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CASE REPORT

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Osseous Involvement in Rosai Dorfman Disease: A Case Series of Orthopaedic Manifestations and Review of the Literature

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ABSTRACT

Introduction

Rosai-Dorfman disease (RDD) is a rare benign histiocytic disorder that can affect every organ system, although commonly presents as bilateral painless lymphadenopathy of the head and neck region. Primary bone RDD is even more rare; less than 10% of RDD patients exhibit bone-only disease, and this presentation is reported less than 50 times in the literature.

Case Presentations

A 76 year old female presented with an 11-month history of atraumatic, intractable low back pain with radiation to the right hip. A 28 year old female with remote history of Epstein-Barr Virus complained of two years of atraumatic left hip pain. A 53 year old female with history of diabetes complained of four months of intermittent, atraumatic left sided low back pain. A 46 year old female with a remote history of diffuse large B-cell lymphoma (DLBCL), presented with two months of intermittent right arm pain and night sweats. A 15 year old male presented with a five week history of constant right lateral knee pain exacerbated by movement. All received different treatment regimens, and all are alive with no evidence of disease progression at last follow up.

Conclusion

Due to the highly variable nature of disease, it is important for orthopaedic oncologists to keep RDD in mind and include it on differential diagnosis for a patient with solitary or multiple marrow-replacing bone lesions, especially with more common diagnoses ruled out. With advanced detection techniques and an increased physician understanding, delays in diagnosis and unnecessary repeat biopsies and testing can be avoided which will ultimately lead to optimal patient outcomes.

Introduction

Rosai-Dorfman disease (RDD) was first described in 1965 in four cases of massive cervical lymphadenopathy found in children and young adults. Four years later, it was characterized in a larger cohort of patients as sinus histiocytosis. Today, it is understood as a rare benign histiocytic disorder that can affect every organ system, although most commonly presents with soft tissue involvement. RDD is more common in African American males with an average age of onset of 20.6 years old, although can occur in any demographic group. Primary bone involvement in RDD is especially rare, reported in less than 10% of patients [1-7].

The classic presentation of RDD is one of bilateral painless lymphadenopathy in the head and neck region, with additional findings of fevers, night sweats, and weight loss. Laboratory abnormalities such as leukocytosis, elevated ESR, anemia, and hypergammaglobulinemia are often also included in the clinical presentation. Primary bone RDD frequently presents with bone pain and lesions located in the metaphysis or diaphysis. Differential diagnoses should include chronic osteomyelitis, fibrous dysplasia, lymphoma, and bone malignancy (both primary or metastatic). Progression of disease tends to be slow, occurring over many years with multiple relapses in a lifetime. Despite the chronic nature of this disease, it doesn't always require treatment due to its benign and often indolent nature [8,9].

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While the cause of RDD is not entirely understood, many RDD cases are characterized by pathological extracellular signal-regulated kinase (ERK) activation driven by activating somatic mutations in the mitogen-activated protein kinase (MAPK) pathway genes. This aberrant pathway results in the development of histiocytic-rich lesions within soft tissue or bone. In about 10% of cases, RDD also has been associated with immunologic diseases such as systemic lupus erythematosus, idiopathic juvenile arthritis, and autoimmune hemolytic anemia. Some studies have linked RDD with viral infections including Epstein-Barr virus, cytomegalovirus, and HIV, but a definitive association has not been proven [10].

Due to the rarity of its presentation in bone and associated non-specific symptoms, diagnosis cannot be made based on radiographs alone and requires tissue biopsy to be confirmatory. Histologic analysis will demonstrate large histiocytes with ample pale cytoplasm, often with "cell in cell" emperipolesis. These cells will selectively stain positive for S100 and macrophage marker CD68, as well as stain negatively for dendritic cell marker CD1a.

There is currently no well-accepted treatment of choice for primary bone RDD, as severity of presentation can vary considerably. Due to the benign nature of the disease and its often indolent symptomatology, RDD doesn't always require treatment unless symptoms become intolerable. Evidence exists to support corticosteroid therapy in decreasing nodal size and improving symptoms, but the durability of disease control with corticosteroids is questionable, as relapse tends to occur. Chemotherapy has also been administered in more severe cases, particularly those with visceral involvement. Surgical excision of the diseased bone with reconstruction/prophylactic stabilization has demonstrated positive outcomes and can be appropriate when the patient meets indications for surgical treatment. Due to the paucity of literature on this topic, this report aims to describe five cases of primary bone RDD treated at our institution and review the available literature on this unique diagnosis [11].

Case Reports

Case 1

A 76 year old female presented with an 11-month history of atraumatic, intractable low back pain with radiation to the right hip. She endorsed a 28-pound weight loss over the past year. CT scan of the chest, abdomen, and pelvis revealed thoracolumbar marrow-replacing bone lesions, concerning for metastatic disease, with no evidence of primary malignancy. Bone scan and PET scan noted multiple hypermetabolic osseous lesions in the thoracolumbar vertebrae, bilateral calvarium, and left femoral neck. Core needle biopsy was performed of the L3 vertebrae lesion, which demonstrated bone and bone marrow with trilineage hematopoiesis, no obvious neoplasm or malignancy. Open biopsy of the left femur was then performed, which revealed marked fibrosis and mixed chronic inflammatory cells, but was negative for malignancy. The patient had no pain in this area. The orthopaedic oncology and medical oncology teams recommended close observation with surveillance PET scan.

6 months later, a new painful hypermetabolic bone lesion was noted within the left iliac bone on PET (Figure 1). A CT guided core needle biopsy revealed atypical S100 positive cells in a background of mixed inflammatory cells and fibrosis. Some cells were highlighted by CD163, CD48, CyclinD1 and OCT2. After review with pathologists at the National Institutes of Health, a diagnosis of RDD was confirmed. The patient was treated with bisphosphonate therapy and cladribine 3.75mg/m2/day, in hopes of controlling painful inflammation and preventing progression. After 1 year of bisphosphonate treatment, Nephrology recommended discontinuation of bisphosphonate therapy due to rising creatinine. She continued on cladribine at a renally-adjusted dose of 3mg/m2/day and is still taking this regimen currently. PET scans have been stable since initiation of this drug, demonstrating scattered foci of bone-only disease without visceral involvement. She will continue to follow up with routine PET scans to monitor disease progression and response to treatment.

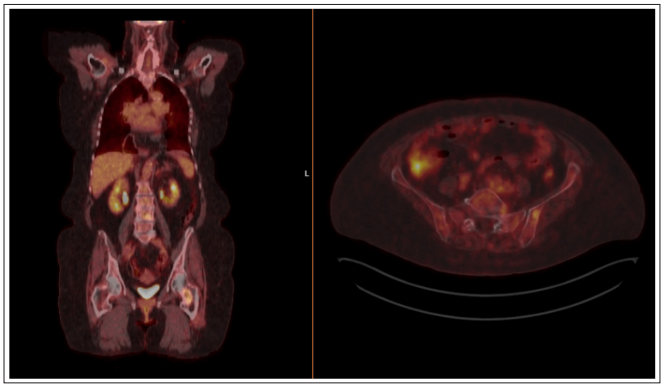

Figure 1: Coronal (left) and axial (right) Positron Emission Tomography (PET) scan images of osseous Rosai-Dorfman Disease, within left femoral neck (left) and left ilium (right).

Case 2

A 28 year old female with remote history of Epstein-Barr Virus complained of two years of atraumatic left hip pain with radiation down the thigh, that had been unresponsive to pain medication and oral corticosteroids. MRI of left hip revealed an aggressive appearing bone lesion in the greater trochanter and intertrochanteric area of the left proximal femur with endosteal scalloping, possible cortical breakthrough, bone marrow edema, and periosteal edema. An open biopsy of this site was performed by orthopaedic oncology the day after her initial presentation, and histopathology of the specimen demonstrated a histiocytic infiltrate and mixed inflammatory cells. Prominent emperipolesis was present. The histiocytic cells were positive for CD68, CD163, and S100, and negative for CD1a, confirming the diagnosis of RDD (Figure 2). The patient underwent prophylactic cephalomedullary fixation of the left femur for stabilization of her impending fracture.

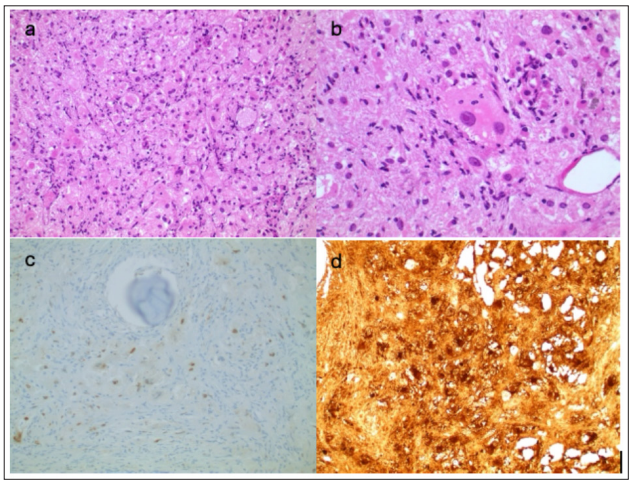

Figure 2a: 20x H&E stain demonstrating histiocytic infiltrate consistent with RDD. Cells have abundant eosinophilic cytoplasm and round vesicular nuclei; 2b: 40x H&E stain, demonstrating emperipolesis, entrapment of a cell inside another's cytoplasm ("cell in cell"). This is a characteristic finding in RDD; 2c: 20x CyclinD1 stain, highlighting the nuclei of cells 17 overexpressing this protein; 2d: 20x S100 stain, hi ghlighting the strongly positive (darker brown) histiocytes. This stain is commonly positive in RDD, though not specific for this disease.

Following this RDD diagnosis, the patient underwent a whole body bone scan which revealed no other sites of skeletal involvement. CT of the chest, abdomen, and pelvis was also negative for visceral disease. The patient reported resolution of pain following prophylactic fixation. After consideration of her negative staging workup and consultation with the medical oncology service, systemic therapy was deferred. A year postoperatively, the patient's bone scan and CT demonstrated no evidence of recurrence or systemic disease. She continues yearly surveillance with the orthopaedic oncology service.

Case 3

A 53 year old female with history of diabetes complained of four months of intermittent, atraumatic left sided low back pain with radiation to the left buttock and waist. She endorsed a recent 15-pound weight loss. MRI scan of her pelvis noted a 1.8 x 1.1 x 2cm lesion within the left posterior superior iliac spine that was hyperintense on T2 weighted images, with surrounding marrow edema and cortical breakthrough. Bone scan demonstrated abnormal uptake of the left ilium, left sphenoid wing, and upper body of sternum. Core needle biopsy was performed, which was nondiagnostic but somewhat suggestive of plasmacytoma. An open biopsy of the left ilium was then performed by orthopaedic oncology, and frozen section initially was interpreted to be consistent with plasmacytoma, as many plasma cells were present on frozen section. However, permanent histologic analysis demonstrated numerous histiocytes with abundant vacuolated cytoplasm, admixed with large numbers of plasma cells. Emperipolesis was noted, as was positive staining for CD68 and S100 within the histiocytes. These findings confirmed the diagnosis of RDD. A sternum core needle biopsy revealed possible involvement but was nondiagnostic.

Indications were considered for definitive surgical treatment versus radiation therapy to the left posterior ilium lesion, but ultimately, conservative management and close imaging surveillance was agreed upon by the patient due to relatively minimal pain. After 3 months, a new PET scan demonstrated decreased metabolic activity in the left iliac and sternal lytic lesions. While pain at these areas has waxed and waned over the years, no further treatment has been needed. The patient is currently 9 years from original diagnosis, continues yearly imaging surveillance, and remains free of further progression of disease.

Case 4

A 46 year old female with a remote history of diffuse large B-cell lymphoma (DLBCL), presented with two months of intermittent right arm pain and night sweats. The patient had been following up annually with imaging for DLBCL diagnosed 5 years prior at an outside facility. Initial diagnosis of DLBCL was made from a mediastinal mass and she was treated with 6 cycles of DA-EPOCH-R chemotherapy, radiation, and stem cell transplant, resulting in complete remission. Her most recent PET scan 3 months prior reported a hypermetabolic lesion in the right proximal humeral metadiaphysis as well as a more subtle lesion in the T3 vertebral body and healing subacute fractures of the left posterior 4th rib and left anterior 5th rib.

An MRI of the right humerus noted an extensive contrast enhancing lesion in the right humeral shaft with bone marrow replacement. Core needle biopsy confirmed the diagnosis of RDD with histology demonstrating a prominent population of histiocytes with emperipolesis. Immunohistochemical staining reported positive markers for S100 and cyclin D1 within the histiocytes. The CD4:CD8 ratio was decreased, ruling out DLBCL. Following the new RDD diagnosis, the patient was considered for radiation versus surgical treatment, and ultimately radiation was pursued. She was treated with a total of 3,600 cGy of radiation over 18 fractions to the right humerus. At this time, she is now 4 months post-radiation therapy. She will continue to follow up with medical oncology to monitor further disease progression.

Case 5

A 15 year old male presented with a five week history of constant right lateral knee pain exacerbated by movement. He reported an audible pop after twisting his knee while playing football five weeks prior. An MRI of the knee revealed multiple marrow replacing lesions within the distal femur, proximal tibia, and proximal fibula involving the epiphysis and metaphysis (Figure 3). Plain radiographs showed no obvious bone lesions. Open biopsy of the right tibia demonstrated diffuse histiocytic infiltrate with cellular atypia, but no frank pleomorphism or signs of malignancy. However, the diagnosis was inconclusive from pathology due to the bony nature of the specimen.

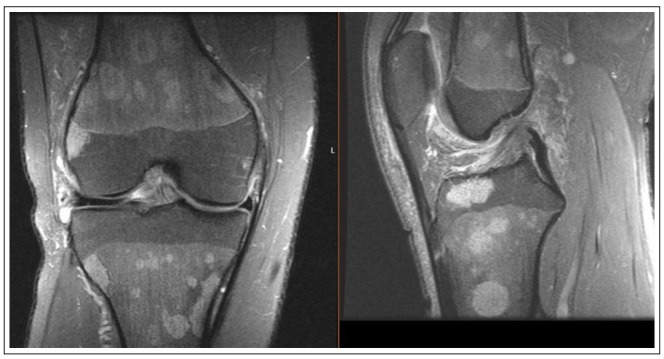

Figure 3: Coronal (left) and sagittal (right) T2 fat saturated magnetic resonance imaging (MRI) images of diffuse osseous involvement of Rosai-Dorfman Disease in distal femur and proximal tibia.

The patient sought a second opinion at an outside facility. A whole body MRI reported diffuse bone lesions throughout the axial and appendicular skeleton with asymmetric lymphadenopathy in the neck, mediastinum, periaortic, and inguinal regions, suggestive of leukemia or lymphoma. A right cervical lymph node biopsy confirmed the diagnosis of RDD with increased histiocytes and noted emperipolesis. Immunohistochemical staining reported histiocytes were positive for CD68, S100, and CD163, while negative for CD1a and Langerin. He initiated systemic therapy, with 12mg/day dexamethasone and 2.5mg/m2/day sirolimus, which he tolerated well. Surveillance MRI of the knee performed 6 months later revealed improvement but persistent presence of the multiple lesions. Over a year has passed, and he remains asymptomatic despite radiographic persistence of these lesions on recent MRI.

Discussion

Primary bone Rosai-Dorfman Disease is a rare disease that can pose challenges in identification, diagnosis, and treatment. Due to its limited incidence, non-specific and highly variable symptom presentation, and nondiagnostic imaging findings, RDD is difficult to diagnose and may result in delayed treatment. Approximately 43% of RDD patients will present with extra-nodal disease, however less than 10% will present as primary bone disease. Especially in these cases, a high degree of suspicion is often required to make this diagnosis, since their osseous presentation is much more consistent with a diagnosis of metastatic carcinoma of lymphoma of bone. With advanced detection techniques and an increased physician understanding, we are able to present five cases of primary bone extra-nodal RDD treated at our institution.

Primary bone RDD frequently presents with persistent bone pain as demonstrated in all five cases. Due to its ability to affect every organ system, patients occasionally also report other nonspecific symptoms such as weight loss which was present in two of our cases. Radiographic diagnosis remains difficult as many patients have nonspecific imaging findings. MRI may show marrow-replacing bony lesions that are hyperintense on T2 with surrounding edema, while PET scan may demonstrate hypermetabolic activity. Biopsy of these lesions is the next step in diagnosis. Immunohistochemistry rules out metastatic carcinoma, and further workup demonstrates S100 positivity, CD68 positivity, and C1a negativity on histiocytes. Emperipolesis is another noteworthy finding that may clue physicians into a possible diagnosis of RDD. Despite these clues, initial biopsy results often remain nondiagnostic as demonstrated in three of our cases. As a result, physicians must persist in obtaining larger specimens, often requiring open biopsy, to establish a diagnosis. In addition to metastatic carcinoma, the differential diagnosis usually includes Ewing sarcoma, giant cell tumor, fibrous dysplasia, chronic osteomyelitis, and lymphoma. After these diagnoses have all been ruled out, the healthcare team must keep RDD in mind, and put it on the differential as a rare mimicker that is often missed.

Prognosis of primary bone RDD is generally considered good, and all 5 of our patients remained alive and relatively healthy at last follow up. However, there is no standard of care treatment in the current literature, which makes management of this systemic disease somewhat challenging. Many cases are suitable for observation, once the potential need for stabilization of the affected bone is addressed, while other cases require aggressive, systemic therapy for years. In our series, Cases 2 and 3 did not receive intervention but rather are solely being observed, while Case 1 was treated empirically with a purine analog chemotherapeutic agent and a bisphosphonate, Case 4 with radiation, and Case 5 with a combination of immunosuppression and oral corticosteroids. These five cases highlight the variability of treatment paradigms that exist for this disease, and emphasize the multidisciplinary, patient-centered approach that must be taken to treatment planning; “one size does not fit all”. The authors recommend that the care team consider two questions: (1) the severity of symptoms related to the bone lesion(s) in question, and (2) how severe/extensive the skeleton is involved in the disease. In consideration of the first question, if the patient is suffering considerable pain from the bone lesion, local treatment with either surgery or radiation should be performed. Prophylactic fixation is indicated to avoid pathologic fracture if the orthopaedic oncologist deems fracture to be impending (as was performed in Case 2). If pathologic fracture is not deemed to be imminent, palliative radiation can be pursued, as was performed in Case 4.

Consistent with available literature, a dose of approximately 30-36 Gy with 2Gy per fraction is an effective dose with minimal adverse effects. To guide decision making regarding the risk of impending pathologic fracture, the authors recommend considering Mirels Criteria as a guide, as well as using the presence of functional pain specifically as a relative indication for prophylactic fixation. In addressing the second question, consultation with the medical oncology team is critical to indicate the patient for systemic treatment, based on the skeletal and visceral burden of disease, along with considering the adverse effects of systemic therapy relating to the patient’s other comorbidities [12,13].

Despite their varied presentations and treatment strategies, currently all five of our patients remain stable, with no progression of disease. They remain at risk of local or distant progression, and annual radiographic surveillance is critical. The authors hope that the contribution of these five cases to the sparse available literature on RDD will allow for increased awareness and understanding of this diagnosis.

Conclusion

Primary bone extra-nodal RDD is an atypical form of a rare

disease, and even within this small subgroup of patients, the presentation, diagnosis, and treatment vary greatly from case to case. Proper diagnostic workup should be initiated for patients who present with atraumatic, persistent bone pain with associated systemic symptoms and the radiographic findings described above. Due to the highly variable nature of disease, it is important for orthopaedic oncologists to keep RDD in mind and include it on differential diagnosis for a patient with solitary or multiple marrow-replacing bone lesions, especially when the more common explanations (metastatic carcinoma, infection, lymphoma) are ruled out. Maintaining a high index of suspicion and involving a multidisciplinary care team will avoid delays in diagnosis and unnecessary repeat biopsies and testing, and will ultimately lead to optimal patient outcomes.

Learning Point of the Article

Primary bone extra-nodal Rosai Dorfman disease is an underrecognized, rare form of a disease that should be included in a differential diagnosis of atraumatic persistent bone pain with associated systemic symptoms in an attempt to optimize patient diagnosis and treatment.

Clinical Message

Primary bone extra-nodal RDD is an atypical form of a rare disease with a presentation, diagnosis, and treatment regimen that varies greatly from case to case. A high index of suspicion from orthopaedic oncologists and a multidisciplinary care team diagnostic approach and treatment are integral in timely diagnosis and optimal patient outcomes.

Consent

This is a case series and no IRB approval was needed. All patient information was de-identified and patient consent was not required. Patient data will not be shared with third parties.

Competing Interests

Authors declare that there is no competing interest.

Authors' Contributions

MH analyzed and interpreted the patient data regarding RDD. MC analyzed and interpreted the patient data regarding RDD. GZ provided histological examination of RDD manifestations and was a major contributor to writing the manuscript. CG provided interpretation and guidance of patient data regarding RDD. All authors read and approved the final manuscript.

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