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Review

The clinical spectrum of IgG4-related disease

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ABSTRACT

IgG4-related disease (IgG4-RD) is an emerging immune-mediated disease with the capability of involving essentially any organ. The epidemiology of this disease has not been explored in detail. A majority of patients reported in the literature to date are from Japan, but the condition has been described all across the world and there is no strong evidence to suggest a predilection for Asian populations. The mean age at diagnosis is approximately 60 years and there is a decided male predominance for many clinical features, with an overall male:female ratio of 8:3. A cardinal feature of IgG4-RD is single or multiple organ swelling that often raises concern for malignancy. IgG4-RD should be suspected in patients presenting with unexplained enlargement or swelling of one or more organs. Presenting features vary substantially according to the specialty to which patients present first; in addition, the disease can be diagnosed unexpectedly in pathological specimens or identified incidentally on radiology studies. Involvement of major organs is common and IgG4-RD may lead to organ failure, particularly in the pancreas, liver and biliary tree, kidneys, thyroid gland, lungs, and aorta. The diagnosis of IgG4-RD relies on the coexistence of various clinical, laboratory and histopathological findings, although none is pathognomonic by itself.

Contents

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1. Historical overview and definition

IgG4-related disease (IgG4-RD) is a systemic immune-mediated disease described in Japan in the first years of the 21st century [1]. The disease is characterized pathologically by the infiltration of IgG4-bearing plasma cells into involved organs [1]. IgG4-RD is not a new disease because many previously-recognized single- and even multi-organ conditions, once regarded as entirely separate disorders, are now known to comprise parts of the IgG4-RD spectrum. Such conditions include "Mikulicz disease", "Küttner tumor", Riedel thyroiditis, and Ormond disease, among others.

In 2001, Hamano et al. [2] linked the finding of high serum levels of IgG4 with a specific form of organ involvement, namely "sclerosing pancreatitis", now known as type 1 (IgG4-related) autoimmune pancreatitis. In 2003, Kamisawa et al. [3] employed the term "IgG4-related autoimmune disease," following the recognition that patients with autoimmune pancreatitis could have extensive organ involvement beyond the pancreas and therefore represented a previously unidentified systemic disorder. In 2012, an international multidisciplinary study group proposed the name "IgG4-RD" [4] in preference to alternative names such as "IgG4-related systemic disease," "IgG4-related sclerosing disease," or "IgG4-positive multiorgan lymphoproliferative syndrome." IgG4-RD has now been reported in nearly every organ, though it was first identified in the pancreas and salivary glands [5–7]. Few data exist on the epidemiological and clinical features of large series of patients. This review addresses current knowledge about the clinical spectrum of IgG4-RD, focusing principally on the specific characteristics of each organ involved.

2. Geoepidemiology of IgG4-RD

IgG4-RD is generally regarded as an uncommon disorder but it is likely that substantial under-recognition of the disease exists because many physicians remain unfamiliar with this diagnosis. A recent study estimated that approximately 8000 patients had IgG4-RD in Japan in 2009 [8], representing an estimated prevalence in the Japanese population of 6 cases per 100,000 people. Fig. 1 summarizes the geographic origin of 3482 reported cases (MEDLINE search of articles published through March 24, 2014, excluding small series and isolated cases). The country of origin was specified in 2504 cases, of which 1856 (74%) were from Japan. It remains unclear if the disease is more common among Japanese or if Japanese investigators have simply written most extensively about IgG4-RD because the disease was identified first in Japan. The authors favor the second explanation, and note that cases of IgG4-RD have been now described in nearly all racial and ethnic groups.

The epidemiology of IgG4-RD has not been described definitively, and multiple knowledge gaps remain. The mean age at diagnosis of the reviewed cases was 61.4 years, with a clear male predominance (2451/3366 cases, or 73%). Only two studies found a mean patient age of less than 50 years, and only the study by Nakazawa et al. [9] reported a mean age of greater than 70 years. The youngest patient reported to date was 14 years of age at presentation [10], and the oldest 88 [11].

3. Clinical spectrum of IgG4-RD: organ-by-organ characterization

3.1. Pancreas

The pancreas was the first organ reported in the context of IgG4-RD [2,3] and perhaps as a result this organ has been reported most frequently in the literature. Type I autoimmune pancreatitis was described in 345/840 (41%) systemic cases reported (Table 1). Eight studies including 1245 patients have focused on IgG4-related pancreatitis [10,12–18]. Four studies [10,12,15,18] have detailed the main presenting symptoms, which included jaundice in 97/129 (75%) patients, abdominal pain in 49/103 (48%), pruritus in 7/30 (23%), steatorrhea in 13/83 (16%), and new-onset diabetes mellitus in 11/83 (13%) patients.

Cross-sectional imaging such as computed tomography (CT) is particularly useful in the evaluation of pancreatic disease. Imaging findings can be highly suggestive of type 1 autoimmune pancreatitis. The typical features are a sausage-shaped pancreas with enhancement around the rim of the organ, representing edema secondary to inflammation. Among the patients in this study, abdominal CT showed pancreatic enlargement, more frequently focal (56%) than diffuse (44%) [10,15]. Pancreatic atrophy, either diffuse or distal, has also been reported [10]. Other infrequent radiological findings have been acute pancreatitis, a normal-size gland with diffusely decreased enhancement, or even a normal pancreas [10].

3.2. Biliary tree and gallbladder

Involvement of the biliary tree was reported in 152/781 (19.5%) patients with systemic disease (Table 1). Seven studies including a total of 647 patients have focused on descriptions of IgG4-related sclerosing cholangitis [9,12,19–23]. Because a close relationship exists between IgG4-related pancreatitis and IgG4-related biliary tract disease, 127 (83%) of the 153 patients reported to have IgG4-related sclerosing cholangitis had concomitant autoimmune pancreatitis [12,19,20,23], and 66 (40%) of the 166 patients with autoimmune pancreatitis also had IgG4-related sclerosing cholangitis [12,13,15,17].

Nearly 60 cases of IgG4-related cholecystitis have been reported (Table 2). Among patients with IgG4-related pancreatitis or cholangitis, gallbladder thickening was also reported in more than 50% of patients, and histopathological analyses of the gallbladder showed transmural lymphoplasmacytic inflammatory infiltrates and extramural inflammatory nodules [12]. Most cases of gallbladder involvement are asymptomatic and constitute surprise findings when the gallbladder is removed incidentally at the time of other procedures. It is likely that IgG4-related cholecystitis is commonly overlooked.

3.3. Major salivary glands

Major salivary glands are among the organs affected most commonly by IgG4-RD (Table 1); 321 (40%) of the 799 cases of systemic disease showed salivary gland involvement. IgG4-related sialoadenitis has been specifically studied in 10 studies [11,12,17,24–30], including 158 patients with Mikulicz disease (defined as the bilateral swelling of at least two major salivary or lachrymal glands) and 42 with Küttner disease (also known as chronic sclerosing sialadenitis, affecting the submandibular glands). Glandular swelling, often subacute, was the key sign on examination. The submandibular glands were affected in 137/145 (94%) patients, the parotid glands in 38/133 (29%), and the sublingual glands only in 8 cases [52]. Sublingual gland enlargement, however, is more difficult to detect on examination than are parotid and submandibular gland enlargements. Sicca symptoms are common in IgG4-RD patients with sialadenitis (56/90 patients; 62%) but tend to respond well to treatment with glucocorticoids, in contrast to patients with Sjögren's syndrome.

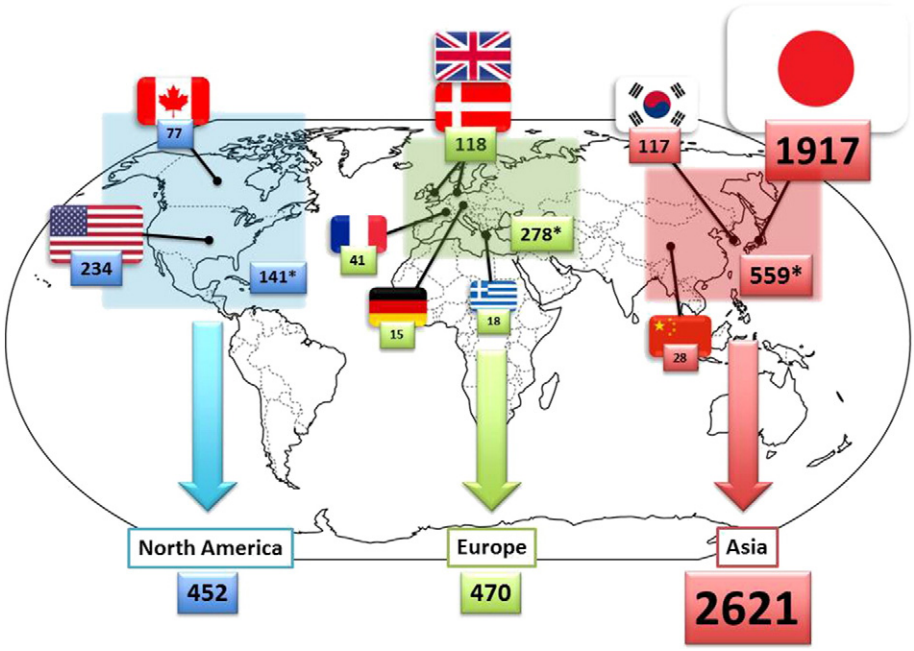

Fig. 1. Geographical origin of 3482 reported cases of IgG4-RD. There may be overlapping data in some multicenter studies. One study* detailed the number of cases by geographical area (North America, Europe and Asia).

3.4. Ophthalmic involvement

Ophthalmic involvement, usually centered on the lachrymal glands (dacryoadenitis), was reported in 163 (29%) of 567 patients in this study with systemic disease (Table 1). Seven studies including a total of 161 patients have focused on IgG4-related ophthalmic involvement [31–37]. Nearly half of the patients described have had isolated involvement of the lachrymal glands, mainly bilateral [36]. The main clinical feature was a painless eyelid swelling (unilateral or bilateral). Other clinical presentations included visual disturbances due to optic neuropathy (anopsia, hemianopsia), ocular movement restrictions, exophthalmos, and ptosis. Inflammatory eye disease (scleritis) has been reported in some cases (one in a patient with concomitant uveitis). Features such as corneal ulceration, eye pain, or epiphora are infrequent.

3.5. Lungs, pleura and mediastinum

Pulmonary involvement has been reported in 75 (12%) of 620 patients with systemic presentations (Table 1). Two studies including a total of 39 patients have been focused on IgG4-related pulmonary disease [38,39], including 35 patients with lung disease and 11 with pleural involvement (7 patients had involvement of both the lung parenchyma and pleura). Pulmonary involvement is often asymptomatic at presentation and was diagnosed incidentally by imaging studies in no fewer than 62% of patients. However, pulmonary disease can worsen dramatically over time, leading to severe interstitial lung disease, large airway compromise, and other complications. When clinical symptoms are present (38% of those with radiologic lung disease at presentation), they usually consist of cough and/or sputum (dyspnea and chest pain are less frequent).

Pleural involvement, consisting principally of nodular pleural thickening that mimics mesothelioma, has been reported in 28% of patients with IgG4-related pulmonary disease [38,39]. Pleural effusions are unusual and seldom dominate the clinical picture.

The most frequent mediastinal involvement consisted of lymph nodes (hilar and/or mediastinal lymphadenopathy accompanies most cases of pulmonary disease). Mediastinal fibrosis (soft tissue masses in paravertebral regions) has been reported in a total of 7 patients

Table 1
Main features of patients with IgG4-RD according to the nature of patient collection (unselected or selected by organ): figures obtained in series including unselected cases of IgG4-RD (systemic series), series including patients with salivary and lacrimal glandular involvement (glandular series), series including patients with autoimmune pancreatitis or sclerosing cholangitis (pancreatobiliary series), and series including other organ-specific IgG-4 related disease (other series).

	Systemic series	Glandular series	Pancreatobiliary series	Other series
Number of patients	887	361	1892	342
Mean age at diagnosis (years)	61.65	58.80	62.28	62.49
Asian patients	729 (82%)	327 (91%)	1254 (66%)	250 (73%)
Males	542/755 (72%)	179 (50%)	1446/1847 (78%)	240 (75%)
Single-organ involvement	130/296 (44%)	59/139 (42%)	79/138 (57%)	41/184 (22%)
Autoimmune pancreatitis	345/840 (41%)	43/237 (18%)	1368/1398 (98%)	95/242 (39%)
Salivary gland involvement	321/799 (40%)	227/278 (82%)	46/264 (17%)	102/232 (52%)
Lacrimal involvement	163/567 (29%)	188/294 (64%)	6/96 (6%)	33/160 (21%)
Lymphadenopathy	154/593 (26%)	45/227 (19%)	48/297 (16%)	134/230 (58%)
Cholangitis	152/781 (19%)	13/237 (5%)	685/813 (84%)	28/342 (8%)
ENT involvement/atopy	44/261 (17%)	47/237 (20%)	2/260 (1%)	40/242 (17%)
Retroperitoneal involvement	87/667 (13%)	26/237 (11%)	22/313 (7%)	39/255 (15%)
Renal involvement	86/667 (13%)	21/237 (9%)	18/313 (6%)	121/266 (45%)
Lung involvement	75/620 (12%)	18/237 (8%)	6/313 (2%)	75/253 (30%)
Aortic involvement	35/375 (9%)	0/237 (0%)	5/313 (2%)	36/268 (13%)

Table 2
List of involvements of organs and clinical presentations reported in IgG4-RD. In parenthesis, number of cases reported in studies including >10 patients.

1. Pancreas (n = 1849)
- Autoimmune pancreatitis
- Pancreatic enlargement[a]
- Pancreatic atrophy[a]
- New-onset diabetes mellitus

2. Biliary tree (n = 876)
- Sclerosing cholangitis
- Biliary strictures[a]

3. Gallbladder (n = 58)
- Sclerosing cholecystitis
- Gallbladder tumor/nodule[a]
- Gallbladder thickening[a]

4. Major salivary glands (n = 610)
- Swelling of submandibular glands
- Swelling of parotid glands
- Swelling of sublingual glands
- Sicca syndrome

5. Ocular involvement (n = 486)
- Swelling of lachrymal glands (dacryoadenitis),
- Eyelid swelling
- Visual disturbances
- Optic neuropathy
- Ocular movement restrictions
- Orbital myositis
- Exophthalmus
- Ptosis
- Corneal ulcer
- Epiphora
- Scleritis
- Uveitis

6. Pulmonary involvement (n = 174)
- Respiratory symptoms (cough, increased sputum)
- Asthma
- Pulmonary solid nodules[a]
- Thickening of bronchovascular bundles and interlobular septa[a]
- Interstitial involvement[a]
- Round-shaped ground-glass opacity[a]

7. Pleural involvement (n = 5)
- Nodular pleural thickening[a]
- Pleural effusion[a]

8. Mediastinal involvement (n = 5)
- Mediastinal adenopathies[a]
- Mediastinal fibrosis[a]
- Paravertebral soft tissue masses[a]

9. Thymus (n = 1)[a]
- Thymic tumor-like mass[a]
- Diffuse thymic fibrosis[a]

10. Renal involvement (n = 246)
- Altered renal parameters (creatinine, proteinuria, hematuria)
- Nephrotic syndrome
- Renal swelling[a]
- Renal atrophy[a]
- Solitary nodules or cysts[a]
- Tubulointerstitial nephritis
- Membranous nephropathy
- IgA nephropathy
- Focal and segmental proliferative glomerulonephritis
- Membranoproliferative glomerulonephritis
- Mesangial proliferative glomerulonephritis

11. Retroperitoneal involvement (n = 174)
- Retroperitoneal fibrosis[a]
- Periaortic masses[a]
- Periiliac masses[a]
- Pericaval masses[a]
- Presacral masses[a]
- Retrovesicular masses[a]
- Perirectal masses[a]

12. Urinary tract and bladder (n = 7)
- Hydronephrosis
- Urinary bladder pseudotumor[a]
- Interstitial cystitis

13. Mesenterium (n = 6)
- Sclerosing mesenteritis or pseudotumor[a]
- Omental involvement similar to peritoneal carcinomatosis[a]

Table 2 (*continued*)

14. Aorta (n = 76)
- Aortitis[a]
- Periaortitis[a]
- Aortic dilation[a]
- Aneurysm[a]
- Dissection

15. Arterial involvement (n = 2)
- Coronary arteries
- Iliac arteries
- Carotid arteries
- Vertebral artery
- Intracerebral aneurysms

16. Meninges (n = 10)
- Headache
- Cranial nerve palsies
- Visual disturbances
- Motor weakness
- Limb numbness
- Sensorineural hearing loss
- Seizures
- Hypertrophic pachymeningitis[a]

17. Cranial nerves (mixed with other involvements)
- Optic nerve
- Trigeminal nerve (supra/infraorbital branches)
- Facial nerve palsy
- Other cranial nerves (VII, VIII, X, and XII)

18. Vertebral nerve roots[b]
- Lumbar spinal nerves[a]
- Sacral spinal nerves[a]
- Cervical spinal nerves[a]

19. Brain (n = 2)
- Inflammatory cerebral pseudotumor[a]
- Intracerebral aneurysms[a]

20. Pineal gland (n = 11)
- Hypopituitarism
- Central diabetes insipidus
- Enlargement of the anterior pituitary gland and/or stalk[a]

21. Thyroid involvement (n = 30)
- Hypothyroidism
- Autoimmune thyroiditis
- Thyroid gland swelling[a]
- Thyroid nodules[a]
- Thyroid atrophy[a]

22. Prostate (n = 24)
- Urinary retention
- Prostatitis
- Prostate hypertrophy[a]
- Prostate mass[a]

23. Breast (n = 3)
- Mastitis
- Painless breast mass/nodule

24. Testes (n = 1)[b]
- Scrotal mass
- Epididymo-orchitis
- Paratesticular pseudotumor

25. Allergic processes (n = 133, mixed with ENT)
- Drug reactions
- Urticarial
- Conjunctivitis
- Rhinitis
- Dermatitis
- Asthma

26. ENT involvement (n = 133, mixed with allergy)
- Nasal crusting/obstruction
- Rhinorrhea
- Anosmia
- Nasal polyposis[a]
- Rhinitis
- Sinusitis
- Otitis media
- Nasolacrimal duct involvement[a]
- Hearing loss
- Larynx
- Mastoiditis[a]

27. Skin involvement (n = 19)
- Skin plaques
- Subcutaneous nodules
- Brown papules

Table 2 (*continued*)

27. Skin involvement (n = 19)
— Dermatitis
— Skin itching
28. Lymph nodes (n = 377)
— Cervical adenopathies
— Hilar adenopathies[a]
— Mediastinal adenopathies[a]
— Intraabdominal adenopathies[a]
— Inguinal adenopathies[a]
— Axillary adenopathies
— Systemic lymphadenopathy resembling lymphoma
29. Esophagus[b]
— Esophagitis
30. Stomach (n = 1)[b]
— Pseudotumor/focal mass of the stomach[a]
— Gastric ulcers
— Gastritis
31. Small intestine[b]
— Major duodenal papilla pseudotumor[a]
— Pseudotumor of an ileal conduit[a]
32. Large intestine (n = 4)
— Colonic pseudotumor
— Colonic polyposis
— Cecum and sigmoid colon nodular lesions
33. Liver (n = 43)
— Inflammatory pseudotumors of the liver[a]
34. Spleen (n = 1)
— Spleen enlargement[a]
35. Articular involvement (n = 5)
— Arthralgias
— Destructive bone involvement of the orbit[a]
— Involvement of temporal, maxillary, or mastoid bones[a]
— Remodeling of adjacent bones[a]
— Paravertebral masses[a]
36. Pericardium (n = 4)
— Pericardial pseudotumor
— Constrictive pericarditis
37. Peripheral nerves[b]
— Sensory-motor polyneuropathy
— POEMS
— Multiplex mononeuritis

[a] Features reported in imaging studies.
[b] Included in isolated reports.

[39–43]. Thymus involvement, including tumor-like mass or diffuse thymic fibrosis, has been rarely reported [28].

3.6. Kidneys

Intrarenal disease has been described in 13% of patients reported with systemic involvement at presentation (Table 1). Four studies including a total of 115 patients have focused on IgG4-related kidney disease [44–47]. Fewer than 10% of patients with renal disease had their kidney manifestations as the first clinical feature of IgG4-RD [44–47]. IgG4-RD is nearly always present in other organ systems at the time renal disease is identified but in some cases extra-renal disease (e.g., in the submandibular glands) has been overlooked.

The cardinal renal manifestations that bring IgG4-RD to medical attention are azotemia resulting from tubulointerstitial nephritis and asymptomatic findings on radiology tests. Elevated serum creatinine levels have been reported in 58 (69%) of the 84 patients on whom such data were available. Proteinuria, generally sub-nephrotic unless concomitant glomerular disease is present, is reported in approximately half of all patients with renal disease (39/83; 47%). Hematuria is somewhat less common but still occurs in approximately one third of patients with IgG4-related renal disease (more than 1+ in 35/108, 32%). Nephrotic syndrome is decidedly less common in IgG4-RD and likely represents membranous glomerulonephropathy occurring either in isolation or concomitantly with IgG4-related TIN.

3.7. Retroperitoneum, mesentery, and urinary tract

Retroperitoneal fibrosis has been reported in 87 (13%) of 667 patients presenting with systemic features (Table 1). When retroperitoneal fibrosis is present, it is the first clinical manifestation of IgG4-RD in nearly half the cases [48]. The most common presenting symptoms were back and flank pain, followed by lower extremity swelling [48]. The locations of the retroperitoneal masses were mainly periaortic (83%) and periiliac (67%); some patients had additional involvement in pericaval, presacral, retrovesicular, or perirectal locations [48]. Hydronephrosis (unilateral more frequent than bilateral) was found in 33% of patients [48]. Some cases of mesenteric fibrosclerosis (fibrosing mesenteritis), pseudotumor or omental involvement (soft-tissue mass resembling peritoneal carcinomatosis) have been reported. The urinary bladder is rarely affected by pseudotumors, although a recent study of idiopathic interstitial cystitis identified 4 IgG4-RD patients with bladder involvement in a series of 44 total patients with idiopathic interstitial cystitis [49].

3.8. Lymph nodes

Lymphadenopathy occurs commonly in IgG4-RD and may precede, coexist with, or follow extranodal manifestations of the disease [50]. Lymphadenopathy has been reported in 154 of 593 (26%) patients with systemic presentations (Table 1). Three studies including a total of 82 patients have focused specifically on IgG4-related lymphadenopathy [50–52]. The location of lymphadenopathy in IgG4-RD often correlates with the presence of regional IgG4-related extranodal disease. Thus, the most frequent locations of lymphadenopathy among patients with salivary gland enlargement are cervical. Similarly, hilar/mediastinal or intra-abdominal lymphadenopathy is most common in patients with pulmonary involvement or pancreatitis/cholangitis, respectively. Inguinal or axillary lymphadenopathy is also common. Diffuse lymphadenopathy suggesting lymphoma is occasionally the presenting feature of IgG4-RD.

3.9. Vascular involvement: aorta and periarterial lesions

Aortic involvement, reported in 35/375 (9%) systemic patients (Table 1), is a major form of vascular involvement in IgG4-RD. Aortitis is often detected in imaging studies (periaortitis, aortic dilation, aneurysms), although some patients may present with aortic dissection or even sudden death caused by rupture. Other periarterial lesions involving carotid, coronary, pulmonary, celiac, mesenteric, iliac, or vertebral arteries, as well as intracerebral or peripheral (femoral or popliteal) aneurysms, have been reported rarely [41,42].

3.10. Neurological involvement: meninges and cranial nerves

Central nervous system (CNS) involvement is reported infrequently in IgG4-RD but when present has a specific predilection for the meninges and cranial nerves. Hypertrophic pachymeningitis, reported in 8/620 (1.3%) systemic patients (Table 1), refers to inflammation leading to a localized or diffused thickening of the cranial or spinal cord dura mater. Lu et al. [53] have recently reviewed the characteristics of 33 patients and found that headache (67%), cranial nerve palsies (33%), vision disturbances (21%), motor weakness (15%), limb numbness (12%), sensorineural hearing loss (9%) and seizures (6%) were the main clinical symptoms at presentation. Imaging studies were likely to disclose either linear dural thickening or a bulging mass.

Involvement of cranial nerves often results from adjacent tumoral masses. The best examples are the involvement of the optic nerves and trigeminal branches (supra/infraorbital nerves) by ocular masses; involvement of VII, VIII, IX, X, and XII cranial nerves by pachymeningitis/mastoiditis; or involvement of the spinal nerve roots by paravertebral masses, including lumbar (n = 3), sacral (n = 3) or cervical (n = 1)

spinal nerves. Impairment of cranial nerves IX, X, and XII is of particular concern given the importance of these nerves in coordinating airway protection during deglutition [53]. Inflammatory cerebral pseudotumor has been reported in only one case [43].

3.11. Thyroid

Several different forms of thyroid disease are known or speculated to be associated with IgG4-RD. First, Riedel's thyroiditis has been proven to be a manifestation of IgG4-RD in a small case series of patients. In addition, fibrosing Hashimoto's thyroiditis, the pathology of which overlaps substantially with that of Riedel's, has also been linked to IgG4-RD.

More controversial is the suggestion that Hashimoto's thyroiditis, the most common autoimmune disease in the general population, is also (in at least some cases) a form of IgG4-RD. A recent study [54] identified 19 IgG4-related thyroiditis from 70 patients with Hashimoto thyroiditis who underwent total thyroidectomy (mainly for gland swelling, tracheal stenosis or suspicious of malignant lymphoma). Anti-thyroid autoantibodies – both anti-thyroglobulin and anti-thyroid peroxidase antibodies – were significantly higher among patients with "IgG4 thyroiditis" compared to those whose thyroiditis was judged not to be associated with IgG4-RD. Watanabe et al. [55] found hypothyroidism in 22 (19%) of 114 patients with IgG4-RD.

In summary, the relationship between both Riedel thyroiditis and fibrosing Hashimoto's and IgG4-related disease is solid. Further studies are required to validate or refute the notion that another entity, "IgG4 thyroiditis", also exists and accounts for a subset of patients now diagnosed with Hashimoto's thyroiditis.

3.12. Hypophysis

Involvement of the hypophysis is a typical though rare form of IgG4-RD (8/550 systemic cases, 1.5%). Bando et al. [56] have recently reviewed 29 cases that presented with hypopituitarism (n = 7), diabetes insipidus (n = 4), or both (n = 17). Magnetic resonance imaging studies typically reveal enlargement of the anterior pituitary and/or stalk.

3.13. Prostate, breast, and testes

Involvement of the prostate has also been reported in approximately 2% (10 of 488 patients) of systemic disease (10/488, 2%). Most patients described in the literature to date were diagnosed retrospectively with IgG4-related prostatitis on the basis of histopathologic findings following transurethral resection for symptoms of severe urinary retention [57]. Biopsy-proven IgG4-related prostatitis presenting as a prostate mass has also been reported [19]. Painless breast masses confirmed to be IgG4-related mastitis have been reported in 5 cases and are consistent with the concept that IgG4-RD has a tendency to form tumefactive lesions [47,58]. Testicular involvement can occur as a scrotal mass (paratesticular pseudotumor) or epididymo-orchitis [44,59].

3.14. Allergy and ENT involvement

Allergic processes or an atopic background has been reported in 44/261 (17%) systemic patients (Table 1). No homogeneous definition was used across the studies, but the majority included pulmonary (asthma), cutaneous (dermatititis, drug reactions, urticaria), ocular (conjunctivitis), or ENT (rhinitis, sinusitis) [60] involvement. It is likely that allergic manifestations of IgG4-RD are underestimated because of the failure of many clinicians to recognize that longstanding symptoms of atopy may be linked to IgG4-RD. Della Torre et al. [60] have suggested that the subset of patients with a history of atopy may have an abnormal Th2 response with an increased number of circulating memory cells.

ENT involvement has been recently included in the clinical spectrum of IgG4-RD. Two studies have analyzed nasal involvement specifically [61,62]. The main nasal symptoms reported were nasal crusting (n = 10), rhinorrhea (n = 9), postnasal drip (n = 8), nasal polyposis (n = 7), nasal obstruction (n = 3) and anosmia (n = 1). Rhinitis (often in an allergic/atopic context) and sinusitis are overwhelmingly the main ENT diagnosis. Nasal biopsy has been suggested as a safe and useful diagnostic tool. Other infrequent ENT manifestations include hearing loss, mastoiditis, otitis media, and laryneal involvement (supraglottic nodules) [63].

3.15. Skin involvement

Specific IgG4-related involvement of the skin has been reported in 4/488 (1%) patients with systemic presentations (Table 1). The two main types of cutaneous lesions are erythematous plaques and subcutaneous nodules [64], although other lesions such as brown papules similar to prurigo nodularis and toe nodules have been reported. Most reports of cutaneous lesions thus far describe findings on the skin of the head region, including periauricular, eyelid, cheek, temporal and mandible locations. Other locations (forearm, abdomen, chest, waist) have been reported in isolated cases.

3.16. Gastrointestinal involvement

Recent studies have reported isolated cases of digestive tract involvement, including esophagitis, gastric involvement (pseudotumor, focal masses, nodular lesions, gastric ulcers or gastritis), pseudotumor of the major duodenal papilla, nodular lesions of the ileum, and colonic involvement (pseudotumor, colonic polyposis, nodular lesions of sigmoid colon or cecum) [65]. Inflammatory pseudotumors of the liver mimicking a primary malignant hepatic tumor have been reported in 43 cases. Splenic involvement has been reported once to date (Table 2).

3.17. Miscellaneous organ manifestations

Joints and bones appear to be affective by IgG4-RD extremely rarely. The most frequent finding is remodeling of bones (erosion or sclerosis) adjacent to the lesions without signs of destruction. Destructive bone involvement has been reported in isolated cases, affecting the bones of the orbit, or the temporal, maxillary, or mastoid bones. Arthralgias have also been reported. Pericardial involvement (pericardial pseudotumor or constrictive pericarditis) has been reported in isolated cases. Isolated cases of peripheral neuropathy have been reported (sensory-motor polyneuropathy, POEMS and multiplex mononeuritis).

4. Conclusions

IgG4-RD is an increasingly-recognized condition in adults, with a heterogeneous clinical presentation affecting a wide range of organ systems. This review shows that clinical studies have a low level of evidence, especially with respect to the lack of a homogeneous diagnostic approach. The body of evidence relies predominantly on series including a range of 10–50 patients in 80% of selected studies. Although a long list of features involving the majority of organs and systems has been reported in the last decade, few studies have attempted to characterize the systemic presentation of IgG4-RD in large series of patients. Moreover, the studies that have done so found differing results, which may be due to the small number of patients analyzed, the different sets of classification criteria used and, especially, the lack of a standardized definition of IgG4-RD involvement in most organs. The main sources of bias we found were the heterogeneous definitions of each organ involvement (or even a lack of definition in some studies) and the heterogeneous diagnostic approach used (clinical, radiological or histopathological).

This review found that the prevalence of specific organ involvement varied widely between studies, and was principally influenced by the

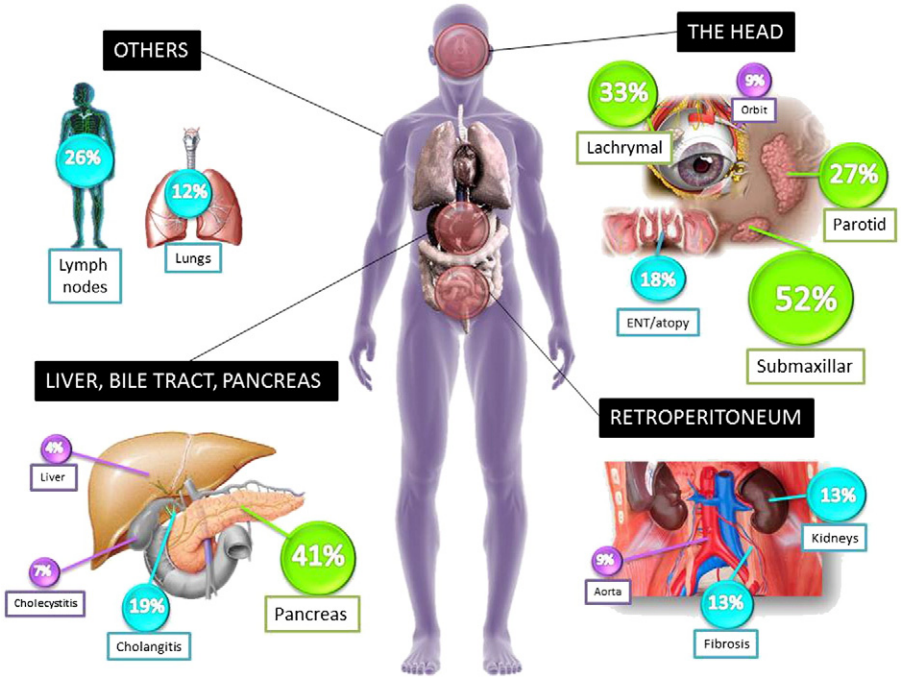

Fig. 2. Frequencies of the main organ involvements obtained in series including unselected cases of IgG4-RD (systemic series).

nature of patient collection (unselected or selected by organ) (Table 1). Nearly 40 organs have been reported to be involved by IgG4-RD (Table 2), but the most closely studied organs to date are the pancreas (the organ in which IgG4-RD was first identified), the salivary/lacrimal glands and the liver and biliary tree [66–69] (Fig. 2). There remain few data about the symptoms leading to suspicion of the disease. The diagnostic approach to specific organ system involvement has not been detailed in the majority of studies. Greater understanding of the etiopathogenesis of IgG4-RD and active multidisciplinary collaboration promoting international multicenter registries and clinical guidelines may help improve the knowledge of systemic involvement of this emerging immune-mediated systemic disease.

Take-home messages

- IgG4-related disease is a systemic immune-mediated disease described in the 21st century
- The disease is characterized by the infiltration of IgG4-bearing plasma cells and raised IgG4 levels
- The cardinal clinical feature of IgG4-RD is single or multiple organ swelling
- Nearly 75% of cases have been reported in Japan
- More than 40 different organs have been reported to be involved in IgG4-RD
- The organs more frequently involved are the pancreas, salivary/lacrimal glands, biliary tree, kidneys, thyroid gland, lungs, and aorta.

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