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Thoracic involvement and imaging patterns in IgG4-related disease

Romain Muller ^{1,13}, Paul Habert^{2,13}, Mikael Ebbo¹, Julie Graveleau³, Mathieu Groh⁴, David Launay ⁵, Sylvain Audia⁶, Gregory Pugnet⁷, Fleur Cohen⁸, Antoinette Perlat⁹, Audrey Benyamine¹⁰, Boris Bienvenu¹¹, Lea Gaigne¹, Pascal Chanez¹², Jean Yves Gaubert² and Nicolas Schleinitz ¹

¹Dept of Internal Medicine, Aix Marseille University, APHM, CHU La Timone, Marseille, France. ²Dept of Radiology, Aix Marseille University, APHM, CHU La Timone, Marseille, France. ³Dept of Internal Medicine, CH Saint Nazaire, Saint Nazaire, France. ⁴Dept of Internal Medicine, CH Foch, National Referral Center for Hypereosinophilic Syndromes (CEREO), Suresnes, France. ⁵Univ. Lille, Inserm, CHU Lille, Service de Médecine Interne et Immunologie Clinique, Centre de référence des maladies autoimmunes systémiques rares du Nord et Nord-Ouest de France (CeRAINO), U1286 - INFINITE - Institute for Translational Research in Inflammation, Lille, France. ⁶Dept of Internal Medicine, CHU Dijon, Dijon, France. ⁷Dept of Internal Medicine and Clinical Immunology, CHU Toulouse, Toulouse, France. ⁸Dept of Internal Medicine, APHP, CHU Pitié-Salpêtrière, Paris, France. ⁹Dept of Internal Medicine, CHU Rennes, Rennes, France. ¹⁰Dept of Internal Medicine, Aix Marseille University, APHM, CHU Nord, Marseille, France. ¹¹Dept of Internal Medicine, CH St Joseph, Marseille, Marseille, France. ¹²Dept of Pneumology, Aix Marseille University, APHM, CHU Nord, Marseille, France. ¹³These authors contributed equally to this work.

Corresponding author: Nicolas Schleinitz (nicolas.schleinitz@ap-hm.fr)



Shareable abstract (@ERSpublications)

Thoracic and lung involvements of IgG4-RD are heterogeneous and under-evaluated. Peribronchovascular involvement and lymph node enlargement are most frequent patterns. Interstitial disease pattern seems to be associated with a lower rate of treatment response. <https://bit.ly/3B54HiR>

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Abstract

Objective Immunoglobulin G4-related disease (IgG4-RD) is a rare orphan disease. Lung, pleura, pericardium, mediastinum, aorta and lymph node involvement has been reported with variable frequency and mostly in Asian studies. The objective of this study was to describe thoracic involvement assessed by high-resolution thoracic computed tomography (CT) in Caucasian patients with IgG4-RD.

Methods Thoracic CT scans before treatment were retrospectively collected through the French case registry of IgG4-RD and a single tertiary referral centre. CT scans were reviewed by two experts in thoracic imagery blinded from clinical data.

Results 48 IgG4-RD patients with thoracic involvement were analysed. All had American College of Rheumatology/European League Against Rheumatism classification scores ≥ 20 and comprehensive diagnostic criteria for IgG4-RD. CT scan findings showed heterogeneous lesions. Seven patterns were observed: peribronchovascular involvement (56%), lymph node enlargement (31%), nodular disease (25%), interstitial disease (25%), ground-glass opacities (10%), pleural disease (8%) and retromediastinal fibrosis (4%). In 37% of cases two or more patterns were associated. Asthma was significantly associated with peribronchovascular involvement ($p=0.04$). Among eight patients evaluated by CT scan before and after treatments, only two patients with interstitial disease displayed no improvement.

Conclusion Thoracic involvement of IgG4-RD is heterogeneous and likely underestimated. The main thoracic CT scan patterns are peribronchovascular thickening and thoracic lymph nodes.

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a systemic fibro-inflammatory disorder characterised by unifying histopathological findings [1]. Virtually all organs can be involved. In most case series, involvement of pancreas, bile ducts, salivary and lachrymal glands, retroperitoneum, lungs, kidneys, and aorta are reported with the highest frequencies [2–4]. Preferential clinical phenotypes have been suggested by cluster analysis [5]. Pulmonary involvement, usually from imaging studies, is reported in up to 14% of patients in large cohorts, with a higher frequency in patients with salivary gland and systemic involvement [6, 7].



In case series, the frequency of the different types of thoracic involvement is variable and the lesions observed are not specific for IgG4-RD. Lymph node enlargement is reported in 40–90% of patients, and pleura or lung involvement in 14–51% [8–13]. However, only few case series have precisely described pulmonary and thoracic involvement, especially in non-Asian patients [14].

The aim of our study was to precisely describe thoracic computed tomography (CT) scan abnormalities in patients with well-characterised IgG4-RD, and to correlate the thoracic lesions and patterns observed with other organ involvements, respiratory disease such as asthma, and responses to treatment.

Materials and method

Patients

Patients with thoracic involvement were identified from the French case registry of IgG4-RD patients. This registry is the result of a multidisciplinary multicentric collaboration, which collects prospectively clinical, biological, radiological and pathological data from patients with IgG4-RD. When thoracic involvement was declared, physicians were asked to send the DICOM (Digital Imaging and Communications in Medicine) of CT scans performed at diagnosis before treatment (group 1, see Supplemental Figure S1). The case registry is authorised by the French authorities (Commission Nationale de l'Informatique et des Libertés). We also systematically reviewed all available thoracic CT scans from patients followed in a single tertiary centre without referenced thoracic involvement. All patients presenting with thoracic abnormalities were included in the study (group 2, Supplemental Figure S1). Only patients fulfilling both comprehensive diagnostic criteria and the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2019 classification criteria (score ≥ 20) were included in the study [4, 15]. Age, gender, time to diagnosis, organ involvements, biological evaluation, treatments and outcome were collected.

Thoracic CT scan and reviewing methodology

Patients from our centre underwent CT scan on the same system (Revolution EVO, GE Healthcare, WI, USA). CT scans were acquired in profound and maximal inspiration with the following parameters: detector collimation: 0.625 mm; field of view: 500 mm; matrix: 512×512; pitch: 1.375; gantry speed 0.35 s; 120 Kv; 1 mAs·kg⁻¹ with care dose modulation, reconstruction in slices of thickness 1:1 mm. We applied dose modification manually according to the patient template, which means 140 kV or 100 kV if their weight were more than 120 kg or less than 60 kg. All imaging data were reconstructed using high-resolution and standard algorithms. Concerning patients from the other centres, physicians were asked to send the anonymised DICOM of CT scans performed at diagnosis before treatment. All imported imageries included thin-section CT scans and high-resolution reconstruction filters. Subsequently, the system and the parameters were not available for imported CT. Monitors were used to view both mediastinal (width, 400 HU; level, 20 HU) and lung (width, 1600 HU; level, -600 HU) windows. The pre-established top anatomic border was the lower part of the neck. The pre-established anatomic bottom boundary was the estimated location of the adrenal glands below the costophrenic angle. CT data were sent to an archiving and communicating system (Centricity Universal Viewer, GE Healthcare, WI, USA). All CT scans were reviewed by two thoracic radiologists blinded from clinical data and discrepancies were reviewed by the two radiologists together to reach a consensus.

Abnormalities were described according to the Fleischner glossary [16] as following: bronchiolitis (tree in bud or alveolar nodules), bronchiectasis, solid nodules, ground-glass opacities (GGO), areas of consolidation, pleural effusion or thickening, peribronchovascular thickening, mediastinal lymph nodes, mucoid impactions, septal thickening, honeycombing, reticulations, architectural distortion, and retromediastinal fibrosis (paravertebral soft tissue band). Subsequently, they were classified into four patterns as previously reported: nodular, round-shaped GGO, interstitial disease and peribronchovascular involvement [14]. Lymph node enlargement, pleural disease and retromediastinal fibrosis patterns were added to define a total of seven patterns of thoracic involvement (Supplemental Table S1). Nodular pattern was defined by the presence of multiple solid nodules; round-shaped GGO pattern by the presence of multiple GGO; interstitial disease pattern by the presence of septal thickening, honeycombing, reticulations or architectural distortion; peribronchovascular involvement pattern was defined by the presence of peribronchovascular thickening, bronchiolitis, area of consolidation or mucoid impaction; lymph node enlargement pattern by bilateral mediastinal lymph nodes; and pleural involvement pattern by pleural effusion or pleural thickening and retromediastinal fibrosis pattern by the presence of retromediastinal fibrosis. The specificity between thoracic involvement and IgG4-RD was also analysed according to the criteria of CORCORAN *et al.* [6]: thoracic biopsy-proved was necessary for “definite” IgG4-RD-related thoracic involvement; a typical imaging finding with no alternative explanation and response to treatment was defined as “highly probable” IgG4-RD-related thoracic involvement; typical radiology with no

alternative explanation was defined “probable” IgG4-RD-related thoracic involvement; and radiology potentially consistent with IgG4-RD but with a plausible alternative cause was identified defined as “possible” IgG4-RD-related thoracic involvement. Response to treatment of thoracic lesions was defined by CT scan comparative analysis before and after treatment: complete response was retained if all thoracic abnormalities disappeared after treatment, no response was retained if thoracic abnormalities remained unchanged and partial response was retained in all cases with improvement of thoracic lesions without complete disappearance.

Statistical analysis

Quantitative variables were expressed as mean or median, standard deviation and range. Qualitative variables were expressed as numbers, proportions and percentages. The differences between groups were compared by the chi-square or Fisher’s exact tests for qualitative variables, and by the Mann–Whitney test for quantitative variables. A $p < 0.05$ was considered significant.

Results

Patients’ characteristics

At the time of the study, 222 patients were included in the French national cohort of IgG4-RD (Supplemental Figure S1). A thoracic involvement was notified in 56 of them (25%), among whom CT scans at diagnosis could be collected in 28 (50%) cases (group 1). We also systematically reviewed the CT scans from 26 patients without notified thoracic involvement followed in our tertiary referral centre. This analysis revealed thoracic abnormalities in 20/26 IgG4-RD patients (77%) (group 2).

After pooling patients from groups 1 and 2, a total of 48 patients with CT scan thoracic involvement were analysed (table 1). All patients fulfilled ACR/EULAR classification criteria with a score ≥ 20 (range: 25–75) [4], even if six patients (13%) presented with eosinophilia $> 3\,000\text{ cells}\cdot\text{mm}^{-3}$. Mean age was 60 ± 15 years, with male predominance (81%). Nine patients (19%) were smokers or former smokers, 18 (37%) reported atopy, and one was exposed to asbestos. Respiratory symptoms were reported in 14 patients and consisted

TABLE 1 Clinical and biological characteristics of 48 patients with immunoglobulin G4-related disease (IgG4-RD) thoracic involvement

Characteristic	Patients (n=48)
Demographic data	
Male	39 (81)
Median age at onset (years)	60 (23–83)
Median diagnostic delay (months)	6 (1–240)
Smoker or former smoker	9 (19)
History of atopy	18 (37)
Organ involvement of IgG4-RD	
Median number of organs affected	3 (1–6)
Lymph nodes	30 (62.5)
Pancreatitis	15 (31.2)
Tubulointerstitial nephritis	15 (31.2)
Sialadenitis	15 (31.2)
Retroperitoneal fibrosis	10 (20.8)
Sclerosing cholangitis	10 (20.8)
Aortitis	8 (16.6)
Dacryoadenitis	6 (12.5)
Prostatitis	3 (6.2)
Biological characteristics	
Elevated serum IgG ($> 1400\text{ mg}\cdot\text{dL}^{-1}$)	43 (89.5)
Elevated serum IgG4 ($> 135\text{ mg}\cdot\text{dL}^{-1}$)	43 (89.5)
Elevated serum IgG4 $> 2 \times \text{N}$	32 (66.7)
Median serum IgG4 level ($\text{mg}\cdot\text{dL}^{-1}$)	430 (23–2040)
Hypocomplementaemia	13 (27)
Elevated CRP ($> 5\text{ mg}\cdot\text{L}^{-1}$)	39 (81.2)
Positive ANA ($> 1/160$)	9 (18.8)

Data are presented as n (%) or median (range). ANA: antinuclear antibody; CRP: C reactive protein.

of wheezing (64%), cough (21%), thoracic pain (14%) or dyspnoea (14%). Thoracic involvement was reported at diagnosis in 13 patients (27%), and during follow-up (at a relapse) in 34 patients (72%). The relapses occurred during maintenance therapy in 19 patients and in the absence of any treatment in the others.

Most patients presented with systemic involvement, defined by three or more organs involved (63%, mean 3 ± 1.5 organs involved). Isolated thoracic involvement with histological confirmation was observed in only one patient (figure 1). The main extra-thoracic associated organ involvements consisted of lymph nodes (62%), pancreas (31%), salivary glands (31%), kidneys (31%), bile ducts (21%) and retroperitoneum (21%). The mean serum IgG4 level was $700 \pm 680 \text{ mg} \cdot \text{dL}^{-1}$, median $425 \text{ mg} \cdot \text{dL}^{-1}$. Hypocomplementaemia was reported in 27% of patients, and elevated serum C reactive protein (CRP) level ($>5 \text{ mg} \cdot \text{L}^{-1}$) in 81%. Hypereosinophilia $>1500 \text{ cells} \cdot \text{mm}^{-3}$ was observed in 11 patients (22%), ranging from $1600 \text{ cells} \cdot \text{mm}^{-3}$ to $18\,000 \text{ cells} \cdot \text{mm}^{-3}$. The six patients with hypereosinophilia $>3000 \text{ cells} \cdot \text{mm}^{-3}$ were maintained in the study because they presented with definite IgG4-RD and no other diagnosis related to eosinophilia.

Thoracic imaging features

CT features of IgG4-RD thoracic involvement are presented in Supplemental Table S1. Lung involvement, defined as peribronchovascular thickening, GGO, nodular or interstitial disease pattern, was present in 43/48 patients (89%). Peribronchovascular thickening and lymph nodes were observed in 54% of patients. When thoracic abnormalities were classified by patterns, peribronchovascular involvement pattern (56%) and lymph node enlargement pattern (31%) were the most frequent. Nodular and interstitial disease patterns were present in 25%. GGO, pleural disease and retromediastinal fibrosis patterns were less common in 10%, 8% and 4% of patients, respectively. 18 patients (37%) had at least two types of thoracic involvement patterns (table 2). The peribronchovascular involvement pattern was isolated in 13/27 cases (48%), while the nodular pattern in 3/7 cases (43%), the interstitial disease pattern in 2/7 cases (29%) and the lymph node enlargement pattern in 3/15 cases (20%). GGO and pleural disease patterns were never isolated. Both patients with a retro-mediastinal fibrosis pattern (paravertebral soft-like band) had no other thoracic involvement. No patient had pericardial involvement on thoracic CT.

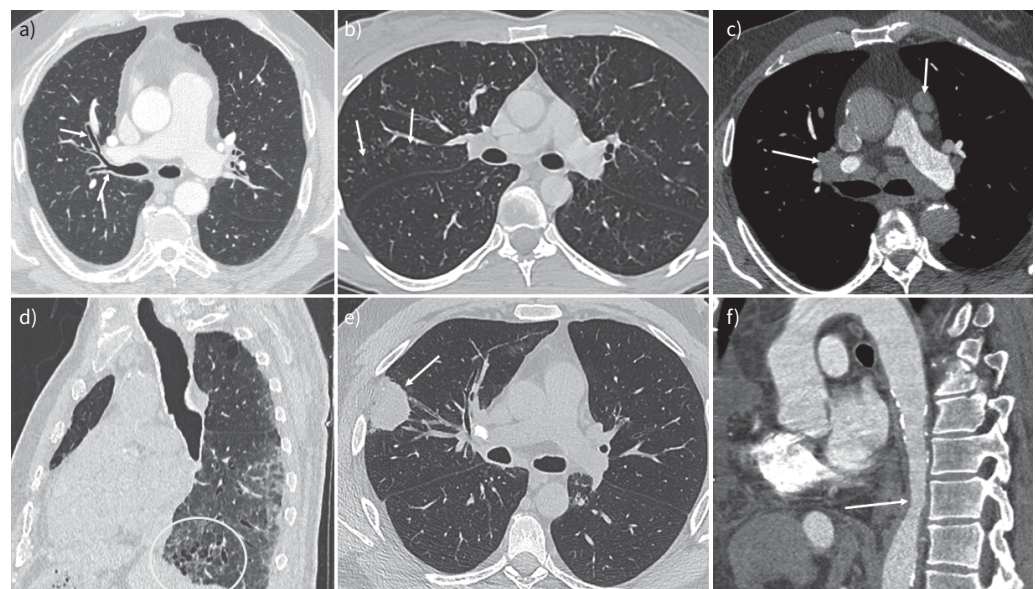


FIGURE 1 Various imaging patterns of immunoglobulin G4-related disease thoracic involvement (each computed tomography (CT) scan section comes from a different patient). **a)** Axial contrast-enhanced thoracic CT scan showing an important bronchial thickening of the segmental right superior lobe bronchi (arrows). **b)** Axial unenhanced thoracic CT scan showing nodular ground-glass opacities in the posterior segment of the right superior lobe (arrows). **c)** Axial enhanced thoracic CT scan showing lymph nodes enlargement in the mediastinum in situation 5 and 10R (arrows). **d)** Sagittal reconstruction of thoracic CT scan showing distal bronchial distension and traction bronchiectasis in the interstitial lung pattern (circle). **e)** Axial unenhanced thoracic CT scan showing a mass in the right superior lobe (arrow). **f)** Sagittal enhanced aortic CT scan showing a stenosis of descending aorta and aortic wall thickening due to posterior mediastinitis (arrow).

TABLE 2 Association between immunoglobulin G4-related disease (IgG4-RD) thoracic involvement patterns.

	Nodular	Interstitial disease	Peribronchovascular involvement	Ground-glass opacities	Lymph node enlargement	Retro mediastinal fibrosis	Pleural disease
Nodular	7						
Interstitial disease	1	7					
Peribronchovascular involvement	2	3	27				
Ground-glass opacities	0	1	3	5			
Lymph node enlargement	3	3	9	0	15		
Retromediastinal fibrosis	0	0	0	0	0	2	
Pleural disease	0	3	3	1	2	0	4

Causal relationship between CT scan lesion and IgG4-RD

According to the criteria of CORCORAN *et al.* [6] (table 3), we classified 23 patients (48%) as definitive, nine (19%) as highly probable, 15 (31%) as probable and one (2%) with possible involvement. No differences in thoracic involvement pattern, age, gender, serum IgG4 level, history of smoking or exposure to asbestos were observed between groups. Histologic features of the 23 patients with definitive involvement are shown in Supplemental Table S2.

Correlations of thoracic CT scan lesions with IgG4-RD characteristics

Characteristics of patients classified in the seven different CT scan patterns (nodular, interstitial disease, peribronchovascular involvement, round-shaped GGO, lymph node enlargement, pleural disease and

TABLE 3 Classification of immunoglobulin G4-related disease (IgG4-RD) thoracic involvement according to the criteria of CORCORAN *et al.* [6]

Category of thoracic involvement	Number of patients (group 1/group2)	Thoracic patterns	Age at diagnosis, years median \pm SD	Male n/N (%)	Elevated serum IgG4 level n/N (%)	Smoking history >10 pack years n/N (%)	Industrial or environmental exposure to asbestos n/N (%)
Definite Biopsy proved thoracic involvement	23/48	15 lymph node enlargement 13 peribronchovascular involvements Seven nodular Four interstitial disease Two GGO	59 \pm 14	20/23 (87)	20/23 (87)	3/23 (13)	0/23 (0)
Highly probable Typical radiology with no alternative explanation and response to treatment	9/48	Seven peribronchovascular involvement Four lymph node enlargement Three GGO One nodular One interstitial disease	49 \pm 17	8/9 (89)	8/9 (89)	1/9 (11)	0/9 (0)
Probable Typical radiology with no alternative explanation	15/48	Eight peribronchovascular involvements Three lymph node enlargement Three nodular	65 \pm 16	10/15 (66)	14/15 (93)	3/15 (20)	0/15 (0)
Possible Radiology potentially consistent with IgG4-RD but plausible alternative cause identified	1/48	One interstitial disease	76	1/1 (100)	1/1 (100)	0/1 (0)	1/1 (100)

GGO: ground-glass opacity; SD: standard deviation.

TABLE 4 Clinico-biological characteristics of patients according to the immunoglobulin G4-related disease (IgG4-RD) thoracic pattern.

Characteristic	Nodular n=7 n (%)	Interstitial disease n=7 n (%)	Peribronchovascular involvement n=25 n (%)	Round-shaped GGO n=5 n (%)	Lymph node enlargement n=15 n (%)	Retromediastinal fibrosis n=2 n (%)	Pleural disease n=4 n (%)
Male	5 (70)	6 (86)	20 (80)	4 (80)	13 (87)	2 (100)	3 (75)
Smoking history	2 (29)	0 (0)*	8 (32)	2 (40)	5 (33)	1 (50)	0 (0)
Asthma	1 (14)	2 (29)*	8 (32)*	0 (0)	2 (13)	0 (0)	1 (25)
Pancreatitis	2 (29)	2 (29)	8 (32%)	4 (80)*	3 (20)	0 (0)	1 (25)
Cholangitis	1 (14)	1 (14)	6 (23%)	1 (20)	3 (20)	0 (0)	0 (0)
Nephritis	2 (29)	1 (14)	10 (40)*	1 (20)	3 (20)	0 (0)	0 (0)
Orbital tumour	0 (0)	0 (0)	3 (12)	1 (20)	1 (7)	0 (0)	0 (0)
Dacryoadenitis	2 (29)	0 (0)	4 (16)	1 (20)	4 (27)	0 (0)	0 (0)
Sialadenitis	3 (43)	1 (14)	8 (32)	1 (20)	8 (53)*	0 (0)	0 (0)
Retroperitoneal fibrosis	2 (29)	1 (14)	5 (20)	0 (0)	2 (13)	0 (0)	1 (25)
Aortitis	1 (14)	2 (29)	5 (20)	0 (0)	4 (27)	1 (50)	1 (25)
Prostatitis	0 (0)	0 (0)	3 (12)	1 (20)	0 (0)	0 (0)	0 (0)
IgG4 >135 mg·dL ⁻¹	6 (86)	7 (100)	23 (92)	4 (80)	15 (100)	1 (50)	4 (100)
CRP >5 mg·L ⁻¹	5 (71)	5 (71)	21 (84)	4 (80)	13 (87)	2 (100)	4 (100)
Hypereosinophilia >1500 cells/mm ³	1 (14)	5 (71)*	9 (36)	2 (40)	2 (13)	0 (0)	2 (50)
EULAR score mean (min-max)	42.3 (35–70)	41.8 (27–64)	41.6 (25–75)	36.5 (25–54)	41.7 (27–70)	42 (39–45)	45 (27–50)

GGO: ground-glass opacity; CRP: C reactive protein; EULAR: European League Against Rheumatism. *: p<0.05.

retromediastinal fibrosis) groups are presented in table 4. Asthma, defined from medical records, was found associated with peribronchovascular involvement pattern (p=0.041). The round-shaped GGO pattern was associated with IgG4-related pancreatitis (p=0.013). The lymph node enlargement pattern was associated with sialadenitis (p=0.041). Hypereosinophilia was associated with the interstitial disease pattern (p=0.031).

Response to treatment of IgG4-RD thoracic involvement

Eight patients underwent multiple longitudinal evaluations with a thoracic CT scan with thin sections before and after treatment. The mean time of follow-up was 30 months (from 6 to 73 months). Patterns of IgG4-RD thoracic involvement before treatment were: nodular (n=1), interstitial disease (n=2), peribronchovascular involvement (n=4), GGO (n=2), retromediastinal fibrosis (n=1) and lymph node enlargement (n=1). Patients were treated for IgG4-RD by prednisone (n=2), rituximab (n=1), prednisone and rituximab (n=4) or prednisone and azathioprine (n=1). Complete remission of thoracic abnormalities was observed in two patients treated with prednisone or prednisone and rituximab (Supplemental Figure S2). Partial remission was observed in four patients treated with rituximab (n=1), prednisone and rituximab (n=2), and prednisone and azathioprine (n=1), respectively. In two patients with an interstitial disease pattern treated with prednisone or prednisone and rituximab, their lesions remained unchanged.

Discussion

We describe thoracic CT scan abnormalities and IgG4-RD thoracic involvement patterns in 48 IgG4-RD patients fulfilling ACR/EULAR classification criteria [4, 15]. To our knowledge, this is the largest series reported to date. Almost half of the patients (n=23) had a thoracic biopsy (lymph nodes, lung or pleura). Pathological confirmation of IgG4-RD was obtained from extra-thoracic organ biopsies in others and all these patients presented with otherwise typical IgG4-RD involvement.

The most frequent lesions observed were peribronchovascular thickening (54%) and mediastinal lymph nodes (54%). The other thoracic lesions were: solid nodules (33%), areas of consolidation (25%), bronchiectasis (19%), bronchiolitis (15%), septal thickening (15%), reticulations (15%) and GGO (13%) (Supplemental Table S1). Pleural effusion or thickening and mediastinal fibrosis were less frequent than lung involvement. Further classification by patterns, according to predominant thoracic abnormalities, found that peribronchovascular involvement (56%) and lymph node enlargement (31%) patterns were the most frequent [14]. All patients, except the two with mediastinal fibrosis, presented more than one pattern (table 2).

We found no preferential association within different patterns. In addition, there were no major differences in gender, age, IgG4 level, asbestosis or tobacco exposure between patterns. We confirm as reported from other series that lung involvement in IgG4-RD is heterogeneous [6, 7, 11–14, 17–20]. The discrepancies with other series between the frequencies of lung abnormalities observed suggests either a bias related to retrospective data collection, the lack of central imagery reviewing in some studies or a role of ethnic background. SARAYA *et al.* [21] reported GGO in 69% (n=16) compared to only 13% in our series. The study from KANG *et al.* [22] (n=37) with a classification in five radiologic subtypes found that solid nodular and alveolar consolidative were the most frequent (30% each). None of these patterns are specific for IgG4-RD. However, we could suggest that the association of two or more patterns in a patient (observed in 37% of patients of this series) should be considered as an argument in favour of IgG4-RD [23].

IgG4-RD should be evoked frequently in cases of lung CT scan abnormalities, especially in the assessment of multisystem disease. A complete patient workup including the search for other organ involvement and biological and pathological assessment should be always considered. Other lung diseases need to be excluded because of the lack of specificity and the diversity of patterns. The patients in this study had a long follow-up and extensive diagnostic workup, responding to the ACR/EULAR criteria. The exposition to tobacco use (19%) or occupational or environmental toxicants (2%) were not frequent. When we categorised the patients based on the probability of lung involvement related to IgG4-RD as done by CORCORAN *et al.* [6], 47/48 had at least probable involvement (table 3). This makes us confident that the lesions observed here, before any treatment, were related to IgG4-RD. Asthma, hypereosinophilia and absence of smoking were significantly associated with interstitial disease pattern. Atopy or asthma has a close relationship to IgG4-RD and is reported in one third of IgG4-RD patients [2, 24, 25]. Of note in our study, six patients had an eosinophil count $\geq 3\ 000\ \text{cells}\cdot\text{mm}^{-3}$, which is considered as an exclusion criteria in the ACR/EULAR classification. We believe that these presented with *bona fide* IgG4-RD in the absence of an alternative diagnosis. These patients, as others, presented with various patterns: peribronchovascular involvement 4/6, interstitial disease 2/6, GGO 2/6 and lymph node enlargement 2/6.

This wide range of lung lesions in IgG4-RD suggests various pathophysiological mechanisms. Interestingly, pathological findings in the lungs are slightly different from those reported in other organs in IgG4-RD with inflammation of the interstitium and alveolar space, sometimes obliterative arteritis and less frequently storiform fibrosis or obliterative phlebitis [1, 12, 26]. The pattern of fibrosis in the lung is less storiform than reported in other organs and associated with fibroblast proliferation. Studies of broncho-alveolar lavage fluid reported lymphocytosis [11]. The lesions revealed by CT scans confirm that some lesions in IgG4-RD, as in sarcoidosis (thickening of the perilymphatic interstitium, thoracic lymph nodes, peribronchovascular and pleural involvement), are related to the involvement of the lymphatic system [27]. Some patterns were associated here with particular extra-thoracic organ manifestations: GGO pattern and pancreatitis, peribronchovascular involvement pattern and nephritis, interstitial disease pattern, and eosinophilia and lymph nodes enlargement pattern with sialadenitis (table 4). Such associations on a limited case series are weak but could mirror variations observed in pathological lesions in between organs in the disease [28]. We compared the phenotype of organ involvement and biological variables from the 48 patients with patients from the case registry without thoracic involvement (n=166) (Supplemental Table S3). The only differences observed were a higher number of organs involved (3.04 *versus* 2.53, $p=0.04$), higher serum CRP levels ($\text{CRP}>5\ \text{mg}\cdot\text{L}^{-1}$, 73% *versus* 81%, $p<0.02$) and hypergammaglobulinemia (89% *versus* 70.3%, $p<0.01$) suggesting an ongoing systemic form of the disease. However, as will be discussed later, this comparison is hampered by the lack of systematic review of CT scans from patients of the registry outside of our centre.

Assessing the diagnosis of IgG4-RD lung involvement is important because patients usually respond to steroid therapy. As discussed above, the patterns observed may represent different pathological mechanisms and therefore the response to treatment or the risk of relapse could vary depending on the type. This has been shown for instance for interstitial lung disease in systemic sclerosis classified in non-specific interstitial pneumonia or usual interstitial pneumonia, both reported in IgG4-RD [27]. The first pattern is more frequent but the second is associated with aggressive interstitial lung disease with a poorer outcome [29]. We evaluated CT scans before and after treatment in eight cases and observed that only interstitial disease pattern did not improve. KANG *et al.* [22] reported that alveolar interstitial type showed the lowest response rate. Of note, CORCORAN *et al.* [6] reported from their series that in 4/7 patients who died thoracic pathology was recorded on the death certificate. IgG4-RD thoracic involvement was not responsible for death in all these cases but it suggests that lung involvement should be carefully investigated in IgG4-RD.

We were surprised by the high frequency of thoracic involvement observed after expert review of CT scans from patients for which thoracic involvement was not considered at the initial IgG4-RD evaluation. The review of CT scans from 26 patients (without initially recorded thoracic abnormalities) identified lesions in

20 of them (76%, group 2). Lesions un-noticed previously were mediastinal lymph nodes (55%), peribronchovascular thickening (50%) and bronchial abnormalities (bronchiectasis or bronchiolitis, 25%). Conversely, patients with GGO, pleural involvement or retromediastinal fibrosis were well diagnosed as having thoracic involvement from the first CT scan evaluation. This suggests a high frequency of thoracic involvement in IgG4-RD probably being under-evaluated in case series without systematic imagery reviews [6, 14]. The specific focus on thoracic imagery by experts and the production of thin CT slices in this study probably account for this frequency.

From this study, we think that it is useful to evaluate thoracic CT scans when IgG4-RD is suspected. At the very least, we suggest that the thoracic CT scans frequently performed at initial staging of the disease should be carefully investigated. Identifying peribronchovascular thickening and soft band-like tissues, considered as more specific, will help diagnoses according to ACR/EULAR classification criteria. Multiple organ involvement in IgG4-RD is a risk factor for relapses, therefore identifying thoracic involvement can have an impact on prognosis. We do not think that low-dose CT scans are a valuable tool in IgG4-RD because the low quality of soft tissue analyses could miss small GGO lesions and interstitial lung abnormalities, do not allow accurate evaluation of bronchial wall thickening and can underestimate mediastinal lymph node involvement. We also suggest that, because some abnormalities reported are subtle and could be easily missed, CT scans should be reviewed by specialist radiologists with expertise in the field. In this study, we did not analyse 18-fluorodeoxyglucose (18FDG) positron emission tomography (PET) CT, which has been shown to be a reliable technique for assessing IgG4-RD activity and detect clinically asymptomatic IgG4-RD organ involvement in the thorax (lung or pleura) [30]. PET CT is also useful to assess treatment response but clinical–radiological discrepancies with 18FDG uptake have been reported for lung lesions and lymph nodes [31].

This study has some limitations, mainly related to the retrospective collection of data and to the lack of systematic pathological documentation of lung involvement. Moreover, lung functional tests were lacking and only a few patients could be analysed after treatment. Not all CT scans from the whole case registry were retrospectively reviewed and therefore the comparison between patients with and without thoracic involvement could be biased. Because the inclusion criteria required an ACR/EULAR score >20 we probably missed patients with definite isolated lung involvement. Their absence in the analysis focusing mainly on patients with multiorgan involvement introduces a potential bias in our analysis.

Strengths of this study are the central and systematic reviews by experts of thin-section thoracic CT scans from patients characterised by the recent IgG4-RD ACR/EULAR classification criteria.

Conclusion

The thoracic and, in particular, lung involvement of IgG4-RD is heterogeneous and probably under-evaluated. Peribronchovascular involvement and lymph node enlargement are the most frequent patterns. Nodular disease, interstitial disease, GGO, pleural disease and mediastinal fibrosis are less frequent. None of these patterns are specific. The interstitial disease pattern seems to be associated with a lower rate of treatment response and both interstitial disease and peribronchovascular involvement patterns are associated with asthma.

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