Intrathoracic manifestation in Rosai Dorfman Disease (RDD): A case report with review of the literature

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ABSTRACT

Rosai-Dorfman disease, previously known as sinus histiocytosis with massive lymphadenopathy (SHML) is one of the rare benign idiopathic proliferative diseases of phagocytic histiocytes. Majority of the patients present with painless massive cervical lymphadenopathy but intrathoracic involvement is rarely reported. Here, we report the case of a 57-year-old male with a history of chest pain, shortness of breath and generalized weakness of two-month duration. The diagnosis was formed by core biopsy of the axillary lymph node with typical emperipolesis and Immunohistochemistry markers.

Keywords: *Emperipolesis, Immunohistochemistry,. Rosai Dorfman disease.*

Destombes-Rosai-Dorfman disease (DRDD) also called as Rosai-Dorfman disease (RDD) is a rare disease first described by Destombes in 1965 and then by Rosai and Dorfman in 1969, who captioned it sinus histiocytosis with massive lymphadenopathy [1]. It predominantly affects children and young adults, commonly males. Most of the patients present with painless cervical lymphadenopathy with varying size. Few authors have reported the size of the lymph node as big as six centimeters leading to respiratory compromise [2]. The usual sites of extra-nodal manifestation are soft tissue of head and neck, paranasal sinuses and nasal cavity seen in up to 43% of patients, while the intra-thoracic involvement is rare and is seen in about 2% of cases [3]. Due to difficulty in diagnosis, thoracic manifestations of RDD have been reported sporadically in the literature. Here, we report a case of Rosai-Dorfman disease with intrathoracic manifestation.

CASE REPORT

A 57-year-old, diabetic male presented with a history of on and off low-grade fever, chest pain, shortness of breath, abdominal distention, generalized weakness and significant weight loss of 2 months duration. He was a non-alcoholic but a chronic smoker for more than 20 pack years.

On physical examination, the patient was febrile (axillary temperature-100 F), sinus tachycardia with a pulse of 110 beats/min and oxygen saturation was 88% at room air. There was facial puffiness and bilateral axillary lymph nodes were palpable. On auscultation of the chest, breath sound was reduced bilaterally, more reduced on the right side. Abdominal examination showed a distended abdomen with moderate ascites.

Laboratory investigations revealed normal blood and biochemical reports. Chest X-ray showed cardiomegaly,

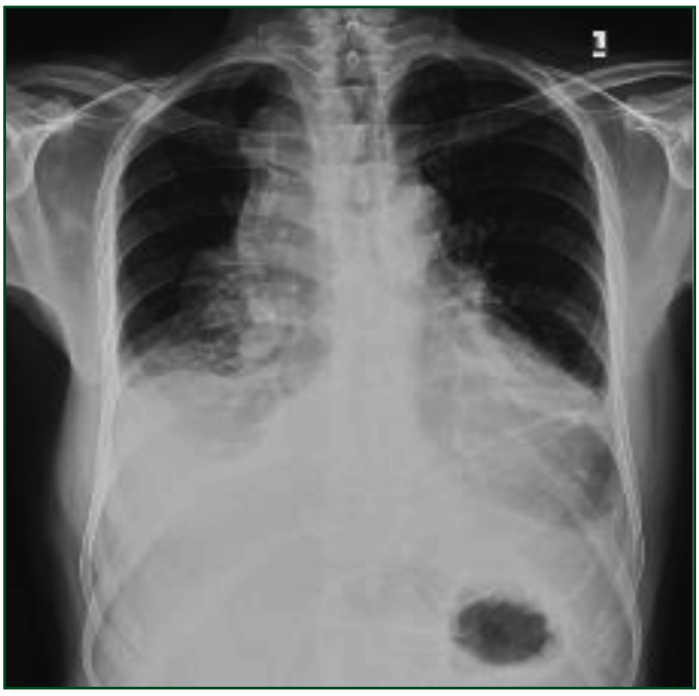

Figure 1: Chest X-ray showing cardiomegaly, mediastinal widening and bilateral pleural effusion

mediastinal widening, and bilateral pleural effusion as shown in Figure 1. High-resolution computed tomography (HRCT) chest revealed pericardial effusion, large necrotic anterior mediastinal lymph nodes along with paratracheal and multiple axillary lymphadenopathies with vascular encasement likely lymphoma or thymoma. Pericardiocentesis to aspirate pericardial fluid was performed. The aspirate mainly showed red blood cells along with hemosiderin laden macrophages. Abdominal ultrasound showed chronic liver disease with moderate ascites. Ascitic fluid tapping was done, which showed no malignant cells. Pulmonary function test revealed severe obstruction (FEV1/FVC ratio=19%).

Axillary lymph node biopsy showed mild nodal architectural distortion with thick capsule and expanded sinus filed with distinct histiocytes with emperipolesis noted, consistent with sinus histiocytosis with lymphadenopathy (Destombes-Rosai-Dorfman Disease). Immunohistochemistry revealed histocytes expressing CD68 and S100 protein. Bone marrow aspiration and biopsy revealed hypoplastic marrow with trilineage hemopoiesis, adequate megakaryocytic and no evidence of granuloma, parasites and malignant cells. FIP1L1-PDGFRa Fusion Assay (Qualitative) by reverse transcriptase-polymerase chain reaction (RT-PCR) and gel electrophoresis was tested which was negative. Hence, a diagnosis of Destombes-Rosai-Dorfman disease was established.

Short term steroid (Prednisolone 1mg/kg per day for four weeks) regimen was initiated and was planned for six cycles of CVP (Cyclophosphamide, Vincristine and Prednisolone) based chemotherapy. After four cycles of the chemotherapy treatment, there was a subsequent improvement of the condition but the patient defaulted treatment and lost to follow-up.

DISCUSSION

Rosai-Dorfman disease is usually a benign condition which clinically manifests with low-grade fever, bilateral cervical painless lymphadenopathy and generalized weakness which was also seen in our case. In the present case, along with the usual symptoms, intrathoracic manifestations like chest pain, shortness of breath were present. Radiologically, intrathoracic involvement includes mediastinal widening along with multiple large necrotic lymph nodes.

The differential diagnosis of RDD with intrathoracic involvement includes primary mediastinal lymphoma, thymoma, lung cancer, sarcoidosis, Wegener's granulomatosis and infectious processes including tuberculosis [4]. The clinical features along with histopathological findings, particularly, features of 'emperipolesis' [5,6] (ie. lymphatic sinuses occupied by numerous lymphocytes and histiocytes with vesicular nucleus and abundant clear cytoplasm with phagocytized lymphocytes, neutrophils or plasma cells) and immunohistochemistry showing the cells positive for protein S-100, α-1-antitrypsin and pan-macrophage antigens (CD68 and HAM56), and negative CD1a7, aid in forming the diagnosis of RDD. Our case was also diagnosed on the basis of clinical features and histopathology of the biopsy taken from the lymph node.

There is no specific laboratory test to establish the diagnosis of RDD [7], similarly, in our case the blood and biochemical reports were normal, serological tests were negative for hepatitis B, hepatitis C and HIV, blood and sputum culture were also negative for Klebsiella and Brucella. The pleural and ascitic fluid analysis showed normal adenosine deaminase (ADA) level with no features of tuberculosis. Bone marrow aspiration flow cytometry showed a few scattered reactive T-cell component. Immunoglobulin level was not tested in the present study.

The differential cytological diagnosis includes Haemophagocytic syndrome, Langerhans cell histiocytosis, reactive lymph node hyperplasia, and lymphoma. In the haemophagocytic syndrome, phagocytosis of the red cell by histiocytes is seen while Langerhans cell histiocytes have grooved and twisted nuclei with cd1a positivity. The reactive lymphadenopathy does not show emperipolesis and immunohistochemistry shows negative S-100 while Hodgkin lymphoma typically shows Reed-Sternberg cells [8,9].

The pathogenesis of RDD is poorly understood although many authors suggest its association with infection and immunodeficiency [10,11,12] Viral infections such as Epstein-Barr virus, parvovirus B19, herpes virus type 6, polyomavirus, Klebsiella, Brucella, and cytomegalovirus have been suspected as the cause but not clearly linked. The other mechanism includes immune dysfunction or an aberrant exaggerated immune response to an infectious agent or an antigen that causes a proliferation of histiocytes.

Many cases of RDD show spontaneous regression [13]. Hence, observation is reasonable, while in some cases, disease progression is seen which requires treatment to prevent major organs dysfunction. The intrathoracic manifestation of RDD is rare and includes mediastinal lymphadenopathy, tracheobronchial disease, pleural effusion, cystic and interstitial lung disease [14] which was also seen in our case. It results in significant morbidity and reported mortality of 45% [15], hence necessitating upfront treatment to prevent organ dysfunction.

There are some reports of successful treatment of Rosai Dorfman disease with a combination of chemotherapy such as alkylating agents and vinca alkaloid with prednisone [16] which were also used in our treatment protocol (CVP regimen). There are reports of systemic non-Langerhans cell histiocytosis being treated successfully with target therapy [17] by Imatinib for c-kit and PDGFR positive cases. Our case was evaluated for the same but was found to be negative. In refractory cases, analysis of NRAS, KRAS, HRAS, MAP2K1, BRAF and ARAF mutations in the lesional tissue has been suggested for the use of targeted therapies [15]. Recently, on 16th October 2016, the Rare Histiocytosis Steering Committee and Working group of Histiocyte Society during its 32nd Annual Meeting in Dublin, Ireland, made the first consensus multidisciplinary recommendation for the diagnosis and management of RDD.[15]

CONCLUSION

Rosai-Dorfman Disease with intrathoracic involvement may manifest as pulmonary nodules with mediastinal lymphadenopathy which might be difficult to diagnose and differentiate from other similar pathologies. Clinicians should be aware of this rare entity. A good pathological laboratory facility is essential to diagnose this condition. Although benign in nature, treatment with chemotherapy is the modality of treatment.

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