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Research Article

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Clinical Manifestations and Radiological Characteristics on Rosai-Dorfman Disease: A Retrospective Observational Study

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Abstract

Background and Objective: *Rosai-Dorfman disease (RDD) are usually misdiagnosed because of rarity and nonspecific clinical and radiological features. The aim of our study is to explore the clinical and imaging characteristics of RDD to improve diagnostic accuracy.*

Methods: *Clinical and imaging data in 10 patients with RDD were retrospectively analyzed. 7 patients were underwent CT scanning and 3 patients were underwent MR examination.*

Results: *8 (8/10) patients presented with painless enlarged lymph nodes (LNs) or mass. 3 cases were involved with LNs, 5 cases were involved with extra-nodal tissues, and the remaining 2 cases were involved with LNs and extra-nodal tissue simultaneously. In enhanced CT images, enlarged LNs displayed mild or moderate enhancement, and 2 cases showed heterogeneous ring-enhancement. MR features of 3 patients with extra-nodal RDD, 2 cases showed a mass located in the subcutaneous and anterior abdominal wall respectively, and 1 case showed an intracranial mass. Besides, all lesions showed high signal foci on DWI images, and were characterized by marked heterogeneous enhancement with blurred edge. The dural/fascia tail sign and dilated blood vessels could be seen around all the lesions on enhanced MRI. Radiological features of 2 cases with LN and extranodal tissue involved, one case presented with the swelling and thickening of pharyngeal lymphoid ring and nasopharynx, meanwhile with enlarged LNs in bilateral submandibular area, neck and abdominal cavity, and also companied with osteolytic lesion in right proximal humerus. All these LNs displayed mild and moderate enhancement on CT images. Another case showed enlarged LNs in bilateral neck accompanied with soft tissue mass in the sinuses.*

Conclusions*: RDD occurred commonly in young and middle-aged men and presented with painless enlarged LNs or mass.RDD had a huge diversity of imaging findings, which varied with different location. The radiological features, such as small patches of high signal foci in the masses on DWI images, heterogeneous enhancement and blood vessels around the masses, are helpful in diagnosis of extranodal RDD.*

Keywords: Rosai-Dorfman disease; Computed Tomography; Magnetic Resonance Imaging; Lymph Node

Abbreviations

RDD: Rosai-Dorfman disease

CT: Computed Tomography

MR: Magnetic Resonance Imaging

DWI: Diffusion Weighted Imaging

WBC: White Blood Count

LNs: Lymph Nodes

ESR: Erythrocyte Sedimentation Rate

Introduction

Rosai–Dorfman disease (RDD) known as sinus histiocytosis with massive lymphadenopathy (SHML), was a rare but well defined clinicopathologic entity first described in 1969 [1]. Although originally described as a nodal disorder, extranodal disease has occurred in up to 40% of cases, with disease sites including the skin, central nervous system, upper respiratory tract, orbit and eyelid, and gastrointestinal tract [1, 2]. RDD usually presents as painless lymphadenopathy, fever, leukocytosis and weight loss [3]. Although lymph node is the most common sites of involvement, extra nodal disease is seen in up to 43% of RDD cases, leading to a wide range of imaging features. RDD is usually misdiagnosed

because of rarity and nonspecific radiological characteristics. Additionally, the etiology and pathogenesis of RDD are currently unknown, resulting in more challenge to RDD diagnosis. Here, the clinical and imaging data of 10 RDD patients were enrolled and analyzed retrospectively, in order to raise the awareness and improve the accuracy of preoperative diagnosis.

Materials and Methods

Patients

10 patients with RDD diagnosed by surgery and pathology in hospital from February 2010 to April 2018 were enrolled. These patients included 7 men and 3 women, whose age ranged from 8 to 54 years, with average age was (32±16) years. 7 patients were performed CT examination, and one of them was underwent X-ray examination simultaneously, the remaining 3 patients were underwent MR examination. Of the 10 patients, 5 cases occurred in the neck, 2 cases occurred in the subcutaneous tissue, 1 case occurred in the cerebellum, 1 case occurred in the liver, and the remaining 1 case occurred in the submandibular salivary gland. According to pathogenic involvement, RDD was classified into nodal, extra-nodal and mixed sub-types. All patients underwent surgery for total or subtotal resection of lesions. None of these patients underwent radio- or chemo-therapy post-operation.This retrospective study was approved by the institutional review board (Ethics committee of the Foshan First People's Hospital).

Imaging examination

MRI

Patients underwent MRI examination with 3.0T MR scanner (GE Signa Excite HD-MR imaging system, USA) .The standard institutional imaging protocol for 3 patients included high-resolution spin-echo (SE) T1-weighted(T1WI) and fast spin-echo (FSE) T2-weighted (T2WI) imaging with 1mm spacing, 5mm sections, 2 to 3 number of excitation (NEX), field of view (FOV) 240x240mm. SE-T1WI imaging acquisition parameters were: repetition time (TR)=400-600ms, echo time (TE)=15-20ms; FSE-T2WI imaging acquisition parameters were: TR=4000-5000ms, TE=100-120ms. On axial diffusion-weighted imaging (DWI), a SE echo planar imaging sequence was used with TR=3700 ms and TE=102 ms, b-values of 0 and 1000, slice thickness 5mm, slice increment 2mm, and FOV 256 mm x256mm. Patients were injected contrast agent (Gd-DTPA) with concentration 0.5mol/L and dose 0.1ml/kg. The enhanced scanning was begun at 30 sec after injection into elbow vein of contrast agent. MR angiography observations were performed by workstation (GE, AW4.5) equipped with angiography analysis software.

CT and X-ray

Patients underwent computed tomography (Philips 256 iCT with following parameters: 120kV, 250mA, FOV 512mmx512mm; slice thickness 5mm; slice increment 2.5mm. For contrast-enhanced CT, 90-100mL iopamidol injection (30 g (I)/100mL/bottle, 1mL/kg) was injected at 2.5-3.5mL/s. Arterial phase and venous phase were delayed performance at 25s and 60s respectively.The patient were underwent the front and oblique radiographs of humerus by using Germany Simons AXIOM Artistos MX DR.

Imaging Analysis and Pathology

The analysis of image was performed by two senior radiologists with rich experience (10 years of clinical experience) in imaging diagnosis. The features of CT or MR imaging of lesions in detail were analyzed and recorded, and a discussion was made to reach a consensus when their diagnosis was inconsistent. Postoperative specimens were stained with hematoxylin, eosin and immunohistochemical staining to detect antibodies for CD1a, S-100 protein, and CD68. The antibody S-100 was purchased from Maixin Company in Fuzhou, and the CD68 and CD1a were from Lycra Company. Positive and control groups of antibody were established.

Results

Clinical characteristics

Leukocyte count and erythrocyte sedimentation rate were normal in 8 cases and were increased in 2 cases. 8 RDD cases presented with painless enlarged LNs and one of them had fever. One case with a craniocerebral lesion only felt pain. 4 RDD cases were accompanied by other systemic involvement as listed below: enlargement of axillary LNs, hypertrophic nasopharyngeal mucosa, a mass in sinus, and liver or spleen involvement, respectively. Of 10 RDD cases, 7 cases were misdiagnosed as malignant tumor before surgery. 3 cases were misdiagnosed as eosinophilic granuloma (craniocerebral lesion), necrotizing lymphadenltis (cervical lesion) and pleomorphic adenoma (submaxillary lesion) respectively.

Radiological Features

10 RDD cases were divided into nodal group (3 cases), extranodal group (5 cases) and mixed group (2 cases), according to the involvements.

1) Nodal group: 3 cases displayed unilateral (1 case) or bilateral (2 cases) enlargement of cervical LNs, and one of them was accompanied with enlargement of retropharyngeal LNs. One case showed extensive lymphadenopathy with inhomogeneous density and mild to moderate enhancement. The lesions in the other 2 cases showed necrosis obviously and ring-enhancement (**Figure 1**).

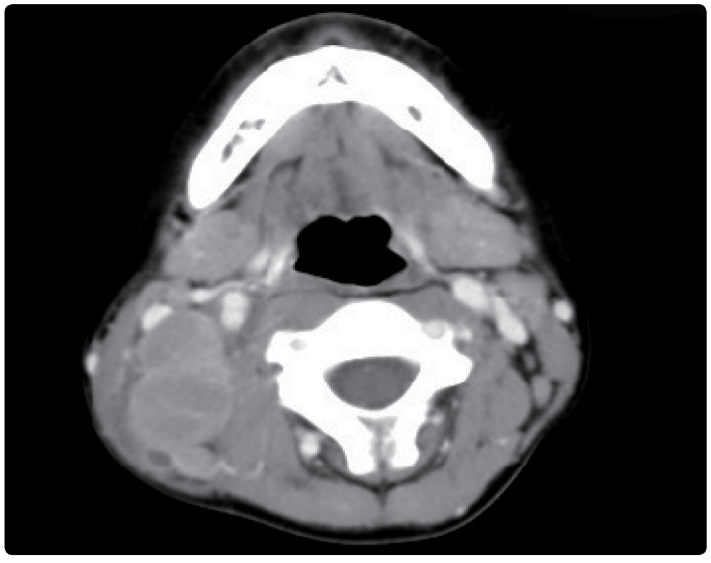

Figure 1: Nodal RDD in the neck. Axial CT enhanced image showed multiple enlarged right cervival lymph nodes with moderate and heterogeneous ring-enhancement.

2) Extranodal group: Of 3 cases underwent MR examination, one case presented with a intracranial lesion, and 2 cases presented with subcutaneous lesions. The intracranial lesion presented as soft tissue masse invading the inner and outer plates of the skull. The masse showed iso- or hypo-intense signal on T1WI (**Figure 2A**) and heterogeneous hypo-intense signal on both T2WI (**Figure 2B**) and DWI (**Figure 2C**). On Gd-DTPA enhanced MR images, these lesions showed intense enhancement with blurred edge and dural/fascia tail sign (**Figure 2D**). Lesios of 2 RDD cases occurred in cutaneous and were characterized by a irregular mass on the left shoulder and anterior abdominal wall. The maximum diameter of them were 7.1cm and 7.5cm, respectively. All the lesions in extranodal group had similar MR features, which showed multiple low signal linear septations within the tumor on all sequence (**Figure 3A**), and had abundant hyperplasia of feeding arteries around tumors (**Figure 3B**). Besides, a masse located in the left lobe of liver showed low density on the non-enhanced CT image (**Figure 4A**), and showed obvious enhancement in arterial phase (**Figure 4B**), then faded away in the portal and delayed phases. Overall, it demonstrated "fast washing out" feature in multi-phase enhanced scanning (**Figure 4C**). Additionally, one mass occurred in the right submandibular gland showed enlargement of submandibular gland with homogeneous, and displayed mild to moderate enhancement on the CT images.

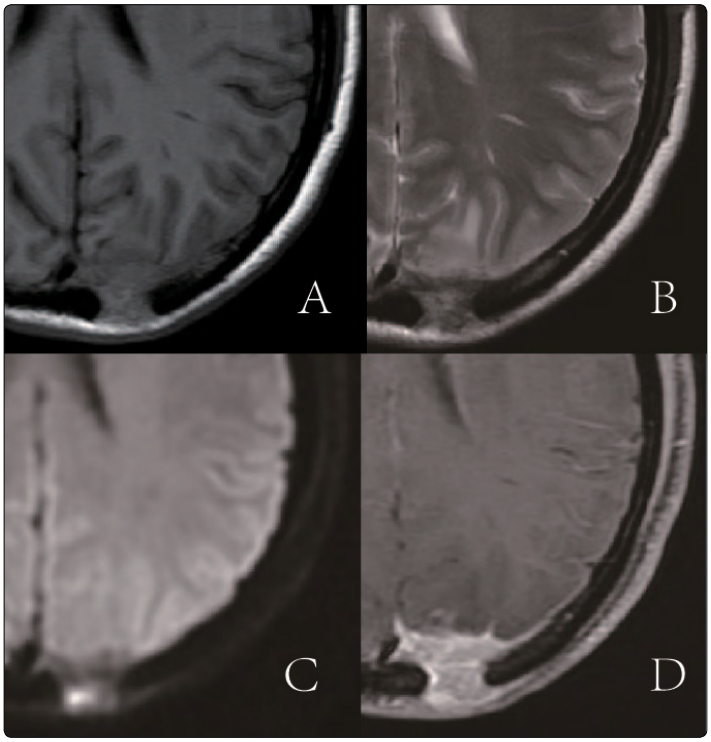

Figure 2: Cerebral RDD, showed partial skull destruction and soft tissue mass in the left occipital region, involving the meninges and brain parenchyma. The masses showed iso-orhypo-intense signal on T1WI(A) and heterogeneous hypo-intense signal on both T2WI (B) and DWI(C).On Gd-DTPA enhanced MR imaging, they showed intense enhancement with blurred edge and dural/fascia tail sign (D).

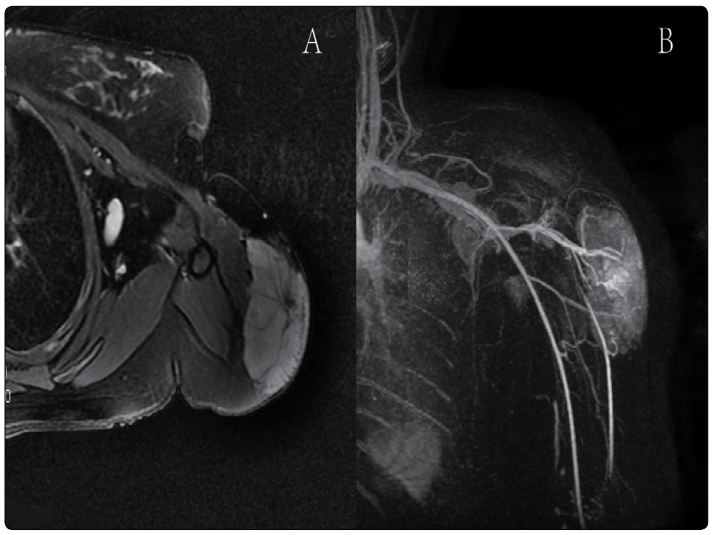

Figure 3: Cutaneous RDD manifested irregular mass on left shoulder which showed iso-or slightly hyperintense signal with low signal lace on T2WI(A). On the coronal reconstructed image of MRA ,hyperplasia of feeding arteries, the thoracoacromial arteries can be seen around the lesions(B).

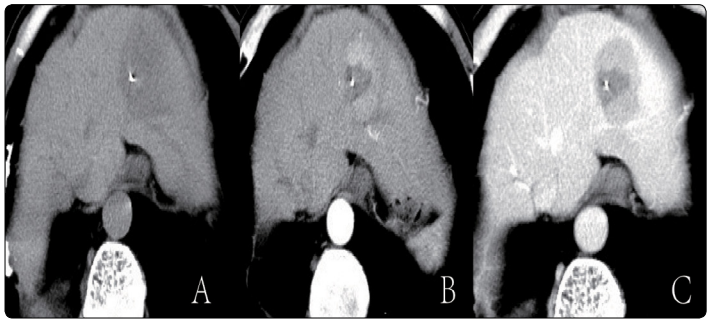

Figure 4: The lesion in the left lobe of the liver showed low density mass with blurred boundary on the non-enhanced CT(A). Some areas of the lesion showed no enhancement(changes after radiofrequency ablation) in artery phase.Beyond that, the lesion showed patchy intense enhancement in arterial phase(B) and faded away in the portal and delayed phases, demonstrating some degrees of "fast washing out" phenomenon(C).

3) Mixed group: The lesion in one case manifested swelling and thickening of pharyngeal region and nasopharynx. Meanwhile, enlarged LNs were found in bilateral submandibular area, neck and abdominal cavity with mild and moderate enhancement. It was also accompanied with hepatosplenomegaly and multiple osteolytic destruction in the pelvis. On the X-ray imaging, patchy osteolytic destructions without periosteal reaction and soft tissue mas were observed in the marrow cavity of the right middle-part humeral fractures, meanwhile were associated with heterogeneous osteosclerosis (**Figure 5**). Another case presented with enlarged LNs in bilateral neck and a mass in the sinusess with mild to moderate enhancement.

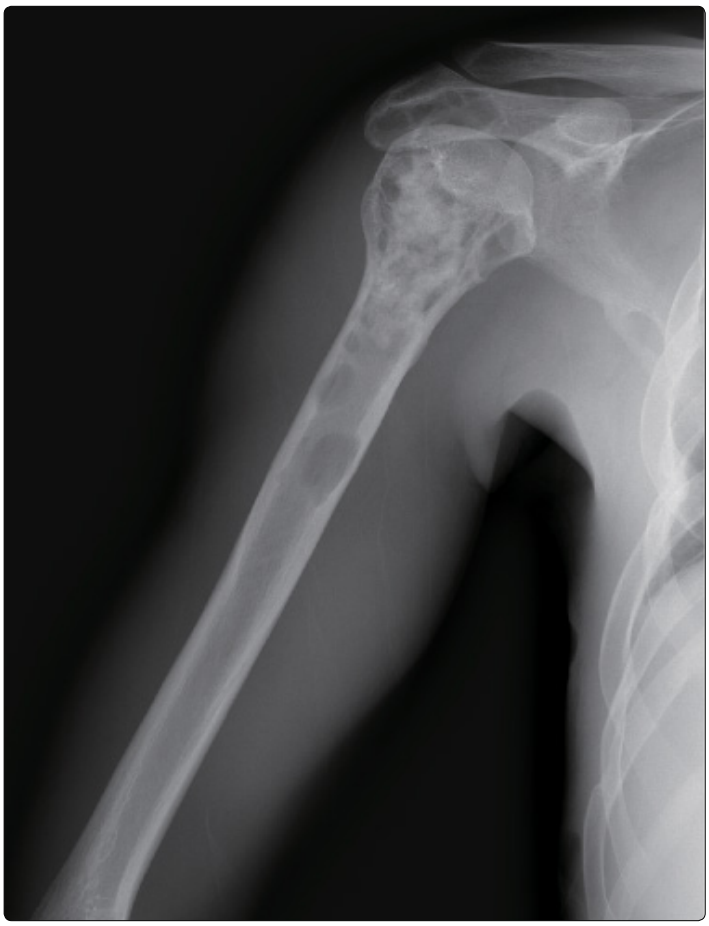

Figure 5: The extranodal RDD always involved multiple systems. On the oblique X-ray imaging, some bone destructions was showed in the right humerus with osteosclerosis.

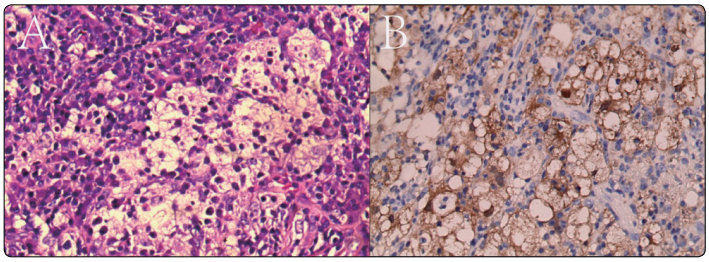

Figure 6: The RDD lesions under optical microscope manifestation as the infiltration of foamy sinus tissue cells among which can find the a great deal of lymphocytes and plasmocyte(A) .The cytoplasm and cell nucleus marked by S100 protein showed positive(B).

4) **Manifestation of pathology and immunohistochemistry** Patients underwent excisional biopsy followed by pathological examination of excised tissue. Tissue samples under optical microscope displayed diffuse infiltration of foamy sinus tissue cells, and interspersed with numerous lymphocytes and plasma cells (**Figure 6A**), meanwhile the phenomenon of emperipolesis was also observed. In the immunohistochemistry, the cytoplasm and cell nucleus were both positive for S-100 protein by immunohistochemistry (**Figure 6B**).

Discussion

Clinical features of RDD

RDD is a rare chronic inflammatory mucosal and self-limiting disease. RDD tends to develop in children and young adult. The disparity between the sexes is still undefinable.The results of this study showed that the majority of RDD patients were young and middle-aged. RDD was more likely to happen in male, which was different from previous reports [2, 4]. We supposed that this difference was related to the number of cases enrolled. In this study, 2 RDD cases presented with an increasing of leukocyte and erythrocyte sedimentation rate (ESR), and one of them was accompanied with repeated low fever. The manifestations of most patients were disaccorded with the clinical features described in previous reports, which included increasing of leukocyte, rising of ESR and hyperglobulinemia of IgG [1, 2, 5, 6]. We supposed that the disaccord was related to objective individual differences. Our results showed that 80% RDD patients presented with painless, growing slowly mass or enlarged LNs. These manifestations could be with high specificity for RDD diagnosis. However, RDD is usually misdiagnosed as malignant tumor, because the lesions always showed multiple enlarged LNs or soft tissue masses. In our results, 7 (70%) RDD cases were misdiagnosed as malignant tumor. Nowadays, the definite diagnosis of RDD depended on pathological examination. Because of the raity of RDD, almost all reports were case reports, more data should be collected for further summarization about clinical features [4, 7-9].

Radiological Features of RDD

The radiological characteristics of RDD are mostly derived from case studies [10-13]. Our results showed that 3 cases had similar CT features with multiple lymphadenopathy, which was consistent with previous studies [4, 10]. These patients presented with one or more groups of enlarged LNs without fusion, these LNs showed mild to moderate enhancement with necrosis. We believed that these features were helpful for RDD diagnosis. The similar MR features of extranodal RDD cases were similar and were summarized as follows:

1) The boundaries of these lesions were blurred, such as inflammatory lesions that invade adjacent tissues. The fascia tail sign occurred in 2 cases (2/3) of cutaneous RDD in this study. The pathological feature demonstrated that this sign was related to the hyperplasia of sinus and inflammatory involving the nearby tissues [4, 12, 14].

2) High signal inhomogeneity was observed in the lesions on DWI images, and this feature was also reported by previous studies, however, the pathologic basis is still unknown [10, 12]. It was supposed to due to the existence of suppurate. Our results showed a large number of inflammatory cell infiltration supported the above view. Whether this MR feature can be as the diagnostic evidence for RDD, further examinations are still needed.

3) Multiple low signal lace were observed in subcutaneous mass on T2WI images. In this study, this feature was observed in one case who had a history of more than 10 years and with a large mass. It demonstrated that fibrous stripes could more often be found in extranodal RDD patients with a long course.

4) The parenchymal areas of lesions were markedly enhanced and with some feeding arteries surrounding. These features occurred in 3 cases (2 cases in subcutaneous masses, one cases in intracranial mass), and could be specific characteristic of RDD. However, in view of too little case collected, this conclusion was yet to be confirmed.

Hepatic RDD presented as a mass with abundant blood vessels, similar to hepatocellular carcinoma. This case was misdiagnosed and performed radiofrequency ablation. However, it was finally diagnosed as RDD by surgery and pathology, and has a good prognosis. Hepatic RDD is so rare that only 7 cases have been reported in nearly 20 years [15]. Preoperative diagnosis of hepatic RDD is very difficult because of the rarity of salivary RDD and no specificity of laboratory examination and imaging tests. Salivary RDD case in this study presented with a submandibular mass with mild to moderate enhancement, and was misdiagnosed as aspleomorphic adenoma preoperation.

A case report which consisted of 423 RDD cases by Yale Medical Records Room found that 43% of the cases affected extra-nodal site, seldom with bone involvement (7%), and only 3 cases (0.7%) manifested as isolated lesions in the bone. One case in this study with bone involvement showed osteolysis destruction in the humerus and ilium with blur or clear edge, and no soft tissue mass or periosteal reaction was observed. All audiological features characterized as benign bone disease that was consistent with the X-ray findings of long bone RDD reported previously. However, contrary to previous results, osteosclerosis could be seen on the edge of destruction in the humerus in this case. We supposed that this case had about one-year course, osteosclerosis was caused by osteogenesis for bone repair. Therefore, the course of disease should be considered, referring to the X-ray features of osteal RDD. The clinical features of this case included local swelling with pain, low fever, rising of WBC and ESR, which were similar to inflammatory reaction. As a result, it was misdiagnosed as chronic osteomyelitis, lymphadenoma or metastasis per-operation. We supposed that the major factors leading to misdiagnosis were as follows: Firstly, rarely seen both LNs and bones involvement simultaneously, and lacks of in-depth understanding about RDD. Secondly, bone X-ray and body CT examinations in this patient were separated by long time, so it is difficult to form a systematic understanding. About 25-40% of the extranodal RDD involve the nasal cavity and paranasal sinuses [16-18]. One case represented enlarged cervical LNs with ring-enhanced and soft tissue mass in the nasal cavity, which was consistent with features reported in previous [14, 16]. These cases were misdiagnosed as necrotizing lymphadenitis, and it ascribabled to too much attention on the neck LNs and lgnore nasal tumors. Therefore, in order to improve the level of preoperative diagnosis, RDD firstly should be regarded as a systemic disease attention, every system in the human body needs a thorough examination and the clinical manifestations and laboratory indicators should be closely combined.

Differential Diagnosis

The radiological features was variety in different types of RDD. Therefore, each type of RDD requires differential diagnosis. Nodal RDD should be differentiation mainly from the following diseases:

(1) Lymphadenoma: The density or signal of the lesions are relatively homogeneous, with little necrosis and mild enhancement. Fusion of LNs can often be found.

(2) Necrotizing lymphadenitis: More common in young women, and often accompanied by high fever and pain[18]. There is a history of viral infection, swollen LN necrosis with ring enhancement are obvious.

(3) Meningeal Neoplasms: Differentiation should be made between cerebral RDD and meningeal neoplasms. Meningioma often shows mild hyposignal signal on T2WI and markedly enhancement.

It seldom shows multiple lesions. Whereas, cerebral RDDs usually show lower signal, display various performances on enhanced scanning and with multiple lesions. Subcutaneous type of RDD should be identified mainly from the following diseases:

(1) Nodular fasciitis: Patients always feel pain. The lesions show homogeneous density or signal, and display the reverse target sign. Besides, muscle space is often involved, the lesion showed enhancement markedly often accompanied with fascial tail sign.

(2) Desmoid type fibromatosis: It develops more often in middle-aged women or the patients underwent surgical history. The lesions show homogeneous density or signal with no necrosis. The boundary of tumor is unclear and infiltrates into the surrounding area, showing a "crab-like" change. It shows delayed significant enhancement. The hepatic RDD should be mainly identified from hepatocellular carcinoma.

Limitations

However, this study had some limitations. The sample size was small, particularly for patients with extranodal RDD. Further studies with larger samples are therefore needed. Besides, only the valuable imaging features were analyzed for different subgroups of RDD, no statistical analysis was used. Moreover, this study was a retrospective observational study, clinical and imaging data were fragmente so that it was not helpful for the establishment of diagnostic criteria.

Conclusions

To sum up, RDD tended to develop more often in young adult and mainly manifested painless enlarged LNs and mass. LNs in RDD mainly displayed one or several groups of enlarged LNs with mild or moderate enhancement (heterogeneous ring-enhancement in some cases). The characteristics of extranodal RDD were that patchy high signal on DWI, intense but inhomogeneous enhancement with dilated blood vessels around the lesions, and the dural/fascia tail sign could be found in soft tissue mass. RDD could accompanied by involvement of multiple system, therefore, accurate preoperative diagnosis is very difficult. It is necessary to comprehensively combine imaging, pathology and clinical features to improve the diagnostic accuracy.

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