

Case Report

Extranodal Rosai-Dorfman disease presenting as recurrent soft tissue masses: a case report and review of literature

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Abstract: Rosai-Dorfman disease (RDD) is a rare benign disease which usually characterized by painless cervical lymphadenopathy and systemic manifestations. Currently no guidelines are available for the management of this disease. Here a very rare case of RDD in a 14-year-old female presenting as recurrent soft tissue masses on the thigh is presented. The patient received repeatedly surgical removal of the masses, and a favorable clinical outcome was obtained. The present case is also discussed in light of literature review in terms of clinical features, histological origin, diagnosis, differential diagnosis, treatment and prognosis.

Keywords: Soft tissue Rosai-Dorfman disease, recurrent, diagnosis, treatment

Introduction

Rosai-Dorfman disease (RDD) is a rare benign histiocytosis disease, which was first reported by Rosai and Dorfman in 1969 [1]. It is usually present with painless cervical lymphadenopathy, fever, leukocytosis, and hypergamma globulinemia [2]. RDD mainly occurs in lymph nodes. Less than 20% of patients have extra-lymphatic lesions without lymphadenopathy, while less than 3% of patients have soft tissue RDD [3, 4]. Here, a very rare case of STRDD in a 14-year-old female presenting as repeatedly treated with recurrent painless masses on the thigh is reported. The Ethics Committee of Huzhou Central Hospital approved this report, and a written informed consent was obtained from the patient.

Case report

A 14-year-old female presented to Huzhou Central Hospital with a 2-years history of an enlarging right thigh mass in August 2011. The mass increased progressively, without pain, redness or fever, and no weight loss during the period. She denied the history of hypertension, diabetes or tuberculosis. Family history was no different. Physical examination revealed a

tough mass on the inner side of the right thigh, about the size of the egg, partially protruding the surface of the skin. The skin at the mass was slightly cyan, the border was clear, no tenderness, and the activity was acceptable. No abnormalities in chest, abdomen, and pelvis computed tomography (CT) scan. No abnormalities in blood routine, liver, and kidney function were observed. Ultrasonography of the mass indicated there was a substantial mass in the adipose layer of the middle right thigh (**Figure 1**), and the CT enhancement of the right thigh suggested that there was multiple flaky density in the subcutaneous adipose layer of the right thigh, with poorly defined boundary, and fibrotic lesions may occur (**Figure 2**).

On the 3rd day after hospitalization, the patient underwent right thigh mass resection. Intra-operative cryosection showed fibrous tissue hyperplasia, lymphocytic infiltration, but it was not clear whether the mass was benign or malignant. One week after operation, paraffin pathological results showed that the lesions were consistent with Rosai-Dorfman disease (Two masses, the sizes were 7*7*4 cm and 5*3*2.8 cm, respectively). The surrounding margin was positive. Immunohistochemistry: S-100 (+), CD68 (+), CD1a (-), CD21 (-), CD99 (+), ALK-1

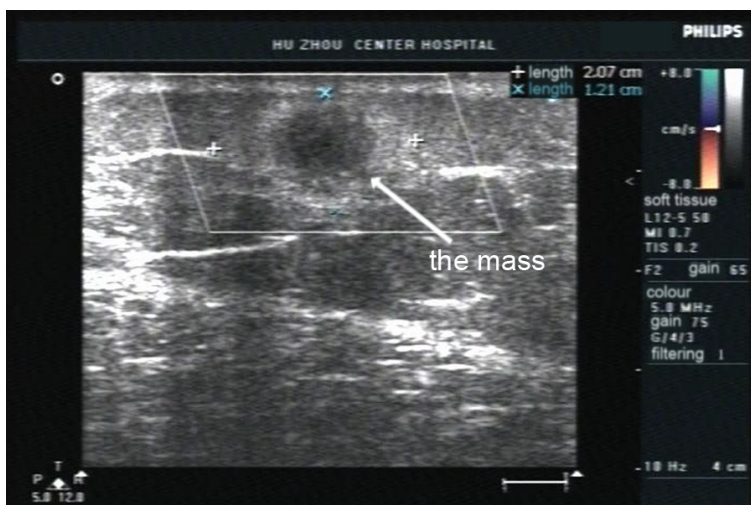


Figure 1. Ultrasonography of STRDD. Substantial mass in the adipose layer of the middle right thigh.

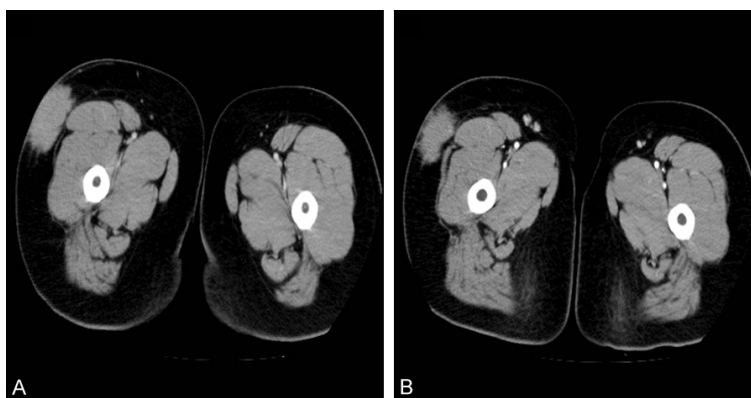


Figure 2. CT enhancement of STRDD. A. Multiple flaky density in the subcutaneous adipose layer of the right thigh, and the mass boundary is not clear. B. After injection of iodinated contrast agent, enhancement of the mass can be noted.

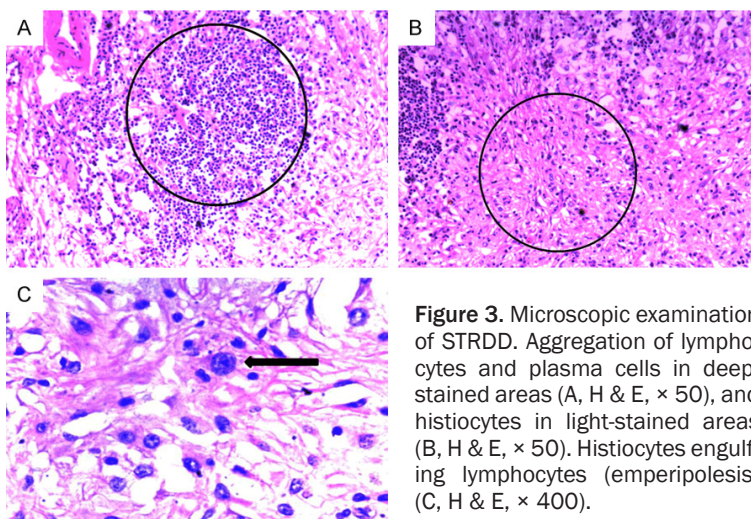


Figure 3. Microscopic examination of STRDD. Aggregation of lymphocytes and plasma cells in deep-stained areas (A, H & E, × 50), and histiocytes in light-stained areas (B, H & E, × 50). Histiocytes engulfing lymphocytes (emperipolesis) (C, H & E, × 400).

(-), Vim (+), SMA (-) (Figures 3, 4). Therefore, the patient underwent extended resection. Postoperative pathology showed that the incision margin was negative. After the incision healed, she was discharged without other treatment.

In July 2012, a mass was found in the left thigh during the follow-up period. The magnetic resonance imaging (MRI) enhancement of the left thigh showed that 1.6*1.5 cm abnormal signal type round nodule was seen in the subcutaneous fat of the upper left thigh with a low signal intensity on T1-weighted image and high signal intensity on T2-weighted image. Diffusion weighted image (DWI) showed a high signal intensity, the edge was not smooth, the surrounding space was not clear, and the lesion was strengthened after the enhancement, considering the performance of sinus histiocytosis (Figure 5). Therefore, the mass resection was performed again, and the conventional pathology was in accordance with RDD, and the size of the mass was about 2*1*1 cm.

The patient continue to be followed up regularly by ultrasonography. One year later (July 2013), the right thigh mass was found again (not in the original surgical area). Further MRI enhancement of the right thigh prompted two abnormal signal nodes in the subcutaneous fat of the right upper thigh. The stove was about 1*1*1 cm in size, respectively. The mass resection was performed for the third time. The postoperative pathology still considered RDD.

After continued follow-up, no other special treatment were carried out and the patient has

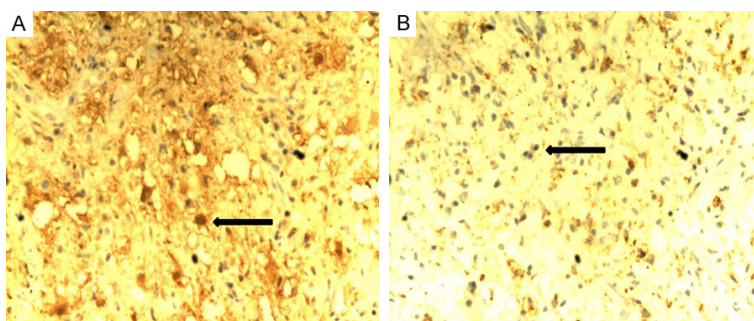


Figure 4. Immunohistochemical staining of STRDD. Immunohistochemical stains shows positive for (A) S-100 and (B) CD68 ($\times 200$).

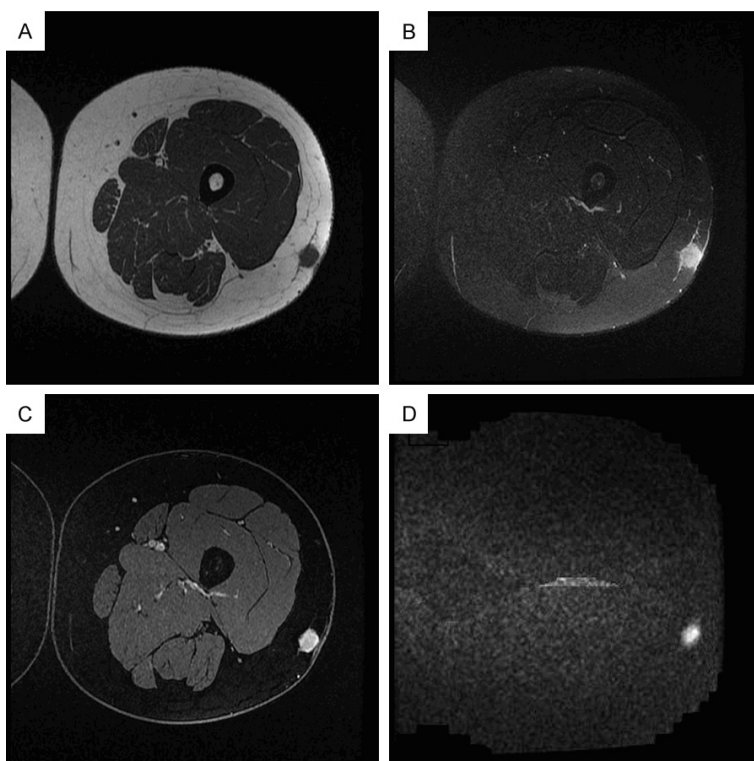


Figure 5. MRI enhancement of STRDD. A. The mass has a low signal intensity on T1-weighted image. B. High signal intensity on T2-weighted image. C. After injection of gadolinium contrast agent, a strong enhancement can be noted. D. High signal intensity on DWI.

been in generally good condition. No mass is found in the whole physical examination.

Discussion

Clinical features

Rosai-Dorfman disease, also known as sinus histiocytosis with massive lymphadenopathy (SHML), was first described systematically by Rosai and Dorfman in 1969. It is a rare benign disease with typical clinical manifestation of painless enlargement of bilateral cervical ly-

mph nodes with a protracted clinical course in up to 90% of the patients [1, 2]. Clinical studies on the maximum sample size of RDD were based on 423 cases of clinical data collected by Foucar, Rosai and Dorfman in 1990, of which only 13 were simple soft tissue lesions without lymph node and other organ involvement, and patients with soft tissue involvement without lymphadenopathy accounted for 3% of all RDD patients [2]. Lymph node RDD occurred in young male patients, while soft tissue RDD cases were older (24 to 66 years old), and female gender advantage was nearly 3:1. It is basically consistent with 18 clinical studies reported by Al-Daraji, W [5]. Soft tissue RDD (STRDD) usually has no obvious symptoms in clinical practice, it only shows local soft tissue mass, occasionally mild tenderness. It can be an isolated solid mass or multiple masses. In this case, the patient was also treated for recurrent masses, no other symptoms during the onset. When it comes to vital organs, intervening measures include corticosteroid management, chemotherapy, radiation therapy, and surgical resection. Due to its low incidence, there is no standardized treatment plan, and the prognosis is still not clear.

Histological origin

The cause of RDD is still unclear, and some scholars believe that it may be related to HHV-6, EBV or SV40 infection [6-9]. Some scholars also have observed that the disease often coexists with immune-mediated diseases such as asthma, systemic lupus erythematosus, rheumatoid arthritis and hemolytic anemia, and thus the disease is considered to be an autoimmune disease. The relationship between this disease and IgG4 disease is still controversial [10, 11]. Cloning analysis by Paulli M by polymerase chain reaction suggests that RDD

is not a neoplastic disease but is more prone to inflammatory diseases [12]. According to the extent of lesion involvement, RDD is divided into lymph node type, extranodal type, and mixed type (the lymph node and extranodal organs are involved at the same time). The orbit, eyelids, skin, bone, central nervous system, and soft tissue are the most frequently involved sites in the extranodal RDD, but the incidence of soft tissue RDD is very low, accounting for less than 3% of patients [3, 13-16].

Diagnosis

Because the clinical manifestations, laboratory and imaging examinations of patients with soft tissue RDD have no obvious specificity, this disease is mainly diagnosed by pathological examinations. Although the soft tissue RDD outside the lymph nodes is significantly different from the typical lymph node involvement RDD, the pathological findings are consistent with the characteristics of typical lymph node RDD. Soft tissue RDD histopathology is characterized by diagnostically significant RDD cells, which are mostly fusiform or polygonal, with large cell volume, rare nuclear division, active cytoplasmic phagocytosis accompanied by the proliferation of a large number of collagen fibers, and the proliferating collagen and histiocytes form a typical "striated" structure. A typical "striated" structure consists of fiber-separated and elongated spindle-shaped tissue cells, and obese fusiform tissue cells are interspersed between rich collagen fibers. In the cytoplasm of histiocytes, swallowed lymphocytes with different numbers and complete morphology can be seen, which is called emperipolesis of lymphocytes [10]. However, the RDD in the lymph nodes often has lymphatic sinus expansion accompanied by cell proliferation in the sinus, and the emperipolesis phenomenon is easier to find. The extranodal type lack true lymphatic sinus structure, and the emperipolesis phenomenon is obviously reduced, and there is more significant fibrosis in the interstitium [17]. Immunohistochemical staining showed that S-100 and CD68 were expressed in the lesion cells, while negative staining of CD1a, CD21 and CD35 suggested that the lesion cells had no dendritic cell characteristics [18-20]. In this case, the immunohistochemical results were consistent with this conclusion. Therefore, the "striated" structure, emperipolesis of lympho-

cyte, and S-100, CD68 positive are characteristics for the diagnosis of RDD [21, 22].

Differential diagnosis

Pathologically, it is also necessary to differentiate from the following diseases: ① Fibrohistiocytic tumors of soft tissue: Benign fibrous histiocytoma is characterized by larger nuclear cytoplasm and deeper staining. The "striated" structure is more typical, but there is no lymphocyte emperipolesis phenomenon. Dermatofibrosarcoma protuberans, malignant fibrous histiocytoma has more obvious anaplastic, and pathological division of nucleus can be seen. Inflammatory malignant fibrous histiocytoma can have a typical "striated" structure and a large amount of inflammatory cell infiltration. However, the anaplasia in neoplastic tissue are obvious. Immunohistochemical staining of S-100 protein positively contributes to the establishment of soft tissue RDD when histology is difficult to identify. ② Langerhans cell histiocytosis (LCH): LCH consisting of varying amounts of eosinophils, histiocytes, neutrophils and small lymphocytes with distinct cell margins and pink granular cytoplasm with Birbeck granules. No emperipolesis is found. Immunohistochemistry of LCH shows S-100 and CD1a positive. ③ Lymphoma involving the lymphatic sinus: Such as anaplastic large cell lymphoma, diffuse into lymphocytes infiltration, cell morphology is single or polymorphic, obvious atypia, but lack of a large number of tissue cells, no emperipolesis phenomenon. Immunohistochemistry shows that CD30 is positive. ④ Chronic inflammatory lesions: Chronic inflammatory changes dominated by lymphocyte under light microscopy. Fibroblasts and small blood vessels may proliferate. Histiocytes occasionally appear vacuolar, but small in size. Immunohistochemistry shows that S-100 protein is negative. ⑤ Granulomatous diseases: It includes juvenile xanthogranuloma and plasma cell granuloma, which is characterized by foam cells on the background of granuloma but no emperipolesis phenomenon. Immunohistochemistry shows that S-100 protein is negative. **Table 1** details a comparison of the pathology and immunohistochemistry appearance of soft tissue RDD and other soft tissue tumors. In conclusion, typical histiocytes and positive expression of S-100 protein and CD68 in RDD may be important for definitive diagnosis, which

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Table 1. Pathological characteristics of STRDD and other soft tissue tumors

	Rosai-Dorfman disease	Fibrohistiocytic tumors of soft tissue	Langerhans cell histiocytosis	Lymphoma involving the lymphatic sinus	Chronic inflammatory lesions	Granulomatous diseases
Pathology	RDD cells, “striated” structure, emperipolesis of lymphocyte	“striated” structure, pathological division of nucleus, no emperipolesis	varying amounts of eosinophils, histiocytes, neutrophils and small lymphocytes with distinct cell margins and pink granular cytoplasm with Birbeck granules, no emperipolesis	diffuse into lymphocytes infiltration, cell morphology is single or polymorphic, obvious atypia, but lack of a large number of tissue cells, no emperipolesis	chronic inflammatory changes dominated by lymphocyte under light microscopy, fibroblasts and small blood vessels may proliferate, histiocytes occasionally appear vacuolar, but small in size, no emperipolesis	foam cells on the background of granuloma but no emperipolesis
Immunohistochemistry	CD1a (-), S-100 (+), CD68 (+)	S-100 (-)	CD1a (+), S-100 (+)	CD30 (+)	S-100 (-)	S-100 (-)

S-100, protein 100% soluble in ammonium sulfate; CD68, cluster of differentiation 68; CD1a, cluster of differentiation 1a; CD30, cluster of differentiation 30.

can reduce misdiagnosis and missed diagnosis.

Treatment and prognosis

Due to the limited data available on RDD treatment, there is no uniform treatment standard. The disease has a certain self-limiting nature. It is reported that about 20% of untreated patients can recover on their own [23, 24]. Conservative treatment can be taken if there are no clinical symptoms or significant organ involvement. In the case of disease progression or life-threatening conditions, active treatment should be taken, whether it is inside the lymph nodes or outside the lymph nodes. Currently, a variety of methods have been reported in the literature, and for patients with extranodal RDD involving significant organs or local symptoms, it is advocated that surgical resection can rapidly improve the symptoms of patients [25, 26]. Adrenal glucocorticoids are the most commonly used drugs. About one third of RDD patients with lymph node and extranodal type have been reported to respond to hormone therapy [27]. There are also reports of radiation therapy [28], chemotherapy [29], and interferon therapy [30-32]. Shrirao N believes that comprehensive treatment plays an important role in improving the prognosis of RDD [33].

In all of the above treatment options, early surgical resection is preferred. On the one hand, early surgical resection can directly remove the lesion and send the pathology to confirm the clinical diagnosis and formulate the corresponding repair plan. On the other hand, in the early stage of the mass discovery, the volume is small, and the surrounding tissue destruction and invasion are relatively less. Early removal of the mass can reduce the difficulty of surgical resection, and also reduce the surgical incision and decrease postoperative incision scar. It has been reported that after complete resection of RDD or subtotal resection of important tissues attached to the surrounding area, it can effectively alleviate clinical symptoms and stabilize the condition, and it is suggested that regular follow-up should be conducted after operation without any special treatment [10, 34]. This case was followed up for 5 years without evidence of recurrence.

Conclusion

In summary, this is a very rare case of recurrent masses with histologically confirmed as

STRDD. The clinical manifestation of STRDD is lack of specificity. It needs to be differentiated from other soft tissue masses to avoid misdiagnosis. Pathological diagnosis is the only way to diagnose the disease. Surgical resection is also the most direct and effective treatment at present. Furthermore, close clinical follow-up of STRDD is necessary.

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Disclosure of conflict of interest

None.

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