Case report

Clinical challenges in the diagnosis and management of disseminated Rosai-Dorfman Disease presenting with chronic severe anemia

Thiraya Akeboonyuen

Department of Medicine, Phrapokklao Hospital

Abstract:

Rosai–Dorfman Disease (RDD) is an uncommon non-Langerhans cell histiocytic disorder, with varying clinical presentations and often complicate diagnosis, particularly in extranodal cases resembling other medical conditions. Moreover, standard treatment guidelines have not been well-established due to its rarity. We report the case of a 59-year-old woman, initially presenting with severe anemia and subsequent bone pain, hypercalcemia, renal impairment, small lymphadenopathy, and ulcerated nodular skin lesions. Histopathologic examination of a skin biopsy revealed histiocytic cell infiltration that was stained positively for S100 and CD68 but negatively for CD1a and Langerin, supporting the diagnosis of RDD. Following corticosteroid therapy combined with mercaptopurine, the cutaneous lesions showed a favorable response, and all laboratory parameters improved progressively during follow-up.

Keywords : ● *Rosai-Dorfman disease* ● *Histiocytic disorder* ● *Extranodal disease* ● *Hypercalcemia* ● *Anemia*

J Hematol Transfus Med. 2026;36:xxx.

Received ..... Corrected ..... Accepted .....

Correspondence should be addressed to Thiraya Akeboonyuen, MD., Department of Medicine, Phrapokklao Hospital, 38 Leabneon Road, Tambon Watmai, Meung, Chanthaburi, 22000

รายงานผู้ป่วย

ความท้าทายทางคลินิกในการวินิจฉัยและรักษาโรคโรไซดอร์ฟแมนแบบแพร่กระจายที่มาด้วยโลหิตจางรุนแรงเรื้อรัง

ธิรยา เอกบุญยืน
แผนกอายุรกรรม โรงพยาบาลพระปกเกล้า

บทคัดย่อ

โรคโรไซดอร์ฟแมน เป็นโรคในกลุ่มความผิดปกติของเซลล์ฮิสติโอไซต์ที่พบไม่บ่อย มีความท้าทายในแง่การวินิจฉัยเนื่องจากมีอาการแสดงที่หลากหลาย โดยเฉพาะกรณีที่เป็นโรคนอกต่อมน้ำเหลือง สามารถแสดงอาการใกล้เคียงโรคในกลุ่มอื่นได้ เนื่องจากเป็นโรคที่พบน้อย ปัจจุบันยังไม่มีแนวทางการรักษามาตรฐานสำหรับโรคนี้ รายงานผู้ป่วยนี้เป็นผู้ป่วยหญิงอายุ 59 ปี มาตรวจครั้งแรกด้วยภาวะโลหิตจางรุนแรง และต่อมามีอาการปวดหลัง แคลเซียมในเลือดสูง ไตวาย มีต่อมน้ำเหลืองโตเพียงเล็กน้อย และผื่นผิวหนังผิดปกติ ผลตรวจชิ้นเนื้อจากรอยโรคที่ผิวหนังพบเซลล์ฮิสติโอไซต์ ที่ย้อมอิมมูโนฮิสโตเคมี พบเอสร้อย (S100) และ ซีดีหกแปด (CD68) เป็นบวก โดยย้อมไม่ติดซีดีวันเอ (CD1a) และแลงเกอริน (Langerin) ยืนยันการวินิจฉัยโรคโรไซดอร์ฟแมน ผื่นผิดปกติที่ผิวหนังตอบสนองดีมากหลังรักษาด้วยยาสเตียรอยด์และเมอร์แคปโตพิวรีน ส่วนผลเลือดอื่นค่อยๆ ดีขึ้นตามลำดับ

คำสำคัญ : *● โรไซดอร์ฟแมน ● โรคฮิสติโอไซติค ● โรคนอกต่อมน้ำเหลือง ● แคลเซียมสูง ● โลหิตจาง*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2568;36:xxx.

Introduction

Rosai-Dorfman Disease (RDD) is characterized by the proliferation of activated histiocytes that are positively stained for S100 and CD68, but negatively for CD1a. RDD was initially described among children and young adults presenting with cervical lymphadenopathy, sometimes accompanied by systemic symptoms like fever, night sweats and weight loss.[4,17] However, the disease can present with a variety of clinical features, ranging from single organ lesions to multisystem extranodal involvements, for which the latter could mimic chronic inflammatory diseases; thereby, challenging diagnosis and delaying management. Subsequent studies[2,3] have shown that extranodal involvement is more common than nodal involvement, particularly among adults. In Thailand,[5,6] most of the reported cases involved cutaneous RDD, while cases with multiple organ involvement were rare. The case discussed here highlights atypical features and expands the understanding of the clinical spectrum of extranodal RDD.

Case report

A previously healthy 59-year-old woman presented with a three-month history of chronic fatigue, anorexia, and unintentional weight loss. She had been treated with packed red cell transfusions at another hospital for severe anemia of unknown etiology. At initial evaluation, she presented with fever without localizing symptoms. Laboratory investigations revealed severe microcytic anemia with Hb 5.9 g/dL, Hct 20%, MCV 67 fL, WBC 19,700/mm^3 (N 73.2%, L 16.9%, Mono 7.1%), and platelets 183,000/mm^3. Blood chemistry indicated normal renal function and a lactate dehydrogenase level of 200 U/L (135-214). Liver function tests revealed a total protein level of 7.4 g/dL (6.6-8.7), increased globulin at 5.3 g/dL, low albumin at 2.1 g/dL (3.5-5.2), and elevated alkaline phosphatase at 408 U/L (35-104). Hemoglobin typing revealed hemoglobin E trait. Iron studies showed elevated serum ferritin levels 563 ng/mL (13-150) with low serum iron levels 9.6 mcg/dL (33-193) and decreased total iron-binding capacity 163.6 mcg/dL (228-428). Empirical treatment for fever of unknown origin was prescribed and a septic workup yielded negative results.

She was re-admitted due to recurrent fever and symptomatic anemia. Bone marrow study revealed hypercellular trilineage marrow and the presence of a few micromegakaryocytes. Given persistent leukocytosis and mild hepatosplenomegaly on ultrasonography, myelodysplastic/myeloproliferative neoplasm (MDS/MPN) was suspected. Ten months later, she reported worsening fatigue and developed lower back pain. Physical examination revealed enlarged lymph nodes 1-2 cm in the supraclavicular, posterior cervical, and bilateral inguinal regions. Lymph node biopsy demonstrated necrotizing granulomatous inflammation. Laboratory investigations revealed hypercalcemia (corrected calcium 12.4 mg/dL), acute kidney injury (serum creatinine 4.4 mg/dL), hyperphosphatemia (5.2 mg/dL), iPTH 6.8 pg/mL (15-65), globulin 6.3 g/dL, albumin 2.5 g/dL and ALP 712 U/L. Bone survey revealed diffuse osteolytic lesions with cortical thinning. A repeat bone marrow study revealed hypercellularity and an increase in interstitial mature plasma cells. Serum protein electrophoresis, immunofixation, and serum free light chain analysis revealed polyclonal gammopathy. Given the differential diagnosis of plasma cell neoplasm, she was treated with intravenous calcitonin and high dose dexamethasone (40 mg/day). Four months later, she attended the plastic surgical department presenting a chronic ulcerative nodule on the chin. Skin biopsy showed dense dermal infiltration by large polygonal histiocytes with abundant eosinophilic cytoplasm, vesicular nuclei, and evidence of emperipolesis. Immunohistochemical staining was positive for S100 and CD68, but negative for CD1a and Langerin–confirming the diagnosis of RDD. Autoimmune workup revealed a positive antinuclear antibody (ANA) test with a titer of 1:640, demonstrating fine speckled and cytoplasmic staining patterns. The imaging studies showed no evidence of underlying malignancy.

Treatment with prednisolone 0.5 mg/kg/day was prescribed and resulted in partial improvement of the cutaneous lesion within two weeks. However, a new 3 to 4 cm lesion developed on the neck and oligoarthritis. Prednisolone 20 mg/day and methotrexate 20 mg/m^2/week were initiated. Unfortunately, methotrexate toxicity necessitated treatment discontinuation. During a short treatment-free period, she subsequently developed bilateral knee pain, lower back pain, low-grade fever and new necrotic lesions on the left elbow. Treatments were resumed with prednisolone and the addition of mercaptopurine 50 mg/day, resulting in complete resolution of cutaneous lesions within two months. Her clinical symptoms and laboratory parameters gradually improved. At the recent follow-up visit (26 months after diagnosis), laboratory studies demonstrated significant improvement with Hb 13.4 g/dL, Hct 42.3%, MCV 75.4 fL, WBC 6,620/mm^3, and platelets 417,000/mm^3. Biochemical parameters showed creatinine 1.6 mg/dL, albumin 4.0 g/dL, globulin 4.0 g/dL, and alkaline phosphatase 153 U/L. The patient remains clinically stable on maintenance therapy with low-dose corticosteroids and mercaptopurine for more than 12 months after initiating treatment.

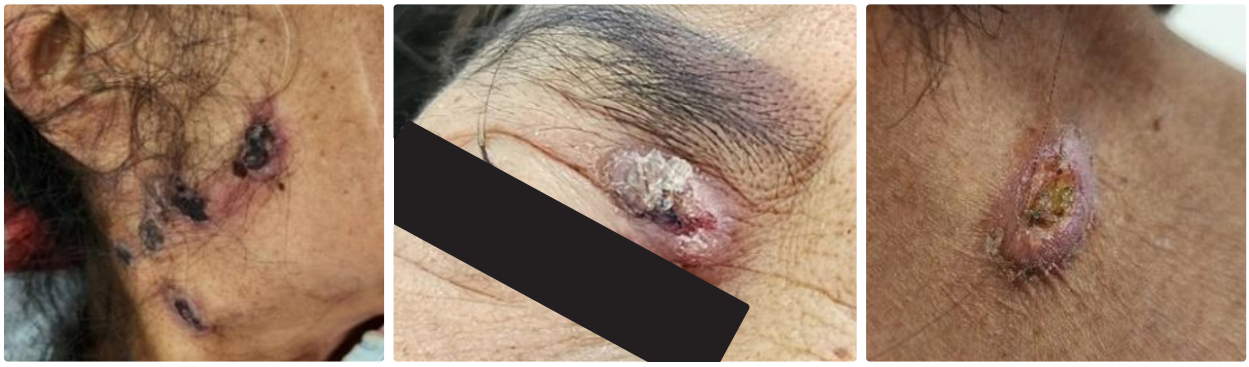

Figure 1 Skin lesions of this patient showing an infiltrate erythematous nodule with a central ulcer on the upper eyelid and neck

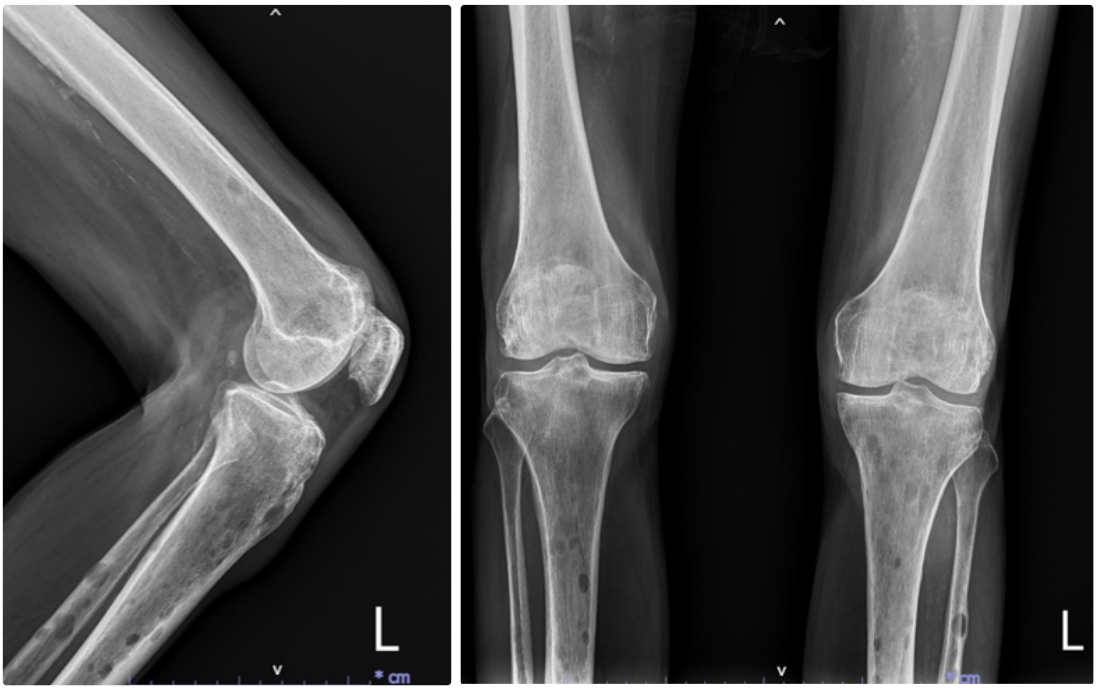

Figure 2 Osteolytic lesions with cortical thinning involving metaphysis, epiphysis and diaphysis of the distal femur, tibia, and fibula

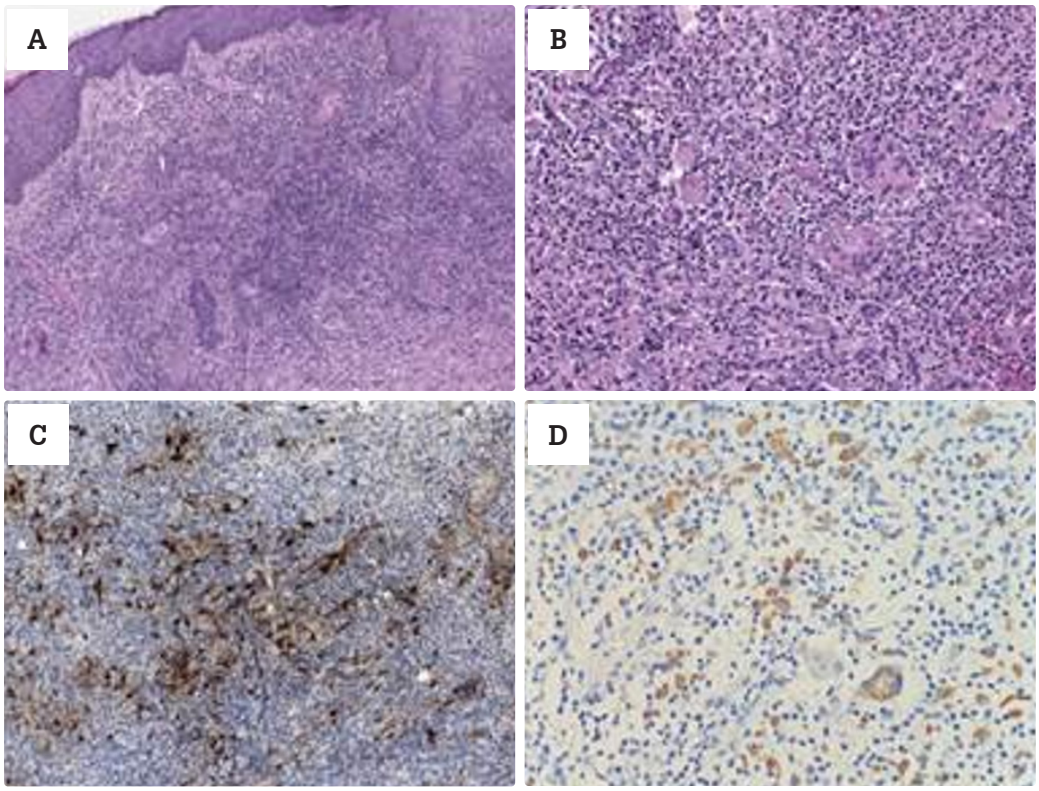

Figure 3: Histopathology of skin: H&E stain (A-B) showing dense dermal infiltrate of large polygonal histiocytes admixed with inflammatory cells. The histiocytes have abundant, lightly eosinophilic cytoplasm, vesicular nuclei and exhibit emperipolesis, characterized by the engulfment of inflammatory cells. Immunohistochemistry showing positive staining for S100 (C) and CD68 (D)

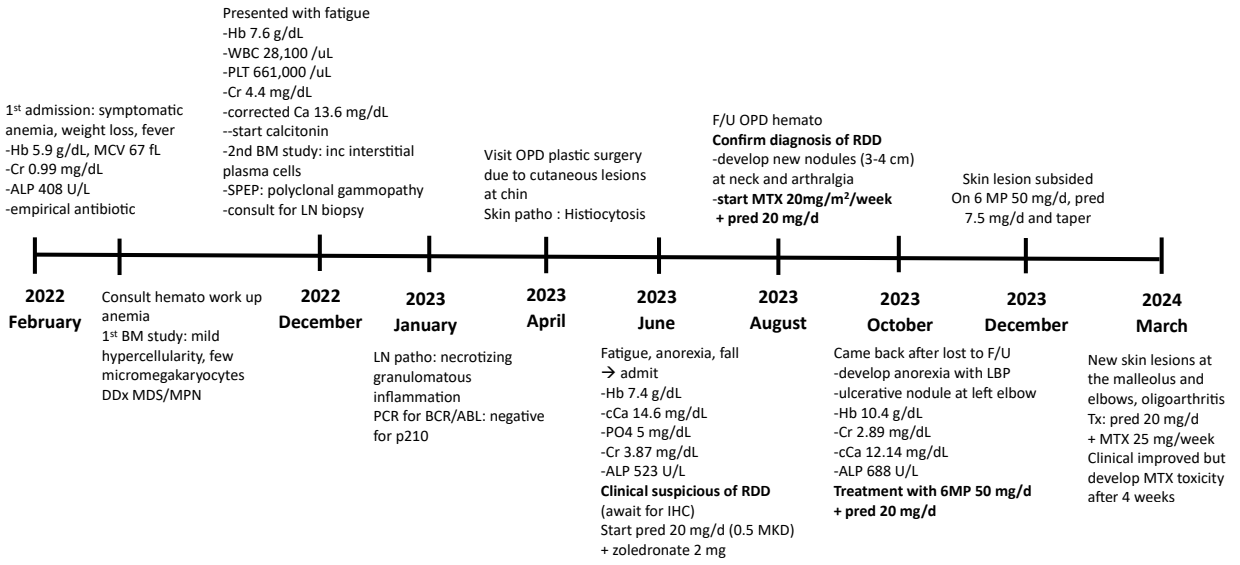

Figure 4 Patient journey through clinical presentation, diagnosis and treatment.

Discussion

RDD is an infrequent non-Langerhans cell histiocytosis, previously regarded as a benign condition and sometimes self-limiting. Recently,[1,12,13] molecular analysis data have identified somatic mutations involving the MAPK signaling pathway including *KRAS*, *MAP2K1*, *NRAS and ARAF* in nearly one half of cases, indicating a clonal neoplastic process. According to the updated 2016 histiocytic disorder classification system,[14] RDD was categorized within the "R group" encompassing both inherited and non-inherited variants. Additional subcategories include nodal, extranodal disease, or associated

The clinical features of RDD had significant variability, from localized self-limiting asymptomatic skin lesions to widespread systemic disease affecting multiple organs, and presentation patterns that may differ in various populations and racial groups.[2,14] Among Asians, particularly in Thai case reports,[5,6] skin lesions were the most common presented feature typically coinciding with mild anemia and variable lymph node involvement. A study from MD Anderson Cancer Center[3] reported fever in 75% of cases, with approximately one half of patients experiencing anemia, thrombocytopenia, or bone pain. The Mayo Clinic series reported hematologic abnormalities in two-thirds of patients, but severe anemia and B-symptoms were uncommon.[2] Thorough evaluation of our case showed no evidence of autoimmune hemolysis or primary bone marrow disease, pointing to anemia of chronic inflammation as the underlying cause. The presence of microcytosis was explained by coexisting hemoglobin E trait and functional iron deficiency induced by severe inflammation, and MCV values improved following RDD treatment. The bone marrow specimen exhibited increased interstitial plasma cells, but clonality analysis was not performed. The polyclonal gammopathy found on serum protein studies corresponded to the presumed polyclonal plasma cell expansion in this patient. Hypercalcemia is thought to result from increased bone resorption due to local inflammatory cytokines or extrarenal calcitriol production. In this case, hypercalcemia alongside elevated alkaline phosphatase levels and multifocal osteolytic lesions suggested extensive skeletal involvement. However, the measurement of 1,25-dihydroxyvitamin D (calcitriol) levels to elucidate the underlying mechanism was not performed in this patient. The patient had widespread osteolytic bone lesions throughout the various anatomical regions of long bones (epiphysis, metaphysis, diaphysis) and within the tarsal bones. The constellation of osteolytic lesions, hypercalcemia, renal failure, and anemia during the initial evaluation mimicked the clinical diagnosis of multiple myeloma. However, the diagnosis of multiple myeloma was against using the presence of lymphadenopathy, which is uncommon, and significantly, the finding of polyclonal gammopathy.

The ulcerative nodular skin lesions observed in our patient constituted less common findings, as most literature described skin lesions as papulonodular, plaques, tumor-like or eruptive xanthoma-like.[1,2] Histologic diagnosis[14] requires identification of characteristic large histiocytes with pale cytoplasm, hypochromatic nuclei, and/or emperipolesis. Immunohistochemical analysis reveals that these cells presented S100, OCT2, cyclin D1, CD68, and CD163, but were absent for CD1a and CD207 that must be present in Langerhans cell histiocytosis, where the involved tissues often contain a dense background of polyclonal plasma cells and lymphocytes.

The pathogenesis of RDD remains incompletely understood. A subset of patients has co-existing autoimmune conditions including systemic lupus erythematosus, rheumatoid arthritis, autoimmune hemolytic anemia or polymyalgia rheumatica.[8] Some extranodal RDD cases had also demonstrated increased numbers of IgG4-positive plasma cells. Leukocytosis and thrombocytosis observed in this patient were likely associated with chronic inflammatory processes, as supported by the combination of anemia of inflammation, polyclonal gammopathy and a positive ANA. However, without confirmed molecular testing, the underlying pathophysiology remained inconclusive, whether of a clonal disease process or associated autoimmune disease.

Due to its rarity and variable presentations, standard treatment guidelines for RDD are not well-established. Based on available data, management should be individualized according to disease severity and organ involvement. Corticosteroids are the most commonly used first-line therapy, which can induce partial or complete responses. Other immunosuppressive agents, chemotherapy or purine analogues are treatment options for nodal or systemic disease.[1-4] Combining low-dose prednisolone and mercaptopurine in our patient resulted in sustained clinical and laboratory improvements

with acceptable side effects. Extended combination immunosuppressive therapy with gradual dose reduction over 6 to 12 months was recommended to control the disease as relapsing symptoms were observed during abrupt treatment discontinuation.

Conclusion

This case highlights the diagnostic challenges of extranodal RDD, particularly among patients presenting nonspecific systemic symptoms of severe nonhemolytic anemia, anorexia, weight loss and laboratory abnormalities preceding the development of overt cutaneous lesions. Clinical features such as hyperglobulinemia, osteolytic bone lesions, renal dysfunction and hypercalcemia can mimic plasma cell neoplasms. A comprehensive diagnostic workup is essential to exclude alternative etiologies including granulomatous, inflammatory and malignant diseases. Pathologic confirmation remains the key to a definite diagnosis; therefore, a careful physical examination is critical to identify subtle cutaneous or nodal lesions, and obtaining tissue for histopathology is essential. Our patient responded well to combining low dose corticosteroids and mercaptopurine, with dramatic resolution of skin lesions and sustained disease control for 12 months. This atypical case features has contributed more information to the extranodal presentations of RDD and emphasized the importance of a multidisciplinary approach in managing this rare disorder.

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