

TITLE PAGE

Respiratory Medicine – Research Paper submission

Title:

Thoracic involvement in IgG4-related disease in a UK-based patient cohort

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IgG4-RD = Immunoglobulin G4-related disease; AIP = autoimmune pancreatitis; MDT = multidisciplinary team; HISORT = Histology, Imaging, Serology, Other organ involvement, Response to treatment; NHS = National Health Service; HRA = Health Research Authority; CT = computed tomography; CXR = chest X-ray

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MAIN TEXT

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ABSTRACT

IgG4-related disease (IgG4-RD) is a multi-system fibro-inflammatory disorder with classical histopathological findings, often in the context of elevated serum IgG4 levels. The thoracic manifestations of IgG4-RD are numerous and can mimic several common and better known conditions. The objective of this study was to outline the frequency and nature of thoracic involvement in a prospective cohort of IgG4-RD patients who met defined diagnostic criteria. Over 40% of IgG4-RD patients had clinicoradiological and/or histological evidence of thoracic involvement, predominantly mediastinal lymphadenopathy, the majority associated with multi-system disease outside the chest. Thoracic involvement was associated with a higher serum IgG4 level, potentially representing greater disease activity or spread. Our data highlight the diverse nature of thoracic IgG4-RD, and the importance of knowledge and recognition of the condition among respiratory physicians who are likely to encounter this disease entity on an increasing basis.

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is an increasingly recognised fibro-inflammatory disorder originally described in association with autoimmune pancreatitis (AIP) [1], but subsequently found to involve multiple organs either synchronously or asynchronously [2, 3]. The condition is often seen in the context of elevated serum IgG4 levels (between 70 and 80% of cases), and is characterised by typical histopathological changes (storiform fibrosis, obliterative phlebitis and lymphoplasmacytic infiltration) that are broadly similar regardless of the site of disease [4, 5]. It remains unclear whether these IgG4 antibodies are themselves pathogenic, or more likely represent a marker or by-product of the immune-mediated inflammatory process.

There is a growing body of literature describing the wide-ranging pulmonary manifestations of IgG4-RD that include interstitial lung disease, inflammatory pseudotumours, fibrosing mediastinitis, lymphadenopathy and pleural disease [6-8]. Previously published data suggest that thoracic involvement may be seen in anywhere between 10 and 50% of patients with IgG4-RD, with up to half of these individuals being symptomatic as a result [7]. Lung involvement in IgG4-RD can be seen in isolation or association with other organ disease, and represents a diagnostic and therapeutic challenge in the absence of long-term follow-up data and consensus as to what should be regarded as a true manifestation of the condition. This is often a consequence of the frequent absence of classical pathological features in the lung, which are more commonly seen in solid organs [9].

The objective of this study was to describe the frequency with which intrathoracic abnormalities, either as a symptomatic presenting feature of IgG4-RD or an incidental asymptomatic finding on imaging, were present in a prospectively recruited patient cohort.

METHODS

The authors' regional IgG4-RD service is the largest UK centre treating patients with this condition, with specialist clinics and multidisciplinary team (MDT) meetings operating alongside an active research programme. Patients referred to the service from 2005 onwards and confirmed as having a diagnosis of IgG4-RD were included in this study. Diagnoses were made via a robust MDT process using established clinical criteria (HISORT for AIP, and Japanese International Consensus Diagnostic Criteria for systemic

disease [9-11]); tissue specimens were evaluated using the Boston histopathological consensus criteria, where available [5]. The above clinical criteria were applied to the cohort retrospectively where appropriate, in order to confirm the diagnosis in patients who were diagnosed with IgG4-RD before the criteria were established. All patients were followed prospectively; demographic and clinicopathological data relating to features such as clinical presentation, diagnostic investigations, treatment, clinical progress and outcomes including disease relapse and death were stored in a secure database with the consent of participants (NHS HRA ethics reference 10/H0604/51).

Patients with either histologically or clinicoradiologically proven symptomatic thoracic IgG4-RD were identified from MDT records. In patients without symptomatic thoracic manifestations of IgG4-RD but proven extra-thoracic disease, routine clinical imaging (computed tomography (CT) +/- chest X-ray (CXR)) was reviewed for evidence of incidental asymptomatic pulmonary disease. Cases and thoracic imaging were double scored by independent clinicians and allocated into one of five diagnostic categories based on the likelihood of thoracic involvement by IgG4-RD (**table 1**). The interpretation of thoracic imaging was then compared with the original radiological report and/or records of MDT discussion for consistency; in those cases without consensus a third independent clinician from the study team acted as a final arbitrator.

Patients with histological evidence from a thoracic site and a consistent clinical presentation were considered to have “definite” thoracic IgG4-RD. Patients with probable thoracic IgG4-RD were identified on the basis of typical radiology and clinical features, alongside proven extra-thoracic disease and the absence of an alternative cause (for example, a negative screen for other causes of interstitial lung disease including extended auto-immune profile, clinical assessment and medication review). These cases were subdivided on the basis of clinical and radiological evidence of treatment response being present (“highly probable”) or not (“probable”). Statistical analysis was performed using SPSS version 19; tests of significance including t-test, analysis of variance and Fisher’s exact test were used with a p value of <0.05 defined as significant.

RESULTS

71 IgG4-RD patients were consented to be part of the wider study cohort; of these, 53 (74.6%) had undergone cross-sectional thoracic imaging during their clinical diagnostic work-up and were included in this analysis. 41/53 (77.4%) patients were male; mean age was 62.4 years (range 24-85; SD 14.8) with a median follow-up period from time of diagnosis of 41 months (range 2-120).

The majority of patients (37/53, 69.8%) presented with gastrointestinal issues including abdominal pain, jaundice, abnormal liver function, and/or diarrhoea. 12/53 (22.6%) patients reported respiratory symptoms including dyspnoea, chest pain and persistent cough at the time of their initial consultation; in six patients these symptoms were their primary reason for having presented to a healthcare professional in the first instance. 18/53 (34.0%) patients were documented as being ex- or current smokers with a ≥ 10 pack year history; whilst 16/53 (30.2%) patients reported an environmental or industrial risk factor for lung disease, with the majority (12 cases) of these being occupational exposure to asbestos.

22/53 (41.5%) patients were categorised as having either definite or probable thoracic involvement by IgG4-RD on the basis of radiology, histology and/or other clinical information (**table 1**). Large volume (≥ 1 cm short axis diameter) mediastinal lymphadenopathy was the most common manifestation, seen in 19/22 (86.4%) patients with thoracic involvement. 2/22 (9.1%) patients had isolated thoracic involvement (1 pleural effusion and thickening; 1 inflammatory pseudotumour); all other cases had clinicoradiological evidence of multisystem IgG4-RD.

The clinical characteristics, treatment and outcomes of those patients with definite (n=5) or highly probable (n=2) thoracic IgG4-RD are detailed in **table 2**. Of those patients (n=15) with probable thoracic IgG4-RD, all had evidence of multi-system disease with pancreatic (6 patients), submandibular and/or parotid (5), biliary (5), and renal (2) involvement being the most common sites for extrathoracic IgG4-RD.

The mean serum IgG4 level in patients (n=22) with either definite or probable thoracic involvement by IgG4-RD was 9.38 g/L (range 0.01-54.1; SD 12.2); this was significantly higher than the mean serum IgG4 level (3.21 g/L; range 0.14-8.03; SD 2.7) in patients (n=22) with no evidence of thoracic involvement (unpaired *t*-test, *p*=0.03). There were no other statistically significant differences identified between the patient populations with and without evidence of thoracic involvement with respect to either demographic or clinical characteristics (**table 1**). 7/53 (13.2%) patients died during follow-up (median 13 months; range 2-120). In 4/7 cases chest pathology was included on the death certificate; in 2 cases this was as the primary cause of death (both pneumonia, diagnosed clinicoradiologically); whilst in 3 cases this was as a secondary co-morbidity likely to have contributed to the patient's death (all interstitial lung disease; 2 NSIP and 1 UIP pattern). There was no significant difference in mortality between those patients with and without thoracic IgG4-RD during the study follow-up period. No cases of primary thoracic malignancy were identified during follow-up.

DISCUSSION

The results of this study show that thoracic involvement may be found in almost half of patients diagnosed with IgG4-RD. Our findings are consistent with those from previous studies [3, 6, 8, 13, 14] and highlight the importance of thoracic manifestations in IgG4-RD, with particular reference to a European population. Whilst mediastinal lymphadenopathy is the most common manifestation in our cohort, a finding also reported by other groups, our data illustrate the wide range of appearances and apparent pathologies with which IgG4-RD can present to respiratory physicians (**figure 1**). Although the proportion of patients with an elevated serum IgG4 was similar for those with and without thoracic involvement by IgG4-RD, the former group had significantly higher levels on average. The clinical significance of this observation is uncertain, but may be a marker of more active or widespread disease.

Establishing a diagnosis of IgG4-RD is challenging due to variations in clinical presentation, the wide differential of other common conditions, and the need to meet pre-specified diagnostic criteria [10-12]. Neither elevated serum IgG4 levels, nor an increased number of IgG4-positive plasma cells on tissue biopsy, are specific enough to make a diagnosis in isolation; instead, the identification of key histopathological findings alongside an IgG4/IgG plasma cell ratio of >40% [5], with consistent clinicoradiological features are usually thought to be necessary. It is important, however, to recognise that lung pathology in IgG4-RD should be considered different to that of more "solid" organs such as pancreas or kidney. The storiform fibrosis and obliterative phlebitis typical of IgG4-RD is frequently inconspicuous or non-existent in lung tissue affected by a more diffuse process (e.g. interstitial lung disease). Instead, the interstitium and alveolar spaces may demonstrate characteristic inflammatory change, sometimes including neutrophilic aggregates that elsewhere in the body would be considered inconsistent with a diagnosis of IgG4-RD. Obliterative arteritis, a feature reported as unique to the lung in IgG4-RD among other organs, may also be present; particularly in solid lesions such as inflammatory pseudotumours [5, 9].

The differential diagnosis at presentation in the context of suspected thoracic involvement by IgG4-RD is broad and ranges from other multisystem diseases (e.g. sarcoidosis, connective tissue disease), to those with similar clinicoradiological features (e.g. interstitial lung disease, neoplasm) or that can also be seen with local and systemic inflammation alongside elevated IgG4 tissue levels (e.g. Churg-Strauss disease,

multicentric Castleman's disease). Nonetheless, establishing the correct diagnosis is critical since the majority of patients with IgG4-RD will, at least initially, respond to corticosteroid treatment [4, 15, 16].

It is increasingly recognised from longer-term observational studies of patients with IgG4-RD that a significant number will require additional immunosuppression with a steroid-sparing agent [15, 16]. This may be as a result of the need to reduce the risk of steroid toxicity in those patients requiring long-term maintenance therapy, or frequently due to disease relapse. A variety of agents have been utilised; these include azathioprine, mycophenolate mofetil, methotrexate, and cyclophosphamide. However, clinical practice is highly variable in terms of agent choice and dosing strategy, and largely based on an individual clinician's preference and/or experience in the absence of any prospective data [16]. The use of rituximab as a rescue and, less frequently, induction therapy is also well reported [15-17]. Whilst its likely mode of action in depleting B-cells, plasmablast precursors and thereby IgG4 production is accepted, there is again no clear consensus on the optimum timing or frequency of treatment needed to achieve and maintain disease remission [15, 16]. The use of other biological therapies aimed at B- and T-cell lines or other molecular targets are in their infancy but may in time provide alternative strategies in more resistant disease.

The recognition of this condition less than two decades ago [1, 2] means there is a lack of data describing the long-term prognosis of patients with IgG4-RD. This is true for those individuals with thoracic IgG4-RD, either in isolation or as part of a multisystem process. The available data suggest that thoracic IgG4-RD behaves similarly to extra-thoracic manifestations in terms of both its initial steroid responsiveness, and tendency to relapse [6-9, 14]. Our own limited observations support this (**table 2**), with a number of our patients requiring second-line steroid-sparing therapy to achieve longer-term remission [18]. A notable exception seen by other groups [7, 9] and in one of our patients (**table 2** - case #5), appears to be those individuals who present with an isolated inflammatory mass and are only diagnosed with IgG4-RD after surgical resection for suspected malignancy. We observed no significant difference in mortality between those patients with and without evidence of thoracic involvement by IgG4-RD in our cohort (**table 1**). Our knowledge of prognosis in this condition is likely to only be furthered by the passage of time and coordinated multicentre studies that can draw on a larger cohort of patients.

The authors have adopted a standardised approach to the treatment of these patients, based on local experience and the available literature. Following discussion at the MDT meeting, we typically initiate treatment with oral prednisolone at a daily dose of between 30 and 50mg (0.5mg/kg), dependent on the patient's size and clinical symptoms. Steroids are gradually weaned according to clinical response; additional immunosuppressive agents, usually mycophenolate mofetil or azathioprine, are introduced in those patients considered to be high-risk and/or with evidence of refractory or relapsing disease. Rituximab is utilised as a third-line treatment on a case-by-case basis when other conventional immunosuppressive therapy has proven unsuccessful. Failure to make the diagnosis and the subsequent delay in treatment risks progressive fibrosis and irreversible organ damage, as seen in our own cohort [18]. The authors recognise there is a lack of robust evidence to guide treatment choice in this field, and further research including international multi-centre clinical trials of treatment in IgG4-RD are urgently needed to standardise both therapeutic regimens and measures of disease response.

The limitations of this work include the retrospective evaluation of thoracic disease, in a prospectively collected cohort of IgG4-RD patients, and the relatively small sample size. Furthermore, the clinical categorisation used meant those patients with "probable" IgG4-related thoracic involvement did not have histopathological confirmation and could have had alternative pathology. However, the robust MDT-led

process meant that all these patients had a secure diagnosis of IgG4-RD on the basis of proven extra-pulmonary disease; increasing the likelihood that their thoracic abnormalities were a manifestation of the same process.

In conclusion, almost half of patients with proven IgG4-RD have evidence of potential thoracic manifestations of this disease. All patients with an established diagnosis of extra-thoracic IgG4-RD should undergo routine cross-sectional imaging to include the chest, regardless of their original presentation or symptoms. Respiratory physicians should be aware of this condition and its varying manifestations, particularly in the context of other systemic issues, and recognise that the absence of classical pathological changes usually associated with extra-thoracic IgG4-RD do not necessarily preclude diagnosis in the lung.

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LEGENDS

- Figure 1: Imaging from three patients (see table 1) with histology-proven thoracic IgG4-RD illustrating variation in clinical presentations; from left to right: (A) case #4, NSIP-pattern interstitial lung disease (see arrows) subsequently responsive to steroid therapy; (B) case #3, pleural thickening and effusion with partial response to steroids and methotrexate; (C) case #5, inflammatory pseudotumour (see arrows) diagnosed following surgical excision (right lower lobectomy for presumed malignancy).
- Table 1: Categorisation of thoracic involvement in 53 patients with proven IgG4-RD based on established diagnostic criteria and cross-sectional imaging available for assessment.
- Table 2: Clinical characteristics, treatment and outcomes in patients with definite (n=5) or highly probable (n=2) IgG4-RD

TABLE 1

Category of thoracic involvement (including brief descriptive outline)	Number of patients	Description of key thoracic abnormalities identified	Age at diagnosis (mean, SD) p = 0.279	Male p = 0.759	Elevated serum IgG4 level (>1.3 g/L) p = 0.303	Smoking >10 pack years p = 0.929	Industrial or environmental risk factor for lung disease p = 0.856	Death during follow-up p = 0.862
DEFINITE <i>Biopsy-proven thoracic involvement by IgG4-RD with MDT consensus and typical radiology</i>	5/53 (9.4%)	4 large volume mediastinal lymph nodes (≥1cm diameter) 3 pleural effusion & thickening 1 ILD (NSIP pattern) 1 inflammatory pseudotumour	65.7 years (9.7)	17/22 (77.3%)	20/22 (90.9%)	8/22 (36.4%)	7/22 (31.8%)	4/22 (18.2%)
HIGHLY PROBABLE <i>Typical radiology with no alternative explanation for abnormalities seen AND evidence of radiological and/or symptomatic response to treatment</i>	2/53 (3.8%)	2 large volume mediastinal lymph nodes 1 ILD (NSIP pattern) 1 multiple soft-tissue nodules						
PROBABLE <i>Typical radiology with no alternative explanation for abnormalities seen</i>	15/53 (28.3%)	13 large volume mediastinal lymph nodes 3 ILD (NSIP pattern) 1 mediastinal soft tissue mass (FDG-PET avid)						
POSSIBLE <i>Radiology potentially consistent with IgG4-RD, but either atypical and/or plausible alternative cause identified for radiological changes</i>	9/53 (17.0%)	7 multiple small volume mediastinal lymph nodes (6- 9mm diameter) 2 multifocal micro-nodularity 1 ILD (UIP pattern) 1 isolated soft-tissue nodule	63.7 years (11.5)	8/9 (88.9%)	7/9 (77.8%)	3/9 (33.3%)	2/9 (22.2%)	1/9 (11.1%)
NONE <i>Normal thoracic imaging or atypical imaging with definite alternative cause identified for radiological changes</i>	22/53 (41.5%)	N/A	58.6 years (19.3)	16/22 (72.7%)	16/22 (72.7%)	7/22 (31.8%)	7/22 (31.8%)	2/22 (9.1%)

TABLE 2

DEFINITE THORACIC IgG4-RD <i>(biopsy-proven thoracic involvement with MDT diagnostic consensus and typical radiology)</i>								
Case no.	Age at diagnosis (years)	Gender	Smoking history	Serum IgG4 at diagnosis (normal <1.3g/L)	Description of thoracic CT findings	Site of biopsy and description of histological findings	Evidence of extrathoracic IgG4-RD	Clinical treatment and outcome
1	68	Female	Never	10.9	Right-sided pleural effusion; scattered areas of ground glass opacification; large volume (>1cm) mediastinal adenopathy	Thoracoscopic pleural biopsy: fibrosis with lymphoplasmacytic infiltrate, obliterative phlebitis and numerous IgG4-positive plasma cells, mean 57 per high-power field	Suspected liver disease with abnormal biochemistry and imaging; subsequent biopsy non-diagnostic for IgG4-RD	Observation only (declined trial of steroids in absence of significant symptoms); clinically stable after 21 months.
2	76	Male	Ex-, 15 pack years	5.8	Left-sided pleural effusion with smooth parietal pleural thickening; large volume mediastinal adenopathy	Thoracoscopic pleural biopsy: fibrosis with lymphoplasmacytic infiltrate and basket weave pattern; numerous plasma cells with IgG4 positivity, >50 per high-power field and IgG4:IgG ratio of 80%	Retroperitoneal fibrosis seen on CT abdomen/pelvis; no biopsy but presumed secondary to IgG4-RD	Initial oral steroid therapy with good clinical response; switched to mycophenolate mofetil after one year as steroid-sparing agent. Clinically stable after 24 months.
3	64	Male	Never	2.8	Right-sided pleural effusion with smooth parietal pleural thickening	Thoracoscopic pleural biopsy: fibrous thickening with prominent lymphoplasmacytic infiltrate; mean 73 IgG4 positive plasma cells per high-power field with IgG4:IgG ratio >40%	No clinicoradiological evidence	Oral steroid therapy with good clinical response; already on methotrexate for psoriatic arthritis at time of diagnosis. Died after 20 months due to mesenteric ischaemia (presumed thromboembolic aetiology).

4	80	Male	Never	26.1	Widespread subpleural reticulation and ground glass with no honeycombing; more confluent areas of right upper lobe consolidation; large volume mediastinal adenopathy	Thoracoscopic lung biopsy: right upper and lower lobe wedges show lymphoplasmacytic infiltration of interstitium with florid vasculitis involving arteries and, to a lesser extent, veins; small foci of fibrosis seen within lung parenchyma; large number of IgG4 positive plasma cells seen within interstitium and vessel walls, >100 per high-power field in many areas	Abnormal biochemistry and appearance to biliary tree and pancreas on imaging (CT, MRCP, ultrasound) in keeping with IgG4 sclerosing cholangitis and autoimmune pancreatitis.	Short course of oral steroids with early switch to oral methotrexate as longer-term maintenance therapy with good symptomatic response. Clinically stable after 15 months.
5	64	Male	Ex-, 30 pack years	3.3	Right lower lobe mass lesion with smaller satellite nodules; large volume mediastinal adenopathy	Thoracoscopic resection of right lower lobe mass: fibroinflammatory lesion with focal obliterative arteritis and venulitis; copious plasma cells; mean 103 IgG4 positive plasma cells per high-power field	No clinicoradiological evidence	Surgical resection of inflammatory pseudotumour; no pharmacological therapy. No evidence of relapse or recurrence after 15 months.
HIGHLY PROBABLE THORACIC IgG4-RD <i>(typical radiology with no alternative explanation for abnormalities seen AND evidence of radiological and/or symptomatic response to treatment)</i>								
1	69	Male	Never	5.06	Symmetrical diffuse subpleural reticulation and ground glass change; few areas of early fibrosis without traction or honeycombing; large volume mediastinal adenopathy	No intrathoracic histology. Prior biopsy from biliary tree inconclusive; diagnosis of IgG4-RD made on basis of multi-system disease with typical radiology and clinical features.	Abnormal biochemistry and appearance to biliary tree and pancreas on imaging (CT, MRCP, ultrasound) in keeping with IgG4 sclerosing cholangitis and autoimmune pancreatitis.	Roux-en-Y biliary bypass at time of presentation; subsequent steroid therapy with good clinical response including reduction in ground glass and mediastinal lymph nodes on interval imaging. Died after 10 years follow-up from community acquired pneumonia (clinicoradiological diagnosis).
2	65	Male	Ex-, 30 pack years	2.11	Multiple soft-tissue nodules spread throughout both lungs; large volume mediastinal adenopathy. FDG avid on subsequent PET scan.	No intrathoracic histology. Prior biopsy from nasal septum highly suggestive of IgG4-RD (dense fibrosis with lymphoplasmacytic infiltrate and IgG4-positive plasma cell predominance)	Abnormal histology (sinonasal) and imaging (PET showing large vessel vasculitis) in keeping with multi-system IgG4-RD involvement.	Initial oral steroid therapy with clinical response including reduction in size, number and avidity of pulmonary lesions; switched to methotrexate as steroid-sparing / second-line agent in context of disease relapse. Clinically stable after 18 months.

FIGURE 1

