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Review Article

IgG4-related skin diseases: A brief review

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ABSTRACT

Immunoglobulin G4-related disease (IgG4-RD) is an increasingly recognized syndrome which shares similar pathologic, serologic, and clinical features in the affected organs. Subacute development of a mass or diffuse enlargement of the organ is a common presenting feature. It is more commonly seen in middle-aged or older men. Lymphadenopathy is common in them. Tissue infiltration with lymphoplasmacytic collection, predominantly of IgG4-positive plasma cells, accompanied by "storiform" pattern of fibrosis, obliterative phlebitis, and increased tissue eosinophils are the hallmark histologic findings. Rapid response to systemic steroids is characteristic. If present, the typical cutaneous findings such as papulonodules or plaques in the head-and-neck region may serve as an initial clue to the underlying systemic involvement in IgG4-RD. Hence, dermatologists need to be aware of this entity for early recognition of underlying organ involvement and thus the prompt management.

Keywords: Immunoglobulin G4-related disease, IgG4-RD, Cutaneous plasmacytosis, Pseudolymphoma, Angiolymphoid hyperplasia with eosinophilia

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a newer immune-mediated fibro-inflammatory disease affecting various organs and tissues. Its characteristic features are organ infiltration with IgG4+ plasma cells (seen in all the cases) and elevated serum levels of IgG4 (seen in a large proportion of cases).[1] It is a multiorgan disease with the disease being reported in almost all the organs including the pancreas, thyroid, lacrimal and salivary glands, lymph nodes, biliary tract, kidneys, lungs, aorta, meninges, pituitary gland, and skin.[2]

HISTORY

IgG4-RD was first described in Japan. In 2001, Hamano *et al.* described the association of high serum concentration of IgG4 in 20 patients with sclerosing pancreatitis in comparison to other diseases of the pancreas or biliary tract.[3] Since then, there have been numerous published literature from different parts of the world on similar association of tissue infiltration and elevated serum levels of IgG4, though majority of the cases are reported from Japan. Certain conditions such as Mikulicz's syndrome, Küttner's tumor, Riedel's thyroiditis, and Ormond's disease which have been described earlier are now considered under this category. The term "IgG4-related autoimmune disease" was first used by Kamisawa *et al.*, in 2003, to describe the multiorgan infiltration with IgG4-positive plasma cells in patients with autoimmune pancreatitis. The current nomenclature of immunoglobulin G4-related disease (IgG4-RD) was proposed in an International Symposium on IgG4-related disease (IgG4-RD) which was held in Boston in 2011

to describe the conditions previously termed as "IgG4-related systemic disease," "IgG4-related sclerosing disease," and "IgG4-positive multiorgan lymphoproliferative syndrome."[2]

EPIDEMIOLOGY

The disease being a recently described one, the exact prevalence and incidence of the disease are not yet known. Even though IgG4-RD is described in nearly all racial and ethnic groups, around 75% of reported cases are from Japan with a prevalence of 6 cases/100,000 people in the Japanese population. According to a recent analysis of two international cross-sectional cohorts, people of Asian origin are more predisposed to develop IgG4-RD limited to the head-and-neck region, whereas pancreatic-hepatobiliary disease and retroperitoneal disease are more common in Caucasians. A male predominance is seen in the studies (62–83%) and is more common in the 5th to 6th decades of life. Age of presentation as early as 14 years has also been reported. Females are more likely to have disease limited to the head-and-neck region. The time to diagnose after the symptom onset varies from 1 to 2 years.[4-6] Multiorgan involvement is more common and single organ involvement is seen in only 4.2% of cases in a study.[7] Cutaneous features are seen in 6.3% and 4.2% of cases of IgG4-RD in a study on Japanese and Chinese patients, respectively.[7,8] More population-based studies are needed to know in detail about the epidemiology of the condition.

ETIOPATHOGENESIS

IgG4 is an immunoglobulin molecule with unique biological properties. It constitutes <5% of the IgG subclass in human serum. The etiopathogenesis of IgG4-RD is not yet fully understood. According to the currently available literature, various mechanisms are being postulated.

GENETIC ASSOCIATION

Based on the studies on autoimmune pancreatitis (AIP), several susceptibility loci have been identified. The HLA-DRB1*0405 and HLA-DQB1*0401 haplotypes were found to be common in Japanese patients with AIP.[9] A different haplotype was found in Korean population with AIP.[10] Other susceptibility loci are identified on ABCF1 (adenosine triphosphate (ATP)-binding cassette subfamily F), FCRL3 (Fc receptor-like 3), and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) regions.[11-13] Familial clustering of IgG4-RD is rare.

IMMUNE MECHANISMS

The role of both the innate and adaptive immune systems has been studied. The presence of immune complex deposits with a predominance of IgG4 in the involved organs along with circulating immune complexes and hypocomplementemia indicates a role of complement system activation in the pathogenesis.[14] Components of the innate immune system, specifically Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) in association with B-cell activating factor of the TNF family (BAFF) and a proliferation-inducing ligand (APRIL), induce the production of IgG4 by the B-cells.[15] A modified Th2 response and the cytokines IL-10 and IL-4 enhance IgG4 production.[16,17]

RISK FACTORS

Risk factors for IgG4-RD include ethnicity and certain environmental factors such as exposure to tobacco and asbestos.[5,18] Atopy and history of malignancy are also potential risk factors.[19,20]

CLINICAL FEATURES

According to a systematic review on cutaneous manifestations of IgG4-RD, more than 60% of the cases were from Japan and comprised predominantly of males in their sixth decade of life. IgG4-related specific involvement of the skin is rare. Skin manifestations are seen along with other systemic features. Rarely, cutaneous lesions can be the initial clinical presentation and can precede the systemic features by 4 months up to 9 years.[8] Cutaneous features present most commonly on the head-and-neck area.[21] Neck, scalp, pinna, postauricular area, zygomatic, and submandibular regions are the usual sites.[22] Trunk and extremities are less commonly involved and IgG4-RD on the buttocks and genitals are extremely rare. The presence of erythematous papules, plaques, and nodules of the head-and-neck region is the characteristic skin findings of IgG4-RD. Pruritus was reported in most of the cases in a study.[23] Other morphological presentations are purpura, rash, and patches. Prurigo nodularis-like lesions are also seen.[8] Macules and bulla associated with IgG4-RD are not yet reported.[21] Unilateral presentation is more common.[24] Rarely, IgG4-related systemic disease may present with features of hypocomplementemic urticarial vasculitis.[25]

In recent review, IgG4-related skin disease was divided into seven types: (1) Cutaneous plasmacytosis (multiple papulonodules or indurations on the trunk and proximal part of the limbs), (2) pseudolymphoma and angiolymphoid hyperplasia with eosinophilia (plaques and papulonodules mainly on the periauricular, cheek, and mandible regions), (3) Mikulicz disease (palpebral swelling, sicca syndrome, and exophthalmos), (4) psoriasis-like eruption (mimicking psoriasis vulgaris), (5) unspecified maculopapular or erythematous eruptions, (6) hypergammaglobulinemic purpura (bilateral asymmetrical palpable purpuric lesions

on the lower extremities) and urticarial vasculitis (prolonged urticarial lesions occasionally with purpura), and (7) ischemic digit (Raynaud phenomenon and digital gangrene). The first three subtypes are categorized as primary lesions with massive direct infiltration by plasma cells and the rest of the subtypes are categorized as secondary lesions, in which the plasma cell mass formation is not seen. Primary lesions fulfill the comprehensive diagnostic criteria of infiltration of IgG4 plasma cells with a ratio of IgG4+ to IgG+ cells greater than 40% and greater than 10 IgG4 plasma cells/high-power field, whereas secondary lesions show plasmacyte infiltration with a ratio of IgG4+/IgG+ plasma cells > 40% and/or perivascular IgG4 deposition.[26]

Organ-specific diagnostic criteria are used for IgG4-related Mikulicz's disease, IgG4-related autoimmune pancreatitis, and IgG4-related kidney disease. At present, there are no organ-specific criteria for the diagnosis of cutaneous IgG4-RD. In 2011, Umehara *et al.* proposed comprehensive diagnostic criteria. This used in combination with organ-specific criteria increases the sensitivity of the diagnosis of IgG4-RD of specific organs.[27] This criterion, as well as provisional diagnostic criteria by Masaki *et al*., is used for IgG4-RD of the skin [Table 1].[8,21]

SYSTEMIC FEATURES

IgG4-RD is a multiorgan disease and can involve almost all the organs in the body organs including the pancreas, thyroid, lacrimal glands, salivary glands, lymph nodes, biliary tract, kidneys, lungs, aorta, meninges, pituitary gland, and skin. In this review, the discussion is limited to systemic features associated with cutaneous involvement. Systemic involvement of the head-and-neck area is significantly associated with cutaneous IgG4-RD. Involvement of submandibular gland, parotid gland, lacrimal gland, and orbit is common and can manifest as swelling or inflammation of these organs with sialadenitis and dacryoadenitis.[23] Cutaneous IgG4-RD generally lack pancreaticobiliary involvement (16% of cases), which by contrast is a predominant manifestation in systemic IgG4-RD (60% with pancreaticobiliary involvement).[24] Other organ system involvements such as hematologic, lymph node, and gastrointestinal and respiratory tract are not significantly associated with cutaneous IgG4-RD.[21]

Table 1: Comprehensive diagnostic criteria for IgG4-related disease (proposed by Umehara *et al.*).[27]

Comprehensive diagnostic criteria for IgG4-related disease
(1) Clinical – diffuse or localized swelling or masses in single or multiple organs on physical examination;
(2) Laboratory – elevated serum IgG4 concentration (≥135 mg/dL), noted similarly in the literature
(3) Histopathology – (a) marked lymphocyte and plasma cell infiltration and (b) fibrosis and infiltration of IgG4 plasma cells: Ratio of IgG4+ to IgG+ cells greater than 40% and greater than 10 IgG4 plasma cells/high-power field.
Definite case meets all three criteria;
Probable case meets the first and third criteria; and
Possible case meets the first and second criteria

DIFFERENTIAL DIAGNOSIS

The differential diagnosis include Cutaneous plasmacytosis, Sjogren's syndrome, angiolymphoid hyperplasia with eosinophilia, Rosai-Dorfman disease, histiocytosis, sarcoidosis, pseudolymphomas, and lymphomas – primary cutaneous marginal zone B-cell lymphoma (PCMZL), granuloma faciale, and erythema elevatum diutinum.[21,28-31] Histopathological features with specific immunostaining and elevated serum levels of IgG4 help in the diagnosis.

Some of these entities such as granuloma faciale or rarely erythema elevatum diutinum, PCMZL,[32] and cutaneous pseudolymphoma[33] may have elevated IgG4 levels and may share some features of IgG4-RD.[30,34] In fact, Tokura *et al*.[26] have categorized pseudolymphoma and angiolymphoid hyperplasia with eosinophilia, which satisfy the diagnostic criteria for IgG4-RD into subtype 2 IgG4-related skin disease.

HISTOPATHOLOGY

Histopathological findings of IgG4-RD are similar irrespective of the organ involved. Fibrosis and a dense lymphoplasmacytic infiltrate are two invariable histopathological features needed for the diagnosis of IgG4-RD.[21] IgG4-positive plasma cells infiltrate the dermis and can extend deep into the subcutaneous tissue. Perivascular and periadnexal infiltrations may be seen in some. Numerous lymph follicles and germinal center formations can also be present. This is more common in biopsies of skin, lacrimal glands, and salivary glands in comparison to other involved organs.[35] The numbers of infiltrating IgG4-positive cells vary widely. Plenty of lymphocytes, few eosinophils, and histiocytes are other cell populations described. The extent of fibrosis also varies and can be mild to moderate. On immunohistochemical staining, plasma cells show a predominance of IgG4-positive cells. According to a consensus statement on the pathology of IgG4-related disease, the critical histopathological features are a dense lymphoplasmacytic infiltrate, a storiform pattern of fibrosis, and obliterative phlebitis and the number of IgG4 cells should be at least 200/high-power field.[36] Fewer numbers of cells are seen in cutaneous plasmacytosis.[29] Monoclonality of these cells is not seen and this finding helps to differentiate it from pseudolymphoma which is a close differential diagnosis.[8] Obliterative phlebitis is less common in cutaneous IgG4-RD than in systemic types. Cutaneous IgG4-RD has to be

differentiated from other skin conditions that show plasma cell infiltration such as cutaneous plasmacytoma, Kimura disease, and angiolymphoid hyperplasia with eosinophilia (ALHE).[37] Predominant IgG4 positivity helps to differentiate them.

INVESTIGATIONS

Serum levels of IgG and specifically IgG4 are found to be elevated.[8] For the diagnosis of IgG4-RD serum, IgG4 concentration should be more than 135 mg/dl.[27] Studies on flow cytometry have shown that the levels of circulating plasmablasts (CD19 + CD38 + CD20- CD27+) are highly elevated even in IgG4-RD patients with normal serum IgG4 levels and levels decrease following successful treatment with rituximab. Hence, measurement of circulating plasmablasts is a useful biomarker than serum IgG4 levels for the diagnosis, to assess disease activity, treatment response and to plan retreatment.[38-40] Eosinophilia and raised levels of serum IgE are also reported.[8] Biochemical parameters (LFT and RFT) may be elevated depending on the organ systems involved. Hypocomplementemia is reported in 40% of patients with systemic IgG4-RD.

Imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), or 18F-FDG positron emission tomography (PET) play a role in the evaluation of systemic involvement. Enlargement of the involved organs with increased 18F-FDG uptake can be seen.[41]

TREATMENT

Treatment options include systemic and topical corticosteroids, intralesional corticosteroids, rituximab, azathioprine, and methotrexate. Initial response in the manner of reduction in size, number, and resolution of skin lesions while on systemic corticosteroids was seen in the majority of patients followed by relapse on tapering steroids.[23] In such cases, slow tapering of steroids, switching to another agent was found to be partially useful. In those patients who are refractory to 40 mg/day of prednisolone or cannot be tapered below 5 mg/day dosage and in patients with strong contraindications for systemic steroids, some authors suggest rituximab over conventional antimetabolite immunosuppressants (e.g., methotrexate, azathioprine, and mycophenolate mofetil). A complete response without a relapse can be achieved by excising the lesion.[21]

PROGNOSIS

The natural history and prognosis are not well described. If untreated, the cutaneous lesions persist or increase in size.[24] Prognosis of IgG4-RD, in general, depends on the organs involved and the degree of fibrosis. After the initial rapid response to systemic steroids, most patients relapse on tapering steroids. Progressive inflammatory and fibrotic changes in affected tissues may lead to significant organ dysfunction. The risk of malignancy in IgG4-RD is not well studied.

CONCLUSION

IgG4-RD is an increasingly recognized syndrome which shares similar pathologic, serologic, and clinical features in the affected organs. If present, the characteristic cutaneous findings such as papulonodules or plaques in the head-and-neck region may serve as an initial clue to the underlying systemic involvement in IgG4-RD. Hence, dermatologists need to be aware of this entity for early recognition of underlying organ involvement and thus the prompt management.

Declaration of patient consent

Not required as there are no patients in this article.

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Conflicts of interest

There are no conflicts of interest.

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