Rosai-Dorfman disease in 6 years old child: presentation, diagnosis, and treatment

Authors:
Kalpana Giri
kalpana688@gmail.com
B.P Koirala Memorial Cancer Hospital, Chitwan

Ashok Baral
Ashokbaral012@gmail.com
National Medical College, Birgunj

Niva Tiwari
neevat@gmail.com
B.P Koirala Memorial Cancer Hospital, Chitwan

Krishna Sagar Sharma
akrish630@gmail.com
B.P Koirala Memorial Cancer Hospital, Chitwan

Corresponding author:

Kalpana Giri
B.P Koirala Memorial Cancer Hospital, Chitwan
kalpana688@gmail.com
Phone: 9860974093

Running title: Rosai-Dorfman in a child

Abstract:
Rosai-Dorfman disease (RDD) is referred to as Sinus Histiocytosis Massive Lymphadenopathy (SHML) of unknown origin. We are reporting a rare case of Rosai Dorfman disease, a case of 6 years old male with a history of multiple painless bilateral submandibular and cervical lymphadenopathy.

Key Words

Rosai-Dorfman disease; Histiocytosis; lymphoproliferative; lymphadenopathy; neck swelling

Introduction:

Rosai-Dorfman disease (RDD) known as Sinus Histiocytosis with Massive Lymphadenopathy (SHML) is a benign systemic histio proliferative disease presented clinically with bilateral painless cervical lymphadenopathy, fever, and have leukocytosis on blood examination. Histopathological examination shows pericapsular fibrosis with dilated sinuses, large histiocytes with intact phagocytosed lymphocytes heavily infiltrated with large histiocytes, lymphocytes, and plasma cells in the background[1]. It is common in children and young adult[2]. RDD is an idiopathic disorder, but its occurrence has frequently been observed after infection, possible viral etiology, like Epstein-Barr virus (EBV), human herpes 6, parvovirus B19 (HHV-B19), and polyomavirus, has been suggested by several authors, supported immunohistochemistry, PCR, and in place hybridization studies[3]. About 43 percentage of RDD have extranodal involvement mostly in the head and neck. with similar morphological features as nodal RDD[4]. They can also be found in skin soft tissues, upper airways, bones, brain. S-100 protein can be demonstrated in diagnostic immunohistochemistry in sinus histiocytes[5]. It is mostly a self-limiting disease however, surgical resection remains the mainstay of treatment for symptomatic disease. Several studies have shown that the combination of cytotoxic agents and prednisolone also shown to be effective for treatment.

Case Report:

A 6 years old male, first presented to the otorhinolaryngology clinic of a peripheral hospital 6 months back with complaints of bilateral neck swelling for 1 month. Histological examination of a biopsy showed lymphoproliferative disease. He received Prednisolone 30 mg for 5 months but the lesion did not respond to Prednisolone then referred to our cancer hospital. At presentation general condition is fair; fever, night sweats, weight loss, cough, and other general symptoms were absent. Physical examination revealed enlarged bilateral multiple cervical and submandibular lymph nodes, difficulty in neck movement due to swelling. Neck swelling on palpation: firm, mobile, non-tender with the largest size measuring 8*10 cm (figure 1,2,3).

On systemic examination: No hepatosplenomegaly; cardiovascular, respiratory, and nervous systems were found normal. Family history was unremarkable. Lab investigation: hemoglobin 9.1% with total leucocyte count 17,700/mm3, Platelet count: 5,48,000/mm3. Peripheral Blood smear(PBS) revealed increased on smear with neutrophils: 87%,

lymphocytes: 10%, eosinophils: 2%, monocytes: 2%. Biochemistry reports sodium; 129.18 mmol/l, magnesium; 1.7 mg/dl, calcium; 7.9mg/dl, SGPT/ALT; 5 U/L. Random blood glucose (RBS), urea, creatinine, lactate dehydrogenase, alkaline phosphatase, electrocardiography, bleeding time, clotting time, prothrombin time(PT)/international normalized ratio(INR), Human Immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg), Hepatitis C virus (HCV), Polymerase chain reaction (RT-PCR) for covid were in the normal range. Ultrasound of neck revealed a few enlarged bilateral cervical lymph nodes noted at all levels (anterior, mid, and posterior region) largest one measuring about 30 * 20 mm in right and measuring about 46 * 26 mm in left [figure 4 (A and B)].
Plain and contrast enhanced helical scan of neck, chest, abdomen and pelvis revealed multiple bilateral cervical at level IB, II, III, IV, V, and VI, bilateral supraclavicular, mediastinal, bilateral axillary and retroperitoneal lymphadenopathies (figure 5,6,7).
Lymph node biopsy under Intravenous anesthesia (IVA) was done. Histopathology report revealed lymph node with follicular hyperplasia and distension of sinuses with the proliferation of foamy histiocytes engulfing lymphocytes and red blood cells (figure 8). Atypical cells not seen. On Immunohistochemistry, these cells displayed a positive reaction to CD68 and S-100 protein, whereas the reaction to CD1a was negative. These findings confirmed the diagnosis of Rosai Dorfman Disease. The patient was treated with the first cycle of chemotherapy. He received 1st cycle of (Injection vinblastine 4mg I/V) and got discharged with oral prednisolone-30 mg for 5 days in divided doses. Patient is on close follow-up, doing well and the lymph node size is decreasing.

Discussion:

RDD is a rare, benign disorder proliferative histiocytic disorder recognized clinically and pathologically in 1969 through a publication by Rosai and Dorfan[1]. The etiology of RDD is unknown. Over the years there are many theories attempting to elucidate RDD's pathogenesis, but each of them has led to conflicting results. Researchers have indicated infectious agents have potential causes of RDD, like human herpesvirus-6 (HHV-6)[6,7], human herpesvirus-8 (HHV-8), parvovirus B19, Epstein-Barr virus (EBV)[7], cytomegalovirus (CMV), varicella zoster virus (VZV), Brucella, and Klebsiella; however, there's no conclusive evidence to verify this theory. It had been observed that primarily infected lymphocytes induce a secondary histiocytic reaction that eventually causes the characteristic microscopic image of RDD, suggested by the authors in one of the articles[8]. Ju et al reported a case of RDD in a 26-year-old man with cervical and mediastinal lymphadenopathy with pleural effusion in 2009[9]. Studied done by Atin Agarwal et al in India Includes seven cases (5 nodal and 2 extranodal) of SHML over a 5-year period whose slides and blocks were reviewed. which showed one of them developed histiocytic sarcoma[10]. Zhu et al found Of the 13 cases sample (77%) were purely extranodal RDD, 15%were both nodal and extranodal, 8%was purely nodal. The locations of the 10 purely extranodal RDD lesions included the central nervous system nasal cavity and paranasal sinuses (30%), and the cutis (10%)[11]

RDD is significantly more common among Caucasians and blacks than among Asians[12]. It is most commonly seen in children and young adults[13]. RDD in children may mimic malignancy because of rapidly progressive lymphadenopathy as presentation[14]. The patient

mostly presents with bilateral painless cervical lymphadenopathy (87%). Initially, lymph nodes are mobile and discrete but later become large, multinodular, and adherent. The axillary (23.7%), inguinal (25.7%) and mediastinal (14.5%) regions may be affected, though not as severely as the cervical region[15]. Our patient also presented with painless cervical lymphadenopathy. Extranodal tissue involvement is documented in 43% of RDD patients, especially of the skin, soft tissues, brain, upper airway, bones, urogenital system, lower airway, and oral cavity[4]. Fever is one of the clinical manifestations of 30% of RDD patients[16] but in our case fever was absent. Some patients present with immunological abnormalities including leukocytosis, altered T4 lymphocytes and T8 lymphocytes ratios (T4/T8), decreased lymphocyte mitogenic responses, and hypergammaglobulinemia. In these cases, extranodal involvement is present in about half of the cases[17]. RDD is frequently associated with a high BSR and polyclonal hypergammaglobulinemia (up to 90% of cases), anemia, and neutrophilic leukocytosis[18]. Our patient presented with cervical lymphadenopathy, neutrophilic leukocytosis (87%), and anemia (Hb = 9.1 mg/dl).

The origin, pathogenesis of the disease, and histogenesis of the proliferating cell are still unknown or uncertain. The cell of Rosai-Dorfman disease can still not be classified as a Langherans type dendritic cell or as a non Langherans phagocytic histiocyte[17]. Some authors have found some viruses like human herpesvirus-6 (HHV-6), and Epstein Barr virus (EBV) and some bacterial infection klebsiella to be associated with its etiopathogenesis[19,20,,21]. But the cause is still not proved[17]. The diagnosis of RDD is based on the physical examination, clinical history, and confirmed by histopathological examination. Specimens could also be obtained by open surgical biopsy or fine-needle aspiration. Fine needle aspiration is considered a sensitive and reliable diagnostic method and has the advantage of being possible in the outpatient setting. Excised lymph nodes are greyish white with capsular fibrosis. If the lymphadenopathy has been present for a long time it may have architectural disruption. lymph nodes have sinusoids which are found to be distended with mixed cell-like lymphocyte, plasmacyte, and histiocyte .marked proliferation of foamy histiocytes. foamy histiocytes are large irregular with abundant eosinophilic and vacuolated cytoplasm. foamy histiocytes engulfing lymphocytes and erythrocytes are found. Atypical cells are not seen.

Because of its self-limiting nature as well as less incident rate, no standard treatment protocol has been made for RDD. A review of the literature revealed that 50% of patients with RDD require no treatment and that 82% of untreated patients experience spontaneous and complete disease regression[21]. Some reports showed disease control in children without therapy[22]. In such a case, after careful analysis of the biopsied specimen, a conservative approach was adopted with progressive reduction of the lymphadenopathy. Pulsoni et al reviewed case reports of 80 patients who received various modes of treatment[21]. Systemic corticosteroids are usually helpful in decreasing nodal size and symptoms; however, they can be quite immunosuppressive and RDD lesions can recur after a short period of interruption[21]. Oka et al reported an effective prolonged course of low-dose prednisolone in a case of RDD with skin and lymph node involvement with respiratory obstruction, its role cannot be generalized[23]. There are not any specific treatment modalities. Corticosteroids, chemotherapy, antibiotic therapy, radiation therapy, and surgical treatment are found to be used[24]. Our patients who had clinical and histopathologic features classic for SHML have received

chemotherapy and prednisolone therapy and the disease state has been stable for several months.

Conclusion:

This is the case of Rosai Dorfman disease that involves both submandibular and cervical lymph nodes in a child, without extranodal localization. Clinically presents with painless submandibular and cervical lymphadenopathy with neutrophilic leukocytosis. Histology shows lymph nodes with follicular hyperplasia and distension of sinuses with the proliferation of foamy histiocytes engulfing lymphocytes and red blood cells. Immunohistochemistry shows histiocytes positive for CD68 and S-100 protein, and negative for CD1a. Most cases with this disease will not require treatment. For those who require treatment, chemotherapy, steroid, as in this case should be given. Also radiation therapy, surgery have been required for those who don't respond to medical therapy. RDD should be included in the differential diagnosis of submandibular and cervical lymphadenopathy even in very young children.

Declarations:

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Ethics approval and consent to participate:

There is no need for ethical approval for a case report according to the local ethical guideline. Written informed consent was taken from the patient in the Nepali language to include clinical details in this article.

Contributors: Fill authors name in blank space

KG conceived the idea for this paper. KG, AB, NT and KSS wrote and prepared the original draft with figures, revised the manuscript critically for intellectual contents. All the authors have provided final approval of the version for publication.

Declaration of Interest:

All other authors declare that they have no competing interests concerning the content published in this manuscript.

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Figure legends:

Figure 1: Multiple massive, firm, non tender, mobile lymph nodes bilaterally largest measuring 8*10cm in the cervical and sub mandibular region with scars of biopsy

Figure 2: Cervical lymphadenopathy with scar of biopsy on Right side of neck

Figure 3: Multiple massive cervical lymphadenopathy on left side of neck

Figure 4 (A and B) Ultrasound of Neck showing few enlarged bilateral cervical lymphadenopathies at all level (anterior, mid and posterior region) largest one measuring about 30 * 20mm in in right and measuring about 46 * 26mm in left.

Figure 5: CT scan of neck showing bilateral cervical lymphadnopathies are notes at level IA, IB, II, III, IV, V, and VI, one measure 37* 20mm

Figure 6: CT scan chest showing multiple enlarged bilateral supraclavicular (20 * 15 mm), pretracheal, paratracheal aortopulmonary lymphnodes are noted, one measuring 17 * 14 mm

Figure 7: CT scan abdomen showing few paraaortic, paracaval, external and internal iliac and mesenteric lymphadenopathies are noted, one measuring 39*16 mm in left iliac region

Figure 8: Histopathology examination showing lymph node with follicular hyperplasia and distension of sinuses with the proliferation of foamy histiocytes engulfing lymphocytes and red blood cells