nature reviews rheumatology

https://doi.org/10.1038/s41584-025-01240-x

Review article

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IgG4-related disease and other fibro-inflammatory conditions

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Abstract

IgG4-related disease (IgG4-RD) is a fibro-inflammatory disorder usually characterized by multi-organ involvement. Its pathogenesis is complex and involves genetic and environmental factors, while immune responses usually mediate organ damage and promote fibrosis, which is a key feature of the disease. IgG4 responses, however, are not exclusive to IgG4-RD and can be encountered in other diseases with phenotypes that partially overlap that of IgG4-RD. Although IgG4-RD has clinical and histological hallmarks, the lack of validated diagnostic criteria often makes the diagnosis challenging, requiring a multi-dimensional approach that integrates clinical, radiological and serological data. The present Review covers recent advances in the understanding of disease drivers and its clinical phenotypes, mainly focusing on the differential diagnosis with potential IgG4-RD mimickers, namely histiocytoses, lymphoproliferative disorders, systemic vasculitides and other immune-mediated conditions. The Review also provides a schematic approach to IgG4-RD treatment, including a brief overview of glucocorticoid-sparing agents and emerging therapies, from B cell-depleting monoclonal antibodies to cytokine-targeting drugs, the majority of which are currently under investigation in randomized clinical trials.

Sections

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Key points

- IgG4-related disease (IgG4-RD) is a fibro-inflammatory disease characterized by slow-growing and often pseudotumoural lesions that can be solitary or occur in multiple organs.
- The diagnosis of IgG4-RD requires the exclusion of a wide array of neoplastic, infectious and autoimmune disorders as well as of rare proliferative conditions such as histiocytoses and Castleman disease.
- The different subphenotypes of IgG4-RD (Mikulicz, head-and-neck limited, pancreato-hepato-biliary, retroperitoneal and/or aortic disease) differ in terms of patients' demographic features, clinical manifestations and serum IgG4 levels.
- Treatment of IgG4-RD is based on the use of glucocorticoids, but B cell-depleting therapies (for example, rituximab or inebilizumab) are being incorporated into the standard therapeutic regimens.
- IgG4-RD is a chronic–relapsing disorder and therefore requires careful and long-term follow-up.

Introduction

The initial report of an 'IgG4-associated' disease dates back to 2001, when Hamano et al.[1] showed that patients with autoimmune pancreatitis had polyclonal hypergammaglobulinaemia with a marked increase in IgG4. In 2002, the same group demonstrated $IgG4^+$ plasma-cell infiltration of the pancreatic and ureteral lesions of individuals with autoimmune pancreatitis associated with retroperitoneal fibrosis[2]. In 2003, Kamisawa et al.[3] reported that, in patients with sclerosing pancreatitis, $IgG4^+$ plasma-cell infiltration could also affect other sites of the digestive tract (for example, the biliary tree, stomach or colon) as well as remote organs such as the salivary glands, lymph nodes and bone marrow, thus introducing the concept of a systemic disease. It then became clear that several seemingly distinct entities, including sclerosing pancreato-cholangitis, Riedel thyroiditis, Mikulicz disease (chronic dacryoadenitis and sialoadenitis) and orbital pseudotumour could be grouped under the umbrella of what was defined as 'IgG4-related disease' (IgG4-RD). These entities all shared key pathological features, namely pseudotumoural lesions, $IgG4^+$ plasma-cell infiltration, fibrosis and chronic lymphoplasmacytic inflammation[4].

During the past two decades, considerable advances were made in understanding the pathophysiology and clinical aspects of IgG4-RD. However, owing to the lack of validated diagnostic criteria and disease-specific biomarkers, the boundaries of the IgG4-RD spectrum are not yet well defined and several diagnostic issues have arisen. Fibro-inflammatory lesions that often lack a prominent IgG4 response (that is, tissue infiltration by $IgG4^+$ plasma cells and/or increased serum levels of IgG4), such as pachymeningitis and retroperitoneal fibrosis, are nevertheless considered to be IgG4 related because of their histological and clinical similarities to typical IgG4-RD lesions[5]; conversely, pronounced IgG4 responses have been recognized in other inflammatory conditions (for example, idiopathic multicentric Castleman disease (iMCD)), whose clinical manifestations can mimic those of IgG4-RD[6]. Finally, substantial overlap has emerged between IgG4-RD and other autoimmune or proliferative disorders such as histiocytoses and systemic vasculitis[7,8]. These and other aspects make IgG4-RD a puzzling condition and have implications for its diagnosis and management. Herein, we review the latest developments in IgG4-RD clinical phenotyping, pathophysiology and management, with a focus on the main disease mimickers and on how to approach the challenging issues related to differential diagnosis.

Clinical presentation and disease phenotypes

General features of IgG4-RD

IgG4-RD is a systemic, immune-mediated, fibro-inflammatory disorder. It usually has an insidious onset and can lead to silent and irreversible organ damage. The clinical presentation of IgG4-RD differs from that of other systemic autoimmune conditions with a rapidly progressive course such as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis or giant-cell arteritis (GCA). However, other conditions that mimic IgG4-RD, such as histiocytosis, can also have an indolent presentation. IgG4-RD occurs more frequently in men than in women (male:female ratio 2:1–3:1), with men usually experiencing more severe disease[9].

IgG4-RD has clinical and histological hallmarks. The lesions usually have a pseudo-tumoural growth pattern and often present as tumour-like masses; organ damage can result from the compressive effects that these lesions exert on neighbouring structures (for example, ureteral obstruction by retroperitoneal fibrosis or common bile-duct obstruction by focal sclerosing pancreatitis). In other instances, organ damage is attributable to diffuse parenchymal infiltration, as occurs in IgG4-related tubulointerstitial nephritis or diffuse sclerosing pancreatitis[10]. Another distinguishing feature of IgG4-RD is its vascular tropism: involvement of large and medium-sized arteries such as the aorta and the carotid, mesenteric and coronary arteries is seen in approximately 50% of cases (Table 1). Interestingly, small vessels can also be involved: fibrous sheathing of arterioles or capillaries and inflammation of small veins are also frequent[11]. These findings suggest that IgG4-RD can be a vasculitis affecting vessels of variable size[12–14]. Histologically, IgG4-RD lesions almost invariably harbour fibrous and chronic inflammatory components (Fig. 1), with their relative proportions accounting for the different activity of the lesions on metabolic imaging studies (such as ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET–CT[15]. The coexistence of fibrosis and chronic inflammation is almost a prerequisite for the diagnosis of IgG4-RD.

Main clinical manifestations of IgG4-RD

The most common IgG4-RD lesions are listed in Table 1. A detailed analysis of clinical manifestations and radiology findings is beyond the scope of this Review. The main clinical signs and symptoms depend on which organs are affected and can be extremely variable (Fig. 2), further complicating the differential diagnosis. Pancreato-biliary involvement (Fig. 2e) can cause jaundice, pruritus, abdominal pain, steatorrhea and new-onset diabetes mellitus[16]. Bilateral swelling of lacrimal and major salivary glands indicates Mikulicz disease[17], whereas other commonly affected sites in the head and neck include cervical lymph nodes, thyroid[18], ocular tissues and annexes, extraocular muscles, orbital fat and trigeminal nerve, possibly manifesting with chronic swelling of the orbit and proptosis[19] (Fig. 2b). Skull-base involvement can also occur, with cranial neuropathies being its most common presentation[20]. Both thoracic and abdominal peri-aortitis, as well as peri-arteritis of the main aortic branches (for example, epi-aortic vessels), are frequent. Abdominal peri-aortitis can range from thin peri-aortic and/or peri-iliac sheathing to large peri-aorto-iliac masses that can encase the ureters, traditionally

Table 1 | Clinical manifestations of IgG4-RD and its main mimics[7,22,24,25,84–110]

Characteristic	IgG4-RD	ECD	iMCD	Sarcoidosis	Large-vessel vasculitis	GPA
Median age at diagnosis	55–65 years	45–55 years	50–55 years	45–50 years	TA: 25–35 years; GCA: 70–80 years	50–60 years
Male-to-female ratio	1.5–4:1	2.5–3:1	0.5–1.5:1	0.5–1:1	0.1–0.25:1	1–1.5:1
Head and neck						
Pachymeningitis	Very rare	Rare	Very rare	Very rare	Very rare	Rare
Pituitary involvement	Very rare	Moderately frequent	Very rare	Very rare	Very rare	Very rare
Retro-orbital infiltration	Rare	Moderately frequent	Very rare	Very rare	Very rare	Rare
Lacrimal and/or salivary gland involvement	Frequent	No data available	Very rare	Very rare	No data available	Rare
Chronic rhinosinusitis	Rare	Frequent	No data available	Very rare	No data available	Frequent
Chest						
Thoracic (peri-)aortitis	Rare	Frequent	No data available	Very rare	Moderately frequent	Rare
Mediastinitis	Very rare	Rare	Rare	Very rare	No data available	No data available
Lung involvement	Rare	Moderately frequent	Frequent	Frequent	Very rare	Frequent
Cardiac involvement	Rare	Moderately frequent	No data available	Very rare	Very rare	Rare
Abdomen						
Hepato-biliary involvement	Rare	Very rare	Rare	Rare	Very rare	Very rare
Spleen involvement	Very rare	Very rare	Frequent	Rare	No data available	Very rare
Pancreatitis	Frequent	Very rare	Very rare	Very rare	No data available	Very rare
Mesenteritis	Very rare	Rare	No data available	Very rare	Rare	No data available
Retroperitoneal fibrosis (peri-aortic and/or peri-iliac)	Moderately frequent	Frequent	Very rare	Very rare	Rare	Very rare
Peri-renal fibrosis	Very rare	Frequent	No data available	Very rare	No data available	No data available
Parenchymal renal involvement	Rare (80% TIN, 15% MN)	No data available	Very rare (case reports of renal mass or GN)	Very rare (80% TIN)	No data available	Frequent (GN)
Other						
Skin lesions	Very rare	Moderately frequent	Rare	Rare	Very rare	Moderately frequent
Bone involvement	Very rare	Frequent	Rare	Very rare	Very rare	No data available
Lymphadenopathy	Moderately frequent	Rare	Frequent	Frequent (thoracic)	No data available	Rare

'Very rare' manifestations have been reported in case reports or have a frequency <10%; 'rare' manifestations have a frequency <25%; 'moderately frequent' manifestations have a frequency 25–50%, and 'frequent' manifestations have a frequency >50%. ECD, Erdheim–Chester disease; GCA, giant cell arteritis; GN, glomerulonephritis; GPA, granulomatosis with polyangiitis; IgG4-RD, IgG4-related disease; iMCD, idiopathic multicentric Castleman disease; MN, membranous nephropathy; TA, Takayasu arteritis; TIN, tubulointerstitial nephritis.

referred to as retroperitoneal fibrosis[13,21]. Typical symptoms of retroperitoneal fibrosis include abdominal, flank or lumbar pain, lower-limb oedema, lower urinary tract symptoms, mild fever and weight loss[21]. Retroperitoneal fibrosis can also develop at atypical sites such as the pre-sacral area or the peri-renal space (Fig. 2). The renal parenchyma can be affected by IgG4-related tubulointerstitial nephritis, which is usually characterized by mild proteinuria and variable degrees of kidney-function impairment[22,23]. Less frequent manifestations include non-specific skin lesions, mesenteritis (Fig. 2h), pachymeningitis, hypophysitis, lung involvement and prostatitis[10].

IgG4-RD sub-phenotypes

IgG4-RD is clinically heterogeneous and comprises different sub-phenotypes. A cluster analysis run on an international cohort including 493 patients identified four distinct disease sub-phenotypes: pancreato-hepato-biliary disease, retroperitoneal fibrosis and/or aortitis, disease limited to the head and neck and classic Mikulicz disease with systemic involvement[24]. The different groups were primarily defined by the different distribution of organ involvement. Nevertheless, other notable differences were highlighted: for instance, the head-and-neck-limited disease cluster was characterized by a predominance of

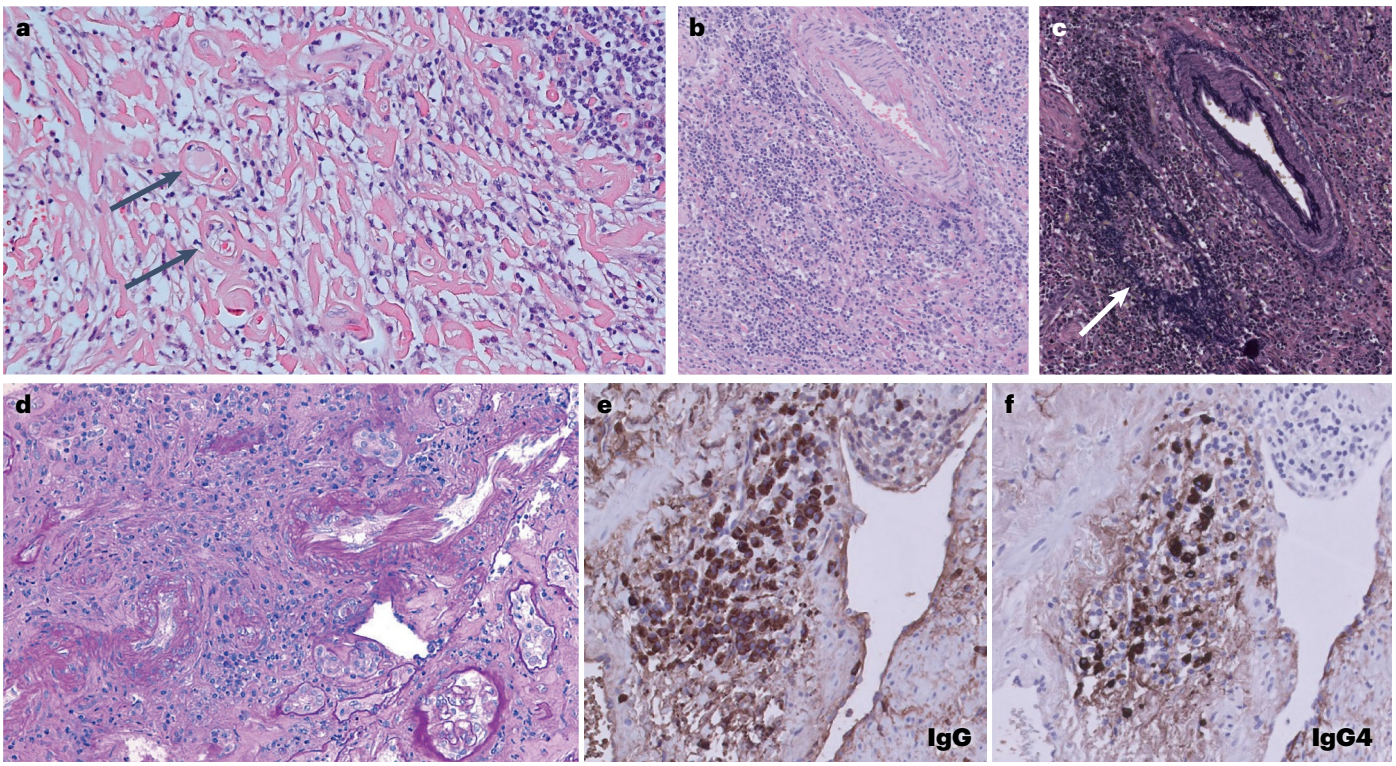

Fig. 1 | Main histological findings in IgG4-related disease. a, Retroperitoneal tissue from a patient with retroperitoneal fibrosis shows pronounced fibrosis with irregular distribution of the fibrous bundles, which often encircle small vessels (arrows) (haematoxylin and eosin (H&E) stained; original magnification ×20). **b**, Retroperitoneal tissue showing a dense lymphoplasmacytic infiltrate and an intact artery (stained with H&E; original magnification ×10). **c**, The same tissue area shown in **b**, in a section stained with Elastica van Gieson, reveals the presence of obliterative phlebitis (arrow) (original magnification ×10). **d**, Kidney tissue from an individual with IgG4-related tubulointerstitial nephritis showing interstitial storiform fibrosis and a chronic tubulointerstitial inflammatory infiltrate (periodic acid-Schiff stained; original magnification ×20). **e**, IgG staining in salivary-gland tissue of a patient with IgG4-related sialoadenitis showing IgG-positive cells (anti-IgG antibody stained; original magnification ×20). **f**, The same biopsy area shown in **e** reveals that a substantial proportion of cells are IgG4-positive (anti-IgG4 antibody stained; original magnification ×20).

younger, female and Asian individuals, whereas white male patients more frequently had hepato-biliary involvement and/or peri-aortitis. The highest serum IgG4 levels were found in the Mikulicz's disease with systemic involvement cluster, the lowest in the retroperitoneal fibrosis cluster[24] (Supplementary Table 1). Other studies on IgG4-RD sub-phenotypes found similar results, with multisystemic disease being characterized by higher serum IgG4 levels[5,25].

Within the past year, a distinction between fibrotic and proliferative (or inflammatory) features of IgG4-RD has been proposed[26,27]. Retroperitoneal fibrosis, mediastinitis, Riedel's thyroiditis, orbital pseudotumour and pachymeningitis were classified as fibrotic manifestations, whereas pancreato-biliary, lacrimal-salivary and kidney involvement were included among the proliferative manifestations. This separation is based on several assumptions: the elevation of serum levels of IgG, IgG4 and inflammatory markers is less prominent in the fibrotic subtype than in the proliferative subtype; fibrotic lesions have only scanty inflammatory infiltrates and low-to-absent metabolic activity on PET; and the improvement of fibrotic lesions (in terms of size and metabolic activity) in response to glucocorticoids or B cell targeting therapies is less brilliant than that seen with proliferative lesions. Although these considerations might hold true for specific manifestations (for example, pachymeningitis), other manifestations, such as retroperitoneal fibrosis, mediastinitis and orbital involvement, are usually metabolically active and respond swiftly to therapy. Thus, we believe that such a distinction should not be clearcut and, more importantly, should not discourage the treatment of fibrotic lesions.

Pathogenesis

IgG4-RD is a complex disorder. Genetic, environmental and lifestyle-related factors confer predisposition to the disease, and its immunopathogenesis involves complex immune responses orchestrated by T cells, B cells and plasma cells (Fig. 3). Varying combinations of genetic and environmental agents, together with different potential autoantigens, could account for the clinical diversity of IgG4-RD, although no studies have compared the pathogenic drivers of the different disease sub-phenotypes[23].

Genetic susceptibility and other risk factors

The genetic susceptibility to IgG4-RD has not been extensively investigated, probably owing to the rarity of the disease and the paucity of familial cases. Common variants of individual susceptibility genes such as *CTLA4*, *PRSS1*, *SPINK1* and *FGFBP2* have been identified in

small cohorts, but most of these studies included mainly patients with predominant pancreatic involvement[28–32]. In a 2024 report of familial IgG4-RD, all three affected family members shared variants of the transcription factor IKAROS, encoded by *IKZF1*, and of the E3 ubiquitin ligase UBR4, encoded by *UBR4*. Both variants were found to functionally enhance T cell activation and T helper 2 (T_H2) responses, and UBR4 was associated with IgG4 class-switch[33].

Large-scale genetic studies have also been performed. A genome-wide association study involving 850 Japanese individuals with IgG4-RD identified *HLA-DRB1* and *FCGR2B* as susceptibility loci[34]. Another genome-wide study performed using the Immunochip platform in 327 patients with retroperitoneal fibrosis clearly showed that the disease-associated locus was *HLA-DRB1*03*, a traditional marker of autoimmune diseases[35]. Notably, this study also showed that the amino acid variant Arg74, which is structurally involved in the peptide-binding groove of the HLA-DRβ molecule, was associated with disease susceptibility[35].

Regarding the association between environmental agents and IgG4-RD, exposure to industrial oils, metals and cigarette smoking is frequently reported in patients' history, although compelling evidence

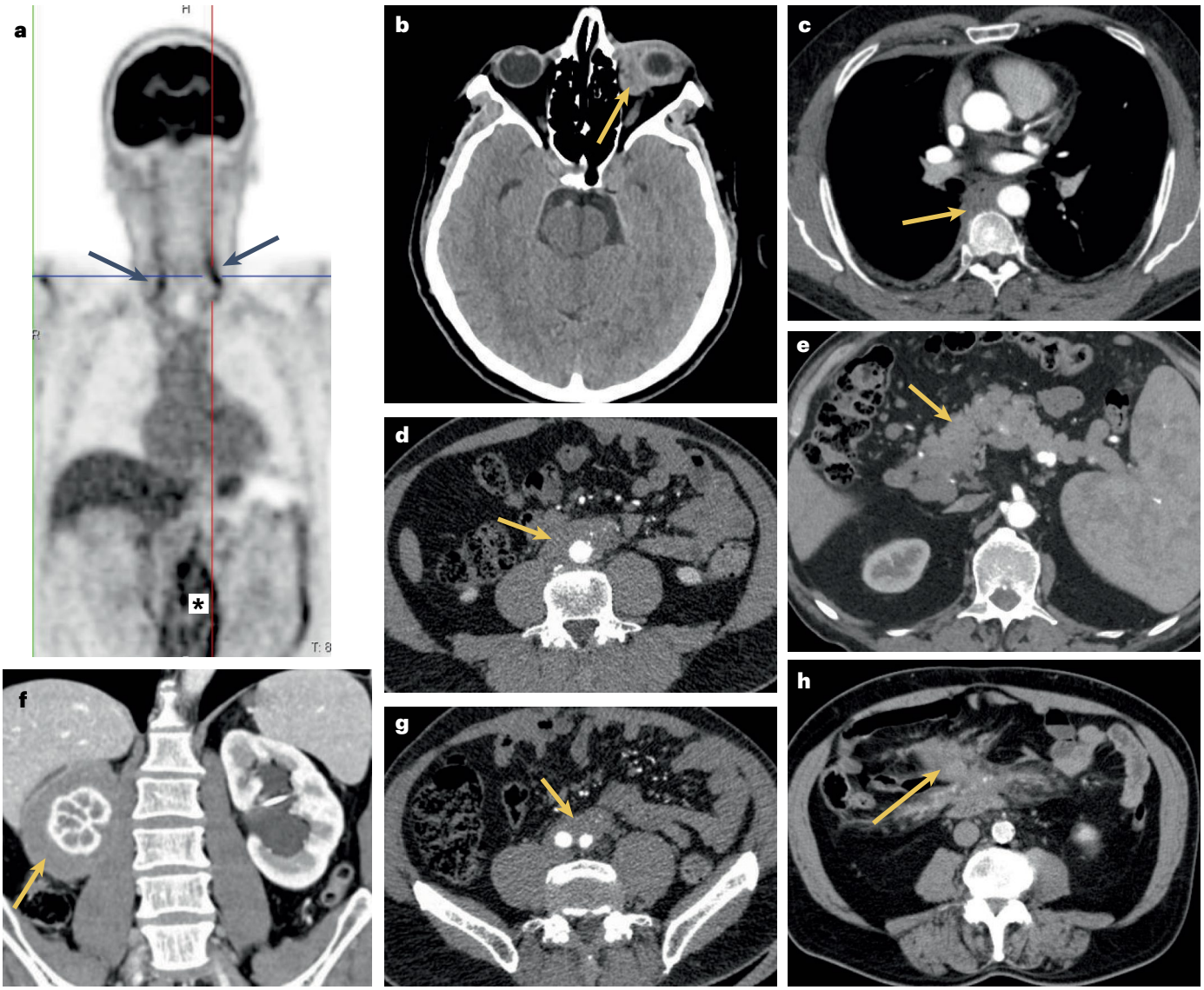

Fig. 2 | Radiological findings in IgG4-related disease. a, PET image (coronal view) showing increased uptake of fluorodeoxyglucose around the abdominal aorta (asterisk) and the common carotid arteries (arrows). **b**, Head CT image (axial view) showing orbital involvement (arrow). **c**, CT image of the chest (axial view) showing mediastinal fibrosis, which appears as a pre-vertebral, muscle-isodense tissue (arrow) adjacent to the descending thoracic aorta. **d**, Abdominal CT image (axial view) showing peri-aortitis (arrow) developing on the antero-lateral sides of the abdominal aorta. **e**, Abdominal CT image (axial view) showing diffuse enlargement of the pancreas due to sclerosing pancreatitis (arrow). **f**, Abdominal CT image (coronal view) showing a right-sided peri-renal tissue (arrow) due to IgG4-related disease, peri-renal infiltration, as well as left-sided hydronephrosis (secondary to retroperitoneal fibrosis). **g**, In the same case shown in **d**, the peri-aortic tissue also surrounds both iliac arteries (arrow). **h**, Abdominal CT image (axial view) showing diffuse thickening of the mesentery due to sclerosing mesenteritis (arrow).

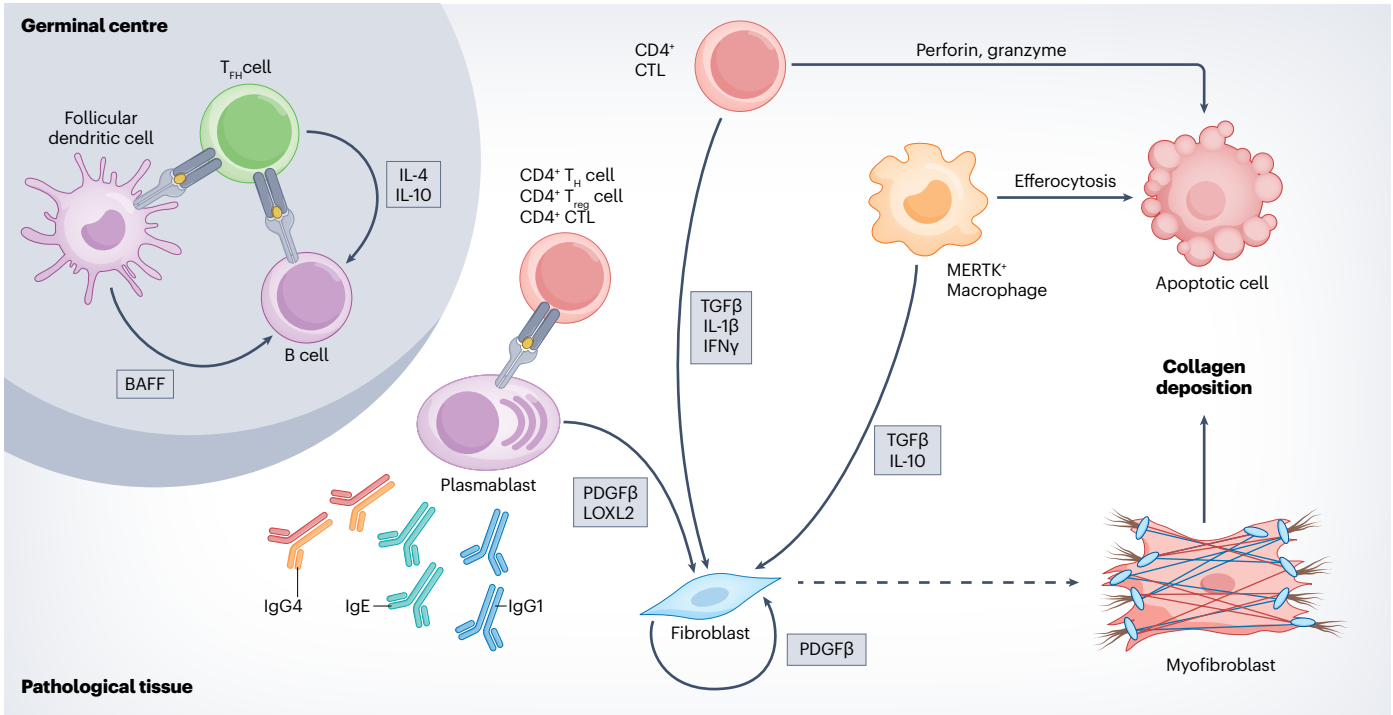

Fig. 3 | Immunopathogenesis of IgG4-related disease. Collagen deposition within pathological tissues in IgG4-related disease results from the activation of fibroblasts through a complex crosstalk involving activated B cells, plasmablasts, $CD4^+$ T cells and macrophages. Within germinal centres, oligoclonal expansion of autoreactive B cells is promoted via the presentation of autoantigens by T follicular helper (T_{FH}) cells and follicular dendritic cells. T_{FH} cells are thought to drive IgG4 class-switching through the production of IL-10 and IL-4, together with B cell activating factor (BAFF)-producing dendritic cells. Activated B cells migrate into pathological tissues, eventually promoting $CD4^+$ T lymphocyte activation and differentiation. $CD4^+$ cytotoxic T lymphocytes (CTLs) determine apoptosis within infiltrated tissues by releasing pro-apoptotic molecules (e.g. perforin and granzyme); moreover, they contribute to the activation of resident fibroblasts through the expression of transforming growth factor-β (TGFβ), IL-1β and IFNγ. $MERTK^+$ macrophages clear apoptotic cell debris through efferocytosis and release IL-10 and pro-fibrotic molecules such as TGFβ. Oligoclonally expanded B cells and plasmablasts also contribute to fibroblast activation through the secretion of platelet-derived growth factor-β (PDGFβ) and lysyl oxidase homologue 2 (LOXL2). Plasmablasts and plasma cells secrete increased amounts of IgG1 and IgG4 in the majority of patients, and increased amounts of IgE in a subset of them. MERTK, proto-oncogene tyrosine-protein kinase MER; T_H cell, T helper cell; T_{reg} cell, regulatory T cell.

of causality is lacking[36,37]. By contrast, case–control studies in patients with retroperitoneal fibrosis have consistently shown that exposure to asbestos and smoking is associated with a high risk of developing the disease, and that co-exposure has a multiplicative effect on risk[38,39].

Autoantigens, autoantibodies and the role of IgG4

The increase in serum levels of IgG4 and other IgG subclasses (especially IgG1) and the oligoclonal expansion of plasmablasts and plasma cells in affected tissues have been regarded as proof of autoimmunity in IgG4-RD[40,41]. Yet, the search for autoantigens has failed to identify a unique causative candidate and rather disclosed a variety of self-antigens including carbonic anhydrase II and IV, lactoferrin, amylase-α-2A, pancreatic trypsinogens and, more recently, galectin-3, annexin-A11, laminin-511 and prohibitin[42–44]. Although this evidence suggests a broad breakdown of immunological tolerance in IgG4-RD, each of the autoantibodies against the aforementioned antigens is found in less than one-third of patients and are also found in other autoimmune disorders; thus, they lack adequate specificity for IgG4-RD[45]. It goes without saying that their pathogenic role is as yet unproven. Nonetheless, people with IgG4-RD who produce antibodies against more than one autoantigen present with more prominent IgG elevations, complement consumption and visceral-organ involvement than those who have antibodies against one or no autoantigens, suggesting that broader autoimmunity might be associated with more severe disease[45]. The pathogenicity of the IgG4 subclass remains controversial. In general, IgG4 acts as a neutralizing antibody in autoimmune, infectious or allergic conditions, being responsible for the containment of immune responses[46,47]. In contrast to other IgG subclasses, IgG4 molecules harbour an inhibitory Fc portion that does not activate complement and poorly engages activating Fcγ receptors[48]. Accordingly, in a mouse model of autoimmune pancreatitis, patient-derived IgG4 mitigated IgG1-induced pancreatic and salivary gland inflammation[49]. In contrast to myasthenia gravis and pemphigus vulgaris, a direct contribution of IgG4 to the pathology of IgG4-RD seems unlikely. The switch from more abundant IgG subclasses to IgG4 is driven by T_H2 and regulatory T cell responses[4]; however, it is still unclear why some IgG4-RD manifestations have more prominent IgG4 signatures than others.

B cells, T cells and other cell subtypes

The landscape of immune cells in IgG4-RD has been investigated in detail, with particular attention to the B cell and T cell compartments and their contribution to tissue fibrosis. The observation of clinical improvement following treatment with B cell targeting therapies

provides the most compelling evidence to implicate B cells as drivers of IgG4-RD[50–52]. Among the many B cell subsets studied, circulating plasmablasts and $IgD^{-}CD27^{-}$ double-negative B cells were found to be oligoclonally expanded in patients with IgG4-RD, to infiltrate tissues, and to secrete pro-fibrotic molecules such as platelet-derived growth factor β and lysyl oxidase homologue 2 (refs. 41,53,54). Yet, because many aspects of B cell responses depend on collaboration with T helper cells, single-cell sequencing and multicolour immunofluorescence have been used to examine T cell subsets of interest for cognate B cell activation. In this regard, four distinct T cell phenotypes have been identified in patients with IgG4-RD, including $LAG3^{+}$ and $BATF^{+}$ T follicular helper cells and $CD4^{+}$ and $CD8^{+}$ cytotoxic T lymphocytes (CTLs)[55–58]. T follicular helper cells might drive IgG4 class-switching and B cell responses in lymphoid follicles via the production of IL-10 and IL-4 in combination with BAFF-producing dendritic cells[56,58]. CTLs contribute to tissue damage and fibrosis by inducing apoptosis and by secreting pro-fibrotic molecules such as TGFβ, IL-1β and IFNγ[59]. The reduction of circulating CTLs following B cell-directed therapy does indeed support the concept that B cells act as antigen-presenting cells to these pathogenic T cells[60]. In addition to B cells and T cells, MERTK-expressing macrophages also infiltrate the affected tissues[61]. These $MERTK^{+}$ macrophages probably efferocytose apoptotic cells and produce pro-fibrotic cytokines, thus participating in the resolution of inflammation and fuelling tissue fibrosis[61] (Fig. 3).

Diagnosis

IgG4-RD is usually a systemic disease, but it can also be limited to single organs. In such cases, the diagnosis is more challenging, especially when a biopsy cannot easily be performed or when serum levels of IgG4 are normal or only slightly increased[62]. In addition, an increase in serum IgG4 level is neither sensitive nor specific for IgG4-RD[5,62], and the typical histopathological features of the disease can also be encountered in other conditions whose clinical manifestations overlap with those of IgG4-RD[6,63,64]. Therefore, the diagnostic approach requires a combination of clinical, serological and histological findings, and the exclusion of a wide array of mimics.

Classification and diagnostic criteria

The American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) proposed in 2019 a shared classification algorithm for IgG4-RD[65]. This algorithm requires that a patient with suspected IgG4-RD shows typical (for example, tumour-like) involvement of at least one of the 11 most commonly affected organs ('entry criteria'; Fig. 4) or typical pathology at these sites. Second, a set of 32 clinical, serological, radiological and pathological 'exclusion criteria' must be checked (Fig. 4); if any exclusion criterion is met, the patient cannot be classified as having IgG4-RD. The exclusion criteria suggest alternative diagnoses, although some of them (such as splenomegaly or lack of response to glucocorticoids) have poor specificity. If a patient meets one or more entry criteria and has no exclusion criteria, then eight 'inclusion criteria' domains (comprising clinico-pathological, serological and radiological items) must be scored. A 20-point score threshold has a specificity of ~98% and a sensitivity of ~82% for IgG4-RD classification[65]. In a Chinese study that externally validated these criteria, their specificity was 98% but their sensitivity was only 77%[66]. It is important to underline that such criteria were developed only for the purpose of classification (that is, to create homogeneous patient cohorts for clinical studies) and not for diagnostic purposes. However, even when used for classification, they have limitations. First, if the disease is confined to atypical sites (for example, the musculoskeletal system or sino-nasal structures)[67–69], it cannot be classified as IgG4-RD because it would not meet the entry

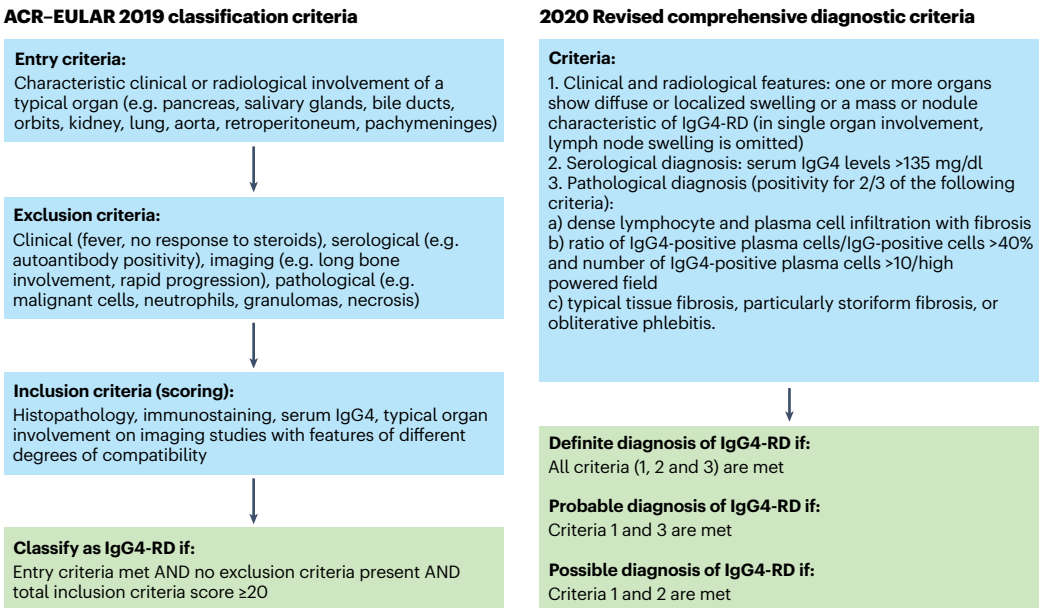

Fig. 4 | Classification and diagnostic criteria for IgG4-RD. The classification of IgG4-related disease (IgG4-RD) according to 2019 American College of Rheumatology–European League Against Rheumatism (ACR–EULAR) criteria[65] follows a three-step process, with successive entry criteria, exclusion criteria and scored inclusion criteria. The patient is classified as having IgG4-RD if a total score ≥20 is reached. The application of these criteria enables the categorization of patients for research studies. The revised comprehensive diagnostic criteria for IgG4-RD[76], published in 2020, comprise three different domains; a diagnosis of IgG4-RD is considered definite when patients fulfil the criteria in all three domains.

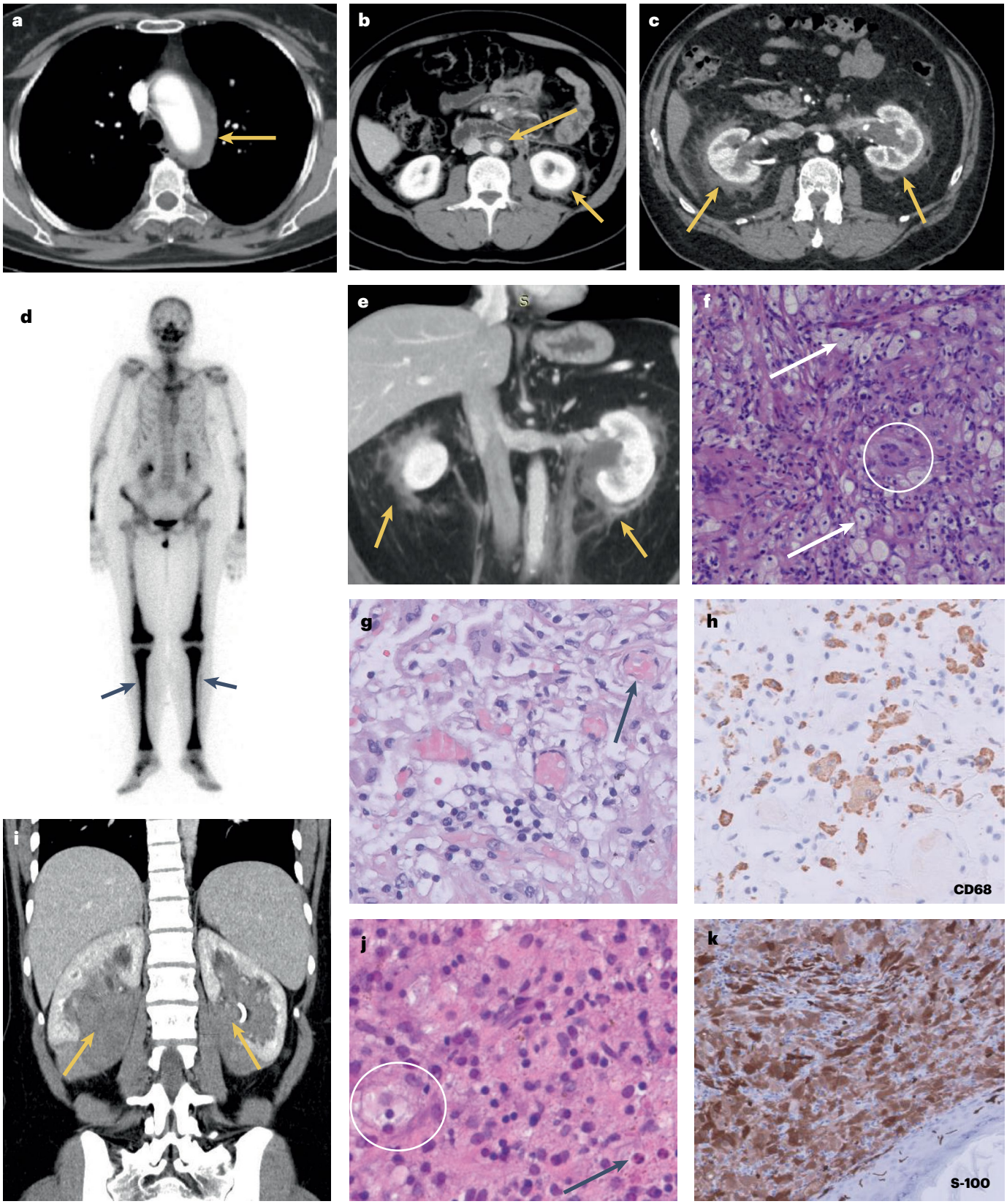
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Fig. 5 | Radiological and histopathological findings in histiocytoses mimicking IgG4-related disease. a, Chest CT scan (axial view) showing thoracic peri-aortitis involving the aortic arch (arrow) in a patient with Erdheim–Chester disease (ECD). **b**, Abdominal CT scan (axial view) showing peri-aortic (long arrow) and peri-renal (short arrow) infiltration in a patient with ECD. **c**, Abdominal CT scan (axial view) showing typical infiltration around both kidneys ('hairy kidneys') (arrows) in a patient with ECD. **d**, ^{99m}Tc bone scintigraphy showing bilateral uptake of tracer in the long bones of the lower limbs (arrows), a typical sign of ECD. **e**, Coronal view of a CT scan showing peri-renal infiltration in a patient with ECD (arrows). **f**, Retroperitoneal biopsy in a patient with ECD shows diffuse fibrosis, with a focal storiform pattern, and infiltration by foamy histiocytes (arrows) and multinucleated Touton giant cells (circle) (haematoxylin and eosin (H&E) stained, magnification ×20). **g**, Retroperitoneal biopsy in a patient with ECD shows fibrous bundles around small vessels (arrow) (H&E stained; magnification ×20). **h**, Retroperitoneal biopsy in a patient with ECD shows diffuse positivity for the histiocyte marker CD68 (anti-CD68KP1 antibody stained; magnification ×20). **i**, Coronal view of a CT scan showing massive and bilateral infiltration of the renal pelvis (arrows) extending to the calyces in a patient with Rosai–Dorfman disease (RDD). **j**, Peri-renal RDD lesion showing diffuse mononuclear cell infiltrates with signs of emperipolesis (circle) and scattered eosinophils (arrow) (H&E stained; magnification ×20). **k**, Skin biopsy in a patient with RDD displaying the presence of numerous S-100$^+$ cells (anti-S100 antibody stained; magnification ×10).

criteria. Second, the criteria exclude the possibility that a patient with IgG4-RD has an overlapping autoimmune disease such as systemic lupus erythematosus or ANCA-associated vasculitis (meaning that positivity for specific autoantibodies that suggests an alternative diagnosis represents an exclusion criterion), even though overlap cases have been extensively reported in the literature[70–72]. Third, typical disease lesions that usually show mild tissue and serum IgG4 responses (for example, retroperitoneal fibrosis, Riedel thyroiditis or mediastinal fibrosis) generally do not reach a sufficiently high score to be classified as IgG4-RD, when they occur in isolation[5,14,73–75]. This is indeed a conceptual issue: given the weakness of their IgG4 responses, it is probably incorrect to incorporate such lesions in IgG4-RD. Finally, the criteria place a substantial weight on histology and immunostaining, which becomes an issue, especially when biopsies are not available. These limitations notwithstanding, the ACR–EULAR 2019 criteria[65] represent the result of a large international effort and are flawed mainly because of the lack of diagnostic biomarkers and the intrinsic clinical variability of the disease.

In parallel with the American College of Rheumatology–European League Against Rheumatism criteria, in 2020 Japanese researchers revised the Comprehensive Diagnostic (RCD) criteria for IgG4-RD[76], updating a first set that was formulated in 2011[77]. The 2020 RCD criteria include three domains: clinical and radiological features, with demonstration of involvement of at least one organ; serological findings, namely elevated IgG4 levels; and histological diagnosis. A diagnosis of IgG4-RD is considered 'definite' when all three conditions are met, 'probable' when the first and third conditions are met and 'possible' when only the first two conditions are met (Fig. 4). Unlike the American College of Rheumatology–European League Against Rheumatism (classification criteria, which were developed using sizeable discovery and validation cohorts, the RCD criteria are based mainly on expert opinion. They have a high sensitivity and a low specificity (100% and 50%, respectively), and require validation[78].

Differential diagnosis

The differential diagnosis is one of the earliest and most important steps in the diagnostic approach to IgG4-RD, and some differential diagnoses (particularly autoimmune diseases) should be considered not only because they can mimic IgG4-RD but also because they can be associated with it.

Infections and neoplasms. First, it must be ruled out that lesions suspected as being IgG4-RD are infectious or neoplastic. Mycobacterial infections are indeed an important differential diagnosis, especially when they show systemic involvement (particularly pulmonary, lymph node, meningeal); retroperitoneal and/or prevertebral lesions mimicking retroperitoneal fibrosis might also be tubercular (for example, owing to an extension of Pott disease)[79] or triggered by mycobacterial infections occurring at remote sites such as the lung and mediastinal lymph nodes[80]. Syphilis can also cause a wide variety of clinical manifestations that mimic IgG4-RD, including cutaneous, neurological and aortic involvement. In general, chronic bacterial, fungal or viral infections should be ruled out in patients with suspected IgG4-RD.

The possibility of solid and haematological neoplasms also needs to be excluded as these conditions often mimic IgG4-RD or can coexist with it. Lymphoma is a common differential diagnosis[81]: it can be a systemic condition affecting nodal and extra-nodal sites, often presenting as mediastinal or retroperitoneal masses and showing polyclonal hypergammaglobulinaemia. However, even localized extranodal lymphoma (for example, orbital mass) could resemble IgG4-RD. Interestingly, patients with gain-of-function variants of *IKZF1* (encoding IKAROS) have been reported to develop both IgG4-RD and B cell malignancies[82].

Solid neoplasms must also be screened: metastatic diseases can mimic the systemic presentation of IgG4-RD, but obviously localized neoplasms must be excluded too. It has been consistently shown that the risk of both haematological and solid neoplasms is higher in patients with IgG4-RD than in the general population, with the frequency of malignancies peaking within the first 3 years after IgG4-RD diagnosis[81]. This pattern could be attributable to misdiagnosis or increased screening due to more frequent investigations, although it cannot be excluded that IgG4-RD per se predisposes to malignancies[81,83].

Histiocytoses and other proliferative disorders. Table 1 reports the frequencies of disease manifestations in IgG4-RD and other systemic inflammatory or non-malignant proliferative disorders[7,22,24,25,84–110]. Among these conditions, histiocytoses such as Erdheim–Chester disease (ECD) and Rosai–Dorfman disease (RDD; also known as sinus histiocytosis with massive lymphadenopathy, or Rosai–Dorfman–Destombes disease) are important differential diagnoses. ECD is a non-Langerhans cell histiocytosis that usually affects adults but only rarely affects children, and is characterized by tissue infiltration by foamy histiocytes[111,112]. ECD has a slowly progressive course and ranges from limited asymptomatic disease to systemic, aggressive forms. ECD is a perfect mimic of IgG4-RD (Table 1). It affects large and medium-sized vessels, often causing peri-arteritis; the so-called 'coated aorta' (that is, peri-vascular infiltration of the thoracoabdominal aorta) is an iconic feature of ECD (Fig. 5). Vascular involvement can also extend to the epi-aortic[113], coronary[114], renal[7] and mesenteric[115]

vessels and can be indistinguishable from that of IgG4-RD. One main differentiating feature of abdominal peri-aortitis in IgG4-RD versus ECD is its distribution, which is generally on the anterolateral sides of the aorta in IgG4-RD but presents as a thin circumferential thickening in ECD[116]. Retroperitoneal infiltration is also common in both conditions: in IgG4-RD, it commonly involves the peri-aorto-iliac space and causes medial deviation and/or stenosis of the lower third of the ureters[117], whereas in ECD it involves the peri-renal space (giving rise to the typical 'hairy kidney' appearance), the renal vessels, the proximal ureters and the renal sinuses[7] (Fig. 5). However, infiltration of the peri-renal space, including the pelvis and the vascular peduncle, can also occur in IgG4-RD (Fig. 3). Other features shared by ECD and IgG4-RD are mesenteric, mediastinal, pleural and peri-cardial involvement, retro-orbital masses, paranasal sinus involvement, pachymeningitis and hypothalamic–pituitary involvement[111,118]. Altogether, these overlapping features make differential diagnosis particularly difficult. A distinguishing feature of ECD (and absent in IgG4-RD) is long-bone infiltration, which is symmetrical, mainly involves the femurs and tibia, and causes osteosclerotic lesions that have a high uptake of tracer on ^{99m}Tc bone scintigraphy and FDG-PET (Fig. 5). The final diagnosis of ECD is histological (see below, paragraph on biopsy), and molecular analysis of the pathological tissue is required to investigate underlying somatic mutations, which are found in ~90% of patients; somatic mutations have not been reported in IgG4-RD, although specific studies are probably lacking[119,120]. IgG4 responses have not been systematically investigated in ECD, but high IgG4 levels and prominent IgG4$^+$ plasma-cell infiltration have been reported in case reports and case series of ECD[5,63,121].

RDD is an additional, important differential diagnosis. It is also a systemic histiocytosis but is clinically and histologically distinct from ECD, although ECD–RDD overlap is recognized[122]. Somatic mutations are found in <50% of RDD cases[123]. RDD usually affects the lymph nodes but the involvement of extra-nodal sites, such as meninges, upper respiratory tract, orbit, bone and salivary glands, is common[123,124]. Retroperitoneal peri-renal infiltration usually has a predilection for the renal hila and the proximal ureters, without peri-capsular involvement[8]. RDD can be misdiagnosed as IgG4-RD owing to the frequent detection of polyclonal hypergammaglobulinaemia with increased IgG4 levels, and of numerous IgG4$^+$ plasma cells in the affected tissues[125,126]. The diagnosis of RDD is essentially histological, with demonstration of tissue infiltration by histiocytes often showing signs of emperipolesis (Fig. 5), a non-destructive form of phagocytosis.

iMCD is a lymphoproliferative disorder of unknown aetiology hallmarked by lymphadenopathies, without evidence of human herpesvirus 8 infection. Its plasmacytic subtype, iMCD-idiopathic plasmacytic lymphadenopathy (iMCD-IPL), presents clinically with diffuse lymphadenopathy and an acute-phase reaction characterized by polyclonal hypergammaglobulinaemia (frequently with high IgG4 levels), high C-reactive protein levels and thrombocytosis. Histologically, iMCD-IPL very frequently shows nodal infiltration by IgG4$^+$ plasma cells and can mimic IgG4-RD lymphadenopathy[6].

Systemic vasculitides and other immune-mediated diseases. Large-vessel vasculitis (LVV) syndromes, namely GCA and Takayasu arteritis, share with IgG4-RD tropism for large arteries (Table 1). Unlike IgG4-RD, GCA usually has an abrupt presentation with cranial symptoms and sudden visual loss, and requires urgent management. However, a subset of individuals with GCA that have predominant large-vessel (aorta and epi-aortic arteries) involvement and systemic symptoms is well recognized[127]. If temporal artery biopsy is not diagnostic, as often occurs with the large-vessel phenotype of GCA, magnetic resonance angiography, CT angiography and FDG-PET are crucial in the differentiation between GCA and IgG4-RD, with GCA showing more intense and diffuse vascular involvement and a higher frequency of carotid, subclavian and axillary artery involvement than IgG4-RD[128]. Interestingly, IgG4-RD can also involve the temporal arteries, although in most cases it is peri-arteritis and not transmural arteritis, as is commonly observed in GCA[129].

Takayasu arteritis is another LVV syndrome that affects younger individuals. It usually involves the thoracic aorta and the epi-aortic arteries, but also other vessels including the abdominal aorta and its branches. The onset of Takayasu arteritis is usually insidious and therefore similar to that of IgG4-RD; unlike IgG4-RD, however, it commonly causes severe stenosis of the large vessels, especially the epi-aortic and renal arteries[130]. Takayasu arteritis should be considered in patients with suspected IgG4-RD, especially when they have isolated peri-aortitis of the thoracic and/or abdominal aorta[13]. Ureteral and/or inferior vena-cava encasement by abdominal peri-aortitis distinguishes between IgG4-RD and LVV[11].

Small-vessel vasculitides, particularly granulomatous forms of ANCA-associated vasculitis such as granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) can also mimic some manifestations of IgG4-RD. Notably, both syndromes involve increased serum levels of IgG4 in a remarkable proportion of cases (~80% of patients with active EGPA and ~30% with active GPA)[64]. Although differentiating IgG4-RD from EGPA might be more straightforward, as EGPA is hallmarked by marked eosinophilia, onset in adult years, severe asthma and nasal polyposis[131], GPA has a broader overlap with IgG4-RD; GPA can indeed involve the orbit, pachymeninges and pre-vertebral areas and occasionally cause peri-aortitis or mediastinitis[132] (Table 1). However, GPA usually has a faster course than IgG4-RD, with aggressive manifestations such as rapidly progressive glomerulonephritis, alveolar haemorrhage or sensorimotor peripheral neuropathy[132]. ANCA positivity is generally considered an exclusion criterion for the classification of a disease as IgG4-RD. However, it must also be emphasized that, despite their profound histological and pathophysiological differences, ANCA-associated vasculitides and IgG4-RD might coexist[70,133]. The exact nosology of these cases remains to be determined but it is important to be aware that patients with such composite phenotypes can be encountered in clinical practice.

Other granulomatous disorders, such as sarcoidosis (Table 1), can also overlap with systemic IgG4-RD manifestations, such as lymphadenopathy, lung involvement, tubulo-interstitial nephritis and orbital lesions[98]. Histology is usually essential for the differential diagnosis. Serum levels of chitotriosidase and angiotensin-converting enzyme can help in the differential diagnosis, being elevated in most patients with active sarcoidosis[134], but their specificity is low and they have not been tested in IgG4-RD. IgG4-RD has also been described, although anecdotally, in patients with a previous diagnosis of sarcoidosis[72].

Finally, other immune-mediated or haematological conditions (such as Sjögren disease, amyloidosis and hypereosinophilic syndrome) must be considered in the differential diagnosis, mainly because they can also be systemic and the sites they affect are shared with IgG4-RD[62]. However, the diagnostic approaches to these conditions are usually well defined and IgG4 responses are generally weak.

Histopathology

IgG4-RD has key histopathological features that are quite uniformly present in all affected organs: dense lymphoplasmacytic infiltrates

comprising T and B cells and plasma cells, often forming germinal centres, along with scattered eosinophils; fibrosis, usually with a storiform appearance; and phlebitis, which may or may not be obliterative. Hyaline rings surrounding small arteries or capillaries and peri-vascular fibrosis of medium-sized and large arteries is also common[135] (Fig. 1). Histopathological features considered to be against a diagnosis of IgG4-RD include granulomas, necrosis, neutrophil-dominant inflammation and, obviously, lesions compatible with infections or malignancies[65]. Immunostaining for IgG4 and IgG is mandatory; a ratio of $IgG4^+$ to IgG^+ plasma cells of >40% is considered suggestive of IgG4-RD, although it is neither sensitive nor specific, and can vary from organ to organ[135].

Histiocytoses mimic IgG4-RD because of their clinical and histopathological aspects and their tendency to form neoplasms of various sizes in a great variety of organs. Similar to IgG4-RD, in which the presence of $IgG4^+$ plasma cells is key to the diagnosis, histiocytoses are classified on the basis of a particular cell having a pivotal role in the composition of the lesion. And just like in IgG4-RD, the lesional cells of the histiocytoses represent only a small proportion of the total number of cells present in the lesions, and are surrounded and sometimes overshadowed by a non-specific, inflammatory mononuclear cell infiltrate[136,137]. For these reasons these entities present a diagnostic challenge for the pathologist. Especially with biopsy-obtained specimens, via which only a small sample of the lesion is obtained, the first impression is that of a non-specific inflammatory lesion. In contrast to IgG4-RD, the lesional cells in histiocytoses are considered to be variants of the commonly occurring histiocytes due to mutations of genes involved in the MAP kinase cell-signalling pathway. Whereas histiocytoses are characterized by positivity for the histiocyte-macrophage marker CD68, the lesional cells can be identified with additional immunohistochemistry testing, mainly for S100 and CD1a expression: ECD involves $CD1a^-$ $S100^{+/-}$ histiocytes, RDD mainly $CD1a^-$ $S100^+$ cells and Langerhans cell histiocytosis $CD1a^+$ $S\text{-}100^+$ cells[137] (Fig. 5).

Overlapping histological features between ECD and IgG4-RD include fibrosis, which sometimes has a storiform pattern and surrounds small vessels, and chronic lymphoplasmacytic infiltrates (Fig. 5). When detected, foamy histiocytes and multinucleated Touton giant cells indicate ECD. The histopathological differentiation between RDD and IgG4-RD can also be challenging: hallmark features of RDD such as emperipolesis might be absent in RDD biopsy-obtained specimens; similarly, storiform fibrosis and obliterative phlebitis are rare in IgG4-RD lymphadenopathy. As stated above, $IgG4^+$ plasma cells can be abundant in RDD[116]. For both ECD and RDD, molecular analysis of the lesional tissue can suggest the diagnosis of histiocytosis if disease-related somatic mutations (for example, in *BRAF*, *NRAS*, *KRAS* or *MAP2K1*) are detected[120,123].

iMCD-IPL also poses histopathological challenges. Both iMCD-IPL and IgG4-RD are marked by prominent $IgG4^+$ responses in the lymph nodes. Histologically, the background of iMCD-IPL is often different from that of IgG4-RD lymphadenopathy, with hyperplastic germinal centres and sheet-like proliferation of mature plasma cells in expanded interfollicular areas[6].

Histological examination is crucial in the differentiation between IgG4-RD and granulomatous disorders such as sarcoidosis, GPA or EGPA, as the demonstration of granulomatous lesions or, in the case of vasculitic syndromes, fibrinoid necrosis are strong arguments against IgG4-RD[135].

The role of imaging and serological findings

Radiological assessment is also important for the diagnosis and staging of IgG4-RD, is guided by clinical manifestations and differs on the basis of the organs involved. Ultrasonography, CT and MRI all contribute to the assessment of most disease manifestations. In whole-body imaging, an important role is also played by ^{18}F-FDG-PET, which detects metabolically active lesions[138,139] (Fig. 2). ^{18}F-FDG-PET could also have prognostic relevance for specific disease manifestations (for example, retroperitoneal fibrosis), as ^{18}F-FDG-avid lesions seem to be more sensitive to immunosuppressive therapies than ^{18}F-FDG-negative lesions[15,140]. Whole-body CT or MRI and ^{18}F-FDG-PET should be performed in all patients for a thorough initial assessment, whereas during follow-up, CT and MRI should focus only on the affected sites (for example, brain MRI for cerebral or meningeal lesions, and high-resolution chest CT for lung or pleural lesions); ultrasonography can be a reliable, non-invasive and cheap technique for monitoring complications such as hydronephrosis due to retroperitoneal fibrosis. The optimal imaging strategy, however, varies from patient to patient.

Among laboratory parameters, a high serum level of IgG4 is the most distinctive laboratory finding of IgG4-RD. However, as reported above, an increase in serum IgG4 level can also be found in a wide spectrum of inflammatory, allergic, infectious and proliferative disorders[5,141,142]. The specificity of IgG4 increases when its levels are more than twofold the upper limit of normal, and is high with levels more than fivefold the upper limit of normal. Serum IgG4 levels swiftly decline after glucocorticoid and/or immunosuppressive therapy; high levels at baseline are generally associated with multi-system involvement[5], although the disease phenotype also matters[24] (Supplementary Table 1). Other serological markers that correlate with disease extent and activity include serum levels of IgG1, IgE and complement; a reduction in serum levels of C3 and C4 is associated with multisystem disease and particularly with lymph-node, pulmonary, renal and pancreato-biliary involvement[143].

Treatment

General principles of treatment

Given the slowly progressive course of IgG4-RD, urgent treatment is seldom required, with the exception of specific situations that might necessitate interventional procedures (for example, ureteral or biliary stent placement for the treatment of ureteral obstruction or biliary tract stenosis, respectively) (Fig. 6). Prompt treatment is needed for symptomatic patients and for asymptomatic patients with evidence of progressive disease in vital organs. Individuals with asymptomatic, limited disease warrant careful monitoring[144]. Current therapies are aimed at curbing the inflammatory process, eventually preventing tissue fibrosis. Glucocorticoids are the mainstay of therapy. Nevertheless, the disease frequently relapses, and long-term glucocorticoid maintenance is associated with severe adverse effects, especially considering that IgG4-RD usually affects elderly individuals. Thus, interest is growing in glucocorticoid-sparing agents. The overall treatment approach should take into account the chronic–relapsing course of the disease, comorbidities and potential treatment-related adverse effects. Courses of glucocorticoids of 9–12 months are usually used; whether glucocorticoids can be tapered to withdrawal or maintained at low doses is debated. The introduction of B cell-targeting therapies will most likely obviate the long-term use of glucocorticoids.

Glucocorticoids and glucocorticoid-sparing agents

Medium-to-high-dose glucocorticoids (~0.6 mg/kg per day of prednisone or equivalent) are recommended as first-line therapy for IgG4-RD if there are no contraindications, although the choice of this initial dose is based mainly on expert opinion (Fig. 6). A significant

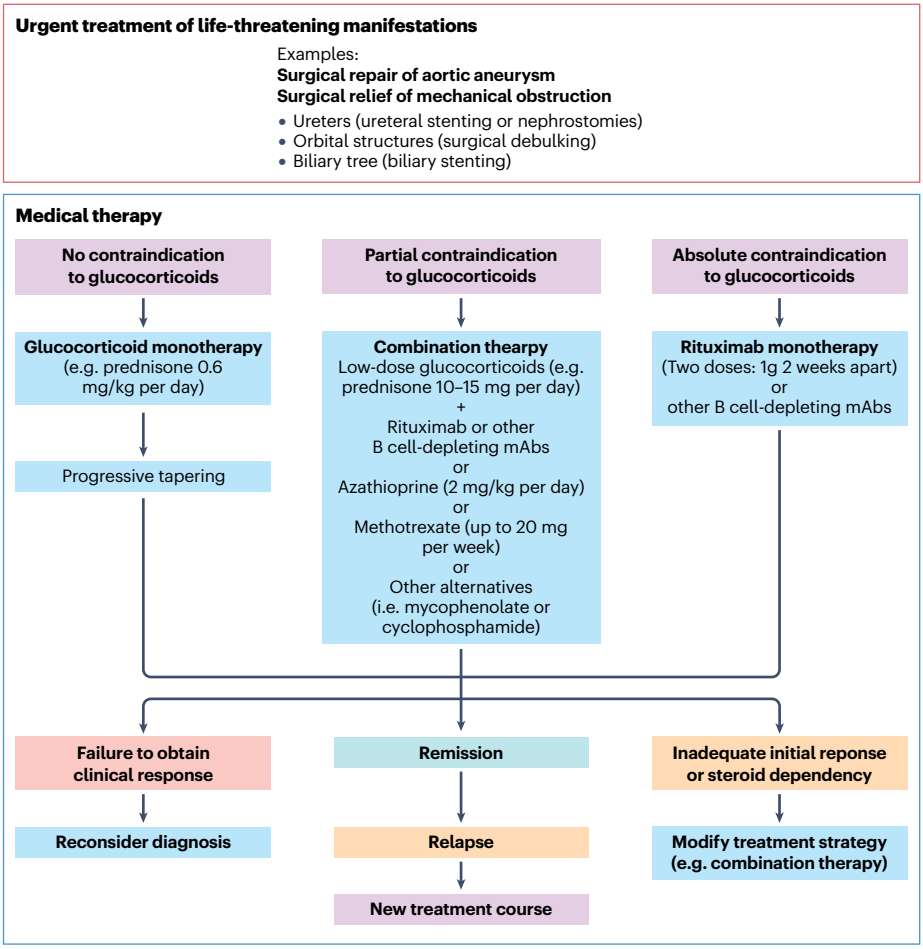

Fig. 6 | Treatment algorithm for IgG4-related disease. The flowchart provides a structured approach to the treatment of IgG4-related disease, guiding therapeutic decisions on the basis of clinical presentation and response to therapy. Initial treatment depends on the urgency of the condition, which might require prompt surgical intervention, and on contraindications to glucocorticoid use. Patients without contraindications to glucocorticoids typically receive glucocorticoid monotherapy, whereas those with partial or absolute contraindications are managed with steroid-sparing agents or B cell-depleting monoclonal antibodies (mAbs). In cases of inadequate response, relapse, or steroid dependency, treatment modification is recommended.

improvement in symptoms is usually observed within days to weeks of the initiation of glucocorticoid therapy, whereas the reduction or normalization of radiological and serological findings could take weeks to months. Lack of response to glucocorticoids is an exclusion criterion for the classification of IgG4-RD according to the ACR–EULAR criteria[65] (Fig. 4), which underscores the importance of glucocorticoid sensitivity in IgG4-RD. Both retrospective and prospective studies report response rates to glucocorticoid that exceed 85%; refractoriness to glucocorticoids, which therefore occurs in <15% of the patients, is thought to be attributable to predominantly fibrotic lesions. Glucocorticoids are also effective in reducing relapse rates when used as maintenance therapy[145,146]. In a randomized controlled trial, prednisone was superior to tamoxifen (which was initially thought to be a valid alternative to glucocorticoids because of its presumed immunomodulatory and antifibrotic effects) for the maintenance of remission in patients with idiopathic retroperitoneal fibrosis[147]. With the aim of limiting the cumulative dose of glucocorticoids, several traditional immunosuppressants (such as azathioprine and methotrexate) have been investigated for the treatment of IgG4-RD. Evidence comes from retrospective studies and proof of their efficacy in inducing and maintaining remission is limited[148–150]. Nonetheless, observational studies have reported that the addition of other steroid-sparing agents (cyclophosphamide and mycophenolate mofetil) is associated with a lower relapse rate when compared with glucocorticoid monotherapy[151].

Emerging therapies

B cell-targeting agents. Since the publication of a first case report in 2008 (ref. 152), retrospective and prospective studies have demonstrated that rituximab and other anti-CD20 monoclonal antibodies can induce remission in up to 80% of cases of IgG4-RD. Data from a meta-analysis indicate a lower relapse rate following such treatments when compared with other immunosuppressants[153]. The mounting evidence regarding the pathogenic role of B cells in IgG4-RD strengthens the rationale for the use of anti-CD20 and other B cell-targeting agents.

Rituximab is frequently used in combination with glucocorticoids as first-line treatment, especially in patients with multisystemic disease and/or vital organ involvement and in patients who cannot tolerate medium-to-high doses of glucocorticoids because of comorbidities (such as diabetes mellitus, obesity or depression) (Fig. 6). Patients who have an inadequate response to glucocorticoids, who relapse after glucocorticoid-induced remission or who cannot satisfactorily reduce their glucocorticoid dose are also commonly prescribed rituximab. Finally, rituximab can also be used as monotherapy for remission induction in patients with absolute contraindications to glucocorticoids, and is a valid option for maintenance therapy as well[154–156]. For remission induction, rituximab is commonly used at a dose of 1 g intravenously every 15 days for a total of two doses, whereas maintenance regimens and dosing strategies are heterogeneous; observational studies demonstrated that systematic rituximab infusions can improve relapse-free

survival[154]. Despite its recognized efficacy in IgG4-RD, rituximab has not been tested in randomized controlled trials and is used off label.

The role of serum levels of IgG4 in predicting response to rituximab or other therapies is controversial. For at least some manifestations (for example, retroperitoneal fibrosis) rituximab is also effective in patients with no elevation in serum IgG4 levels or histological evidence of IgG4$^+$ plasma-cell infiltration[5,157].

Beyond rituximab, the most promising drugs currently under investigation are inebilizumab and obexelimab. Inebilizumab, a B cell-depleting anti-CD19 monoclonal antibody, has been evaluated in MITIGATE, a phase III randomized placebo-controlled trial that enrolled adults who were receiving glucocorticoid treatment for a current IgG4-RD flare[158]. Inebilizumab (at a dose of 300 mg) or placebo was administered by intravenous infusion on days 1 and 15 and at week 26 and identical glucocorticoid tapers were used in both treatment groups (with the aim of withdrawal by week 8). The results, published in late 2024, indicate that the primary end point (time to first flare) was met: inebilizumab reduced the risk of IgG4-RD flare by 87% compared with placebo over 52 weeks. Serious adverse events during the treatment period were seen in 18% and 9% of the patients who received inebilizumab and placebo, respectively[158].

Obexelimab is a humanized monoclonal antibody that ligates CD19 with its Fab portion, whereas its Fc portion is engineered to engage the inhibitory FcγRIIb receptor. The co-ligation of CD19 and FcγRIIb leads to inhibition of B cells without inducing B cell depletion. Encouraging results from a phase II open-label study[159] led to a phase III randomized placebo-controlled trial, which is currently enrolling (NCT04540497).

Other B cell-targeting drugs currently under investigation as potential treatments for IgG4-RD include the Bruton tyrosine kinase inhibitors rilzabrutinib (NCT04520451) and zanubrutinib (NCT04602598); telitacicept, a recombinant fusion protein comprising the extra-cellular domain of T cell activator and calcium-modulating ligand interactor, and capable of neutralizing both BAFF and APRIL[160]; and belimumab (NCT04660565), a recombinant monoclonal antibody against soluble BAFF, the levels of which are increased in active IgG4-RD[161].

T cell-targeting agents. T cell activation also represents a promising target in IgG4-RD. Abatacept is a synthetic analogue of cytotoxic T lymphocyte antigen 4 (CTLA4) that binds CD80–CD86 and prevents T cell activation by competing with the costimulatory molecule CD28 expressed by T cells. In a prospective open-label study that included ten patients with active IgG4-RD (seven of whom were treated with abatacept alone), abatacept demonstrated efficacy in five patients[162]. The monoclonal antibody elotuzumab, which targets SLAMF7, was investigated in a prospective trial that was terminated early because of a lack of efficacy (NCT04918147).

Cytokine-targeting agents. Levels of several cytokines correlate with IgG4-RD activity and their expression is enhanced in affected tissues; thus, these cytokines represent potential therapeutic targets. Eosinophils are frequently observed in IgG4-RD lesions and blood concentrations of these cells are increased in one-third of cases of IgG4-RD; however, the use of mepolizumab or benralizumab, which target the IL-5–IL-5 receptor axis, thus hampering the maturation, activation and survival of eosinophils, proved ineffective[163]. IL-4 and IL-13 were both described to be involved in IgG4-RD and the development of tissue fibrosis; nevertheless, blocking the IL-4–IL-13 receptor pathway with dupilumab in IgG4-RD led to conflicting results[164,165]. Janus kinase (JAK) inhibitors represent a promising alternative: tofacitinib proved effective in inducing either complete or partial responses in two patients with IgG4-RD and two patients with idiopathic retroperitoneal fibrosis[166]. Two trials of JAK inhibitors for the treatment of IgG4-RD are ongoing, investigating tofacitinib (NCT05625581) and baricitinib (NCT05781516), respectively.

Conclusions

IgG4-RD is a complex and multifaceted fibro-inflammatory disease and its clinical phenotype ranges from organ-limited to disseminated multisystemic forms. The lack of disease-specific biomarkers and diagnostic criteria often pose challenges for the diagnostic approach. After infections and malignancies have been ruled out, a number of systemic conditions, mainly histiocytoses, vasculitis, granulomatous and lymphoproliferative diseases, must be considered in the differential diagnosis, as their clinical and histological presentations can overlap with that of IgG4-RD and also because they might harbour pronounced IgG4 responses. The spectrum of IgG4-RD also includes forms with mild IgG4$^+$ plasma-cell infiltration and normal serum levels of IgG4, the nosology of which is still uncertain.

Glucocorticoids and B cell-depleting agents induce clinical responses in the vast majority of cases of IgG4-RD. However, the most appropriate remission-induction and remission-maintenance strategies still need to be established. Advances in the comprehension of the pathogenesis of IgG4-RD have prompted the development of novel therapies, mainly targeting B cells, T cells and cytokines, which are being tested in clinical trials. Future areas of scientific research should explore diagnostic biomarkers, disease-specific and organ-specific prognostic factors, and cost-effective treatment strategies, the development of which requires the involvement of patients and the analysis of patient-reported outcomes.

Published online: 7 April 2025

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Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41584-025-01240-x.

Peer review information *Nature Reviews Rheumatology* thanks Fleur Cohen-Aubart, Yoshito Nishimura and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.