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Case Report

Infantile Rosai-Dorfman disease: an unusual case of neck swelling and a literature review

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Abstract: Rosai-Dorfman disease (RDD) is a benign, rare histiocytic disorder presenting as a wide clinical spectrum, which mainly affects bilateral dilated lymph node enlargement. This study aimed to show an infantile RDD and review the clinicopathologic features, imaging, and histological features of RDD, including pitfalls in diagnosis. We report here an infant who had a 3-month history of painless bilateral cervical masses progressed to tracheal compression. Postoperative immunohistochemical results with positive characteristic staining of CD68 and S-100, negative for CD1a, which helped to determine the diagnosis. This peculiar case is the youngest case of RDD presenting with painless massive lymph node progressing to severe dyspnea due to tracheal compression. The optimal treatment still remains challenging. Future research should focus more on etiology and pathogenesis of RDD, especially relapsing cases.

Keywords: Rosai-Dorfman disease, neck masses, infant

Introduction

Rosai-Dorfman disease (RDD) was first reported by Rosai and Dorfman in 1969 [1]. RDD was defined as being quite distinct with non-neoplastic histioproliferative disorders of dubious etiology that is predominantly accompanied with bilateral, massive, and nontender lymphadenopathy in the neck [2]. Clinically, it can also be found extranodally and usually is associated with a wide spectrum of clinical features such as fever, anemia, leukocytosis, and elevated inflammatory markers including polyclonal hypergammaglobulinemia and erythrocyte sedimentation rate [3]. The most frequent sites of extranodal RDD are skin, central nervous system, upper respiratory tract, bone, genitourinary system, oral cavity, breast, soft tissue, eyes and ocular adnexa, salivary gland, tonsil, and heart [4-6].

Even though RDD is considered as a benign and self-limited disease in most cases, fatalities can also happen. Due to its huge size and location, it can mimic malignancy. Accurate diagnosis of RDD relies on key histopathologic features characterized by the emperipolesis presented, which contain large histiocytes with abundant clear cytoplasm and engulfed inflammatory cells or S-100 immunostain positivity [7, 8]. The differential diagnoses of RDD usually include Langerhans cell histiocytosis, granulomatous lesions, Hodgkin lymphoma, and some special infections causing adenopathy (tuberculosis, atypical mycobacteria, toxoplasma, rhinoscleroma cytomegalovirus, and Epstein-Barr virus) [9].

We reported the youngest case of RDD which primarily presented with almost total tracheal compression, causing a life-threatening situation in the course of the disease and needed emergency tracheal intubation. In this case, diagnostic pitfalls and therapeutic challenges surrounding this disease were repeated because of the clinical characteristic and laboratory tests supporting a diagnosis of lymphadenitis.

Case presentation

We reported an 8-month-old boy who presented to our outpatient department with com-

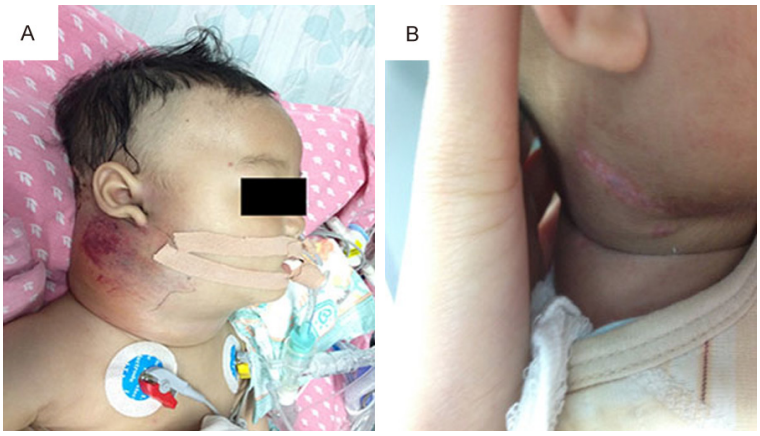

Figure 1. A. On admission, the patient showed massive cervical lymph node enlargement with obvious edema and bleeding treated by intubation and mechanical ventilation. B. Postoperative photograph showing bilateral cervical lymphadenopathy reduced significantly and removed intubation.

plaints of gradually enlarged cervical lymph nodes of 3-months with coughing and phlegm for one week. The cervical mass progressed to swell when the patient had a fever or other infectious signs but shrink when antibiotics were used. He had a history of pneumonia, and had fevers, chills, or other constitutional symptoms such as poor appetite malaise. A good response to antibiotics and recurrent episodes of enlarged cervical lymph nodes led to being highly suspicious for infective diseases or malignancy. On the second hospital day, the patient, whose cervical masses swelled with severe bleeding appeared with progressive cyanosis and serious breathing difficulty with airway obstruction. Immediate emergency tracheal intubation was administered (**Figure 1A**).

On physical examination, we found bilateral cervical enlarged lymph nodes the size of 2×3 inches, accompanied by tenderness, inflamed hot pain, and unclear boundaries. Lymph nodes were also palpated in groin and axillary regions. His blood investigations were entirely abnormal including significantly increased white blood cells of 33.7×10^9/L (ref: 4-10 10^9/L), the erythrocyte sedimentation rate (ESR) of 34 mm/h (ref: 0-25 mm/h), procalcitonin of 2.85 ng/ml (ref: 0-0.5 ng/ml), C-reactive protein (CRP) of 179.3 mg/L (ref: 0-10 mg/L), and IgM antibody of Epstein-Barr virus of 82.5 u/ml (ref: 0-20 u/ml). Bronchoalveolar lavage fluid (BALF) indicated Pseudomonas infection. The cervical computed tomography (CT) demonstrated that diffuse masses with solid or cystic arising from lymph nodes and extrinsic compression of oropharyngeal airway corresponding to swollen area (**Figure 2**).

A biopsy was performed on a cervical node as an initial suspected diagnosis of chronic lymphadenitis made on significantly increased infection index. The core biopsy specimens revealed granulation tissue with extensive acute and chronic inflammation. Postoperative histopathological analysis of the cervical revealed that emperipolesis (lymphocytes phagocytosis by histiocytes) was abound in the specimens (**Figure 3**). In addition, hemorrhage necrosis was widely spread in lymph nodes and there was a massive amount proliferation of mild polymorphous histiocytes, some of which contained the engulfed intact lymphocytes in their cytoplasm. The immunohistochemistry of the specimen confirmation reported histiocytes that were positive staining for S-100 and CD-68, but they were negative for CD1a, MPO, CD20, and CD3 (**Figure 4**). The histopathological diagnosis was concordant with the clinical symptoms and photographic results. Based on histological and immunohistochemical analysis of the excision, the diagnosis of RDD was confirmed.

After the patient was started on 80 mg daily of methylprednisolone for 3 days, his symptoms were relieved with the standard of extubate achieved (**Figure 1B**). Ultimately, we gradually tapered the dose of steroids and long-term low dose predenisolone as maintenance therapy for 1 year. After a 2-year follow-up, the patient had no recurrence and no further treatment was requirement.

Discussion

RDD is a rare, benign, and self-limited proliferative disease with about 1,000 cases reported in the English language literatures by 2014 [10]. Foucar et al. reported a clinical course of stable disease in 54%, spontaneous regression in 21%, and progressive disease in only 1% of the patients [11]. It is important to recognize

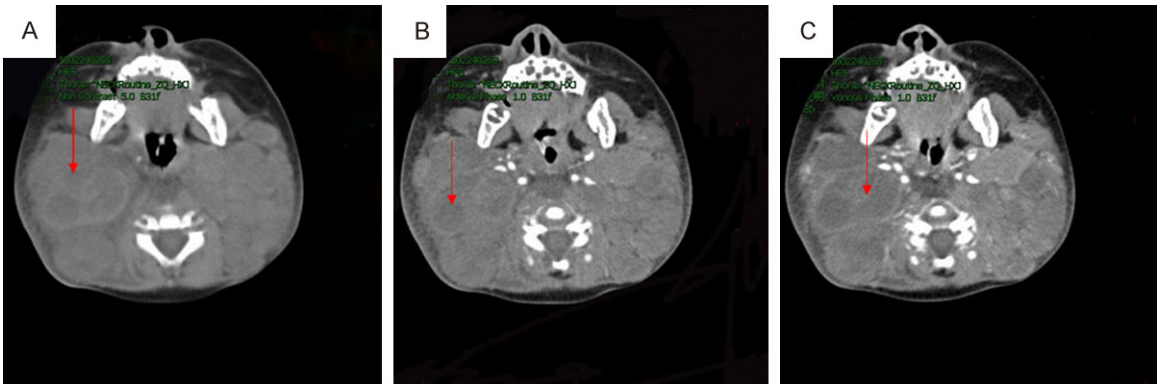

Figure 2. The patient underwent a cervical computed tomography (CT) which presented diffuse and multiple lymphadenopathies of the bilateral neck with the airway and vascular compression and in the CT plain scan (A), arterial phase (B), and venous phase (C).

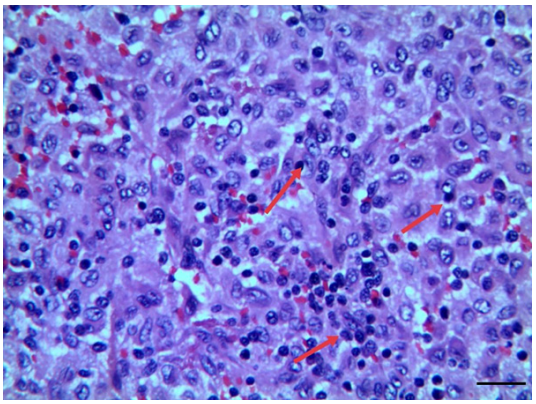

Figure 3. Histopathology images of RDD. Emperipolesis is displayed with intact lymphocyte or plasma cell engulfed within large histiocyte cells and normal lymph nodes construction has been destroyed with hemorrhagic infarction. Bar = 20 μm.

that RDD can mimic malignancy and be fatal in exceedingly rare cases. This disease can occur at any age and has a higher prevalence in males, with the mean onset age of 20.6 years [12]. Massive, painless cervical swollen lymph nodes and histiocytic infiltration of the lymph node are the most hallmark presenting symptoms. It usually is accompanied with other systemic symptoms such as a fever, malaise, night sweats, and weight loss in the short term [4, 12]. Extranodal involvement was common, and 43% of cases were extranodal and most common sites were skin, upper respiratory, orbits, testes, and bones [11].

The imaging findings and laboratory data of RDD are nonspecific, so the diagnosis of RDD can be challenging and usually requires histological confirmation. Histopathologically, RDD characteristically exhibits the existing of emperipolesis which is the hallmark of RDD and the prominent histologic feature [13]. The biological phenomenon of emperipolesis as the diagnostic investigation is the nondestructive phagocytosis of multiple types of complete bone marrow cells, such as lymphocytes, plasma cells, erythrocytes, or polymorphonuclear leukocytes. However, emperipolesis which limited in a distinguishing feature of RDD is not distinct to RDD and can also appear in hematological disorders, including lymphoma, Langerhans histiocytosis, hemophagocytic syndrome, and infection [9]. Immunostains in large foamy histiocytes of RDD can be positive for S-100 and CD68 while CD1a is typically negative and are conducive to distinguish RDD from other lesions, such as LCH in which the histiocytes are CD1a-positive [14]. Some studies pointed out that RDD might be an unusual variant of LCH [10].

RDD has been classically considered a non-neoplastic lesion of unknown exact aetiology. Some pathogens such as Epstein-Barr virus, the human papillomavirus-6, Brucella, Polyomavirus, Parvovirus B19, and cytomegalovirus played a role in the pathogenesis through immune dysregulation, or an aberrant exaggerated immune response results in histiocyte expansion and activity [7, 12]. The pathogenesis of RDD is likely multifactorial and involved with autoimmune diseases, post-infectious conditions, hematological malignancies, and immune dysfunction [10]. The disturbance of homeostasis either preceding or after the

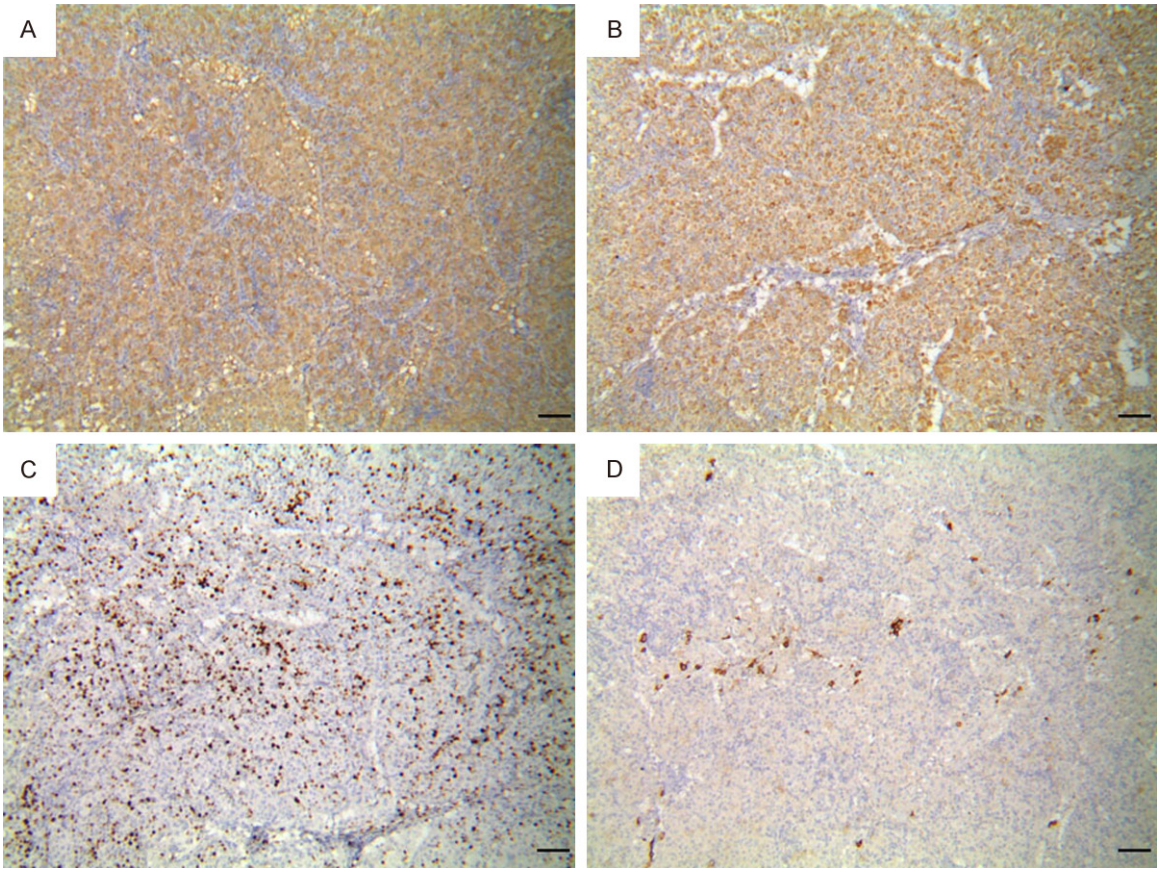

Figure 4. Immunohistochemical staining of RDD. A. S-100 was all (+). B. CD68 was all (+). C. ki-67 was about 10-20% (+). D. CD1 a was all (-). Bar = 50 μm.

onset of RDD which induced by pathogens usually contributes to the initiation of the immune disorder and results in a poor prognosis, sometimes even a fatal outcome. In our case the cervical mass rapidly reduced and infectious indicators lowered after meropenem was used at the beginning of therapy, but sudden discontinuation of meropenem resulted in longer or more severe symptoms. The first step of treatment is to actively control the infection and reduce inflammatory activation of cytokines to recover immune balance.

The standard treatments for RDD are still unknown and include surgical resection, chemotherapy, radiotherapy, steroids, and low dose interferon [12, 15]. RDD is a self-limited clinical course and the prognosis is generally favorable. Fifty percent of patients often undergo close observation or conservative treatment aimed at controlling local manifestations in the absence of vital organ involvement [10]. Some cases also indicated that the RDD might affect multiple organ systems and be highly fatal [2]. Shrirao et al. found that surgical excision is recommended for symptomatic, progressive, and surgically accessible lesions, and systemic corticosteroids, chemotherapy, or radiotherapy is preferred in life threatening cases [15]. Constitutive activation of the mitogen-activated protein kinase (MAPK) pathway as a crucial pathogenic mechanism in RDD, Jacobsen E initiated treatment with cobimetinib which is MAPK kinase (MEK) inhibitors targeting RDD, A repeat CT scan showed a substantial response [16].

We presented the youngest rare case with RDD which caused massive lymph nodes with compressive oropharyngeal airway in a life-threatening situation. Definitive diagnosis requires a histopathology feature and immunohistochemistry (IHC) which included positive for CD68 and S100 and negative for CD1a. This case had systemic symptoms and was dependent on steroid-treatment during the strict follow-up peri-

od. The CRP was elevated in our case and had a positive relation with the mass size, and a significant increase when the steroid was stopped. The certain diagnosis of RDD is debatable. Only elaborate histopathologic features and IHC findings are considered as the key points for the diagnosis of RDD.

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An informed consent was obtained from the patient for publication. The article was approved by the institutional research ethics committee of Guangdong Medical University.

Disclosure of conflict of interest

None.

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