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ROSAI-DORFMAN DISEASE: A CASE STUDY AND LITERATURE REVIEW

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ABSTRACT

Rosai-Dorfman Disease (RDD) is a disorder that does not occur commonly; involving the macrophages of the body, characterized by histiocytosis and general lymphadenopathy (especially involving the cervical lymph nodes). Its involvement is divided broadly into two categories: nodal and extra-nodal. A case of this rare disease presented in the surgical department of the Pakistan Institute of Medical Sciences (PIMS). She was a 13- year-old female who had been experiencing respiratory signs and symptoms for the last 2-3 years, had multiple visits to various hospitals, and even had multiple pleural taps to relieve her pulmonary symptoms. She came to the general surgery department when her symptoms were aggravating and there was no drainage via a chest tube already in place. She received apt treatment for her disease including Video-Assisted Thoracic Surgery (VATS) and decortication of pleural scar tissue. She was discharged on 12th post-op. day with no post-operative complications and

instructions to have follow-ups with her physicians.

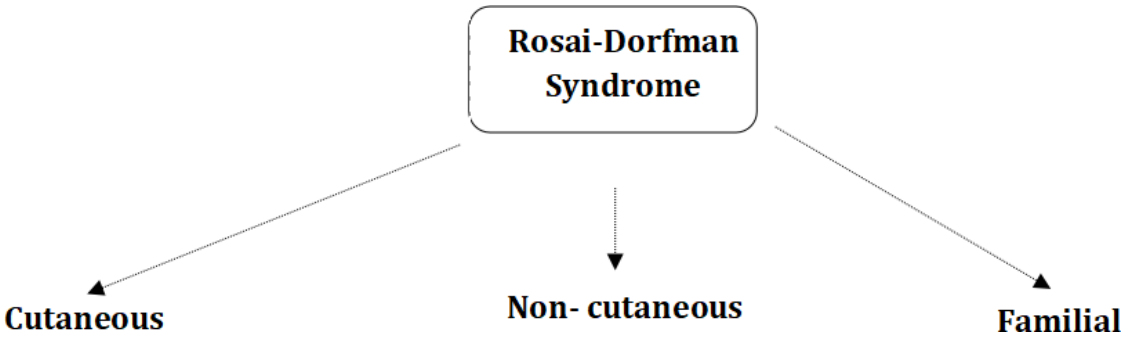
KEYWORDS: Rare Disorder, Histiocytosis, Lymphadenopathy, Video-Assisted Thoracic Surgery, Decortication

AIM

Advancements in medical and surgical fields are parts of an undying process. The aetiology, progression, and/or treatment protocols are not entirely understood for the common disorders in general and those of rare diseases in particular. This case report is a small step in understanding one of these rare diseases i.e. Rosai-Dorfman Disease and more importantly, the intrathoracic manifestations of this disease. These complications are seen in less than 3% of the patients affected by RDD so they are seldom reported in literature. Henceforth, we aim to pave the path of forthcoming studies in better understanding the enigma of this ailment.

LITERATURE REVIEW

RDD is one of the rare disorders i.e. less than 200k cases are reported per annum. In this disorder, there is a proliferation and accumulation of specialized White Blood Cells (WBCs) called histiocytes in lymph nodes (particularly bilaterally enlarged cervical lymph nodes). There can be aggregation of histiocytes in other places as well; like in the integumentary, renal, nervous, and/or digestive systems. It is usually a self-limiting and benign illness. It primarily affects children and young adults. The mean onset age of Rosai-Dorfman Disease is 20.6 years[1]. The Histiocytes Society has divided the manifestation of this disease in the following manner[2]:



The non-cutaneous is further divided into nodal, extra-nodal, neoplasia-associated, and autoimmune-associated.

The signs and symptoms of the disease depend upon where the histiocytes have deposited. These

range from being asymptomatic, skin paleness, rashes, visual disturbances, chronic rhinitis to seizures and dyspnea[3]. The precise cause of Rosai- Dorfman Disease is still undiscovered but

several precipitating factors have been identified. Recent studies have identified many kinase mutations associated with Rosai- Dorfman Disease. Though it is most commonly diagnosed in the 1st decade of life, it is also found in adults, affecting men and women almost evenly. The most common involvement sites are ophthalmic and nasal tissue, followed by osseous tissues, and CNS (where it primarily affects the dura-mater). Radiographs can reveal bony involvement as well-circumscribed lytic lesions with pronounced sclerotic margins. Lab results of patients with Rosai-Dorfman reveal a raised ESR, raised TLC, gammaglobulinemia, and results mimicking auto-immune hemolytic anaemia. Several studies have reported its relation with certain autoimmune and infectious disorders. There is a known association with an assortment of viruses such as Epstein-Barr virus, varicella-zoster, cytomegalovirus, herpes virus, etc. Another known risk factor for this disease is having a sibling with Hirshsprung's disease. The differential diagnoses for Rosai-Dorfman Disease include Langerhans cell histiocytosis (LCH), Meningiomas, Lymphomas, and Lyme disease amongst others. The differentiating points of LCH and RDD are given in Table 1.

Category	**Langerhans Cells Histiocytosis**	**Rosai–Dorfman Disease**
Age	Childhood	**Childhood/ Early Adulthood**
Cutaneous Involvement	Dark red to brown lesions	**Reddish-brown to yellowish lesions**
Skeletal Manifestation	Osteolysis	**Rare (10%)** **Osteolytic changes with Cortical Thinning**

Lymph node Involvement	**Restricted lymph node involvement**	**Massive Lymphadenopathy**[4]

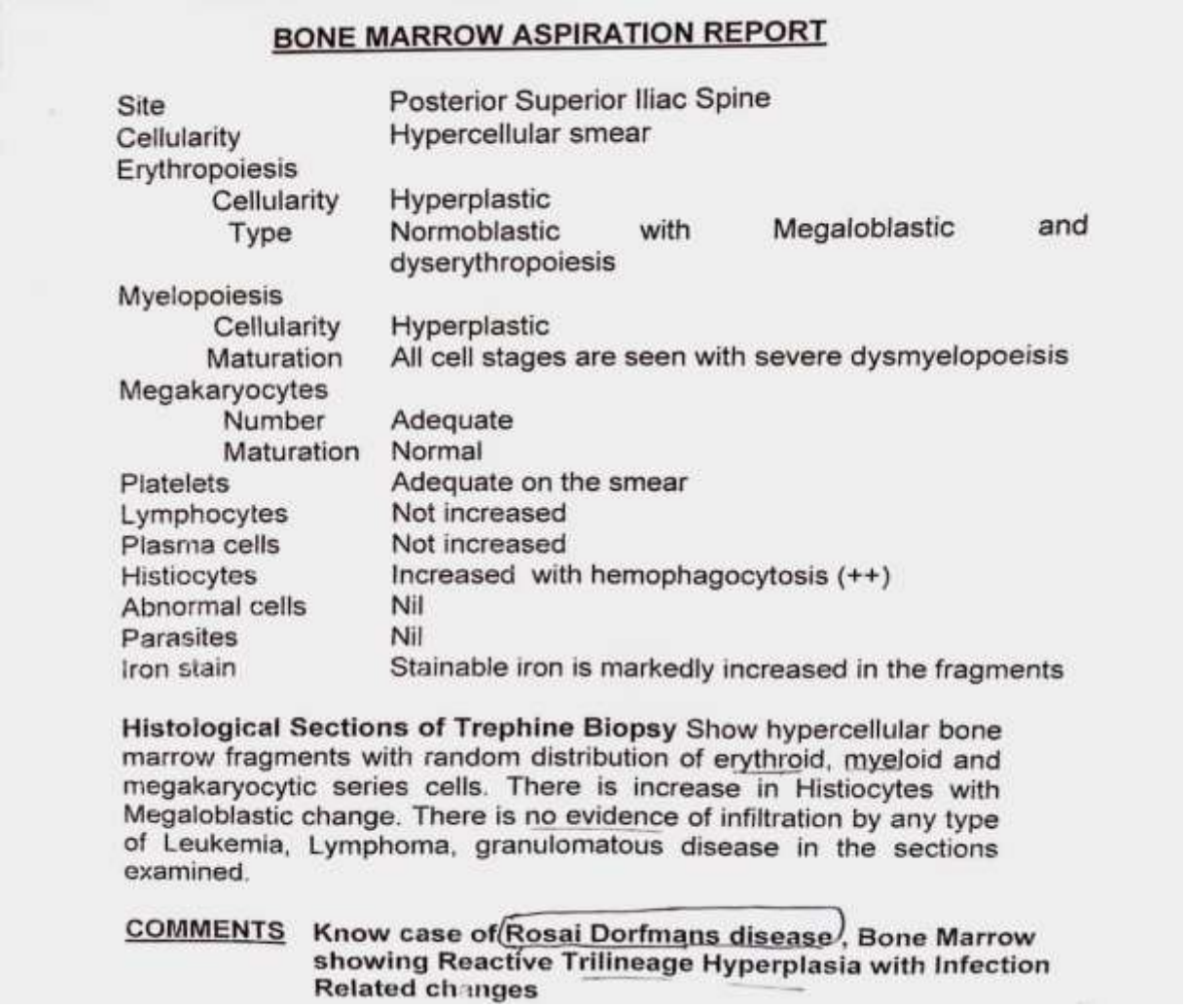
Table 1. Comparative Analysis of Langerhans Histiocytosis and Rosai-Dorfman Syndrome

More than 80% of the patients with Rosai-Dorfman Disease undergo spontaneous resolution. An assortment of chemotherapy regimens, the most common being Cladrabine and Clofaradine have been employed over the years. Even radiotherapy has been used as an alternative to systemic therapy, both as primary treatment and as post- surgical treatment. However, in the absence of vivid guidelines or treatment protocols, the exact treatment of RDD remains elusive. Most patients respond to the steroids but the combination of vinca alkaloids, alkylating anti-neoplastic agents, and/or corticosteroids appear to be the most effective according to most research done. Some researchers also state the importance of using anti-virals and interferons in the treatment of this disease. Hence, in advanced disease, chemo/ radiotherapy is a generally accepted modality of treatment and surgical intervention is only done in cases of recurrent, refractory or complicated disease[5].

CASE PRESENTATION

A 13-year-old female, known case of Rosai-Dorfman Disease, and resident of district Nowshera, Pakistan, presented with shortness of breath (NYHA grade III) that exacerbated on effort and alleviated while lying down. These symptoms were associated with pleuritic chest pain, dry cough, and orthopnoea. She had these symptoms continually with varying intensities for the last five years.

In late 2019, the patient had multiple, painless, and enlarged cervical lymph nodes. These swellings were gradually increasing in size and were associated with odynophagia, hoarseness of voice, and weight loss. She also had occasional episodes of Fever (undocumented, intermittent) with rigours. There was an evanescent erythematous rash in the genital area as well. Keeping all her signs and symptoms in view, her physician recommended GeneXpert MTB Assay along with some other tests. GeneXpert MTB Assay was negative so a CT- neck + chest with contrast was done that revealed hyper-enhancing cervical lymphadenopathy with mild pleural effusion, which was likely suggestive of lymphoproliferative disorder. A Complete Blood Count done during this time showed severe hemolytic anaemia with raised ESR. However, she was soon diagnosed as a case of Rosai-Dorfman Disease in 2020 by an FNAC of her enlarged cervical lymph node. A bone marrow aspiration was also done shortly afterwards.



BONE MARROW ASPIRATION REPORT

Site	Posterior Superior Iliac Spine
Cellularity	Hypercellular smear
Erythropoiesis	
Cellularity	Hyperplastic
Type	Normoblastic with Megaloblastic and dyserythropoiesis
Myelopoiesis	
Cellularity	Hyperplastic
Maturation	All cell stages are seen with severe dysmyelopoeisis
Megakaryocytes	
Number	Adequate
Maturation	Normal
Platelets	Adequate on the smear
Lymphocytes	Not increased
Plasma cells	Not increased
Histiocytes	Increased with hemophagocytosis (++)
Abnormal cells	Nil
Parasites	Nil
Iron stain	Stainable iron is markedly increased in the fragments

Histological Sections of Trephine Biopsy Show hypercellular bone marrow fragments with random distribution of erythroid, myeloid and megakaryocytic series cells. There is increase in Histiocytes with Megaloblastic change. There is no evidence of infiltration by any type of Leukemia, Lymphoma, granulomatous disease in the sections examined.

COMMENTS **Know case of Rosai Dorfmans disease, Bone Marrow showing Reactive Trilineage Hyperplasia with Infection Related changes**

Figure 1. Bone Marrow Aspiration Report

After being diagnosed with RDD and exacerbation of the symptoms, a pan-CT was done. It showed that there was Grade 3 splenomegaly with splenic varices and, generalised lymphadenopathy with moderate right-sided pleural effusion. Multiple pleural taps were done from 2020 to 2023, during this time the MTB and cytology for atypical or malignant cells remained negative and the pleural fluid routine examination also gave a transudative picture (according to light's criteria). All this while, she was often put on broad-spectrum antibiotics.

Various manifestations of RDD in CVS and the musculoskeletal system were ruled out from time to time. The ECHO (conducted at multiple times during the course of the treatment) was grossly normal and the possibility of JIA (ANF, anti-RF, and anti-CCF were negative) was eliminated.

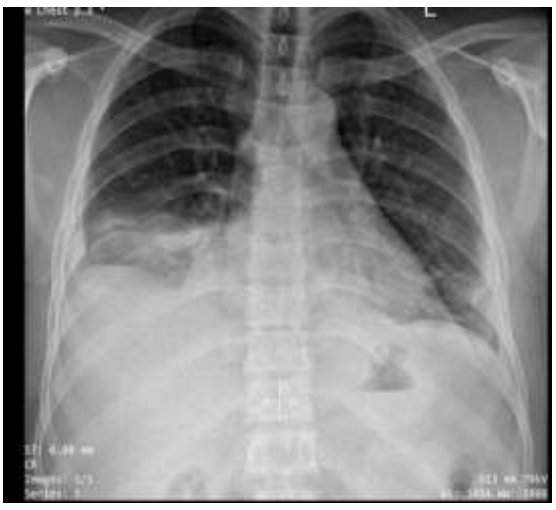
Physical examination done at the time of presentation to the surgical unit showed generalized pallor of the skin and mucous membranes. The patient had multiple enlarged palpable lymph nodes.

*A 2*2 cm palpable lymph node (LN) was present in the right submandibular region.*
*Bilateral posterior cervical lymph nodes were palpable, 3 on the left side and 2 on the right side. The largest of which was about 3*2 cm.*
*Bilateral (B/L) supraclavicular LN were palpable. Each of which was about 1*1 cm.*
*B/L axillary lymph nodes were palpable. Right central of about 3*3 cm. Left central of about 1*1 cm.*
*Left inguinal LN OF ABOUT 1*1 cm was palpable.*
All LN were firm, non-tender and discrete.

Signs of dullness to percussion, low tactile fremitus, asymmetrical expansion of the chest and reduced breath sounds were present bilaterally but more on the right side.

Abdominal examination showed right hypochondrium tenderness and revealed hepatomegaly (moderate grade: 6 cm below right costal margin) with a liver span of 16 cm.

She presented to the hospital with aggravating symptoms and there was no drainage via a chest tube already in place and various pleural taps. The decision to perform a Video- Assisted Thoracic Surgery (VATS) was made after discussion with and examination by the Anesthesia Team. Anesthesia administration was fairly easy as there was no soft tissue extension into the trachea, which is a concern for RDD patients. An attempt to perform VATS was made but eventually, open thoracotomy with decortication was done because of widespread adhesions in her pleural cavity and extensive loculation of the empyema present.



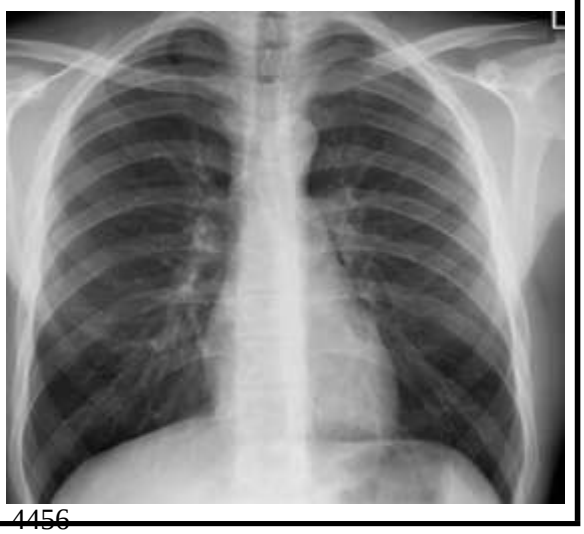


Figure 2 One of the Pre-op CXRs and 60th Post-op. Day CXR

She was taking vancomycin and steroids prescribed by her physician preoperatively, which were also continued post-op. She stayed in the hospital till her 12th post-op. day and then she was discharged as she was vitally and clinically stable. The intensity of her pain was reduced to 2 from 8 and there was no odynophagia as well. She was discharged with instructions to have follow-ups with her physicians and weekly follow- ups with the surgical department for a month.

DISCUSSION

Rosai-Dorfman disease (RDD) is a peculiar form of non-Langerhans cell histiocytosis, characterized by the presence of CD68-positive, S100-positive, and CD1a-negative histiocytes with recurring emperipolesis (presence of an entirety of a cell within a host cell's cytoplasm). This illness was first discovered in 1965 by Destombes in four African children who had signs of general lymphadenopathy. As the presence of lipid-rich histiocytes was noted in the retrieved tissue samples, this disorder was labelled as

'adenitis with lipid excess'. In 1969, Dorfman and Rosai individually reported four patients with colossal cervical lymphadenopathy and discrete histopathological features; they regarded this ailment as "sinus histiocytosis with massive lymphadenopathy". Since then, few cases of this malady have been reported. An extensive analysis of approximately four hundred cases, which were reported in international cache, was done in 1990. This study enlightened nodal and extra-nodal complexities of RDD[6]. Since then, not many efforts have been put in order to understand the mysteries of Rosai-Dorfman Disease.

In the last decennium, our knowledge of histiocytic disorders like Erdheim-Chester disease (ECD) and Langerhans cell histiocytosis (LCH) has significantly improved. This is because of the discovery of repetitive BRAF and mitogen-activated protein kinase–to- extracellular signal-regulated kinase (MAP-ERK) track mutations. These particular mutations have also been found in both ECD and LCH. Hence, this provides additional proof regarding the 'somewhat neoplastic' attributes of these conditions, rather than being entirely reactive inflammatory in nature. Furthermore, there is evidence of reciprocally exclusive KRAS and MAP2K1 mutations that ascertain the neoplastic characteristics of this disorder even more. However, due to the rarity of RDD, the clinical scope, prognosis, and treatment outcomes remain poorly described.

Most patients with RDD report bilaterally enlarged lymph nodes in the neck. These nodes are mostly painless but can become quite swollen. Swellings may also be present in the regions of the groin, armpits, and central chest area with accompanying fever. In approximately half of patients, RDD extends beyond the lymph nodes, involving other systems e.g. the skin, soft tissues, nasal cavities, eyes and eyelids, bony tissues, salivary glands, and central nervous system[7]. In rare cases, the effects may extend to the kidneys, liver, lungs, breast, heart, and alimentary canal.

Rare manifestations of Rosai-Dorfman Disease may render a direct effect on the haematological system, exhibiting a decrease in red blood cell counts that result in varying severities of anaemia. This causes patients to appear pale, feel lethargic, or experience shortness of breath. Moreover, a decline in the number of platelets may lead to easy bruisability and/or bleeding, while a drop in white blood cells increases the probability of life-threatening infections. Non-specific symptoms may include

- weight loss,
- blockage or discharge of the nose with nosebleeds, and collapsed nasal bridges resulting in saddle-nose deformity,
- tonsilitis or sinusitis,
- difficulty or pain in swallowing or speaking,
- added high-pitched breathing sounds,
- proptosis with visual field disturbances,
- Headaches and seizures,
- night sweats,
- Paraplegias and paralysis,
- Arthralgias

In terms of treatment, cladribine is the most commonly used chemotherapeutic agent. It is administered at a dose of about 5 mg/m^2/day for 5 days every month, usually for 3 to 4 cycles. Cladribine has been used as a second-line medication with improving response seen in 2/3rd of the total patients of RDD. It is also to be noted that patients who respond to cladribine, do not generally relapses. Prednisone, in association with 6-mercaptopurine, azathioprine, or methotrexate, has proven to be the best 1st line treatment. An interesting study was conducted for the possible administration of rituximab, in conjunction with corticosteroids that produced a miraculous overall response rate of 100%. However, such studies are greatly delimited by the small number of cases.[8]. Keeping a rising trend in the number of patients being reported, an international repository of the description of such rare disorders should be made so that further

research into them can be done.

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