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PRIMARY INTRAOSSEOUS MANIFESTATION OF ROSAI-DORFMAN DISEASE: 2 CASES AND REVIEW OF LITERATURE

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Rosai-Dorman disease (RDD) is a rare disorder of proliferative histiocytes with an unknown etiology. It is also known as sinus histiocytosis with massive lymphadenopathy. Most patients present with painless cervical lymphadenopathy due to accumulation of histiocytes in the lymph nodes, often in conjunction with fever, elevated leukocyte count and erythrocyte sedimentation rate. Isolated skeletal involvement is very rare.

Key-word: Sinus histiocytosis with massive lymphadenopathy – Rosai Dorfman disease – musculoskeletal system – MRI.

Since it was first described by Rosai and Dorfman in 1969, there are multiple cases known in which other organ systems are also involved (40%). The most frequently affected extranodal sites include skin, sinonasal area, orbit, eyelids, salivary glands, upper airways, bone, and genitourinary system. Extranodal manifestation can occur without lymphadenopathy (28%). Isolated skeletal involvement is very rare, occurring only in 2-8% of all the patients reported to date.

Two new cases of isolated osseous RDD presented in our hospital, which will be reported in this article.

Cases

Case 1

A 72-year-old Caucasian man presented to an orthopedic surgeon in a referring clinic with complaints of pain in his right knee. Conventional radiographs of his knee showed no abnormalities. Magnetic Resonance Imaging (MRI) was performed because of ongoing complaints.

MRI (Fig. 1A) showed a lobular lesion anterolaterally in the proximal metaphysis of the tibia. The tumor had an intermediate signal intensity on the T1-weighted images and an increased signal intensity on the T2-weighted fat-suppressed images as compared to muscle. After intravenous contrast administration the lesion showed distinct and homogenous enhancement.

There was cortical interruption and a discrete soft-tissue extension. Subsequently, the patient was referred to our university hospital on suspicion of a primary bone tumor.

Additional clinical examination revealed no evidence of lymphadenopathy or other organ involvement.

Based on the age of the patient and the radiographic findings the differential diagnosis of chondrosarcoma, chondromyxoid fibroma, lymphoma, metastasis or plasmacytoma was made. Because of these considerations no biopsy was performed. Surgery was planned, but, unfortunately, at that time the patient suffered from a severe stroke which led to considerable delay in further histological diagnosis and treatment. It was decided to follow the patient with conventional radiographs and MR imaging. After 2 years the lesion decreased slightly in size (Fig. 1B).

After 4 years, however, the lesion again demonstrated an increase in size on MRI and was now also visible on conventional radiographs (Fig. 1C and Fig. 2). MR imaging showed anterior cortical scalloping (Fig. 3A,B). In addition, a dynamic MR study during intravenous contrast administration was performed. There was very rapid enhancement (within 6 seconds after enhancement of the artery) and also a washout phenomenon, suggestive of an aggressive lesion. The tumor was then resected.

Histologically, the lesions showed the classic features of Rosai-Dorfman disease (Fig. 4). One year follow up images showed no signs of recurrence or other lesions.

Case 2

A 59-year-old Caucasian woman presented with short term shoulder complaints. Conventional radiographs demonstrated an ill-defined osteolytic lesion in the right humeral diaphysis with a permeative pattern of bone destruction (Fig. 5A), suggestive of a malignancy.

The lesion showed a markedly increased uptake of the tracer on bone scintigraphy (Fig. 6) without other skeletal lesions. MRI showed a lesion with an intermediate signal intensity on T1- and a heterogeneous increased signal intensity on T2-weighted fat-suppressed images as compared to muscle. In addition there was cortical involvement and some edema of the surrounding soft tissues (Fig. 7). Metastasis of an unknown primary malignancy, plasmacytoma, lymphoma, and even sarcoma were in the radiological differential diagnosis. A biopsy was performed.

Again, the diagnosis of Rosai-Dorfman disease was made by histology.

Because of the benign histology and a decrease in symptoms a wait-and-see policy was agreed upon.

Approximately 6 months later, she progressively suffered from complaints of pain in her upper arm. A follow-up radiograph showed an increase in size and a progressive periosteal reaction (Fig. 5B).

Treatment is now under discussion.

Discussion

Rosai-Dorfman disease (RDD) is a rare and non-neoplastic disorder. The classical clinical presentation of RDD is massive and painless cervical lymphadenopathy. Often it presents with fever and increased leukocyte

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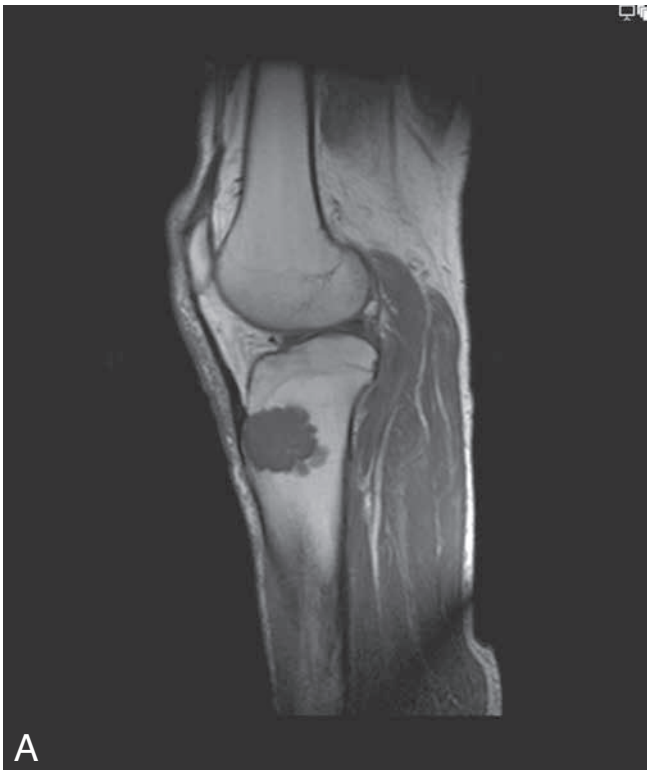
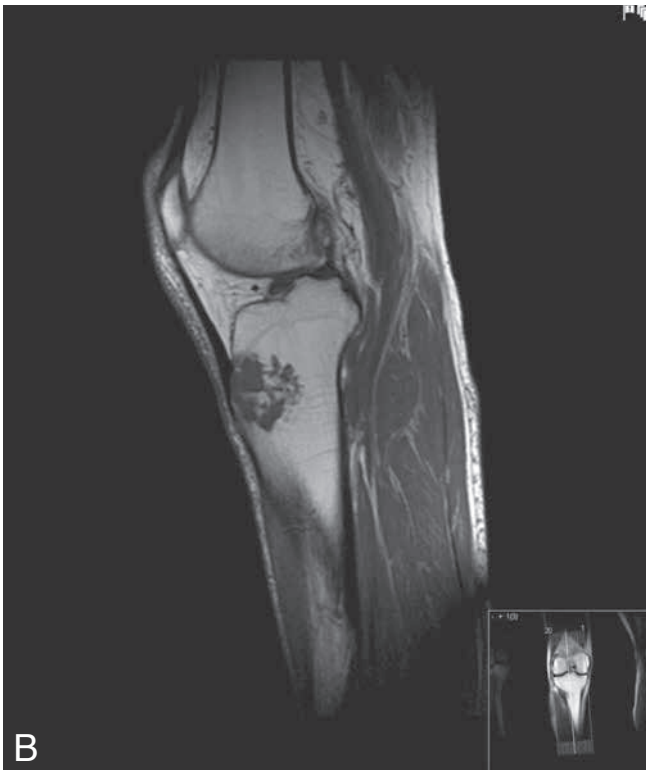




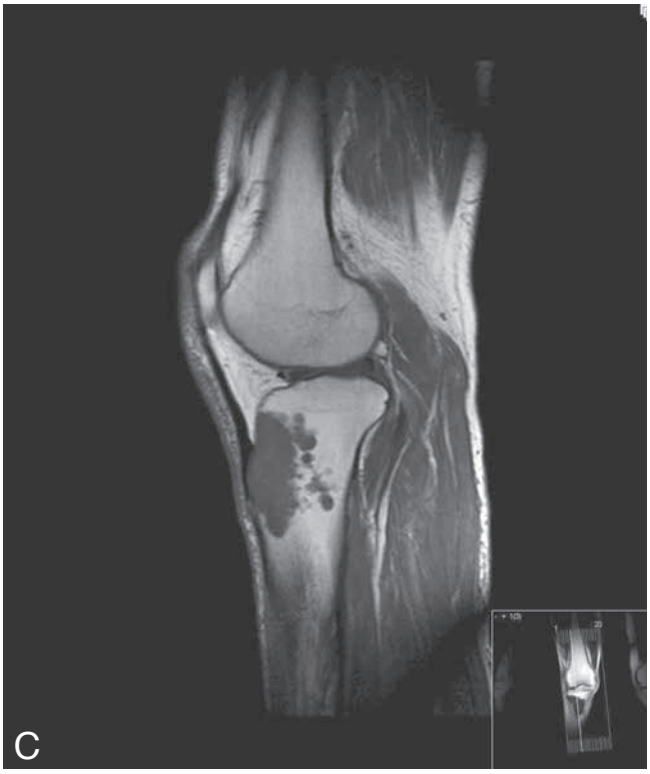


Fig. 1. — Case 1. Sagittal T1 weighted images at the time of presentation in 2006 (A), of 2008 (B) and of 2011 (C) showing a lobulated lesion anterolaterally in proximal metaphysis of the tibia with an intermediate signal intensity. Image (B) demonstrates slight decrease of the lesion compared to image (A). Compared to initial images, the lesion has increased in size on image (C).

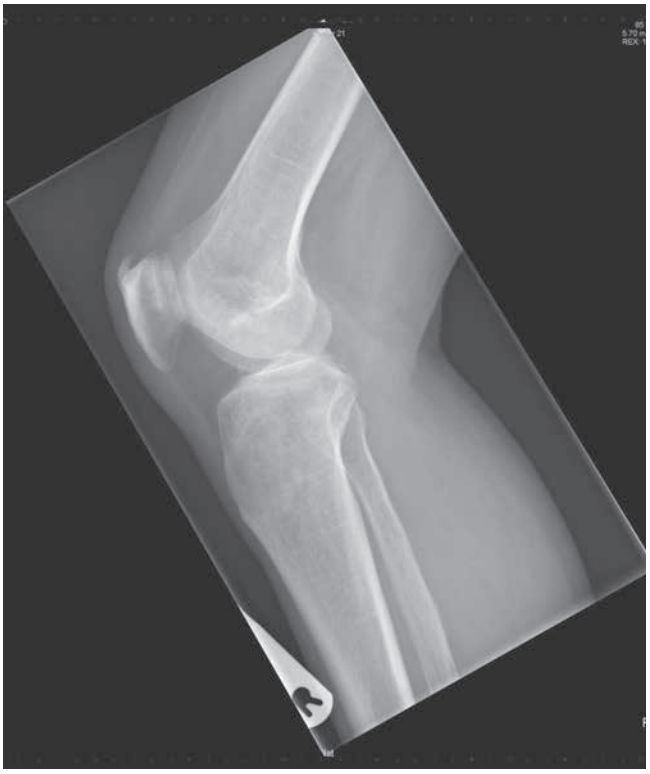


Fig. 2. — Case 1. Lateral radiograph of the knee: an osteolytic lesion in the anterior aspect of the proximal metaphysis of the right tibia.

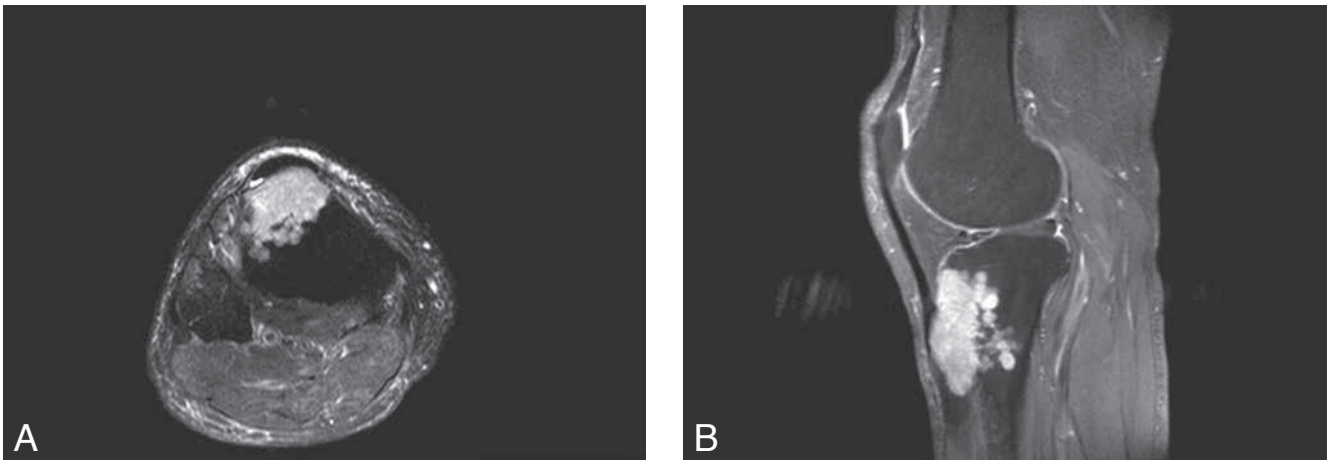


Fig. 3. — Case 1. Axial T2-(fat suppressed) and sagittal T1-(with fat suppression and after contrast) weighted images of 2011: The lesion has a high signal intensity on the T2 fat suppressed image (A) and homogenous enhancement after contrast (B). Cortical interruption and a discrete soft-tissue extension can be seen.

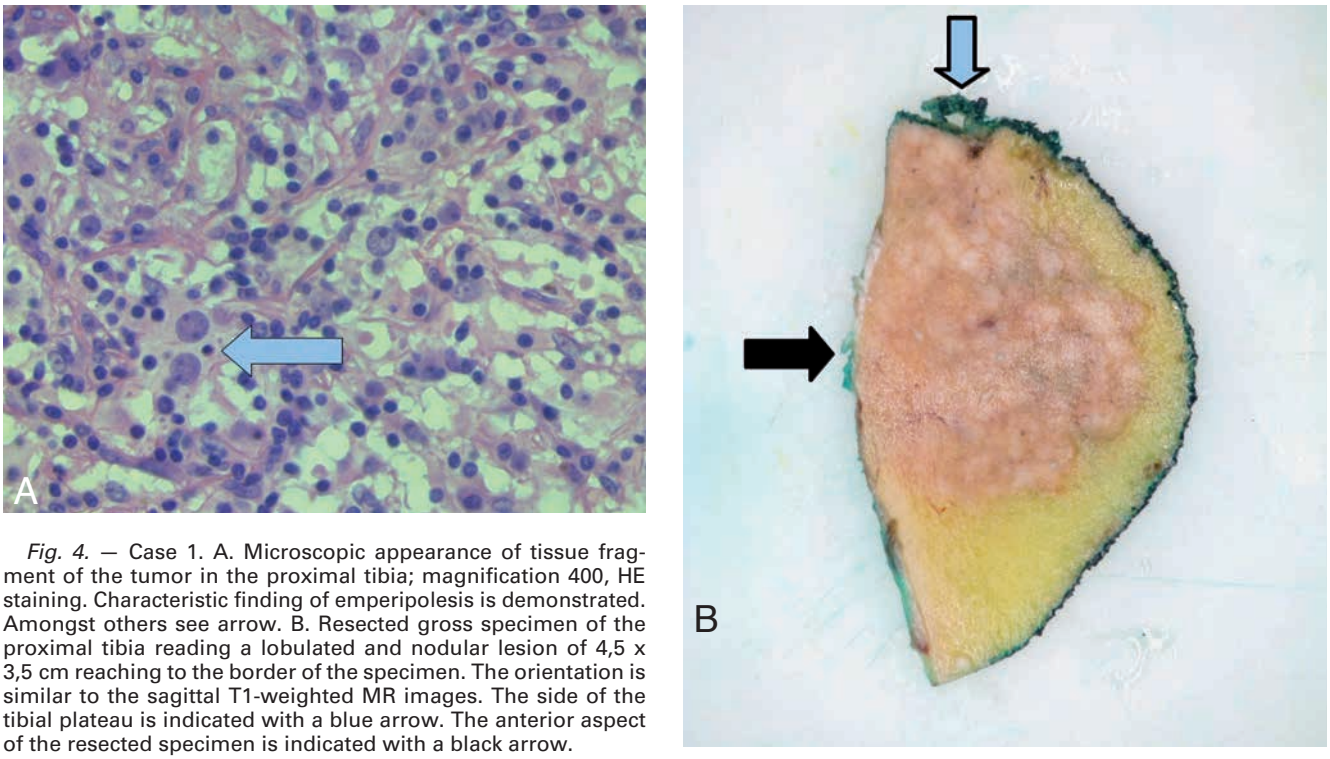


Fig. 4. — Case 1. A. Microscopic appearance of tissue fragment of the tumor in the proximal tibia; magnification 400, HE staining. Characteristic finding of emperipolesis is demonstrated. Amongst others see arrow. B. Resected gross specimen of the proximal tibia reading a lobulated and nodular lesion of 4,5 x 3,5 cm reaching to the border of the specimen. The orientation is similar to the sagittal T1-weighted MR images. The side of the tibial plateau is indicated with a blue arrow. The anterior aspect of the resected specimen is indicated with a black arrow.

count and erythrocyte sedimentation rate (1, 2).

Usually it affects young patients, the mean age of onset in 395 patients was 20.6 years of age (1). The two cases we described were both of a higher age which is uncommon and not often reported in the literature (3, 4). It occurs slightly more often in males. RDD has no racial predilection and has a morphologic and clinical overlap with Langerhans Cell Histiocytosis, both characterized by often multisystem infiltrates of non-specific inflammatory cells containing a distinctive histiocyte population. The two entities, however, can be clearly differentiated by their immunophenotype.

In approximately 30% of the known cases of RDD, other organ systems were affected without lymphadenopathy, especially skin, sinonasal area, orbit, eye lids, salivary glands, upper airways, bone, and genitourinary system (1). In less than 10% the skeleton is affected, sometimes due to secondary involvement, and there are only a few cases of isolated osseous involvement without lymphadenopathy (2-8%). In the largest study of 423 cases, only 9 patients had isolated intraosseous RDD (1). Until 2010, 39 additional cases of primary intraosseous RDD were described (5). It can occur everywhere in the skeleton (5). The disease may be multifocal (6, 7).

Most patients present with pain in the affected site, most frequently in the long bones (5). In case of RDD extending into the vertebral canal it

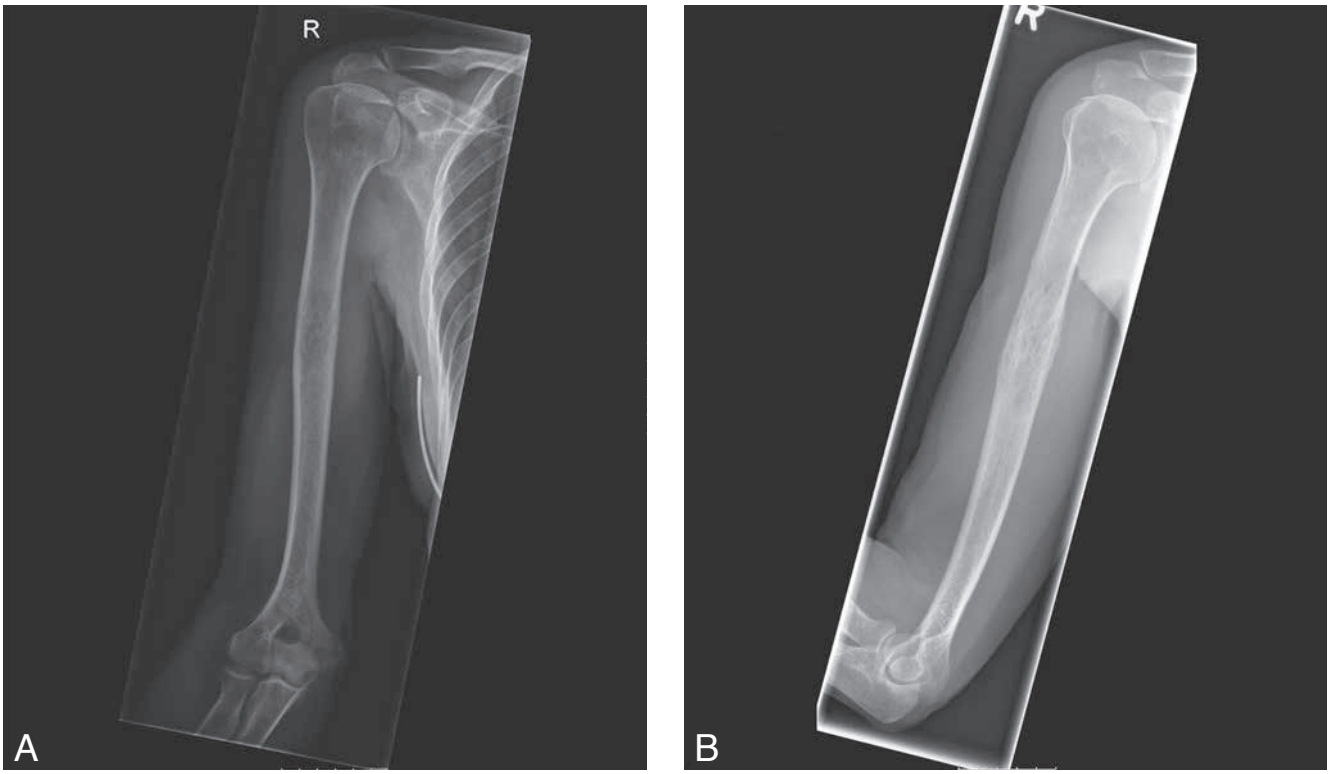


Fig. 5. — Case 2. A. Radiograph of the right humerus: ill-defined osteolytic lesion located centrally in the diaphysis of the right humerus. B. Radiograph six months later, the lesion has increased in size and progressive periosteal reaction can be seen.

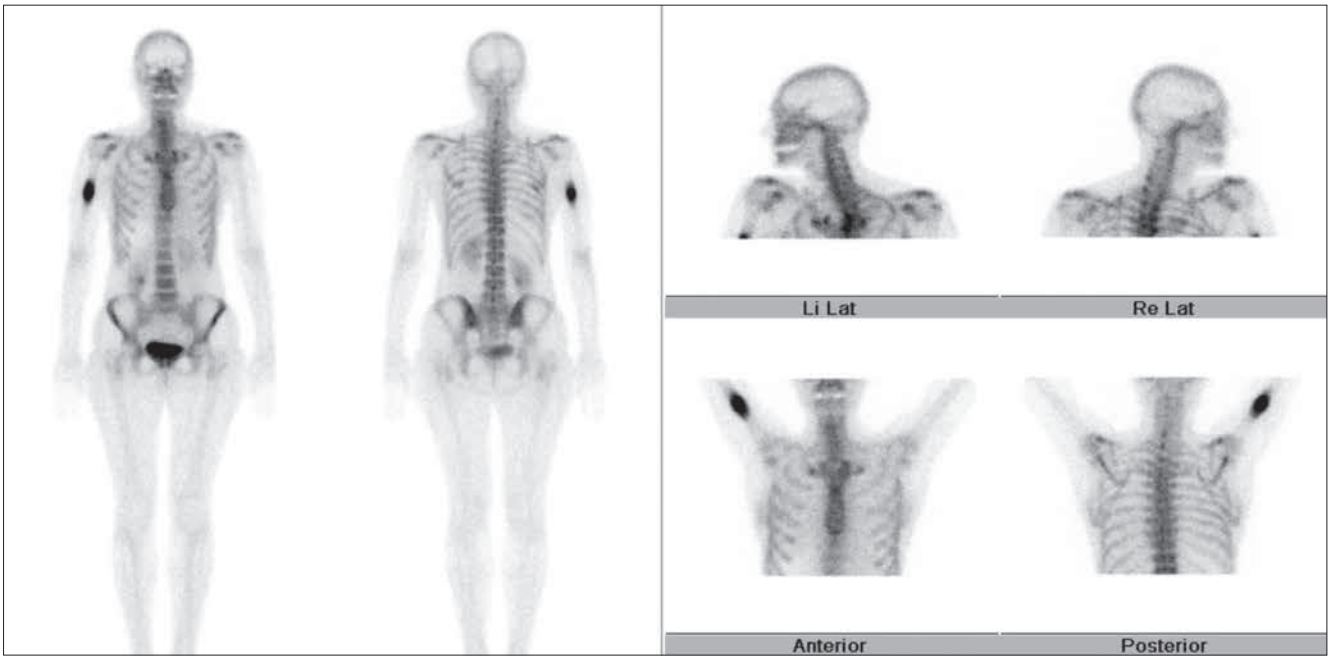
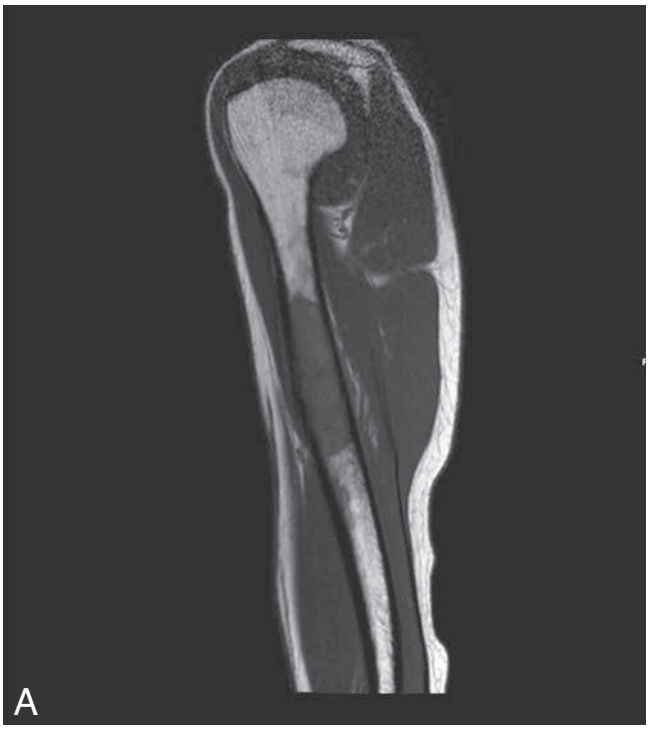
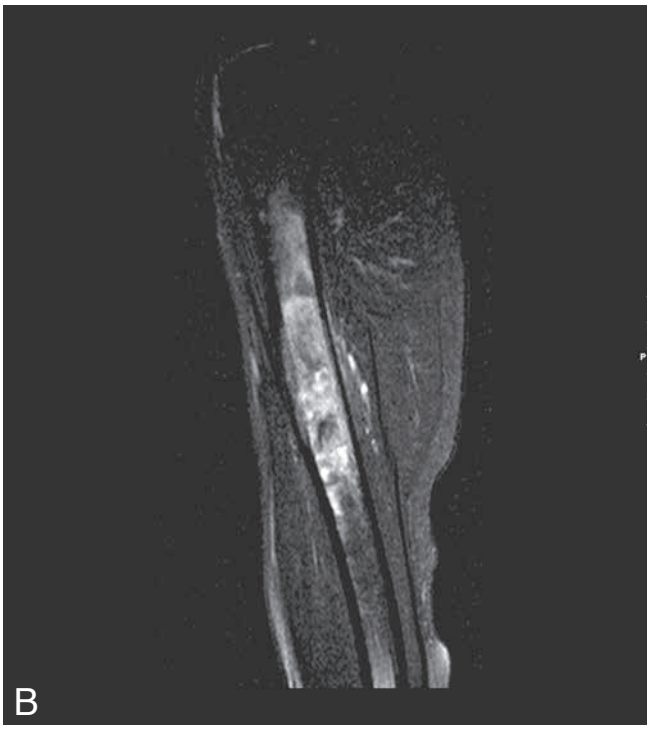


Fig. 6. — Case 2. Bone scintigraphy shows markedly increased uptake of radiopharmacon in the humeral diaphysis. No other skeletal localizations.





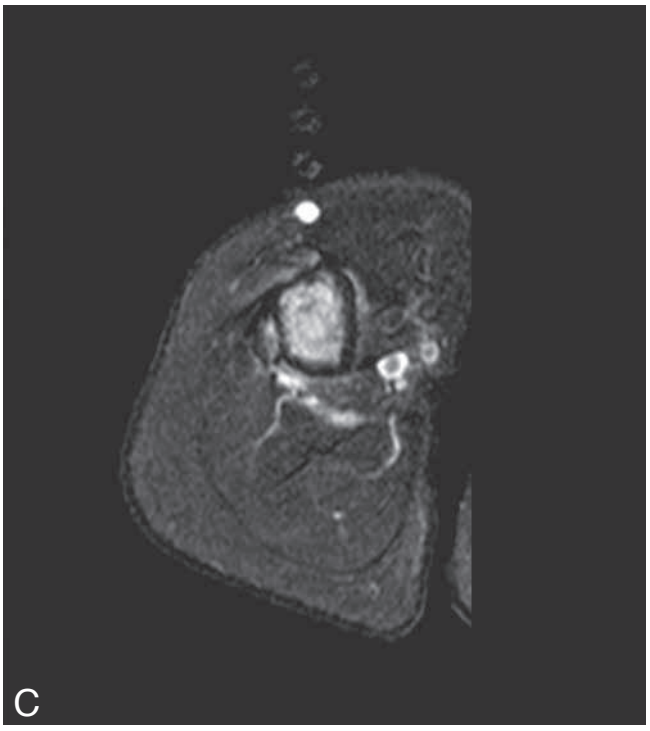


Fig. 7. — Case 2. Sagittal T1 and axial and sagittal T2-weighted (fat suppressed) images of the right humerus: a lesion in de medullary cavity of the proximal diaphysis with cortical infiltration and soft tissue reaction, possibly edema. The lesion has an intermediate signal intensity on T1 (A) and a heterogeneous increased signal intensity on T2 fat suppressed images (B,C).

can cause neurological symptoms (8, 9).

The clinical course can be variable with alternating episodes of worsening and relief of symptoms (4). In the first case we described, this was supported follow-up by MR studies which showed a subtle variation in size of the lesion.

Imaging typically shows an osteolytic lesion but there are examples of lesions with an osteoblastic or mixed osteolytic and osteoblastic appearance (4, 10). In case of long bone involvement the lesions most often are located in the metaphysis. Extension into the epiphysis is also reported (5). However, as in our second patient, a diaphyseal localization may occur. The lesion can be well-defined or demonstrate a moth-eaten or permeative pattern of bone destruction. The contours can be smooth or lobulated. Cortical interruption has also been described before (4, 6, 10).

MRI findings were first described in 1996 (11). Further MR characteristics were reported in 2012 (7).

MR imaging shows intermediate T1- and predominantly high T2-signal and a marked enhancement after contrast administration. Dynamic MR during intravenous contrast administration in our first case showed rapid enhancement and a washout phenomenon. To our knowledge this MR feature has not been reported before.

Rittner et al describe the use of whole body diffusion weighted imaging for staging and follow up, especially in severe cases or in case of progressive disease. They suggest ADC quantification to determine disease activity (7).

Bone scintigraphy can also be used to detect skeletal multifocality, lesions show markedly increased uptake of radiopharmacon (12).

Because of the rarity, the relatively nonspecific radiologic appearance and the clinical course with pain and fever, the diagnosis is often difficult and the lesion can be confused with more common disorders like osteo-

myelitis or Langerhans Cell Histiocytosis, specifically in the younger patient.

Malignancy, such as metastasis, plasmacytoma, lymphoma and even sarcoma, specifically in the older patient, granulomatous disorders or storage diseases are often in the radiological differential diagnosis.

RDD has, however, a distinctive microscopic appearance which shows a diffuse heterogeneous infiltrate of histiocytes, lymphocytes, and plasma cells. The characteristic finding is emperipolesis: engulfment of lymphocytes or plasma cells by large histiocytes, which are typically positive for immunochemical staining S100 and CD68 protein and negative for CD1A.

The diagnosis in our two cases was also based on this typical histological appearance. Goel et al. described FNA to obtain the histopathological diagnosis (13).

The etiology of the disorder is still unknown but the leading hypothesis is that it has an infectious cause and that it can be related to the parvovirus (B19). But no certain agent has yet been found (14).

The prognosis depends on the extent, the associated extranodal system involvement, and co-morbidity (particularly immunologic disease). Usually RDD has a good prognosis with spontaneous regression. In the literature, however, four patients were reported who died as a result of the disease (1, 2), three of these had involvement of bone.

The ideal treatment is unknown, as would be expected in a disease with such low prevalence, but ranges from a wait-and-see policy to surgery, chemotherapy, and radiotherapy. Pulsoni et al. concluded that surgery can be used when possible or necessary in case of vital organ compression or (impending) pathologic fracture. He reported 80% (32 out of 40 cases) in which the patient was cured.

Radiotherapy and especially chemotherapy has shown limited efficacy. Further research must be done to define the role of interferon alpha (15).

Conclusion

Primary involvement of Rosai Dorfman disease of bone without lymphadenopathy is very rare. Although it usually affects younger patients, two patients with isolated osseous involvement in an older age group are described in this article. It has a relatively nonspecific radiological appearance which causes diagnostic challenges and can lead to the erroneous diagnosis of a malignancy. Biopsy and histological examination by an experienced pathologist is mandatory for the final diagnosis. Treatment is still a matter of debate.

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