ROSAI-DORFMAN DISEASE- A RARE ENTITY

Abstract

Rosai Dorfman Disease (RDD) is a rare disorder of histiocytes.[1] It is predominantly seen in males affecting younger age groups but patients of all the age groups are known to be affected by this disease.[2] The most common presentation is bilateral massive lymphadenopathy which is non-tender and self-limiting. Head and neck region as the most commonly affected regions.[3] Apart from involvement of lymph nodes in head and neck regions, it has been reported to involve inguinal, retroperitoneal and mediastinal lymph nodes also. Extranodal manifestation has been seen over 40% patients, but it may occur in older patients even in the absence of nodal disease. Exact pathogenesis of RDD has not been known. It was thought to be a reactive, non-neoplastic histiocytic disorder lacking clonality.[5] RDD is believed to be a reactive process, and an undefined immunological defect is thought to be initiated by some other organism which is believed to be responsible for this disease.[9] The most common differential for RDD are Langerhans cell histiocytosis (LCH), lymphoma and nonspecific sinus hyperplasia.

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I. INTRODUCTION

Rosai Dorfman Disease (RDD) is a rare disorder of histiocytes. In 1965, it was described initially by Destombes among four children in Africa presented with lymph node swelling and named it "Adenitis with lipid excess". In the year 1969, Rosai and Dorfman described it in a series of four patients with massive cervical lymphadenopathy with specific histopathological features and named it as "sinus histiocytosis with massive lymphadenopathy". Further in the year 1990, it has been reported as nodal and extranodal forms of the disorder.[1] Till now, only 1000 cases are reported around the world, hence the exact incidence and prevalence are not known for this disease.[1] It is predominantly seen in males affecting younger age groups but patients of all the age groups are known to be affected by this disease.[2] The most common presentation is bilateral massive lymphadenopathy which is non-tender and self-limiting. Head and neck region as the most commonly affected regions.[3] It is associated with fever, weight loss and night sweats. Although the most common presentation in patient suffering from this disease is swelling in head and neck region, but can also presents as swelling in extranodal sites like- skin, soft tissue, CNS and GIT system.[4] Apart from involvement of lymph nodes in head and neck regions, it has been reported to involve inguinal, retroperitoneal and mediastinal lymph nodes also. Extranodal manifestation has been seen over 40% patients, but it may occur in older patients even in the absence of nodal disease. On laboratory investigation, elevated ESR, leucocytosis, hypergammaglobinemia are observed. Patients with cutaneous form of RDD presents in the older age group than compared to nodal one. The disease is more likely to be localised lesion, despite of long term follow up and it lacks any association with systemic or extracutaneous disease.[5] It is a benign proliferative histiocytic disorder morphologically characterized by 'emperipolesis'.[3] Working Group of the Histiocyte Society in 1987 has recently reclassified the histiocytosis based on new insights into the pathological, genetic and molecular features of these disorders. This classification includes familial RDD, sporadic RDD and non-LC histiocytosis. RDD forms a part of 'R group' of histiocytiosis and cutaneous RDD has been classified separately as part of 'C group' of histiocytosis. RDD can be diagnosed generally on Hematoxylin & eosin stained sections and may need a group of immunohistochemical markers for further confirmation. In some instances, the diagnosis becomes challenging when patient presents with extranodal presentation or cases in which there is extensive fibrosis or scant emperipolesis.[5] Exact pathogenesis of RDD has not been known. It was thought to be a reactive, non-neoplastic histiocytic disorder lacking clonality.[5] Among neoplastic lesions, lymphomas, leukaemia, malignant histiocytosis, Langerhans Cell Histocytosis (LCH) and Erdheim-Chester Disease (ECD) are found to have a close association with RDD. Idiopathic juvenile arthritis, Systemic lupus erythematosus, autoimmune haemolytic anaemia and HIV are found to be associated with Rosai Dorfman disease.[5] Histopathologic evaluation is the core diagnostic method in the diagnosis of RDD.[6] Histopathologically it is characterised by the frequent emperipolesis with CD68-positive, S100-positive, and CD1a-negative histiocytes.[1] Spontaneous regression has been reported in numerous cases and therefore a "watch and wait" approach is recommended. Surgery and systemic treatment with steroids are being used as initial mode of treatment in case of symptomatic cases, but in rare cases it may need chemotherapy. But still, the reliability and stability of these treatment is unpredictable with unspecified duration of treatment.[2] Generally, this disease has a very stable and benign course, but in rare cases due to its wide spread and involvement of vital organs like kidney and liver or presence of immunological abnormalities it carries poor prognosis.[8] The clinical spectrum and treatment outcomes are not

well known as this disorder being uncommon. Hence, we undertook this study to evaluate this case with cytological and histopathological correlation.

II. CASE DETAILS

A young female presented with a painless swelling of cervical lymph node for 2 months with no complain of fever or another swelling in the body. Clinical examination revealed no evidence of hepatosplenomegaly or any evidence of any swelling in the body. Ultrasonography for swelling over right cervical region reported as Infection/inflammatory. Among the various laboratory investigation done, ESR was found to be raised, total leucocyte count and other parameters were normal. On examination, swelling was firm, non-tender on posterior cervical region and measures 2.5x 2cm. Fine needle aspiration cytology revealed a cellular smear with proliferated large histiocytes with numerous intracytoplasmic lymphocytes and plasma cells. These histiocytes have abundant cytoplasm, large nuclei and prominent nucleoli displaying emperipolesis. Background shows population of lymphoid cells, plasma cells, multinucleate giant cells and erythrophagocytosis. It was reported as Rosai Dorfman Disease. Later patient underwent surgery for the swelling (cosmetic purpose).

1. **Histopathology:** Gross examination shows an enlarged lymph node measuring 3.5x2x1.5 cm. Cut section shows a tan –yellow solid homogenous mass. Microscopic examination shows a normal architecture of lymph node which is partially altered with massive sinusoidal dilatation, polymorphous population of lymphoid cells, numerous histiocytes, plasma cells, multinucleate giant cells. These histiocytes showing emperipolesis as well as erythrophagocytosis. Cortex shows the appearance of alternating dark and light zones, which is composed of numerous activated B cells, plasma cells and follicles along with the presence of histiocytes.

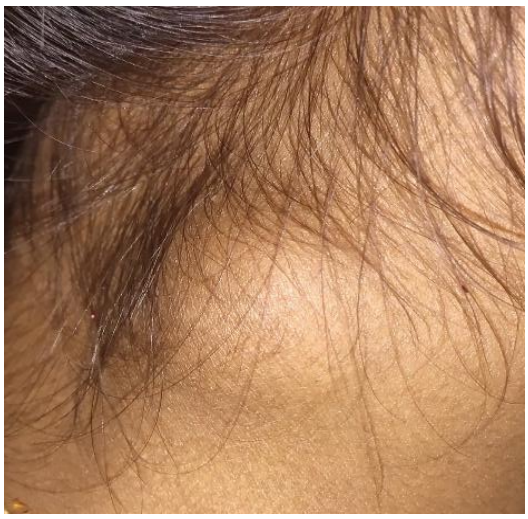

Figure 1: Large Single Swelling Over Right Posterior Cervical Region

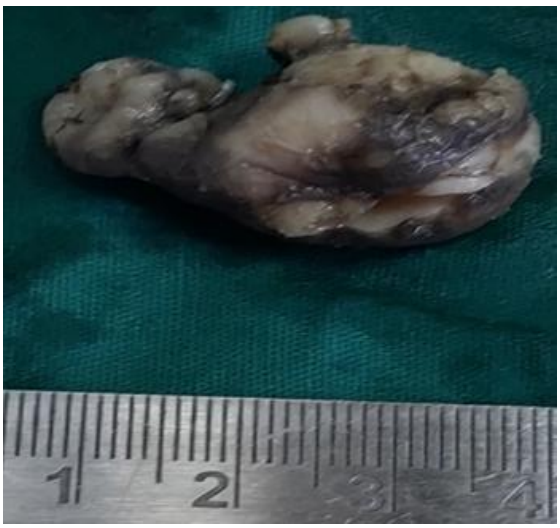

Figure 2: Gross: Excised Large Lymph Node

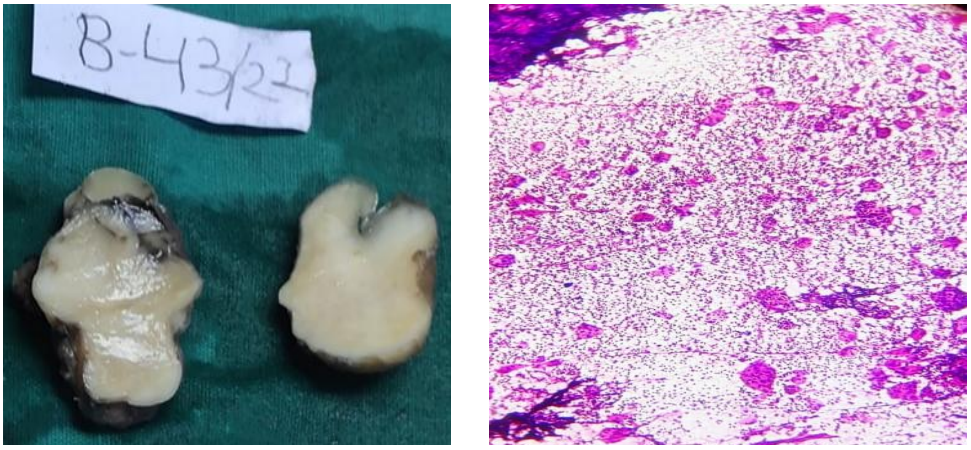

Figure 3: Cut Surface-Solid Homogenous Tan Areas With Entire Capsule.

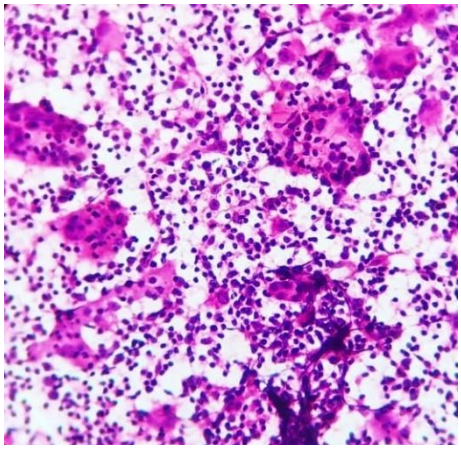

Figure 5: Histiocytes Showing Emperipolesis with Lymphocytes, Plasma Cells and Multinucleate Giant Cells. H&E-1000X

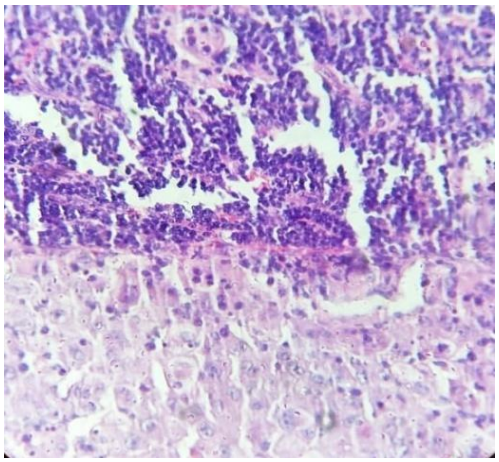

Figure 6: Displaying Characteristics Alternating Dark and Light Areas. H&E 100X

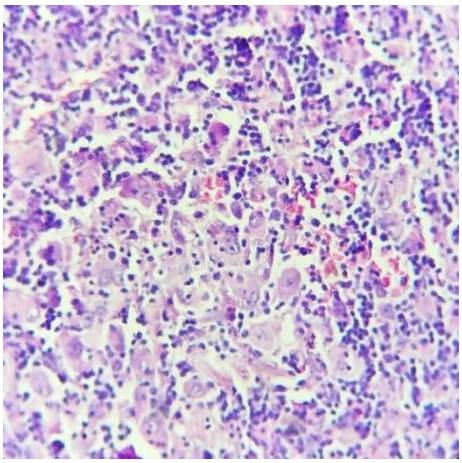

Figure 7: Numerous Histiocytes Displaying Emperipolesis with Lymphocytes, Multinucleate Giant Cells and Plasma Cells. H&E 100X

III. DISCUSSION

RDD is a rare disease seen with varying course and presentation. Although it has a varying clinical presentation, but the most common site is nodal involvement and has been reported in about 90% of cases. Extra nodal involvement occurs in less than 50% cases.[2] Less commonly it may also involve the skin, orbits, eyelids, salivary glands, peritoneum, bone, kidneys and testis. Patient can presents with varying features like- fever, weight loss, tonsillitis, nasal discharge and obstruction.[9]. Histiocytes are positive for immunohistochemical stains like- CD68 and S100 and are typically negative for CD1a.[2] RDD is believed to be a reactive process, and an undefined immunological defect is thought to be initiated by some other organism which is believed to be responsible for this disease.[9] The most common differential for RDD are Langerhans cell histiocytosis (LCH), lymphoma and nonspecific sinus hyperplasia. Immunohistochemical stains help in diagnosing Rosai Dorfman disease. In RDD, histiocytes are strongly positive for S-100 protein, negative for CD1a and variably positive for CD68. In case of nodal involvement we must rule out the other nodal disease which can often coexist with RDD like- lymphoma, ECD and LCH. So to diagnose a lesion as RDD, one must rule out LCH which is the most common entity by doing immunohistochemical staining which should be negative for CD1a or CD207 for histiocytic infiltrate. The presence of characteristics elongated grooved nuclear with lack of plasma cell points towards LCH and thus morphologically helps us to differentiate RDD from LCH.

RDD also closely mimics Anaplastic large cell lymphoma (ALCL) which can be differentiated on morphological features on H&E stained slides and further can be confirmed by Immunohistochemistry. ALCL shows negativity for S100 with CD30 positivity. Although less commonly but one should also have other differential diagnosis in cases with nodal involvement like Whipple's disease, Hodgkin's lymphoma and Gaucher's disease. Gaucher's disease can be differentiated by existance of characteristics finely fibrillar histiocytes with tissue paper like cytoplasm and lack of emperipolesis. Whipple's disease is characterised by Periodic Acid Schiff positive diastase resistant bacilli in the macrophages. Hodgkin's Lymphoma characterised by typical Reed-Sternberg cells and further can be confirmed by immunohistochemistry which shows CD15 & CD30 positivity and negative for S100.[5] Till now pathogenesis has not been understood completely to classify it as benign or a neoplastic disorder. According to a recent study, it has been reported to have MAP –ERK pathway alternations which has been found among 33% of RDD patients.[1]

The Consensus recommended to detect Mitogen Activated Protein Kinase by targeted next generation sequencing in patients with severe or refractory diseases. ARAF, MAP2K1, NRAS and KRAS are also found in some patients with nodal and extranodal presentation of Rosai Dorfman Disease which was reported in a recently published article.[5]

IV. CONCLUSION

Classical clinical presentation and morphological features in cytology and histopathology help in recognising the Classical cases of RDD. But in difficult cases, it may need to be differentiated from other disease entity mimics closely with RDD. Most of the differentials can be ruled out by lack of emperipolesis, dark and light zone appearance and negativity for immunohistochemical stain for S100. But in longstanding cases with

extranodal involvement, it may show extensive fibrosis with scant emperipolesis which causes pitfalls in the diagnosis of RDD. As RDD mimics IgG4 related diseases, which is not possible to make an accurate diagnosis and hence a full clinical history with investigation and histopathological study should be included. This is as per recommended by the expert panel on consensus guidance published in 2015 on the management of IgG4 related disorders. The histiocyte society has recommended to perform an immunohistochemical stain for IgG4 in all such cases.[5]

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