IgG4-Related Disease

Mimickers and Diagnostic Pitfalls

Eduardo Martín-Nares, MD, MSc, Gabriela Hernández-Molina, MD, MSc,**
Diego Federico Baenas, MD,† and Sergio Paira, MD‡

Background: The tendency of IgG4-related disease (IgG4-RD) to form pseudotumors, as well as its multisystemic nature, makes it the perfect mimicker of many conditions. Moreover, some clinical, serological, radiological, or histological features of the disease might be shared with some mimickers.

Recently, 4 clinical phenotypes have been identified, and patients grouped in each phenotype have distinctive demographic, clinical, and serological features and outcomes, and, as expected, for each phenotype, a set of differential diagnoses should be considered.

Summary of the Literature: The main differential diagnoses for the pancreato-hepato-biliary phenotype are pancreatic adenocarcinoma and cholangiocarcinoma. Other differential diagnoses include type 2 autoimmune pancreatitis and primary sclerosing cholangitis. In patients with retroperitoneal/aortic phenotype, inflammatory conditions such as idiopathic retroperitoneal fibrosis and large vessel vasculitides should be ruled out, and most of the time, a biopsy will be needed to exclude malignancies. In head and neck limited phenotype, autoimmune conditions (eg, granulomatosis with polyangiitis, Graves orbitopathy, sarcoidosis), malignancies, and histiocytosis should be ruled out, whereas the main differential diagnoses of the Mikulicz/systemic phenotype are Sjögren syndrome, granulomatosis with polyangiitis, and multicentric Castleman disease.

Conclusions: Approaching a patient with probable IgG4-RD through a clinical phenotype framework will ease the diagnostic algorithm and facilitate the prompt recognition of the disease. There are certain clinical, serological, radiological, and histological features in each clinical phenotype that, if present, increase the likelihood that a patient may have IgG4-RD instead of the mimicker condition. Those clues that point toward IgG4-RD diagnosis should be actively sought in the workup of patients.

Key Words: IgG4-related disease, clinical phenotypes, differential diagnosis, mimickers

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IgG4-related disease (IgG4-RD) is a fibroinflammatory disease characterized by mass-forming lesions and pseudotumors, high serum IgG4 levels, and characteristic histological features, namely, lymphoplasmacytic infiltrate, fibrosis arranged in a storiform pattern, obliterative phlebitis, and IgG4+ plasma cells.[1,2] The recognition of IgG4-RD as a unified entity happened only this century when the different manifestations of the disease were linked together by similar histological findings across organs and high serum IgG4 levels.[1–3]

IgG4-RD can affect practically every organ or anatomic region with a tendency to involve lacrimal and major salivary glands, orbital structures, pancreas, biliary tract, kidney, and retroperitoneum.[1,2] The tendency of IgG4-RD to form pseudotumors and to produce the thickening of tubular organs and its multisystemic nature makes it the perfect mimicker of many inflammatory, neoplastic, hematological, and infectious conditions, and many patients have a considerable delay in diagnosis of the disease, leading to permanent damage.[4–6] Moreover, none of the clinical, serological, radiological, or histological features of the disease is specific enough for the diagnosis of IgG4-RD, and some features might be shared with some mimickers.

Thus, early recognition is of paramount importance, and physicians of all specialties must recognize the clinical presentation and the differential diagnoses of IgG4-RD.

Recently, 4 clinical phenotypes have been identified.[4] These phenotypes are pancreato-hepato-biliary, retroperitoneal fibrosis (RPF) with or without aortitis, head and neck limited disease, and classic Mikulicz syndrome with systemic involvement.[4,6,7] Patients grouped in each phenotype share distinctive demographic, clinical, and serological features and outcomes.[4,6] As expected, each phenotype has a set of differential diagnoses (Table).

Approaching a patient with a suspected diagnosis of IgG4-RD through a clinical phenotype framework is expected to improve the recognition of IgG4-RD. In this review, we will dissect the differential diagnosis of IgG4-RD according to each of the clinical phenotypes, and we will provide clues that point toward or against its diagnosis.

PANCREATO-HEPATO-BILIARY PHENOTYPE

The pancreato-hepato-biliary phenotype refers to involvement of pancreas, biliary tract, gallbladder, and liver, and its prevalence among IgG4-RD cohorts has a range of 13% to 45%.[4,6–8] Patients belonging to this phenotype are usually male, older than 60 years, have high IgG4 and IgE levels, and are diagnosed faster than other phenotypes.[4,6–8]

Type 1 autoimmune pancreatitis (AIP) is among the most frequent manifestations of IgG4-RD.[4,9] The diffuse pattern (enlarged "sausage-shaped pancreas," surrounded by a low-enhancing capsule-like rim, and the loss of lobulations) is the most common (Fig. 1A). Other patterns include focal and multifocal pseudotumors.[10] It can present insidiously or subacutely with painless obstructive jaundice, weight loss, or abdominal pain.[11] In advanced cases, type 3c diabetes may appear due to endocrine insufficiency and steatorrhea due to malabsorption.[11]

Because of the clinical presentation of obstructive jaundice and weight loss in an elderly patient, type 1 AIP is usually misdiagnosed as pancreatic ductal adenocarcinoma (PDAC) (Table).[5,11] Clinical clues that point toward IgG4-RD are the presence of other organ involvement and atopic manifestations, and the finding of high

From the *Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; †Servicio de Reumatología, Hospital Privado Universitario de Córdoba, Córdoba; and ‡Sección de Reumatología, Hospital José María Cullen, Santa Fe, Argentina.

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Correspondence: Eduardo Martín-Nares, MD, MSc, Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vasco de Quiroga No. 15, Col. Sección XVI, Tlalpan, 14080, Mexico City, Mexico. E-mail: eduardomartinnares@gmail.com.

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TABLE. Differential Diagnosis of IgG4-RD According to Clinical Phenotype

Pancreato-Hepato-Biliary	Retroperitoneal and Aortic
• Type 2 AIP • Follicular pancreatitis • Primary sclerosing cholangitis • Secondary sclerosing cholangitis (eg, HIV cholangiopathy, Caroli disease, biliary trauma) • Pancreatic adenocarcinoma • Neuroendocrine tumors • Cholangiocarcinoma • Gallbladder carcinoma • Hepatocellular carcinoma	• RPF: ○ Idiopathic RPF ○ Drug-induced RPF (eg, methysergide, ergotamine, methyldopa) ○ Anti–PD1-associated RPF ○ Radiotherapy-induced RPF ○ Retroperitoneal sarcoma ○ Primary retroperitoneal lymphoma ○ Erdheim-Chester disease ○ Tuberculosis ○ Histoplasmosis • Aortitis: ○ Isolated aortitis ○ Large vessel vasculitides: TA, GCA ○ Aortitis associated with systemic autoimmune diseases: RA, AS, Cogan syndrome, RP, AAV, Behçet disease ○ Atherosclerotic aneurysms ○ Infectious aortitides: syphilis, salmonella
Head and Neck Limited	**Mikulicz and Systemic**
• Sjögren's syndrome • AAV (GPA, EGPA) • Sarcoidosis • Graves' orbitopathy • Idiopathic orbital inflammation • Idiopathic hypertrophic pachymeningitis • Head and neck cancer • Lymphoma • Adult xanthogranulomatous disease of the orbit • Erdheim-Chester disease • Rosai-Dorfman disease • Inflammatory myofibroblastic tumor	• Sjögren's syndrome • AAV (GPA, EGPA) • Systemic lupus erythematosus • Sarcoidosis • Idiopathic multicentric Castleman disease • Lymphoma • Erdheim-Chester disease • Disseminated Rosai-Dorfman disease • Hypereosinophilic syndrome

AS, ankylosing spondylitis; EGPA, eosinophilic granulomatosis with polyangiitis; GCA, giant cell arteritis; HIV, human immunodeficiency virus; RA, rheumatoid arthritis; RP, relapsing polychondritis.

serum IgE and hypereosinophilia that can appear in up to 40% of patients.[11] There are radiological features that help distinguish these 2 diseases.[11,12] For example, magnetic resonance (MR) cholangiopancreatography may detect stricture of the pancreatic portion of the common bile duct with thickening and enhancement, which signifies associated IgG4-related sclerosing cholangitis (IgG4-SC), whereas the penetrating duct sign or icicle sign (smooth narrowing of the upstream pancreatic duct) favors stricture by type 1 AIP.[12,13] Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}FDG PET/CT), besides showing the "sausage-shaped" pancreas with intense ^{18}FDG uptake (Fig. 1E), can also show systemic manifestations of IgG4-RD.[14]

Focal or multifocal involvement may be indistinguishable from PDAC in some clinical settings (Fig. 1F).[11,12] For this reason, an essential requirement is a strict correlation of extrapancreatic clinical manifestations, imaging patterns, elevated serum IgG4 levels, tumor markers such as CA19-9 (frequently negative in IgG4-RD), and histological findings.[11–13] A needle biopsy should be performed with a core needle (Figs. 1C–D) because a fine-needle is insufficient to show histological changes of IgG4-RD.[15,16] Samples can also be obtained laparoscopically. If the diagnosis remains unclear, and no histological material can be obtained from another organ, a therapeutic test with prednisone can be performed since, whereas type 1 AIP will respond to steroids, PDAC will not.[11,12]

Other differential diagnoses of pancreatic involvement are type 2 AIP, follicular pancreatitis, and neuroendocrine tumors.[17] Type 2 AIP or idiopathic duct centric pancreatitis may present in a similar fashion than type 1, but differences do exist. Type 2 AIP presents at a younger age (<50 years), most commonly with acute pancreatitis and focal features in imaging and is frequently associated with inflammatory bowel disease; furthermore, elevation of serum IgG4 and other organ involvement are not features of this type of AIP.[12,18]

Approximately 25% to 50% of AIP 1 cases are associated with hepatobiliary disease, which includes IgG4-SC and IgG4-related hepatopathy.[16] Cholangiogram-based classification of IgG4-SC includes 4 subtypes of presentations. Subtype 1 involving distal common bile duct stricture is the most frequent pattern and often accompanies AIP (Fig. 1B).[16] The main differential diagnoses of IgG4-SC are primary sclerosing cholangitis (PSC), secondary sclerosing cholangitis (e.g., human immunodeficiency virus cholangiopathy),and cholangiocarcinoma.[16] In particular, type 2 IgG4-SC resembles PSC. In the absence of a biopsy, clues that point toward PSC are age (<40 years), presence of pANCA, serum IgG4 <140 mg/dL, a beaded or pruned-tree appearance, and short band-like strictures at cholangiogram, association with IBD and absence of other organ involvement.[16]

A multidisciplinary approach that includes internists, rheumatologists, gastroenterologists, radiologists, and surgeons is critical to the correct diagnosis of pancreato-hepato-biliary IgG4-RD and to exclude neoplasms. In this way, pancreatectomies and other unnecessary surgeries can be avoided, thus reducing morbidity and mortality.[11]

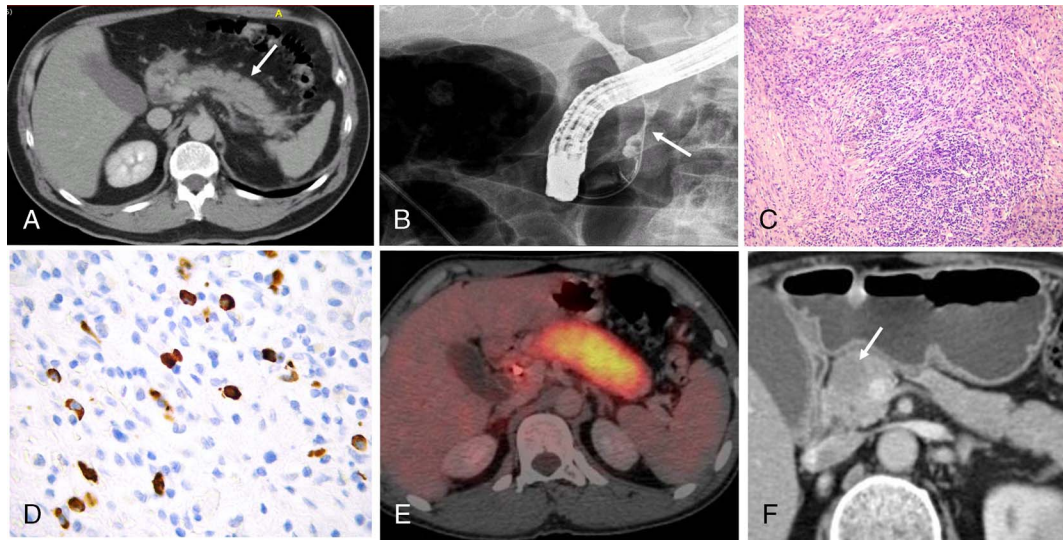

FIGURE 1. A 67-year-old man presented with abdominal pain, jaundice, and rhinosinusitis; (A) axial contrast-enhanced abdominal CT revealed a diffusely enlarged pancreas (arrow); swelling predominates in the head of the pancreas, and (B) cholangiogram showed distal common bile duct stricture (arrow); (C) pancreatic biopsy showed storiform fibrosis and lymphoplasmacytic infiltrate (hematoxylin-eosin, ×300), and (D) immunostaining revealed abundant IgG4+ plasma cells (×400). E, ^{18}FDG PET/CT from a 41-year-old patient with type 1 AIP showing sausage-shaped pancreas with intense ^{18}FDG uptake. F, Axial contrast-enhanced abdominal CT from a 69-year-old man showing a hypodense mass in the head of the pancreas diagnosed with biopsy as type 1 AIP. Color online-figure is available at http://www.jclinrheum.com.

RETROPERITONEAL FIBROSIS WITH OR WITHOUT AORTITIS PHENOTYPE

The prevalence of this phenotype has a range of 19% to 26% in different cohorts, being less frequent in the Latin American population (11.4%).[4,6–8]

In this phenotype, the aorta may be encased by the fibrous tissue arising from the adventitia ("periaortitis"), which includes RPF, or patients might have inflammation that involves predominantly the media and/or intima of the aorta, usually referred to as "aortitis."[19,20]

The main feature of RPF/periaortitis is chronic inflammation and fibrosis of retroperitoneal tissues. Compression of retroperitoneal veins and lymphatics may present with deep vein thrombosis and lower-limb edema, and ureteral obstruction leads to postrenal acute kidney injury.[21] Nowadays, it has been recognized that approximately 10% to 50% of idiopathic retroperitoneal fibrosis (IRPF) cases are indeed patients with IgG4-related retroperitoneal fibrosis (IgG4-RPF), being the abdominal aorta the most affected, specifically the infrarenal region and the iliac arteries.[21–23] Conversely, in the cases of aortitis, the thoracic aorta is involved twice as often as the abdominal aorta, affects approximately 8% of IgG4-RD patients, and represents 7% to 9% of noninfectious thoracic aortitis.[24,25]

Among the 4 IgG4-RD phenotypes, patients with RPF and/or aorta involvement had the lowest serum IgG4 and IgE concentrations, but the highest C-reactive protein (CRP) and erythrocyte sedimentation rate levels, and hypocomplementemia is rare.[4,26]

The diagnosis of IgG4-RD requires a multidisciplinary approach and truly represents a challenge for the clinician, as it requires an extensive exclusion of other causes (Table).[2,25]

Some clues that point toward IgG4-RPF are the presence of other organ involvement and allergic diseases.[4,26,27] Most of the studies have described that these patients also show a greater male predominance, even higher than in IRPF cases (4.8:1 vs 1.1:1); are older; with a longer interval between symptom onset and diagnosis; and have a higher incidence of hydronephrosis, postrenal acute kidney injury, and arterial hypertension when periaortic fibrosis is present, and although pain was associated with IRFP in one study, another one found a higher prevalence in IgG4-RPF.[26–30] Patients with IgG4-related aortitis also tend to be older, whereas thoracic aortitis in young patients should alert for Takayasu arteritis (TA), Behçet disease, syphilis, or ankylosing spondylitis.[23] Also, the presence of high IgG4 and IgE levels and hypereosinophilia favors the diagnosis of IgG4-RPF and/or aortitis. Histologically, IgG4-RPF and/or aortitis have a higher IgG4+ plasma cell count and IgG4/IgG ratio, obliterative phlebitis, and storiform fibrosis, as well as higher tissue eosinophils compared with idiopathic forms.[29,30] As opposed to this, IRPF cases tend to have rather hypocellular or hyaline fibrosis and variable mild lymphocytic inflammation without formation of lymphoid follicles in most cases.[31] The presence of granulomas or neutrophilic aggregates is against IgG4-RD and should lead the investigations to granulomatous aortitis such as giant cell arteritis and TA.[19,20]

On imaging, IgG4-RPF patients exhibit a nonbulky, single homogenous mass, lateral and anterior to the aorta, with neither aortic displacement or elevation nor muscle or bone infiltration, that causes medial deviation of the ureters with or without obstruction (Figs. 2A–C). It usually develops below the origin of renal arteries, rather than above this level (more common in malignancy). IgG4-RPF and IRPF cannot be distinguished solely on imaging features (Fig. 2D). By contrast, malignancies may show periaortic soft tissue infiltration with anterior displacement of the aorta (Fig. 2E), as well as infiltration of bone, muscles, and confluent lymphadenopathy.[31] On the other hand, the presence of perirenal fibrotic tissue, thickening of renal fascia and perinephric fat stranding (the hairy kidney sign), and concentric soft tissue encasing the aorta ("coated aorta") are findings highly specific for Erdheim-Chester disease (Fig. 2F).[32] Furthermore, it has been reported that an ^{18}FDG PET/CT might be helpful, as a lower FDG retroperitoneal intake is seen in lymphoma and metastases.[33] Finally, IgG4-related aortitis is radiologically characterized by severe wall thickening, but stenosis is not usually observed as in TA.[25] Even if a patient with suspected TA is young, if other inflammatory or tumefactive lesions are present, IgG4-RD should be ruled out.

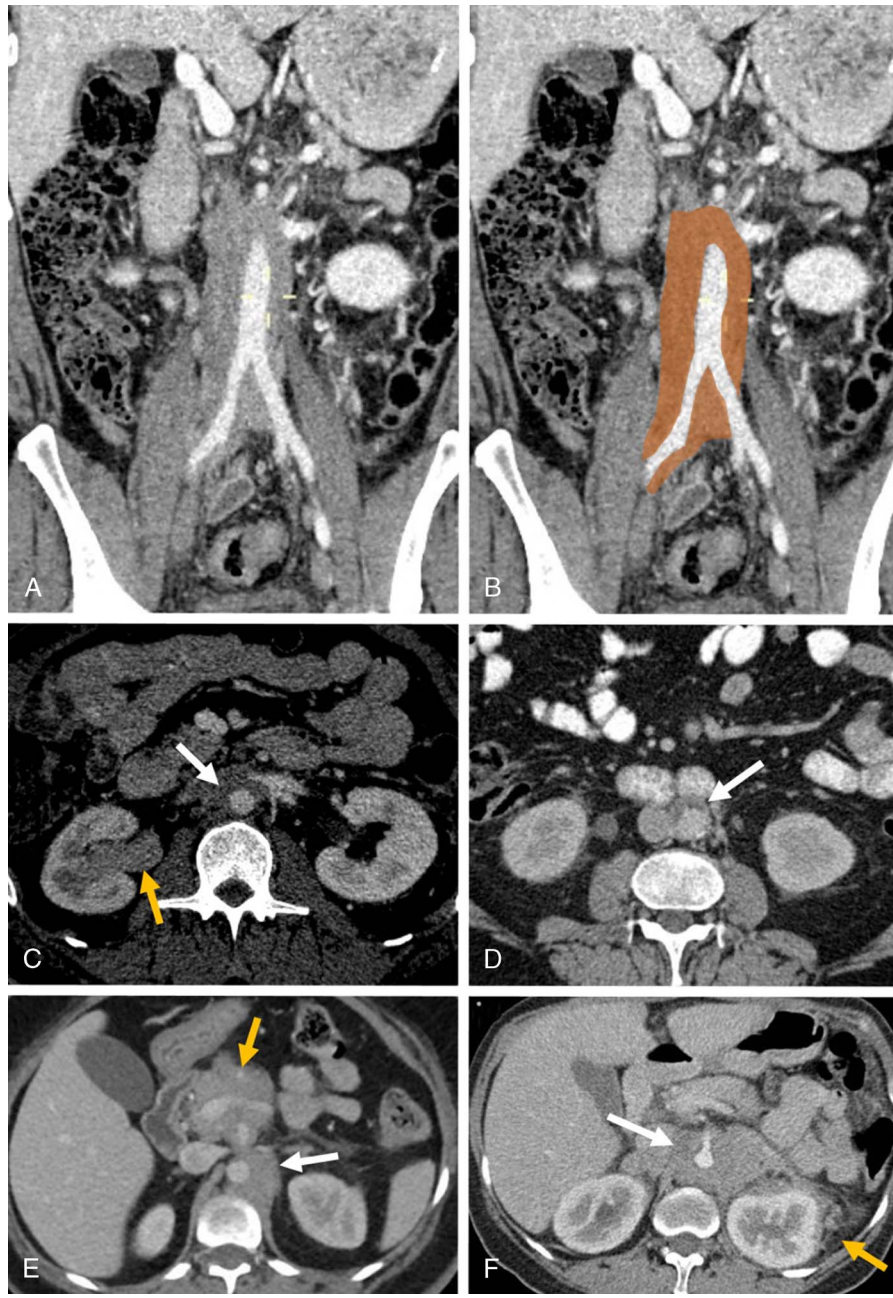

FIGURE 2. A and B, Contrast-enhanced coronal CT images showing retroperitoneal tissue adjacent to the infrarenal abdominal aorta and iliac arteries (orange shadow) in a 56-year-old man presenting with abdominal pain, weight loss, and elevation of inflammatory markers. C, Axial CT image from the same patient showing retroperitoneal tissue (arrow) that encases the abdominal aorta lateral and anteriorly and the right ureter, leading to pyelectasis (yellow arrow); serology and biopsy confirmed IgG4-RPF. C, Axial CT image showing retroperitoneal tissue (arrow) that encases the abdominal aorta lateral and anteriorly in a patient with IRPF. E, Contrast-enhanced axial CT image of the abdomen shows left para-aortic retroperitoneal tissue with anterior displacement of the aorta (white arrow) in a 54-year-old woman with follicular lymphoma; a mass at the mesenteric root is also shown (yellow arrow). F, Contrast-enhanced axial CT image of the abdomen shows a "coated aorta" appearance (white arrow) and left "hairy kidney" in a 46-year-old man with Erdheim-Chester disease. Color online-figure is available at http://www.jclinrheum.com.

HEAD AND NECK LIMITED PHENOTYPE

Head and neck limited phenotype refers to involvement usually limited to the head and neck anatomy including lacrimal and major salivary glands, orbital inflammation, pachymeninges, hypophysis, paranasal sinus, thyroid, and mastoid.[1,4] Incomplete Mikulicz syndrome and Mikulicz syndrome without systemic involvement are part of this clinical phenotype, and they may resemble the clinical presentation of Sjögren syndrome (SjS).[3]

The frequency of this phenotype has a range of 24% to 31%.[4,6–8] Younger age, female sex, and atopy history are more frequent in

this phenotype compared with others.[4,6–8,34] Juvenile-onset IgG4-RD patients present more frequently with this phenotype.[35,36] Clinical, serological, radiological, and histological correlation is of paramount importance to diagnose this phenotype due to the myriad of differential diagnoses (Table).[2,37,38]

This phenotype often presents with normal IgG4, normocomplementemia, and imaging findings are not specific enough.[7,8] Furthermore, many diseases in the differential may have high IgG4 serum levels.[9] Consequently, most of the time a biopsy is needed to reach a diagnosis. However, some imaging findings may suggest IgG4-RD.

IgG4-related ophthalmic disease (IgG4-ROD) may present with extraocular muscle and orbital fat involvement, and is usually misdiagnosed as Graves orbitopathy (GO).[39] Imaging features that indicate IgG4-RD by CT and MR are the combination of lacrimal gland and lateral rectus involvement (Fig. 3A) and when the lateral rectus is the most enlarged among all the rectus muscles (Fig. 3B).[39,40] Conversely, GO should be considered when there is the combination of orbital fat and inferior rectus involvement, when the inferior rectus is the most enlarged among all the rectus muscles and when there is optic nerve elongation and destruction of adjacent bone.[39] Tendons of the extraocular muscle are usually spared in both diseases.[39,40] Also, the presence of autoimmune thyroid disease and/or positive thyroid-stimulating immunoglobulin makes a GO diagnosis more likely.

Compared with orbital lymphoma, IgG4-ROD presents with regular rather than irregular lesion borders, presents more frequently with lacrimal gland involvement, and with bilateral and multiple lesions according to a CT study from Taiwan.[41] However, another study in German patients did not find any CT imaging differences between both diseases.[42]

An imaging finding highly suggestive of IgG4-ROD is the involvement of the trigeminal nerve branches, especially the infraorbital nerve (Fig. 3C), which has not been found in GO, orbital lymphoma, reactive lymphoid hyperplasia, idiopathic orbital inflammation, or adult xanthogranulomatous disease.[39,43–45] This is usually an asymptomatic finding.

IgG4-RD is among the most common etiologies of hypertrophic pachymeningitis (HP) (Figs. 3D–E).[46] IgG4-RD should be suspected in cases of asymptomatic or pauci-symptomatic HP.[47] A Japanese study suggested some clinical and serological features that may distinguish IgG4-related HP from mimickers such as idiopathic HP and ANCA-associated vasculitis (AAV). The presence of double vision and absence of otological symptoms, fever, and erythrocyte sedimentation rate elevation favored IgG4-RD diagnosis over AAV; however, IgG4-related HP behaved similarly to the idiopathic form.[46] In most of the cases, a biopsy will be required to attain a proper diagnosis (Fig. 3F).

Head and neck limited phenotype resembles the clinical presentation of granulomatosis with polyangiitis (GPA) in the head and neck. Both conditions may present with orbital, major salivary gland, paranasal sinus, mastoid, optic perineuritis, and HP, and no head-to-head study is available about imaging features that may help to differentiate between them. As such, it has been suggested that in limited GPA, especially when ANCA negative, IgG4-RD should be ruled out.[48] The presence of ANCA should orient to the diagnosis of GPA; however, the decision to diagnose a case as GPA in the absence of histological confirmation should be made if PR3-ANCA or MPO-ANCA are present, as ANCA by immunofluorescence are not rare in IgG4-RD.[49]

IgG4-RD may mimic non-Langerhans cell histiocytosis such as adult xanthogranulomatous disease of the orbit and Erdheim-Chester disease. Clinically, the histiocytosis present with eyelid xanthelasmas and radiologically with eyelid infiltration and patchy infiltrative lesions in the orbit. Although they might have prominent fibrosis and IgG4+ plasma cell infiltrate in tissue, the presence of

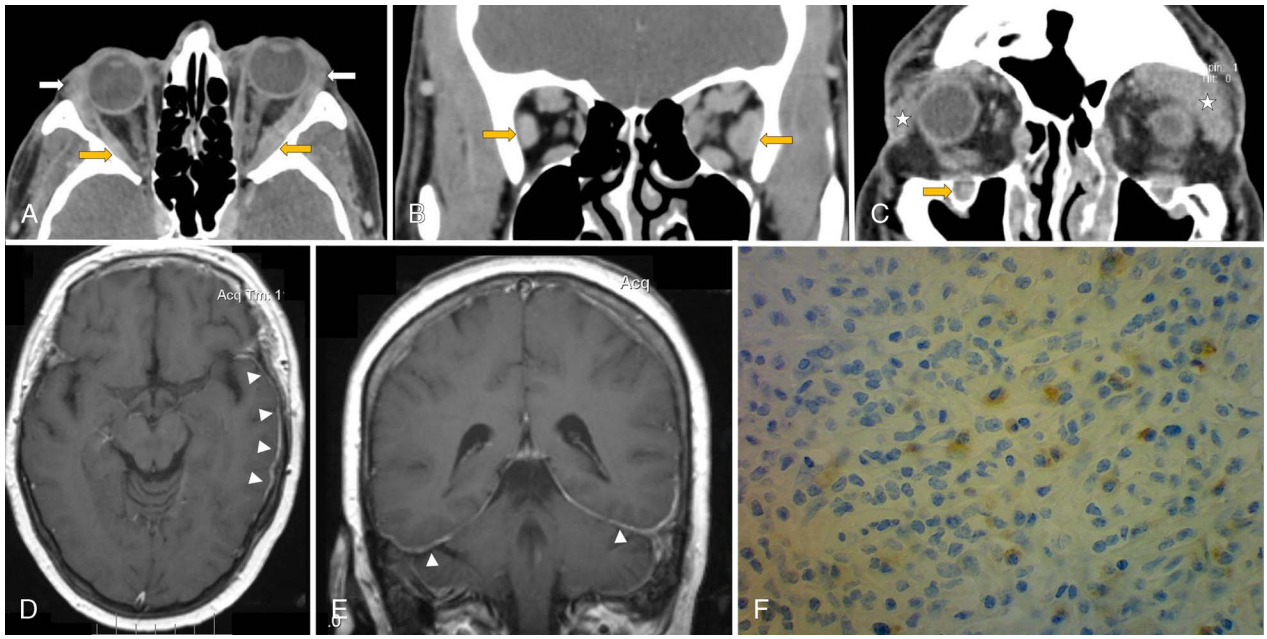

FIGURE 3. A, Axial CT showing bilateral lacrimal gland (white arrows) and lateral rectus enlargement (yellow arrows), more evident in the left eye causing proptosis in a 46-year-old man. B, Coronal CT image from the same patient shows superior, lateral, and inferior rectus enlargement bilaterally; the lateral rectus is the most enlarged among the rectus muscles (yellow arrow). C, Coronal CT image from 48-year-old patient with infraorbital nerve enlargement (yellow arrow) and bilateral lacrimal gland enlargement (stars). Axial (A) and coronal (B) contrast-enhanced MR imaging of the brain showing hypertrophic pachymeningitis in a 45-year-old woman hospitalized due to quadriplegia, visual alterations, and headache; (C) dural biopsy revealed >30 IgG4+ plasma cell/HPF with an IgG4/IgG ratio >40 (×400). Color online-figure is available at http://www.jclinrheum.com.

Touton giant cells, necrobiotic xanthogranuloma, and fat necrosis orients to their diagnosis.[45]

Rosai-Dorfman disease (RDD), another group of non-Langerhans cell histiocytosis, most commonly presents with bilateral painless cervical lymphadenopathy (classical or nodal RDD). The extranodal form may present with nasal cavity, orbit and salivary gland involvement, or with pachymeningitis.[50,51] Histologically, up to 40% of cases exhibit >10 IgG4+ plasma cell/HPF and varying degrees of fibrosis, termed IgG4-associated RDD.[50,51] As such, RDD in the head and neck region may mimic IgG4-RD. Features that point toward RDD are constitutional symptoms such a fever, night sweats, and weight loss; younger age; tissue IgG4/IgG ratio <40%; absence of storiform fibrosis, obliterative phlebitis, and eosinophils; and the presence of emperipolesis (erythrocytes, plasma cells, and lymphocytes engulfed by histiocytes) with S100+ histiocytes.[50,51]

MIKULICZ/SYSTEMIC PHENOTYPE

The Mikulicz/systemic phenotype refers to classic Mikulicz syndrome (involvement of 2 or more pairs of glands: lacrimal, parotid, submandibular, sublingual) with involvement of thoracic and/or abdominal organs. Sometimes only one pair of glands may be affected. It usually presents with different degrees of hypergammaglobulinemia and hypocomplementemia and has the highest serum IgG4 levels among clinical phenotypes.[1,4] The frequency of this phenotype has a range of 14% to 22% in different cohorts.[4,6–8]

The clinical presentation of major salivary and lacrimal gland enlargement with sicca symptoms and hypergammaglobulinemia resembles the clinical picture of SjS (Table).[5,38] In this sense, Mikulicz syndrome was considered a "less highly developed variant" of SjS before the recognition of IgG4-RD as a unified entity.[52]

Mikulicz/systemic phenotype is more common in men than in women in contrast to the striking overrepresentation of female patients in SjS.[3,4,6–8] Regarding clinical presentation, although both diseases may involve all pairs of glands, IgG4-RD more commonly presents with submandibular and lacrimal gland enlargement rather than parotid enlargement (Fig. 4A and E). The classic presentation of bilateral parotid gland enlargement of SjS is quite rare in IgG4-RD. In a cohort of 42 patients with IgG4-related sialadenitis, only 11.9% had this presentation.[53] Furthermore, while gland enlargement is usually persistent and painless in IgG4-RD, it is recurrent and painful in SjS.[3] Likewise, sicca symptoms and objective signs of lacrimal and salivary dysfunction are less pronounced or even absent in IgG4-RD.[3] Other clues in the head and neck region that should lead to the diagnosis of IgG4-RD are orbital inflammation and paranasal sinus involvement, which are very rare in SjS.[4,7,54]

Various imaging modalities have been evaluated to distinguish IgG4-RD from SjS. Changes in the submandibular glands by ultrasound, so-called reticular and nodal patterns, orient toward IgG4-RD (Fig. 4B).[55] ^{18}FDG PET/CT uptake tends to be higher in IgG4-RD. As opposed to this, imaging findings in the salivary glands characteristic of SjS are atrophy, dot-like calcifications on CT, and small multiple cystic areas on T2-weighted MR imaging (salt-and-pepper appearance).[55]

As the name of this phenotype implies, systemic involvement is always present, mainly in the form of pancreatic, lung, kidney, and lymph node involvement.[4,7] These organs may also be involved in SjS, leading to similar clinical scenarios; however, imaging findings may discriminate between both diseases. Although SjS may rarely cause acute pancreatitis and often overlaps with primary biliary cholangitis, the classic sausage-shaped pancreatic swelling, the characteristic imaging findings of IgG4-SC (Fig. 4D), and the absence of antimitochondrial antibodies help to differentiate it from IgG4-RD.[12,13,16,54] At lung level, IgG4-RD presents with a myriad of different imaging findings, being peribronchovascular (Fig. 4C), and septal thickening the most common; lungs cysts, however, are not reported in IgG4-RD and should lead the investigations to SjS.[56] In addition, although both diseases may cause

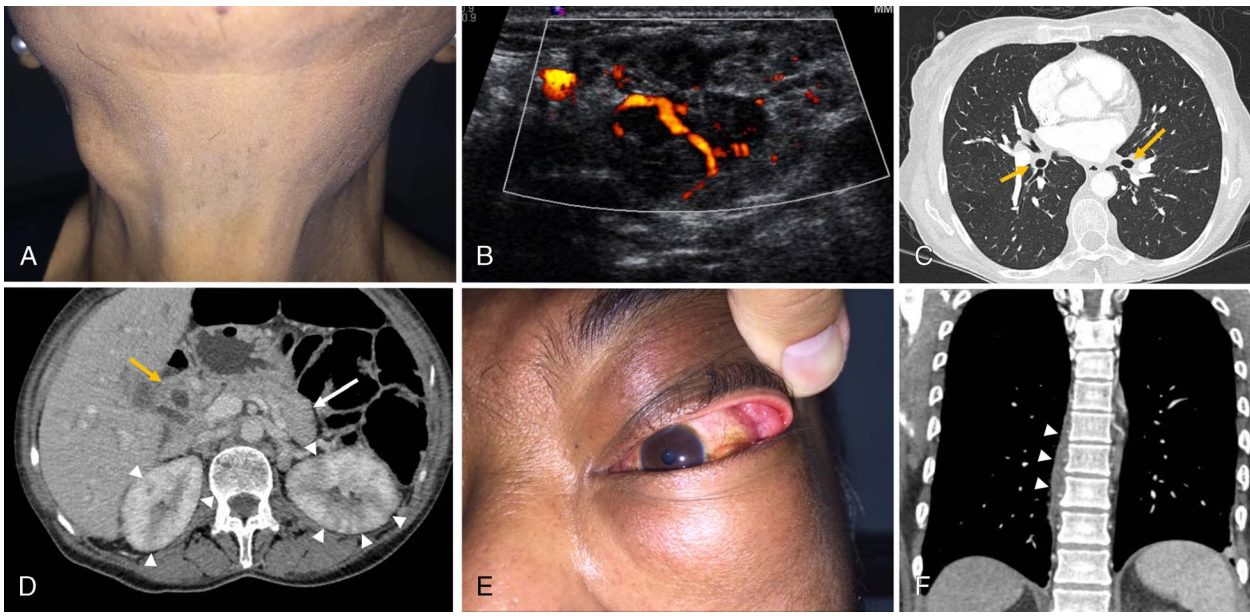

FIGURE 4. A 62-year-old woman presented with (A) bilateral submandibular gland enlargement; (B) left submandibular gland ultrasound showing reticular and nodal pattern; (C) axial thoracic CT showed peribronchovascular bundle thickening (yellow arrow) and (D) contrast-enhanced axial CT of the abdomen revealed an enlarged pancreas with loss of lobulations (white arrow), common bile duct dilation with concentric wall thickening with smooth lumen surface (yellow arrow), and multiple wedge-shaped, low-attenuation cortical lesions in both kidneys (arrowheads); she had hypocomplementemia, serum IgG4 levels were 7020 mg/dL, and pancreas and common bile duct biopsy corroborated IgG4-RD diagnosis. E, Left dacryoadenitis in a 42-year-old man. F, Coronal CT image showing a left paravertebral mass in a 60-year-old man. Color online-figure is available at http://www.jclinrheum.com.

tubulointerstitial nephritis, only IgG4-RD presents with typical imaging CT findings (Fig. 4D).[57] Paravertebral lesions (band-like soft tissue usually in the right side of the thoracic vertebrae 8–12) are strongly suggestive of IgG4-RD and typically present in multisystemic disease (Fig. 4F).[57–59]

Finally, regarding laboratory features, both diseases may present with hypergammaglobulinemia, hypocomplementemia, and positive rheumatoid factor and antinuclear antibodies, but the presence of high IgG4 and IgE levels and hypereosinophilia, and the absence of anti-Ro/SSA and anti-La/SSB antibodies, direct toward IgG4-RD.[3,4,38,57] Other biomarkers have been investigated in this setting with conflicting results. Serum soluble IL-2 receptor and immunoglobulin free light chains (sFLCs) were not helpful in distinguishing between both diseases, whereas Umeda et al found that higher levels of serum thymus and activation-regulated chemokine could discriminate between IgG4-RD and SjS.[60–62]

Other systemic inflammatory diseases that may mimic the Mikulicz/systemic phenotype are AAV, especially GPA.[2,48] Regarding clinical behavior, Kawashima et al[63] suggested that the presence of fever, ear/nose, lung, and kidney involvement and higher CRP was indicative of GPA, whereas lacrimal and salivary gland, retroperitoneum, and pancreas involvement was suggestive of IgG4-RD.[63] However, all those organs can be affected in both diseases, IgG4-RD may present with high CRP, and, in the authors' experience, patients starting with multisystemic involvement may present with intermittent low-grade fever.[7,57] A clue to GPA is the presence of vasculitic manifestations such as diffuse alveolar hemorrhage, rapidly progressive glomerulonephritis, peripheral neuropathy, and palpable purpura. In most cases, a biopsy will be needed to ascertain the correct diagnosis, and the presence of necrotizing vasculitis in tissue will help to establish an AAV diagnosis. The presence of ANCA should direct toward the diagnosis of AAV, although, as previously mentioned, PR3-ANCA and MPO-ANCA should be positive to make a correct diagnosis of AAV in the absence of histopathology confirmation, as ANCA by immunofluorescence may be positive in IgG4-RD, especially in the Mikulicz/systemic phenotype.[49]

In the same sense, sarcoidosis may present in a similar fashion to the Mikulicz/systemic phenotype, but the presence of musculoskeletal, skin, liver, and spleen involvement should lead to the former diagnosis as they are rare in IgG4-RD.[2,4] As in SjS, serum soluble IL-2 receptor and sFLC were not helpful in distinguishing between IgG4-RD and sarcoidosis.[62,64] Imaging tools to discriminate among these conditions have been investigated. In a study in Japanese patients, gallium-67 scintigraphy was useful in differentiating between both diseases showing uptake in mediastinal and supraclavicular lymph nodes, and muscle in patients with sarcoidosis, and in pancreas and submandibular glands in IgG4-RD.[65] Likewise, in a study using ^{18}FDG PET/CT, the IgG4-RD group showed higher incidence of FDG accumulation in the lacrimal glands, submandibular glands, pancreas, prostate, periurethral, and periarterial regions, and the sarcoidosis group in the supraclavicular and abdominal lymph nodes, muscles, and soft tissues.[66] Granuloma formation is exceptional in IgG4-RD, and its presence suggests the diagnosis of sarcoidosis.[15]

Idiopathic multicentric Castleman disease (iMCD) may also mimic systemic IgG4-RD both clinically and histologically, especially the plasma cell type. Clinically, findings suggestive of iMCD are the presence of fever, high CRP, IL-6, and IgA levels and the absence of orbital, salivary gland, and pancreatic involvement. At the histology level, findings compatible with iMCD are the presence of IgA positive cells, expression of IL-6 and hemosiderin deposition, and the absence of eosinophil infiltrate and obliterative phlebitis or arteritis in lymph nodes and other tissues such as the lung.[67–70]

CONCLUSIONS

The differential diagnosis of IgG4-RD is vast due to the diverse clinical manifestations of the disease. No single clinical, serological, radiological, or pathological feature is by itself specific enough to diagnose IgG4-RD. A correct diagnosis will require the integration and proper interpretation of all those findings. IgG4-RD needs a multidisciplinary approach formed by internists, rheumatologists, surgeons, gastroenterologists, oncologists, ophthalmologists, radiologists, and pathologists, among others, and truly represents a challenge for the clinician, as it requires an extensive exclusion of other causes. Approaching a patient with probable IgG4-RD through a clinical phenotype framework will ease the diagnostic algorithm and facilitate the prompt recognition of the disease.

There are certain clinical, serological, radiological, and histological features in each clinical phenotype that, if present, increase the likelihood that a patient may have IgG4-RD instead of the mimicker condition. Those clues that point toward IgG4-RD diagnosis should be actively sought in the workup of patients.

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