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Dermatological Manifestations of IgG4-Related Disease: Insights into the Immunopathogenesis and Clinical Spectrum

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ABSTRACT

This review aims to provide insights into the immunopathogenesis and clinical spectrum of dermatological manifestations in IgG4-related disease (IgG4-RD), a systemic fibroinflammatory disorder characterized by tissue infiltration of IgG4-positive plasma cells. Through comprehensive immunohistochemical analyses of skin biopsies from patients with IgG4-RD-associated cutaneous lesions, researchers endeavor to understand the role of IgG4-mediated immune responses, cytokine signaling, and fibrotic pathways in driving skin inflammation and fibrosis. Moreover, this research seeks to characterize the clinical presentation and treatment response of IgG4-RD-related dermatological manifestations to immunomodulatory therapies. Understanding the complex immunopathogenic mechanisms underlying IgG4-RD-related skin lesions may contribute to the refinement of diagnostic criteria and therapeutic strategies for managing this emerging autoimmune condition. Future research directions could include exploring novel biomarkers, identifying potential therapeutic targets, and investigating the long-term outcomes of dermatological involvement in IgG4-RD.

Keywords

IgG4-Related Disease, Dermatological Manifestations, Immunopathogenesis, Cutaneous Involvement, Autoimmune Disorders, Skin Lesions, Histopathology.

Introduction

IgG4-Related Disease (IgG4-RD) represents a unique clinical entity characterized by chronic fibroinflammatory conditions, affecting various organs with a marked presence of IgG4-positive plasma cells. Dermatological manifestations, although less commonly reported compared to other organ involvements, provide critical insights into the broader immunopathological spectrum of IgG4-RD. This review focuses on delineating the immunopathogenesis underlying these cutaneous manifestations and exploring their clinical implications, diagnostic challenges, and therapeutic responses.

IgG4-RD is defined by specific pathological features, including tissue infiltration with IgG4-positive plasma cells, tumefactive lesions, storiform fibrosis, and often elevated serum IgG4 levels [1]. The disease can affect virtually any organ, with the pancreas, biliary tree, salivary glands, and kidneys being commonly involved. However, skin involvement in IgG4-RD, manifesting as rashes, nodules, or plaques, underscores the systemic nature of this condition and necessitates a comprehensive clinical evaluation [2].

The significance of dermatological manifestations in IgG4-RD lies in their ability to provide accessible insights into the disease's

underlying immune mechanisms. The skin, as an external organ, offers a unique window to study the localized immune response characteristic of IgG4-RD. Immunohistochemical analyses of cutaneous lesions have revealed a predominance of IgG4-positive plasma cells, providing a direct correlation to the systemic immunopathogenesis of IgG4-RD [3].

The role of IgG4-mediated immune responses in the pathogenesis of IgG4-RD is paradoxical. While IgG4 is considered the least inflammatory of the immunoglobulin subclasses due to its inability to activate complement effectively, its overexpression in IgG4-RD is associated with extensive tissue fibrosis and damage [4]. This contradiction highlights the complexity of IgG4-RD's immunopathogenesis, where IgG4 plays a dual role in anti-inflammatory processes and pro-fibrotic pathways.

Cytokine signaling, particularly the profibrotic actions mediated by Th2 cytokines like IL-4, IL-5, and IL-13, and regulatory cytokines such as IL-10 and TGF-β, is central to the fibrosis observed in IgG4-RD. These cytokines facilitate the recruitment and proliferation of fibroblasts, leading to excessive collagen deposition and tissue remodeling [5]. In the skin, this cytokine milieu contributes to the development of distinctive fibrotic and inflammatory dermatological manifestations, varying from papules and plaques to nodular lesions.

The objectives of this review are twofold. Firstly, to delve into the immunopathogenesis of dermatological manifestations in IgG4-RD, examining the interplay between IgG4-positive plasma cells, cytokine networks, and fibrotic pathways. Secondly, to elucidate the clinical spectrum and treatment responses of these cutaneous presentations, thereby aiding in the comprehensive management of IgG4-RD. By investigating the dermatological aspects of IgG4-RD, this review aims to enhance the understanding of its complex immunopathogenesis, contribute to refining diagnostic criteria, and facilitate the development of targeted therapeutic strategies for this enigmatic disease.

Discussion

Immunopathogenesis of Dermatological Manifestations in IgG4-RD

The immunopathogenesis of dermatological manifestations in IgG4-Related Disease (IgG4-RD) presents a complex interplay of immunological processes that contribute to the distinctive features of the disease, including tissue infiltration by IgG4-positive plasma cells, IgG4-mediated immune responses, cytokine signaling pathways, and fibrotic processes. Tissue infiltration by IgG4-positive plasma cells is a hallmark of IgG4-RD, observed across various organs, including the skin. This infiltration plays a pivotal role in the pathogenesis of the disease and is believed to result from a specific immune response that mistakenly targets self-antigens, leading to chronic inflammation and subsequent fibrosis [2,6]. Unlike other types of plasma cells, IgG4-positive cells produce antibodies that have reduced ability to form immune complexes and have a limited capacity to activate complement, suggesting a unique pathogenic mechanism [2,7]. The exact triggers of this abnormal immune response remain unclear, but infections and genetic predispositions have been proposed as potential factors [6]. Furthermore, the skin, being an external organ, may exhibit these pathological changes more prominently, serving as a useful site for biopsy and diagnosis.

IgG4-mediated immune responses are characterized by their supposed anti-inflammatory properties, yet in the context of IgG4-RD, they contribute to disease pathology. The unique structural and functional characteristics of IgG4, including its ability to undergo Fab-arm exchange and limited ability to activate complement, suggest a complex role in immune regulation [7,8]. This property may contribute to their inability to cross-link antigens effectively, potentially explaining the non-inflammatory nature of the antibody response in IgG4-RD [8]. However, this same characteristic might also contribute to the persistence of antigenic stimulation and ongoing tissue damage [2,9]. The role of regulatory T cells (Tregs) in promoting IgG4 production and the potential anti-inflammatory effects of IgG4 in suppressing other types of immune responses are areas of active research, suggesting complex regulatory mechanisms at play.

Cytokine signaling is central to the pathogenesis of IgG4-RD, with a particular impact on skin inflammation and fibrosis. Th2 cytokines, such as IL-4, IL-5, and IL-13 are prominently involved in the promotion of fibrosis and the recruitment of IgG4-positive plasma cells within affected tissues [5,10]. These cytokines not only recruit these plasma cells but also stimulate the production of collagen and other extracellular matrix components, contributing to the thickening and hardening of the skin. Additionally, IL-6, known for its pro-inflammatory effects and its ability to promote B cell differentiation and antibody production, has been implicated in IgG4-RD’s pathology [11]. The involvement of Treg-derived cytokines, particularly IL-10 and transforming growth factor-beta (TGF-β), is also noteworthy. In the context of IgG4-RD, these cytokines induce fibroblast proliferation, resulting in the organ dysfunction and tissue damage that are characteristic of this disease [12,13]. The upregulation of these cytokines in IgG4-RD skin lesions underscores their importance in driving the fibrotic process.

The fibrosis observed in IgG4-RD is a result of complex interactions between cytokines, growth factors, myofibroblasts, and fibroblasts. The process of fibrosis in IgG4-RD is thought to be a consequence of both direct immune-mediated damage and the body's attempt to repair that damage. The persistent activation of fibroblasts and myofibroblasts, combined with a skewed repair mechanism, leads to the excessive deposition of extracellular matrix and collagenous proteins, culminating in tissue fibrosis [14]. Interestingly, research has highlighted the potential role of platelet-derived growth factor (PDGF) and connective tissue growth factor (CTGF) in contributing to the fibrotic process, indicating that multiple signaling pathways contribute to the fibrotic response in IgG4-RD [15,16].

Moreover, the categorization of IgG4-RD skin lesions into seven subtypes, as identified by Tokura et al., offers insights into its diverse

dermatological manifestations and underlying mechanisms [3]. Subtypes 1 to 3 result from the direct infiltration of IgG4-positive plasma cells, manifesting as plaques, nodules, or tumors. These are primarily observed as cutaneous plasmacytosis, pseudolymphoma, angiolymphoid hyperplasia with eosinophilia, and Mikulicz disease, demonstrating the direct impact of cellular infiltration on skin morphology. Conversely, subtypes 4 to 7 arise through secondary mechanisms, potentially reflecting systemic effects of the disease or indirect consequences of IgG4-positive cell activities. These include psoriasis-like eruptions, unspecified maculopapular or erythematous eruptions, hypergammaglobulinemic purpura with urticarial vasculitis, and ischemic digit phenomena. This differentiation highlights the complex etiology of IgG4-RD, where the expression of skin lesions ranges from direct cellular infiltration phenomena to more indirect, systemic responses that result in fibrosis.

Immune-Related Oncogenesis and Cell Proliferation in IgG4-RD

In addition to immunopathogenesis, exploration of the immune-related oncogenesis and cell proliferation in IgG4-RD is imperative to a discussion of the dermatological manifestations of IgG4-RD. The link between immune dysregulation and oncogenesis has been increasingly recognized in various autoimmune disorders like IgG4-RD and documented in the literature. In IgG4-RD, the accumulation of IgG4-positive plasma cells and resulting fibrotic tissue remodeling have raised concerns about the potential for immune-related oncogenesis. The continuous and unchecked proliferation of these cells, alongside chronic inflammation, can create an environment conducive to tumorigenesis. A prospective cohort study by Tang et al. investigated the incidence, risk factors, and prognosis of malignancies in patients with IgG4-related disease (IgG4-RD). After thoroughly analyzing data from 587 IgG4-RD patients, the study identified 17 cases of malignancy, with a significantly higher standard incidence ratio (SIR) of 2.78 [17]. The results from this study indicate that IgG4-positive plasma cells, while generally associated with anti-inflammatory responses, may contribute to an oncogenic milieu by promoting prolonged cellular proliferation, disrupting normal tissue architecture, and playing a role in malignancy.

Chronic inflammation, a hallmark of IgG4-RD, is well-documented to be a predisposing factor for oncogenesis. In the context of IgG4-RD, persistent inflammation and tissue damage may lead to genomic instability and mutations, providing a fertile ground for cancer development. The role of cytokines, such as IL-4 and IL-10, which are elevated in IgG4-RD, in promoting cellular proliferation and fibrosis is particularly noteworthy. These cytokines are known to stimulate fibroblast proliferation and extracellular matrix deposition, processes that can inadvertently favor the growth of neoplastic cells [18]. Additionally, the presence of regulatory T cells and their associated cytokines, which are also prominent in IgG4-RD, may suppress anti-tumor immunity, further increasing the risk of malignant transformation.

The clinical implications of immune-related oncogenesis in IgG4-RD are profound. Patients with IgG4-RD exhibiting unusual or aggressive cutaneous manifestations should be carefully monitored for signs of malignancy. This includes evaluating the potential for tumor formation in areas of significant IgG4-positive plasma cell infiltration and fibrosis. A review by Chen et al. highlights the potential in the identification of biomarkers associated with tumorigenesis, in the context of IgG4-RD. The review suggests that this could provide valuable insights into the disease's progression and aid in early detection of malignancies [19]. Future research is warranted and should focus on elucidating the exact mechanisms by which IgG4-mediated immune responses contribute to oncogenesis and exploring strategies to mitigate these risks while managing the underlying autoimmune condition.

Comprehensive Immunohistochemical Analyses of Skin Biopsies

Studies using immunohistochemistry (IHC) can detect and examine the presence, distribution, and degree of expression of particular proteins in tissue samples. This provides insightful information on biological mechanisms and disease processes. IHC staining accuracy depends on the careful selection of antibodies that have been shown to identify particular epitopes. Proteins can be distinguished from one another via gel electrophoresis according to their size, charge, or conformation. To resolve cross-reactivity concerns, the proteins are subsequently transferred to a membrane (i.e., western blot) using certain antibodies [20,21]. While negative controls verify certain interactions, positive controls validate staining [20]. By seeing the antibody binding sites under a conventional or fluorescent microscope, the locations can be found. Visualization can be aided by markers such as radioactive elements, enzymes, fluorescent dyes, or colloidal gold [18]. IHC's main goal is to use the least quantity of antibody while staining with the least amount of damage to cells or tissue. IHC has become a key method that is widely used in various clinical diagnostic and medical research contexts. IHC has an advantage over traditional enzyme staining techniques, which can only identify a limited variety of proteins, enzymes, and tissue structures since it depends on specific antigen-antibody interactions [21].

IgG4-RD is an immune-mediated disorder that can impact multiple organs, including the skin. It is characterized by IgG4-positive plasma cell infiltration, fibroinflammatory changes, and high serum IgG4 levels [22]. A biopsy is necessary for diagnosis, particularly in cases when there are cutaneous symptoms. This is because skin involvement frequently occurs after visceral organs and although visceral organ biopsies may be present, they can prove nondiagnostic [19-21]. IgG4-RD cutaneous symptoms tend to be confined to the periauricular, face, and mandibular areas and might appear as nonspecific erythematous papules, nodules, or pruritic plaques [22-24]. Because total IgG stains poorly, immunohistochemical methods are necessary to identify intraepidermal IgG4 deposits [25].

In addition to the skin exhibiting the cutaneous manifestations of IgG4-RD, selection criteria for skin biopsies using tissue registry databases can look for dermatoses associated with elevated levels

of dermal and/or subcutaneous plasma cells, as well as specimens with squamous atypia [23,24]. Comprehensive diagnostic criteria for IgG4-RD were proposed in 2011, with a focus on elevated serum IgG4 levels above 135 mg/ml and abundant IgG4-positive cell infiltration (> 40% of IgG-positive plasma cells being IgG4-positive and > 10 IgG4-positive cells per high power field) in biopsy samples [26]. The ratio of IgG4-positive to IgG-positive cells is regarded as more diagnostically relevant than the absolute quantity of IgG4-positive cells [1]. It is crucial to note that skin biopsies with mildly elevated IgG4+ plasma cell density and IgG4/IgG ratio are not reliable markers of diagnosing IgG4-RD in patients who have conflicting systemic evidence for the disease [24].

Dense lymphoplasmacytic infiltration, a storiform fibrosis pattern, and obliterative phlebitis are important histological hallmarks for diagnosing IgG4-RD, especially when IgG and IgG4 staining are insufficient [1,22,23,27]. Storiform fibrosis is defined as spindle-shaped cells with inflammatory cells and fine collagen fibers while obliterative phlebitis is fibrous venous obliteration with inflammatory cells [1]. Multiple studies have found an IgG4+/IgG+ plasma cell ratio greater than 40% as well as the specific histological hallmarks to be diagnostic of IgG4-RD [1,24,26].

The 2020 revised comprehensive diagnostic criteria for IgG4-RD include three major aspects. The first criterion is diffuse or localized swelling in a mass or nodule, which indicates organ involvement. The second criterion is serum IgG4 concentrations more than 135 mg/dl. The third criterion is the presence of two of the following: dense lymphocyte and plasma cell infiltration with fibrosis, a ratio of IgG-positive cells/IgG4-positive plasma cells >40% and a number of IgG4-positive plasma cells greater than 10 per high powered field, or the presence of storiform fibrosis or obliterative phlebitis [1]. Patients who fulfill the first and third criterion are diagnosed with probable IgG4-RD, whereas those who meet criterion one and two are suspected of having IgG4-RD. Furthermore, patients with probable or possible IgG4-RD who meet organ-specific criteria are also diagnosed with definite IgG4-RD [1]. Combining extensive diagnostic criteria with organ-specific criteria improves diagnostic sensitivity and specificity [1,27].

Being a direct pathogen, IgG4 works without the help of complement or cell-dependent cytotoxicity. A subtype of IgG4-RD with higher inflammatory characteristics, such as numerous organ involvement, strong inflammatory markers, and perhaps increased treatment resistance, is indicated by elevated serum IgG4 levels [24]. While some patients have circulating plasmablasts independent of serum IgG4 levels, others have enhanced IgG4+ plasmablasts [4,28,29]. However, there was a stronger correlation between disease activity and larger elevations in IgG4+ plasmablasts [29]. Increased disease activity was also discovered to be caused by eosinophilia and fibrosis, which are promoted by elevated levels of cytokines, such as interleukin-1β, transforming growth factor-β1, and interferon-γ, and cytolytic molecules, such as perforin, granzymes A and B [29,30]. In addition to being indicators of inflammation and fibrosis, biomarkers such serum IgG2, soluble IL-2 receptor, and chemokine C-C motif ligand 18 can also be used to predict therapy response in IgG4-RD patients [27]. Furthermore, Eotaxin-3 is a recently discovered biomarker for IgG4-RD [29]. IgG4-RD is found to have autoantibodies against autoantigens such as Galectin-3 and Laminin-511-E8, which may possibly be used as possible diagnostic indicators in the future [29]. The pathophysiology of IgG4-RD is further illuminated by the aberrant growth of plasmablasts, CD4+ cytotoxic T cells, and follicular T helper cells, which show changes in the acquired immune system [30].

Clinical Spectrum of IgG4-RD-Associated Dermatological Manifestations

Common cutaneous manifestations of IgG4-RD include pruritic papules, plaques, nodules, and subcutaneous masses. Many patients also report inflammation-induced enlargement of lacrimal and salivary glands. Presentations of IgG4-RD include IgG4-RSD, a related skin disease characterized by sclerotic plaques and nodules, in addition to other presentations such as eosinophilic angiocentric fibrosis and granuloma annulare-like lesions [29]. IgG4-RSD can occur as an isolated case of cutaneous disease, or in association with other systemic IgG4-RD, potentially involving other organs.

IgG4-related skin lesions tend to be firm to the touch, while also exhibiting an indurated texture, both singularly or in multiples. These legions often present with redness (erythema), scaling, or ulceration, and can present across various anatomical sites, most commonly the face, trunk, and extremities. IgG4-RD often present challenges in diagnosis and management as they can morphologically resemble a multitude of other dermatological conditions including sarcoidosis, granuloma annulare, and cutaneous lymphoma, highlighting the importance of histopathological examination in order to obtain accurate diagnosis. Iaccarino et al. identify best practices to assess IgG4-RD, emphasizing comprehensive care and the collaboration between specialists to ensure that a patient's entire clinical history, thorough physical examination, specific laboratory investigations, and appropriate radiology studies have been conducted [31].

As discussed, differential diagnosis of IgG4-RD often includes other dermatological conditions that are inflammatory, neoplastic, or infectious in nature. These differential diagnoses and diagnostic challenges are enunciated by the effect of overlapping clinical and histopathological features of IgG4-RD with other diseases. A review of the literature suggests that characteristic findings from histopathological examination are required in order to achieve a definitive diagnosis of IgG4-related disease. Of note, these findings include lymphoplasmacytic infiltration, obliterative phlebitis, storiform fibrosis, and elevated IgG4-positive plasma cell counts [32]. As a result, a multidisciplinary approach is required with the involvement of numerous medical specialists including dermatologists, rheumatologists, and pathologists, emphasizing the importance of adopting an interdisciplinary approach [2].

Immunomodulatory therapies can include glucocorticoids, rituximab, and other steroid-sparing agents, and tend to be the mainstays of treatment of IgG4-related disease and cutaneous manifestations in general. Patients' response to treatment varies substantially between patients; some patients experience rapid improvement in skin lesion recovery whereas others require long-term maintenance therapies in order to prevent relapse of the disease. Treatment response requires close monitoring of disease activity in order to optimize therapeutic outcomes and reduce the risk of disease progression and recurrence. However, further research is warranted to refine the scientific community's understanding of IgG4-RD and its dermatological manifestations, particularly in the area of establishing guidelines and best practices to further insight into the complex features of this autoimmune disorder [33].

Future Research Directions

The future of research in IgG4-RD presents a promising yet challenging landscape. As our understanding of this complex condition deepens, the focus shifts toward improving diagnostic precision, enhancing therapeutic efficacy, and elucidating the long-term implications of the disease, especially its dermatological manifestations. One of the critical challenges in managing IgG4-RD is the lack of specific biomarkers for early and accurate diagnosis. Current diagnostic criteria heavily rely on histopathological examination and IgG4 serum concentrations, which may not be elevated in all patients or could be elevated in other conditions. Potential areas of future research include the exploration of genetic markers, autoantibodies, or unique cytokine profiles that could distinguish IgG4-RD from other fibroinflammatory and autoimmune diseases.

While current treatments for IgG4-RD, including glucocorticoids and rituximab, have shown efficacy in managing the disease, they do not offer a cure and are associated with significant side effects. The identification of novel therapeutic targets is crucial for developing more effective and safer treatments. Research should delve into the molecular and cellular mechanisms underlying IgG4-RD pathogenesis, with a particular focus on the role of specific cytokines, growth factors, and signaling pathways in driving fibrosis and inflammation. Investigating the potential of targeting T-cell subsets, B-cell maturation, or specific cytokine receptors could guide the development of immunomodulatory therapies that address the underlying immune dysfunction in IgG4-RD.

The long-term outcomes of dermatological involvement in IgG4-RD are poorly understood. Future longitudinal studies are needed to assess the prognosis of patients with skin manifestations, including the risk of progression to systemic disease, the impact on quality of life, and the long-term efficacy and safety of current treatments. Research in this area should also explore the potential for skin lesions to serve as a prognostic indicator or marker of disease activity in IgG4-RD. By focusing on these key areas, we can anticipate significant advancements in the diagnosis, management, and understanding of dermatological manifestations of IgG4-RD, ultimately improving patient care and outcomes.

Areas for Future Research

Current diagnostics of IgG4-RD involve clinical and histopathological features, along with elevated IgG4, although this is non-specific. Due to the technical challenges and invasive nature of biopsies, several biomarkers are under investigation to improve diagnostics. In one study of orbital IgG4-RD, elevated IgG2 was found to be elevated, which may prove to be an indicator of IgG4-RD disease activity [34]. Similarly, soluble Interleukin-2 Receptor was found to be elevated in a small study of patients with IgG4-RD, and may emerge as an indicator of disease activity [35]. CC-Chemokine Ligand 18 was similarly correlated with IgG4-RD in a small study [36]. There is limited evidence that other markers of inflammation, including ESR and CRP, may correlate with IgG4-RD [37]. Future research in larger patient cohorts is needed to validate the use of these novel biomarkers.

Although B cells, plasmablasts, and T cells have been implicated in the pathophysiology of IgG4-RD, the exact mechanism of the disease, including the role of IgG4 and T cells, has not been fully elucidated [2,38]. Further mechanistic studies are needed to fully understand the pathophysiology of IgG4-RD, which may also reveal novel biomarkers or therapeutic targets for IgG4-RD.

While IgG4-RD are classically treated with glucocorticoids or glucocorticoid-sparing agents such as rituximab, there has been no consensus on the treatment of dermatologic involvement of IgG4-RD [39]. Although a recent case report showed evidence of improved dermatologic manifestation with dupilumab, an IL-4 and IL-13 antagonist [30], further randomized controlled trials are needed to determine the efficacy of treatments in patients with IgG4-RD with dermatologic manifestations. Finally, as IgG4-RD is a newly recognized autoimmune disorder with emerging treatments, longitudinal studies are needed to assess disease progression and treatment response.

Conclusion

Our review helps uncover further knowledge of IgG4-RD regarding its immunopathogenesis and clinical spectrum of dermatological presentation. This information can guide clinicians as they diagnose and treat IgG4-RD. We highlight the complex autoimmune cytokine signaling in IgG4-RD, which leads to skin inflammation and subsequent fibrosis. Skin biopsy is essential for IgG4-RD diagnosis; and key histopathological features include a dense lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis. Cutaneous manifestations of this disease include pruritic papules, plaques, firm nodules, enlarged lacrimal and salivary glands, and subcutaneous masses. Since these dermatological presentations are common to many other conditions, such as sarcoidosis, granuloma annulare, and cutaneous lymphoma, a multidisciplinary approach is crucial for diagnosis. Histopathology of skin biopsies in conjunction with imaging and IgG4 serum concentrations help uncover IgG4-RD. The current treatment guidelines include immunomodulatory agents like glucocorticoids and rituximab with close monitoring to ensure improvement and prevent recurrence. As we look to the future for this complex disease, discovering a discrete biomarker

would provide immense clarity for diagnostic purposes and guide clinicians toward prompt treatment. In addition, treatments for this condition do not guarantee a cure; thus, novel therapeutic strategies are necessary to improve patient outcomes.

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