Cutaneous and systemic IgG4-related disease: a review for dermatologists

Adele Shenoy[1] BA, Nirupa Mohandas[2] MD, Alice Gottlieb[3] MD PhD

Affiliations: [1]New York Medical College, School of Medicine, Valhalla, New York, USA, [2]Division Chief, Department of Rheumatology, NYC Health+ Hospitals/Metropolitan, New York, New York, USA, [3]Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, New York, USA

Corresponding Author: Adele Shenoy BA, School of Medicine, New York Medical College, 40 Sunshine Cottage Road, Valhalla, NY, USA. Email: adeleshenoy@gmail.com

Abstract

Immunoglobulin G4-related disease (IgG4-RD) is a chronic inflammatory condition characterized by IgG4+ plasma cell infiltration of the skin and other organs. Cutaneous forms of the disease may be under recognized owing to poorly defined diagnostic criteria and relatively recent recognition in the literature. The aim of this review is to describe the clinical, histological, and serological presentations of cutaneous IgG4-RD, and to provide an overview of its systemic manifestations for dermatologists. Cases of cutaneous IgG4-RD identified in the literature review were compared to control cases. Clinically, plaque morphology and systemic involvement of the orbit, submandibular gland, lacrimal gland, and parotid gland were associated with a diagnosis of cutaneous IgG4-RD. Histologically, lymphoplasmacytic infiltrate and percentage of IgG4+ plasma cells/IgG+ plasma cells > 40% were associated with the diagnosis. Serologically, neither elevated serum IgG4 nor IgE concentrations were associated with the diagnosis. Dermatologists should consider IgG4-RD as part of the differential diagnosis for nodules, papules, and plaques with an IgG4+ plasma cell infiltrate, especially in middle-aged and elderly males with systemic manifestations of the disease. Diagnosis requires thorough investigation of both cutaneous and systemic clinical and histological presentations.

Keywords: IgG4-related disease, IgG4, lymphoplasmacytic infiltrate

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a rare, chronic inflammatory disorder characterized clinically by tumor-like enlargement of organs and histologically by lymphoplasmacytic infiltrate with IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis. The disease can affect multiple organs simultaneously or at different times. Extracutaneous presentations include swelling of the lacrimal and salivary glands (Mikulicz disease), chronic sclerosing sialadenitis (Küttner tumor), retroperitoneal fibrosis (Ormond disease), type 1 autoimmune pancreatitis, thyroiditis, aortitis, sclerosing cholangitis, pneumonitis, nephritis, and lymphadenopathy [1].

In 2011, comprehensive diagnostic criteria for IgG4-RD were introduced to establish guidelines for organs such as the skin that lack well-defined, organ-specific diagnostic criteria [2]. These comprehensive diagnostic criteria include: (1) swelling or masses; (2) serum IgG4 levels > 135mg/dl; and (3) histology showing marked lymphocyte and plasmacyte infiltration and fibrosis, >10 IgG4+ plasma cells/high powered field, and percentage of IgG4+ plasma cells/IgG+ plasma cells >40%. The diagnosis is definite when criteria (1), (2), and (3) are fulfilled, probable when criteria (1) and (3) are fulfilled, and possible when criteria (1) and (2) are fulfilled [2].

However, the diagnosis of cutaneous IgG4-RD is particularly difficult owing to its rare presentation and relatively recent recognition in the literature. Skin lesions were identified in only 6.3% of cases of IgG4-RD in a study of 80 Japanese patients [3],and in only 4.2% of cases in a study of 118 Chinese patients [4]. By applying the comprehensive diagnostic

criteria to reported cases of cutaneous IgG4-RD in the literature, we aim to describe the clinical, histological, and serological manifestations of cutaneous IgG4-RD. Furthermore, because skin presentation rarely occurs in isolation and the skin may not be the first system affected by the disease [3, 5], we build upon prior reviews by discussing systemic manifestations so that dermatologists can better suspect and establish a diagnosis of IgG4-RD based on the holistic, multi-organ clinical and histological presentation.

Search strategy for systemic IgG4-RD

Separate searches on PubMed were performed for each organ system. Keywords in respective searches included: "Mikulicz disease," "Sjögren syndrome," "Küttner tumor," "autoimmune pancreatitis," "IgG4-RD of the orbit," "sclerosing cholangitis," "IgG4-RD of the kidney," "IgG4-RD of the thyroid," "IgG4-RD of the lung," "retroperitoneal fibrosis," "IgG4-RD of the aorta," and "IgG4-RD and malignancy." References cited in articles from the initial search were scanned for additional articles.

Search strategy for cutaneous IgG4-RD

Our methods were derived from a previous review of cutaneous IgG4-RD [6]. A search of the literature for cutaneous manifestations of IgG4-RD was performed using PubMed (**Figure 1**). Key words included "IgG4-related disease," "IgG4-related skin disease," "IgG4-related systemic disease," "IgG4-related sclerosing disease," OR "IgG4" AND "skin," "dermatology," "dermatologic," OR "cutaneous." This initial search was supplemented by using the Similar Articles feature of PubMed and by scanning reference sections of articles from the initial search. Articles published in a language other than English, published before the year 2000, and focused on nonhuman studies were excluded. The following sections regarding article selection, data extraction, and data analysis apply to cutaneous disease only.

Article selection

Articles were screened based on title and abstract. Review articles, articles that were irrelevant to IgG4-RD or its differential diagnosis, articles that lacked skin presentation of IgG4-RD, and articles that could not be obtained through the library system (a list is provided after the Reference section) were excluded from full-text assessment. Full text articles that lacked sufficient cutaneous data to apply the comprehensive diagnostic criteria were excluded [2].

Data extraction

From each full-text article reviewed, the following data were extracted: country and year of publication; general characteristics of patients (age, sex, ethnicity); clinical presentation (location and morphology of cutaneous and systemic lesions); serum studies (IgG, IgG4, IgE, anti-Ro, anti-La); histological analysis of cutaneous lesions (description of biopsy with location of infiltrate and fibrosis, IgG4+ plasma cells/high power field, percentage of IgG4+ plasma cells/IgG+ plasma cells); and treatment used and response. The comprehensive diagnostic criteria [2] were then used to characterize the lesions as cutaneous manifestations of IgG4-RD or controls.

Search strategy for controls

The differential diagnosis for cutaneous IgG4-RD has been described in previous reviews of the disease and includes conditions that resemble IgG4-RD clinically with erythematous nodules, papules, and plaques, and histologically with lymphoplasmacytic infiltrate and increased IgG4+ plasma cells [6, 7]. Control cases included in our review resulted from the same search and article selection as cases of cutaneous IgG4-RD (as depicted in **Figure 1**) and were subject to the same data extraction as described above. Thus, the controls analyzed in this review included Castleman disease, angiolymphoid hyperplasia with eosinophilia, cutaneous plasmacytosis, and Kimura disease, but did not include all conditions that are part of the differential diagnosis for cutaneous IgG4-RD.

Cutaneous IgG4-RD

Characteristics of included studies

The initial search for cutaneous IgG4-RD found 440 articles that were screened based on title and abstract (**Figure 1**). Of these, 67 full text articles were reviewed, and 37 articles with sufficient data to apply the comprehensive diagnostic criteria to cutaneous lesions were included in the data analysis. There were 52 cases of cutaneous IgG4-RD [3, 5, 8-38], as

well as 23 control cases [35, 39-42]. The characteristics of cutaneous IgG4-RD and controls are summarized in **Table 1**.

Patient characteristics

The mean age was 60.0 years in cases diagnosed with IgG4-RD and 49.3 years in controls, which was significantly different between the two groups (P<0.001). Male sex comprised 76.9% of IgG4-RD cases and 60.1% of controls and was not significantly associated with diagnosis (P=0.173).

Morphology and location

Among cases with IgG4-RD diagnoses, the majority presented with nodules (40.4%), papules (36.5%), and plaques (32.7%), though only plaques (P=0.042) were significantly associated with IgG4-RD diagnosis. Cutaneous lesions were predominantly located on the head and neck in IgG4-RD cases (73.1%), and were less commonly reported on the trunk (38.5%) and extremities (28.9%). Most cases associated with IgG4-RD also reported pruritus (61.1%).

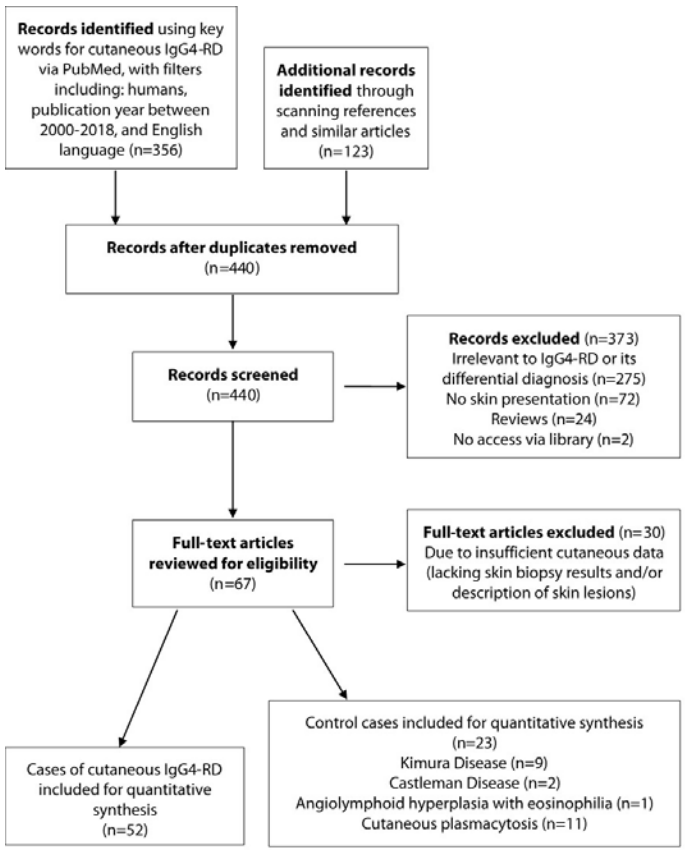

Figure 1. *Search strategy for cutaneous IgG4-related disease (RD) and controls.*

Serum studies

There was no significant difference in serum IgG4 or serum IgE between cutaneous IgG4-RD cases and controls (P=0.051 and P=0.914, respectively).

Histology

In cases with IgG4-RD, lymphoplasmacytic infiltrate (90.4%, P=0.038), infiltration in the subcutaneous tissue (51.1%, P<0.001), and percentage of IgG4+ plasma cells/IgG+ plasma cells >40% (94.2%, P<0.001) were significantly associated with the diagnosis. The majority of cases with IgG4-RD had infiltration in the dermis (86.7%) and many cases reported fibrosis (43.5%), but neither was associated with diagnosis (P=0.319 and P=0.800, respectively).

Systemic manifestations with cutaneous IgG4-RD

Systemic manifestations prior to, subsequent to, and/or concurrent with cutaneous presentation were found in the majority of IgG4-RD cases (92.5%), and systemic involvement was significantly associated with diagnosis (P<0.001). Involvement of the submandibular gland (30.8%, P=0.002), lacrimal gland (30.8%, P=0.002), parotid gland (41.0%, P=0.009), and orbit (17.9%, P=0.021) were significantly associated with diagnosis.

The prevalence of systemic manifestations of IgG4-RD reported in the literature is shown in **Table 2**. Of note, the prevalence of IgG4-RD is poorly established and often reported from studies of only single populations [4, 43, 44]. Compared to larger studies of IgG4-RD, almost all systemic presentations occurred less frequently in the cases of cutaneous IgG4-RD included in this review. This includes the lacrimal gland (30.8% of cutaneous IgG4-RD cases versus 50.8% reported in the literature), salivary glands (58.9% versus 64.6%), pancreas (7.69% versus 38.1%), biliary tract (0% versus 17.8%), kidneys (10.3% versus 24.6%), thyroid (0% versus 1.7%), lung (7.69% versus 27.1%), retroperitoneum (2.56% versus 26.3%), aorta (0% versus 36.3%), and lymph nodes (25.6% versus 63.5%), [4, 44]. The exception was orbital involvement, which was reported in 17.9% of cutaneous IgG4-RD cases compared to 17% reported in the literature [43].

Furthermore, because the lacrimal and salivary glands are often involved in Sjögren syndrome (SS),

Table 1. *The characteristics of cutaneous IgG4-related disease (RD) and controls.*

Characteristics				
Mean age, years (SD)	56.7 (12.8)	60.0 (12.1)	49.3 (11.2)	<0.001
Male	54 (72.0)	40 (76.9)	14 (60.1)	0.173
Clinical Presentation				
Morphology				
Nodule	32 (42.7)	21 (40.4)	11 (47.8)	0.617
Papule	25 (33.3)	19 (36.5)	6 (26.1)	0.435
Plaque	19 (25.3)	17 (32.7)	2 (8.70)	0.042
Other	7 (9.33)	1 (1.92)	6 (26.1)	0.003
Pruritus	22 (57.9)	22 (61.1)	0	0.171
Location				
Head/Neck	53 (70.1)	38 (73.1)	15 (65.2)	0.585
Extremities	24 (32.0)	15 (28.9)	9 (39.1)	0.427
Trunk	33 (44.0)	20 (38.5)	13 (56.5)	0.207
Systemic Involvement				
Systemic	43 (68.3)	37 (92.5)	6 (26.1)	<0.001
Lymphadenopathy	15 (24.2)	10 (25.6)	5 (21.7)	1
Submandibular	12 (19.4)	12 (30.8)	0	0.002
Lacrimal	12 (19.4)	12 (30.8)	0	0.002
Orbit	8 (12.9)	7 (17.9)	0	0.021
Parotid	18 (29.0)	16 (41.0)	2 (8.70)	0.009
Other	7 (11.2)	7 (17.9)	0	0.04
Serum Studies				
IgG4, avg mg/dl (SD)	732 (590)	786 (589)	405 (515)	0.051
IgE, avg IU/dl (SD)	1902 (1721)	1762 (1349)	2440 (2853)	0.914
Histopathologic				
IgG4/IgG > 40%	46 (70.8)	49 (94.2)	7 (30.4)	<0.001
IgG4/HPF > 10	54 (94.7)	36 (94.7)	18 (94.7)	1
Lymphoplasmacytic	63 (84.0)	47 (90.4)	16 (69.6)	0.038
Dermal infiltrate	53 (89.3)	39 (86.7)	14 (100.0)	0.319
Subcut infiltrate	23 (39.0)	23 (51.1)	0	<0.001
Fibrosis	29 (42.0)	20 (43.5)	9 (39.1)	0.800
Therapy				
Systemic steroid	34 (69.4)	29 (74.4)	5 (50.0)	
Skin response	22 (81.5)	22 (81.5)	NR	
Systemic response	11 (84.6)	11 (84.6)	NR	
Skin relapse	14 (93.3)	14 (93.3)	NR	
Systemic relapse	6 (85.7)	6 (85.7)	NR	
Other therapy	14 (28.6)	13 (33.3)	1 (7.14)	
Azathioprine	4 (8.16)	4 (10.2)	0	
Rituximab	4 (8.16)	4 (10.2)	0	
Thalidomide	2 (4.08)	2 (5.12)	0	
Surgical resection	3 (6.12)	3 (7.69)	0	
Response to other	13 (92.9)	9 (90.0)	0	

"All" denotes cases of IgG4-RD and controls. "IgG4-RD" denotes all cases of definite, probable, or possible IgG4-RD. All values are denoted as: Number (percentage), unless otherwise specified. IgG4/IgG > 40% indicates that >40% of IgG+ plasma cells were IgG4+. IgG4/HPF indicates the number of IgG4+ plasma cells per high powered field. Skin response to therapy included decrease in size, decrease in number, or resolution of skin lesions. Systemic response to therapy included decrease in swelling and/or resolution of symptoms in affected organs. NR = not reported. Cases included in analysis are cited in references [3, 5, 8-38], and controls included cases with similar clinical and histological presentation [35, 39-42].

we reviewed whether any cases or controls were incorrectly diagnosed with SS. Only one of the cutaneous IgG4-RD cases had previously been misdiagnosed as SS. Five cases of IgG4-RD (9.61%) reported anti-SS-A/Ro and anti-SS-B/La antibody testing; all were negative.

Therapy and response to therapy

Systemic corticosteroids were used in the majority of IgG4-RD cases (74.4%), with 81.5% reporting a cutaneous response (decrease in size, decrease in number, or resolution of skin lesions) and 84.6% reporting a systemic response (decrease in swelling and/or resolution of symptoms in affected organs). Upon taper or discontinuation of systemic corticosteroids, 93.3% of IgG4-RD cases reported relapse of skin lesions and 85.6% reported relapse of systemic symptoms. Other therapies used for cutaneous IgG4-RD either alone or in combination with corticosteroids included azathioprine in 10.2% of cases, with response in 25.0%; rituximab in 10.2% of cases, with response in 100.0%; thalidomide in 5.12% of cases, with response in 100.0%; and surgical resection in 7.69% of cases, with response in 100.0%.

Systemic IgG4-RD

The prevalence, clinical, and histological characteristics of systemic IgG4-RD are summarized in **Table 2**.

Lacrimal, parotid, and submandibular glands: Mikulicz disease and Küttner tumor

Mikulicz disease (MD) presents with persistent, symmetrical, and painless enlargement of the lacrimal, parotid, and/or submandibular glands. Clinically, patients can have dry eyes and dry mouth and histologically, glands show lymphoplasmacytic infiltrate with fibrosis [45, 46].

Although Mikulicz disease and Sjögren syndrome have similar presentations, there are several clinical, serological, histological, radiological, and therapeutic factors that distinguish the two diseases. Clinically, the incidence of xerostomia, xeropthalmia, and arthralgia are significantly lower in Mikulicz disease versus SS, but allergic rhinitis and autoimmune pancreatitis (discussed below) are more frequently associated with Mikulicz disease [47]. Serologically, rheumatoid factor, antinuclear antibody, antiSS-A/Ro, and antiSS-B/La antibodies were significantly lower in Mikulicz disease compared to SS, but IgG, IgG4, and IgE levels are higher in Mikulicz disease [47]. Histologically, only Mikulicz disease shows marked infiltration of IgG4+ plasma cells and Sjögren syndrome is associated with more cell apoptosis [46-49]. Radiologically, only Sjögren syndrome demonstrates the "apple-tree sign" on sialography, indicative of contrast spilling from degenerated glands [46]. Therapeutically Mikulicz disease can regain salivary function after corticosteroids, whereas Sjögren syndrome does not [46, 47].

Küttner tumor, or chronic sclerosing sialadenitis, presents with asymmetrical and firm swelling of the salivary gland, most often of the submandibular gland. It can be painful or asymptomatic and histology can show lymphoplasmacytic infiltrate, storiform fibrosis, and/or obliterative phlebitis [50].

Orbit

Immunoglobulin G4-RD of the orbit presents with swelling of the lacrimal gland, soft tissue, extraocular muscles, palpebrae, optical nerve, or orbital bone, but typically spares the conjunctiva [43]. Although vision loss is uncommon, swelling can lead to proptosis and compression of local nerves [51]. Histologically, there is lymphoplasmacytic infiltrate, fibrosis and lymphoid follicle formation, but characteristic obliterative phlebitis is less common [43, 52].

Pancreas: autoimmune pancreatitis

Autoimmune pancreatitis (AIP) associated with IgG4-RD presents most commonly in elderly males and may be asymptomatic or present with mild abdominal symptoms and obstructive jaundice. Eventually, some patients lose endocrine function of the pancreas and can develop secondary diabetes [53]. Histologically, AIP typically has the characteristic triad associated with IgG4-RD: lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis [54, 55]. Imaging with CT or MRI shows diffuse, segmental, or focal enlargement of the pancreas with a low-density rim [54].

Biliary ducts: sclerosing cholangitis

Sclerosing cholangitis often presents concurrently with AIP. It can be asymptomatic or present with

obstructive jaundice, abdominal pain, weight loss, and/or steatorrhea [56]. Histologically, it also presents with the characteristic triad associated with IgG4-RD [56]. Imaging most often shows obstruction of the lower common bile duct [57]. The condition can be difficult to distinguish from primary sclerosing cholangitis (PSC). However, IgG4-RD has elevated serum IgG4 whereas PSC does not, and PSC is more often associated with inflammatory bowel disease [57]. IgG4-RD sclerosing cholangitis can also be confused with cholangiocarcinoma, but the latter has higher serum bilirubin and CA19-9 [58].

Kidney: tubulointerstitial nephritis and membranous nephropathy

Kidney disease associated with IgG4-RD is often detected through abnormal urinary analysis, radiological studies, or kidney function tests obtained during workup of extrarenal symptoms [59]. Renal involvement includes tubulointerstitial nephritis (TIN) and membranous nephropathy. Histology of TIN shows lymphoplasmacytic infiltrate, fibrosis, and tubular atrophy; CT imaging shows enlarged kidneys and hypodense lesions [59]. Unlike other manifestations of IgG4-RD, TIN is associated with hypocomplementemia [59]. Membranous nephropathy can be concurrent with TIN and presents with nephrotic range proteinuria and hypoalbuminemia [60].

Thyroid

Reidel thyroiditis is an inflammatory condition characterized by fibrosis of the thyroid gland leading to destruction of the tissue and invasion into adjacent structures. A relationship between Reidel thyroiditis and IgG4-RD has been proposed based on shared features including lymphoplasmacytic infiltrate, obliterative phlebitis, tissue eosinophilia, and fibrosis [61].

A fibrosing variant of Hashimoto thyroiditis has also been associated with IgG4-RD [62]. In comparison to IgG4-negative thyroiditis, IgG4-RD thyroiditis presents serologically with higher levels of anti-thyroglobulin and anti-thyroid peroxidase antibodies [63], radiologically with diffuse low echogenicity on ultrasound [63], and histologically with dense infiltrate of IgG4+ plasma cells [63, 64].

Lung

Immunoglobulin G4-RD of the lung has a diverse clinical presentation; it can present with cough, dyspnea, and chest pain, or without symptoms. The disease is divided into four radiological subtypes: solid nodular, bronchovascular, alveolar interstitial, and round-shaped ground glass opacity [65]. Histologically, there is lymphoplasmacytic infiltrate in all subtypes, but obliterative phlebitis is more common in the solid nodular type [65, 66]. The solid nodular type may be confused with sarcoidosis, but IgG4-RD is not associated with elevated angiotensin converting enzyme (ACE) levels [65].

Retroperitoneal fibrosis

Retroperitoneal fibrosis, historically known as Ormond disease, presents with a retroperitoneal mass that can lead to hydronephrosis, flank pain, and/or back pain [67]. Histologically, it displays the same classic triad found in AIP and sclerosing cholangitis: lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis [67, 68]. IgG4-related retroperitoneal fibrosis must be distinguished from secondary causes of retroperitoneal fibrosis, such as malignancy, infections, and radiation therapy.

Aortitis

IgG4-RD is associated with inflammatory abdominal aortic aneurysms, which may present with abdominal and lower back pain [69]. IgG4-RD aortitis and periaortitis most often involve the infra-renal aorta and can extend into the iliac arteries and periaortic tissue [44]. Histologically, there is obliterative phlebitis, lymph follicle formation, and eosinophilia [69, 70]. Thoracic aortitis can lead to aneurysm formation or dissection, though it is often asymptomatic and detected only by imaging [70].

Lymphadenopathy

Lymphadenopathy associated with IgG4-RD can be generalized or localized to disease-affected organs. Typically, the nodes swell to less than 2cm and patients remain afebrile [71]. Histologically, most nodes do not have storiform fibrosis, but rather fall within five morphological subtypes: Castleman disease-like, reactive follicular hyperplasia, interfollicular plasmacytosis and immunoblastosis, progressive transformation of germinal center-like,

and inflammatory pseudotumor-like morphologies [72]. Although lymphadenopathy is common, biopsy is not typically used to establish the diagnosis of IgG4-RD because of the histological diversity of affected nodes.

Prognosis

The prognosis of IgG4-RD depends on the organs involved and the severity of fibrosis. There can be irreversible fibrosis of vital organs including the biliary tree, aorta, and retroperitoneum if undetected, but asymptomatic lymphadenopathy or mild submandibular enlargement may be relatively benign. In general, affected organs respond to corticosteroids. Although there have been no randomized controlled trials for treatment of the disease, a general consensus supports corticosteroids as first-line therapy to induce remission and lower-dose maintenance therapy to prevent relapse when necessary [73].

Studies examining the relationship of IgG4-RD with malignancy have conflicting results. Some studies have found an increased risk of malignancy associated with IgG4-RD compared to the general population [74, 75], whereas others have not [76]. Interestingly, one study found that history of malignancy increases subsequent risk of IgG4-RD [77].

Discussion

Our review found that cutaneous IgG4-RD most commonly presented with pruritic nodules, papules, and plaques in middle-aged or elderly male patients with systemic forms of the disease, and histologically with lymphoplasmacytic infiltrate and percentage of IgG4+ plasma cells/IgG+ plasma cells >40%. However, not all these characteristics are specific to cutaneous IgG4-RD and dermatologists should be aware that diagnosis requires clinical and histological evaluation of both the skin and systemic organs in order to distinguish the disease from similar conditions.

Specifically, Kimura disease presents with lymphadenopathy and subcutaneous nodules of the head and neck region and can also have abundant IgG4+ plasma cell infiltration. It can be distinguished from IgG4-RD histologically by reactive vascular proliferation and eosinophilic microabscesses in lymph nodes. Clinically, Kimura disease typically affects younger patients (median age of 44.5 in one study) compared to IgG4-RD and rarely affects organs such as the pancreas [41]. Other conditions, such as pemphigus vulgaris, can also have cutaneous lesions with a percentage of IgG4+ plasma cells/IgG+ plasma cells > 40% [78]. Thus, although skin biopsy is an important factor in diagnosis of cutaneous IgG4-RD, it should not be used in isolation.

Similarly, despite the inclusion of elevated serum IgG4 (>135mg/dl) as part of the comprehensive diagnostic criteria for IgG4-RD, its specificity and reliability for diagnosis are debated. We did not find a significant difference in serum IgG4 between cases and controls. This result is not surprising; serum IgG4 can be elevated in many other conditions, including recurrent infection, systemic autoimmune conditions, and unrelated disease of the lungs, biliary tract, pancreas, liver, and vasculature [79, 80].

Our review also found that systemic IgG4-RD, particularly of the orbit and submandibular, lacrimal, and parotid glands, was associated with a cutaneous IgG4-RD diagnosis. Our results support those from previous reviews showing an association between cutaneous IgG4-RD diagnosis and systemic involvement of the head and neck [6, 7]. For this reason, it is important to understand why Mikulicz disease is considered a systemic manifestation of IgG4-RD rather than a subtype of Sjögren syndrome. Mikulicz disease has increased serum IgG, IgG4, and IgE, dense IgG4+ plasma cell infiltrate, and therapeutic response to corticosteroids, whereas Sjögren syndrome does not; Sjögren syndrome is associated with increased rheumatoid factor, antinuclear antibody, anti-SSA/Ro, and anti-SS-B/La antibodies, increased apoptotic cells on histology, and demonstrates the "apple tree sign" on sialography, features that are not found in Mikulicz disease [46, 47, 49]. One possible explanation for these histologic, radiologic, and therapeutic differences is that lymphocytic infiltration in SS, but not in Mikulicz disease, is associated with autoimmune-mediated glandular destruction. Acinar cells in lacrimal glands affected by Sjögren

syndrome have demonstrated much greater expression of proteins associated with apoptosis, including APO2.7, FasL, and Fas compared to acinar cells affected by Mikulicz disease [49]. This may explain the lack of functional improvement despite corticosteroid therapy in Sjögren syndrome[46, 47].

Recognizing systemic forms of the disease discussed in our review can help dermatologists suspect the diagnosis of cutaneous IgG4-RD and understand its prognosis based on the comprehensive, multi-organ presentation. However, there are limitations to our review; because extracutaneous involvement of IgG4-RD can occur after cutaneous presentation, the cases we included may have excluded manifestations of disease that occurred after publication. Furthermore, our sample size is small and larger analyses of cutaneous and systemic IgG4-RD are necessary to fully characterize the disease and establish diagnostic criteria for the skin. However, our review may help alert dermatologists to this rare disease that requires thorough, multi-disciplinary clinical and histological evaluation.

Conclusion

Diagnosis of IgG4-RD is difficult, especially in organs such as the skin that lack well-established diagnostic criteria. It requires integration of both cutaneous and systemic presentations. Dermatologists should consider IgG4-RD as part of the differential diagnosis for nodules, papules, and plaques with IgG4+ plasma cell infiltrate, especially in middle-aged and elderly male patients with systemic manifestations of the disease involving the orbit, lacrimal glands, and salivary glands.

Potential conflicts of interest

The authors declare no conflicts of interests.

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Table 2. *Overview of the clinical presentation, histology, and differential diagnosis for systemic forms of IgG4-related disease (RD).*

Systemic Location	Clinical Presentation	Histology	Differential Diagnosis	References
Lacrimal, Parotid, and Submandibular glands *Prevalence* [4]: Dacryoadenitis: 50.8% Sialadenitis: 64.4%	**Mikulicz Disease**: Persistent, symmetrical, painless enlargement of at least 2 glands: lacrimal, parotid, or submandibular. Dry eyes, dry mouth.	Lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis (but not often found in parotid)	Sjögren Syndrome	[45–49]
	Küttner tumor: Firm mass in the submandibular gland. Asymptomatic or painful	Lymphoplasmacytic infiltrate, storiform fibrosis, lymphoid follicles, obliterative phlebitis sometimes present	Sjögren Syndrome, salivary tumor	[50]
Orbit *Prevalence* [43]: 17%	Swelling that can lead to proptosis and can compress nerves. Can involve the lacrimal gland, soft tissue, extraocular muscles and nerves. Visual impairment is uncommon	Lymphoplasmacytic infiltrate, lymphoid follicle formation, patternless fibrosis. Obliterative phlebitis and storiform fibrosis uncommon	MALT lymphoma, follicular lymphoma, diffuse large B-cell lymphoma	[43, 51, 52]
Autoimmune pancreatitis *Prevalence* [4]: 38.1%	Mostly in elderly males, mild abdominal symptoms, no acute attacks of pancreatitis, occasional obstructive jaundice. Can have secondary loss of endocrine function (diabetes).	Lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis	Type 2 AIP, pancreatic head cancer, cholangiocarcinoma	[53–55]
Sclerosing cholangitis *Prevalence* [4]: 17.8%	Abrupt obstructive jaundice, weight loss, abdominal discomfort, often associated with autoimmune pancreatitis	Lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis	Primary sclerosing cholangitis, cholangiocarcinoma	[56 –58]
Kidney disease *Prevalence* [4]: 24.6%	**Tubulointerstitial nephritis**: Commonly detected from abnormal urinary analysis, renal dysfunction, or radiographic abnormalities detected from workup for extrarenal manifestations. Hypocomplementemia	Lymphoplasmacytic infiltrate, eosinophils, fibrosis, tubular atrophy. Obliterative phlebitis is rare.	ANCA-associated vasculitis, Rosai-Dorfman disease, Castleman disease	[59]
	Membranous nephropathy: Nephrotic range proteinuria.	Subepithelial deposits in a membranous pattern		[60]
Thyroid disease *Prevalence* [4]: 1.7%	**Reidel thyroiditis**: Growing thyroid mass, can compress local structures resulting in dyspnea, dysphagia, hoarseness, cough.	Lymphoplasmacytic infiltrate, fibrosis with destruction of thyroid architecture, obliterative phlebitis	Non IgG4-related Reidel thyroiditis	[61]
	Fibrous variant of Hashimoto thyroiditis: Hypothyroidism	Lymphoplasmacytic infiltrate, fibrosis, follicular degeneration, lymph follicle formation	Non IgG4-related Hashimoto thyroiditis	[62–64]
Lung disease *Prevalence* [4]: 27.1%	Asymptomatic or cough, dyspnea, chest pain. Radiologically: can be solid nodular, bronchovascular,	Diffuse lymphoplasmacytic infiltration in all presentations, but	Sarcoidosis, Castleman disease, lung cancer	[65, 66]

	alveolar interstitial, or round-shaped ground glass opacity	irregular fibrosis and obliterative phlebitis more common in solid nodular type		
Retroperitoneal fibrosis *Prevalence* [4]: 26.3% (retroperitoneal fibrosis or periaortitis)	Retroperitoneal mass, can have hydronephrosis, flank pain, back pain.	Lymphoplasmacytic infiltrate, storiform fibrosis, eosinophilia, sometimes obliterative phlebitis.	Idiopathic, secondary causes (drug exposure, infection, malignancy)	[67, 68]
Aortitis/Periaortitis *Prevalence* [44]: 36.3%	**Abdominal aorta**: may have poorly localized abdominal, back, or thigh pain. Usually localized to the infrarenal portion and continues to the iliacs, can have aneurysm formation. **Thoracic aorta**: often asymptomatic, aneurysm or dissection. Can have saccular formation, fibrous adhesion to surrounding tissue	Lymphoplasmacytic infiltrate, irregular fibrosis, sometimes eosinophilia and obliterative phlebitis.	Other noninfectious inflammatory aortitis (Takayasu, ANCA-associated vasculitis)	[44, 69, 70]
Lymphadenopathy *Prevalence* [4]: 65.3%	Regional swelling (around other organs affected) or systemic. Typically no larger than 2 cm. Lacks fever and B symptoms	Castleman disease-like, reactive follicular hyperplasia, interfollicular plasmacytosis and immunoblastosis, progressive transformation of germinal center-like, inflammatory pseudotumor-like. Often lack storiform fibrosis and obliterative phlebitis	Castleman disease, lymphoma, other malignancies	[71, 72]

AIP, autoimmune pancreatitis; ANCA, antineutrophil cytoplasmic antibody; MALT, mucosa-associated lymphoid tissue.