Rosai-Dorfman Disease- A rare entity

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Introduction

Rosai Dorfman Disease is a rare entity of lymph nodes. It was originally described by Destombes in 1965 among four children in africa with lymphadenopathy and described it as "Adenitis with lipid excess". Later it was described by Rosai and Dorfman as a separate series of four patients with massive cervical lymphadenopathy with specific histopathological features in the year 1969 and named it as "sinus histiocytosis with massive lymphadenopathy". In the year 1990, it was reported as nodal and extranodal manifestations of the disease.[1]

Till now, only 1000 cases has been reported so far across the world, hence the exact incidence and prevalence has not been known for this disease.[1] It is predominantly seen in males affecting younger age group but patients of all age group are also reported to have this disease.[2] The most presentation is bilateral massive lymphadenopathy which is non-tender and self-limiting commonly seen in head and neck region.[3] It is associated with fever, loss of weight and night sweats. Although it is commonly seen as the swelling in head and neck region, but also present in extranodal sites like- skin, soft tissue, CNS and GIT system.[4] Apart from involvement of lymph nodes in head and neck regions, inguinal, retroperitoneal and mediastinal lymph nodes can also be involved. Extranodal disease has been seen over 40% cases but it may rarely occur in older patientswith different demographics in absence of nodal disease. On laboratory investigation, elevated ESR, leucocytosis, hypergammaglobinemia and autoimmune haemolytic anaemia are observed. Patients with Cutaneous form of RDD presents at a older age group than compared to nodal one. The disease tend to be localised despite long term follow up and lacks 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 of 1987 has recently reclassified the histiocytoses based on new insights into the pathological, genetic and molecular features of these disorders. This classification includes familial RDD, sporadic RDD and non-LC histiocytoses RDD forms a part of 'R group' of histiocytoses,. Cutaneous RDD has been classified separately as part of 'C group' of histiocytoses. Diagnosis of RDD can be made generally on routine Haematoxin & Eosin stained sections and may need panel of immunohistochemical markers for further confirmation. Sometimes the diagnosis can be becoming challenging when patient presents with extranodal forms or cases in which there is extensive fibrosis or scant emperipolesis.[5]

The exact aetiopathogenesis of Rosai Dorfman disease has not been known. It was thought to be a reactive, non-neoplastic histiocytic disorder lacking clonality.[5] Sporadic form is the most common presentation and it is seen in 3 forms- classic nodal form, extranodal, neoplasia-associated and immune disease-associated. Among the Neoplastic lesions, lymphomas,

leukaemias, malignant histiocytoses, Langhans Cell Histocytosis(LCH) and Erdheim-Chester Disease (ECD) are found to have a close association with RDD . Among immune disorders, Systemic lupus erythematosus, idiopathic juvenile arthritis, autoimmune haemolytic anaemia and HIV are associated with Rosai Dorfman disease.[5]

Histopathologic evaluation is the core diagnostic method in the diagnosis of RDD.[6] Rosai-Dorfman disease characterized histopathologically by the accumulation of CD68-positive, S100-positive, and CD1a-negative histiocytes with frequent emperipolesis.[1] S100 stain is useful in identifying the histiocytosis in Sinus Histiocytosis with massive Lymphadenopathy (SHML).[7]

Spontaneous regression has been observed in many cases and hence the "watch and wait" approach is advocated. Surgery and systemic treatment with steroids are being used as first line treatment protocol in case of symptomatic cases and but rare cases may need chemotherapy. But still, the reliability and durability of such treatment is unpredictable with unknown duration of treatment.[2] Generally, this disease has a very stable and benign course. In rare cases, it carries poor prognosis due to its wide spread dissemination and involvement of vital organs like kidney and liver or presence of immunological abnormalities.[8]

The clinical spectrum and treatment outcomes are not well defined because of rarity of this disease. Hence, we undertook this study to evaluate our institutional experience with RDD patient with cytological and histopathological correlation.

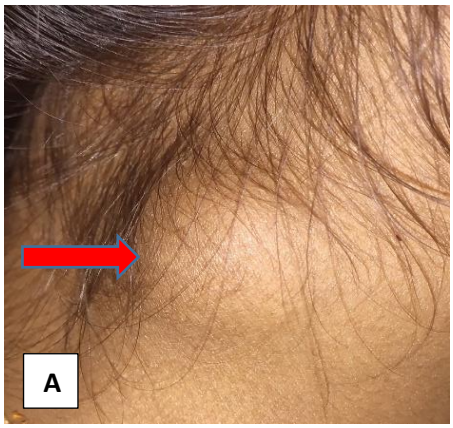
Case Details

A 21 year old female presented with a painless swelling of right cervical lymph node for 2 months. History revealed no complain of fever or another swelling in the body. Clinical examination revealed no evidence of organomegaly or any other 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 (40 mm/hour), total leucocyte count and other parameters were normal. On examination swelling was firm non tender on right 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 showing emperipolesis. Background shows polymorphous population of lymphoid cells, plasma cells, multinucleate giant cells and erythrophagocytosis. It was reported as Rosai Dorfman Disease. Later patient underwent surgery for swelling over neck (cosmetic purpose).

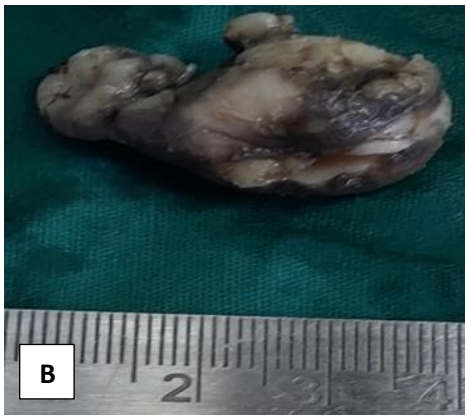
Histopathology

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 and erythrophagocytosis. Cortex shows the

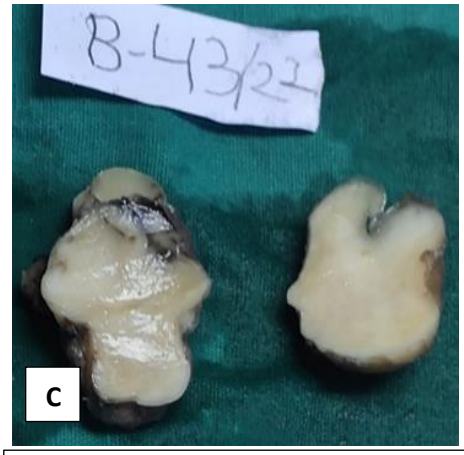
appearance of alternating dark and light zones which is composed of numerous activated B cells, plasma cells and follicles along with the presence of histiocytes.



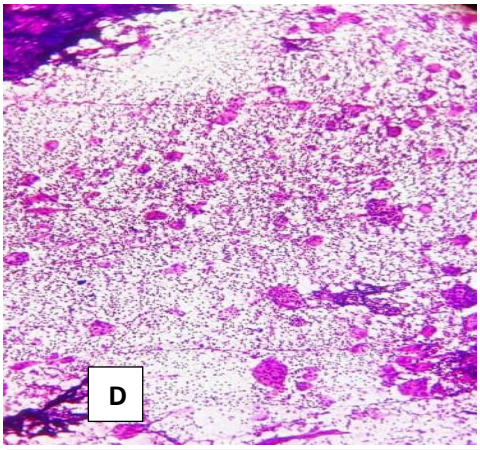
A- Large single swelling over right posterior cervical region



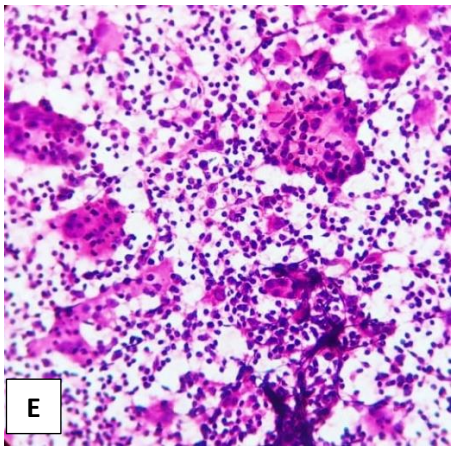
B- Gross: Excised large nodular mass



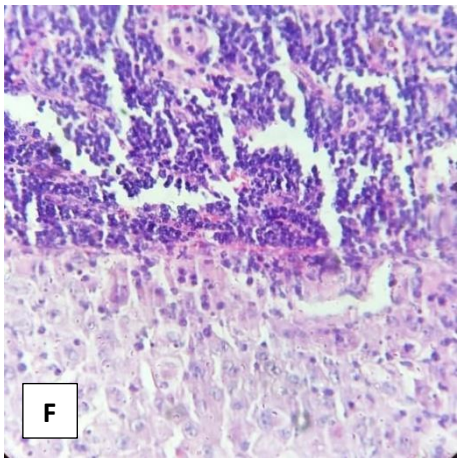
C- Cut surface-solid homogenous tan area with intact capsule.



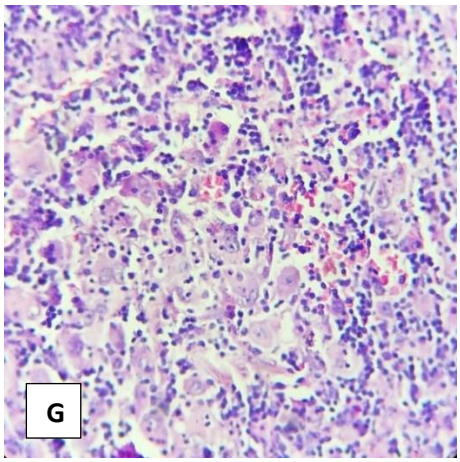
D- Numerous histiocytes with multinucleate giant cells, lymphocytes and plasma cells. H&E-100X



E- Histiocytes showing Emperipolesis with mixture of multinucleate giant cells, lymphocytes and plasma cells. H&E-1000X



F-Alternating light and dark areas characteristics of Rosai-Dorfman disease, H&E 100X



G- Numerous histiocytes showing Emperipolesis with mixture of lymphocytes and plasma cells. H&E 100X

Discussion:

RDD is also known as Sinus histiocytosis with massive lymphadenopathy, which is a rare disease with a variable course and presentation. Although it has variable clinical presentation, but the most common site is nodal involvement which is painless bilateral cervical lymphadenopathy which is being reported in about 90% of cases. Extra nodal involvement most commonly seen in skin, gastrointestinal tract, eyes, external and internal ear, skeletal system, upper and lower respiratory tracts, oral cavity, paranasal cavities, and the central nervous system and it 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 present with varying features like- fever, weight loss, tonsillitis, nasal discharge and obstruction.[9]Laboratory findings includes leukocytosis, neutrophilia, normocytic anemia, thrombocytosis, an elevated CRP, ESR, ferritin levels and hypergammaglobulinemia. Histiocytes are positive for immunohistochemical stains CD68 and S100 and are typically negative for CD1a.[2] It has been believed to be a reactive process, and infection by a virus or an undefined immunological defect initiated by some other organism is believed to be responsible for the disease.[9]

Differential diagnoses includes- Langerhans cell histiocytosis (LCH), lymphoma and nonspecific sinus hyperplasia, lack lymphophagocytosis. 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 absence of plasma cell give clue for 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 Gaucher disease, Whipple disease and Hodgkin's lymphoma. Gauchers disease can be differentiated by presence of characteristics finely fibrillar histiocytes with tissue paper like cytoplasm and absence of emperipolesis. Whipple's disease is characterised by Periodic acid Schiff positive diastase resistant bacilli in the macrophages. Hodgkin's Lymphoma characterised by presence of typical Reed-Sternberg cells and further can be confirmed by immunohistochemistry which shows CD15 & CD30 positivity and negative for S100.[5]

Although pathogenesis has not been understood completely whether it should be classified as benign or a neoplastic disorder. Previous studies suggest RDD to be polyclonal in nature. It has been reported to have MAP –ERK pathway alternations according to a recent study which has been found in about a third of RDD patients. Thus it suggests it nature to neoplastic rather a benign entity.[1]

In case of severe or refractory diseases, it has been advised by Consensus recommendation to detect Mitogen Activated Protein Kinase by targeted next generation Sequencing. Also in recently published articles, ARAF, MAP2K1, NRAS and KRAS are also found in patients with nodal and extranodal RDD.[5]

Conclusion

The Classic RDD can be recognised by its classical clinical presentation and morphological features seen on cytology and histopathology. But in difficult cases, it may need to be differentiated from other disease entity mimics closely with RDD. Most of the differential can be ruled out by absence of emperipolesis with absence of dark and light zone appearance and negative 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 as IgG4 related diseases which is not possible to make accurate diagnosis a full clinical history with investigation and histopathological study should be included. This is as per the recommendation of Expert panel on consensus guidance published in 2015 on the management of IgG4 related disorers. Histiocyte society has recommended to perform a immunohistochemical stain for IgG4 in all such cases.[5]

References:

1. Goyal G. Clinicopathological features, treatment approaches, and outcomes in Rosai-Dorfman disease. Haematologica. 2020; 105(2):348-357.

2. Amiji I, Mohammed U, Salum H, et al. Rosai Dorfman Disease —A rare case of cervical lymphadenopathy. Clin Case Rep. 2020; 8:2712–2715. https://doi.org/10.1002/ccr3.3255.

3. Sachdev R, Setia N, Jain S. Sinus histiocytosis with massive lymphadenopathy.Is the lymph node enlargement always massive?. Med Oral Patol Oral Cir Bucal 2007;12:E198-200.

4. Dalia S et al. Rosai–Dorfman Disease: Tumor Biology, Clinical Features, Pathology, and Treatment. Cancer Control. 2014; 21(4): 322-327.

5. Bruce-Brand C, et al. J Clin Pathol 2020; 73:697–705. doi:10.1136/jclinpath-2020-206733.

6. Yaam AA et al. Rosai–Dorfman Disease: A Rare Clinicopathological Presentation and Review of the Literature. Head and Neck Pathology. 2021; 15:352–360.

7. Joshi S. Otorhinolaryngology Clinics: An International Journal, September-December 2014; 6(3):121-122.

8. Ekhar VR, Shelkar RN, Rane S, Anand A, Lanjewar K, Jain SKT. Rosai-Dorfman Disease: A Rare Cause of Cervical Lymphadenopathy. Int J Head Neck Surg 2014;5(3): 152-154.

9. Santra G, Das B K, Mandal B, Kundu S S, Bandopadhyay A. Rosai-Dorfman disease. Singapore Med J 2010; 51(10) : e173-e175.