A rare case of extra nodal Rosai-Dorfman disease with isolated multifocal osseous manifestation

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Abstract
Sinus histiocytosis with massive lymphadenopathy (SHML) or Rosai–Dorfman disease is a non-neoplastic condition which typically presents as massive, bilateral cervical lymphadenopathy and can involve multiple extranodal organ systems such as skin, eyes, and upper respiratory tract in about 28% cases. Bone lesions in association with nodal disease are seen in less than 10% cases. Isolated bone involvement as the only manifestation of SHML is extremely rare, with less than 50 cases reported in the literature. We report a very uncommon case of Rosai–Dorfman disease with isolated multifocal osseous involvement as the only presenting feature, involving about 10 different sites with no lymphadenopathy or other organ system involvement.

Key words: Extra nodal; histiocytes; Rosai-Dorfman

Introduction
Rosai-Dorfman disease (RDD) is a rare non-neoplastic histiocytic proliferative disorder.[1] Patients typically present with bilateral painless cervical lymphadenopathy, fever, leukocytosis with neutrophilia, elevated erythrocyte sedimentation rate (ESR), and hypergammaglobulinemia.[2] Analysis of the registry of 423 worldwide cases of RDD showed a mean onset age of 20.6 years with 58% cases reported in males and 42% cases reported in females.[3] Extranodal disease can occur in the upper respiratory tract, salivary glands, eyelids, and skin in about 28% cases.[1,3] Osseous involvement in association with nodal disease can be seen in less than 10% cases.[1,3] Isolated multifocal osseous involvement only without any other systemic involvement is however very rare. This case highlights the significance of including RDD as an uncommon but well-documented differential diagnosis when evaluating multifocal osseous lesions.

Case Report
A 44-year-old African-American female was admitted to the hospital with chief complaint of right hand pain. White blood cell count was elevated at 14.8 K/µl, and ESR and C-reactive protein (CRP) were elevated at 81 mm/h and 56.90 mg/L, respectively. Patient’s serum uric acid level was also elevated at 7.6 mg/dl at the time of presentation. The patient had pain and swelling of the right third metacarpophalangeal joint, raising the suspicion of gout. Joint aspiration was attempted to rule out crystal arthropathy and/or septic joint. However, adequate fluid could not be aspirated. Radiograph of the right hand showed a 1.6 cm mixed lytic sclerotic lesion with narrow zone of transition at the base of the third metacarpal, without periosteal reaction. No erosive changes at the third MCP joint were seen [Figure 1]. Magnetic resonance imaging (MRI) (Siemens Trio 3T, Germany) was recommended for further evaluation, which showed confluent low T1 signal and narrow edema within the metacarpal, with a small T2-hyperintense central area of non-enhancement suggesting
an abscess [Figure 2]. Diffuse periosteal edema and enhancement was also noted.

No joint space abnormality was seen. Based on a combination of clinical and radiologic findings, a diagnosis of osteomyelitis with abscess was made. Findings were, however, felt to be atypical for osteomyelitis due to absence of systemic infection or overlying soft tissue ulceration. The patient was nevertheless treated for osteomyelitis with intravenous Vancomycin and Ertapenem antibiotics and was discharged.

After 1.5 years of being lost to follow-up, the patient presented to the outpatient orthopedic clinic for evaluation of left knee and left elbow pain. Radiograph of the left knee showed a large expansile mixed lytic sclerotic lesion involving distal left femoral metaphysis with narrow zone of transition and sclerotic borders [Figure 3A and B].

Follow-up MRI (GE medical’s GE 1.5 T LX, USA) of the knee showed an expansile lytic lesion occupying much of the medial femoral condyle with multiple areas of cortical breakthrough and extension into the adjacent soft tissues [Figure 3A and B].

Based on the imaging findings, infection, aggressive giant cell tumor, brown tumor, acute phase of eosinophilic granuloma, and metastatic disease were included in the differential diagnosis.

Work-up included renal function tests and serum calcium and parathyroid hormone levels which were normal. A surveillance computed tomogram (Phillips Brilliance 16 slice scanner) (CT) of chest, abdomen, and pelvis with contrast did not show a primary tumor. Multiple osteolytic lesions involving left inferior pubic ramus, right clavicle, and left posterior seventh rib were seen on the CT. Follow-up whole-body bone scan was performed [Philips Medical Systems Jet Stream after 23.7 mCi Technetium-99m hydroxymethylene diphosphonate intravenous administration]. It showed additional foci of increased radiotracer uptake in the right parietal skull and right ankle and hind foot [Figure 5].

Patient presented again with right foot pain for which radiograph was obtained which showed multiple well-circumscribed rounded lucent areas that were interspersed with linear areas of sclerosis.

Open biopsy of the distal left femur was performed. The diagnosis of extranodal Rosai–Dorfman was made based on pathology, which showed exuberant histiocytic proliferation with foci of emperiplois [Figure 6]. On immunohistochemistry, there was diffuse expression of S-100 protein by the larger histiocytes and all cells were negative for cytokeratin AE1/AE3 and CD1a. Additionally, Gomori methenamine silver (GMS) and acid fast bacillus (AFB) special stains were negative for organisms.

**Discussion**

The initial cases of sinus histiocytosis with massive lymphadenopathy were reported by Juan Rosai and Ronald Dorfman.[4] Since then, more than 400 cases have been reported.[3] In the classic form, RDD presents with painless massive lymphadenopathy, leukocytosis, elevated ESR, anemia, and hypergammaglobulinemia. The typical age
group affected is from second to third decade of life. There have been reports of delayed initial presentation in later decades such as in our patient who was 44 years old.[1]

Extranodal involvement occurs in about 28% cases to sites including orbit, eyelids, upper respiratory tract, salivary gland, skin, testes, and bones.[1,3] Osseous involvement occurs in 5-10% of cases, although isolated involvement of bones is rarely seen.[1,3,5-10] In 2010, Demicco et al. described 15 cases of primary RDD of bone involving up to two bones in two of their cases.[1] They also alluded to 24 other previously described cases of isolated bony involvement of which only two cases had involvement of up to three bones. To the best of our knowledge, this is the first case presenting with 10 different osseous sites, in a slightly older age patient, thus raising the possibility of metastasis higher on the differential.

Bony lesions tend to be expansile lytic or mixed lytic sclerotic, often with a narrow zone of transition. However, lesions can appear more aggressive and have associated cortical breakthrough with soft tissue extension as was seen with the femur lesion in our case. The usual location is metaphyseal or diaphyseal. MRI usually shows nonspecific low T1 and high T2 marrow signal, thus making this modality not very helpful in diagnosing the disease. Lesions can show increased radiotracer uptake on bone scan as well.
Differential diagnoses based on the clinical and imaging findings include osteomyelitis, eosinophilic granuloma, metastasis, and lymphoma. Other conditions varying from benign to malignant such as giant cell tumor, fibrous dysplasia, and Ewing sarcoma/primitive neuroectodermal tumors (PNET) have also been described in the differential. In patients who show lytic bone lesions and clinically present with fever, elevated ESR, leukocytosis, and pain, findings can resemble osteomyelitis, as was the case with our patient. Several cases of misdiagnosis of RDD confused with osteomyelitis have also been reported. Specific histochemical attributes of RDD help distinguish it from osteomyelitis. RDD involves histiocytes which are positive for S-100 and also depict emperipolesis or inflammatory cells “passing through” the cytoplasm of the large histiocytes [Figure 6].

Prognosis of primary osseous RDD is good, although there is no consensus within the medical community for effective treatment. Curettage or resection has been considered most effective with good overall outcome. Radiation and chemotherapy have also been tried in some cases.

In summary, RDD is a rare disease of marrow hematopoietic stem cell origin, with painless massive lymphadenopathy being the classic finding. However, about 28% of patients have extranodal presentation with less than 10% showing pure osseous involvement. Although this rare isolated multifocal osseous involvement has been previously reported in up to 2-3 bones, isolated multifocal lesions involving up to 10 different bony sites as seen in our case is extremely rare and, to the best of our knowledge, has not been previously reported. Thus, radiologists should be aware of the possibility of this rare but well-documented entity when evaluating multifocal bone lesions. Radiographically, multifocal lytic or mixed lytic sclerotic lesions with variable morphology are seen. S-100 positive histiocytes along with emperipolesis (inflammatory cells “passing through” the cytoplasm of the large histiocytes) on biopsy confirms the diagnosis.

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References


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