Rosai-Dorfman disease associated with myasthenia gravis

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Abstract

We present the case of a 29-year-old patient with a prior diagnosis of myasthenia gravis at age 20, who years later developed skin lesions compatible with Rosai-Dorfman disease on histopathological testing.

She initially had a stable lesion on her right auricle, and then progressed with new lesions on her right buttock, thigh and knee. With the onset of multifocal, recurrent lesions, oral corticosteroid therapy cycles were started, achieving a transient reduction in the size and color of the lesions, but with recurrence when the treatment was stopped.

Currently, the patient is stable, having received multiple corticosteroid cycles over the last few years. The association of these two conditions is extremely rare and points to a possible immunopathological interrelationship. This case illustrates the difficulties in effective long-term management of the skin lesions associated with Rosai-Dorfman disease, which in this particular case required multiple corticosteroid cycles with a transient benefit.

Studies of more sustainable treatments and/or with a better response profile are needed. Communicating these rare cases encourages the exchange of knowledge and experiences among specialists.
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Keywords: *Rosai-Dorfman, myasthenia gravis, steroid therapy.*

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Introduction

Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a rare disease of unknown origin characterized by excessive proliferation of histiocytes in the lymph nodes and other extranodal tissues. It was first described in 1969 by Rosai and Dorfman (1). The disease most commonly occurs in children and young adults but may develop at any age. It is characterized by massive lymphadenopathy, mainly in the neck and supraclavicular region. However, it can also affect other systems like the skin, bones, central nervous system and other organs (2).

Histopathologically, RDD is characterized by the presence of large histiocytes with abundant cytoplasm and emperipolesis, which is the inclusion of hematopoietic cells within the histiocytic cytoplasm. There is also a mixed inflammatory infiltrate composed of lymphocytes, plasma cells and polynuclear cells (3).

There is no established standard treatment for RDD, due to its rarity and clinical diversity. Some cases have shown spontaneous resolution, while others require therapeutic intervention (4). Corticosteroids, like prednisone, tend to be the first-line treatment. However, in refractory cases or those with severe extranodal manifestations, other treatment approaches may be used, like radiation, chemotherapy, immunomodulating agents or surgery (5).

Myasthenia gravis is a chronic autoimmune disease that affects the neuromuscular junction and is characterized by weakness and muscle fatigue. This disease is caused by autoantibodies that interfere with nerve impulse transmission to the muscle, leading to fluctuating muscle weakness and fatigue. This disease can affect people of any age but is most common in young women and older men. The symptoms may range from weakness in the eye and facial muscles to weakness in the neck, arm and leg muscles. In severe cases, the weakness may affect the respiratory muscles, which is potentially fatal (6). The exact mechanism of onset of myasthenia gravis is not fully understood but is thought to involve a complex interaction between genetic, immunological and environmental factors. The autoantibodies are mainly directed against the acetylcholine receptors in the neuromuscular junction, which leads to decreased muscle response (7).

The coexistence of myasthenia gravis and RDD is extremely rare, and only one case has been reported to date in a patient with thymus involvement (8). The coexistence of these two diseases is interesting from a clinical point of view and suggests a possible interaction between the

immunological mechanisms involved in both conditions (9). However, the exact relationship between myasthenia gravis and RDD has not been clearly established, and more research is needed.

It is important to present this clinical case to highlight the clinical relevance of these two diseases coexisting in a young patient. In addition, the fact that the patient did not respond adequately to the standard treatment highlights the need to explore alternative treatment approaches.

Case presentation

This was a young (29-year-old) patient who had been diagnosed with myasthenia gravis at age 20 and developed progressive generalized muscle weakness, asthenia and high acetylcholine receptor antibody titers. Initial treatment with pyridostigmine was effective, and the patient had no relevant complications.

At age 25, the patient developed a lump on her right ear with well-defined borders, no pain and no signs of inflammation, along with a purplish hue in the surrounding skin (Figure 1). In addition, the patient complained of a constant feeling of fullness in the ear and decreased hearing. The lump was biopsied, and the findings were compatible with RDD, showing dense connective tissue with primary lymphoid collections and mixed infiltrate made up of lymphocytes, plasma cells and histiocytes with emperipolesis. Immunohistochemistry tests were positive for S100 (Figure 2).

The ear lesion remained stable; however, three years after diagnosis, the patient began to develop lesions in other parts of her body, including the right gluteus and thigh, as well as the ipsilateral knee. The gluteal lesion continued to grow and therefore required surgical removal.

In view of the constant growth of the skin lesions and appearance of new lesions, oral corticosteroids were started. The cycles consisted of 1 mg/kg doses of oral prednisone daily for one to three-month periods, followed by gradual tapering until the treatment was suspended. While the corticoids were being administered, there was a notable reduction in the size and color of the skin lesions. However, there was an undesirable effect after tapering and suspending treatment, as the lesions that had improved reappeared and showed new growth. This led to restarting short cycles of oral corticosteroid therapy several times.

The patient is currently stable, with skin lesions that, while not disappearing, have stayed the same size, with no new lesions during at least the last year. The patient had received two cycles of oral steroid therapy in 2023, at the time of this writing.

Furthermore, the myasthenia gravis symptoms have been successfully controlled and have disappeared with pyridostigmine treatment alone. However, given the recurrence of the Rosai-Dorfman skin lesions after discontinuing steroids, the patient is under constant monitoring in order to look for new treatment options if the disease reactivates.

Discussion

The combination of RDD and myasthenia gravis in the same patient is a rare and very interesting clinical finding. Although RDD is not itself an autoimmune disease, there seems to be an association between this disease and several autoimmune disorders. An association between RDD and

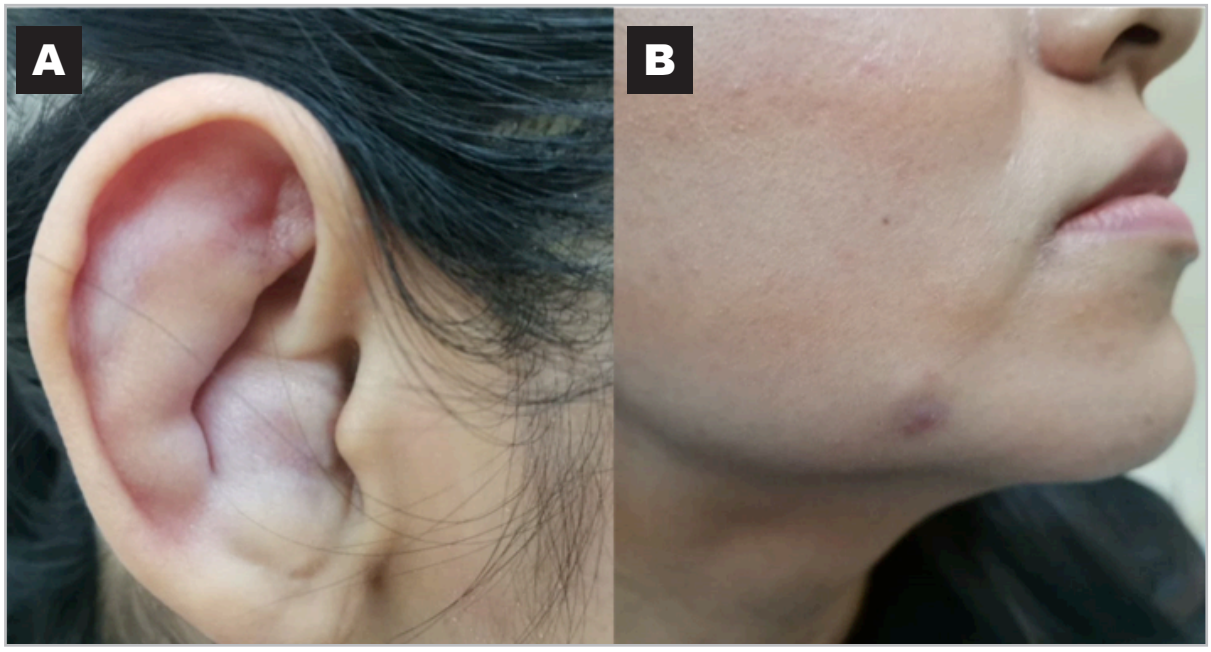

Figure 1. *Skin lesions in the patient.* ***A:*** *The ear lesion shows poorly defined borders with a purplish hue covering almost the entire pinna.* ***B:*** *The jaw lesion has well defined borders with a deeper purplish hue. Both photos highlight the wide morphological variety of skin lesions in Rosai-Dorfman disease.*

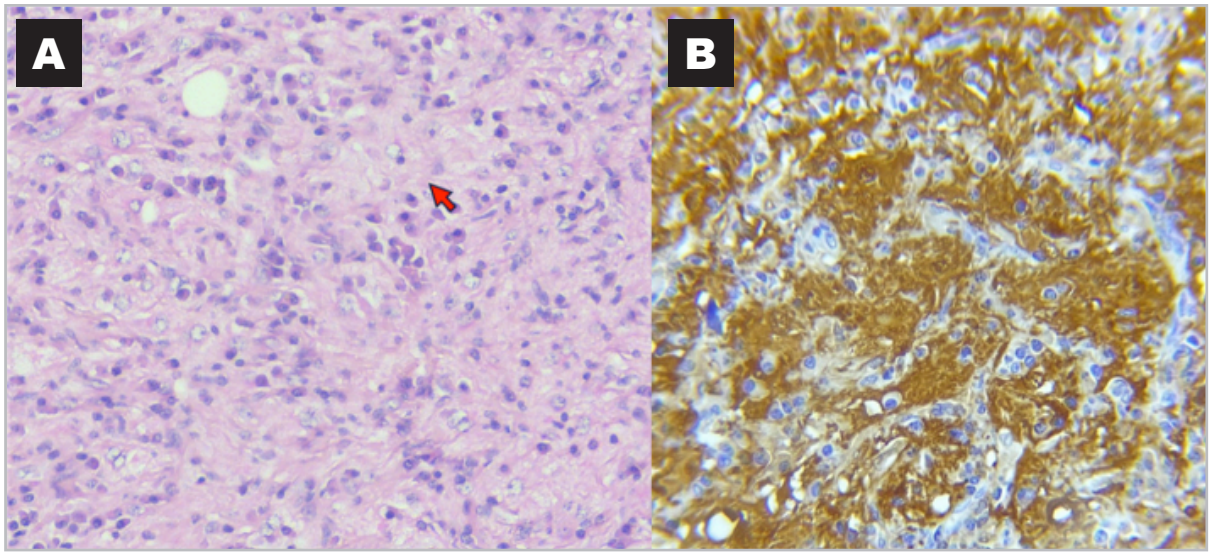

Figure 2. ***Microscopic view of the lesions. A:*** *A mixed inflammatory infiltrate with giant histiocytes highlighting emperipolesis (red arrow).* ***B:*** *S100 positive*

autoimmunity has been mentioned in approximately 10% of cases, with entities like systemic lupus erythematosus, idiopathic juvenile arthritis, autoimmune hemolytic anemia, autoimmune lymphoproliferative syndrome (10) and IgG4-related diseases (11) in a subgroup of patients. This is shown by the reported coexistence of RDD with these diseases, as well as cases of RDD in the context of somatic and germline mutations linked to autoimmune processes. While the exact mechanisms relating RDD and autoimmune disorders have not been completely elucidated, these findings point to a possible common pathogenic basis in some patients (12).

Treating the skin lesions associated with RDD can be a challenge. While corticosteroids are usually the first-line treatment, there is often a partial and unsustained response, with frequent relapses when the medication is discontinued (13), as occurred in the case we presented. This underlines the need to consider alternative or complementary treatment options to achieve more long-term control. Surgery may be curative in unifocal cases but is not very useful for multiple recurrent lesions (14). Some reports indicate a benefit with low-dose oral methotrexate (15) or vincristine as a single agent (16). Other immunomodulating drugs like thalidomide (17), lenalidomide (18) or interferon (19) have also shown activity; however, their toxicity profiles must be considered before beginning treatment.

Given the diversity of the disease, there is probably no single approach which is applicable for all patients. More studies are needed to optimize treatment of the refractory skin manifestations of RDD. Meanwhile, the combination of surgical resection, corticosteroids and second-line agents, sequentially or simultaneously, may be a reasonable strategy to achieve longer remissions (12).

In conclusion, while the management of RDD skin lesions may be complex, we have more therapeutic tools available today to help us advance toward a more sustained, long-term control.

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