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CASE REPORT

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Extranodal Rosai-Dorfman disease masquerading as intrathoracic invasive malignancy with ankylosing spondylitis: a case report

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Abstract

Introduction Rosai-Dorfman Disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is an uncommon histiocytic disorder. It may be associated with autoimmune diseases, but there are few reports of concurrent ankylosing spondylitis. RDD is typically characterized by massive bilateral and painless cervical lymphadenopathy, which can also involve extranodal sites and constitutional symptoms, but rarely affect the chest cavity.

Case presentation In this report, we present a case of a patient with a suspicious invasive anterior mediastinal lesion affecting multiple blood vessels and adjacent tissues. The patient has a history of ankylosing spondylitis. Despite extensive radiological and interventional examinations, the possibility of malignancy could not be completely ruled out. Following surgical resection of the tumor, the final pathology diagnosis suggested RDD.

Conclusion Our report emphasizes the importance of considering RDD in the differential diagnosis of invasive thoracic malignancies. Thoracoscopy or mediastinoscopy biopsy can improve diagnostic accuracy. Our study contributes to an improved understanding among clinicians regarding the diagnosis and treatment of intrathoracic RDD and provides relevant evidence for future exploration of potential associations between RDD and ankylosing spondylitis.

Keywords Rosai-Dorfman disease, Mediastinum, Thymus, Ankylosing spondylitis

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Introduction

Rosai-Dorfman Disease (RDD) is a type of rare benign histiocytic disorder of unknown etiology, characterized by abnormal accumulation of histiocytes and numerous lymphadenopathy, especially in the neck, head, and face [1, 2]. Bilateral massive and painless cervical lymphadenopathy is classical. Other lymph nodes, such as mediastinal, retroperitoneal, axillary, and inguinal nodes, may also be involved. However, only about 2% of patients develop intrathoracic RDD [3], often manifesting as pulmonary nodules and mediastinal lymphadenopathy. Except for cervical nodes, the dimension of adenopathy in the other sites is usually smaller. In our case report, we present a young patient with ankylosing spondylitis who was found to have a huge mediastinal mass initially suspected to be an invasive malignancy. Multiple biopsies failed to establish a definitive diagnosis. Ultimately, histopathological examination following surgical resection confirmed a rare case of RDD.

Case presentation

A 23-year-old male patient accidentally found a space occupying the anterior mediastinum during a chest and abdominal plain computed tomography (CT) scan due to pain and discomfort in the lower right abdomen. Upon presentation at our hospital, the patient denied experiencing symptoms including drooping eyelids, difficulty in chewing or swallowing, hoarseness, breathing difficulties, chest tightness, chest pain, mental confusion, and weight loss. Approximately one month ago, he was diagnosed with ankylosing spondylitis through X-ray examination and a positive HLA-B27 test at an external hospital due to persistent back pain. He received irregular treatment with prednisone acetate (20 mg/day) but ultimately discontinued the medication because of adverse effects. He denied any history of EB virus infection and related family history. Enhanced CT revealed an 8.5*5.0 cm soft tissue mass in the anterior mediastinum, with indistinct borders and involvement of nearby blood vessels. Positron emission tomography (PET)-CT showed intense fluorodeoxyglucose uptake in the mass (SUVmax: 8.11), and no evident lesions were found elsewhere in the body (Fig. 1). Due to the large lesion, the patient underwent two mediastinal fine-needle aspiration biopsies. The pathological findings revealed proliferation of spindle-shaped cells accompanied by infiltration of lymphocytes and plasma cells, interstitial collagen formation, and local invasive growth. The results did not provide conclusive diagnostic evidence and could not completely rule out the possibility of malignancy.

Given the size of the tumor and the possible invasion of adjacent blood vessels highlighted by enhanced CT scans, the mediastinal biopsy, despite being performed multiple times, could not conclusively exclude the presence of an invasive malignant tumor. Considering the young age of the patient, we recommend further biopsy under thoracoscopy or mediastinoscopy to establish a definitive diagnosis. However, the patient insisted on surgery. We performed a median sternotomy to excise the anterior mediastinal mass (Fig. 2). Intraoperatively, we found the mass invading the pericardium, aortic arch, superior vena cava, and encasing the left and right innominate veins. After opening the pericardium, the tumor was carefully separated, and the affected pericardium was excised. Intraoperative rapid frozen section pathology indicated benign tissue cell proliferation, ruling out malignant tumor. Due to the intricate vascular involvement and the nature of the pathology, vascular replacement was deemed unfavorable and therefore not pursued. The postoperative pathology revealed significant tissue cell proliferation with lymphocyte and plasma cell infiltration, suggesting RDD. By immunohistochemistry, histiocytes were positive for S100, CD68, Ki-67, Vimentin, Kappa, and IgG, and were negative for CD1a, CK, CD34, Desmin, and ALK (Fig. 3). These morphologic and immunophenotypic findings were diagnostic of RDD. The patient recovered well without any postoperative complications and discharged on the 6th day after surgery with removal of drainage tubes. The patient did not receive any steroid treatment postoperatively. During follow-up, magnetic resonance imaging scans revealed no signs of tumor recurrence. At 24 months post-operation, the patient remained asymptomatic with no evidence of recurrence.

Discussion

RDD is a rare non–Langerhans cell histiocytosis, having a reported prevalence of 1:200,000, and it mostly occurs in young individuals [2]. The exact etiology of RDD is unknown and probably multifactorial. It may be associated with autoimmune diseases (lupus, idiopathic juvenile arthritis, autoimmune hemolytic anemia) [4], tumors (Hodgkin's lymphoma and non-Hodgkin's lymphoma) and infections such as varicella-zoster virus, human herpesvirus 6 [5], Epstein–Barr virus (EBV), cytomegalovirus [4], Parvovirus [6], Klebsiella [7], and Brucella [8], as well as genetic factors (reported germ-line mutations in SLC29A3 in familial cases) [4]. In this case report, we describe a patient with a history of ankylosing spondylitis. To date, very few reports in the literature have described RDD in conjunction with a history of ankylosing spondylitis. The combination of ankylosing spondylitis with lymphadenopathy (sinus histiocytosis) was first reported in 1986 [9]. In 2006, a hospital in Taiwan reported a patient with both RDD and ankylosing spondylitis [10]. As an autoimmune disease, the potential association between ankylosing spondylitis and RDD remains unclear. We report what may be the

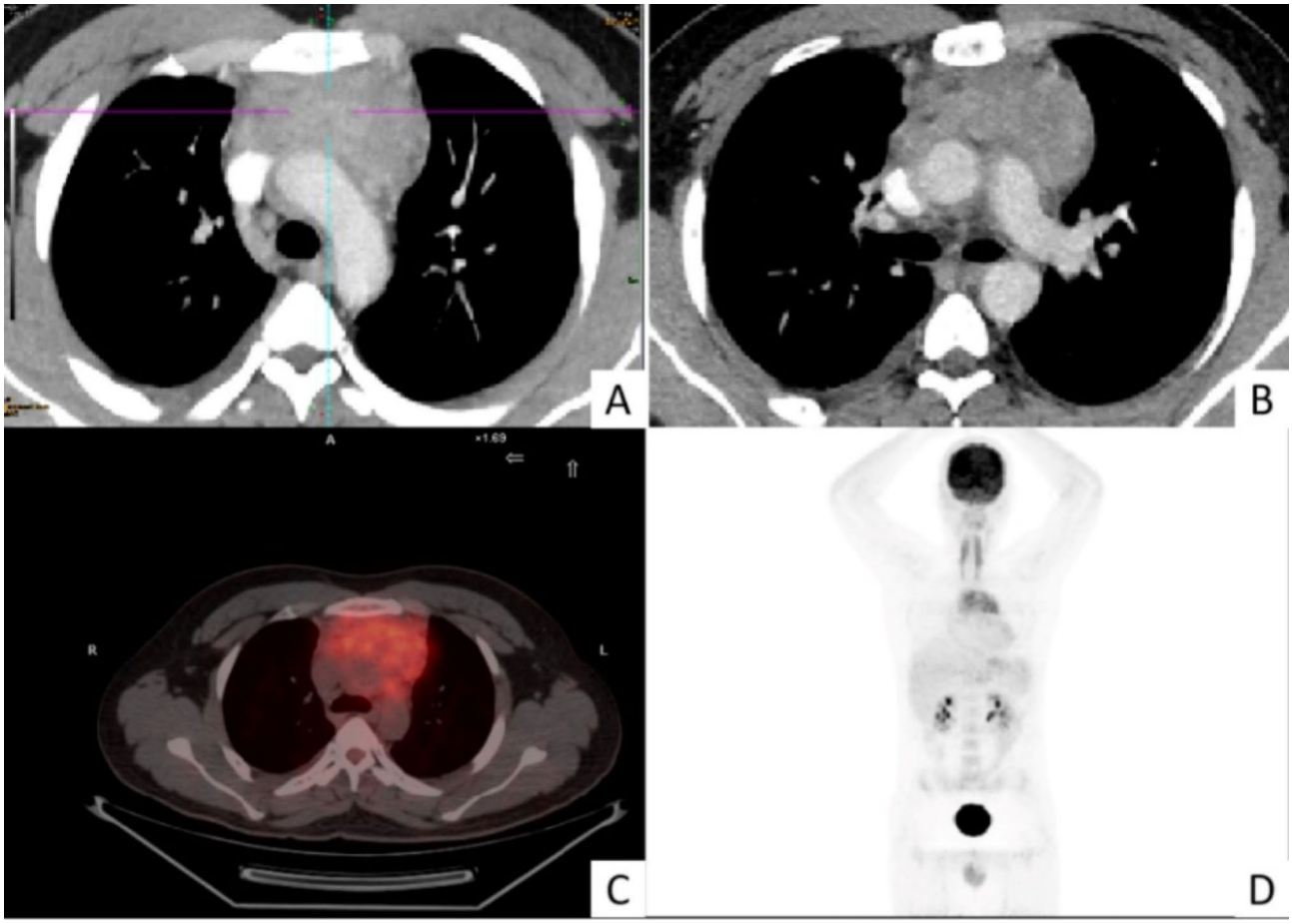

Fig. 1 (**A**, **B**) Contrast-enhanced computed tomography showed a large mass visible in the anterior mediastinum, accompanied by uneven enhancement. (**C**, **D**) Positron emission tomography scan. 18 F- fluorodeoxyglucose (FDC) uptake on mediastinal mass

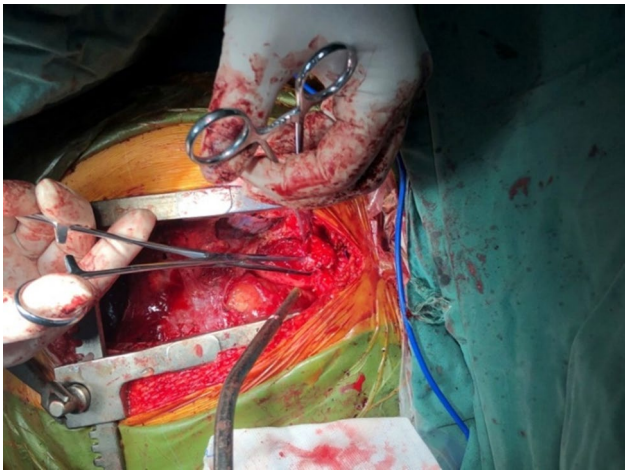

Fig. 2 Midline thoracotomy performed for tumor resection with pericardial opening

first case of intrathoracic RDD in a patient with concurrent ankylosing spondylitis, highlighting this rare but valuable case that provides relevant evidence for further investigation into the relationship between RDD and immune-mediated diseases such as ankylosing spondylitis.

The diagnosis of RDD can be particularly challenging. Patients diagnosed with RDD may exhibit clinical manifestations including fever, night sweats, and weight loss. Additionally, they may present with non-specific laboratory abnormalities such as anemia, leukocytosis with neutrophilia, and polyclonal hypergammaglobulinemia [3, 4]. In lymph node cases, CT shows enlarged nodes with uniform enhancement. Intrathoracic RDD appears as nodular consolidation in lung lobes, possibly with pleural effusion, fibrosis, or nodules [1]. On T1-weighted MRI, affected lymph nodes resemble muscles in signal intensity, while on T2-weighted MRI they appear hyperintense with uniform enhancement. 18 F-FDG PET/CT shows increased metabolic activity [11]. Due to the lack of specific laboratory and radiological findings, early diagnosis of RDD is notably formidable.

Isolated thymic RDD is exceedingly uncommon, as the majority of intrathoracic RDD cases manifest as pulmonary or peritracheal masses and pleural lesions [12, 13]. RDD typically exhibits inert growth, with only rare cases

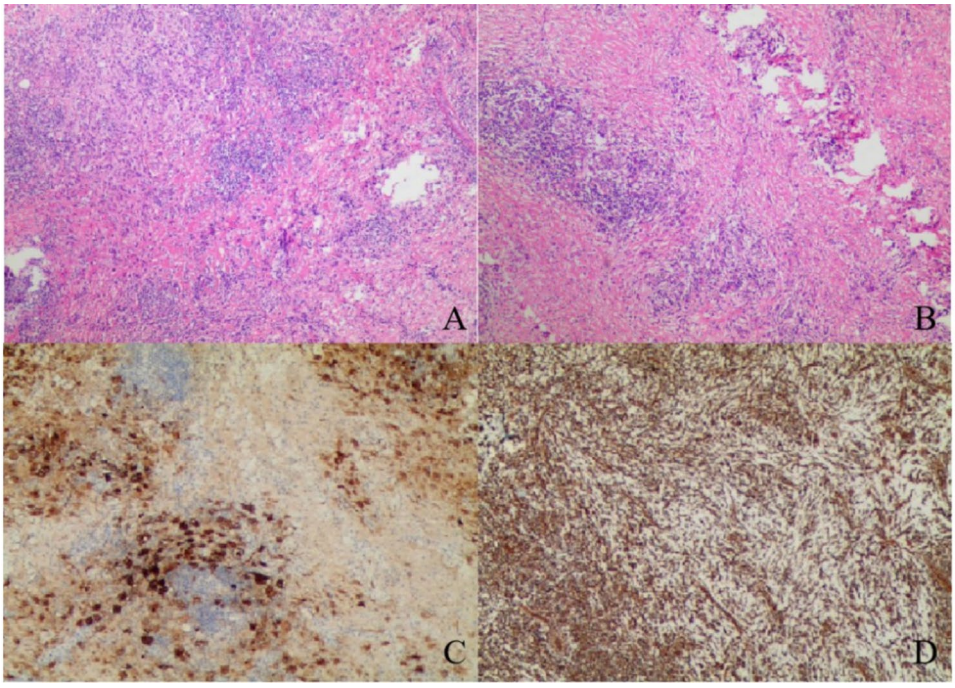

Fig. 3 (**A**, **B**) The morphological characteristics of the mass and its immunohistochemical features. Histologic examination 100×. Nodal Rosai-Dorfman disease shows marked fibrosis which may be storiform. (**C**) S100 protein immunohistochemical stain 100×. The S100 highlights the histiocytes as well as the emperipolesis. (**D**) CD68 protein immunohistochemical stain 100×. The CD68 highlights the histiocytes

showing invasive growth. Mediastinal RDD represents an exceedingly small fraction, comprising just 0.5% or less of all lesions occupying the mediastinal space [14]. Currently reported anterior mediastinal RDDs are mostly isolated mediastinal masses, with less vascular invasion [15, 16]. RDD in the thymus shares similarities in appearance, FDG avidity, and distribution with several other diseases. It poses a wide range of potential differential diagnoses, including thymoma, lymphoma, metastatic disease and proliferative inflammatory diseases like inflammatory myofibroblastic tumor [12]. Zhang et al. [16] also reported a case of RDD presenting as an anterior superior mediastinal mass. Initially, they diagnosed it as thymoma, but the final pathological result confirmed it to be a mediastinal RDD with KRAS mutation. In our clinical practice, huge anterior mediastinal masses are often invasive, especially thymomas, which typically show vascular infiltration on enhanced CT and increased FDG uptake on PET-CT [11]. In this case, the patient did not show typical clinical symptoms of RDD or abnormal results from preoperative laboratory tests. Two previous mediastinal biopsies did not provide conclusive evidence for a diagnosis, posing a challenge to diagnosis. Due to the patient's young age, we proposed a mediastinal biopsy under thoracoscopy, but the patient refused. Considering the typical signs of malignancy and vascular invasion in the anterior mediastinal mass, we eventually opted for surgical treatment.

Diagnosis of RDD requires sufficient tissue samples, and biopsies should be reviewed by a pathologist familiar with RDD [3].Histologic examination of nodal RDD reveals sinus expansion by large histiocytes, with abundant pale or "watery-clear" cytoplasm (a large hypochromatic nucleus with a prominent nucleolus [3]. Extranodal lesions exhibit more fibrosis, fewer RDD histiocytes, and less emperipolesis. The immunophenotype of RDD histiocytes includes positivity for S100 and fascin, variable positivity for CD68, CD163, CD11c, and CD14, and negativity for CD1a and CD207. Plasma cells express markers such as CD38, CD138, MUM1, and IgG4 [1–4]. BCL-2 and OCT2 are commonly expressed in RDD cases [17, 18]. As primary thymic RDD is extremely rare, clinicians and radiologists often find it difficult to make a definite diagnosis without definitive pathological findings. RDD exhibits typical cytological features, making fine needle aspiration cytology (FNAC) a commonly used diagnostic tool for RDD. However, diagnosing extranodal RDD through FNAC may be more challenging. In our case, despite two attempts at needle biopsy, the limitations of the FNAC meant that we did not obtain definitive evidence of RDD in the early stages of treatment. Its nonspecific clinical presentation, subtle variations, atypical features, and rarity may lead cytopathologists to overlook or misinterpret the condition. In contrast to the limited tissue samples obtained through FNAC, thoracoscopic biopsy yields tissue specimens that are more likely to preserve adequate tissue architecture. Through direct visual

inspection and multi-angle sampling, it offers more comprehensive and diverse diagnostic information. Therefore, we consider that for young patients with mediastinal masses difficult to diagnose conclusively via FNAC, further refinement with thoracoscopy or mediastinoscopy biopsy may be a more appropriate diagnostic step.

Treatment for RDD varies depending on individual clinical circumstances. While spontaneous resolution occurs in 50% of cases, about 10% may face complications leading to death [1]. Asymptomatic patients can be monitored, and surgical resection is an option for those with specific symptoms or solitary extranodal lesions. Systemic treatments such as glucocorticoids, sirolimus, radiotherapy, chemotherapy, and immunomodulatory therapy may be viable options for patients with multifocal or unresectable lesions [1, 4, 19]. Immunotherapy with TNF-α inhibitors, thalidomide, and lenalidomide have also been attempted due to elevated levels of TNF-α and interleukin-6 in RDD patients [4, 19]. For inoperable and refractory RDD, treatment with thalidomide may be an exciting option. The report by Hoyo-Muñoz et al. [20] suggests that thalidomide therapy may induce remission in patients who have failed fourth-line systemic chemotherapy. If relevant driver mutations are identified, targeted therapies like tyrosine kinase inhibitor(imatinib) [21], BRAF inhibitor (dabrafenib) [22], and MEK inhibitor (trametinib) [23] have shown some efficacy in treating refractory RDD patients. Overall, a multidisciplinary approach is recommended for optimal outcomes.

Conclusion

This case report describes a patient with a history of ankylosing spondylitis, who presented with an anterior mediastinal mass exhibiting features of an invasive malignant tumor. It emphasizes the importance of considering Rosai-Dorfman disease (RDD) in the differential diagnosis of anterior mediastinal masses. Thoracoscopy or mediastinoscopy biopsy can improve diagnostic accuracy. Obtaining clear preoperative pathological evidence enables the formulation of more effective multidisciplinary treatment strategies. Our study contributes to an improved understanding among clinicians regarding the diagnosis and treatment of intrathoracic RDD, particularly in young patients, and provides relevant evidence for future exploration of potential associations between RDD and ankylosing spondylitis.

Abbreviations

RDD	Rosai-Dorfman Disease
CT	Computed Tomography
PET	Positron Emission Tomography
EBV	Epstein-Barr virus
FNAC	Fine Needle Aspiration Cytology

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Author contributions

Conceptualization, Methodology, Writing – Original Draft Preparation J.X. and T.X.; Investigation, Writing – Original Draft Preparation Z.L.; Investigation, Writing – Review & Editing J.Z.; Supervision, Funding Acquisition, Writing – Review & Editing S.J. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This project has been approved by the Ethics Committee of the First Affiliated Hospital of Soochow University, and has obtained written consent from the patient.

Consent for publication

Written informed consent has been obtained from the patient and their family members for publication of relevant clinical information by the authors in pertinent medical publications.

Competing interests

The authors declare no competing interests.

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