Case Report

A rare triad of Rosai-Dorfman disease: A case report

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ABSTRACT

Rosai-Dorfman disease (RDD) is a rare, benign non-Langerhans cell histiocytosis characterized by the accumulation of $CD68^+$, $S100^+$, and $CD1a^-$ histiocytes, typically presenting as massive, painless cervical lymphadenopathy. Pulmonary involvement in RDD is exceedingly rare. It may manifest with respiratory symptoms, such as chronic cough, dyspnea, and chest pain. We describe the case of a 23-year-old male with immune-related RDD and coexistent juvenile idiopathic arthritis (JIA), who presented with fever, chronic cough, and progressive dyspnea. Imaging revealed extensive bilateral pulmonary involvement and lymph node histopathology confirmed RDD. During hospitalization, the patient developed a right-sided secondary spontaneous pneumothorax, a complication not previously reported in pulmonary RDD. This case highlights the unusual co-occurrence of RDD and JIA with extensive pulmonary involvement culminating in spontaneous pneumothorax. It underscores the importance of considering RDD in the differential diagnosis of atypical pulmonary presentations in young patients, particularly those with underlying autoimmune rheumatic diseases.

Key words: Cervical lymphadenopathy, Emperipolesis, Juvenile idiopathic arthritis, Non-Langerhans cell histiocytosis, Pulmonary Rosai-Dorfman disease, Rosai-Dorfman disease, Spontaneous pneumothorax

Non-Langerhans cell histiocytosis (NLCH) is a rare group of disorders characterized by the abnormal proliferation of histiocytes that lack CD1a and express S100 positivity, distinguishing them from Langerhans cell histiocytosis (LCH) [1]. NLCH encompasses entities, such as Erdheim-Chester disease and Rosai-Dorfman disease (RDD), both of which can involve multiple organ systems [2]. RDD, also known as sinus histiocytosis with massive lymphadenopathy, is a rare idiopathic histiocytic disorder histopathologically defined by the presence of $CD68^+$, $S100^+$, and $CD1a^-$ histiocytes with emperipolesis [3]. First described by Destombes in 1965 and later characterized by Rosai and Dorfman in 1969, it typically presents with bilateral, painless cervical lymphadenopathy and systemic symptoms, such as fever, night sweats, and weight loss [2]. Goyal *et al*. reported that extranodal involvement is seen in approximately 25–40% of cases, most frequently affecting the skin, subcutaneous tissues, bones, and head and neck region [3]. Although pulmonary involvement in RDD is rare, it has been reported in isolated cases and may manifest with non-specific symptoms, such as cough, dyspnea, or chest pain [4]. According to Cartin-Ceba *et al*. [4], the most common radiological intrathoracic finding is mediastinal lymphadenopathy. Other documented thoracic manifestations include interstitial pneumonitis, parenchymal nodules, cystic lung changes, solitary pleural-based lesions, and airway abnormalities, such as air trapping and bronchiectasis [5]. High-resolution computed tomography (CT) may reveal bilateral subpleural reticular opacities, scattered ground-glass attenuation, and mild traction bronchiectasis [5]. Unlike pulmonary LCH, which is strongly linked to cigarette smoking, pulmonary RDD has no known association with tobacco exposure [4]. RDD has also been categorized into three subtypes: Neoplasia-associated RDD, immunoglobulin G4-related RDD, and immune-related RDD [3]. The immune-related subtype has been associated with various autoimmune conditions, including systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, warm autoimmune hemolytic anemia, and multiple sclerosis [2]. However, its coexistence with juvenile idiopathic arthritis (JIA) remains exceedingly rare and sparsely reported.

Here, we present a unique case of immune-related RDD in a young adult with rheumatoid factor (RF)-negative polyarticular JIA, complicated by significant pulmonary involvement and a secondary spontaneous pneumothorax. To our knowledge, this is the first reported case of intrathoracic RDD manifesting with such a complication, highlighting the need for increased

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awareness of this rare presentation and its potential association with autoimmune rheumatic diseases.

CASE REPORT

A 23-year-old male was admitted with complaints of high-grade fever and productive cough for the past 2 months, persisting despite initial empirical treatment. He also reported exertional breathlessness, with oxygen saturation dropping to 84% on room air, disproportionate to the degree of dyspnea. He was a non-smoker and non-alcoholic, with no history of anti-tubercular therapy or prior COVID-19 infection. He was appropriately vaccinated as per the recommendations. The patient had a history of polyarthralgia involving the small joints of the hands for the past 8 years, associated with early morning stiffness. He had been treated intermittently with non-steroidal anti-inflammatory drugs and had received Ayurvedic therapy for approximately 6 months. There were no other significant comorbidities or contributory family history.

On examination, he was of moderate build and nutrition. Vital signs revealed fever, tachycardia, and tachypnea. Notable findings included mild pedal edema and a right-sided cervical lymph node (single, firm, freely mobile, with well-defined borders). Ulnar deviation at the metacarpophalangeal joints of both hands was observed. There were no spinal deformities, bony tenderness, or other septic foci. Cardiovascular, abdominal, and neurological examinations were unremarkable. Pulmonary examination revealed bilateral basal crackles and occasional rhonchi. The trachea was midline, and the bilateral thoraces were equally mobile.

A chest radiograph showed bilateral multiple nodular opacities (Fig. 1a). Contrast-enhanced CT of the thorax revealed patchy and confluent areas of air-space opacification in the right upper lobe, left upper lobe, right middle lobe, lingula, and bilateral lower lobes. Internal air bronchograms and adjacent centrilobular nodules were present, along with multiple enlarged mediastinal lymph nodes, the largest measuring 14 mm in short axis diameter (Fig. 2). Based on clinical and radiological findings, differential diagnoses included tuberculosis, sarcoidosis, septic emboli, and malignancy.

Sputum smear and GeneXpert testing for *Mycobacterium tuberculosis* were negative. Serum angiotensin-converting enzyme and 24-h urinary calcium levels were within normal limits, making sarcoidosis unlikely. No septic foci were identified, and there was no history of skin boils or intravenous drug use. Fine-needle aspiration cytology (FNAC) of a right supraclavicular lymph node suggested granulomatous inflammation. Due to the non-diagnostic FNAC, a surgical excision biopsy of the lymph node was performed for histopathological and immunohistochemical evaluation.

While awaiting the biopsy report, autoimmune serology revealed a significantly elevated anti-cyclic citrullinated peptide antibody level (431 IU/mL) and low-titer RF positivity (4.8 IU/mL). Long-standing joint symptoms and positive serology helped in establishing a diagnosis of RF-negative polyarticular JIA.

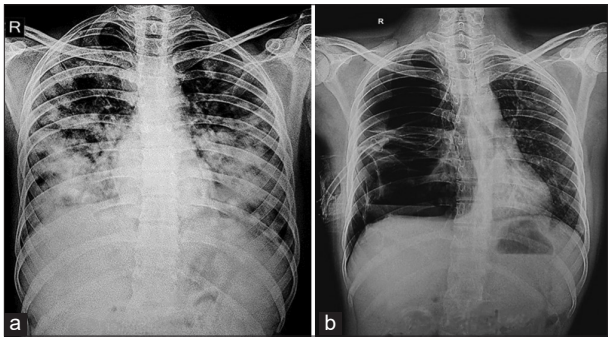

Figure 1: X-ray chest suggestive of bilateral middle and lower zone patchy consolidation

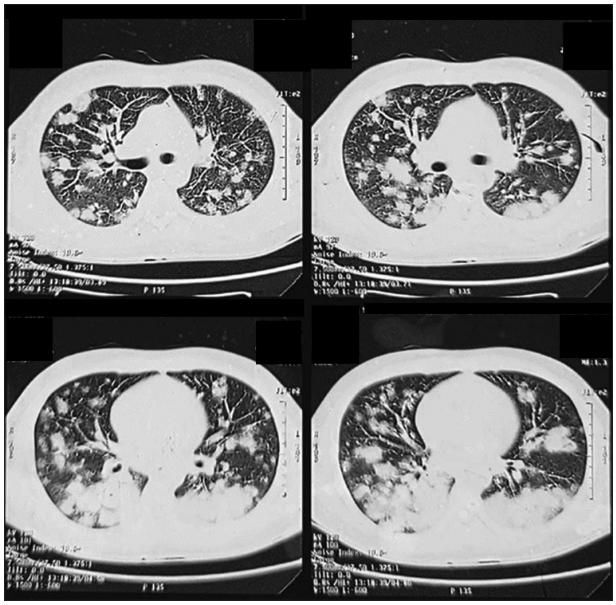

Figure 2: Computed tomography images showing large nodules with "feeding vessel sign" with septal thickening, with peri-septal nodules

Bronchoscopy was performed and showed no endobronchial abnormalities. Histopathological examination of the excised lymph node revealed preserved follicular architecture with markedly distended sinuses containing numerous large histiocytes exhibiting emperipolesis (engulfment of intact lymphocytes and plasma cells) (Figs. 3 and 4). Immunohistochemistry was positive for S100 and CD68, and negative for CD1a, confirming a diagnosis of RDD (Fig. 5).

Given the coexistence of inflammatory arthritis and seropositivity, a final diagnosis of immune-related RDD with associated JIA was established. The patient was started on oral methylprednisolone at 0.75 mg/kg/day initially, which led to symptomatic and radiological improvement over the following days and was gradually tapered over a month.

However, during the hospital stay, the patient developed sudden-onset dyspnea and right-sided pleuritic chest pain. Examination revealed absent breath sounds on the right side. A chest radiograph confirmed a large right-sided secondary spontaneous pneumothorax, which

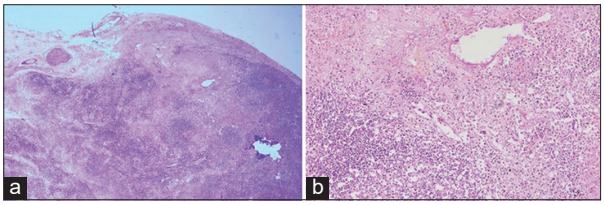

Figure 3: Histopathological examination of the left cervical lymph node showing (a) preserved follicular architecture with (b) markedly dilated sinusoids

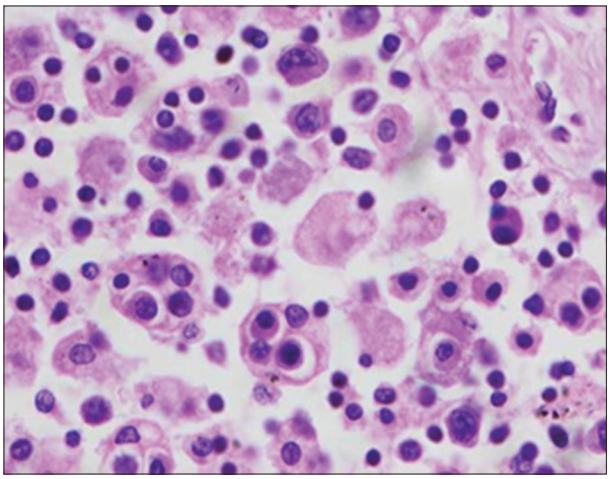

Figure 4: Lymph node biopsy shows emperipolesis with intact lymphocytes seen within histiocytes

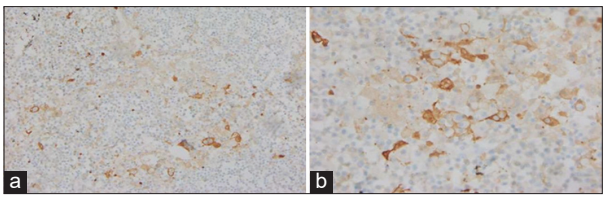

Figure 5: Immunohistochemistry (a) ×10 and (b) ×40 applied on the biopsy specimen showed histiocytes' nuclear/cytoplasmic S100 positivity and the appearance of emperipolesis

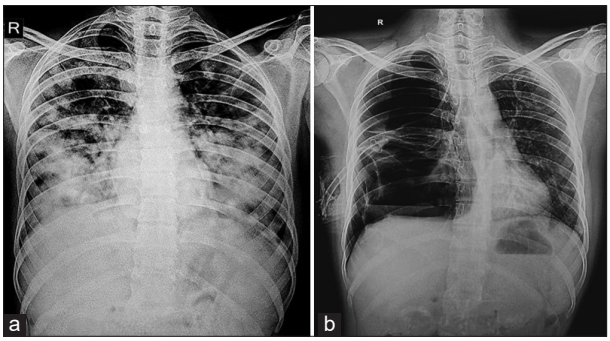

Figure 6: Serial X-ray chest suggestive of healed parenchymal lesions with cyst formation and right sided hydropneumothorax with intercostal drainage tube *in situ*

was managed with intercostal drainage tube insertion (Fig. 6).

Follow-up imaging revealed healing parenchymal lesions with areas of cyst formation and early cavitation (Fig. 7). After a total hospital stay of 45 days, the patient was discharged with the chest drain *in situ*. He showed near-complete radiological resolution at the time of discharge.

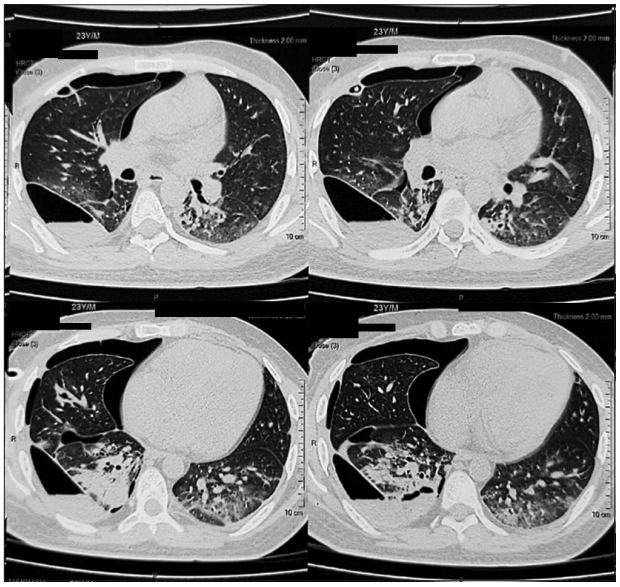

Figure 7: Serial contrast-enhanced computed tomography thorax lung window: Bilateral lower lobe healed parenchymal lesions with residual disease, with right-sided hydropneumothorax with an intercostal drainage tube *in situ*

DISCUSSION

We report a rare case of immune-related RDD in a 23-year-old male with RF-negative polyarticular JIA, who presented with fever, cough, and exertional dyspnea. Imaging revealed diffuse interstitial and nodular pulmonary involvement with mediastinal lymphadenopathy. Differential diagnoses included tuberculosis, sarcoidosis, septic emboli, and malignancy.

Histopathological examination of an excised cervical lymph node confirmed RDD. Notably, the clinical course was complicated by a right-sided secondary spontaneous pneumothorax, which converted into hydropneumothorax, an event not previously reported in association with RDD. The patient responded favorably to corticosteroid therapy.

RDD is a rare, benign, idiopathic histiocytic proliferative disorder, typically presenting in children and young adults, with a male predominance. While it classically involves lymph nodes, especially cervical, extra nodal involvement is seen in up to 40% of cases [6]. The etiology remains uncertain, with proposed mechanisms, including infections, genetic predisposition, and immune dysregulation [7]. Immune-related RDD has been associated with conditions, such as systemic lupus erythematosus [8], rheumatoid arthritis, Sjögren's syndrome [9], multiple sclerosis, and autoimmune hemolytic anemia. However, co-occurrence with JIA is exceedingly rare.

Pulmonary involvement in RDD is exceptionally uncommon, seen in <3% of cases, and often presents a diagnostic challenge. Intrathoracic manifestations include mediastinal lymphadenopathy, interstitial lung disease (ILD), pulmonary nodules, tracheobronchial disease, and pleural effusions [2,4]. These are often associated with an obstructive pattern on pulmonary

function tests. In most series, honeycombing and cystic changes were uncommon. Reported symptoms range from chronic dry cough and progressive dyspnea to acute respiratory failure. A few case reports have described RDD mimicking bronchogenic carcinoma [10], while others have presented with pleural involvement [11]. This underscores the heterogeneity of pulmonary manifestations in RDD and the importance of considering it in the differential diagnoses of atypical thoracic presentations. However, to our knowledge, no previous RDD case has been reported with spontaneous pneumothorax.

Pulmonary RDD is frequently misdiagnosed as infections (e.g., tuberculosis, fungal, mycobacterial), granulomatous diseases (sarcoidosis, granulomatosis with polyangiitis), autoimmune ILD (e.g., RA-associated lung disease), or neoplastic processes. In our patient, the differential included septic emboli, tuberculosis, and sarcoidosis based on initial imaging. The eventual histological diagnosis of RDD, confirmed by emperipolesis and S100+/CD68+/CD1a−immunophenotype, redirected the treatment strategy.

Cartin-Ceba *et al*. [4] documented that intrathoracic lymphadenopathy is the most frequent thoracic finding in RDD, followed by pleural effusion and interstitial changes. However, cystic changes and spontaneous pneumothorax have not been previously reported. In our case, cystic changes in the lung parenchyma are likely predisposed to pneumothorax through rupture of subpleural cysts. We hypothesize that this occurred within the inflammatory milieu of immune-related RDD associated with JIA, reflecting a potentially aggressive pulmonary phenotype.

In a multicenter analysis, mortality related to lower respiratory tract involvement in RDD approached 45%, underscoring the need for early recognition and intervention. Management is individualized. Asymptomatic nodal RDD may not require therapy, while systemic corticosteroids are the first-line treatment for symptomatic or systemic involvement. Refractory disease may require immunomodulators, chemotherapy, or MEK inhibitors [1,5]. Complete surgical resection is indicated for localized disease, and external-beam radiation therapy may be considered for symptomatic, unresectable, steroid-refractory extra nodal lesions [1]. Our patient was successfully managed with oral methylprednisolone, resulting in both clinical and radiologic improvement.

This case expands the clinical spectrum of intrathoracic RDD, particularly in the setting of autoimmune disease. To our knowledge, it is the first RDD case complicated by spontaneous pneumothorax to be reported and among the very few documenting its association with JIA. It emphasizes the importance of considering RDD in the differential diagnosis of unexplained pulmonary presentations in patients with systemic autoimmune features and highlights the value of a multidisciplinary approach in achieving timely diagnosis and optimal management.

CONCLUSION

We described a case of RDD presenting with JIA, ILD, and mediastinal lymphadenopathy as the primary clinical features and secondary spontaneous pneumothorax as a complication. The rarity and protean manifestations of pulmonary RDD, especially in the context of autoimmune disease, present a diagnostic challenge. This case emphasizes the importance of maintaining a broad differential and underscores the need for a multidisciplinary approach for timely diagnosis and appropriate management.

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