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Authors

Vecerek, Natalia

Henderson, Gregory P

Pascucci, Anabella

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CLINICAL VIGNETTE

Primary Cutaneous Rosai-Dorfman with Uveitis

Natalia Vecerek, Gregory P. Henderson, M.D. PhD, and Anabella Pascucci, MD

Introduction

Rosai-Dorfman disease (RDD) is an idiopathic, benign proliferation of histiocytes. Originally described as a nodal disease, extranodal disease is common. Isolated cutaneous disease is rare.

The first description of RDD, also known as sinus histiocytosis with massive lymphadenopathy, came from Destombes et al. in 1965 with his study of four patients with unexplained adenitis.¹ As further cases accumulated, Rosai and Dorfman were able to characterize RDD as a clinicopathological entity beginning in 1969.^{2,3} Rosai and Dorfman observed that most cases exhibited painless, bilateral, cervical lymphadenopathy, with elevated erythrocyte sedimentation rate (ESR), fever, leukocytosis with neutrophilia and hypergammaglobulinemia.³ On pathological examination, involved lymph nodes demonstrated pericapsular fibrosis, intrasinus histiocytes with clear cytoplasm, and abundant plasma cells. A consistent finding in all patients, which now pathologically defines RDD, was the presence of phagocytosed inflammatory cells within the cytoplasm of histiocytes.³ This pathologic finding has since been termed emperipolesis.⁴

Although the underlying etiology of RDD remains unknown, the course of the disease has been well described in the literature. RDD is a benign disease of histiocyte infiltration into either lymph nodes or extranodal tissue.⁴ While RDD generally has an affinity for lymph nodes, it can present in other sites, most commonly the skin, soft tissue, central nervous system, and the gastrointestinal tract.⁴ RDD involves extranodal sites in 43% of cases, with skin being the most common site affected.⁵ RDD limited to the skin is a rare occurrence, representing only 3% of all cases.⁶ When RDD does affect the skin it usually appears as a combination of papules, plaques, nodules and pustules that have been described as xanthelasma-like, acneiform, and rosacea-like.⁶

RDD has a broad differential, including malignancies (such as lymphoma, melanoma and leukemia), other histiocytic disorders (such as Langerhans cell histiocytosis), sarcoidosis, and tuberculosis.⁴ On histology, emperipolesis suggests RDD. Immunological studies are often useful in diagnosing RDD as the RDD histiocytes will typically stain positive for S100 and negative for CD1a, helping to differentiate it from other histiocytic disorders.⁴ Other macrophage/monocyte lineage markers may also be positive including CD68 and CD163.

We present a case of primary cutaneous RDD without nodal involvement that is associated with uveitis and occurred after chemoradiation for breast cancer.

Case

A 47-year-old Hispanic woman presented to UCLA Dermatology for a second opinion of a facial rash previously diagnosed as granulomatous rosacea.

The patient had a history of bilateral breast cancer diagnosed two years prior. She required a bilateral mastectomy, two rounds of taxotere and cyclophosphamide chemotherapy, and two rounds of radiation. She has been on maintenance aromatase inhibitor (first anastrozole then exemestane) since completion of chemoradiation. She noted that a facial rash began to appear approximately one year after she completed chemo-radiation. Concurrently, she developed uveitis requiring multiple steroid injections. CT scans have been negative for any lymphadenopathy.

On dermatologic examination, she had numerous erythematous non-scaly dermal papules and nodules on her bilateral cheeks (Figure 1).



The remainder of her skin examination was normal. She notably did not have any lymphadenopathy on physical exam. The patient complained that the rash was pruritic. She reported no history of fever, weight loss, or night sweats. A prior outside

biopsy had revealed moderate chronic perifollicular granulomatous inflammation with telangiectasias, consistent with granulomatous rosacea. A year of treatment with ivermectin cream, metronidazole gel, risaborole and minocycline showed very slight or no improvement. Laboratory work-up revealed an elevated ESR of 58. Work up for autoimmune disorders including anti-nuclear antibody, anti-double stranded DNA anti-bodies, anti-smooth muscle antibodies, anti-SSA, anti-SSB, anti Scl-70, and rheumatoid factor was all negative. Angiotensin converting enzyme, C3, and C4 levels were all within normal limits. Testing for possible infectious causes including rapid plasma reagin, bartonella, West Nile virus, and Lyme disease was all negative.

Repeat biopsy of her right cheek showed dense dermal histiocytic inflammation. This included multinucleate histiocytes exhibiting emperipolesis. The associated histiocytes were positive for both CD68 and S100 on immune-histochemistry. The histiocytes within the lesion were negative for CD1a and pan-cytokeratin. Periodic acid–Schiff, Wade–Fite, and acid-fast stains were all negative. Based on this histology and immunohistochemistry, the patient was diagnosed with RDD.

Since her diagnosis, she has had larger lesions excised without any adjunctive treatment. She has been stable, without development of new lesions. Follow-up with her oncologist has not revealed any evidence of systemic involvement or new lymphadenopathy.

Discussion

Cutaneous RDD may be a distinct clinical entity from classic RDD with lymph node involvement. There have been case reports in the literature with uveitis occurring concurrently with RDD, with at least two previous cases confirming histiocytic infiltrate in the uveal tract via biopsy.⁷ Our case showed evidence of systemic involvement with uveitis, but our patient did not have a uveal biopsy. This case demonstrates that a high degree of suspicion should be maintained for this unusual diagnosis as RDD can present in various ways and similarly to other more common conditions, such as rosacea.

There is speculation as to the underlying cause of RDD, as the pathogenesis of the disease remains unknown and is based largely on isolated case reports. The histocyte proliferation in RDD is polyclonal, giving rise to speculation that RDD may be a reactive phenomenon. No single trigger has been identified. Case reports include Epstein-Barr virus (EBV), parvovirus B19, human herpes virus-6 (HHV-6) and human herpes virus-8 (HHV-8), and Crohns.⁶ Aberrant activation of cell mediated immunity is likely involved in the pathogenesis as many patients are found to have activated macrophages, polyclonality, and increased IgG4/IgG ratios.⁶ RDD has further been associated with immune system abnormalities including autoimmune disease and HIV infection.⁶ Our patient had a history of breast cancer and had recently completed chemo-radiation therapy. It is interesting to consider a potential link between her prior chemotherapy as taxotere is known to have immunestimulatory effects and can alter levels of cytokines in patients.⁸

Similarly, the association with uveitis supports an underlying immune mediated mechanism for RDD.⁷

Work-up for suspected RDD should include computed tomography of the neck, chest, abdomen, and pelvis to evaluate for systemic involvement, while laboratory workup should include complete blood count, liver and kidney function tests, immunoglobulin panel, ESR, testing.⁴ If appropriate, an infectious and autoimmune workup would include viral testing for EBV, cytomegalovirus, HHV-6, HHV-8, HIV, antinuclear antibodies, and rheumatoid factor.⁴ For patients who are suspected to have cutaneous involvement, biopsy should be performed.⁴ Of particular importance is histopathologic differentiation of RDD from other histiocytic disorders. Malignant histiocytosis will also stain positive for S100, but will generally also exhibit marked cytological atypia with pleomorphism.⁶ The presence of Birbeck granules, eosinophilic infiltrate, and positivity of CD1a and Langerin help differentiate Langerhans cell histiocytosis.⁶ In regards to our patient, the finding of emperipolesis confirmed the diagnosis of RDD, with positive staining for CD68 and S100 supporting the diagnosis.

Because RDD is benign and self-limited, treatment is often only advised in patients with systemic involvement of vital organ systems.⁴ Systemic corticosteroids are considered first line treatment, although response is highly variable.⁴ Radiotherapy has been shown to have limited efficacy, while chemotherapy is generally ineffective.⁹ Localized nodal disease or cutaneous involvement can be treated with surgical excision.⁴ In a series of thirteen patients with cutaneous RDD reported by Brenn et al., three patients with complete follow-up data who underwent surgical excision experienced complete resolution, while one of three patients treated with radiation had resolution of lesions.¹⁰ In three patients treated with steroids, one using oral steroids had resolution, while topical steroid use in two patients led to continued eruption of lesions.¹⁰ Oral methotrexate has also been successfully utilized for cutaneous RDD involvement in a case report described by Sun et al.¹¹

Our patient is being successfully treated with surgical excision of larger lesions and her disease appears to be remitting without further treatment. This case highlights the importance of careful pathological diagnosis as RDD can appear similarly to other disorders. Additionally, this case adds to the literature regarding a potential connection between RDD and uveitis, as well as a possible linkage to prior treatment with chemotherapy.

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