IgG4-related pseudotumours: a series of 12 cases and a review of the literature

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Summary

IgG4-related pseudotumours (IgG4-RPT) represent a distinctive manifestation in the broad spectrum of IgG4-related diseases (IgG4-RD). Due to their wide morphology and rarity, IgG4-RPTs represent a diagnostic challenge in the differential between reactive lesions and a fibrous soft tissue tumours. Thus, our aim was to characterise our cases and review the literature, focusing on the macroscopic and microscopic features of the lesions. In this paper, we summarise the possible presentations and histomorphological features of IgG4-RPT based on data collected from the literature and from cases at our institute and provide an overview of the pathogenesis and histological characteristics based on the knowledge accumulated in recent years.

We collected surgical cases with a diagnosis of IgG4-RPT over the period 2013–2020 at two centres and analysed their macroscopic, histological, and immunohistochemical profiles. Furthermore, we performed a literature research in the MEDLINE and EBSCO databases regarding case reports and studies with the explicit diagnosis of IgG4-RPT.

Our cases consist of nine men and three women, with an average age of 60±14 years, representing about 0.05% of the lesions evaluated at the two departments. The involved sites include the kidney, lung, gallbladder, pterygopalatine fossa, spleen, tongue, mediastinum, and submandibular gland. Grossly, nine lesions showed sharp margins. On histological examination, all the lesions showed an abundant inflammatory infiltrate with lymphocytes and IgG4-positive plasma cells as well as characteristic fibroblastic storiform proliferation. The literature search revealed 266 cases and similar histomorphological features in 23 locations. In 30 of these cases (11%), IgG4-RPTs were multifocal.

IgG4-RPT are exceedingly rare lesions, which makes them challenging to diagnose. They can affect different sites, and the histomorphological presentation may differ.

Key words: IgG4-related; pseudotumour; autoimmune.

INTRODUCTION

IgG4-related disease (IgG4-RD) refers to a chronic inflammatory condition characterised by tissue infiltration of IgG4-secreting lymphocytes and plasma cells, storied fibrosis and a generally rapid response to corticosteroid therapy. It can be a localised but also a multisystem disorder.[1]

This condition was initially described as autoimmune pancreatitis in 2001[2] and later as a separate clinicopathological entity in 2003.[3] However, it became increasingly apparent that virtually any organ system could be involved. Nowadays, several manifestations are known, such as autoimmune pancreatitis, sclerosing cholangitis, sialadenitis, dacryoadenitis, tubulointerstitial nephritis, interstitial pneumonia, mediastinitis, retroperitoneal fibrosis, and inflammatory aortic aneurysm.[4] Many of these different diseases and clinical manifestations have been known and described for many decades but have only recently been recognised as variants of the spectrum of IgG4-RD. For example, Riedel's thyroiditis was first described in 1896,[5] but its association with IgG4-RD was only recognised over a century later.[6]

In addition to predominantly inflammatory conditions, there are rarer forms of solid, more or less sharply defined lesions, known as IgG4-related pseudotumour (IgG4-RPT). The current literature on IgG4-RPTs is restricted to single case reports and series of fewer than 30 cases. This still limited description and documentation of this group of pseudotumours may lead to misdiagnosis of malignancy or other pathologies depending on the site involved.[7] The aim of this study was to analyse the spectrum of IgG4-RPTs in a series of cases from two German centres and to analyse the reported cases in the literature to summarise the affected organs and sites as well as identify potential differences based on location or patients' demographic features.

MATERIALS AND METHODS

Case collection

We collected surgical cases with the diagnosis of IgG4-RPT over a period from 2013 to 2020 from the departments of pathology of the Medical Centre of Augsburg and the Technical University Munich, according to the combined diagnostic criteria proposed by Deshpande *et al.*[8] and Okazaki *et al.*[9] (Supplementary Fig. 1 and 2, Appendix A). In addition, we collected available clinical data and information on follow-up after treatment. All cases were re-evaluated by two pathologists (AM, BM). The study was approved by the internal review board of the Augsburg Medical Centre (Number 2020–5) and was prepared in accordance with the declaration of Helsinki.

Immunohistochemistry

We used the following panel of immunohistochemical antibodies: IgG, IgG4, CD3, CD20, CD34, CD117, CD163, fibronectin, smoothelin, desmin, YAP1, cTGF, and ALK-1. All reactions were developed using the Ventana Benchmark Ultra system, and the reactions were performed using the Ventana Ultravision detection system (Roche Diagnostics, Germany). The clones and dilutions used are reported in Supplementary Table 1 (Appendix A). In this study, a high power field (HPF) refers to an area of 0.31 mm^2.

Statistical analysis

Non-continuous values of two different groups were compared with the Mann–Whitney U test. The chi-square test was used for the categorical variables, such as sex. The Wilcoxon test was used to analyse differences within a single group. Mean values are reported with ± one standard deviation. Statistical analyses were carried out with SPSS Statistics 24 (IBM, Armonk, NY, USA). A p-value of less than 0.05 was considered statistically significant.

Literature search

We performed a literature search in the MEDLINE and EBSCO databases, using the keywords 'IgG4' combined with 'pseudotumour', 'neoplasia' and 'pseudoneoplasia'. Case reports and original reports in English, German, Spanish, and Italian were included. All results were transferred to the citation manager Endnote (Clarivate Analytics, Philadelphia, PA, USA), and duplicates were deleted. The remaining articles were screened by two authors (AM and BG) with regard to the suitability of the topic, language, and publication standard. Discrepancies were resolved through a discussion with a third senior author (BM). Duplicates were excluded. It is important to note that we focused on publications reporting clearly tumour-forming lesions and excluded lesions that reported inflammatory associated tissue alterations (e.g., 'lumen narrowing', simple 'sclerosis' or 'thickening') without a hint of mass-forming lesion. Similarly, articles that did not sufficiently address the histopathological aspects of the IgG4-PT were excluded. Clinical information regarding IgG4 serum values, symptoms, as well as possible associations with autoimmune diseases and malignancies was taken into account in the analysis. Other information included the size, location, and margins of the lesions as well as their histomorphological description, including the assessment of fibrosis and obliterative phlebitis and the evaluation of IgG- and IgG4-positive plasma cells.

RESULTS

Cases series

Case collection and clinical symptoms

The demographic data and the clinical symptoms are summarised in Table 1. Eleven cases of IgG4-RPT from the pathology department of the Medical Centre Augsburg were analysed along with a case provided by the Pathology Department of the Technical University Munich (Table 1). Of these patients, there were nine men (75%) and three women (25%), with a mean age of 60±14 years (range 43–82). Three cases concerned the lung, two concerned the kidney, and one case each concerned the pterygopalatine fossa, submandibular gland, tongue, mediastinum, gallbladder, spleen, and soft

Table 1 Clinicopathological and immunohistological data of own cases

Case no.	Age/ Sex	Organ	Symptoms	Suspected tumour	Other autoimmune diseases	Size (cm)	Margin	Obliterative phlebitis	Eosinophils /HPF	IgG (mean/ HPF)	IgG4 (mean/ HPF)	IgG4/ IgG ratio	CD3	CD20	CD117+ mast cells/ HPF	CD163	YAP1	cTGF
1	62/F	Pterygopalatine fossa	Headache, swelling	None	None	4	Blurred	Yes	15	150	50	0.33	++	+++	3	+++	++	++
2	81/M	Tongue	Dysphagia	Oral cancer	None	2.5	Sharp	Yes	90	200	190	0.95	+	+	43	+++	++	+++
3	57/M	Submandibular gland	Swelling	Oral cancer	Unknown	1.8	Sharp	No	0	150	140	0.93	+++	+++	30	++	+++	+
4	68/M	Axilla	Swelling	Lymphoma	None	2.7	Blurred	No	20	150	100	0.67	+	++	19	++	+	++
5	43/M	Mediastinum	Fever	Thymoma	None	3	Blurred	Yes	0	95	40	0.42	+++	+++	52	+++	+	–
6	76/M	Lung	Incidental findings	Bronchial carcinoma	None	2	Sharp	Yes	5	200	130	0.65	+++	+++	50	+++	++	++
7	55/F	Lung	Incidental findings	Bronchial carcinoma	None	1.5	Sharp	No	4	180	130	0.72	+	+	35	+	+	–
8	49/M	Lung	Incidental findings	Bronchial carcinoma	None	5	Sharp	Yes	0	160	90	0.56	++	++	55	++	++	+
9	58/F	Gallbladder	Cholecystitis	None	Asthma	4	Blurred	No	30	200	120	0.6	+	++	57	+++	+++	+++
10	82/M	Spleen	Incidental findings	Non-Hodgkin lymphoma	Unknown	6	Sharp	No	0	110	80	0.73	+++	++	7	+++	+	++
11	44/M	Kidney	Fever	Renal cell carcinoma	None	4.2	Sharp	No	50	150	60	0.4	+	++	35	+++	+++	+
12	45/M	Kidney	Incidental findings	Renal cell carcinoma	Type I diabetes	3.5	Sharp	Yes	20	130	100	0.77	++	+++	0	+++	+	++

–, absent; +, weak; ++, moderate; +++, strong.

tissue (axilla). One patient (8%) showed an association with another immune disease (allergic asthma). Five patients were completely asymptomatic. Regarding the other seven patients, known symptoms included site-specific symptoms (e.g., cholecystitis in the case of the gallbladder or headache in the case of the pterygopalatine fossa), fever (in the case of the mediastinum and one case involving the kidney), and swelling.

Macroscopy

In all cases, the leading histological aspect was a tumour-forming lesion with a mean diameter of 3.4±1.4 cm (range 1.5–6). Macroscopically, four of 12 lesions (25%) had blurred margins (Fig. 1A), while the remaining nine (75%) showed clear margins and were well delimited by the parenchyma and surrounding tissues (Fig. 1B). The lesions were generally elastic in consistency and had a gray-yellowish, homogeneous cut surface. In all cases, surgical resection led to a complete remission of symptoms. No recurrences occurred.

Histopathology

Inflammatory cells occurred in a medium to high density. The lymphocytes were either scattered or grouped in aggregates, and in five cases (42%) unequivocally organised in follicles (Fig. 2C). B- and T-lymphocytes were equally present (Table 1). There was almost always an eosinophilic infiltrate, with a mean density of 29/HPF±27 (range 4–90/HPF) and a fair number of mast cells (average 35/HPF±18, range 3–57/HPF). A high number of positive plasma cells was consistently observed. The average ratio of IgG4 to IgG-positive plasma cells was 64%±20 (range 33%–95%) with densities of 103 IgG4-positive plasma cells/HPF ± 43 (range 50–190/HPF) and 156 IgG-positive plasma cells/HPF±34 (range 120–250/HPF), respectively (Fig. 2). A constant aspect of all cases was that strong positivity for CD163 was characteristic of M2 macrophages (Fig. 2). ALK and CD34 were negative. All cases showed storiform fibrosis; i.e., an irregularly whorled organisation of fibroblasts radiating from a centre with positivity for the connective tissue growth factor (cTGF) (Fig. 2H) and yes-associated protein 1 (YAP1) (Fig. 2G) were characteristic in all cases. Fibronectin, smoothelin, and desmin showed negative or only weak expression. In six cases (50%) obliterative phlebitis was observed, described a partial or total occlusion of small to medium sized veins through inflammatory infiltrate and extrinsic compression (Fig. 2B).

Desphande and Okazaki criteria

The six cases with locations for which a cut-off IgG4 concentration was defined (Cases 3, 6, 7, 8, 11, and 12) met the diagnostic criteria of Desphande *et al.*, having at least two main diagnostic features (including lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis) and showing an IgG4/HPF concentration above the proposed cut-off. Of the remaining six cases, although no cut-offs were defined for the organs involved, two of the three main features were present. In 11 of 12 cases, the IgG4/IgG ratio was above 0.4. In case one, the IgG4/IgG ratio was 0.33 and fell just below the established cut-off. All 12 cases met the diagnostic criteria proposed by Okazaki *et al.*, with at least conditions (1), (3a), (3b), and (3c) being positive. The serum IgG4 levels were known for seven of 12 patients; of these, three showed a significant serum elevation (Table 1).

Literature review

The literature search revealed a total of 958 publications before April 2020. After the elimination of duplicates, 231 articles remained. Screening by the three authors (AM, BG, BM) resulted in 174 possible eligible papers. Articles and case reports on IgG4-RD that did not clearly mention a pseudotumour (e.g., simple 'sclerosis' or 'thickening' without a hint of mass-forming lesion) were excluded. Similarly, articles were excluded that did not, or did not sufficiently, address the histopathological aspects of the IgG4-RPT. Starting from the bibliographies of the 103 articles obtained from an initial search, another 24 works were selected by screening the cited literature (Fig. 3). Out of 127 articles with a total of 266 reported patients, eight were organ series, while 119 consisted of case reports with one to three cases. The basic demographic data of these patients are summarised in Table 2.

The mean age was 52±16 years (range 5–82), with a slight male predominance of 56%. All age groups were reported, including paediatric[10,11] and adolescent[12] cases. Symptoms were reported in 90 cases (34% of the total) and generally varied according to the organ involved (e.g., paresis in those of the spinal cord and jaundice in those of the biliary tract). Systemic symptoms, such as anaemia, asthenia, fever, and fatigue, were reported in 17 cases. In all of the described cases, remission was observed following surgical resection.

The most frequently mentioned site was the orbit (24%). Other frequent sites were the lungs (20.5%), the stomach (12.1%), and the liver (11%) (Fig. 4). The lesions had a mean

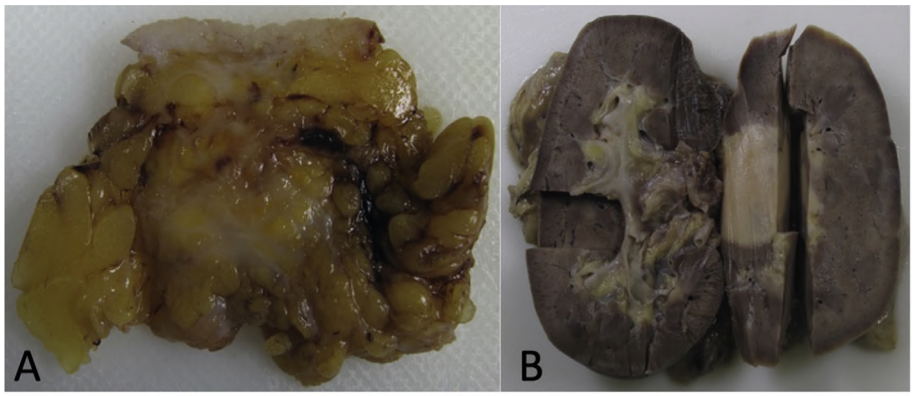

Fig. 1 (A) Macroscopic appearance with blurred margins (Case 4, axilla) and (B) net margins (Case 10, kidney).

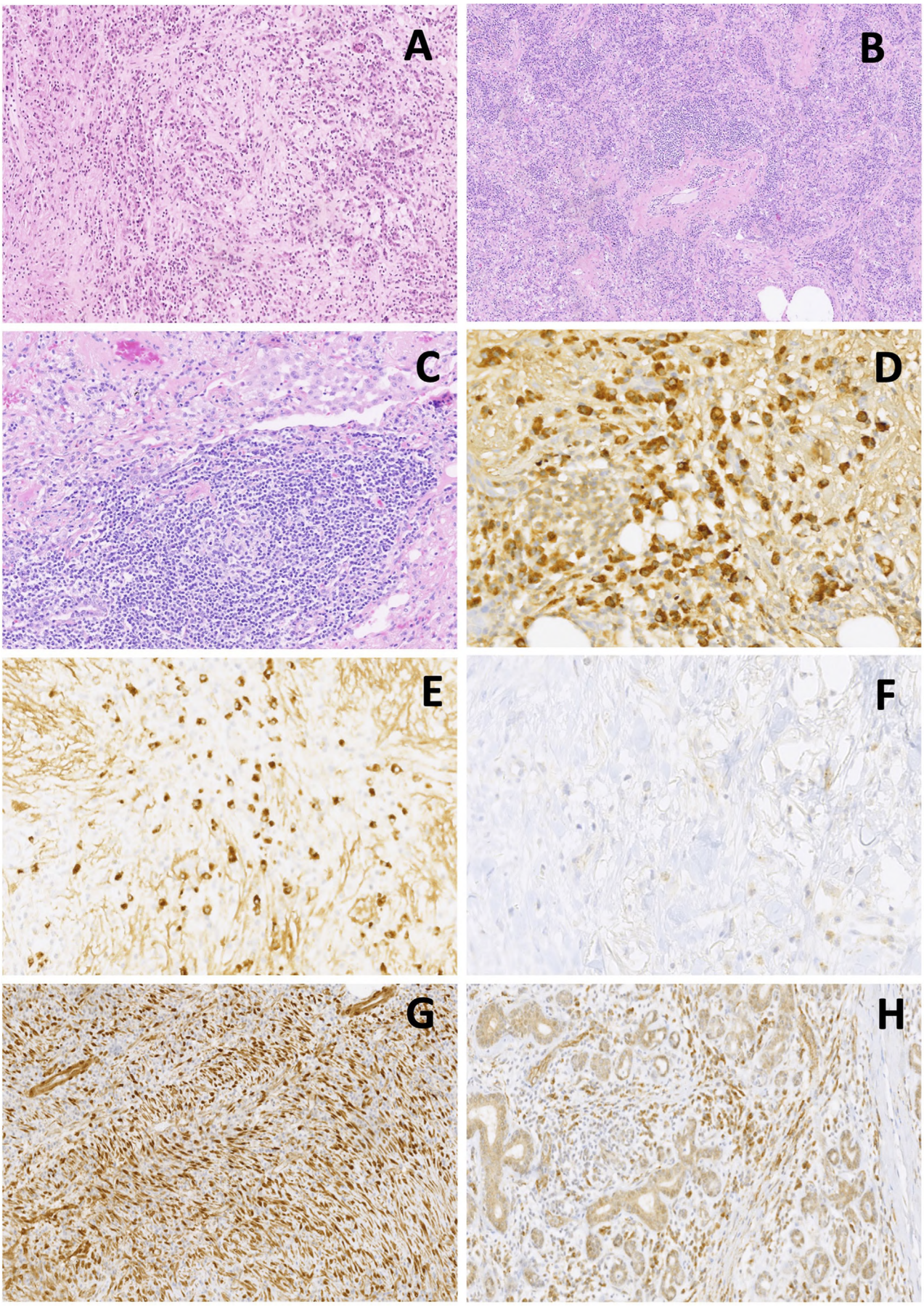

Fig. 2 (A) Storiform fibrosis, Case 11. (B) Obliterative phlebitis, Case 7. (C) Marked lymphocytic infiltrate with follicle organisation in H&E staining, Case 7. (D) Intense positivity in staining for total IgG and (E) IgG4, Case 4. (F) Absence of specific reaction in staining for ALK-1, Case 4. (G) Intense positivity in staining for YAP1, Case 9, and (H) for cTGF, Case 3.

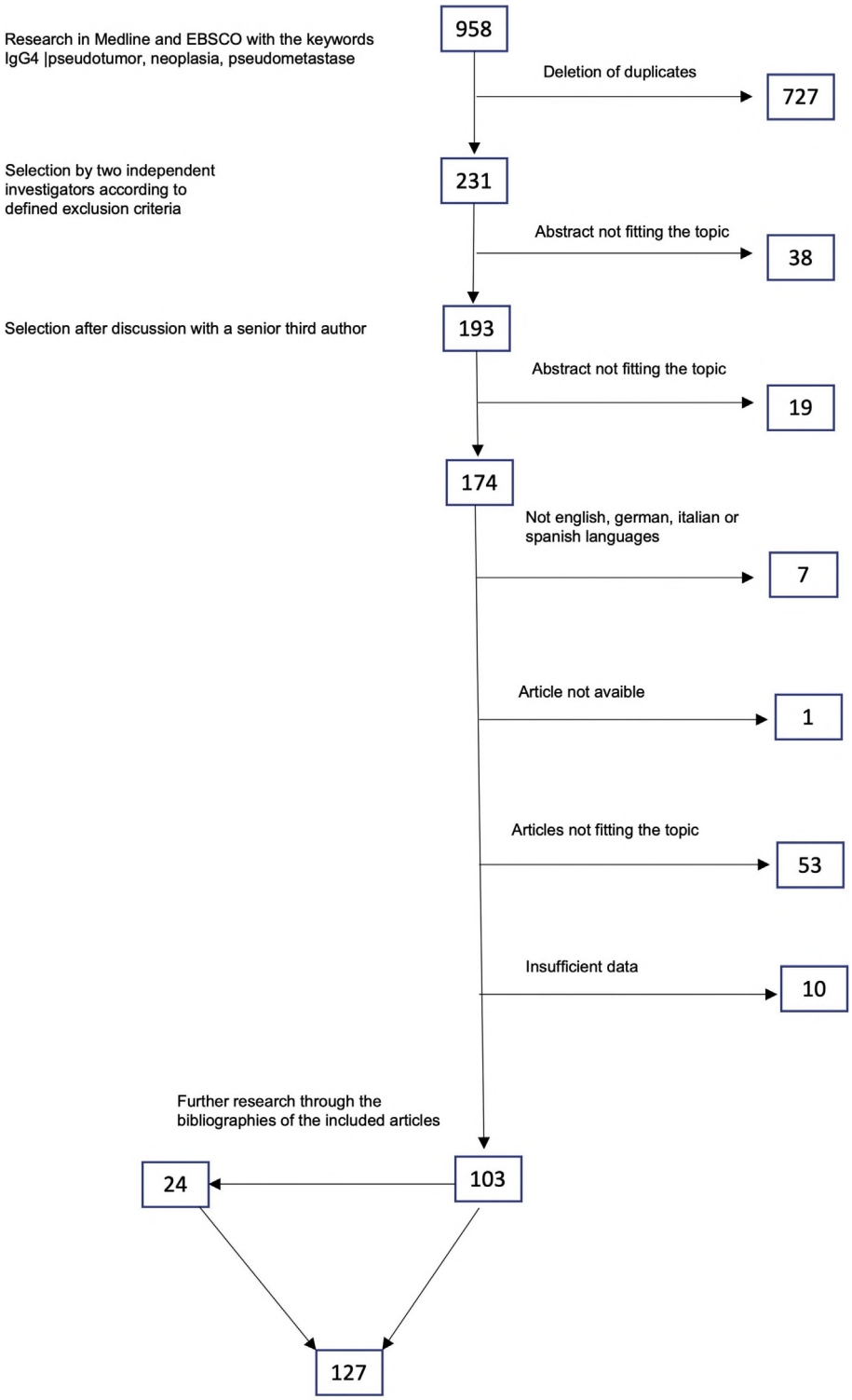

Fig. 3 Flow of analysis based on the retrieved literature.

diameter of 3.6±5.6 cm (range 0.15–21), but the size varied highly from a few millimeters up to 21 cm. In particular, smaller lesions appeared to be more typical in the regions of the orbit, brain, and heart, while the larger ones were found more often in the stomach, urinary tract, and testis. A comparison of the gender distribution, mean sizes, and IgG4 densities with the mean of the entire cohort is presented in Supplementary Table 2 (Appendix A).

Although rarely described macroscopically, ill-defined margins are most frequently observed in soft tissues, such as in orbital tissues.

In seven patients (2.6% of the total), an association with an immune disease other than IgG4-RD was reported, including Sjögren's syndrome, Henoch–Schönlein purpura, Graves's disease, allergic asthma, dermatomyositis, Crohn's disease, and eosinophilic cellulitis (Well's syndrome). Three of these

Table 2 Clinicopathological characteristics of cases reviewed from the literature

Organ	Cases, *n* (%)	Age, years	Sex (M:F)	Diameter, cm	Mean IgG4/HPF	Ratio IgG4/IgG, %	Cut-off point IgG4/HPF [a]
Orbita	62 (24.4%)	50 ± 19 (reported in 46 pt)	22:24 (reported in 46 pt)	1.5 ± 1.5 (reported in 16 pt)	118 ± 97 (reported in 27 pt)	57 ± 15.7 (reported in 42 pt)	>100[b]
Nose and sinus	16 (6.3%)	41 ± 12 (reported in 3 pt)	9:7	NR	25 ± 0 (reported in 2 pt)	NR	NR
Neck	2 (0.75%)	35 ± 13	2:0	2.3 ± 1.8	155 ± 153	52 ± 33.4	NR
Larynx	1 (0.38%)	62	M	NR	50	NR	NR
Trachea	1 (0.38%)	22	F	5	NR	50	NR
Meninges	16 (6.3%)	51.4 ± 17	9:7	4.1 ± 5 (reported in 6 pt)	105.6 ± 127 (reported in 11 pt)	43.5 ± 18.5 (reported in 4 pt)	NR
Periveral Nerves	1 (0.4%)	59	F	NR	128	71	NR
Lung	52 (20.5%)	49 ± 16 (reported in 46 pt)	35:17	2.6 ± 1.2 (reported in 43 pt)	85 ± 40 (reported in 23 pt)	25.4 ± 9.5 (reported in 14 pt)	>50
Thymus	1 (0.4%)	44	M	3.3	80	60	NR
Heart	5 (1.9%)	63 ± 12	2:3	1.4 ± 1.6	110 ± 141	57.4 ± 5 (reported in 4 pt)	NR
Mediastinum	1 (0.4%)	58	M	7	NR	NR	NR
Breast	5 (2%)	57 ± 10	5:0	2 ± 1	212 ± 117 (reported in 4 pt)	NR	NR
Stomach	33 (12%)	54,± 13	11:22	4 ± 4.6 (reported in 29 pt)	128 ± 102 (reported in 29 pt)	69.1 ± 22.9 (reported in 17 pt)	NR
Bowel	2 (0.8%)	46 ± 25	1:1	3 (reported in 1 pt)	50 ± 0	NR	NR
Oesophagus	1 (0.4%)	75	F	7	202	64	NR
Liver	28 (11%)	58 ± 9	24:4	3.9 ± 2.8 (reported in 19 pt)	35 ± 30 (reported in 11 pt)	26.1 ± 10.2 (reported in 9 pt)	NR
Bile duct	3 (1.1 %)	68 ± 8	3:0	2.8 ± 1.8 (reported in 2 pt)	33 ± 15	40 (reported in 1 pt)	>50
Kidney	12 (4.5%)	61 ± 18	6:6	3.9 ± 2 (reported in 11 pt)	179 ± 219 (reported in 6 pt)	44 ± 12.5 (reported in 3 pt)	>30
Urinary system	9 (3.4%)	61 ± 16	5:9	4.4 ± 2.6 (reported in 7 pt)	96 ± 41	66.5 ± 20.9 (reported in 4 pt)	NR
Testicle	10 (3.8%)	38 ± 16	10:0	4 ± 2.1	46 ± 32 (reported in 9 pt)	55 ± 7.1 (reported in 2 pt)	NR
Bone	5 (1.9%)	44 ± 13	3:2	2.8 (reported in 1 pt)	95 ± 72 (reported in 4 pt)	30 ± 28.3 (reported in 2 pt)	NR
Total	266	52 ± 16 (reported in 232 pt)	150 : 105 (reported in 255 pt)	3.6 ± 5.8 (reported in 161 pt)	102 ± 95 (reported in 150 pt)	55.7 ± 20.2 (reported in 108 pt)	

NR, not reported; pt, patients.
[a] According to Deshpande *et al.*[8]
[b] Referred to lacrimal glands.

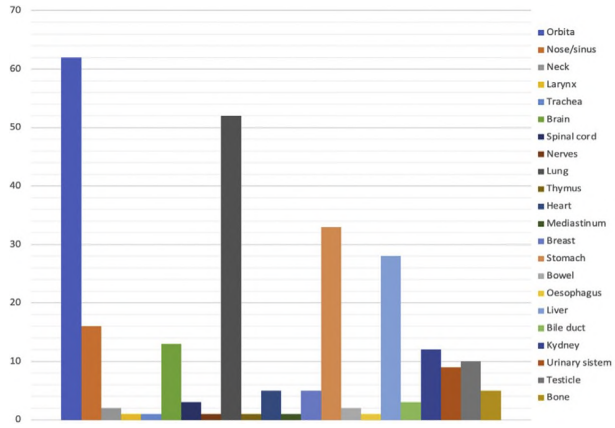

Fig. 4 Graphic distribution of the IgG4-PT cases of literature review in the various organs.

patients were males (42.8%) and four females (57.2%), with an average age of 57±12 years (range 33–73).

In 30 reviewed cases (11.3%) there were multiple pseudotumours (Table 3; Supplementary Fig. 3, Appendix A). In this group, neither the mean age (57±16 years; range 7–77 years) nor the predominance of males (76.6%) were significantly different from the entire cohort of literature cases (p=0.123 and p=0.076, respectively). The affected sites were comparable with the cases of isolated pseudotumours. In 22 cases (73.3%) of patients with multi-organ involvement (Table 3), the head (orbit, pharynx, salivary glands, pterygopalatine fossa, or cavernous sinus) was involved, while the orbit (wall, muscles, or lacrimal glands) was reported in 15 patients (50%). Among the most frequently found associations were the paranasal sinuses with the cavernous sinus and the orbit (Supplementary Fig. 3, Appendix A). Local symptoms were reported in 73 cases (27% of the total) and depended on the location, such as dysphagia in the case of the oesophagus or diplopia and swelling with pseudotumours in the orbital region. The asymptomatic IgG4-RPTs were typically located in organs that can compensate for mass-forming lesions (lung, kidney, and spleen). Systemic symptoms, such as anaemia, asthenia, fever, and fatigue, were reported in 17 cases (6% of the total), which may quickly point to a misdiagnosis of malignancy. In all cases remission was observed following surgical resection. In the literature review, serum IgG4 levels were reported in 29 patients, and the mean value was 801±1039 mg/dL (range 6–4400). In all cases remission was observed following surgical resection.

DISCUSSION

IgG4-RPT is a subgroup of IgG4-RD, characterised by a mass-forming, fibrous lesion with dense chronic inflammatory infiltrate. It can be challenging to diagnose, which is documented in several case reports where IgG4-RPT was misinterpreted as neoplasia.[13–15] The variable symptomatology is often caused by the space occupying effect within the affected organ. Patients with the same affected site may also complain of different disorders or be totally asymptomatic. Symptoms such as weight loss or local lymphadenopathy[16,17] are not uncommon and can increase the suspicion of malignancy. This diagnostic difficulty can be attributed to the low incidence of these lesions and their superficial histopathological description, including a lack of definitions of possible variants or subtypes.[8] The aim of this study was to describe the histopathological and clinical features of a series of 12 cases from our files and to summarise the relevant literature to obtain an overview of these rare lesions.

The entire body of literature comprises 266 cases in 23 locations. The vast majority of these contributions are single case reports. The results highlight the rarity and diversity of these lesions.

There was a male predominance both in our cases (75%) and in those in the literature (59%), similar to the situation for IgG4-RD. IgG4-RPT in the liver had a significantly higher prevalence in males compared to other organs (p=0.015, Table 2). The only exception was the stomach, where we observed a statistically significant prevalence in females (p=0.032). The mean age in IgG4-RPT, however, is about 15 years lower compared with that in IgG4-RD[18] (Supplementary Table 2, Appendix A).

Of the 266 patients reported in the review, seven (2.6%) had an association with an immune disease other than IgG4-RD. Similarly, in 12 of our cases we observed another immune disease.

Macroscopically, in both our cases and those in the literature, sharply demarked lesions were typically observed in hollow and parenchymatous organs. In contrast, ill-defined lesions were restricted to soft tissue, such as axilla and periorbital tissues.

Serum IgG4 concentration is a non-invasive marker that has been shown to be significantly higher in IgG4-associated diseases than in other conditions important in the differential diagnosis.[2,19] Considering normal values of serum IgG4 between 10 and 150 mg/dL,[20] elevated values were observed in about 60% of the reported cases. In light of these results, and in accordance with what has already been reported in the literature,[21,22] the serum IgG4 assay has a very low sensitivity for the existence of IgG4-RD or IgG4-RPT. Moreover, specificity is also suboptimal due to the possibility of several false negatives.[23] This underlines the importance of histopathological examination.

Regarding the reported locations, the most common sites were the orbit, the lungs, the stomach, and the liver in decreasing order (Table 2). How well these numbers represent the situation in the general population is difficult to estimate, and the possibility of reporting bias must be taken into account. This is an explicit limitation of this study. However, given the rarity of these lesions, a more extensive series would not be expected. The spectrum of affected locations in our series differed considerably compared to that of the literature cohort. The lungs were affected in 25% of cases, while the other lesion regions belong to the group of rarely reported locations. To the best of our knowledge, the axilla and the tongue are locations that we describe for the first time here. An interesting aspect of the literature evaluation is the relatively high number of multiple lesions (30 cases, 29 of them simultaneous), indicating a systemic disease. Again, publication bias must be considered, which might increase the likelihood of reporting a case of multiple occurrences. Notably, 11 cases were reported by Ryu *et al.*[24] with restriction to the head and neck regions.

Microscopically, we and others consistently found a storiform proliferation of spindle cells consisting of fibroblasts and myofibroblasts. These proliferations were accompanied by a diverse inflammatory infiltrate, comprising

Table 3 Reported cases with multi-organ involvement

Authors	Age	Sex	Anatomical locations
Tsuboi *et al.*[39]	62	M	Pituitary gland, lung, lymph nodes, pancreas
Takuma *et al.*[40]	76	M	Lacrimal glands, liver, pancreas
Surintrspanont *et al.*[41]	52	M	Kidney, liver
Soloperto *et al.*[42]	75	M	Medial wall of the orbit, crista galli
Ryu *et al.*[24]	60	M	Bilateral lacrimal gland, nasal sinus (bilateral)
Ryu *et al.*[24]	77	M	Nasal sinus, nasopharynx, orbit, petrous apex, infratemporal fossa, cavernous sinus
Ryu *et al.*[24]	7	M	Maxillary sinus, orbit, orbital fissure, pterygopalatine fossa, cavernous sinus, dura mater
Ryu *et al.*[24]	45	F	Lacrimal gland, nasal sinus (bilateral)
Ryu *et al.*[24]	46	F	Orbit, nasal sinus
Ryu *et al.*[24]	55	M	Nasal sinus, orbit, infratemporal fossa, masticatory space, cavernous sinus (bilateral)
Ryu *et al.*[24]	48	M	Nasal sinus, orbit, nasopharynx, pterygopalatine fossa, orbital fissure, cavernous sinus (bilateral)
Ryu *et al.*[24]	42	F	Maxillary sinus, anterior cheek
Ryu *et al.*[24]	34	F	Maxillary sinus, orbit, pterygopalatine, fossa, cavernous sinus, infratemporal, fossa, dura mater
Ryu *et al.*[24]	33	M	Maxillary sinus, pterygopalatine fossa, cavernous sinus, Meckel's cave, masticatory space
Ryu *et al.*[24]	56	M	Lacrimal gland, nasal sinus (bilateral)
Kishi *et al.*[43]	78	M	Orbit, liver
Pal *et al.*[44]	50	F	Orbit, lacrimal glands, kidney, pancreas
Hamed *et al.*[45]	70	M	Bile duct, submandibular gland, prostate
Dhobale *et al.*[46]	69	M	Lung, pancreas, submandibular glands, kidney, lymph nodes
Masterson *et al.*[47]	56	F	Temporal bone, orbit, gall bladder, pharynx, pelvis, omentum,
Hsing *et al.*[48]	66	M	Pituitary gland, salivary glands, lungs, liver, bile duct, gallbladder, pancreas, kidneys, retroperitoneum
Kim *et al.*[49]	58	M	Liver, kidney
Bjørlykke *et al.*[50]	52	M	Liver, pancreas
Choi *et al.*[51]	72	F	Urethra, eyelid (only anamnestic)
Inoue *et al.*[52]	74	M	Stomach, kidney
Hart *et al.*[53]	67	M	Testicle, retroperitoneum, pancreas
Ortuño-Moreno *et al.*[54]	67	M	Stomach, pancreas
Nagashima *et al.*[55]	63	M	Lung, liver
Kanno *et al.*[56]	48	M	Liver, pancreas
Uehara *et al.*[57]	66	M	Salivary glands, kidney
Total	57±16	M:F=23:7	

histiocytes, lymphocytes, eosinophils, and plasma cells. In the literature review, however, storiform fibrosis was found to be less marked in the lachrymal glands and in lymph nodes.[25] The triggering event in the fibrosis seems to be the activation of $CD4^+$ T helper cells, B lymphocytes, and plasma cells, which is followed by, in addition to macrophage and eosinophilic activation, a complex inflammatory cascade consisting of various profibrotic cytokines (e.g., IL-4, IL-10, and IL-13).[25] It has also been suggested that IgG4-positive plasma cells themselves may play a direct role in fibroblast differentiation through IL-6.[25] The presence of eosinophils, sometimes described as eosinophilic angiocentric fibrosis,[26] was explicitly reported in 112 cases (42% of the total) in the literature and appeared to be particularly frequent in the orbit and respiratory tract.[25,27] Additionally, of the 12 cases in our series, at least some eosinophils were found in seven cases (58% of the total), with a mean concentration of 20±26 HPF (range 0–50/HPF). The presence of these cells is mentioned in the diagnostic criteria,[8] although it is considered a feature found in a minority of cases. Based on our results, the presence of eosinophilic granulocytes may be detectable in at least 50% of cases and probably more often, depending on the organ involved. However, a low density must be considered a minor criterion because of its low sensitivity and low specificity.[28]

Another typical phenomenon is obliterative phlebitis (i.e., partial or total occlusion of small to medium-sized veins through inflammatory infiltrate and extrinsic compression). This is also one of the main diagnostic criteria. However, this aspect may not always be present.[29–31] In IgG4-RD, unlike some other types of systemic vasculitis, leukocytoclastic vessel wall necrosis and fibrin deposition are not observed.[25] Positivity for CD163, an M2-macrophage surface marker molecule, has also been described.[32] A significant increase of IgG4-positive plasma cells is a hallmark feature of IgG4-RPTs.

The vast majority of cases, including our collection, showed densities of at least 50 IgG4-positive plasma cells/HPF, often with numbers >100/HPF, while a significantly lower concentration of IgG4 plasma cells was observed in the lungs and liver than in the other organs (Supplementary Table 2, Appendix A). The mean IgG4/IgG ratios were >0.5. Therefore, the diagnostic criteria defined for IgG4-RDs by Deshpande *et al.* and Okazaki *et al.* were met in the majority of IgG4-RPT cases. It should be noted that histopathological aspects may vary, not only according to the site but also according to degree of fibrosis, the inflammatory process, and consequently the time of diagnosis. Indeed, according to some studies the predominance of storiform fibrosis over the cellular component is an indication of a more advanced stage of the disease, while a predominance of the cellular component is typical of an earlier stage.[33] This distinction has particular importance for the pathologist, who may encounter different stages of the disease using bioptic procedures that provide tiny amounts of tissue. It is also

important to note the recent drafting of new classification criteria by the American College of Rheumatology/European League Against Rheumatism.[34] However, we decided not to explore these criteria in our analysis because they do not strictly concern only the histopathological aspect of the lesions, but also focus on clinical and radiological parameters.

Importantly, from a differential diagnostic standpoint, all of the lesions of our series were immunohistochemically negative for ALK-1 and CD34. Therefore, the existence of inflammatory myofibroblastic and solitary fibrous tumours could be ruled out. Melanotic markers like HMB45 or MiTF help to differentiate IgG4-RPTs from angiomyolipoma/PEComa.[35,36] Concerning a possible association with malignancy, evidence has been found either in the literature or in our own cases. Interestingly, in a recent article of Tang *et al.* a slightly increased risk of malignancy, such as rectal and breast cancer, has been described.[37] On the other hand, no significant association between IgG4-RD and cancer has emerged in other studies.[38] Therefore, from our point of view, this is still an open topic that needs further observations and analysis.

This study is limited by the small number of cases in our series and the possibility of a relevant publication bias, which limits the general applicability of the review. However, our analysis provides a comprehensive overview of these exceedingly rare tumour-forming lesions. Knowledge of their existence might be the most important clue for the diagnosis. Immunohistochemical investigations including IgG, IgG4, ALK1, CD34, and melanocytic markers are helpful for excluding other differential diagnoses.

CONCLUSION

IgG4-RPT are exceedingly rare lesions of the IgG4-RD spectrum, which can lead to diagnostic challenges and potential misinterpretation. They occur mainly in the fifth decade of life, with a slight predominance in males, although cases have been described in almost every age group. While every organ system can be involved, they are more frequently observed in orbital tissues as well as in the lung, stomach, and liver. Because of the possibility of multi-organ involvement and recurrence, IgG4-RPT should always be suspected in patients with a positive history of IgG4-RPT and, particularly in males, in the case of known involvement of other sites.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pathol.2021.11.015.

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References

1. Lees JS, Church DN, Langdale-Brown B, Bellamy C, Gibson P, Watson S. IgG4-related disease: a novel, important but easily missed condition. *J R Coll Physicians Edinb* 2013; 43: 126–33.
2. Hamano H, Kawa S, Horiuchi A, *et al*. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001; 344: 732–8.
3. Kamisawa T, Funata N, Hayashi Y, *et al*. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003; 38: 982–4.
4. Brito-Zerón P, Ramos-Casals M, Bosch X, Stone JH. The clinical spectrum of IgG4-related disease. *Autoimmun Rev* 2014; 13: 1203–10.
5. Riedel BM. Die chronische, zur Bildung eisenharter Tumoren fuhrende Entzundung der Schilddruse. *Verh Dtsch Ges Chir* 1896; 25: 101–5.
6. Dahlgren M, Khosroshahi A, Nielsen GP, Deshpande V, Stone JH. Riedel's thyroiditis and multifocal fibrosclerosis are part of the IgG4-related systemic disease spectrum. *Arthritis Care Res* 2010; 62: 1312–8.
7. Chen LY, Mattman A, Seidman MA, Carruthers MN. IgG4-related disease: what a hematologist needs to know. *Haematologica* 2019; 104: 444–55.
8. Deshpande V, Zen Y, Chan JKC, *et al*. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012; 25: 1181–92.
9. Okazaki K, Uchida K, Koyabu M, Miyoshi H, Takaoka M. Recent advances in the concept and diagnosis of autoimmune pancreatitis and IgG4-related disease. *J Gastroenterol* 2011; 46: 277–88.
10. Jariwala MP, Agarwal M, Mulay K, Jariwala MP, Sawhney S. IgG4-related orbital inflammation presenting as unilateral pseudotumor. *Indian J Pediatr* 2014; 81: 1108–10.
11. Kalapesi FB, Garrott HM, Moldovan C, Williams M, Ramanan A, Herbert HM. IgG4 orbital inflammation in a 5-year-old child presenting as an orbital mass. *Orbit* 2013; 32: 137–40.
12. Oles K, Szczepanski W, Skladzien J. IgG4-related inflammatory orbital pseudotumors - a retrospective case series. *Folia Neuropathol* 2015; 53: 111–20.
13. Wang Y, Chen X, Luo R, *et al*. IgG4-related systemic disease mimicking renal pelvic cancer: a rare case. *World J Surg Oncol* 2014; 12: 395.
14. Woo CG, Yook JH, Kim AY, Kim J. IgG4-related disease presented as a mural mass in the stomach. *J Pathol Transl Med* 2016; 50: 67–70.
15. Ahn KS, Kang KJ, Kim YH, *et al*. Inflammatory pseudotumors mimicking intrahepatic cholangiocarcinoma of the liver; IgG4-positivity and its clinical significance. *J Hepatobiliary Pancreat Sci* 2012; 19: 405–12.
16. Baez JC, Hamilton MJ, Bellizzi A, Mortelé KJ. Gastric involvement in autoimmune pancreatitis: MDCT and histopathologic features. *JOP* 2010; 11: 610–3.
17. Ribeiro Ferreira N, Vaz R, Carmona S, *et al*. IgG4-related disease presenting with an epidural inflammatory pseudotumor: a case report. *J Med Case Rep* 2016; 10: 61.
18. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. *Lancet* 2015; 385: 1460–71.
19. Zhao Z, Mou D, Wang Z, *et al*. Clinical features and relapse risks of IgG4-related ophthalmic disease: a single-center experience in China. *Arthritis Res Ther* 2021; 23: 98.
20. Nirula A, Glaser SM, Kalled SL, Taylor FR. What is IgG4? A review of the biology of a unique immunoglobulin subtype. *Curr Opin Rheumatol* 2011; 23: 119–24.
21. Yamamoto M, Tabeya T, Naishiro Y, *et al*. Value of serum IgG4 in the diagnosis of IgG4-related disease and in differentiation from rheumatic diseases and other diseases. *Mod Rheumatol* 2012; 22: 419–25.
22. Takano K, Yamamoto M, Takahashi H, Himi T. Recent advances in knowledge regarding the head and neck manifestations of IgG4-related disease. *Auris Nasus Larynx* 2017; 44: 7–17.
23. Varghese JL, Fung AWS, Mattman A, *et al*. Clinical utility of serum IgG4 measurement. *Clin Chim Acta* 2020; 506: 28–35.
24. Ryu G, Cho HJ, Lee KE, *et al*. Clinical significance of IgG4 in sinonasal and skull base inflammatory pseudotumor. *Eur Arch Otorhinolaryngol* 2019; 276: 2465–73.
25. Della-Torre E, Lanzillotta M, Doglioni C. Immunology of IgG4-related disease. *Clin Exp Immunol* 2015; 181: 191–206.
26. Deshpande V, Khosroshahi A, Nielsen GP, Hamilos DL, Stone JH. Eosinophilic angiocentric fibrosis is a form of IgG4-related systemic disease. *Am J Surg Pathol* 2011; 35: 701–6.
27. Andrew NH, Sladden N, Kearney DJ, Selva D. An analysis of IgG4-related disease (IgG4-RD) among idiopathic orbital inflammations and benign lymphoid hyperplasias using two consensus-based diagnostic criteria for IgG4-RD. *Br J Ophthalmol* 2015; 99: 376–81.
28. Carruthers MN, Stone JH, Khosroshahi A. The latest on IgG4-RD: a rapidly emerging disease. *Curr Opin Rheumatol* 2012; 24: 60–9.
29. Origuchi T, Yano H, Nakamura H, Hirano A, Kawakami A. Three cases of IgG4-related orbital inflammation presented as unilateral pseudotumor and review of the literature. *Rheumatol Int* 2013; 33: 2931–6.
30. Chougule A, Bal A, Das A, Agarwal R, Singh N, Rao KL. A comparative study of inflammatory myofibroblastic tumors and tumefactive IgG4-related inflammatory lesions: the relevance of IgG4 plasma cells. *Appl Immunohistochem Mol Morphol* 2016; 24: 721–8.

31. Johnson JS, Saltzman AF, Treece AL, Cost NG. A case of IgG4-related renal pseudotumor in a child with history of Wilms tumor. *Urol Case Rep* 2018; 22: 107–9.
32. Zen Y, Kawakami H, Kim JH. IgG4-related sclerosing cholangitis: all we need to know. *J Gastroenterol* 2016; 51: 295–312.
33. Della-Torre E, Feeney E, Deshpande V, *et al*. B-cell depletion attenuates serological biomarkers of fibrosis and myofibroblast activation in IgG4-related disease. *Ann Rheum Dis* 2015; 74: 2236–43.
34. Wallace ZS, Naden RP, Chari S, *et al*. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. *Arthritis Rheumatol* 2020; 72: 7–19.
35. Agaimy A, Märkl B. Inflammatory angiomyolipoma of the liver: an unusual case suggesting relationship to IgG4-related pseudotumor. *Int J Clin Exp Pathol* 2013; 6: 771–9.
36. Thway K, Fisher C. PEComa: morphology and genetics of a complex tumor family. *Ann Diagn Pathol* 2015; 19: 359–68.
37. Tang H, Yang H, Zhang P, *et al*. Malignancy and IgG4-related disease: the incidence, related factors and prognosis from a prospective cohort study in China. *Sci Rep* 2020; 10: 4910.
38. Hirano K, Tada M, Sasahira N, *et al*. Incidence of malignancies in patients with IgG4-related disease. *Intern Med* 2014; 53: 171–6.
39. Tsuboi H, Inokuma S, Setoguchi K, *et al*. Inflammatory pseudotumors in multiple organs associated with elevated serum IgG4 level: recovery by only a small replacement dose of steroid. *Intern Med* 2008; 47: 1139–42.
40. Takuma K, Kamisawa T, Tabata T, *et al*. Visual field deficit: a rare initial symptom of autoimmune pancreatitis. *Intern Med* 2011; 50: 887–91.
41. Surintrspanont J, Sanpawat A, Sasiwimonphan K, Sitthideatphaiboon P. IgG4-related pseudotumor of kidney and multiple organ involvement mimicked malignancy. *Urol Case Rep* 2019; 26: 100953.
42. Soloperto D, Fabbris C, Di Maro F, Marchioni D. IgG4-related pseudotumor affecting ethmoid, orbit and anterior skull base. *J Neurosurg Sci* 2019; 63: 238–40.
43. Kishi K, Fujii T, Kohno T, Yoshimura K. Inflammatory pseudotumour affecting the lung and orbit. *Respirology* 2009; 14: 449–51.
44. Pal P, Kalpala R, Reddy DN. An unusual cause of abdominal pain in a female with bilateral proptosis. *Gastroenterology* 2016; 150: 1087–9.
45. Hamed G, Tsushima K, Yasuo M, *et al*. Inflammatory lesions of the lung, submandibular gland, bile duct and prostate in a patient with IgG4-associated multifocal systemic fibrosclerosis. *Respirology* 2007; 12: 455–7.
46. Dhobale S, Bedetti C, Killian P, *et al*. IgG4 related sclerosing disease with multiple organ involvements and response to corticosteroid treatment. *J Clin Rheumatol* 2009; 15: 354–7.
47. Masterson L, Del Pero MM, Donnelly N, Moffat DA, Rytina EL. Immunoglobulin G4 related systemic sclerosing disease involving the temporal bone. *J Laryngol Otol* 2010; 124: 1106–10.
48. Hsing MT, Hsu HT, Cheng CY, Chen CM. IgG4-related hypophysitis presenting as a pituitary adenoma with systemic disease. *Asian J Surg* 2013; 36: 93–7.
49. Kim F, Yamada K, Inoue D, *et al*. IgG4-related tubulointerstitial nephritis and hepatic inflammatory pseudotumor without hypocomplementemia. *Intern Med* 2011; 50: 1239–44.
50. Bjørlykke KH, Eftang LL, Grzyb K, Line PD, Lassen K, Jahnsen J. A man in his fifties with abdominal pain, itching and weight loss. *Tidsskr Nor Legeforen* 2020; 140.
51. Choi JW, Kim SY, Moon KC, Cho JY, Kim SH. Immunoglobulin G4-related sclerosing disease involving the urethra: case report. *Kor J Radiol* 2012; 13: 803–7.
52. Inoue K, Okubo T, Kato T, *et al*. IgG4-related stomach muscle lesion with a renal pseudotumor and multiple renal rim-like lesions: a rare manifestation of IgG4-related disease. *Mod Rheumatol* 2018; 28: 188–92.
53. Hart PA, Moyer AM, Yi ES, Hogan MC, Pearson RK, Chari ST. IgG4-related paratesticular pseudotumor in a patient with autoimmune pancreatitis and retroperitoneal fibrosis: an extrapancreatic manifestation of IgG4-related disease. *Hum Pathol* 2012; 43: 2084–7.
54. Ortuño Moreno MI, Ferri Ñíguez B, Martínez Barba E, Fernández Hernández Á. Pseudotumor gástrico ulcerado con afectación pancreática por enfermedad relacionada con inmunoglobulina G4: descripción de un caso y revisión de la literatura. *Rev Esp Enferm Dig* 2017; 109: 870–4.
55. Nagashima K, Sano I, Kobayashi T, *et al*. IgG4-related lung pseudotumor and pleural inflammation with autoimmune hepatitis. *Intern Med* 2018; 57: 43–8.
56. Kanno A, Satoh K, Kimura K, *et al*. Autoimmune pancreatitis with hepatic inflammatory pseudotumor. *Pancreas* 2005; 31: 4203.
57. Uehara T, Ikeda S, Hamano H, *et al*. A case of Mikulicz's disease complicated by malignant lymphoma: a postmortem histopathological finding. *Intern Med* 2012; 51: 419–23.