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Case Report

Unmasking Rosai-Dorfman disease in a woman with cervical lymphadenopathy: a histopathological insight

Anoushka A. Doshi[1]*, Shruti B. Nelekar[2]

[1]Department of Medicine, Krishna Institute of Medical Sciences, Karad, Maharashtra, India
[2]Department of Medicine, Government Medical College, Baramati, Maharashtra, India

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***Correspondence:**
Dr. Anoushka A. Doshi,
E-mail: anoushkadoshi@outlook.com

ABSTRACT

Rosai-Dorfman disease (RDD) also called as sinus histiocytosis with massive lymphadenopathy is a rare benign proliferative self-limiting disease of the macrophage-histiocyte cell family. Its etiology is unknown and presents with massive lymphadenopathy. We hereby present a case of a female presenting with massive cervical lymphadenopathy, evening rise in temperature and weight loss. It was initially misdiagnosed as tuberculous cervical lymphadenopathy as it is the most common cause of cervical lymphadenopathy in India due to high prevalence of tuberculosis. It was treated with anti-tuberculous drugs, but did not resolve. Eventually neck biopsy was done which showed characteristic histopathologic features including emperipolesis and S100 positivity on immunohistochemistry. The patient was managed conservatively with observation and symptomatic management. Patient underwent spontaneous remission in a few months. The absence of any specific clinical features caused diagnostic difficulty, delaying the diagnosis. This report highlights the importance of considering RDD in the differential diagnosis of cervical lymphadenopathy, particularly in tuberculosis-endemic regions.

Keywords: Histopathology, Cervical lymphadenopathy Rosai-Dorfman, Sinus histiocytosis with massive lymphadenopathy

INTRODUCTION

Rosai-Dorfman disease (RDD) is a rare disorder characterized by overproduction and accumulation of a histiocyte (a type of white blood cell) in the lymph nodes of the body, most often those of the neck causing cervical lymphadenopathy in children and young adults.[1]

In approximately 43 percent of cases, other areas of the body besides the lymph nodes may also be affected (extra nodal).[2]

The symptoms and physical findings associated with RDD vary depending upon the specific areas of the body that are affected. This raises diagnostic and therapeutic difficulties. 20-50% of RDD patients with nodal/cutaneous disease undergo spontaneous remission.[2]

CASE REPORT

A 62-year-old female presented to the outpatient department with complaint of neck swelling for the past 1 year. She also had evening rise in temperature, night sweats and weight loss.

On examination, she had multiple, bilateral enlarged cervical lymph nodes, including level IA, II, III, V on the right side, and level II, III on the left side. The multiple matted lymph nodes were firm and tender on palpitation, with the largest node measuring 23×13 mm in the right

sub mandibular cluster. She had no significant axillary or inguinal lymph node enlargement.

Her CBC revealed elevated WBCs with a neutrophilic preponderance. Her ANA and HCV came back negative. Her direct Coombs test was positive. Her Serum Immunoglobulin levels showed IgA: 906 (normal levels:70-400 mg/dl) and IgG: 4292 (normal levels:700-1600 mg/dl). The bone marrow biopsy revealed hypercellular bone marrow with trilineage hemopoiesis and no evidence of infiltrative disease.

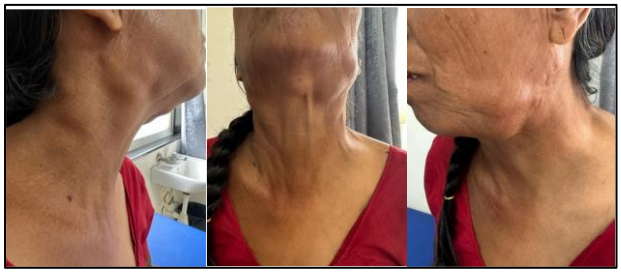

Figure 1: Patient presenting with several enlarged lymph nodes.

An ultrasound of the neck showed enlarged lymph nodes, indicating an infectious etiology. Because tuberculosis had already been ruled out as she had completed a course of anti-tubercular medications, FNAC was performed. The creamish pus like material from the right cervical lymph node displayed moderately cellular smears showing several neutrophils, few macrophages, degenerated cells and reactive lymphoid cells all of which was suggestive of acute lymphadenitis. She was started on appropriate antibiotics.

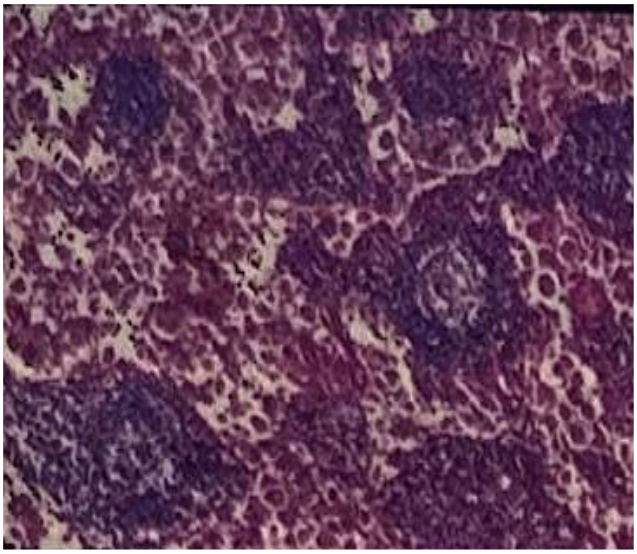

Figure 2: Histopathologic findings of a cervical lymph node involved by RDD (H and E staining) of hallmark histologic finding of RDD: large histiocytes with pale, vesicular nuclei engulfing many small lymphocytes (emperipolesis).

The swelling persisted even after the antibiotic regimen was completed. So, neck biopsy was performed which showed reactive lymphoid follicles with dilatation of sinuses by sheets of foamy macrophages containing intact lymphocytes which is called as emperipolesis (Figure 2). No granulomas or fungal hyphae. All characteristics suggestive of sinus histiocytosis with massive lymphadenitis (Rosai Dorfman disease).

Immunohistochemistry was advised and it shows CD68, S100: Positive in histiocytes, CD1a: Negative, Cd20: Highlights follicles and CD3: Stains T cells (Figure 3).

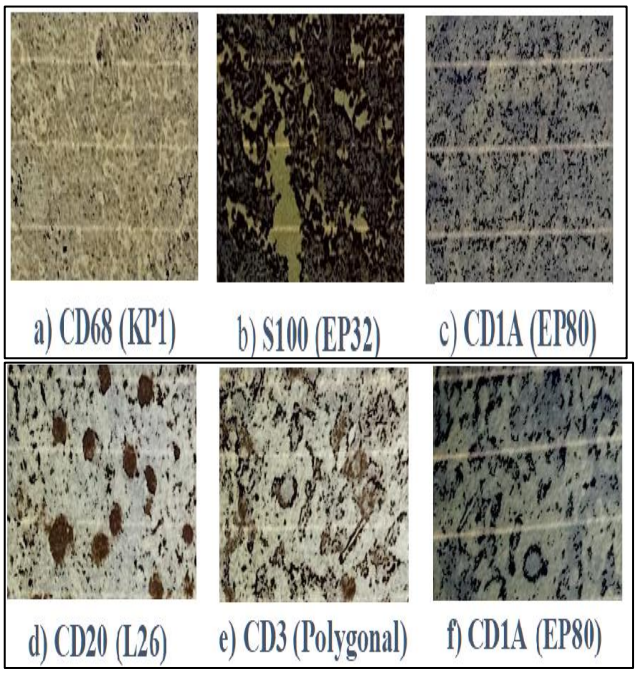

Figure 3 (A-F): Immunohistochemistry findings of RDD. CD68 immunostaining showing strong granular cytoplasmic positivity. Positive S100 immunostaining (both cytoplasmic and nuclear) of the histiocytes in the lymph node with emperipolesis of lymphocytes. negative CD1a immunostaining of the histiocytic cells of the cervical lymph node.

The patient was managed with symptomatic treatment. There was no extra-nodal or multi-system involvement and no systemic cause or associated diseases were identified. The cervical lymphadenopathy spontaneously resolved after eight months without any active treatment.

DISCUSSION

Rosai Dorfman disease is a rare, benign type of non-Langerhans cell histiocytosis, with a prevalence of around 1: 200000.[3] It was first described in 1965 by a French pathologist, Pierre Destombes, and was thought to be a lipid storage disease caused by inflammation. However, four years later, Rosai and Dorfman correctly identified the key roles of histiocytes in the pathogenesis of the disease.[4]

The disease can occur at any age, but mainly affects children and young adults, with a slight male predilection (1.4:1).[2] The pathogenesis of Rosai Dorfman Disease is not completely understood. RDD may occur independently or in combination with other autoimmune, hereditary, and malignant conditions. It can be classified into five subgroups: classical (nodal), familial, extranodal, neoplasia associated, and immune disease-associated. Sporadic nodal form is more common and usually undergoes spontaneous remission. It may be associated with IgG4 lymphoproliferative disorders.[5] The familial RDD includes H syndrome, an autosomal recessive genetic syndrome caused by mutations in the *SLC29A3* gene and autoimmune lymphoproliferative syndrome (ALPS)-related RDD caused by germline mutations in *TNFRSF6.*[6]

The neoplasms frequently associated with RDD include lymphomas, leukemias, malignant histiocytosis, Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease (ECD). Immunologic conditions like systemic lupus erythematous, idiopathic juvenile arthritis and autoimmune hemolytic anemia can be associated in up to 10% of cases.[2]

It typically presents as painless lymphadenopathy - with the cervical lymph nodes being most commonly affected. It may also involve other lymph nodes like the retroperitoneal, inguinal, and mediastinal. It may be accompanied by B symptoms like night sweats, fever, and weight loss. Although, the extra nodal involvement is uncommon, when involved cutaneous RDD is more common along with the nodal involvement. Extranodal RDD can involve skin (10%), nasal cavity (11%), bone (5%–10%), orbital tissue (11%) and central nervous system (5%).[7] An elevated erythrocyte sedimentation rate, leukocytosis, hypergammaglobulinemia and autoimmune hemolytic anemia may also be observed on laboratory studies.

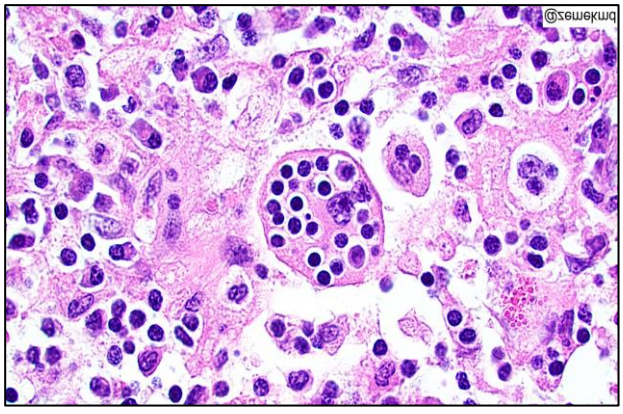

Figure 4: The characteristic 'emperipolesis' seen on H and E staining in RDD.[9]

The diagnosis is usually based on histological findings characteristic to RDD which involves an enlarged node with appearance of extensive sinusoidal expansion. The most striking feature is 'emperipolesis' (Figure 4) – which is the engulfment of the small lymphocytes, erythrocytes and plasma cells by histiocytes without phagocytosis. This can be identified on routine hematoxylin and eosin stains. Small foci of RDD-like histopathology (i.e. histiocytes with emperipolesis) are nonspecific; therefore, it has been recommended that greater than 10% of a specimen should demonstrate Rosai–Dorfman morphology along with appropriate clinical and radiologic context and exclusion of primary malignant disorders is required to constitute a diagnosis.[9] Emperipolesis is not a requirement for the diagnosis and is often unremarkable at extranodal sites.

Immunohistochemical staining is characterized by positivity for S100, which highlights the nuclei and cytoplasm of histiocytes by demarcating the edges and creating a 'halo' effect around mature cells within the cytoplasm showing emperipolesis, along with CD68 positivity and is typically negative for CD1a.[8]

After autoimmune disorders, familial causes, and malignancies have been ruled out, observation is often the treatment of choice. In about 20–50% cases, spontaneous remission occurs.[2] When necessary, treatment is directed at the particular symptom. In some cases, surgery can be done if disease is uni-focal. Corticosteroids, sirolimus, immunotherapy with TNF-α inhibitors, chemotherapy or radiotherapy can also be used with variable results.[9,10]

CONCLUSION

Patients with cervical lymphadenopathy may be mistaken for lymphoma and other infectious disorders like tuberculosis or granulomatous diseases especially in developing countries like in India where tuberculosis is more prevalent and is the most common cause of cervical lymphadenpathy. Inflammatory markers may be elevated and patients may have fever, night-sweats, and weight-loss. As in this case the patient was mimicking symptoms of tuberculosis and lymphoma. Although history, physical examination, laboratory investigation, and imaging studies helped to rule out other potential diagnoses like autoimmune conditions and infections. The definitive diagnosis was made upon histopathologic examination of a lymph node biopsy, causing a delay in diagnosis and treatment. So, RDD should be included in the differential diagnosis of cervical lymphadenopathy.

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