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Rosai dorfman disease: a rare cause of lymphadenopathy

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ABSTRACT

Rosai-Dorfman disease (RDD) is a rare cause of generalized lymphadenopathy due to sinus histiocytosis. This is often confused with infective or malignant aetiologies. We here report a case of a 46 year old female from Eastern India presenting with progressive generalized lymphadenopathy for four years. She had no systemic symptoms like fever. All blood tests including viral serologies were normal. Excision biopsy showed lymph node sinus infiltration with histiocytes and emperipolesis. The histiocytes were CD68 positive and CD1a negative. Thus the case was pathologically diagnosed as RDD. The patient responded to oral prednisolone (1 mg/Kg). There was no extra-nodal involvement. The relevant literature regarding RDD has also been discussed at length.

INTRODUCTION

Rosai - Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a rare cause of generalised lymphadenopathy [1]. Only rarely, the disease involves extra-nodal sites like central nervous system (CNS) or paranasal sinuses. The exact pathogenesis of the disease is still unknown and sometimes, viral infections are implicated. Clinical course of the disease is quite unpredictable and treatment is not always needed [2]. This disease is sometimes clinically and histologically confused with different infective causes and malignancies. RDD has been very rarely reported from India. We here report a case of RDD presenting as generalized lymphadenopathy in a middle aged female from Eastern India.

CASE REPORT

A 46 year old female home-maker from Howrah, West Bengal presented with painless progressive swellings in neck and armpit for last four years. The swellings were insidious in onset and there was no discharge or redness over the swellings. In neck, the swellings started first in bilateral submandibular region. She presented to us as the large masses were causing some wheezing at night and social embarrassment. She had no complaint of arthritis, skin rash, paleness or fever. She was not taking any anti-epileptic drugs. She had taken indigenous medicines and some herbal drugs for the last four years. She had no recent history of travel and there was also no history of congenital metabolic diseases. On examination, there were multiple enlarged firm lymph nodes on both sides of neck (figure 1) with the largest one measuring 6.5 ×6 cm. they were all mobile, non-matted and non-tender. The surface was smooth. There were also bilateral axillary and inguinal lymph nodes with the same characteristics and of similar size. In abdomen, there was no organomegaly. General and systemic examination was otherwise normal.

Laboratory tests revealed hemoglobin of 12.2 gm/dl, total leukocyte count of 7900/cmm (N 75 L20 E3) and platelet count of 120000/cmm. Erythrocyte sedimentation rate was 52 mm in 1st hour. Red cell indices were normal and peripheral blood examination revealed no abnormal cells. Blood sugar/urea/creatinine were 99/20/0.8 mg/dl respectively. Liver function test revealed total bilirubin of 0.7 mg/dl, ALT (alanine aminotransferase) 31 IU/L, alkaline phosphatase (ALP) 400 IU/L (N<360), albumin 4.4 gm/dl and globulin 4 gm/dl. Ultrasonography of abdomen revealed mild enlargement of liver with grade I fatty changes. There was no lymphadenopathy in abdomen and no ascites. Chest X ray was normal without any mediastinal widening or hilar mass. Malaria antigen test was negative; HIV, Hepatitis B and C serology and CMV serology were also negative. Serum LDH was 391 IU/L (N: <360). Blood serology for anti-nuclear factor (ANF) by Hep-2 cell line, Anti-SS-A and B and ANCA were also negative. Serum C - reactive protein (CRP) was 4.6 mg/L (N<6) and serum calcium was 9.2 mg/dl. Thyroid profile was normal. Finally, excision biopsy from the lymph node was done which revealed infiltration by numerous histiocytes into lymph node sinuses (figure 2). The normal architecture of the nodes was altered. The histiocytes were CD68 positive and CD1a negative. S-100 could not be done due to cost factor. On further magnification (figure 3) some of the histiocytes showed lymphophagocytosis (emperipolesis). There

was no granuloma or abnormal cells in the nodes. Thus, the disease was diagnosed pathologically as Rosai-Dorfman disease. CT scan of brain did not reveal any intracranial, paranasalor orbital disease.

The patient was initially followed up without any therapy. However, after three months, as she developed obstructive symptoms like wheezing, she was started on oral prednisolone (1mg/Kg). The size of the lymph nodes decreased considerably over the next months. At six months' follow up, her largest lymph node was measuring 2.5 cm in greatest diameter.

DISCUSSION

Histiocytosis is a rare group of immune system disorders characterized by accumulation of monocytes, macrophages and dendritic cells in the affected tissue: either lymph node or extra-nodal sites without any antigenic stimulation[3]. Table 1 here shows the different types of histocytic disorders.

RDD is characterised by massive lymph node enlargement. Sometimes, the enlarged lymph nodes may resemble bull-neck of diphtheria. [4] Rarely, the extra-nodal sites like retro-orbital tissue, dura mater, upper respiratory tract or parotid gland may be

Table I. Table showing the different types of histiocytosis [3]

Type	Organs affected	Systemic features	Pathologic features
Langerhans cell histiocytosis (LCH)	Bone, scalp, skin, lymph nodes, lungs, mandibles and maxilla, middle ear and posterior pituitary gland.	Fever, diabetes insipidus, facial rash, pathological fractures	The lesions contain aggregates of pathologic Langerhans cells (PLCs), intermediate cells, interdigitating cells and giant histiocytes. The cells are CD1a positive and contain Birbeck granules.
Sinus hyperplasia	Lymph nodes	Variable	Lymph node sinuses dilated and contain histiocytes. Erythrophagocytosis may be present. [3]
RDD	Lymph nodes, rarely CNS, orbits	Low grade fever, high ESR, hyperglobulinemia and leucocytosis.	Emperipolesis, pericapsular fibrosis, sinus infiltration with histiocytes [4]
Hemophagocytic lymphohistiocytosis (HLH)	Skin, liver, spleen, bone marrow	High fever, rash, hepatosplenomegaly, pancytopenia, altered coagulation	Increased histiocytes in sinuses and paracortical areas of lymph nodes. Erythrophagocytosis in bone marrow, liver and spleen.
Familial HLH	Liver, spleen, rarely CNS	Fever, thrombocytopenia, increased ferritin	Erythrophagocytosis; infiltration of lymph nodes and bone marrow with histiocytes.
Hepatosplenic T cell lymphoma	Liver and spleen	Fever	Pulp of spleen and sinusoids of liver contain large lymphoid cells with erythrophagocytosis.
Histiocytic necrotising lymphadenitis(Kikuchi-Fujimoto disease)	Commonly cervical lymph nodes	Fever, arthralgia, myalgia	Necrosis of paracortical areas of lymph nodes with macrophage infiltration
Congenital solitary histiocytoma	Self-healing lesion in skin of infants	None	Infiltration of histiocytes with eosinophils. Birbeck Granules may be present.

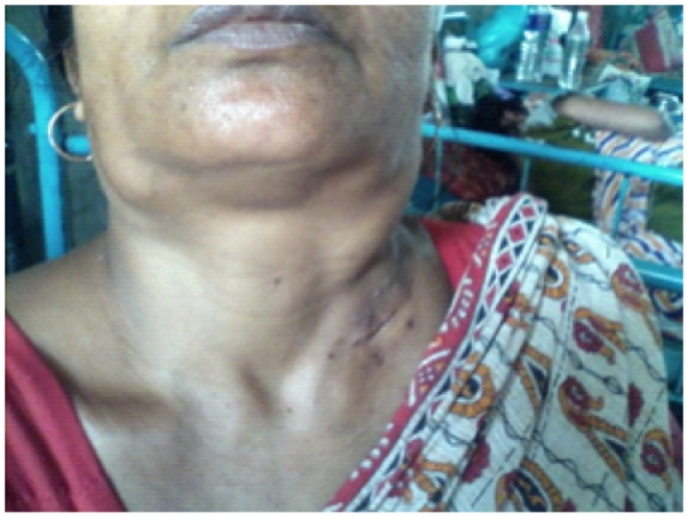

Figure 1: The massive lymph nodes on both sides of neck of the patient

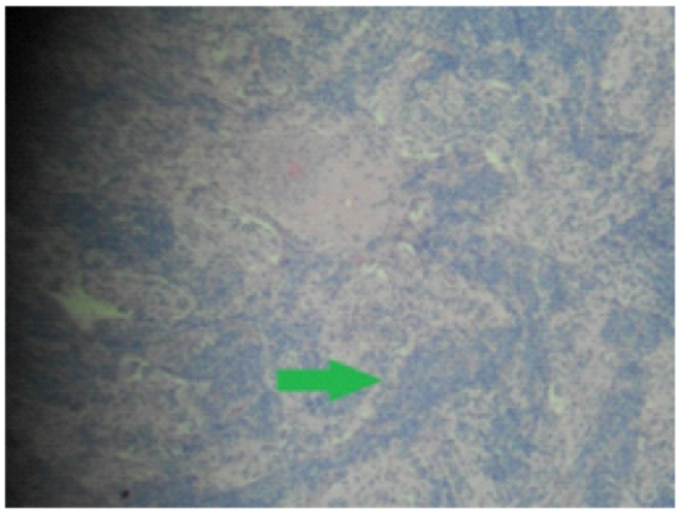

Figure 2: The lymph node biopsy photomicrograph, showing dilated sinuses with numerous histiocytes (green arrow)

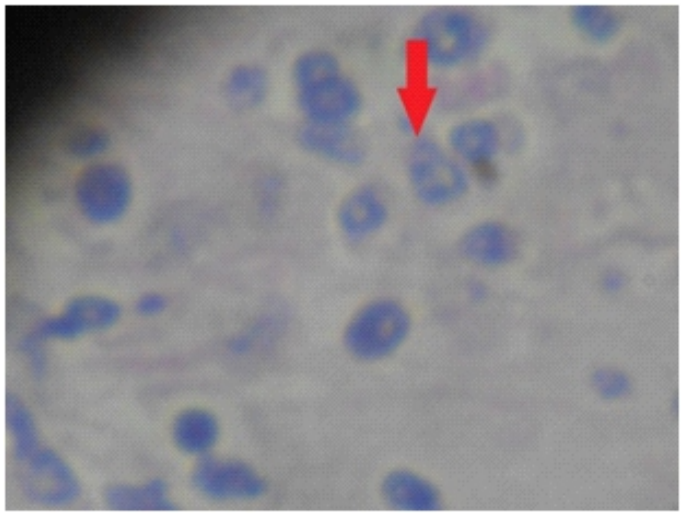

Figure 3: Magnified image (×40) of lymph node biopsy, showing lymphocytes inside histiocyte cytoplasm (red arrow) emperipolesis.

Table 2. IPT differences between RDD and LCH

Marker	RDD	LCH
CD1a	-	+
CD68	+	+
S-100	+	+
CD-163	+	+/- [6]
α1-antitrypsin	+	-

involved [5]. Sometimes, the disease may even start as isolated mediastinal node involvement. In that case, differentiation must be made with malignant conditions like lymphoma. [5] However, in our patient, no extra-nodal involvement was found. Often, systemic features like leucocytosis and elevated ESR are seen. [4] In our case, although elevated ESR was found, the TLC was essentially normal. Sometimes, autoimmune haemolytic anemia is associated with RDD. This can also create confusion with lymphoma [5]. Other close differential diagnosis of RDD includes LCH. This is differentiated by immunophenotyping (IPT) studies of the histiocytes in the lymph node, as shown in table 2.

Presence of these markers, along with emperipolesis, is diagnostic of RDD. In our patient, CD1a was negative.

Treatment of RDD is controversial [2]. In many cases, the disease may resolve by itself. In cases where there are symptoms due to mass effect or progressive enlargement of lymph nodes, steroids, radiation therapy or surgical debulking may be tried. [2] In some cases, even interferon, chemotherapy or a combination of these modalities have been used with variable success. [2]Generally, the disease runs a benign course. However, sometimes it can be fatal due to tracheal obstruction or widespread extra-nodal disease[2, 7].

RDD has rarely been reported from India. One such case reported from Western India was of a 12 year old girl who presented with lymphadenopathy over a long time. [4] She had recurrent episodes of lymphadenopathy over 67 years. Another case of RDD from Delhi presented with lymphadenopathy, pituitary and renal masses. [8]For the pituitary mass, surgery was needed in that case. Finally, one case reported from Kerala showed skin papules along with lymphadenopathy. [9] The clinico-pathological presentations of reported Indian cases have been found to be similar to other Western reports.

CONCLUSION

We here present this case to sensitize clinicians to this rare cause of massive generalized lymphadenopathy. RDD is a pathological diagnosis. It is often confused with haematological malignancy or the more serious LCH. Proper diagnostic tests, including immunophenotyping, can be helpful in arriving at the correct diagnosis.

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