Metachronous Multifocal Osseous Rosai-Dorfman Disease in a Pregnant Woman: Report of an Unusual Case and Brief Review of Pertinent Literature

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Abstract

Rosai-Dorfman disease (RDD) is a rare histiocytosis that most commonly involves the cervical lymph nodes. Extralymphatic involvement occurs in 30-40% of cases and most often in the head and neck region. Prognosis is generally excellent. We present an unusual case of metachronous Rosai-Dorfman disease arising in multifocal bone sites in a 25-year-old pregnant female. She presented with right shoulder pain, frontal headache associated with fever and sweating. Computed Tomography scan and Magnetic Resonance Imaging studies demonstrated well-circumscribed lesions in the proximal humerus followed by a similar lesion in the frontal bone of the skull. Microscopic examination revealed variable numbers of pale-staining histiocytes with emperipolesis and background lymphoplasmacytic infiltrate and fibrosis. Immunohistochemical studies revealed positive staining of these histiocytes for S100 and CD68, but they were negative for CD1a. These findings were characteristic of RDD. Our patient was treated by curettage of both lesions. She is well and alive but with recurrence in both locations.

Keywords: Rosai-Dorfman; Pregnancy; Bone; Multifocal

Introduction

In 1969, Rosai and Dorfman reported a distinct histiocytic disorder in several patients with marked enlargement of the lymph nodes, as well as other symptoms [1]. They named this condition sinus histiocytosis with massive lymphadenopathy, and the name has since come to be known as Rosai-Dorfman Disease (RDD). This rare disorder is characterized by an overproduction and accumulation of histiocytes in lymph nodes. Despite the aforementioned uncertainty, it is classified as a benign reactive lesion [1]. It commonly presents as massive, painless, bilateral cervical lymph node enlargement with systemic symptoms in the first-second decade of life and have a predilection for African Americans. Additional clinical features may include hepatomegaly, fever, pallor, anemia, arthralgia, weight loss, tonsillitis, nasal discharge and nasal obstruction [2]. Occasionally, histiocytes accumulation may occur in the skin, lungs, bones, orbital tissue and peri-orbital tissue, kidneys, peritoneum, testes, central nervous system or the digestive tract [3-5].

Extralymphatic involvement occurs in up to 30-40% of cases; however, pure extralymphatic disease is rare and varies from organ to organ. For example, all patients with salivary gland involvement had associated nodal disease while only 50% of patients with central nervous system disease have lymph node involvement. Because of its rarity and scarcity of large published series, there is no well-established and widely-accepted standard treatment. However, most RDD cases are self-limiting and require no aggressive treatment [1].

We are reporting an unusual case of metachronous multifocal RDD of the bone in a pregnant young woman. In addition, a brief pertinent literature review is offered.

Case Presentation

A 25-year-old Saudi Arabian female patient presented to our hospital with right shoulder pain, and complained of fever and night sweats. Her vital signs were 36.6°C, blood pressure 127/75, heart rate 90/min, respiratory rate 18/min. Her laboratory tests were all within normal range including her ferritin level which was 27 ng/ml. Computed Tomography scan (CT scan) and Magnetic Resonance Imaging (MRI) demonstrated a well-circumscribed lytic bone lesion in the proximal humerus (Figure 1). The lesion had both intra and extramedullary components measuring 4.4×3.8 and 4.1×2.1 cm respectively, with homogeneous enhancement. She was treated by surgical curettage and insertion of bone graft. Microscopically, there was an abundant population of histiocytes admixed with lymphocytes, plasma cells within fibrous stroma. These prominent large histiocytes contained abundant pale to vacuolated cytoplasm and a large nucleus with prominent nucleoli. Many of these cells showed lymphohagocytosis, also known as emperipolesis (Figure 2). The lesional histiocytes were immunoreactive for S-100 protein and CD 68 antibodies but were...
negative for CD1a (Figure 3). Based on these features, the diagnosis of RDD was rendered.

Six weeks after surgery the patient became pregnant and in the middle of her first trimester, she developed persistent headache and pain in the frontal skull bone. MRI showed a lytic lesion of the frontal skull bone, measuring 1.5 cm. (Figure 4). This lesion was curetted under local anesthesia where the pathological features were identical to that seen in the humerus. On a follow up visit while she was in her seventh month of pregnancy, a local swelling was found at the proximal humerus which was considered to be local recurrence. MRI revealed a larger lytic osseous lesion of the proximal humeral bone with extra osseous extension into soft tissue (Figure 5). The patient refused any further intervention during pregnancy and consequently delivered a healthy baby girl. Four months following the delivery, she complained of mild pain in the right shoulder and frontal skull bone. MRI showed recurrence in both locations with slight increase in their size. Resection

Discussion

The commonest symptom of RDD is painless massive lymphadenopathy mostly of the cervical region in up to 90% of patients. Other locations such as inguinal (26%), axillary (24%) and mediastinal lymph nodes (15%) have been reported [6]. Extranodal disease is documented in up to 30-40% of patients, with or without associated lymphadenopathy. The common extranodal sites include skin, nasal cavity and paranasal sinuses, eyelid, orbit, bone, salivary gland and central nervous system [7]. Overall, 36 cases of extranodal soft tissue RDD had been documented since 1969 [8].

The Writing Group of the Histiocyte Society subdivided the histiocytic syndromes based on the nature of these proliferating histiocytes whether they are Langerhans cells in origin or not and whether the process is benign or malignant [9]. RDD has been classified as one of the non-Langerhans cell benign histiocytosis. These histiocytes are usually located in the sinuses of the lymph nodes and less commonly in the interfollicular region. Histologically they are characterized by round or oval vesicular nuclei with well-defined delicate nuclear membranes and a single prominent nucleolus. Similar to what was seen in our patient, nuclear atypia and mitoses are usually absent. Lymphophagocytosis or emperipolesis is considered the hallmark of Rosai-Dorfman disease. It is defined by the presence of viable lymphocytes swallowed and engulfed in well-defined cytoplasmic vacuoles within the cytoplasm of large histiocytes. These
cells are actually activated macrophages that developed exuberant phagocytic abilities as well as immune related properties. They usually express S-100 protein, α1 antitrypsin, α1 antichymotrypsin, lysozyme, Mac 387, Ki-1 (CD 30, Ber-H2), but are non immunoreactive for CD1a (Leu 6) which specifically stains Langerhans type histiocytes RDD involving extranodal sites shows similar morphologic features to its nodal counterpart but they are characterised by the presence of more prominent fibrosis and fewer numbers of histiocytes with emperiplois. Therefore, this latter feature makes the diagnosis of RDD in extranodal sites very challenging [10].

Morphologically, the differential diagnosis includes hemophagocytic syndromes, storage disorders, inflammatory lesions, necrobiocti xanthogranuloma and lymphoreticular malignancies. The main distinguishing features that specify RDD are the presence of benign bland histiocytes with emperiplois, along with the absence of cytological atypia and the demonstration of the characteristic immunohistochemical profile [11].

Although the clinical presentation of RDD is well-recognized, the cause of this disease is still unknown. Possible etiologic factors include bacteria such as Klebsiella, viruses such as Epstein Barr Virus, parvovirus B 19, and Human Herpesvirus-6 (HHV-6) [12,13]. One study pointed towards a viral aetiology as suggested by the immunolocalization of parvovirus B19 (B19) using antibodies against B19 capsid proteins VP1/VP2.12. In addition, immune dysfunction, or an aberrant response to an unspecified antigen such as HHV-6 or EBV has been postulated. The most recent hypothesis is that the defective Fas/Fasl signalling system leading to altered apoptosis may be an important triggering mechanism in this uncontrolled histiocy tic proliferation [14].

RDD is known to have a chronic clinical course with variable frequency of recurrences that may present with acute exacerbations. It has been reported that up to 54% may have stable clinical course and up to 21% spontaneous regression. However, less than 5% may develop progressive disease [15].

RDD during pregnancy has been sporadically documented. To the best of our knowledge and after review of the English language literature, only five cases were reported, including our patient (Table 1). One case has been documented in an 8-month pregnant woman that occurred in the left parietal-occipital bone in the ventricular and periventricular area [16]. Another pregnant patient had a mandibular lesion that was discovered at 4 weeks gestation and showed slow progression of size during pregnancy [17]. Interestingly, Butler et al. reported a patient who during two separate pregnancies experienced clinical relapses of her RDD lesions, with complete disease remission in between [18]. Another nodal RDD case was described where the patient developed relapses in between pregnancies and a trial of anti-CD20 (Rituximab) was relatively successful [19]. Our patient had multifocal bone disease with multiple recurrences during and after pregnancy. Since it has been always believed that pregnancy is associated with an element of immune-suppression, exacerbations in pregnant patients with RDD are expected to occur.

Multifocal Osseous RDD has also been reported in few cases. Sundaram et al., reported a 2-year-old African American child with multiple bone involvement where the lesions affected the foot and wrist [20]. Sundaram et al. reported another case in a 60-year-old woman who presented with multiple lytic bone lesions affecting the lower end of femur and the middle of the fibula [21]. Demicco et al. had reported fifteen cases of primary RDD of bone where they described four cases where the disease was multifocal [22]. Al-Saad et al. reported multifocal bone and epidural involvement causing recurrent spinal cord compression in a 17-year-old boy who suffered from multiple neurological manifestations. He received 7 weeks course of prednisone and showed almost complete radiologic resolution of the epidural and paraspinal masses [23]. Similar patient with multifocal bone involvement by RDD was reported by Rittner et al. [24].

There is no well-established standard treatment for RDD. Options include observation for mild disease or surgical excision or debulking for lesions in surgically accessible locations and in some cases where vital organ function is compromised. Systemic corticosteroids with or without chemotherapy or radiotherapy were also reported as an available option [15,23,24].

We conclude that RDD should always be included in the differential diagnosis of multifocal lytic lesions of bone in pregnant women. Furthermore, this case is a rare example of pregnancy associated RDD.

**References**


