EJCRIM
European Journal
of Case Reports
in Internal Medicine

ROSAI DORFMAN DISEASE: A MYRIAD OF PRESENTATIONS-MULTISYSTEM INVOLVEMENT INCLUDING BONE MARROW

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Received: 22/10/2025
Accepted: 05/11/2025
Published: 03/12/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent was obtained from the patient for publishing their clinical data, reports and results, ensuring anonymisation as much as possible.
Acknowledgments: We thank the patient for completing follow-up and sharing all requested data.
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How to cite this article: Susai Manickam DJ, Pandurangan V, Arthur M, Srinivasan D. Rosai Dorfman disease: a myriad of presentations-multisystem involvement including bone marrow. *EJCRIM* 2025;**12**:doi:10.12890/2025_005930

ABSTRACT

Background: Rosai Dorfman disease (RDD) is a type of histiocytosis which characteristically involves lymph nodes, involvement of other organs is often rare. Histopathological analysis is essential for establishing a definitive diagnosis.

Case report: Our patient had involvement of uncommon sites including bone marrow and spleen at an atypical age of 59 years. Also due to absence of the characteristic CD markers of histiocytes in RDD, we faced certain diagnostic challenges. However, the patient was started on steroids and showed a rapid response. We were able to follow up the patient for nearly a year and have seen improvement in clinical and haematological parameters.

Conclusion: Bone marrow infiltration in RDD is a rare presentation. Improving clinician awareness will lead to earlier detection. Following the guidelines, bone marrow aspiration and biopsy should be done promptly in all patients with cytopenia and will help in early identification of RDD.

KEYWORDS

Rosai Dorfman disease, cytopenia, histiocytosis

LEARNING POINTS

- Histiocytic disorders can mimic a variety of diseases and suspicion must guide us to do tissue biopsy for diagnosis.
- Treatment regimens vary and the patient's response to treatment also can vary irrespective of the extent of the disease.
- Cytopenia in Rosai Dorfman disease or any histiocytosis should prompt early bone marrow examination.

INTRODUCTION

Histiocytes are mononuclear tissue phagocytes, tissue infiltration of these can occur in a variety of diseases broadly grouped as histiocytosis. Currently, histiocytosis is being classified into five subgroups[1]. Rosai Dorfman disease (RDD) comes under the R group of histiocytosis, it can be multifocal and is mostly benign[2]. Nodal presentation of the disease is the most common form of the disease, so much so, that historically the disease was named by Juan Rosai and Ronald Dorfman as sinus histiocytosis with

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massive lymphadenopathy in 1969. We report our patient who suffered the florid presentations of the disease along a timeline of 4 years. This case highlights the different presentations and involvement of rarer sites including bone marrow liver and spleen in our patient. Also unlike other similar cases in the literature[3,4], our patient responded well to steroid therapy.

CASE DESCRIPTION

A 59-year-old female who was a homemaker, with no other background comorbid illness had initially presented 4 years back with multiple swellings over the right leg, bilateral gluteal region and right shoulder, the largest being over the right calf. She underwent radiological imaging including magnetic resonance imaging (MRI) of both legs which revealed intraosseous and extraarticular T1 hypointense and T2 mildly hypointense lesions in the distal metaphyseal ends, mid shaft of tibia and fibula of the right leg, with irregular and ill-defined margins suggestive of a neoplastic malignant aetiology with possibility of intraosseous metastases. It also showed multiple subcutaneous T1 and T2 hypointense nodular lesions in the posteromedial right thigh, posterior aspect of the right leg and anteromedial aspect of the left knee, suggestive of subcutaneous sarcoma. All initial blood investigations including haemogram, renal and liver function tests were within normal limits. Multiple biopsies were taken from the swellings over the right calf and right gluteal region, histopathological examination revealed infiltrates of large foamy histiocytes and plasma cells in the skin and subcutis. The histiocytes were characteristically large and had large vesiculated nuclei with nucleoli and exhibited emperipolesis. Immunohistochemical staining revealed S-100 positivity, CD 68 positivity and CD1a negativity, suggesting a diagnosis of RDD. The patient was started on steroids, and she showed gradual reduction in the size of the swellings. The steroids were gradually tapered with introduction of methotrexate. After this she discontinued her follow-up and medications and a year later, she again presented with multiple subcutaneous swellings. She was initiated on steroids and cyclophosphamide after which swellings started to subside, then the patient was lost to follow- up again.

A year later, she presented with constitutional symptoms such as nausea, weight loss and loss of appetite. There was no fever, no change in bowel habits or other systemic symptoms. There was no history of rashes, joint pains, hair loss or photosensitivity to suggest autoimmune disease. There was no significant familial history of similar illnesses. There was no history of substance abuse. There was no significant exposure to radiation or chemicals.

At presentation to our hospital, she was afebrile and hemodynamically stable. Clinical examination revealed multiple subcutaneous swellings over her torso, upper and lower limbs of varying sizes which were non-tender, mobile, firm with the largest in the right axilla of 7 × 5 cm *(Fig. 1)*. She also had pallor and splenomegaly. No bleeding manifestations/ rash/ joint swelling were noted. The cardiovascular, respiratory and neurological examinations were normal.



Figure 1. Subcutaneous swelling in patient's right arm and forearm during resolution stage after initiation of therapy.

When we started our evaluation, routine investigations showed haemoglobin (7.9 g/dl), neutrophilic leucocytosis (103,740/mm^3) and thrombocytopenia (120,000/mm^3). A peripheral smear showed normocytic normochromic anaemia, leucocytosis-neutrophilic predominance with shift to left, thrombocytopenia. The erythrocyte sedimentation rate (ESR) was elevated 78 mm/h, lactate dehydrogenase (LDH) was 457 U/l. Nutritional screening showed normal iron studies, vitamin B12 and folate levels. Her random blood glucose, glycated haemoglobin, renal and liver function parameters were normal.

In order to rule out autoimmune related RDD, an antinuclear antibody (ANA) test was done which showed 3 plus positivity, but the patient had no other clinical features of any autoimmune disease. Further antibody analysis by Line Immune Assay showed nucleosome +, Ro 52 +, SS-A +, anti double stranded deoxyribonucleic acid + which could not be clinically correlated. The direct Coomb's test was negative. Rheumatoid factor and anti-citrullinated C-peptide tests

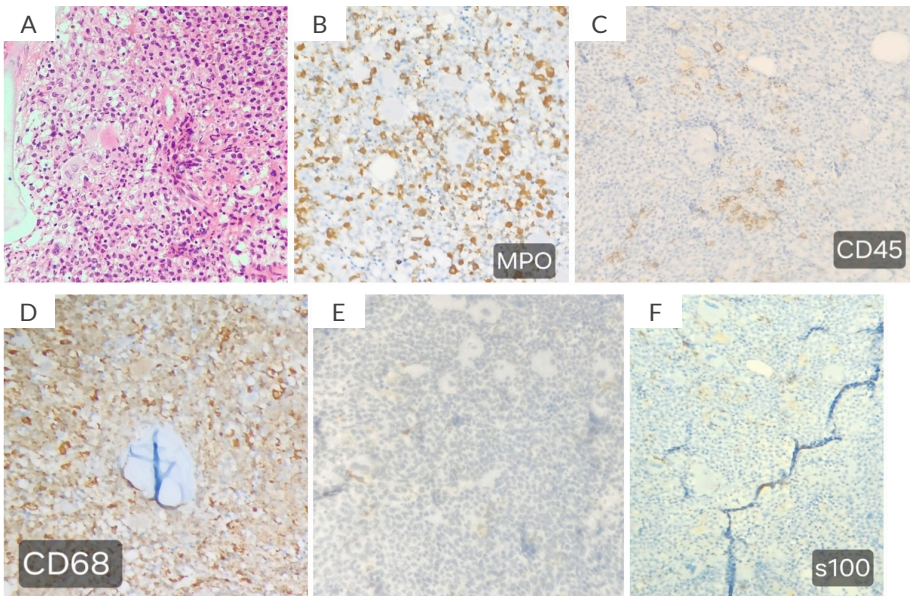


Figure 2. Bone marrow microscopy revealing histiocyte infiltration: A) haematoxylin and eosin showing foamy histiocytes with emperipolesis; B) MPO positivity; C) CD45 positivity; D) CD68 positivity; E) CD1a negativity and F) S-100 negativity
Abbreviations: MPO, myeloperoxidase; CD, cluster of differentiation.

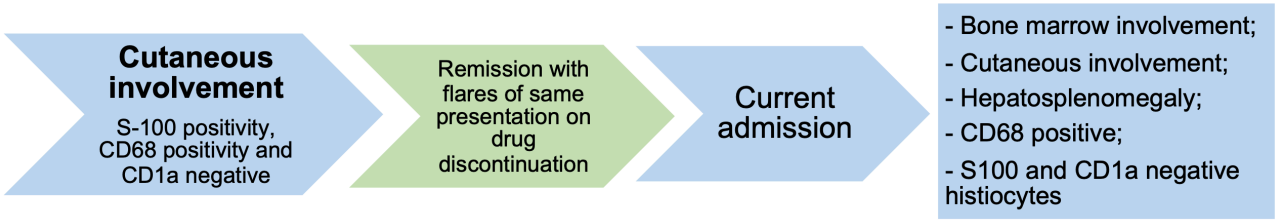


Figure 3. Timeline of the different presentations of our patient.

were negative. Viral serology (Including tests for human immunodeficiency virus, hepatitis B virus, hepatitis C virus, Epstein-Barr virus and cytomegalovirus) were negative.
Against this background, differentials we considered included RDD with bone marrow involvement, myeloproliferative neoplasm, and myelofibrosis.
For ruling out myeloproliferative neoplasm a fluorescence in situ hybridization test for the BCR-ABL gene was done and was negative. In view of new cytopenia, we proceeded with bone marrow aspiration and biopsy, which revealed a hypercellular marrow with diffuse histiocytic infiltration, supressed erythropoiesis, effective myelopoiesis showing all stages of maturation and adequate megakaryocytes. Immunohistochemistry showed CD68 positive but S100 and CD1a negative histiocytes *(Fig. 2)*. This was inconclusive and was in contrast to the previous histiocytic proliferation seen in the same patient as described above, and a clear discrimination between RDD and Langerhan's cell histiocytosis could not be made *(Fig. 3)*.
We did a positron emission tomography-computed tomography (PET-CT) scan to rule out any underlying malignancy *(Fig. 4)*, which revealed: 18 fluorodeoxyglucose (FDG) avid subcutaneous soft tissue nodules throughout the body, hepatomegaly of 17.5 cm with hypodense lesions in the liver- few showing mild FDG uptake, splenomegaly of 16.9 cm with diffuse mild FDG uptake, mild diffuse marrow FDG uptake noted in the axial and appendicular skeleton, focal mild FDG uptake in the right calcaneus.
Based on these findings a diagnosis of RDD was made. Though ANA was positive, it was only an immunological laboratory criterion for autoimmune disease and there were no clear clinical features of autoimmune disease. Also, the other workup for associated causes or secondary RDD were negative, and the diagnosis was likely sporadic RDD.
The patient was started on prednisolone tablets 40 mg once daily. She was discharged with oral steroids. During follow up, she was started on azathioprine, and her steroid dose was tapered down (during last follow-up she was on 50 mg of azathioprine and 10 mg of prednisolone every day).
She has been showing a good response: clinically, a reduction in size of the swellings has been noted, blood investigations over the last 6 months showed improvement in haemoglobin, and platelet count with leucocytosis. A peripheral blood smear done because of leucocytosis showed macrocytic anaemia, adequate platelets and neutrophilic leucocytosis attributable to a steroid related reaction. In view of the B12 deficiency noted during follow-up (the patient switching to a predominantly vegetarian diet and macrocytic anaemia), vitamin B12 therapy was initiated.

DISCUSSION

Histiocytes are cells of monocyte lineage found in connective tissue and consist of tissue macrophages, monocyte derived cells and dendritic cells. Histiocytosis constitutes a heterogenous rare group of diseases due to accumulation of histiocytes[1]. Though there is a clonality of cells confined in a particular place, it could be neoplastic or non-neoplastic[3]. Histiocytosis was previously classified into Langerhans

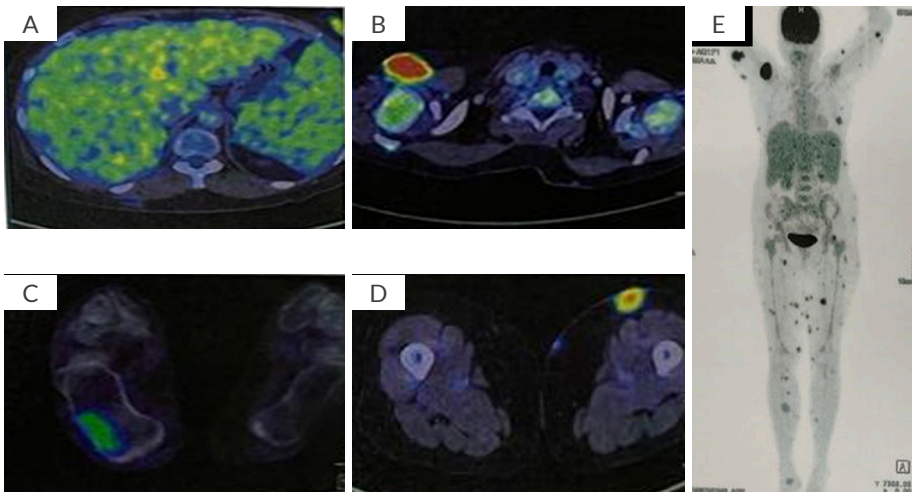


Figure 4. Showing PET CT images of the patient-multifocal and extranodal involvement: A) FDG uptake in liver and spleen; B) FDG uptake in right arm soft tissue swelling; C) FDG uptake in the calcaneum; D) FDG uptake in left thigh soft tissue swelling; E) Multisite involvement in RDD.
Abbreviations: PET-CT, positron emission tomography-computed tomography; FDG, fluorodeoxyglucose; RDD, Rosai Dorfman disease.

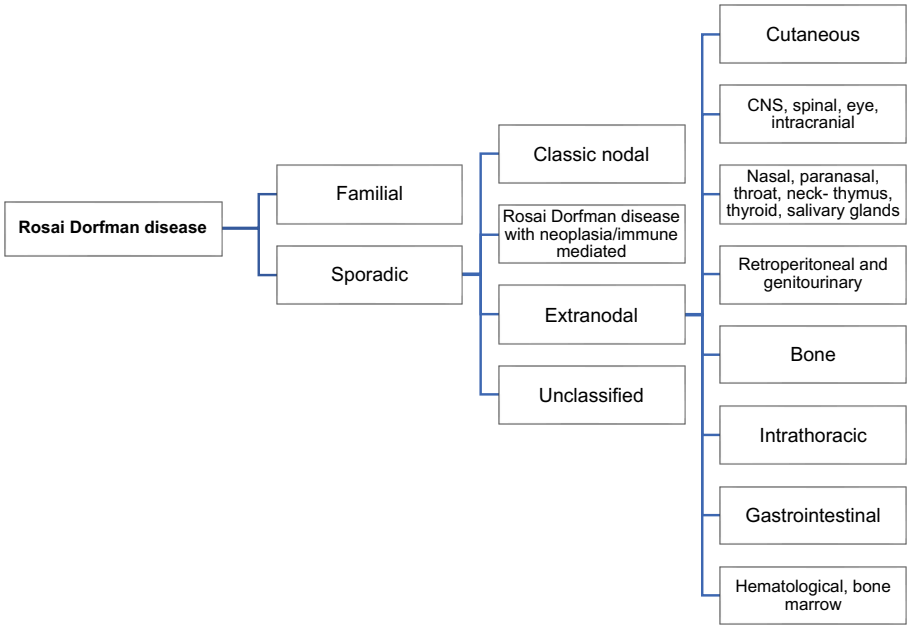


Figure 5. Classification of Rosai Dorfman disease based on disease distribution[3].

cell and non-Langerhans cell histiocytosis. Currently, Society of Histiocyte expert consensus 2016[3] classifies histiocytosis into five groups: 1) Langerhans-related (L group), 2) cutaneous and mucocutaneous group (C group), 3) malignant histiocytosis (M group), 4) RDD (R group) and 5) hemophagocytic lymphohistiocytosis (H group). These groups present with diverse clinical features and differentiation between them is based on tissue diagnosis aided by immunohistochemistry.

RDD most commonly presents as painless massive cervical lymphadenopathy. It is more common in children or younger individuals (mean age 20.6 years) and also more often in males[3]. It is classified into familial and sporadic *(Fig. 5)*. Nodal is the most common presentation of sporadic disease. Extranodal presentation (43%)[5] can cause cutaneous (10%), central nervous system (<5%), head and neck (11%), retroperitoneal and genitourinary, bone (5-10%), gastrointestinal (<1%) and haematological (60% approximately) manifestations.

The prognosis of the disease depends on the sites involved. Haematological manifestations[3,6] commonly seen in RDD include normocytic normochromic anaemia, leucocytosis with neutrophilia, thrombocytopenia, eosinophilia and elevated ESR, but bone marrow infiltration is rare[6,7]. Our patient presented at age 59, although this is considered an atypical age, recent studies are showing a mean age of 48 versus 20 years[8] and extranodal disease has been seen more often in adults[9]. She had involvement of rare sites[3,10] including bone marrow involvement and hepatosplenomegaly whilst also exhibiting subcutaneous manifestations, bone manifestations and lymphadenopathy. Published case reports[3,6] show bone marrow infiltration is associated with a poor prognosis but our patient had a good response to steroids.

RDD is diagnosed based on clinical features. Histopathological examination of affected tissue will show large pale histiocytes with large nucleolated hypochromatic nuclei. The histiocytes are further identified by their immunohistochemical positivity for CD68 and CD163 which are monocyte macrophage markers. The histiocytes are often positive for S100 and newer markers like cyclin D, OCT 2 which are specific for RDD. The histiocytic population in RDD is characteristically negative for the Langerhans cell marker CD1a[3]. Emperipolesis is a phenomenon considered

characteristic but might be subtle or lacking and can also sometimes be found in juvenile xanthogranuloma and Erdheim Chester disease[3]. In our patient we did not find S-100 positivity in one of the presentations. A similar discrepancy in CD markers associated with Langerhans cell histiocytosis has been reported[11].

Evaluation done to identify secondary causes of RDD include ANA, rheumatoid factor, LDH, Coomb's test, bone marrow aspiration/ biopsy and flow cytometry. PET-CT scan is done for prognostication[3].

In case of nodal/cutaneous disease 20-50% can resolve spontaneously[3]. If symptomatic, surgical debulking or other medical therapy[3] can be given. In patients requiring medical therapy, steroids are the first line of therapy. Other regimens used in patients with steroid refractory disease include methotrexate, vinblastine, 6-mercaptopurine with methotrexate combination, combination of low dose methotrexate with 6-mercaptopurine, 6-thioguanine/ prednisone, vinblastine. Azathioprine is an alternative choice for maintaining remission. In refractory disease immunomodulators including thalidomide, lenalidomide, rituximab, imatinib, clofarabine and newer gene-based therapy are currently being tried and tested in clinical trials[3]. Our patient although she presented with multifocal involvement had responded to steroids alone and had a rapid progressive recovery. Azathioprine was introduced to maintain remission and taper down her dose of steroids.

CONCLUSION

Histiocytic disorders are rare and can present in multiple ways and in multiple systems. Classification and understanding of these disorders have been constantly evolving as more and more molecular mechanisms and genetic changes underlying are being discovered. RDD, a histiocytosis characteristically presenting with lymph node enlargement can also present in many other ways. Bone marrow infiltration is a rare presentation, but awareness will help in early suspicion. Following the guidelines, bone marrow aspiration and biopsy should be done promptly in all patients with cytopenia and will help in early identification. Treatment regimens vary and different patients respond to different therapies.

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