Case Report

Unveiling the enigma: Navigating extranodal Rosai-Dorfman disease in the maxilla - A teen's journey

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Abstract

Rosai–Dorfman disease (RDD), a rare histiocytic disorder, typically manifests as widespread lymphadenopathy. We present a unique case of extranodal RDD in a 14-year-old with a solitary maxillary lesion and mild bilateral submandibular lymphadenopathy. Clinical, radiological, and histopathological assessments confirmed RDD, highlighting the importance of a comprehensive approach. Immunohistochemistry, including CD68, CD45, CD 1a, and S100, played a crucial role in diagnosis. Differential diagnoses encompassed Langerhans cell histiocytosis, Erdheim–Chester disease, lymphomas, and histiocytic sarcoma, necessitating meticulous evaluation. Surgical excision was performed due to bone involvement, leading to successful healing in six months. Our case underscores the significance of a multidisciplinary and scientific approach for accurate RDD diagnosis and management, especially in atypical intraoral presentations.

Keywords: Emperipolesis, extranodal Rosai–Dorfman disease, immunohistochemistry, lymphadenopathy, oral cavity, sinus histiocytosis

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INTRODUCTION

Rosai–Dorfman disease (RDD) is an extremely rare histiocytic condition with an undetermined cause that is also referred to as "Sinus histiocytosis" with extensive lymphadenopathy. It was initially discussed by Destombes in 1965,[1] and again in 1969 by Juan Rosai and Ronald F. Dorfman.[2] The Working Group of the 1987 Histiocyte Society had previously defined this entity as a non-Langerhans cell (LC) histiocytosis. RDD belongs to the group of histiocytosis known as the "R group," which comprises sporadic RDD, familial RDD, and other non-cutaneous, non-Langerhans cell histiocytosis.[3] Classical RDD symptoms include bilateral cervical lymphadenopathy, but there are also multiple cases of isolated extranodal involvement. This condition is thought to affect 1 in 2,00,000 people[4] and 40–45% of patients possess extranodal and nodal involvement.[5] About 20% to 25% of cases had isolated extranodal illness.[6] Less than 10% of patients have osseous involvement with nodal illness. However, isolated osseous involvement in extranodal location is uncommon.[7] A distinctive pathologic hallmark of RDD is "Emperipolesis" (Greek word: "to meander inside and outside"). RDD is characterized by a significant amount of histiocytes seen on the histological analysis, along with sporadic giant cells that include whole phagocytized lymphocytes in the background of chronic inflammatory cells. Due to the potential involvement of the oral cavity

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in these uncommon pathologies, there is a need for an oral pathologist's scientific approach.

According to our knowledge, hereby we report the 21st case of extranodal RDD in a 14-year-old boy who had a lesion in the right posterior maxilla and a history of painless bilateral mild submandibular lymphadenopathy.

CASE REPORT

A 14-year-old male presented with painless swelling in the right upper back tooth region for the past four months. His medical and family history was unremarkable. Externally, a smooth swelling of size 4 × 3 cm was evident on the right side of the face, extending anteroposteriorly from the ala of the nose till 1 cm in front of the tragus. It was soft, non-tender, and obscuring the right nasolabial fold [Figure 1a]. Upon palpation, non-tender, and movable submandibular lymph nodes measuring 0.5 × 0.5 cm were evident on both sides. Intra-orally, a 4 × 3 cm soft tissue growth in the right upper posterior region (irt 14, 15, 16, 17,) extended from the distal aspect of 13 to the mesial aspect of 17. It obliterates the vestibule irt the 14, 15, and 16 regions buccally and reaches the midpalatine raphae palatally. The lesion had diffuse borders, a polylobed surface, and caused indentation of the mandibular tooth, as well as palatal displacement of tooth 15. It was soft to firm upon palpation without tenderness [Figure 1b]. Blood investigations revealed normal values.

Radiological examination using CBCT [Figure 2] revealed an irregular expansive hypodense lesion involving the right maxillary alveolus along with the destruction of both buccal and palatal cortical plates. The lesion displaced 15 palatally, 55 superiorly, and there is a breach in the superior floor of the right maxillary sinus, accompanied by thickening of the sinus lining. There is no indication of root resorption. The rapid growth of the lesion, combined with destructive radiographic features, was more indicative of malignant neoplasms rather than an inflammatory lesion, and thus an incisional biopsy was advised, which upon microscopic examination showed hyperplastic stratified squamous epithelium with a lamina propria abundant in dilated and engorged capillaries. The presence of numerous proliferating capillaries and collagen bundles led to a diagnosis of "Angiofibroma" [Figure 3].

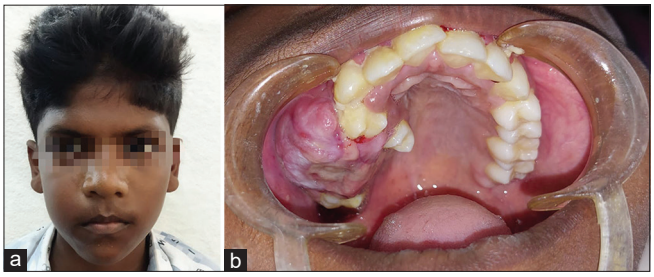

Figure 1: (a) Extra-oral swelling in the right-side middle third of the face. (b) Polylobed soft tissue growth was observed on the right-side posterior region of the maxilla

Following surgical excision, histopathological examination revealed hyperplastic stratified squamous keratinized epithelium. The connective tissue exhibited proliferating blood vessels, chronic inflammatory cells, and tissue macrophages mirroring the incisional biopsy findings. Notably, the granulation tissue displayed numerous multinucleated giant cells with some osteoid-like deposits, indicative of a "Central giant cell granuloma." Surprisingly, closer inspection revealed lymphocytes trapped within multinucleated giant cells, which is a rare phenomenon called "Emperipolesis" [Figure 4a and b].

This observation led us to consider RDD. Further investigation using immunohistochemistry (IHC) markers showed CD68, CD45, and S100 were positive, while CD1a was negative [Figure 5]. These findings, along with unique histopathological features, led to a final diagnosis of RDD with extranodal involvement. [Table 1] lists the differential diagnoses and their distinguishing IHC markers. The patient was treated with surgical curettage, and after 1 year of follow-up, there was no remission, and lymph nodes regressed to normal on their own [Figure 6].

DISCUSSION

RDD is a rare idiopathic histiocytic proliferation mainly affecting cervical lymph nodes and extranodal sites. The cause is unknown. Although Epstein–Barr virus (EBV)

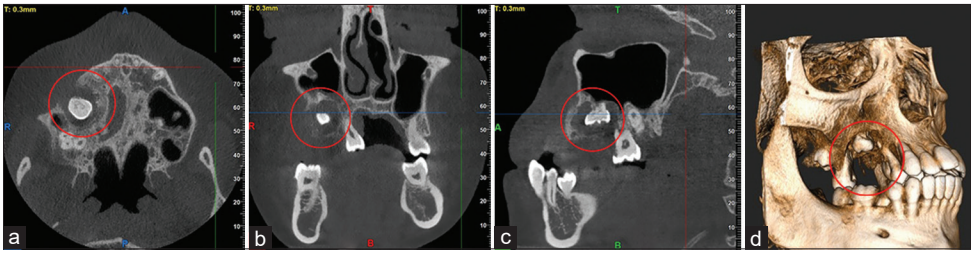

Figure 2: CBCT. (a) axial. (b) coronal. (c) Sagittal. (d) 3D reconstruction

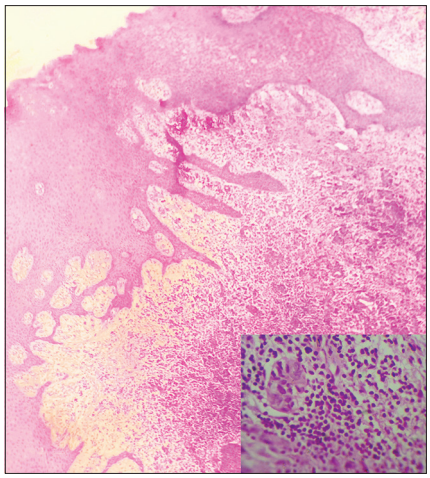

Figure 3: Photomicrograph of incisional biopsy showing the proliferating capillaries and collagen bundles

Table 1: Illustrates the importance of immunohistochemical stains in differentiating RDD, ECD, and LCH

Disease name	Positive IHC Stain	Negative IHC Stain
Langerhans cell histiocytosis (LCH)	CD 68 CD 1a	S100
Rosai–Dorfman Disease (RDD)	CD 68 S100	CD 1a
Erdheim–Chester Disease (ECD)	CD68	S100

was initially considered, many patients tested positive for EBV despite negative *in situ* hybridization results.[8] Recent research indicates that about one-third of RDD patients carry gene mutations impacting the MAPK/ERK pathway, including NRAS, KRAS, MAP2K1, and occasionally BRAF. This suggests a neoplastic rather than a reactive nature. RDD is featured in the World Health Organization's Fifth Edition Classification of Myeloid and Histiocytic/Dendritic Neoplasms.[9] RDD diagnosis typically occurs around the age of 20.6 years, with a male-to-female ratio of 3:2.[2] Painless, bilateral large cervical lymphadenopathy is prevalent, observed in around 87% of cases.[10] Extranodal involvement occurs in 43% of cases, with 75% limited to the head and neck.[2] The extranodal involvement of RDD in the oral cavity and osseous involvement is a super rare entity. To the best of our knowledge, only 20 such cases of oral RDD without involvement of lymphadenopathy have been reported in the literature. Our case represents the 21st instance, as detailed in [Table 2]. Patients often reported discomfort and swelling, though some were asymptomatic. There were no general symptoms like weight loss, malaise, fever, or nasal obstruction. Oral extranodal RDD displays diverse clinical appearances, but a polylobed surface, as in our case, is noted in some literature.[11]

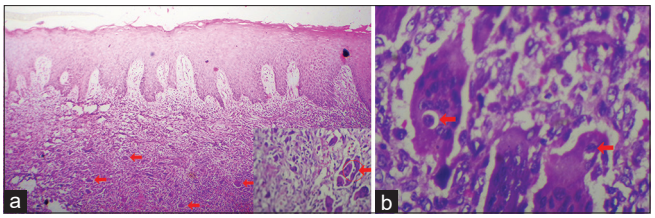

Figure 4: (a) Stratified squamous epithelium with multinuclear giant cells in fibrous connective tissue (indicated by arrows). Insert multinuclear giant cells with emperipolesis of an intact lymphocyte that has wandered outside (arrow). (b) Multinuclear giant cells with emperipolesis (arrows)

In oral cavity it primarily affects the soft and hard palate with nodules, gingiva, and oral mucosal swellings. Other oral symptoms may include tongue enlargement, thickened oropharyngeal mucosa, swollen tonsils, or recurrent tonsillitis. Nonspecific results from laboratory evaluations of patients suspected of having RDD include about 90% exhibiting increased erythrocyte sedimentation rate, leukocytosis, polyclonal hypergammaglobulinemia with elevated immunoglobulin G levels in 83% of cases, anemia in 65%, and a reversal of the CD4/CD8 ratio.[14] Radiographically, prior oral RDD cases showed indistinct osteolytic lesions, eroding cortices without expanding into nearby structures. When linked to teeth, it presented a distinctive "floating tooth" appearance or resulted in root resorption of teeth,[11] as observed in our case.

Typical giant cells and emperipolesis in histopathological examination are the key diagnostic features. In the present case, central giant cell granuloma (CGCG) was considered as a potential differential diagnosis characterized by non-neoplastic vascular tissue, giant cells, and hemosiderin. Emperipolesis is rare in CGCG, and the internalized cells usually do not express CD68.[15] However, in this case, CD68 positivity was observed.

Numerous large histiocytic cells are observed, possibly showing multinucleation, atypia, and occasional mitotic figures. Emperipolesis, lacking specificity, involves intact haemato-lymphoid cells within a vacuole or freely floating in the histiocytic cytoplasm. Background neutrophils may be visible, occasionally forming micro-abscesses, while eosinophils are usually absent. A notable feature is a significant sclerosis with a storiform architecture and lobulation. All these features suggested RDD. If enhanced plasma cells are observed in pathology samples, perform IgG4 immunohistochemistry to exclude IgG4 lymphoproliferative disorder.[3]

RDD histiocytes are notably large, ranging from 50 to 100 microns, and occasionally exceed this size. A mere

Table 2: Reports of extranodal Rosai–Dorfman disease of oral cavity published in English literature

Maxilla				
Ref No	**Age**	**Sex**	**Clinical Features**	**Treatment**
[11]	46	F	Pain, non-healing extraction site	NA
[11]	44	F	Pain, swelling in the maxillary sinus and nasal cavity	Excision, Steroids
[11]	29	F	Pain, swelling	None
[11]	18	M	NA	None
[11]	29	F	Pain, swelling, submucosal mass	Excision
[11]	65	F	Reddish macule, telangiectasia, nodular sessile lesion softened to palpation	Steroids
[11]	47	F	Dental mobility	NA
[11]	56	F	Pain, hard palate swelling involving the right genian region	NA
[11]	39	F	Pain, teeth mobility	Steroids
[12]	20	F	Recurrent lesion, mobile incisors, swelling, no trauma	Curettage, tooth extraction
Present case	14	M	Painless swelling in the right-side posterior maxilla	Surgical curettage
Mandible				
Ref No	**Age**	**Sex**	**Clinical Features**	**Treatment**
[6]	27	F	Right jaw swelling, loosening teeth, localized pain, tender mandible	Reconstruction with fibular flap
[11]	23	F	Pain, swelling, submucosal mass	Excision
[11]	26	F	Pain, mobility	NA
[11]	26	M	NA	NA
[11]	38	F	Gingival mass	NA
[11]	46	F	Bilateral proptosis, sinusitis, saddle nose	Excision
[11]	47	F	Swelling	Excision
[11]	12	M	Pain, swelling, vestibular edema, tenderness, rapid lesion progression	Partial mandibulectomy
[11]	32	F	Pain, swelling, dental mobility, dysphagia	Excision
[13]	25	M	NA	NA

F=Female, M=Male, NA=Not available

five-micron section displaying only a small portion of the RDD histiocytic cytoplasm can pose challenges in accurately identifying the emperipolesis. RDD histiocytes, similar to activated macrophages, are *S100* positive and originate from circulating monocytes and thus express *CD68* positivity. Monocytes serve as antigen-presenting cells, recognizing foreign substances. These features imply that emperipolesis is observed in the late stages of transformation during disease flare-ups.[16] These histiocytes show positive results for *CD68 and S100,*[17] as in the present case. To demonstrate the lymphocyte engulfed within the giant cells, we used the CD45 marker. However, CD45 displayed weak membrane staining in the IHC [Figure 5d]. According to literature, once lymphocytes are engulfed by macrophages or tumor cells, they are broken down by lysosomes, making them short-lived.[18]

To diagnose RDD, the specimen should show RDD features in over 10% of the entire tissue.[3] In the histological context, the potential differential diagnosis for RDD encompasses Langerhans cell histiocytosis (LCH), Erdheim–Chester disease (ECD), lymphomas, leukemias, and malignant histiocytosis.[19]

Distinguishing LCH from RDD is straightforward. Langerhans cells in LCH have thin nuclear membranes resembling coffee beans and a high eosinophil count, unlike RDD. Both are S100 positive, but LCH expresses CD1a and langerin (CD207), while RDD does not. In our case, negative CD1a rules out LCH [Figure 5a]. Birkbeck granules unique to LCH are visible under an electron microscope. Regarding mutations, BRAF V600E is more common in LCH than RDD. The BRAF VE1 clone in immunohistochemistry can identify BRAF V600E. PD-L1 is more frequently positive in LCH compared to RDD.[19]

A comprehensive evaluation, considering clinical, radiological, and molecular aspects, is essential for an ECD diagnosis. Key radiographic features include bilateral osteosclerotic lesions in long bones and aorta sheathing. Histologically, Touton cells, a type of giant cell, are present, surrounded by inflammatory cells, xantho-granulomatous alterations, and fibrosis. Histiocytes in ECD are positive for CD68, CD163, and few for S-100, resembling RDD. Unlike RDD, ECD histiocytes show BRAF mutations (>50% of cases) and lack emperipolesis.[20] S100 immunoreactivity is present in 20% of cases, but is mostly negative. CD1a is typically negative [Figure 5a]. In our case, CD68, CD45, and S100 were positive, playing a crucial role in ruling out ECD [Table 1].

In Hodgkin's lymphoma, Reed–Sternberg and Hodgkin cells aid in identifying the lesion. In lymphomas, background cells usually only show positivity for CD-68, not S-100. However, in our case, both were positive, definitively ruling out lymphoma [Figure 5b and c]. It is crucial to note that Hodgkin and Reed–Sternberg cells

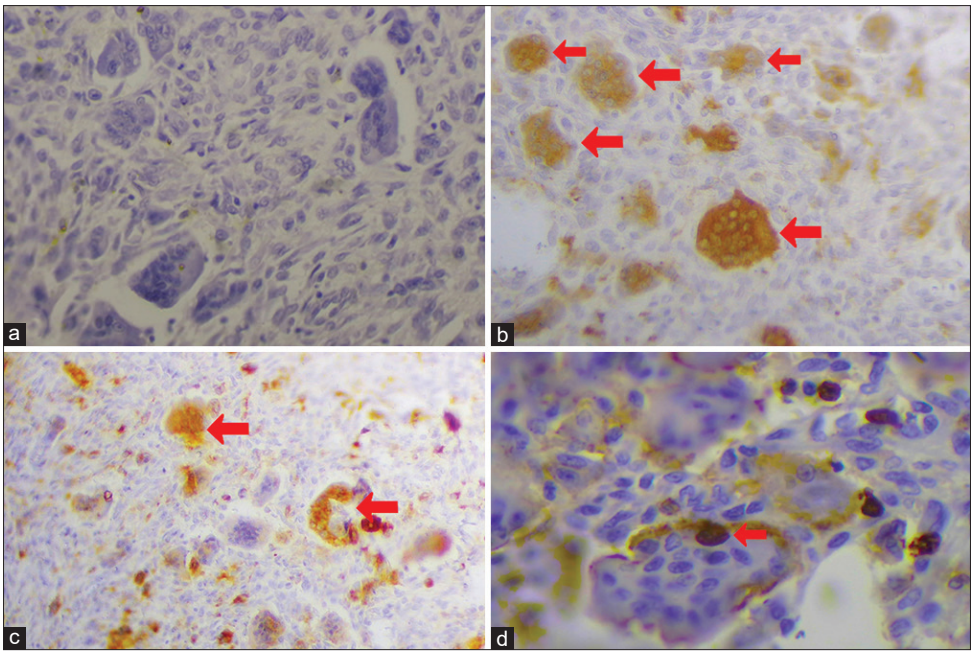

Figure 5: (a) Cd 1a (negative) – 200× magnification. (b) Cd 68 (positive) – 200× magnification (arrows). (c) S100 (positive) – 200× magnification (arrows). (d) CD 45 (positive) – 400× magnification (arrows)

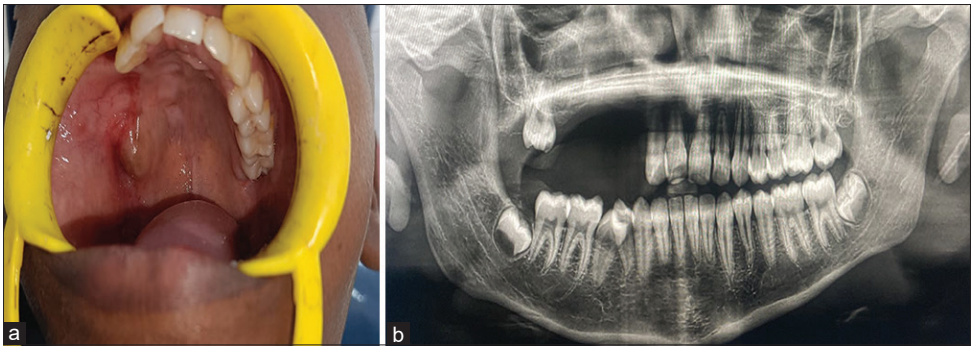

Figure 6: (a) Post-op clinical image revealing completely healed surgical site. (b) Post-op OPG

also exhibit positivity for CD30, CD15, dim PAX5, and MUM1.[19]

Histiocytic sarcoma is marked by atypical histiocyte proliferation, high mitotic activity, and S100 negativity. While rare, emperipolesis indicates an aggressive clinical course. Positive S100 for background histiocytes in this case rules out histiocytic sarcoma.[19]

RDD is typically benign and often self-limiting. If surgical removal is required, it should be approached cautiously, considering the benign nature of the condition. Radical treatment at the outset seems unnecessary, akin to other locally destructive benign lesions.[10] However, surgery remains the most efficient treatment for RDD, especially in cases like the present one involving the bone. Additional treatment possibilities comprise of sirolimus, imatinib, liquid nitrogen, methotrexate, rituximab, acitretin, thalidomide, isotretinoin, dapsone, interferon, chemotherapy, and radiation.[11]

Currently, there is insufficient data to definitively correlate prognosis with underlying molecular changes. Consensus recommendations propose targeted next-generation sequencing for Mitogen-Activated Protein Kinase (MAPK) mutations in severe or refractory cases with possible targeted therapy if driver mutations are identified.[3]

In the present case, surgical removal was done due to bone involvement. After a six-month follow-up, successful healing was observed at the surgical site [Figure 6].

CONCLUSIONS

RDD is a rare, benign condition affecting both nodal

and extranodal regions in the head and neck. Cervical lymphadenopathy is common, but extranodal disease can occur without nodal involvement. Our case shows isolated intraoral disease without lymph node involvement. Immunohistochemical studies help, but pathologists must recognize microscopic features for accurate diagnosis, especially without nodal involvement. Most patients need conservative management, but some may require aggressive treatment. Clinicians should be aware of RDD's diverse presentation and treatment options.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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