

Case Report

Disseminated Rosai-Dorfman Disease with Multiple Extranodal

Involvement: A Rare Case Report

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Abstract:

Sinus histiocytosis with massive lymphadenopathy or Rosai-Dorfman disease (RDD) is an uncommon benign tumor characterized by idiopathic proliferation of phagocytic histiocytes. RDD is usually manifested by the presence of large painless lymphadenopathy; however, extranodal involvement, e.g., the central nervous system, orbits, skin and respiratory tract, is rarely seen. Herein, we reported an elderly man presenting a 3-month history of progressive generalized papules with lymphadenopathies. The pathological findings of the skin, cervical lymph node and bronchial nodule were consistent with RDD. He received a diagnosis of disseminated RDD. Treatment with immunosuppressive therapy using corticosteroid and mercaptopurine resulted in gradually improved symptoms within 3 weeks.

Keywords : ● Disseminated Rosai-Dorfman disease ● Extranodal involvement ● Skin ● Pulmonary ● Bone
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รายงานผู้ป่วย

Disseminated Rosai-Dorfman Disease with Multiple Extranodal

Involvement: A Rare Case Report

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บทคัดย่อ

โรค Sinus histocytosis with massive lymphadenopathy หรือ โรค Rosai-Dorfman จัดเป็นโรคก้อนเนื้อออกที่มีการเพิ่มปริมาณของเซลล์ฮีสทีโอไซต์มากผิดปกติ โรคนี้ส่วนใหญ่มีอาการแสดงนำ คือ มีต่อมน้ำเหลืองโตขนาดใหญ่โดยที่ไม่มีอาการเจ็บที่ต่อมน้ำเหลือง และอาจพบอาการแสดงผิดปกติที่อวัยวะอื่นที่ไม่ใช่ต่อมน้ำเหลืองได้ถึงแม้จะมีโอกาสพบได้น้อย เช่น ระบบประสาทตา ผิวหนัง และทางเดินหายใจ ด้วยเหตุนี้คณะผู้วิจัยจึงได้รายงานผู้ป่วยสูงอายุ เพศชาย มาพบแพทย์ด้วยอาการมีก้อนขึ้นตามผิวหนังทั่วร่างกายและมีต่อมน้ำเหลืองโตมากขึ้นมา 3 เดือน ซึ่งผลตรวจพยาธิสภาพของ ผื่น ต่อมน้ำเหลืองที่คอ และก้อนที่หลอดลมของผู้ป่วยเข้าได้กับโรค Rosai-Dorfman ผู้ป่วยรายนี้จึงได้รับการวินิจฉัยเป็นโรค Rosai-Dorfman ที่มีการแพร่กระจายทั่วร่างกายและได้รับการรักษาด้วยยาสตีรอยด์และยาเคมีบำบัด Mercaptopurine ซึ่งพบว่าผู้ป่วยมีอาการดีขึ้นภายใน 3 สัปดาห์หลังได้รับการรักษา

คำสำคัญ : ● Disseminated Rosai-Dorfman disease ● Extranodal involvement ● Skin ● Pulmonary ● Bone
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Introduction

Sinus histiocytosis with massive lymphadenopathy, also known as Rosai-Dorfman disease (RDD), is a benign entity first recognized and described by two pathologists, Juan Rosai and Ronard Dorfman in 1969.¹ RDD is characterized by massive and painless lymph node enlargement, typically seen among male teenagers and young adults. Clinical course is indolent with spontaneous resolution in a majority of patients. Patients who have disease progression with enlarged lymph nodes causing compressive symptoms on adjacent vital organs are usually managed by simple excision. When surgery is incapable of removing all the involved tissue, treatment with corticosteroids, systemic chemotherapy or immunosuppressive agents have demonstrated promising results.

Extranodal manifestations of RDD account for approximately 40% of all cases and can represent a diagnostic challenge for clinicians and pathologists.² Few case series and individual cases of extranodal RDD have been reported in various organs, mimicking neoplastic entities. We report an extremely rare case of disseminated RDD with multiple organ involvement.

Case report

A previously healthy 63-year-old Thai male presented a 3-month history of asymptomatic erythematous and yellowish papules starting on his face and later on both arms, chest and back. One month after the appearance of skin lesions, he experienced low grade fever, fatigue, and painless bilateral cervical lymphadenopathies. His comorbidities included well-controlled type 2 diabetes mellitus and dyslipidemia. Physical examination revealed multiple discrete erythematous and yellowish dome-shaped papules on the face, chest, back, and both upper extremities (Figure 1) and bilateral cervical lymphadenopathies varying in size around 1 to 2 cm in diameter. Laboratory data were remarkable for mild normochromic

normocytic anemia with hemoglobin of 10.2 mg/dL and polyclonal paraproteinemia. Serum creatinine and lactate dehydrogenase were within normal range. A computerized tomography of the neck, chest and abdomen revealed several small fixed irregular tracheobronchial wall thickening lesions and multiple tiny pulmonary nodules in both lungs (Figure 2). Multiple cervical, axillary, mediastinal, intra-abdominal and inguinal lymphadenopathies were detected with the largest nodes measuring up to 4.2 cm in diameter. Furthermore multiple osteolytic lesions were seen at the ischium, pubic bones, right femoral head, both ilia, manubrium, left clavicular head, right scapula, both ribs and at multivertebral levels.

Skin biopsy was performed and histopathology showed diffuse inflammatory cells infiltration composed of large foamy histiocytes, multinucleated giant cells admixed with lymphocytes, eosinophils and plasma cells. One phenomenon, called emperipoiesis, occurs when lymphocytes and/or plasma cells are engulfed by histiocytes, and Touton giant cells are noted. Immunohistochemistry showed positive CD68 and S-100 but negative

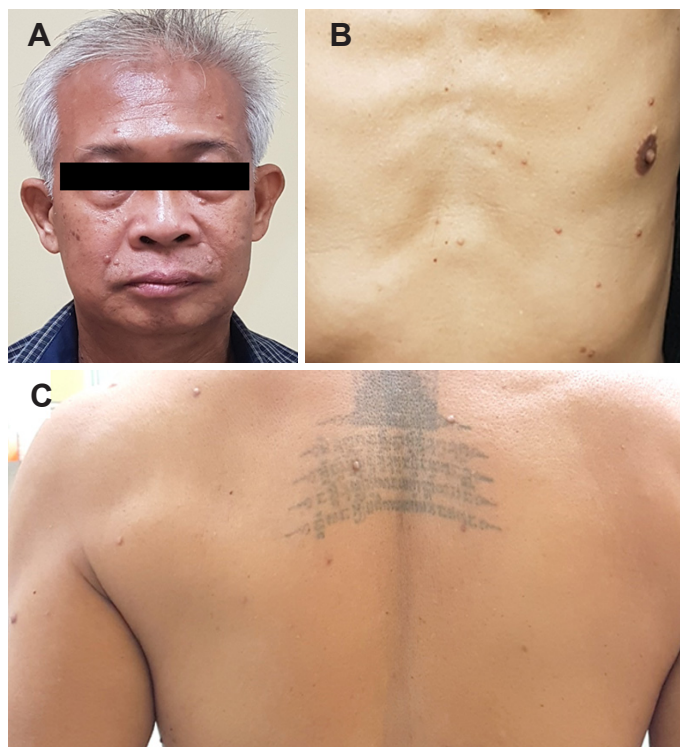


Figure 1 Generalized erythematous and yellowish papules on the face (A), chest (B) and back (C)

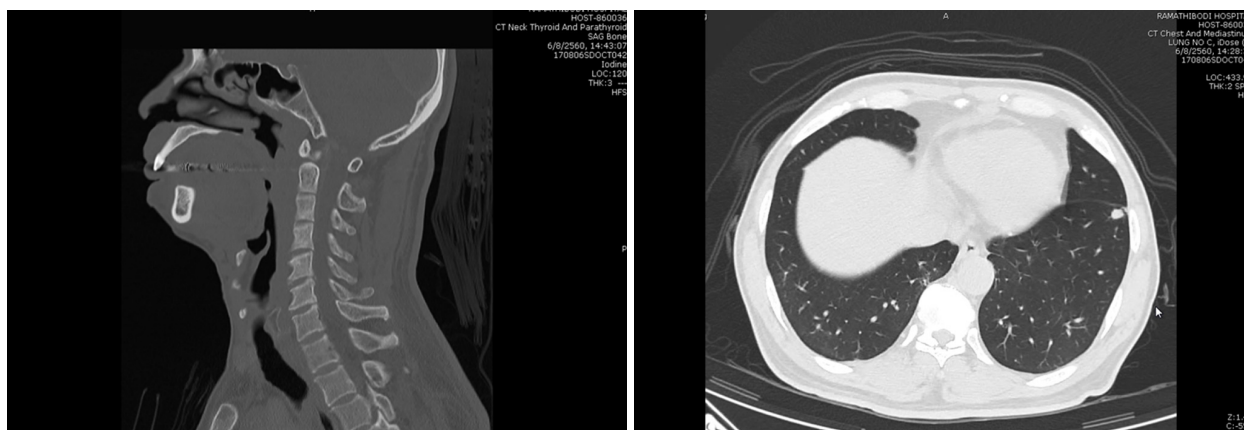


Figure 2 Computerized tomography of the neck in coronal view and chest in horizontal view: irregular tracheo-bronchial wall thickening and multiple tiny pulmonary nodules in both lungs

for CD1a staining (Figure 3). Bronchoscopy with bronchial nodule biopsy was obtained. The bronchoscopic findings showed a nodule at the posterior pharynx and multiple nodules with minimal vascular supply at the trachea and both bronchi (Figure 4). The histopathology of the bronchial nodule was consistent with RDD (Figure 5).

The diagnosis of disseminated RDD with cutaneous, pulmonary (trachea, bronchus and suspected pulmonary nodules) and skeletal involvement was made. He received systemic treatment with corticosteroid (prednisolone 0.5 mg per kg daily (MKD) resulting in no change in size and number of lymph nodes and skin lesions. Mercaptopurine 50 mg daily in addition to increased dosage of prednisolone to 1 MKD was considered. Amelioration of the previous lymphadenopathies and skin lesions by 4-week treatment of prednisolone plus mercaptopurine was observed. We report an extremely rare case of disseminated RDD with multiple organ involvement.

Discussion

RDD is an uncommon nonLangerhans cell histiocytosis, typically seen among children and young adults. The disease is more common among males and individuals of African descent² and is rarely reported in Asian populations.³⁻⁶ The usual clinical presentation is massive lymphadenopathy, especially in the cervical region, associated with fever, night sweat, fatigue and

weight loss. The etiology of RDD remains unknown. The most plausible pathogenesis mechanism involved is genetic alteration and disturbance of homeostasis leading to recruited monocytes, with defects in differentiation and antigen presentation, to inflammatory sites. The activated monocytes produced macrophage colony-stimulating factor (M-CSF), promoting the production of tumor necrosis factor- α , IL-1 β and IL-6.⁷ Coincidentally, RDD cells also express these cytokines. Together with the detection of same myeloid-related protein8 (MRP8) and MRP14 on the surface of both RDD cells and recruiting monocytes, these data indicated that RDD cells may derive from circulating monocytes.⁸ A few inherited conditions, H syndrome (associated with germline mutation in SLC29A3) and autoimmune lymphoproliferative syndrome (ALP) type Ia (associated with germline mutation in the FAS/TNFRSF6), have systemic lesions with histopathology patterns resembling RDD. Recent molecular studies have revealed recurrent mutation involving *KRAS* and *MAP2K1* in one third of RDD cases.⁹ *KRAS* activating mutation results in constitutive activation of the MAPK pathway that may be inhibited by MEK inhibitors. A better understanding of the genetic alterations that contribute to the pathogenesis of RDD may guide potential targeted therapies for this disease.¹⁰

Several observations found an association between RDD and IgG4-related disease and RDD but remains controversial due to the lack of IgG4-related disease

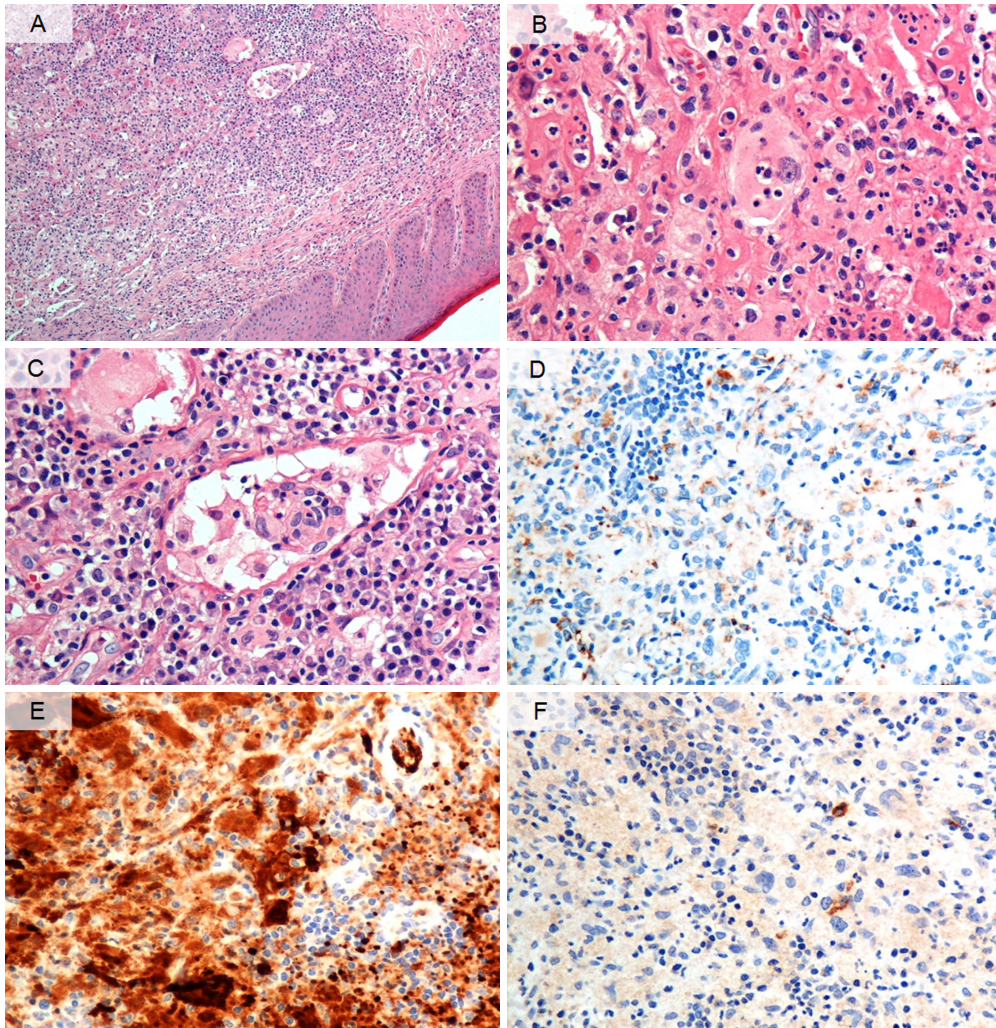


Figure 3 Histopathology of skin: (H&E stain x100): H&E stain x100 demonstrates moderately dense mixed cellular infiltration comprising small lymphocytes, plasma cells and scattered large histiocytes with many admixed neutrophils in this case (A). H&E stain x400 shows large histiocytes have some degree of nuclear atypia (B). Intact leucocytes are in abundant cytoplasm (emperipolesis) (C). Immunohistochemistry expresses positive CD68 (D) and S-100 (E) but negative for CD1a staining (F).

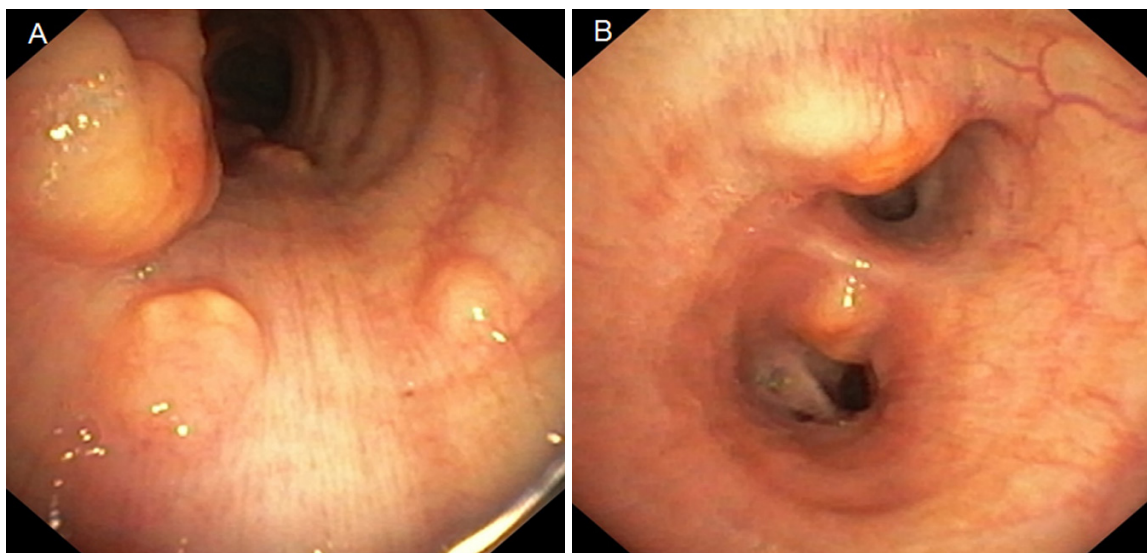


Figure 4 Bronchoscopic findings: multiple nodules with minimal vascular supply at trachea (A) and both bronchi (B)

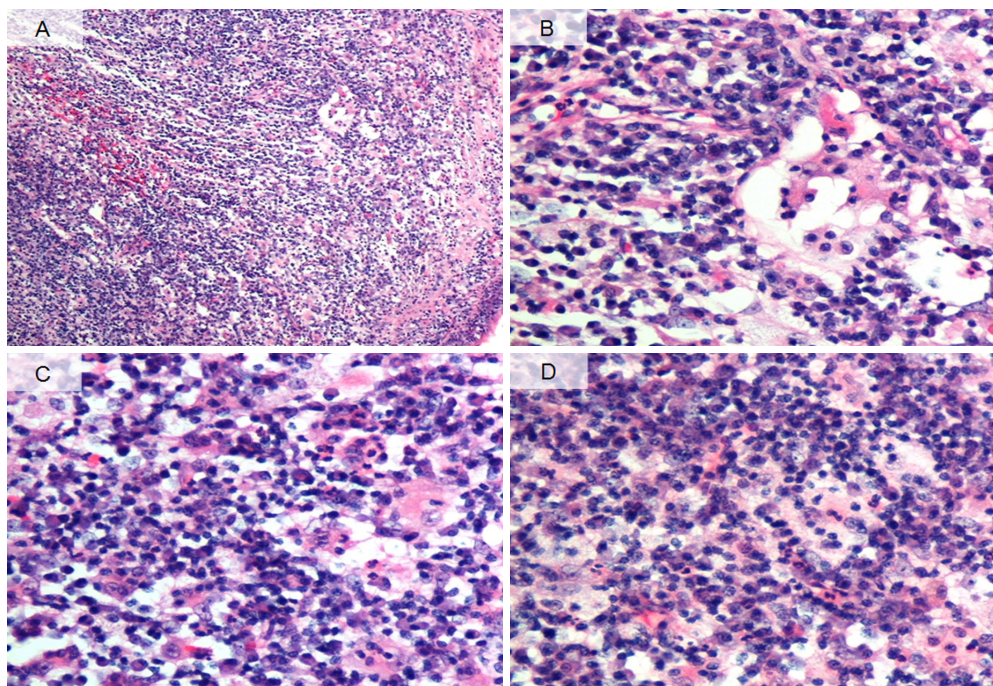


Figure 5 Histopathology of bronchial nodules: H&E stain x100 demonstrates dense cellular infiltration in sub-epithelial area of bronchus with scattered small dilated spaces (A). H&E stain x400 shows mixed lymphocytes, plasma cells and histiocytes. Focal dilated spaces containing histiocytes with ingested intact cells (emperipolesis) (B, C, D)

histologic features such as storiform fibrosis and obliterating phlebitis in RDD cases.¹¹⁻¹³ RDD has been reported concurrently with autoimmune disease, Hodgkin lymphoma, non Hodgkin lymphoma and other histiocytic disorders.¹⁴⁻¹⁶ Extranodal manifestations of RDD have been documented in 43% of all cases², but few clinicopathologic case series have been reported in the literature. The majority of extranodal sites comprise skin lesions, which present as well-defined skin colored papules to palpable masses and confined or distributive lesions. In the scanty case series of extranodal RDD reported in the western literature, most cases are limited to the skin. However, some individual reports of this disease show it occurs in many locations including the nasal cavity, bone, soft tissue, retro-orbital tissue and rarely visceral organs. Cutaneous RDD can vary in size, ranging from less than 1 to 30 cm or more at their greatest dimensions.¹⁷ The lesion characteristics are typically red-brown papules or nodules without confluent infiltrative pattern. The most frequent site of skin involvement is the trunk and back followed by the

head and neck region. Pulmonary involvement of RDD is extremely rare. Twelve cases of tracheobronchial involvement and 2 cases of interstitial infiltration from RDD have been reported.¹⁸⁻²⁰ Some cases presented acute respiratory failure or progressive dyspnea due to airway obstruction. Findings from fiberoptic bronchoscopy revealed tracheobronchial lesions ranged from small nodules to 4 cm.²¹

Laboratory abnormalities of RDD are frequent but nonspecific including elevated erythrocyte sedimentation rate, hypergammaglobulinemia, leukocytosis and anemia.² Radiologic feature of RDD is nonspecific but can mimic various malignancies. The diagnostic roles of computerized tomography (CT) and magnetic resonance imaging (MRI) are still controversial to distinguish between RDD and other entities.^{22,23} Skeletal lesions are typically osteolytic and can be confused with Langerhans cell histiocytosis (LCH). Positron emission tomography (PET) with ¹⁸F FDG plays a role in detecting RDD with extranodal involvement especially visceral organ-based given the suggested inflammatory process

of RDD.²⁴⁻²⁶ However, tissue diagnosis is mandatory in all cases.

The histopathology of RDD, in both nodal and extranodal involvement, is characterized by sinusoidal dilatation filled with histiocytic proliferation. The histiocyte demonstrates single bland-appearing nuclei with well-defined nuclear membranes, homogeneous chromatin, and a single small nucleolus. Its cytoplasm is abundant, eosinophilic to amphophilic, and shows the hallmark feature of this disease, emperipolesis, consisting of the passage of intact lymphocytes through the cell within intracellular vacuoles. These findings are often less apparent in extranodal sites. Prominent eosinophils or necrosis are not features of RDD and usually go against the diagnosis. The lesional histiocytes express both CD68 and S-100 proteins while negativity for CD1a helps to distinguish this condition from Langerhans cell histiocytosis and polyostotic sclerosing histiocytosis (Erdheim-Chester disease). An accurate histopathologic diagnosis of RDD requires appropriate clinical suspicion and is crucial to prevent unnecessarily aggressive therapy.^{27,28}

Management depends on clinical manifestations. In many cases, the lesions remain asymptomatic and regress spontaneously without treatment. Nevertheless, the clinical course may be protracted with nodal and/or extranodal dissemination. The therapeutic options for systemic involvement are corticosteroids alone or in combination with oral methotrexate or mercaptopurine.²⁷⁻²⁹ Other agents including cladribine³⁰, imatinib³¹, rituximab³² and azathioprine³³ have been found to be effective in some refractory cases. Radiotherapy has not shown encouraging results though it has been used in RDD with orbital or central nervous system involvement.

To conclude, disseminated RDD with extranodal involvements are rare, and the pathogenesis of RDD is not well understood. Given the heterogeneous clinical presentations and unpredictable clinical course, confirming the diagnosis by histological and immunohistochemistry staining is crucial. Currently, no standard treatment has been delineated. Systemic corticosteroid

is usually helpful in alleviating constitutional symptoms and decreasing nodal size. Various agents are used as second line therapy for multisystem involvement and relapse/refractory cases.

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