Case Report

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Rosai-Dorfman Disease Presenting With FDG-Avid Breast Masses and Axillary Lymph Nodes on PET-CT in a Patient With Recent Diagnosis of Endometrial Carcinoma: A Diagnostic Dilemma

Jennifer Kudja-Rennick[1], Pai Raghav[2], Cedric Pluguez-Turull[2], Katherine Drews-Elger[3], Cristina Hoyos[2]

[1]Miller School of Medicine, University of Miami, Miami, FL, USA
[2]Department of Radiology, Miller School of Medicine, University of Miami, Miami, FL, USA
[3]Department of Pathology, Miller School of Medicine, University of Miami, Miami, FL, USA

ABSTRACT

Rosai-Dorfman disease (RDD) is a self-limited, idiopathic, non-neoplastic disorder characterized by the proliferation of phagocytic histiocytes, which can mimic malignant lymphoproliferative disease. Cases of RDD most commonly present as bilateral painless cervical lymphadenopathy, with lesser involvement of the axilla, inguinal, and mediastinal lymph nodes. We present the case of a 62-year-old woman with a history of endometrial serous carcinoma who underwent evaluation at a dedicated breast imaging department after positron emission tomography/computed tomography (PET/CT) revealed breast masses and axillary nodes with increased uptake of fluorodeoxyglucose (FDG). Upon clinical examination, she had bilateral palpable lumps in both breasts and axillae. Subsequent dedicated breast imaging with bilateral diagnostic mammography with tomosynthesis and bilateral complete breast ultrasound were suspicious for malignancy detecting bilateral breast masses and axillary lymphadenopathy corresponding to the FDG-avid findings on PET/CT. Ultrasound-guided core needle biopsies, however, revealed a diagnosis of RDD. This case highlights the unique characteristics of RDD with an atypical clinical presentation suspicious for breast cancer both clinically and radiologically.

Keywords: Endometrial carcinoma; primary breast cancer; axillary lymphadenopathy; mammogram; core needle biopsy

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Key Points

- Despite the benign nature of Rosai Dorfman disease (RDD), its clinical presentation can mimic features of malignancy, necessitating thorough diagnostic evaluation. The diagnostic dilemma of our case was intensified by the patient's recent gynecologic cancer, requiring careful oncologic evaluation.
- Diagnosis of RDD relies heavily on histopathology, highlighting features such as sinus infiltration and emperipolesis with key immunohistochemical markers including S-100 and CD68, which aid in distinguishing RDD from other conditions.
- RDD may present as suspicious findings on breast imaging or other imaging modalities, highlighting the need for timely diagnostic evaluation and provider awareness.

Case Presentation

A 62-year-old female without a personal or family history of breast cancer, but recently diagnosed with endometrial serous carcinoma, presented to the dedicated breast imaging clinic for evaluation after staging computed tomography (CT) of the chest revealed concerning findings in the uterus, breast, left abdominal wall and right colon. CT chest showed bilateral axillary lymphadenopathy (LAD) and breast nodules, the largest of which was in the medial right breast up to 2.5 cm (Figure 1). Positron emission tomography (PET)/CT scan subsequently detected bilateral, fluorodeoxyglucose (FDG)-avid, axillary lymph nodes and breast masses, most suspicious within the medial right breast (Figure 2), further corresponding to suspicious masses reported on the prior CT chest. Thus, concern for primary breast malignancy, metastatic disease and lymphoma were all considered in the differential diagnosis.

During diagnostic workup at the breast imaging clinic, she presented with palpable areas of concern in both breasts and axillae. She underwent bilateral diagnostic digital mammography with tomosynthesis which

Corresponding Author:
Jennifer Kudja-Rennick; jenkudjarennick@gmail.com

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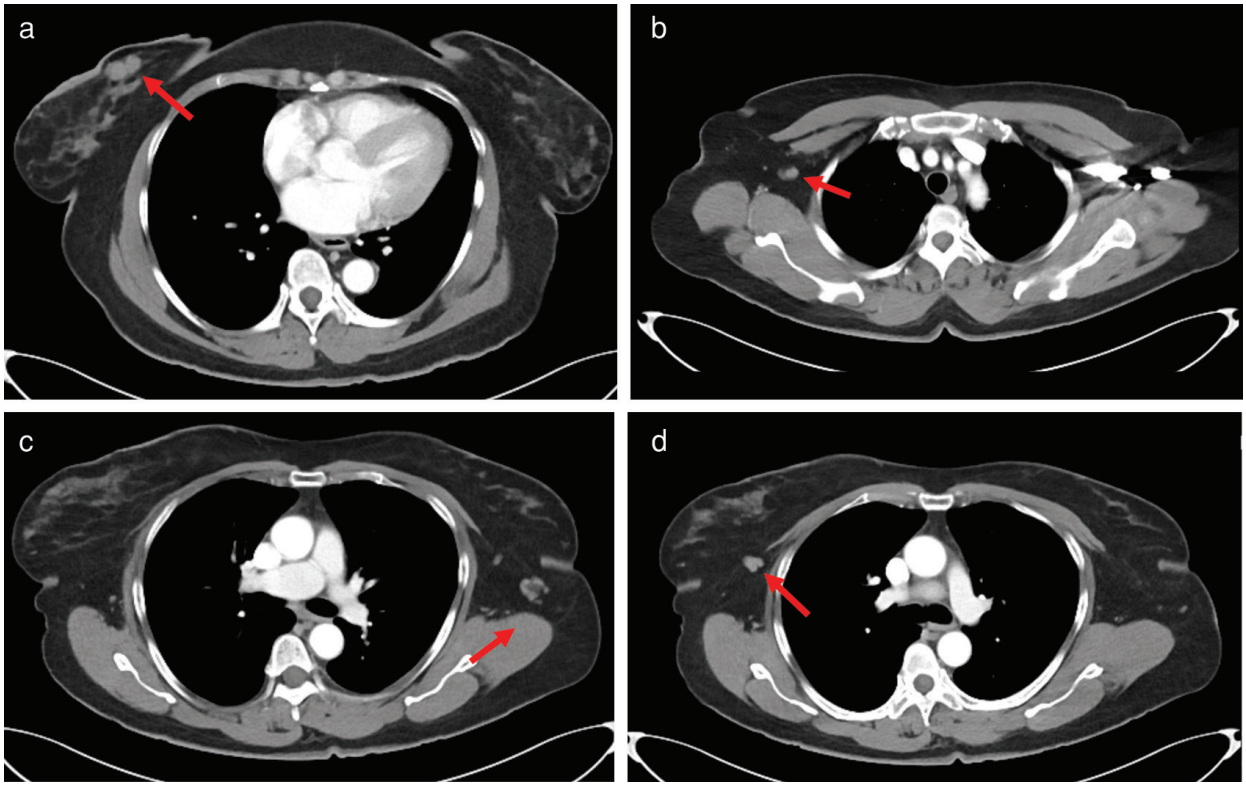

Figure 1. 62-year-old female with recently diagnosed endometrial carcinoma. Staging imaging via CT Chest showing prominent 2.5 cm right breast mass (a), and evidence of bilateral axillary LAD (b). Right axillary node with little fatty hilum and thickened cortex of 0.9 cm (c and d). Additional enlarged nodes of the left axilla, 1.6 cm x 1.5 cm, and right axilla, 1.2 cm x 1.1 cm

CT: Computed tomography; LAD: Lymphadenopathy

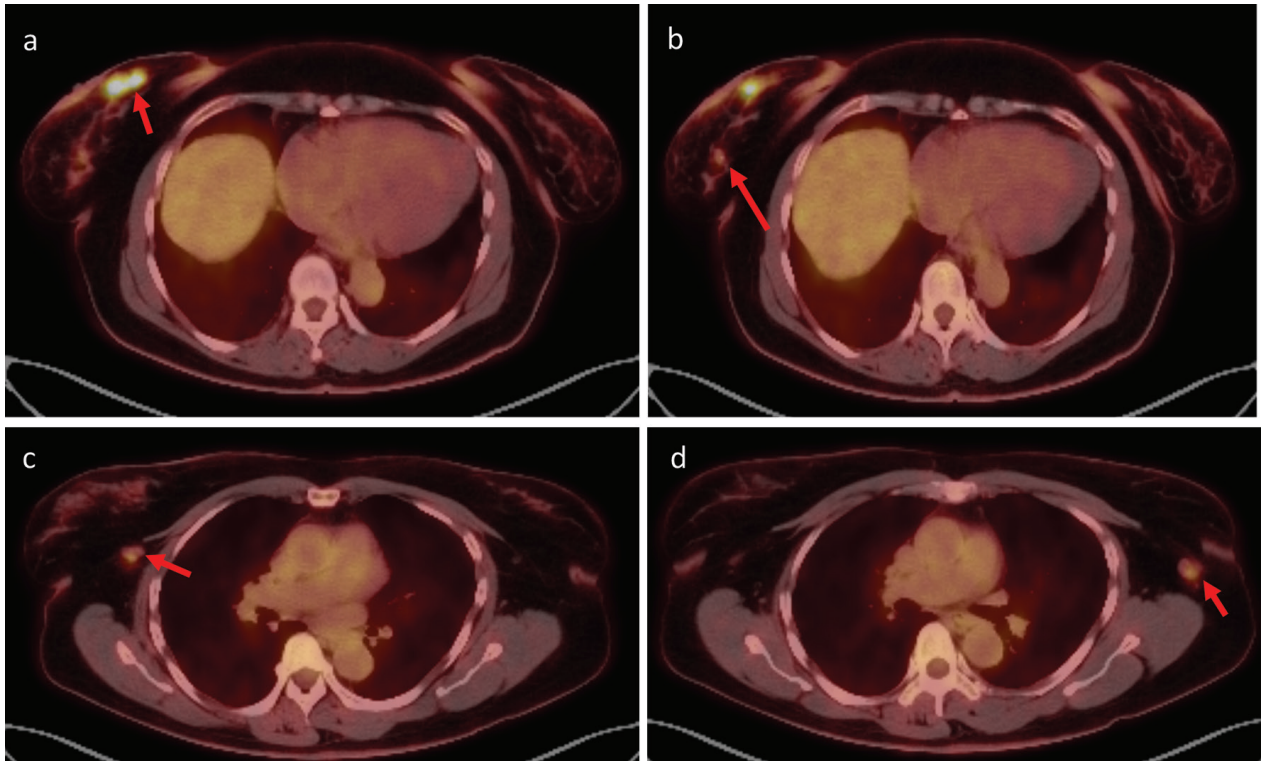

Figure 2. PET/CT showing FDG avid right breast masses SUV 9.5 medially and 7.6 laterally (a and b). Additional views with (c) right FDG avid axillary lymph node with background FDG activity and (d) left axillary node with SUV 2.4

PET/CT: Positron emission tomography/computed tomography; SUV: Standardized uptake value; FDG: Fluorodeoxyglucose

showed scattered areas of fibroglandular breast tissue and bilateral similar-appearing, partially obscured, equal density masses, including a dominant 3.3 cm mass in the right lower inner quadrant at 3-4 o'clock, containing a biopsy marker from a prior reportedly benign biopsy site performed many years ago (Figure 3). Mammography was relevant for a 1.7 cm obscured equal density mass in the right outer breast at 9 o'clock which also contained a biopsy marker at an additional reportedly benign biopsy site. There was an additional 1.8 cm obscured mass with coarse calcifications in the left inner breast at approximately 9 o'clock favoring a benign, involuting fibroadenoma, prominent axillary lymph node, and persistent asymmetry reported in the left outer breast at 3 o'clock (Figure 4). No previous screening or diagnostic images were available for comparison at the time of diagnostic evaluation. Given the areas of palpable concern and mammographic findings within the both breasts and axillae, bilateral breast ultrasound (US) was obtained. US showed multiple breast masses, with the most suspicious including a 3.2 x 1.3 x 1.3 cm oval heterogeneous mass with microlobulated margins and internal vascularity on Doppler ultrasound in the right breast at 3-4 o'clock, 2 cm from the nipple, which corresponded to the mammographic mass with adjacent biopsy marker in the right lower inner quadrant. (Figure 5). There was also an additional 1.0 x 0.7 x 0.9 cm irregular, heterogeneous mass in the left breast at 3 o'clock, 4 cm from nipple (Figure 5). On evaluation of bilateral axillae, an abnormal right lymph node was visualized with up to 0.5 cm of cortical thickening, as well as an abnormal left axillary lymph node with a cortical thickness of 0.7 cm in the mid left axilla (Figure 6). Despite the patient's account of a remote, benign biopsy result corresponding to the right breast mass at 3-4 o'clock, biopsy was indicated given the internal vascularity and FDG avidity. A Breast Imaging Reporting and Data System (BI-RADS)-4 classification was assigned to her breast imaging. Additional core needle biopsy of the abnormal right lymph node was indicated given the corresponding FDG avidity and cortical thickness. Respective biopsies were performed, and post-biopsy imaging confirmed adequate placement of biopsy markers.

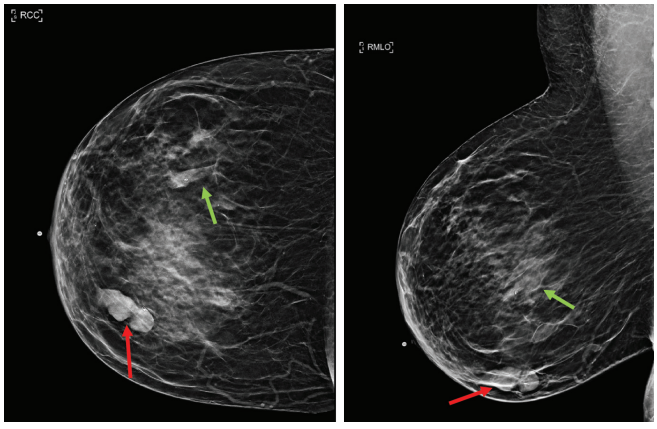

Figure 3. Bilateral diagnostic digital mammography with scattered areas of fibroglandular breast tissue. Right breast cranial-caudal (left image) and medial lateral (right image) views showing 3.3 cm oval circumscribed mass denoted by red arrow in the right lower inner quadrant at 3:00-4:00, also containing a prior biopsy marker. An additional 1.7 cm obscured equal density mass also containing a biopsy marker was noted in the right outer breast, approximately 9:00, denoted by green arrow

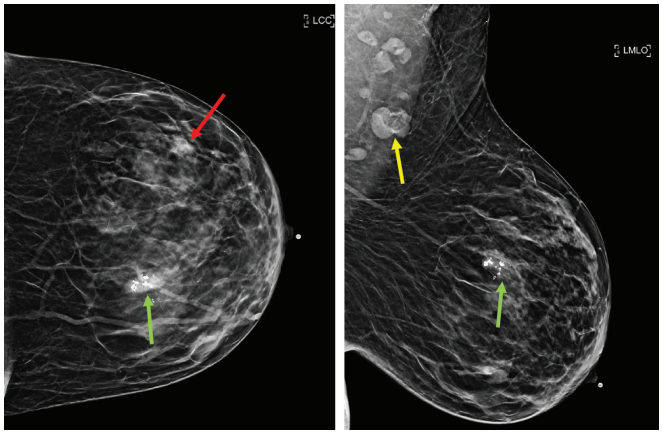

Figure 4. Bilateral diagnostic digital mammography with scattered areas of fibroglandular breast tissue. Left breast cranial-caudal (left image) and medial lateral (right image) views showing a 1.8 cm obscured mass with coarse calcifications in the left inner breast at approximately 9:00 favoring a benign, involuting fibroadenoma (green arrow). Additional persistent asymmetry in the left outer breast, best seen on craniocaudal (CC) view (red arrow), approximately 3:00, middle depth which was further evaluated with spot compression views (Figure 7 below). Prominent left axillary node appreciated on the left medial-lateral oblique (MLO) view (yellow arrow)

Ultimately, histopathological results from the biopsies performed of the right breast and right axillary node demonstrated intramammary lymph nodes with sinus histiocytosis, consistent with RDD, and a benign lymph node with paracortical hyperplasia and sinus histiocytosis. Cytology studies revealed marked paracortical expansion by patchy histiocytic proliferation with round nuclei and small nucleoli, surrounded by abundant pale cytoplasm, with emperipolesis present. There was no evidence of metastatic disease or atypia (Figure 7). Immunohistochemical studies revealed the histiocytes were positive for S-100, OCT2, cyclin D1, and BCL6, and negative for CD1a. Biopsy of the suspicious left breast mass at 3 o'clock was also performed with pathology revealing benign mammary parenchyma with dense stromal fibrosis. The results were concordant with her breast imaging. Patient consent was obtained prior to preparation of the following case and manuscript.

Discussion and Conclusion

RDD, also known as sinus histiocytosis with massive lymphadenopathy, is a benign disorder first described in 1969 (1). RDD is characterized by the non-neoplastic proliferation of activated histiocytes within tissues, often presenting as extensive peripheral lymphadenopathy (2, 3). Diagnosis is largely based on clinical history and pathology.

Cases of RDD are more common within the pediatric population with peripheral lymphadenopathy as the cornerstone of the disease syndrome. When presenting in adults, RDD has been reported to present in the second decade of life with cervical lymphadenopathy, usually bilateral and painless in about 87% of patients (4-6). The axilla, as in our case, has been found to be involved in RDD to a lesser degree, in roughly 23.7% of cases. Involvement of the inguinal (25.7%) and mediastinal (14.5%) regions have also been reported (1, 6-7). Other signs and symptoms of RDD include fever, weight loss, anemia, elevated erythrocyte sedimentation rate, hypergammaglobulinemia, malaise, and night sweats (8-9). RDD has also been shown to affect various extra nodal sites in nearly half of patients with greatest prevalence within the head and neck region, specifically the paranasal sinuses and nasal cavity (4, 8, 10). Additional extra nodal cases of RDD in adults have been reported to present with cutaneous findings without LAD, most often in the form of papules, nodules, and plaques (11). Extra nodal RDD was most frequently reported in older patients

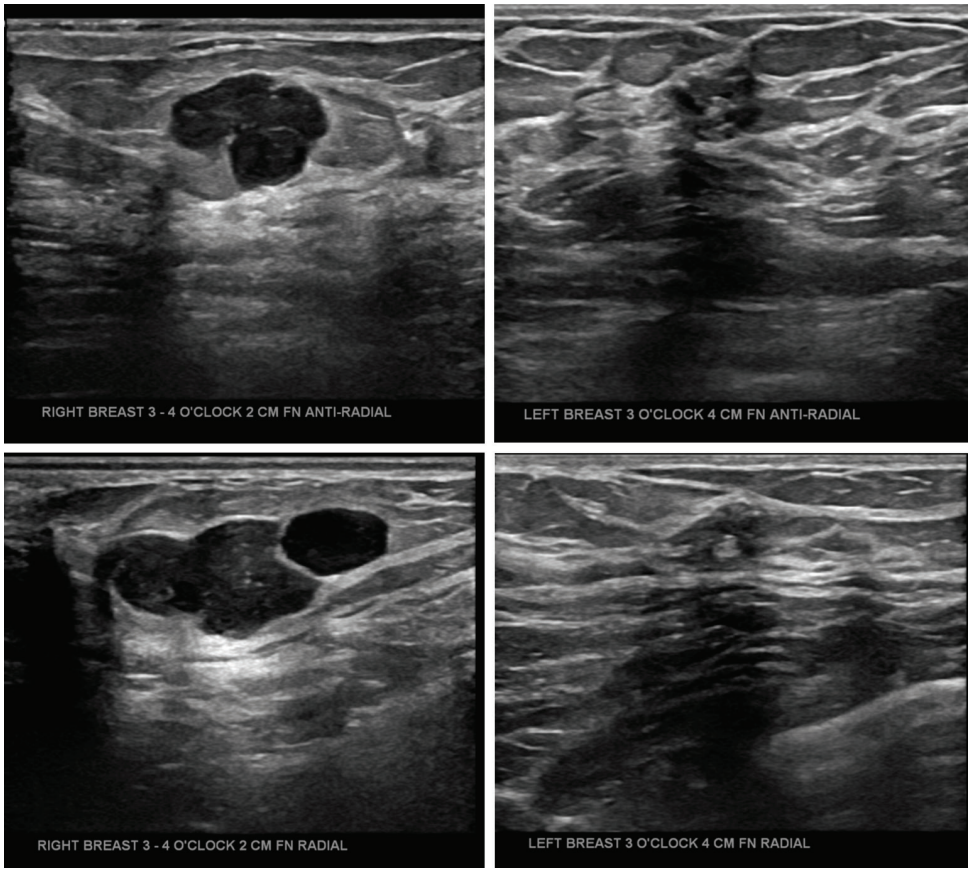

Figure 5. Bilateral complete breast ultrasound with findings of 3.2 x 1.3 x 1.3 cm oval heterogeneous mass with predominantly circumscribed however some micro lobulated margins and internal vascularity in the right breast 3-4:00, 2 cm from nipple, corresponding to the mammographic mass with adjacent biopsy marker in the right lower inner quadrant (left images) and 1.0 x 0.7 x 0.9 cm irregular, heterogeneous mass in the left breast 3:00, 4 cm from nipple, concordant with asymmetry on mammographic images. Core biopsy yielded intramammary lymph nodes with sinus histiocytosis, consistent with Rosai-Dorfman disease

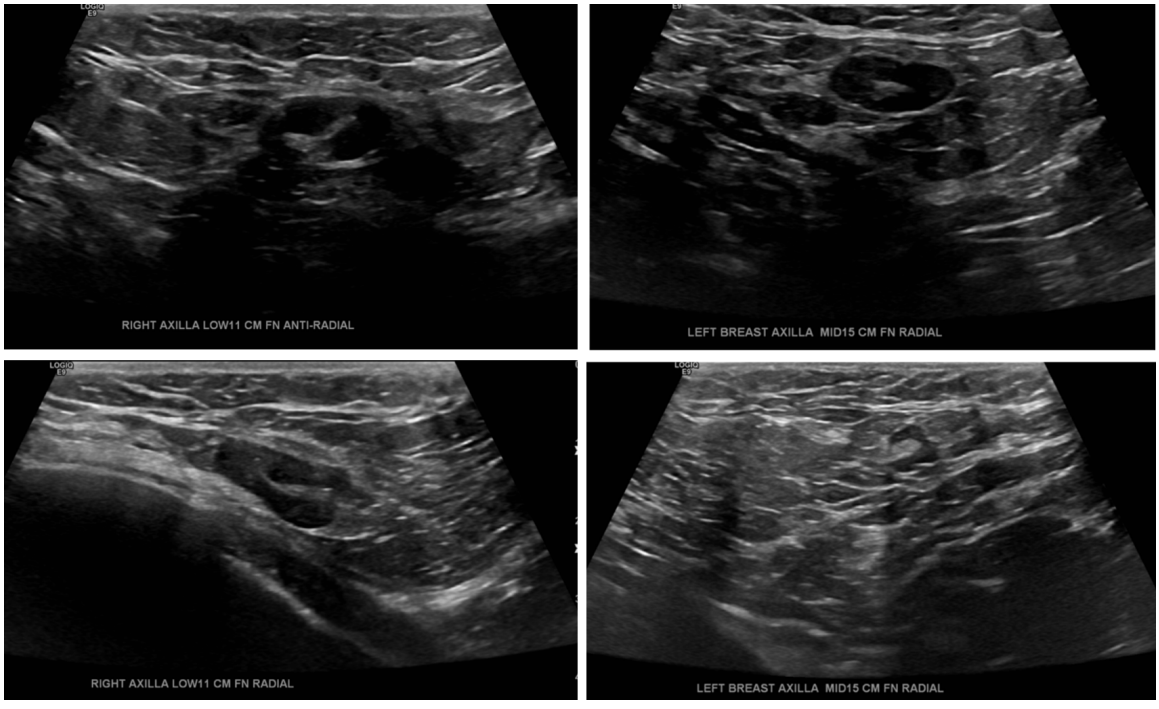

Figure 6. Bilateral complete breast ultrasound with findings of abnormal right lymph node with 0.5 cm cortical thickening in the low right axilla 11 cm from nipple (left images), and abnormal left axillary lymph node with cortical thickness of 0.7 cm and peripheral vascularity in the mid left axilla at 15 cm from nipple (right images). Core biopsy yielded a benign lymph node with paracortical hyperplasia and sinus histiocytosis

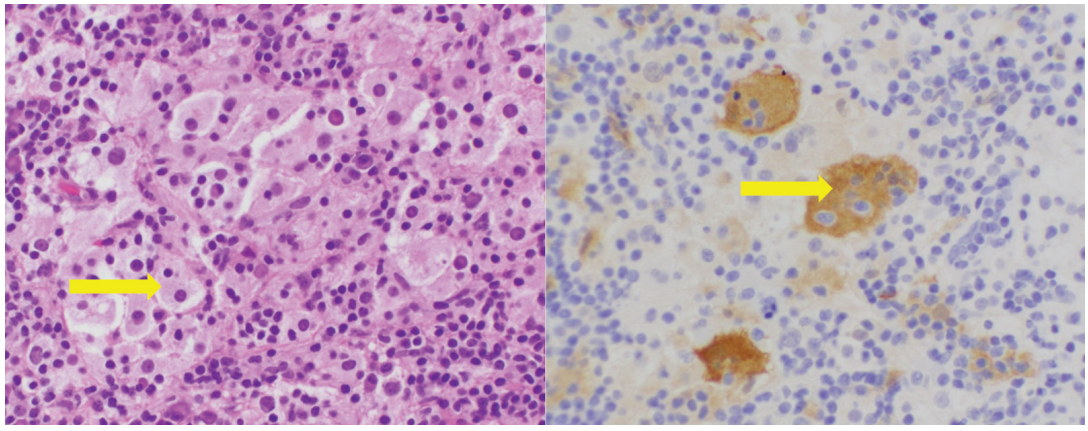

Figure 7. Photomicrographs showing representative histologic section of breast core with marked paracortical expansion and patchy histiocytic proliferation with round nuclei and small nucleoli, surrounded by abundant pale cytoplasm, emperipolesis (left image, yellow arrow, H and E, 600X). Higher power photomicrograph with both H and E (600X) and S100 immunostaining shows diffuse, strong cytoplasmic positivity within histiocytes (right image, yellow arrow)

(1, 5, 8). Rare extra-nodal presentations of RDD are still documented, including cases involving the CNS and breast, exemplifying the vast clinical presentations of RDD.

The histiocytosis of RDD may be sporadic, familial, or cutaneous. Sporadic cases are the most prevalent and may be secondary to neoplasia, seen with hematologic malignancies, or autoimmune related such as with systemic lupus erythematosus or human immunodeficiency virus (3, 12). The etiology of RDD is widely debated, and has also been attributed to an exacerbated immune response to viruses such as Epstein-Barr virus, human herpes virus 6, cytomegalovirus, and parvovirus B19, (8, 13, 14). Histopathologic hallmarks of RDD include sinus infiltration, emperipolesis or pale histiocytic cells containing engulfed lymphocytes, and immunohistochemical features such as positive staining for S-100, alpha1-anti-chymotrypsin, CD68, and staining negative for CD1a (4, 5, 8, 10). While emperipolesis is commonly seen histologically in RDD, it is not pathognomonic nor a requirement for diagnosis. In a study by Hoffman et al. (15), 22 cases of RDD of the breast were analyzed for comparison of histopathologic characteristics with 19/22 showing numerous plasma cells and prominent sclerosis in majority of cases, and 22/22 displaying emperipolesis (15, 16). Histopathology in our case demonstrated emperipolesis with positive staining of S-100 and CD68, and negative staining for CD1a.

Imaging findings of RDD are confounding and often complicate the broad differential diagnoses. Such differentials may include lymphoma, malignant histiocytosis, tuberculosis, noninfectious granulomatosis, and others. CT, magnetic resonance imaging (MRI), PET/CT, and radionucleotide bone scans have been used in diagnostic work-up and surveillance of patients with documented RDD. The lymphadenopathy present in RDD can be well identified using ultrasound, CT, MRI, and PET/CT, as also seen in the presented case. CT findings in patients with RDD may reveal enhancing isolated or disseminated lymphadenopathy. RDD lesions on MRI have been reported to be isointense on T1-weighted images and iso- to hypo-intense on T2-weighted images (18-20). Lymphadenopathy in RDD on ultrasound studies have been reported to mimic malignant appearing nodes, underscoring the importance of histopathologic evaluation (21). On PET/CT, lesions of RDD have been reported to demonstrate increased gallium uptake and increased metabolism of FDG (19). The avidity and high standardized uptake value of 9.5 of the right breast mass in our case further demonstrates this.

RDD of the breast is rare, with only a few cases reported in the literature (22-25). Similar to that of our patient, documented cases often presented with unilateral or bilateral breast masses. Green et al. (22) described seven documented cases of RDD within the breast included disease findings confined to one breast itself, involvement of one breast and ipsilateral axillary nodes, or both breasts with disseminated systemic disease, and all with findings concerning for malignancy (23, 24). On dedicated breast imaging, findings of RDD cases have been classified as suspicious or highly suspicious for malignancy during diagnostic work-up. On mammography specifically, cases of RDD have been reported to present as a high-density, irregular or lobulated mass with circumscribed or ill-defined margins, multiple masses, or even small diffuse breast nodules (23, 24). On breast ultrasound, cases of RDD have been reported to appear with a hypoechoic mass with indistinct or angulated margins with increased vascularity on Doppler (23, 24). A study by Wang et al. (25), noted that breast masses in RDD were categorized as BI-RADS-4 or 5 during workup for all evaluated patients, similar to the degree of suspicion elicited by our case. On targeted breast US, the palpable right breast mass found to be RDD in our case showed an oval heterogeneous mass with microlobulated margins and internal vascularity, further emphasizing the concerning nature to which RDD has been documented in previous cases, both clinically and radiologically.

RDD follows an unpredictable, and often slowly progressive, clinical course with most patients not requiring treatment. Spontaneous remission has been noted in approximately 20–40% of patients after several years, with others showing a chronic pattern of exacerbations and remissions (26, 27). Nodal cases and those of cutaneous disease are more commonly self-limited compared to those with multifocal and extra-nodal RDD (2, 26). A study conducted of 238 cases of RDD revealed mortality due to direct complications, infections, or amyloidosis, in only about 7% of patients (2, 26). Ultimately, a limited number of RDD cases have been documented and studied, creating a challenge when examining effective treatment modalities. Treatments with corticosteroids, surgical resection, systemic chemotherapy, and radiotherapy have been studied without consistent clinical evidence favoring one modality. Symptomatic patients without significant morbidity will most often undergo treatment with steroids as first-line therapy with unpredictable response (28). Given the rarity of the disease and the absence of a definitive therapeutic pathway, treatment is tailored to individual clinical circumstances.

In conclusion, RDD presents a unique diagnostic challenge due to its diverse clinical manifestations and imaging characteristics that can often mimic malignancy. The present case underscores the importance of a thorough evaluation, particularly in patients undergoing oncologic assessments or with concerning history of malignancy. Although benign and sometimes self-limiting, awareness of the diverse clinical presentation of RDD is important for accurate diagnosis, management and to enhance patient care and clinical outcomes.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Footnotes

Authorship Contributions: Surgical and Medical Practices: C.P.T., C.H.; Concept: C.P.T., C.H.; Design: J.K.R., P.R., C.P.T., C.H.; Data Collection or Processing: C.P.T., K.D.E. C.H.; Analysis or Interpretation: J.K.R., P.R., C.P.T., K.D.E., C.H.; Literature Search: J.K.R., P.R.; Writing: J.K.R., P.R., C.P.T., C.H.

Conflict of Interest: No conflict of interest was declared by the authors.

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