Rosai–Dorfman disease simulating metastatic breast carcinoma

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Key words: metastatic breast cancer; monoclonal gammopathy; Rosai–Dorfman disease.

INTRODUCTION

Rosai–Dorfman disease (RDD) is a benign non–Langerhans cell histiocytosis with a predilection for the head and neck lymph nodes, although it may present extranodally in the skin, soft tissue, or the central nervous system. The diagnosis depends on histopathologic features, including the classic finding of emperipolesis, along with immunohistochemical characteristics: $S100^+$ and $CD68^+$ and $CD1a^-$ cells (Table I).[1] RDD has several postulated etiologies, although none have been definitively proven. It has been reported to mimic various metastatic cancers,[2] including 1 reported case of RDD simulating metastatic breast cancer.[3] We present a patient with RDD of the skin and bone simulating presumed recurrent metastatic breast cancer. The correct diagnosis of RDD based on dermatologic and hematologic clues led to a significant change in her treatment.

CASE REPORT

A 67-year-old woman presented to the Department of Dermatology at Michigan Medicine with a papular rash on the upper portion of the left arm. The rash was previously diagnosed as keloids. Her history was notable for breast cancer treated with a left breast lumpectomy and radiation therapy; a subsequent pathologic fracture of the right hip was confirmed with a biopsy specimen as metastatic breast carcinoma to the bone, and was treated with open reduction and internal fixation, radiation, and aromatase inhibitor therapy. Five years later, and shortly before she presented for the skin rash, a routine monitoring positron emission tomography (PET) scan revealed multiple ^{18}F-fluorodeoxyglucose–avid lesions in her left breast, right hip, T6 through T11 spine, and sternum, presumed to be recurrent metastatic breast cancer. She underwent radiation to her sternum and spine and received hormone therapy for the suspected metastases, with persistence of the lesions. She did not have any systemic symptoms at the time of presentation.

The clinical examination of her skin revealed multiple pink, smooth papules on the upper portion of her left arm, overlying a subcutaneous 4- to 5-cm firm, tethered nodule (Fig 1). There was slight tenderness on palpation of the nodule. A thorough examination of the cervical, axillary, inguinal, and popliteal nodes was performed, revealing no appreciable lymphadenopathy. A telescoping punch biopsy specimen obtained through 1 of the papules into the deeper nodular component revealed a dermal and subcutaneous infiltrate of $S100^+$ and $CD68^+$ histiocytes with evidence of emperipolesis, confirming RDD (Fig 2).

Given the reported associations between monoclonal gammopathy and RDD,[4-7] serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) were obtained to determine possible systemic involvement of RDD. A 0.2-gm/dL immunoglobulin A (IgA)-kappa monoclonal M protein spike was detected in the serum, and a free monoclonal kappa light chain was detected in the urine. Her serum kappa to lambda ratio was elevated at 4.79. The patient had no other symptoms of systemic disease and the laboratory studies were

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Funding sources: None.
Conflicts of interest: None disclosed.
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JAAD Case Reports 2019;5:372-4.
2352-5126

https://doi.org/10.1016/j.jdcr.2019.02.021

Table I. Rosai–Dorfman disease: An overview

Natural history	Usually found in childhood to early adulthood, most patients present in good health; 20% have spontaneous clearing; 70% relapse and remit
Pathophysiology	Nonmalignant histiocytes found in lymph nodes or extranodally; cells show characteristic emperiopolesis; no clear pathogenesis, but postulated associations with infectious agents, immune dysfunction, and various lymphomas
Diagnosis	Comprehensive history and physical examination often reveal fever and cervical lymphadenopathy; laboratory workup commonly reveals leukocytosis with neutrophilia, anemia, polyclonal hypergammaglobulinemia, and an elevated erythrocyte sedimentation rate
Management	Typically self-limited without the need for systemic therapies; treatment is advised in symptomatic patients, includes surgery if focal involvement, otherwise steroids, radiotherapy; no clear standard of care for systemic treatment

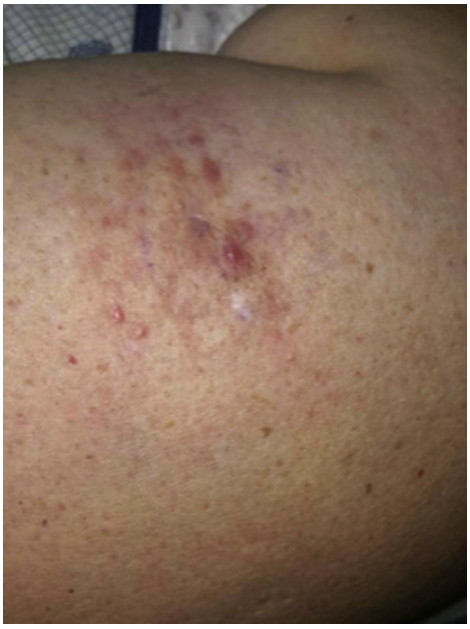

Fig 1. Rosai–Dorfman disease. Left upper arm with multiple keloidal pink smooth papules in a clustered configuration overlying a 4- to 5-cm dermal/subcutaneous firm tethered nodule.

otherwise unremarkable. The patient's SPEP findings, along with her skin lesions, prompted referral to the hematology/oncology clinic for additional evaluation for suspected systemic RDD rather than putative metastatic breast cancer. A repeat PET scan revealed persistent lesions. Sternal biopsy revealed findings diagnostic for RDD.

The patient's cutaneous lesions were treated with intralesional triamcinolone with near complete resolution at 5 months' follow-up. The patient's bone lesions, now confirmed to be RDD, remained persistent but stable on PET monitoring. Hematology/oncology thus recommended trial of a course of rituximab, rather than pursuing further breast cancer treatment.

DISCUSSION

Our patient's rash of smooth erythematous papules and a deep nodule was diagnosed via an obtained biopsy specimen as RDD with characteristic histopathologic and immunohistochemical features. This triggered further systemic workup, including SPEP, that identified an IgA monoclonal gammopathy. The biopsy results and SPEP findings along with stable ^{18}F-fluorodeoxyglucose–avid lesions on PET scans prompted us to obtain a biopsy specimen from the sternum confirming systemic RDD rather than previously suspected additional breast cancer metastases, significantly altering her disease management.

Although the etiology of RDD has not yet been identified, associations of RDD with non-Hodgkin lymphomas and multiple myeloma have been reported in the literature, justifying systemic workup.[8] While SPEP testing is not a standard part of the workup for patients with RDD, it was performed in this case given the known associations of monoclonal gammopathy with systemic RDD.[4-7] Laboratory evaluation in RDD also commonly reveals leukocytosis with neutrophilia and anemia,[9] and approximately 90% of cases present with polyclonal hypergammaglobulinemia and elevated erythrocyte sedimentation rate.[1]

In this patient, the confirmed skin involvement by RDD, along with the finding of IgA monoclonal gammopathy, prompted referral to hematology/oncology to evaluate for possible systemic RDD as opposed to previously presumed metastatic breast cancer. The monoclonal gammopathy also raised concern about possible underlying hematologic

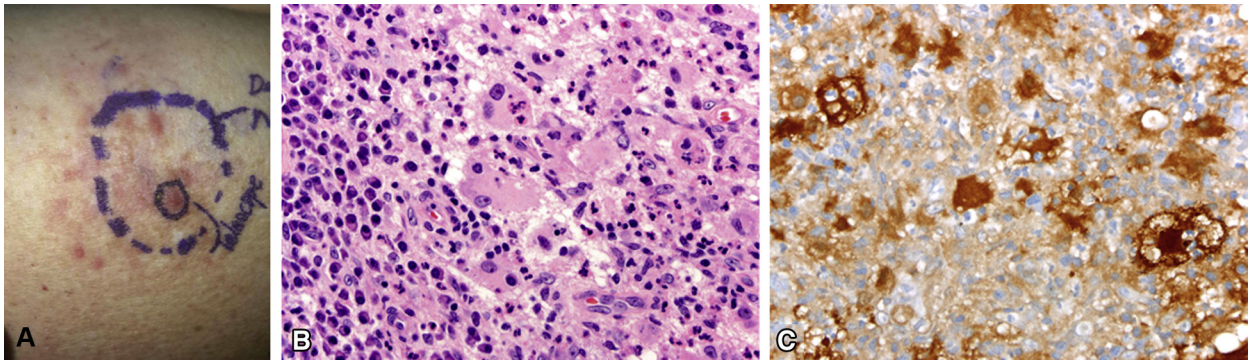

Fig 2. Rosai–Dorfman disease. Telescoping punch biopsy specimen obtained from a nodule on the left upper arm. Both the superficial papule and the deeper subcutaneous nodule (**A**) consist of a dense infiltrate of large pale histiocytes admixed with lymphocytes, plasma cells, and neutrophils. Some of the histiocytes contain intact inflammatory cells (predominantly neutrophils) within the cytoplasm, a process known as "emperipolesis" (**B**). These histiocytes are highlighted by S100 immunostain (**C**). (Original magnification: *A* and *B*, ×40; *C* and *D*, ×400.)

malignancies, such as lymphoma, myeloma, or alternate plasma cell dyscrasia. Although the significance of monoclonal gammopathy in patients with RDD may be indeterminate at the time of diagnosis, SPEP with serial monitoring is indicated as a normal part of work up of monoclonal gammopathy of unknown significance. Because IgA gammopathy has a more aggressive course compared with other monoclonal gammopathy of unknown significance variants, such diagnostic testing may be particularly important.[10]

There are few reported cases of RDD in the bone simulating metastatic cancer[2] and only 1 case simulating metastatic breast cancer similar to our patient.[3] In our patient's case, with a known history of metastatic breast cancer, following the dermatologic clue to perform additional systemic workup to distinguish between new metastases versus RDD bone lesions was critical to her care because it led to drastically different management decisions and averted the potential long-term morbidity associated with further aggressive treatment of presumed metastatic breast cancer. The treatment for RDD can be as minimal as ongoing monitoring or, if persistent, consist of immunomodulatory therapies, such as rituximab,[1] as in our patient. Dermatologists play a critical role in identifying the skin lesions of RDD and initiating the appropriate multidisciplinary workup to determine the presence of systemic disease or underlying hematologic malignancies, and, as in this case, help to diagnose RDD mimicking metastatic breast cancer.

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