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*Case Report*

# Cervical Rosai-Dorfman Disease in a Patient with Blau Syndrome: A Rare Overlap

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## A B S T R A C T

**Introduction:** Rosai-Dorfman disease (RDD) is an uncommon non-Langerhans histiocytosis characterized by massive lymphadenopathy and distinctive histopathological features. Its occurrence in children with complex autoinflammatory conditions is exceptionally rare. Blau syndrome, a monogenic granulomatous disorder caused by NOD2 mutations, leads to early-onset arthritis, uveitis, and cutaneous involvement. The coexistence of RDD and Blau syndrome has not been extensively documented.

**Case presentation:** We report the case of a 13-year-old boy with genetically confirmed Blau syndrome who developed chronic, bilateral cervical lymphadenopathy lasting 10 months. His medical history included polyarthritis, recurrent uveitis, papulonodular skin lesions, and moderate hepatic and renal involvement. He was treated with methotrexate 25 mg/kg weekly and etanercept 30 mg weekly. Despite stable systemic disease, the cervical lymph nodes progressively enlarged. Laboratory testing excluded infectious, autoimmune, and malignant causes. Imaging showed multiple enlarged lymph nodes without necrosis. Excisional biopsy demonstrated S100-positive histiocytes with emperipolesis, consistent with RDD.

**Discussion:** The coexistence of Blau syndrome and RDD poses diagnostic challenges due to overlapping inflammatory manifestations, drug-related lymphoid hyperplasia, and altered immune responses under biologic therapy. Both diseases involve dysregulated macrophage activation, suggesting shared pathogenic pathways. Immunosuppressive therapy may further modulate histiocytic proliferation, complicating disease expression. Biopsy remains the gold standard for diagnosis in persistent lymphadenopathy, particularly in immunomodulated pediatric patients.

**Conclusion:** This case highlights the importance of considering RDD in the differential diagnosis of chronic lymphadenopathy in children with underlying autoinflammatory diseases. Early tissue diagnosis prevents mismanagement and provides essential insight into the interaction between granulomatous and histiocytic disorders. Long-term monitoring is crucial due to the unpredictable course of both conditions.

**Keywords:** Rosai-Dorfman disease; Granulomatous; Histiocytic disorders; Lymphadenopathy; Autoinflammatory diseases

## Introduction

Rosai-Dorfman disease (RDD), described initially by Rosai and Dorfman in 1969, is a rare, benign, idiopathic histiocytic proliferative disorder predominantly affecting children and young adults[1]. The disease classically presents with massive, painless lymphadenopathy, mainly in the cervical region. Histopathology reveals large histiocytes with emperipolesis and immunoreactivity for S100 and CD68, with negativity for CD1a, aiding differentiation from Langerhans cell histiocytosis[2]. Although many cases are self-limited, the variable involvement of extranodal sites and association with immune dysregulation remain poorly understood.

Blau syndrome is a distinct autosomal dominant, monogenic autoinflammatory disorder caused by gain-of-function mutations in the NOD2 gene[3]. It is characterized by early-onset granulomatous arthritis, recurrent uveitis, and papulonodular skin lesions, with occasional involvement of the liver, kidneys, and blood vessels[4]. Management typically requires systemic corticosteroids, methotrexate, and biologic agents such as TNF-α inhibitors[5].

Concomitant presentation of RDD in patients with Blau syndrome is infrequent. Both diseases involve macrophage activation, granulomatous inflammation, and complex cytokine dysregulation, hinting at possible mechanistic overlap. Furthermore, immunosuppressive therapy may alter lymphoid tissue behavior, creating diagnostic ambiguity.

We report a unique case of a 13-year-old child with long-standing Blau syndrome who developed persistent cervical lymphadenopathy ultimately diagnosed as RDD. This case emphasizes the importance of early biopsy in chronic lymphadenopathy in complex immunological contexts and explores potential pathophysiological connections between these two rare diseases.

## Case Presentation

A 13-year-old male followed in paediatric rheumatology since infancy presented with gradually progressive, bilateral cervical lymphadenopathy for 10 months. He had a confirmed diagnosis of Blau syndrome based on a pathogenic NOD2 mutation identified at age two. His past medical history included chronic symmetrical polyarthritis affecting wrists, knees, and small joints; recurrent granulomatous cutaneous lesions; and repeated episodes of bilateral anterior uveitis. He also had low-grade hepatic cytolysis and mild proteinuria attributed to granulomatous involvement **(Figure 1)**.

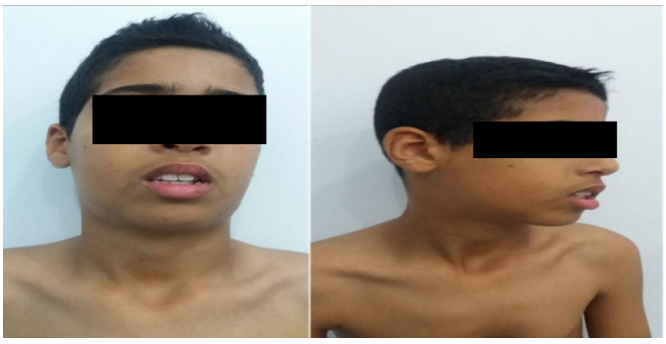

**Figure 1:** Cervical examination of the patient showing cervical swelling.

The patient had been treated with methotrexate 25 mg/kg weekly and etanercept 30 mg/week for the previous year. Under this regimen, his arthritis and uveitis were well controlled, and no significant infectious episodes had occurred.

The cervical swelling was insidious, painless, and progressively noticeable over several months. There were no fevers, night sweats, weight loss, or recent infections. Physical examination revealed multiple mobile, firm lymph nodes bilaterally at levels II and III, the largest measuring approximately 3 cm. There was no hepatosplenomegaly or additional lymphadenopathy.

Initial laboratory tests showed:

- Mild leukocytosis (12,500/mm³)
- ESR: 45 mm/h
- CRP: 18 mg/L
- Normal liver and kidney function tests
- Negative blood cultures

Extended infectious workup was negative for Epstein–Barr virus, cytomegalovirus, HIV, toxoplasmosis, Bartonella, tuberculosis (IGRA), syphilis, and brucellosis.

Autoimmune testing including ANA, ANCA, rheumatoid factor, complement levels, and ACE were unremarkable or unchanged from baseline.

Serum LDH and ferritin were within normal limits, decreasing suspicion for lymphoma or hemophagocytic lymphohistiocytosis.

Cervical ultrasound showed multiple enlarged lymph nodes with preserved fatty hilum and homogeneous echotexture. Contrast-enhanced CT of the neck confirmed bilateral lymphadenopathy without necrosis, calcification, or compression of adjacent structures. No thoracic or abdominal lymph node involvement was detected.

Given persistent lymphadenopathy and inconclusive laboratory results, an excisional biopsy of the largest right cervical lymph node was performed.

Histopathology revealed:

- Dilated sinuses filled with large histiocytes
- Abundant pale cytoplasm with intact lymphocytes and plasma cells inside their cytoplasm (emperipolesis)
- No necrosis or atypical mitotic activity

Immunohistochemistry demonstrated:

- S100-positive histiocytes
- CD68-positive
- CD1a-negative

These findings confirmed the diagnosis of Rosai–Dorfman disease.

A multidisciplinary discussion involving rheumatology, haematology, and paediatrics concluded that the patient did not require new immunosuppressive therapy. Because the disease was confined to lymph nodes and the patient was stable, a conservative approach with observation was chosen.

Over six months of follow-up, the lymphadenopathy gradually decreased in size without complications. His Blau syndrome remained controlled under methotrexate and etanercept. No extranodal RDD manifestations were observed.

## Discussion

This case highlights the unusual coexistence of Blau syndrome and Rosai-Dorfman disease (RDD) in a paediatric patient and raises several diagnostic and pathophysiological considerations.

Children with Blau syndrome often present with chronic inflammatory lymphadenopathy, which is frequently attributed to disease activity or reactive hyperplasia. In addition, immunomodulatory treatments such as methotrexate and TNF-α inhibitors may mask clinical signs that could otherwise suggest infection or malignancy[6]. In our patient, the persistence of lymphadenopathy initially seemed compatible with the underlying inflammatory disease. However, the prolonged evolution in the absence of infectious signs, systemic symptoms, or laboratory abnormalities prompted further investigation. This case therefore illustrates the importance of maintaining diagnostic vigilance in immunomodulated patients, as persistent lymphadenopathy should not automatically be attributed to the primary disease and may require histological confirmation.

From a pathophysiological perspective, a possible link between Blau syndrome and RDD may also be considered. Blau syndrome is a granulomatous autoinflammatory disorder associated with mutations in the NOD2 gene, resulting in chronic activation of macrophages and dysregulation of innate immune pathways[3]. RDD, on the other hand, is a histiocytic disorder characterized by the accumulation of activated histiocytes and altered cytokine signalling[7]. Although these two conditions are distinct, they share several immunological features, including dysregulation of innate immunity, macrophage-dominant inflammation, and activation of NF-κB–related pathways. This overlap raises the possibility that the inflammatory environment associated with Blau syndrome could Favor histiocytic proliferation or immune dysregulation. While a causal relationship cannot be established based on a single observation, the coexistence of these two conditions may warrant further investigation.

Another aspect to consider is the potential influence of immunosuppressive therapy. Agents such as methotrexate and TNF-α inhibitors, including etanercept, can alter lymphoid tissue architecture and modulate immune cell responses[8]. Some reports have described the occurrence of RDD or RDD-like reactions in patients receiving immunosuppressive treatment. Whether such therapy contributed to the development or unmasking of RDD in our patient remains uncertain, but the possibility cannot be excluded. In this case, treatment was maintained because adequate control of Blau syndrome remained necessary. The favourable clinical evolution supports a conservative approach in cases of isolated nodal RDD.

The case also emphasizes the importance of histological confirmation. Imaging findings alone are insufficient to reliably distinguish RDD from other causes of lymphadenopathy such as lymphoma, tuberculosis, sarcoidosis, or Kikuchi disease. Excisional biopsy therefore remains the diagnostic gold standard. In our patient, the identification of characteristic histological features-particularly emperipolesis and S100-positive histiocytes-confirmed the diagnosis[2]. Establishing the diagnosis early also helped avoid unnecessary modifications of immunosuppressive therapy or empirical antimicrobial treatment.

Finally, the management of nodal RDD in children is often conservative. In many cases the disease follows a benign and self-limited course, and systemic treatment is not required unless there are significant symptoms or extranodal involvement[9]. In our patient, careful observation was therefore considered appropriate, and the lymphadenopathy regressed spontaneously over time. Nevertheless, long-term follow-up remains important given the variable and sometimes unpredictable course of both Blau syndrome and RDD.

## Conclusion

The coexistence of Blau syndrome and Rosai–Dorfman disease in this 13-year-old child represents an exceptionally rare and diagnostically challenging scenario. Persistent cervical lymphadenopathy in patients with autoinflammatory disorders should not automatically be attributed to underlying disease activity. This case demonstrates the critical importance of early biopsy in clarifying the aetiology of chronic lymphadenopathy, especially in immunomodulated paediatric patients.

Potential immunopathogenic overlap between Blau syndrome and RDD-both macrophage-centered inflammatory disorders-merits further investigation. Conservative management with close follow-up is often sufficient for isolated nodal RDD. Clinicians should maintain a high index of suspicion and provide long-term monitoring to ensure stable disease course.

## Declarations

### Ethics Approval and Consent to Participate

Not applicable.

### Consent for Publication

Written informed consent was obtained from the patient's family.

### Conflicts of Interest

We stated that there is no conflict of interest to declare.

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