Rosai Dorfman Disease — A Clinico-pathological Presentation

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Abstract
Rosai Dorfman disease (RDD) or sinus histiocytosis with massive lymphadenopathy (SHML) is a rare disorder that typically manifests as lymphadenopathy and systemic symptoms. The authors report a 45 year old lady who presented with nasal mass and generalised lymphadenopathy. Histopathological examination demonstrated lymphophagocytosis (emperipolesis) consistent with a diagnosis of RDD. The clinical and histologic aspects of the disease are discussed as a rare cause of generalised lymphadenopathy. ©

INTRODUCTION
Rosai Dorfman disease (RDD) or sinus histiocytosis with massive lymphadenopathy (SHML) is a rare disorder that typically manifests as lymphadenopathy and systemic symptoms. Physicians very commonly encounter patients with generalised lymphadenopathy with clinical picture representative of malignant lymphoma. Both physicians and pathologists need to be aware of rare conditions which masquerade as lymphoproliferative disorders. Here we describe one such differential diagnosis - “Rosai Dorfman disease” and an approach to such patients.

CASE REPORT
A 45 year old multiparous lady presented with history of progressively increasing painful masses in bilateral axillary, cervical and groin region occurring successively in that order over a period of two years; mild grade fever along with increasing weakness for eight months; and increasing stuffiness of left nasal cavity for three months. On examination she had pallor and lymphadenopathy (bilateral axillary, cervical and inguinal) which were firm, massive, mobile and discrete. Examination of eye including fundus was normal. Endoscopy of left nasal cavity revealed two smooth bulges arising from the septum and the lateral nasal wall, along with hypertrophy of adenoids (Fig. 1).

Hematological investigations revealed Hb - 12 g/dL, TLC - 9600/mm³, DLC - P82L8M9E1, Platelets-2.16 lacs/mm³, GBP - mild anisocytosis with hypochromia, ESR – 105 mm/h and reticulocyte count -<1%. Flowcytometry demonstrated 59% CD3+ cells (474 ×10⁶/L), with CD4/CD8 ratio of 1.2. Other relevant investigations included negative direct Coomb’s test and negative ELISA for HIV.

All imaging investigations including CT scan of head, ultrasound of abdomen, ultrasound B scan of orbits and X-rays of abdomen, chest and nasal sinuses, were within normal limits.

Histopathological examination of a left axillary lymph node biopsy displayed dilated sinuses in the parenchymal region with extensive infiltration consisting of histiocytes and chronic inflammatory cells (Fig. 2a). A large number of lymphocytes could be seen in cytoplasm of histiocytes suggesting lymphophagocytosis - emperipolesis (Fig. 2b). Lymphoid follicles were hypertrophied and showed germinal activity. Immunohistochemical staining of histiocytes was positive for S-100 gene product expression (Fig. 3). Similar histopathological findings were observed in nasal biopsy specimens. In view of the above mentioned observations diagnosis of extranodal Rosai Dorfman disease (RDD) or sinus histiocytosis with massive lymphadenopathy (SHML) was made.

Due to increasing nasal obstruction, the patient was advised to undergo chemotherapy. She underwent three cycles of chemotherapy at intervals of three weeks each comprising of cyclophosphamide (750 mg/m²), vincristine (1.4 mg/m²) and prednisolone (1 mg/kg/day orally for one week). Following chemotherapy, lymph nodes regressed remarkably, with no change in nasal mass. Post chemotherapy the patient developed hypoproliferative anemia with normal iron stores which was managed conservatively.

DISCUSSION
RDD is rare in Indian population with less than a dozen cases being reported in children and none in adults.\textsuperscript{1} Around 43\% of patients of RDD have extranodal involvement;\textsuperscript{2} none being reported in India.\textsuperscript{1}

Generalized lymphadenopathy, most prominent in axillary region, is the commonest presentation of this rare disease.\textsuperscript{1} Extranodal involvement, as evident by the presence of nasal mass in this case, has to be differentiated from diseases like lymphoma, tuberculosis, sarcoidosis, rhinoscleroma, syphilis, nasopharyngeal carcinoma, nasal carcinoma and olfactory neuroblastoma. Biopsy is the next best step in such cases. The differential diagnosis of a chronic inflammatory infiltrate containing numerous large histiocytes includes granulomatous diseases such as Wegener’s granulomatosis, sarcoidosis, Hodgkin’s disease, and Langerhans’ cell histiocytosis (LCH). The classical finding of emperiploesis (active penetration by a smaller cell into or through a larger cell) differentiates it from other diseases but may not be present in all cases of RDD.\textsuperscript{2,3} Although RDD shares several cell markers with LCH, the indolent clinical course of RDD suggests a reactive disorder rather than a neoplastic process which is proven by its polyclonal histiocytic proliferation.\textsuperscript{4}

SHML cells constantly express the S-100 protein, concanavalin agglutinin and peanut agglutinin lectins, and monocyte-macrophage-associated antigens CD 11c, CD 14, CD 33, CD 68, and LN 5.\textsuperscript{5} These cell markers can be used to differentiate SHML from various disorders including lymphoma and LCH.

Autoimmune hemolytic anemia in RDD has been reported\textsuperscript{2,6} but in this case the onset of hypoproliferative anemia, following the first cycle of chemotherapy, with the absence of positive Coomb’s test indicates bone marrow suppression. Immune dysfunction has been postulated to be a cause of death in around 60\% of cases.
in a registry of 14 cases. Low CD4/CD8 ratio may be one of the causes of immune dysfunction as evident in this patient and needs to be further evaluated. ESR is elevated in 88.5% of cases of RDD and was raised in this case too.

Active management of RDD is not required unless the disorder becomes organ or life threatening since it is mostly self-limiting. If required, vinca alkaloid in conjunction with alkylating agent and corticosteroid provide the most efficient chemotherapeutic regimen besides radiation therapy which is also used. The responsiveness in cases of RDD to the two modes of therapy may be inferior to that encountered with other hemopoietic disorders such as malignant lymphoma or histiocytosis X as evident in this case.

To conclude, RDD indeed is a rare finding, especially in Indian subcontinent. Physicians need to have a high degree of suspicion in patients presenting with generalized lymphadenopathy, with or without extranodal involvement, to diagnose RDD. Indolent course, presence of histiocytes with emperiploexis in inflammatory exudates and S100 positive immunohistochemical staining clinch the diagnosis in favour of Rosai Dorfman disease or sinus histiocytosis with massive lymphadenopathy.

REFERENCES