

Case Report

A case report of Rosai Dorfman disease

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ABSTRACT

Rosai-Dorfman's disease also known as sinus histiocytosis with massive lymphadenopathy (SHML) is characterized by distorted lymph node architecture with marked dilation of lymphatic sinuses occupied by numerous lymphocytes, as well as histiocytes with vesicular nucleus and abundant clear cytoplasm with phagocytized lymphocytes or plasma cells, also known as 'emperipolesis'. This disease of unknown etiology progresses with a benign prognosis strictly and only when an early diagnosis and treatment is made. A late diagnosis and a generalized lymph node involvement contribute to a poor prognosis. We reported a case of a 29-year-old Indian female with a 4-month history of painful unilateral cervical mass and low-grade fever with the final diagnosis of Rosai-Dorfman disease. The final diagnosis was made by fine needle aspiration (FNA) biopsy of the cervical lymph node. In conclusion, FNA biopsy can be enough to make the diagnosis in most cases due to the distinct cytological features of SHML, thereby avoiding more invasive approaches that potentially are unnecessary.

Keywords: Rosai-Dorfman disease, Sinus histiocytosis, Massive lymphadenopathy, Fine needle aspiration biopsy

INTRODUCTION

Sinus histiocytosis with massive lymphadenopathy (SHML) or Rosai-Dorfman disease is a rare self-limited and benign disease that was first described in 1969.¹ The clinical features in the classical form include painless enlargement of cervical lymph nodes, fever, leukocytosis, anemia, hypergamma globulinemia and elevated erythrocyte sedimentation rate.² Frequently other lymph nodes can be involved such as axillary, para aortic, mediastinal, inguinal and concurrent extra nodal disease may be evident. Extra nodal disease has a particular predilection for the head and neck region (75% of cases).^{3,4} Involvement of ≥ 1 extra nodal site has been identified in 43% of cases and only 23% have extra nodal disease exclusively.^{1,5} Documented sites of extra nodal involvement include skin, respiratory tract, bone, genitourinary system, oral cavity, central nervous system, eyes and ocular adnexa, salivary gland, tonsil, breast, soft

tissue and heart.⁶⁻⁹ This condition can occur at any age, albeit 80% of the patients are aged 20 years or younger at onset, with a higher prevalence in males.^{8,10,11}

The etiology of the disease is unknown but several theories have been suggested. Some infectious agents have been suspected, including Epstein-Barr virus, Parvovirus B19, Herpes virus type 6 and 8, and Polyomavirus.¹²⁻¹⁶ A relationship with *Klebsiella*, *Brucella* and *Cytomegalovirus* was also suggested, but any attempt to isolate the organisms consistently failed.¹² Other proposed mechanisms include immune dysfunction or an aberrant exaggerated immune response to an infectious agent or an antigen that causes a proliferation of histiocytes.⁶ Stimulation of monocytes/macrophage via macrophage colony-stimulating factor was also involved.¹⁷ These mechanisms suggest an immune misregulation.¹⁸ In addition, 10–12% of patients with SHML exhibit autoimmune phenomena.¹⁹⁻²⁰

The classical histology of this entity is characterized by distorted nodular architecture with marked dilation of lymphatic sinuses, partial effacement of follicles and germinal centers, as well as capsular and pericapsular fibrosis.¹ Lymphatic sinuses are occupied by numerous lymphocytes and histiocytes with vesicular nucleus and abundant clear cytoplasm with phagocytized lymphocytes or plasma cells, also known as 'emperipolesis'.^{5,6,21}

Immunohistochemical analysis revealed the cells were positive for protein S-100, but typically negative for CD1a. These cells also expressed α -1-antitrypsin and other pan-macrophage antigens (CD68 and HAM56).²² The cytological characteristics of SHML are highly distinctive. Consequently, fine needle aspiration (FNA) biopsy may be sufficient to make the diagnosis in most cases thus preventing unnecessary invasive procedures.^{5,6,21,22}

CASE PRESENTATION

In the current study, we present a 29-year-old Indian female patient presenting to the outpatient department of Otorhinolaryngology with a 4-month history of low-grade fever and painful unilateral cervical mass on the left side below the angle of the mandible. On physical examination we found bilateral cervical lymphadenopathy.



Figure 1: A picture of the patient presenting with a single discrete swelling on the left side of the neck.

On examination, a single oval swelling of 4x5cm was noted, mobile in all directions, tender to touch, and no local rise of temperature was noted. Laboratory exams showed anemia and high erythrocyte sedimentation rate. USG neck showed left cervical lymphadenopathy. As the initial suspected diagnosis was a probable lymphoma a FNA biopsy was performed on a cervical node.

The patient's samples were stained to describe morphologic differences by Papanicolaou (Pap) and Diff-Quik stain techniques. The microscopic examination revealed a highly cellular sample with abundant

histiocytes with large eosinophilic cytoplasm, in a reactive lymphocytic background, made up of lymphocytes, plasma cells, and few eosinophils and neutrophils. The cytoplasm of these histiocytes has numerous intact lymphocytes and plasma cells (Figure 2 and 3). Finally, we evaluated a cellular block stained with hematoxylin and eosin and observed the classic histopathological characteristics of this disease as, distorted node architecture with marked dilation of sinuses and partial effacement of follicles and germinal centers. The sinuses are occupied by numerous histiocytes with a vesicular nucleus and abundant clear cytoplasm with phagocytized intact lymphocytes, known as 'emperipolesis' (Figure 4). Following immunohistochemical analysis, the cells were found to be positive for CD68 and negative for CD1a. Following immunohistochemical analysis, the cells were found to be positive for CD68 and negative for CD1a.

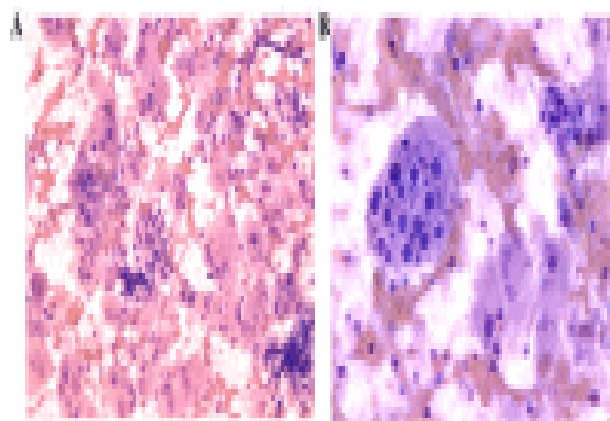


Figure 2: Medium-power (magnification, $\times 10$) stained with the Papanicolaou technique. Hemorrhagic and lymphocytic background of chronic non-specific lymphadenitis, with large macrophages, with abundant cytoplasm and numerous lymphocytes are observed.

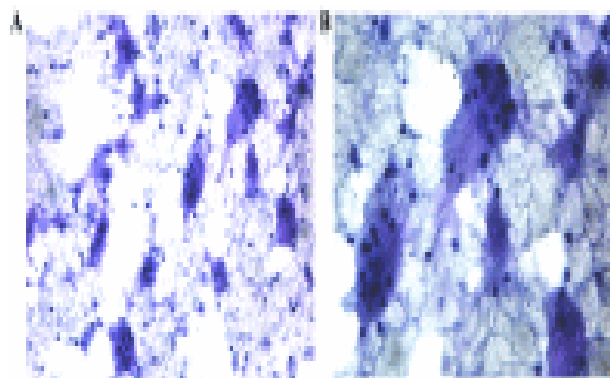


Figure 3: Hemorrhagic and lymphocytic background of chronic non-specific lymphadenitis, with large macrophages, with abundant cytoplasm and numerous lymphocytes are observed, but evaluated with the Diff-Quik stain. [(A) Magnification, $\times 10$; and (B) magnification, $\times 40$].

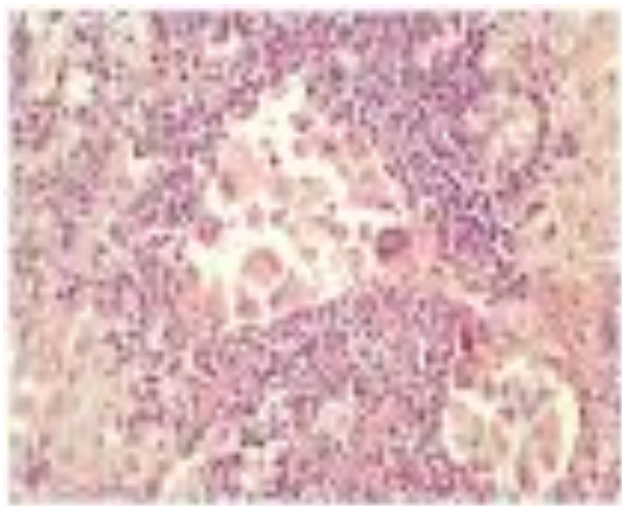


Figure 4: Cellular block with hematoxylin and eosin technique at medium power (magnification, $\times 10$). Fragment of a lymph node with important sinusoidal dilatation, note the histiocytes lining the sinuses. Many of the histiocytes have intact lymphocytes within

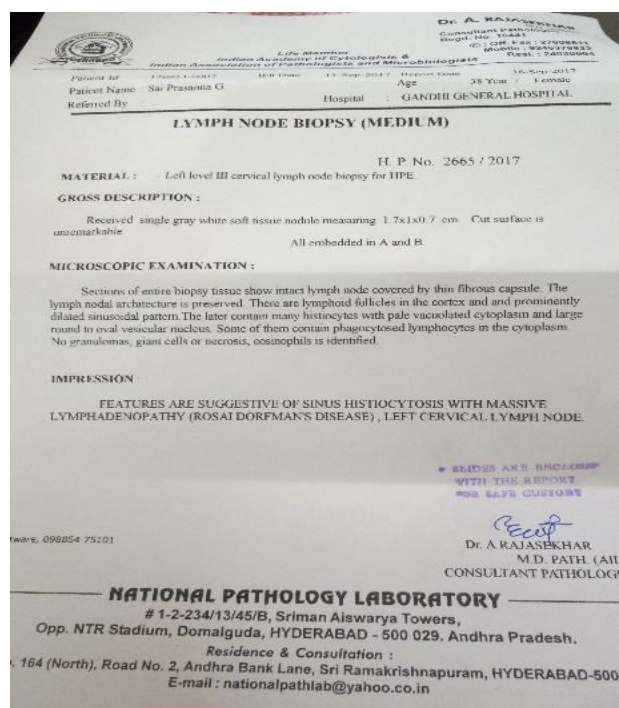


Figure 5: Excision biopsy was done, the histopathological report says Rosai-Dorfman's disease. A set of antibiotic was given to the patient after this.

DISCUSSION

As in histology, cytology from FNA biopsy is usually highly cellular, with numerous histiocytes with vesicular nucleus and abundant clear cytoplasm with fine vacuoles and lymphophagocytosis in a reactive background of

lymphocytes, plasma cells and occasionally neutrophils.^{5,10,23} Lymphatic sinuses are occupied by numerous lymphocytes and histiocytes with vesicular nucleus and abundant clear cytoplasm with phagocytized lymphocytes, neutrophils or plasma cells, also known as 'emperopolesis'.^{5,6}

The chromatin of the histiocytes was satisfactory and evenly distributed, although the nuclear shapes varied from round to extremely bizarre configurations. The nucleoli are usually not prominent.²⁴ Occasionally, atypical morphology may be seen and, when present, it can lead to a misdiagnosis of malignancy.²⁵ Large binucleated and multinucleated forms were also present.²¹ Immunohistochemistry revealed the cells were positive for protein S-100, α -1-antitrypsin and pan-macrophage antigens (CD68 and HAM56), but typically negative for CD1a.^{6,22}

Although the cytomorphological features may be well defined, diagnosis of SHML can be difficult to make, particularly in extranodal sites.²³ Shi et al reviewed 49 cases of Rosai-Dorfman disease diagnosed with FNA cytology, and found a significant misdiagnosis of SHML by FNA more often in extranodal rather than in nodal disease: 12% (3 out of 25) misdiagnosed cases in lymph node aspirations vs. 50% (6 out of 12) misdiagnosed or inconclusive cases in extranodal aspirations.⁵ In addition, diagnosis requires correlation with an appropriate clinical history.

In our case SHML is likely to be mistaken for lymphoma because of its typical presentation as cervical lymphadenopathy accompanied by non-specific signs of immune activation, occasional fever, neutrophilia and a high erythrocyte sedimentation rate. Therefore, SHML should be considered in the differential diagnosis of painless, unilateral or bilateral cervical lymphadenopathy, usually of marked size.¹⁰

The differential cytological diagnosis includes reactive lymph node hyperplasia, infectious lymphadenitis, hemophagocytic syndrome, Langerhans cell histiocytosis, tuberculosis, and lymphoma.²³⁻²⁶ The main differential diagnoses are summarized in Table 1. In the lymph node reactive hyperplasia there are sinusoidal hyperplasia with loose clusters of histiocytes, accompanying lymphocytes, germinal center cells, immunoblasts, and tangible body macrophages; however cytology usually does not show extensive emperipolesis while protein S-100 is negative. Techniques such as Pap and Diff-Quik staining, allow us to observe cellular differentiation between normal and squamous cells, as well as various features. In the case of SHML, techniques last mentioned help improve the cytological characterization.

Mallick et al carried out a cytomorphological and morphometric analysis of 22 cases of SHML, and the authors quantified and compared the cell dimensions and nuclear dimensions of SHML histiocytes with those in

the reactive lymph nodes.²⁴ Morphometric parameters show the mean nuclear diameter of the SHML histiocytes was 16.7 μm compared with the diameter of reactive histiocytes at 10.1 μm , which was statistically significant ($p<0.01$). The median nuclear area in SHML histiocytes

was 163.4 μm^2 and in reactive histiocytes it was 66.14 μm^2 , which was statistically significant ($p<0.001$). SHML histiocytes were also significantly greater in size ($p<0.001$) than those in the reactive lymph nodes.²⁴

Table 1: Common differential diagnoses for Rosai-Dorfman disease and their cytological characteristics compared against other similar diseases.

Differential diagnosis	Cytological/clinical features	Cytological/clinical features of haemophagocytic lymphohistiocytosis
Lymphoma	Atypical lymphoid cells, numerous histiocytes with hemophagocytosis and benign erythrophagocytosis.	Absence of atypical lymphoid cells.
Rosai dorfman's disease	Bilateral massive and painless cervical lymphadenopathy without hepatosplenomegaly	Bilateral cervical, painful lymphadenopathy with hepatosplenomegaly
Langerhans cell histiocytosis	Presence of eosinophils and lobulation or grooving of the nucleus	Absence of eosinophils and lobulation or grooving of the nucleus
Malignant histiocytosis	High nucleocytoplasmic ratio with prominent nucleoli and presence of mitotic figures	Low nucleocytoplasmic ratio, abundant lightly staining cytoplasm with hemophagocytosis, absence of prominent nucleoli and mitotic figures

Hemophagocytic syndromes should be differentiated from Rosai-Dorfman disease on the basis of the presence of hemophagocytosis and absence of emperipolesis. This syndrome has a high association with hematopoietic malignancy and infectious processes and it is presented as systemic failure, frequently with pancytopenia and hepatosplenomegaly. Under microscopic examination, the most relevant, is the phagocytosis of red cells by histiocytes.^{6,27} In Langerhans cell histiocytosis, Langerhans cells have grooved and twisted nuclei and the background has eosinophilic micro abscess. Langerhans cells also express CD1a.²⁸

Following microscopy, we identified tuberculous lymphadenitis and other granulomatous lymphadenitis with cohesive aggregates of epithelioid histiocytes, frequently with associated necrosis but with a lack of phagocytized lymphocytes. Aggregates of epithelioid histiocytes were absent in Rosai-Dorfman disease.^{26,29} Smears from patients with Hodgkin lymphoma show lymphocytes, plasma cells, histiocytes, eosinophils, and Reed-Sternberg cells.³⁰ In non-Hodgkin lymphoma the most important cytological feature is the monomorphic population of lymphoid cells.³¹ Additionally, none of the previously described conditions is characterized by a prominent emperipolesis, as was observed in SHML.

Most patients with SHML have spontaneous remission and some can recur or have persistent disease with asymptomatic but persistent lymphadenopathy. In very few cases it progresses to an aggressive tumor and can be fatal. Involvement of extranodal sites generally carries a poorer prognosis, and disease tends to be chronic and relapsing.^{2,10} A poorer prognosis has been associated with dissemination and involvement of kidney, upper

respiratory airway, liver and patients with underlying immune abnormalities or anemia.²⁰ Death occurs in approximately 7% of patients, linked to a possible defect in the immune system.³²

An ideal treatment for SHML remains to be identified; nevertheless, approximately 50% of the patients require treatment. The management options range from observation for those patients with mild manifestations with no functional or cosmetic abnormalities to surgical resection, systemic steroids and in some cases chemo- or radiotherapy for patients with severe symptoms, as well as compromise of vital organs.^{33,34}

In conclusion, the cytological features of SHML are distinctive in the correct clinical context, whereby biopsy with FNA may be sufficient for diagnosis in most cases, thus preventing unnecessary invasive approaches. Surgical resection for histological diagnosis should be considered in cases with inconclusive cytological findings, or unusual clinical presentation.

CONCLUSION

RDD must be considered in the differential diagnosis of young patients who exhibit massive or multiple lymphadenopathies, especially when involvement of the cervical area occurs. The disease can be diagnosed on the histopathologically and immunohistochemically. In our case, there was a typical presentation of Rosai dorfman's disease but with painful cervical lymph node. The tenderness resolved after a course of antibiotics which proves it might be due to some underlying infection. Excision biopsy was done and course of antibiotics was given.

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