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Case Report

# Extra-Nodal Rosai-Dorfman Disease Presenting as Head And Neck Masses in Children: 5 Cases

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## Abstract

### Introduction

Rosai-Dorfman Disease (RDD), or sinus histiocytosis with massive lymphadenopathy, is a rare, idiopathic disease characterized by a benign proliferation of histiocytes that infiltrates lymph node sinuses, mimicking a neoplastic process. RDD classically presents with bilateral, painless cervical lymphadenopathy; constitutional symptoms; and elevated erythrocyte sedimentation rate. However, an extra-nodal mass is reported in approximately 43% of cases with potential to involve any organ system.

### Objectives

The purpose of our study is to report 5 cases of extranodal RDD to better elucidate RDD's manifestations in the head and neck.

### Methods

We completed a retrospective chart review of patient records from Le Bonheur Children's and St. Jude Children's Research Hospitals in Memphis, Tennessee since 2000 containing a diagnosis of extranodal RDD.

### Results

Five cases were reviewed. Patients were female, aged 1 to 15 years. Presenting signs and symptoms included: nasal congestion, palpable mass, and new onset headaches. Extra-nodal mass sites included: nasal cavity, neck, posterior scalp, frontal skull, dura mater, and orbits. Diagnosis required both histopathology, which showed emperipolesis (e.g. engulfment of cells by phagocytes), and immunohistochemical staining of S-100+, CD68+, CD1a- histiocytes. Management included: observation, surgical excision, systemic corticosteroids, chemotherapy, radiation, or, most frequently, a combination.

### Conclusions

Extra-nodal RDD is rare and has a variable presentation. A high degree of suspicion is required for diagnosis. Diagnosis by frozen sections is not sensitive, and the hallmark of RDD, emperipolesis, may be absent on histopathology in 30% of cases. Thus, immunohistochemical analysis should be included if RDD is suspected. There is no established treatment algorithm. While spontaneous resolution is possible, complete surgical excision of isolated nodules is often curative. RDD should be considered children with a head or neck mass with or without associated lymphadenopathy.

**Keywords:** Rosai-Dorfman; Histiocytosis; Lymphadenopathy; Erythrocyte

## Introduction

Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, was first recognized by Juan Rosai and Ronald Dorfman in 1969 [1]. It is a rare, idiopathic disease characterized by a benign, polyclonal proliferation of histiocytes that infiltrates lymph node sinuses, mimicking a neoplastic process. RDD classically manifests in young adults and adolescents as a triad of bilateral, painless cervical lymphadenopathy; constitutional symptoms; and elevated erythrocyte sedimentation rate (ESR). However, presentation can vary widely as extra-nodal involvement with or without cervical lymphadenopathy is reported in up to 43% of cases with potential to affect any organ system of the body

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[1-3]. Notably, the head and neck area is involved in 22% of cases with predilection for the nasal cavity and parotid glands [2,4,5]. While RDD's classic presentation is well described in the literature, its presentation as an isolated head and neck mass without cervical lymphadenopathy is exceedingly rare. Given this rarity, extranodal RDD can potentially be misdiagnosed as a malignancy, there by unnecessarily exposing patients to the harmful effects of radio- and/or chemotherapy [6,7]. Thus, extranodal RDD is an important disease to report.

We report 5 cases of extranodal RDD in children that all involve the head and neck region. For all cases, biopsy with histopathologic and immunohistochemical analysis were ultimately required to diagnose RDD.

## Illustrative Cases

We conducted a retrospective chart review of patients at Le Bonheur Children's Hospital and St. Jude Children's Research Hospital in Memphis, TN with a diagnosis of extranodal RDD since 2000. Our study was reviewed and approved by both institutions' Institutional Review Boards.

### Case 1

A 12-month-old African American female with birth history notable for isolated elevated c-reactive protein (CRP; 30.90 mg/L) presented with 3 weeks of nasal congestion secondary to a progressively enlarging mass in the left nare lateral to the nasal septum and anterior to the left inferior turbinate. She had a second stable 3 cm submandibular mass present since 3 months of age. Computed tomography (CT) with contrast of the maxillofacial area revealed a large submental node, bilateral maxillary sinus opacification, and a mildly enhancing, well-circumscribed 1.2 x 1.2 cm soft tissue mass in the left nasal cavity.

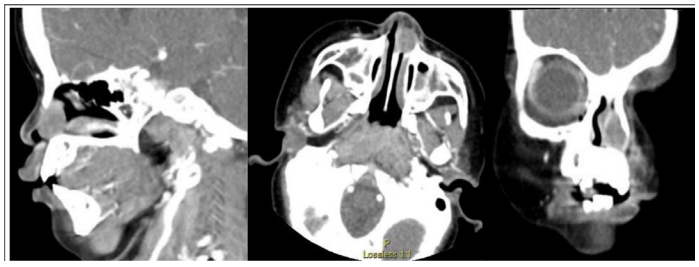

**Figure 1:** Case 1 is an 12-month-old female who presented with nasal congestion secondary to an enlarging nasal mass. CT of the maxillofacial area with intravenous contrast revealed a mildly enhancing 1.2 cm x 1.2 cm soft tissue mass in the left anterior nare. The mass abutted the anterior nasal septum medially and the frontal process of the maxilla and nasal bone laterally. Posteriorly, it is continuous with the left inferior turbinate. There is no evidence of destruction of the nasal bone or nasal septum. These findings are suggestive of a benign mass, such as a nasal polyp or intranasal glioma. Pathology following excisional biopsy revealed RDD.

Frozen sections from both incisional and excisional biopsies of the nasal and submental masses, respectively, revealed an epitheliod/histiocytic neoplasm with lymphophagocytosis, concerning for Hodgkin's lymphoma.

Final pathology revealed submucosal and sinusoidal space infiltration by a proliferation of lymphohistiocytes containing whole cells within the cytoplasm. The cells stained positively for CD68 and S-100. The histiocytes were negative for CD1a, Langerin, CD15, ALK, keratin, and EBER in-situ hybridization. Stains for B (CD45, CD20, PAX5) and T cells (CD45, CD3, CD5) showed a normal distribution of small, mature lymphocytes without any large, immature lymphocytes. These findings were consistent with a diagnosis of RDD. Since her operation, the patient's mother decided against adjuvant chemotherapy, and her nasal mass resolved spontaneously within one year.

### Case 2

A 17-month-old African American female with history of hemoglobin s-c disease presented with 2 weeks of stable left neck swelling that was unresponsive to a 7-day course of oral amoxicillin. Soft tissue CT of the neck revealed 2 contiguous left posterior cervical lymph nodes, with the largest measuring 3 cm in diameter.

With no response following an additional 14-day course of oral amoxicillin-clavulanate, she underwent surgical resection and biopsy of the lymph nodes, and pathology confirmed RDD. The patient remained without signs of disease until approximately 8-months post-operation at which time her mother noticed similar swelling on the left neck. Positron emission tomography-computed tomography (PET-CT) was utilized to evaluate the extent of her disease, and it demonstrated bilateral high cervical lymphadenopathy and mild-to-moderate fluorodeoxyglucose accumulation in the same region. She remains clinically stable without further progression of disease and continues to follow-up routinely.

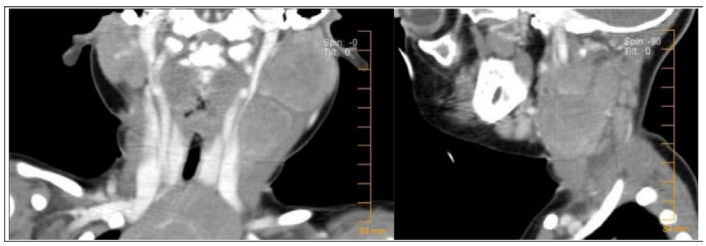

**Figure 2:** Case 2 is a 17-month-old female with hemoglobin-sc disease with 2 weeks of left sided neck swelling. CT of the soft tissue of the neck with intravenous contrast revealed 2 contiguous enlarged left cervical lymph nodes measuring up to 3 cm in diameter.

### Case 3

A 15-year-old African American female presented with a small, tender mass on her posterior scalp. MRI of the head revealed an 8 x 2 cm occipital lesion with bone and meningeal involvement. The lesion was biopsied and

confirmed to be extra-nodal RDD but thought to be non-resectable. She was treated with prednisone and acyclovir, but the lesion progressed. She then received external beam radiotherapy to her occipital calvarium at a total dose of 2160 cGy with minimal response. One year later, she developed 2 adjacent occipital lesions and a rib lesion, and she subsequently began a 4-week cycle of weekly rituximab and decadron without response. The main lesion developed cranial extension, prompting her to undergo wide local excision of the lesions (4 x 4 x 4 cm left parietal and 5 x 5 x 5 occipital) and closure with sternocleidomastoid rotational and scalp rotational flaps. The patient was scheduled to complete a post-operative MRI of the head at 6 weeks post-operation but unfortunately was lost to follow-up.

### Case 4

A 13-year-old female presented with swelling and pain in the vertex of the skull. CT of the head revealed a lytic lesion of the left frontal bone, thought to be consistent with Langerhan's cell histiocytosis. She underwent curettage; however, the diagnosis remained inconclusive. Ultimately, biopsy and subsequent pathologic and immunohistochemical analysis confirmed RDD. She elected to observe her lesion. She remained clinically stable for 1 year but was subsequently lost to follow-up.

### Case 5

A 15-year-old female presented with two yearsof severe fronto-orbital headaches without associated triggers or visual complaints. CT and MRI revealed anterior falcine, posterior falcine, and posterior right temporal lobedural-based nodules, concerning for meningiomas. She began dexamethasone and underwent ethanol embolization of the temporal lesion, which involved the sagittal sinus, with improvement in symptoms. She ultimately underwent craniotomy with resection of the temporal lesion, which pathology confirmed to be RDD.

She continued dexamethasone, but at 1-year post-operation reported orbital pain and exhibited bilateral proptosis, papilledema, splenomegaly, and left paraspinal-lumbar tenderness on physical examination. MRI of the brain and orbits scan revealed newly developed bilateral orbital lesions. CT of the neck, chest, abdomen and pelvis; gallium scan; and plain film of the lumbar spine were unremarkable for additional lesions. She underwent left lateralobitototomy with biopsy of her intraorbital lesions, which were confirmed RDD. She received 4 course of cladribine with good symptomatic response but no radiographic regression of lesions. She underwent optic nerve decompression for continued proptosis. As her disease progressed, she began induction chemotherapy with6 weeks of prednisone and vinblastine and maintenance therapy of 6-mercaptopurine for 1 year with pulses of prednisone and vinblastine every 3 weeks. She remained clinically stable with chronic headaches managed by neurology. Repeat MRI up to 4-years post-operation revealed stable disease.

## Discussion

Extranodal RDD is a rare disease, and we report just 5 cases in almost 20 years at two institutions with the disease involving the head and neck. RDD classically presents as painless, bilateral cervical lymphadenopathy, fever, and elevated ESR. However, extranodal involvement is documented in approximately half of cases and can involve any organ in the body with skin, soft tissue, upper respiratory tract, multifocal bone, eye and retro-orbital tissue being the most common sites [3]. Isolated cases of extranodal RDD without cervical lymphadenopathy have been reported to involve almost every area of the human body, including the nasal cavity, tibia, and kidney [6-11]. Diagnosis requires a high degree of clinical suspicion, particularly in extranodal RDD, as the presentation can mimic several lymphoproliferative, malignancies, and infectious disorders.

The differential diagnosis of extranodal RDD of the head and neck without cervical lymphadenopathy is broad. It includes but is not limited to: infectious histiocytosis, leukemia, Hodgkin and non-Hodgkin lymphoma, nasal polyps, intranasal glioma, dermoid cysts, and encephaloceles. The possibility of malignancy and locally invasive lesions necessitates prompt diagnoses to guide treatment and prevent further complications. RDD is typically thought of as a benign condition with potential to spontaneously resolve, but lesions can destroy local tissue and, in some cases, result in fatality, especially if involving vital organs [12]. In our cases, diagnosis was important as RDD is easily treated surgically with favorable prognosis. Furthermore, a definitive diagnosis prevented further costly and unnecessary procedures or treatments utilized in other lymphoproliferative diseases, namely toxicity associated with chemotherapy and radiation therapy.

Isolated extranodal RDD is frequently misdiagnosed as other lymphoproliferative diseases due to similar presentations [13]. From just our cases RDD mimicked Hodkin's lymphoma, meningiomas, and Langerhan's cell histiocytosis. Notably, intraoperative frozen sections in Case 1 revealed lymphophagocytosis, phagocytosed fragments of leukocytes within histiocytes, a finding most often associated with Hodgkin lymphoma [14]. However, previous literature has reported difficulty in diagnosing RDD with frozen sections alone, and crush cytology has been suggested as either a substitute or adjunct method for intraoperative diagnosis of suspected RDD [15,16]. In all of our cases, histopathology was ultimately diagnostic and revealed emperipolesis, engulfment of whole cells. Emperipolesis is the hallmark of RDD and reported in 70% of cases [17]. These cells remain in intracellular vacuoles and avoid degradation by lysosomes, which is distinct from lymphophagocytosis seen in Hodgkin lymphoma.

Immunohistochemistry is a useful tool that also aids in diagnosis of RDD. The histiocytes stain positively for S-100 and CD-68 but are negative for CD1a, Langerin and Birbeck granules, distinguishing RDD from

Langhans cell histiocytosis [17,18]. Immunohistochemistry will also reveal a polyclonal population of histiocytes, thereby ruling out neoplasia from the differential diagnosis. The findings in our cases were consistent with these histopathologic and molecular characteristics. Thus, given that 30% of RDD cases do not contain emperipolesis, we recommend both histopathologic and immunohistochemical analysis to definitively diagnose or rule-out suspected cases of RDD [17]. In all of our cases, both pathology and immunohistochemistry were ultimately diagnostic, as RDD was not included in the differential diagnosis given the combination of a rare disease with atypical presentations.

Imaging manifestations in RDD are largely nonspecific, and, thus, there are no standard imaging requirements for diagnosis. Radiologic study has largely been limited to central nervous system involvement [21-23]. In regards to Case 5, decreased T2-weighted signal intensity in a dura-based mass and lack of arteriovenous shunting on angiography may distinguish RDD from a meningioma [23]. However, definitive diagnosis can only be obtained with biopsy. As RDD is a systemic disease, PET-CT is an important modality that can potentially detect additional visceral or osseus involvement or disease progression based on the 18F-fluouro-deoxyglucose avidity of a proliferative disorder [23]. Follow-up imaging continues to be useful in identifying recurrence or response to therapy, and we recommend the imaging modality be largely based on the overall clinical picture and the discretion of the treating physician.

No algorithm currently exists for the treatment of RDD. Approximately 20% of cases resolve spontaneously and another 70% of cases experience chronic relapsing and remitting [19,20]. Surgical management is generally indicated for single lesions or to maintain airway patency if involving the respiratory tract as with Case 1[24]. However, surgery is not necessarily curative as sinonasal RDD has been reported to recur following endoscopic excision, but this is likely due to incomplete resection [12]. Thus, while surgery is effective for short-term symptomatic control and restoration of function, follow-up is necessary to evaluate for recurrence of RDD, especially when surgical resection is challenging [8].

Medical management of RDD with radiotherapy, chemotherapy, immunosuppression and systemic or topical corticosteroids can be effective, but response is variable as experienced in Cases 3 and 5 [16]. In one study, only 1/7 RDD patients received complete remission with oral prednisone, and 4/7 had partial response. Radiotherapy resulted in a favorable response in 2 patients who were non-responsive to steroids. Additionally, treatment with several chemotherapeutic agents, namely, imatinib and cladribine, has been met with variable response [25]. Unfortunately, the disease's rarity severely limits clinical trials, and there are no established factors to suggest what patients would respond best to the different modalities. Our patients experienced greatest resolution of symptoms following surgical excision. However, follow-up is necessary to monitor for clinical signs and symptoms or repeat imaging that may suggest recurrence, development of new lesions, and refractory cases that may necessitate additional therapy.

## Conclusion

Isolated extranodal RDD without cervical lymphadenopathy is very rare and delayed diagnosis can ultimately lead to disease progression with local tissue destruction or development of additional lesions. Complete surgical excision is often curative. However, since extranodal RDD mimics several other conditions and intraoperative diagnosis by frozen sections is unreliable, RDD is commonly misdiagnosed. Our cases of RDD manifesting as masses in the head and neck provide multiple teaching points. First, RDD should be considered in the differential diagnosis of any child with a head and neck mass with or without associated lymphadenopathy. Lastly, RDD cannot be effectively ruled out without both histopathologic and immunohistochemical analysis due to the low sensitivity of frozen sections for diagnosing RDD and the possible absence of emperipolesis, the hallmark of RDD.

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