figure 3 Immunohistochemical stained section from wedge biopsy lower lobe right lung using anti-IgG4 (MRQ-44) antibody, x 200 magnification. Illustrating high proportion of scattered IgG4-positive plasma cells (white arrow), exhibiting strong cytoplasmic immunoreactivity for IgG4



persisted on interval CT, leading to a video-assisted surgical lung biopsy, which showed peribronchial interstitial chronic inflammation with nodular lymphoid hyperplasia (Figure 3). Immunohistochemistry demonstrated over 50% IgG-positive cells which were positive for IgG4. IgG subclasses were measured in peripheral blood with a raised IgG4 of 2.77 g/L. A diagnosis of asymptomatic IgG4 pulmonary disease was made. PET did not show increased avidity in the pulmonary nodules or elsewhere. Management was expectant as she was asymptomatic and concerned about corticosteroid use.

Discussion

IgG is the most abundant immunoglobulin in the human immune system, with 4 subtypes. IgG4 is the least prevalent subtype (1–4%) and least understood.[1] Theories about the role of IgG4 include:

- Anti-inflammatory activity due to poor complement activation via C1q and Fc receptors[2]
- 'Blocking antibody' function by competing with IgE for allergens[1]

IgG4-RD is increasingly recognised, with autoimmune pancreatitis one of the first entities described.[3] Pathophysiological mechanisms are still incompletely understood. The main process seems to be fibro-inflammatory characterised by tumour-like lesions, lymphoplasmacytic infiltrate, storiform fibrosis, and elevated serum IgG4.[4] Almost any organ can be involved but common manifestations are pancreatitis, sclerosing cholecystitis, sclerosing sialadenitis, dacryoadenitis, lymphadenopathy and retroperitoneal fibrosis.[4] Intrathoracic manifestations vary from 14–54% in prevalence.[5]

Diagnosis

Several diagnostic criteria exist with biopsy confirmation strongly recommended to also exclude malignancy and vasculitis[6,7] The major histopathological features are outlined in Table 1. These features may be absent or less prominent in certain organs such as the lung.[8]

Other histopathological features are the number of IgG4-positive (IgG4+) plasma cells per high power field (range of 10–200 per hpf) and the ratio of IgG4+/IgG+ plasma cells. The cut-offs depend on the type and site of biopsy, for example in the lung, > 50 IgG4+ per hpf are needed for a surgical specimen vs. > 20 in a needle biopsy.[9,10]

Elevated serum levels of IgG4 (> 1.36 g/l) can be a feature in IgG4-RD;[11] however, 3–30% of patients with IgG4-RD can have normal concentrations.[12–16] Serum IgG4 can be a useful biomarker to monitor disease and response to glucocorticoids if elevated at presentation.[17] More elevated levels can occur in more extensive disease.[18–21] However, raised serum IgG4 levels can be seen in other conditions, e.g. rheumatoid arthritis, limiting its value alone without biopsy.[22,23] Plasmablasts are found in high concentrations in IgG4-RD, regardless of serum IgG4, and may correlate more strongly

Table 1 Diagnostic features in IgG4-related disease

Pathological features	Highly suggestive	Probable	Inconsistent
Dense lymphoplasmacytic infiltrate	Two or more features	One feature	Lack of typical features or low ratio/number of IgG4+ plasma cells
Storiform fibrosis		Additional clinical, serological and radiological evidence	Epithelioid cell granulomas**
Obliterative phlebitis			Prominent neutrophilic infiltrate**
Immunostaining IgG4+/IgG+ plasma cell ratio > 40%	Number of IgG4+ plasma cells per hpf*	Number of IgG4+ plasma cells per hpf*	

*IgG4 counts per high power field required will differ depending on the organ site sampled and method of sampling
**These may represent co-existing disease or alternative diagnoses

with disease activity.[18] Peripheral eosinophilia is present in around 30%[24] with tissue eosinophilia being notable in some cases.[10] Theories of the role of the eosinophil in IgG4-RD include antigen presentation, release of profibrotic factors, and promotion of plasma cell survival for IgG4 production.[25]

IgG4-RD pulmonary and pleural manifestations

IgG4-RD in the lung and pleural cavity[26] can present insidiously and symptoms generally reflect disease location, e.g. dyspnoea, cough, haemoptysis and chest pain. It usually presents in middle to late age with a male preponderance.[4] Individuals may have been treated for asthma with poor treatment response. Patients can present incidentally or diagnosis may be made due to detection of IgG4+ plasma cell infiltration in multiple organs (multi-organ lymphoproliferative syndrome or MOLPS).[27,28] Up to 40% can present with concomitant allergy.[29]

Radiological appearances vary but bronchovascular thickening is characteristic. Other features include pulmonary nodules, ground-glass opacities, pleural thickening, interstitial fibrosis and lymphadenopathy.[30] PET can be helpful in identifying extra-thoracic disease sites such as aortitis, as well as monitoring disease activity.[31]

Management

First-line therapy is usually with systemic glucocorticoids.[17] For remission-induction, prednisolone at a dose of 30–40 mg is commonly started. Pulsed intravenous methylprednisolone (1–3 doses) is an option for induction of multisystem disease. Clinical response is assessed using serial serum IgG4, if elevated at diagnosis, and radiological response. A quick and favourable response to glucocorticoids is usual in most cases, but in some this is not sustained on dose reduction. A case of bronchial disease has been treated successfully with inhaled steroids.[32] Relapse often occurs following glucocorticoid discontinuation.[33] Immunomodulation with azathioprine, methotrexate and mycophenolate mofetil is recommended based on best clinical practice, case series and NHS England guidance, but no prospective controlled data currently exist.[17,26,34] Anti-CD20 monoclonal therapy (rituximab) has also been used with success in refractory cases, with patients demonstrating prompt clinical, radiological and serological responses.[35–37] Rituximab is now approved by NHS England as a third-line agent for highly selected resistant cases.[34]

Conclusion

IgG4-RD is rare but important due to its potential for morbidity if not recognised and treated early. It can mimic more common respiratory conditions such as asthma but go undiagnosed. It should be considered in cases with unexplained chronic inflammatory endobronchial biopsies, refractory asthma or multi-organ inflammation. This paper illustrates three varied respiratory presentations and different diagnostic pathways. Biopsy confirmation and early inter-specialty involvement may be required for optimal management.

References

1 Aalberse RC, Stapel SO, Schuurman J et al. Immunoglobulin G4: an odd antibody. *Clin Exp Allergy* 2009; 39: 469–77.
2 Van der Neut Kolfschoten M, Schuurman J, Losen M et al. Anti-Inflammatory activity of human IgG4 antibodies by dynamic fab arm exchange. *Science* 2007; 317: 1554–7.
3 Yoshida K, Toki F, Takeuchi T et al. Chronic pancreatitis caused by an autoimmune abnormality: proposal of the concept of autoimmune pancreatitis. *Dig Dis Sci* 1995; 40: 1561–8.
4 Stone JH, Zen Y, Deshpande V. IgG4 related disease. *N Engl J Med* 2012; 366: 539–51.
5 Ryu JH, Sekiguchi H, Yi ES. Pulmonary manifestations of immunoglobulin G4-related sclerosing disease. *Eur Respir J* 2012; 39: 180–6.
6 Deshpande V, Zen Y, Chan JK et al. Consensus statement on the pathology of IgG4-related disease. *Mod Path* 2012; 25: 1181–92.
7 Khosroshahi A, Wallace ZS, Crowe JL et al. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. *Arthritis Rheum* 2015; 67: 1688–99.
8 Zen Y, Inoue D, Kitao A et al. IgG4-related lung and pleural disease: a clinico-pathologic study of 21 cases. *Am J Surg Pathol* 2009; 33: 1886–93.
9 Shrestha B, Sekiguchi H, Colby TV et al. Distinctive pulmonary histopathology with increased IgG4-positive plasma cells in patients with autoimmune pancreatitis: report of 6 and 12 cases with similar histopathology. *Am J Surg Pathol* 2009; 33: 1450–62.
10 Zen Y, Kitagawa S, Minato H, et al. IgG4-positive plasma cells in inflammatory pseudotumor (plasma cell granuloma) of the lung. *Hum Pathol* 2005; 36: 710–7.
11 Umehara H, Okazaki K, Masaki Y, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD). *Mod Rheum* 2012; 22: 21–30.
12 Ghazale A, Chari ST, Smyrk TC et al. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. *Am J Gastroenterol* 2007; 102: 1646–53.
13 Carruthers MN, Khosroshahi A, Augustin T et al. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. *Ann Rheum Dis* 2015; 74: 14–8.
14 Takahira M, Ozawa Y, Kawano M et al. Clinical aspects of IgG4-related orbital inflammation in a case series of ocular adnexal lymphoproliferative disorders. *Int J Rheumatol* 2012; 2012: 635473.
15 Tanaka A, Tazuma S, Okazaki K et al. Nationwide survey for primary sclerosing cholangitis and IgG4-related sclerosing cholangitis in Japan. *J Hepatobiliary Pancreat Sci* 2014; 21: 43–50.
16 Saeki T, Nishi S, Ito T et al. Clinicopathological characteristics of patients with IgG4-related tubulointerstitial nephritis. *Kidney Int* 2010; 78: 1016–23.
17 Kamisawa T, Zen Y, Pillai S et al. IgG4-related disease. *Lancet* 2015; 385: 1460–71
18 Wallace ZS, Mattoo H, Carruthers M et al. Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations. *Ann Rheum Dis* 2015; 74: 190–5.
19 Mattoo H, Mahajan VS, Della Torre E et al. De novo oligoclonal expansions of circulating plasmablasts in active and relapsing IgG4-related disease. *J Allergy Clin Immunol* 2014; 134: 679–87.
20 Kamisawa T, Okamoto A. Clinicopathological features of autoimmune pancreatitis in relation to elevation of serum IgG4. *Pancreas* 2005; 31: 28–31.
21 Tabata T, Kamisawa T, Takuma K et al. Serial changes of elevated serum IgG4 levels in IgG4-related systemic disease. *Intern Med* 2011; 50: 69–75.
22 Ebbo M, Grados A, Bernit E et al. Pathologies associated with serum IgG4 elevation. *Int J Rheumatol* 2012; 2012: 602809.
23 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: 232960.
24 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.
25 Diny NL, Rose NR, Cihakova D. Eosinophils in autoimmune disease. *Front Immunol* 2017; 8: 484.
26 Medford AR. Recurrent pleuritis: consider IgG4-related systemic disease. *Respiration* 2013; 85: 265.
27 Horino T, Ogata K, Terada Y et al. IgG4+ MOLPS associated with inflammatory abdominal aortic aneurysm, interstitial pneumonia and interstitial nephritis. *NDT Plus* 2010; 3: 102–3.
28 Michel L, Clairand R, Néel A, et al. Association of IgG4-related disease and sarcoidosis. Thorax 2011; 66: 920–1.
29 Kamisawa T, Anjiki H, Egawa N et al. Allergic manifestation in autoimmune pancreatitis. *Eur J Gastroenterol Hepatol* 2009; 21: 1136–9.
30 Campbell SN, Rubio E, Loschner AI. Clinical review of pulmonary manifestations of IgG4-related disease. *Ann Am Thorac Soc* 2014; 11: 1466–75.
31 Ebbo M, Grados A, Guedj E et al. Usefulness of 2-[18F]-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography for staging and evaluation of treatment response in IgG4-related disease: a retrospective multicenter study. *Arthritis Care Res* 2014; 66: 86–96.
32 To M, Kono Y, Soeda S et al. A case of IgG4-related bronchial disease successfully treated with inhaled corticosteroids. *Am J Respir Crit Care Med* 2014; 189: A5702.
33 Hart PA, Kamisawa T, Brugge WR et al. Long term outcomes of autoimmune pancreatitis: a multi-centre, international analysis. *Gut* 2013; 62: 1771–6.
34 NHS England Specialised Services Clinical Reference Group for Specialised Rheumatology. Clinical Commissioning Policy Reference 16057/P: Rituximab for immunoglobulin G4-related disease (IgG4-RD). December 2016. https://www.england.nhs.uk/wp-content/uploads/2016/12/clin-comm-pol-16057P.pdf (accessed 8/10/17).
35 Hart PA, Topazian MD, Witzig TE et al. Treatment of relapsing autoimmune pancreatitis with immunomodulators and rituximab: the Mayo Clinic experience. *Gut* 2013; 62: 1607–15.
36 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.
37 Khosroshahi A, Carruthers MN, Deshpande V et al. Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. *Medicine* 2012; 91: 57–66.