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CASE REPORT OPEN ACCESS

Wiskott-Aldrich syndrome complicated with IgG4-related Sclerosing disease: A case report and literature review

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Abstract
Wiskott-Aldrich Syndrome (WAS) is an X-linked immunodeficiency characterized by eczema, microthrombocytopenia, and recurrent infections. Immunoglobulin G4-related disease (IgG4-RD) is a fibroinflammatory disorder involving various organs. We present a 34-year-old male with WAS who developed cervical lymphadenopathy and parotid gland swelling. Initial biopsies were inconclusive and imaging suggested pleomorphic adenoma. Given the persistent cervical lymphadenopathy and the underlying immunodeficiency, lymphoma was also considered in the differential diagnosis. However, histopathological examination of excised salivary gland and lymph nodes revealed lymphoplasmacytic and eosinophilic infiltrates, numerous IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis, consistent with IgG4-RD. The patient responded well to prednisone therapy. This case emphasizes the importance of considering IgG4-RD in the differential diagnosis of lymphoproliferative lesions in immunodeficient individuals and highlights the diagnostic value of histopathological evaluation in excisional tissue specimens. To our knowledge, this represents a rare coexistence of WAS and IgG4-RD not previously reported in the literature.

Introduction

Wiskott-Aldrich Syndrome (WAS) is a rare X-linked immunodeficiency characterized by thrombocytopenia, eczema, and recurrent infections, and classified as a syndromic combined immunodeficiency with syndromic features according to the 2022 criteria.[1-3] WAS is caused by mutations in the WAS gene on Xp11.22-p11.23, which encodes WAS protein (WASp), a key regulator of hematopoietic and immune cell function. Disease severity varies by mutation type. While premature termination and deletion mutations usually lead to severe, classic WAS, certain missense mutations result in milder forms and activating mutations may cause severe congenital neutropenia.[4-6] The estimated incidence of classic WAS is approximately 1 in 100,000 live male births.[7] A clinical scoring system (0-5) proposed

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by Zhu et al. incorporates thrombocytopenia, eczema, autoimmunity, immunodeficiency, and malignancy; scores ≥ 3 define classic WAS, while a score of 5 often indicates autoimmunity or malignancy.[8,9] Patients are predisposed to infections, bleeding, autoimmune diseases, and malignancies, particularly B-cell lymphoma and leukemia, with a malignancy risk estimated to be over 100 times higher than in the general population and increasing with age.[5,10]

Immunoglobulin G4-related disease (IgG4-RD) is a rare immune-mediated fibroinflammatory disorder that can affect nearly any organ, and if left untreated, may lead to organ failure and death.[11-13] First defined in 2003, it is histopathologically characterized by dense lymphoplasmacytic infiltrates rich in IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis.[14,15] Diagnosis requires a combination of clinical, radiological, laboratory, and histopathological findings, as serum IgG4 elevation lacks adequate sensitivity and specificity. In 2019, The European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) established classification criteria for IgG4-RD, requiring evidence of involvement of a characteristic organ.[15] Although its chronic course, responsiveness to immunosuppression, and association with autoantibodies suggest an autoimmune basis, there is a lack of any definitive proof.[13,16,17] IgG4-RD typically presents with tumor-like organ enlargement and can affect structures such as the lacrimal and salivary glands, orbits, thyroid, bile ducts, pancreas, retroperitoneum, aorta, lungs, meninges, and kidneys.[13]

This case report presents a unique co-occurrence of two rare diseases, and to our knowledge, it represents the first instance documented in the literature.

Case Report

Our patient was a 34-year old male who had purpuric lesions on his legs (Figure 1A) and eczema since he was a year old. When he presented with thrombocytopenia and eczema along with a strong family history (diagnoses of WAS in his brother and aunt's children), genetic tests were performed, after which he was diagnosed with WAS since the age of four. Our patient did not give consent for curative treatment options because his brother, who was followed up with the same diagnosis, died after bone marrow transplantation for lymphoma. By age 16, he had been put on monthly intravenous immunoglobulin (IVIG) replacement therapy and trimethoprim-sulfamethoxazole prophylaxis due to his frequent sinusitis and upper airways infections. In his 20s, he complained of swelling on the left side of his neck that turned out to be a lymphadenomegaly 3 × 2 cm in size, suggestive of lymphoma. The patient, who had no B symptoms, had undergone fine needle aspiration biopsies performed at repeated intervals several times that showed no evidence of malignancy and findings were suggestive of reactive lymphoid hyperplasia. The lymph node, which was observed with left cervical lymphadenomegaly of 3 × 2 cm in size for the last 4 years, grew to 4 × 3 cm in 2 years. Recently, the patient presented to the Ear, Nose and Throat (ENT) service with increasing pain and swelling on the left side of the neck (Figure 1B); physical examination revealed a significant swelling in the left parotid gland which was accompanied by left cervical lymphadenomegaly measuring 4 cm. The ultrasound of the neck revealed widespread heterogeneous parenchymal echoes within the left parotid gland. A mass lesion measuring 45 × 27 mm was observed in the left submandibular-jugulodigastric area, alongside another mass lesion within the parotid gland measuring 17.5 × 17 mm. In the left cervical chain, lymph nodes with a short axis exceeding 1 cm and thick cortices were noted. Additionally, a thickened cortex supraclavicular lymph node measuring 24 × 11 mm was identified in the left posterior cervical region, along with numerous lymph nodes with a short axis less than 1 cm. Preoperative imaging with nasopharyngeal magnetic resonance revealed a lesion originating from the inferior lobe of the left parotid gland. The mass was superficial, enhanced upon contrast administration, and measured 32 × 52 × 58 mm in dimensions. The characteristics of the mass were suggestive of a pleomorphic adenoma. He started having night sweats and chills. Consequently, the patient underwent a neck exploration due to the suspicion of a pleomorphic adenoma. Samples from the salivary glands and lymph nodes were sent for pathology. Approximately 10 days postoperation, he was admitted to our immunology clinic with complaints of fever, pain, and swelling on the left side of the neck. There was a stiffness on the submandibular region secondary to the operation (Figure 1C). Additionally,

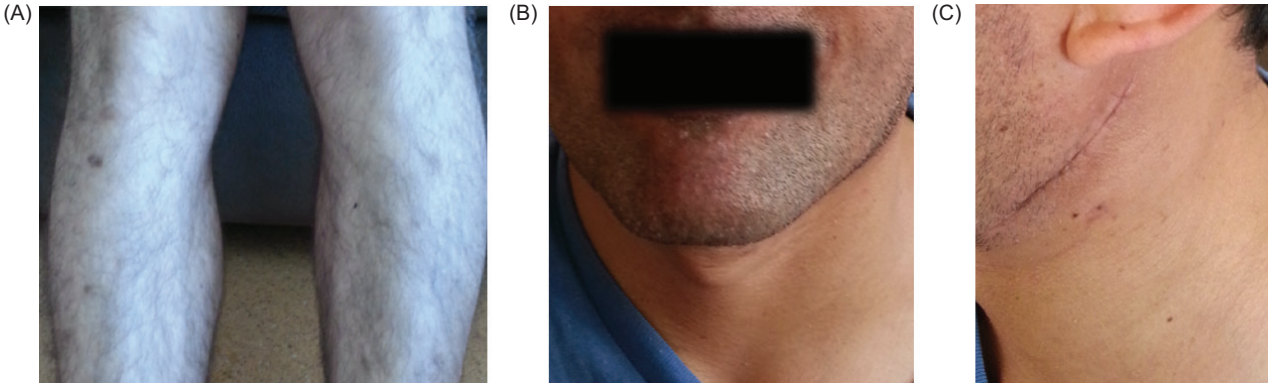

Figure 1 (A) Purpura on the legs; (B) swelling on the left side of the neck before the operation; (C) swelling on the left side of the neck after the operation.

a 20 mm mobile, painful, hard mass was detected around the supraclavicular region. Cultures were taken from the patient and empirical antibiotic therapy was initiated. The patient was screened for any evidence of infection or malignancy. Cultures and imaging studies all came back as negative. During inpatient follow-up, the pathology was compatible with the diagnosis of IgG4-related sclerosing disease (subtype with an inflammatory pseudotumor-like appearance). The pathology report and the laboratory results of the patient, with detailed results of the immunohistochemical staining and whose serum IgG4 level was 0.518 g/L (normal range from 0.039 to 0.864), is provided in Table 1. The patient was under regular immunoglobuline replacement therapy during the immune workup. Based on clinical, pathological, and laboratory findings, the patient was diagnosed with IgG4-RD and subsequently started on prednisone therapy with 60 mg/day. Fever and tenderness resolved within a week. A dramatic response was achieved with the reduction in the size of the enlarged lymph nodes within 5 weeks. The steroid treatment was tapered and discontinued over a period of 10 weeks. Upon recurrence 3 months later, prednisone was reinitiated with 24 mg/day; an effective response was obtained. The prednisone dose was rapidly reduced to 5 mg/day within 6 weeks and was completely discontinued over 12 weeks.

The coexistence of WAS and IgG4-RD in this patient highlights the diagnostic and therapeutic complexity of rare immune disorders, offering valuable insight into clinical immunology.

Discussion

Our patient was a male diagnosed with WAS, classified as one of the combined immunodeficiency with rare syndromic features.[1-3] In patients with WAS, infections, bleeding, autoimmune diseases, and malignancies, primarily lymphomas, as increasingly reported in recent publications, are the major causes of death. The relative risk of malignancy is 100 times greater than normal and increases with age.[10] Our patient was closely monitored due to lymphadenopathy on the left side of the neck, initially investigated for malignancy; recurrent fine needle aspiration biopsies and incisional biopsies suggested reactive lymphoid hyperplasia. Upon growth in lymphadenopathy and accompanying parotid gland swelling, excisional biopsy reported IgG4-RD; he responded dramatically to prednisone treatment. It is crucial to obtain excisional biopsies and provide accurate information to the pathologist. IgG4-RD is a rare, immune-mediated, fibroinflammatory disease that can progress to organ failure and death if left untreated.[11-13,18] As in our patient, common features include subacute tumorous growth in affected organs and a characteristic storiform pattern of fibrosis accompanied by rich IgG4-positive plasmacytic infiltration on pathological examination. It is commonly seen in middle-aged and older men, with high serum IgG4 concentrations present in 60–70% of these patients.[19] Although serum IgG4 level was within the normal range in our case, we emphasize that up to 30–40% of histologically confirmed IgG4-RD cases may have normal serum IgG4 levels, as supported in multiple studies.[18,20,21] Hence, tissue histopathology and clinical-radiological correlation as well as optimum response to specific treatment were decisive in our diagnostic process. It is important to note that serum IgG4 levels are not high in all patients and that elevations in serum and tissue IgG4 concentrations are not specific to IgG4-RD. Elevation of serum IgG4 can be seen in a number of other conditions, including multicentric Castleman disease, allergic diseases, sarcoidosis, and antineutrophil cytoplasmic antibody-associated vasculitis.[18]

Establishing the diagnosis of IgG4-RD can be challenging in patients with inborn errors of immunity due to overlapping clinical features, an increased prevalence of disease mimickers, ongoing immunomodulatory treatments, and underlying immune dysregulation. Our patient was a middle-aged male with a normal serum IgG4 level.

Table 1 The patient's laboratory results and biopsy report of left neck lymph node and salivary gland: Microscopy.

Laboratory results	Platelet	14 × 10^9/L (150–400)	IgG*	16.3 g/L (7.51–15.6)
	MPV	3.8 fL (6.5–10.5)	IgA	1.06 g/L (0.82–4.53)
	Lymphocyte	1.14 × 10^9/L (1.5–4)	IgM	0.264 g/L (0.46–3.04)
	Beta-2-microglobulin	3.65 mg/L (1.09–2.53)	IgG2	5.93 g/L (2.42–7.0)
	Antinuclear antibody	Negative	IgG4	0.518 g/L (0.039–0.864)
	Sedimentation	63 mm/hour (< 15)	CRP	11.1 mg/L (0.0–5.0)
Microscopy report	There is a marked expansion of the interfollicular area within the lymph node with fibrosis notably prominent, especially at the periphery of the lymph node and areas adjacent to the salivary gland. Follicular structures displaying regressive changes in germinal centers are present, alongside vascular proliferation, fibrosis, histiocytic, myofibroblastic, and plasma cells, eosinophils, small lymphocytes, and rare large blastic cells in the interfollicular area. The foci of fibrosis are storiform pattern in places. Focally, the number of IgG4-positive cells at high magnification is over 50 and the overall IgG4/IgG ratio is over 40%. Plasma cell population is significantly increased in CD138 staining, and kappa and lambda staining is polytypical. The findings primarily support a diagnosis of IgG4-related sclerosing disease (subtype with an inflammatory pseudotumor-like appearance). Clinical and laboratory correlation is recommended for a definitive diagnosis.			

MPV: mean platelet volume; Ig: immunoglobulin; CRP: C-reactive protein; mg: milligram; L: liter; dL: deciliter.
*: Immunoglobulins were measured under immunoglobuline replacement therapy.

This highlights the unmet need for additional, easily accessible biomarkers to facilitate the accurate diagnosis of IgG4-RD. IgG2 is an accessible, recently described biomarker for IgG4-RD, and findings from a retrospective descriptive study suggest that serum and tissue IgG2 levels may serve as reliable biomarkers for distinguishing patients with IgG4-RD from healthy individuals.[22,23] Notably, serum IgG2 cutoff value of > 5.3 mg/L yielded a sensitivity-to-specificity ratio of 0.90 in differentiating cases. Our tests confirmed that our patient had relatively high (5.93 g/L) IgG2 levels, even though it was in normal range. IgG2 can serve as a reliable biomarker to differentiate patients with IgG4-RD from healthy individuals; however, the patient's ongoing immunoglobulin replacement therapy constituted a confounding factor in the interpretation of aforementioned findings. A definitive diagnosis requires strict clinical-pathological correlation. The condition is generally sensitive to glucocorticoid therapy, with prednisolone at 0.6 mg/kg/day recommended as the first-line treatment. After two to four weeks of induction dosing, steroids are tapered based on the patient's response, with the goal of discontinuing treatment within 3–6 months. For patients resistant or intolerant to glucocorticoids and other treatments, B-cell directed therapy (Rituximab) can be considered.[18,19] Maintenance therapy with low-dose prednisolone (2.5–5 mg/day), azathioprine (2–2.5 mg/kg/day), calcineurin inhibitors, cyclophosphamide, mycophenolate mofetil, methotrexate, or other agents is recommended for multiorgan disease, significantly elevated serum IgG4 levels, or a history of relapse.[18] To our knowledge, our case is the first reported instance of WAS coexisting with IgG4-RD. The diagnosis of IgG4-RD should be considered in patients with inborn errors of immunity who present symptoms similar to those of lymphoma, such as lymphadenopathy and/or nonspecific edema of the salivary glands.

Conclusion

IgG4-related disease should not be treated merely as part of the differential diagnosis in patients with inborn errors of immunity. On the contrary, especially when clinical findings are suggestive, it should be actively considered as a coexisting diagnosis, regardless of serum IgG4 levels. IgG4-RD is difficult to recognize. In addition to clinicians having an awareness of the disease, it is very important to obtain an excisional biopsy for an accurate histopathological examination. It is also crucial to provide detailed clinical information for the pathologist, especially if IgG4-staining is not routine in the institution. This case is notable not only for the coexistence of WAS and IgG4-RD, but also for the challenging management and diagnostic complexities associated with dual rare pathologies. IgG4-RD may represent a critical codiagnosis in inborn errors of immunity patients and must not be underestimated.

Competing Interests

The authors had no relevant financial interests to disclose.

Author Contributions

All authors contributed equally to this article.

Written informed consent for publication of the case details and accompanying images was obtained from the patient (anonymity has been ensured).

Conflicts of Interest

None.

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