Rosai-Dorfman disease (RDD), or sinus histiocytosis with massive lymphadenopathy (SHML) is a benign lympho-histiocytic proliferative disorder initially described with bilateral painless lymphadenopathy (90 percent), fever, leukocytosis, elevated ESR, anemia, and polyclonal hypergammaglobulinemia (90 percent).¹

RDD presents with cervical adenopathy most commonly in children or young adults (median age, 20 years), in those of African ancestry and male sex.¹ Extranodal disease occurs in 25-40 percent, is often widespread, involving skin, respiratory tract, soft tissue, paranasal sinuses, visceral organs, bone, central nervous system, genitourinary tract, and orbit.²³ Cutaneous RDD (CRDD) is rare with about 3/100 cases of SHML. CRDD has a median age 44 with a female and Asian predominance, and can be in any location. CRDD presents as red-brown-yellow localized or disseminated papules, plaques, or nodules.²⁴

CASE REPORTS

Case 1. A 34-year-old female presented with a 6x8cm reddish-brown plaque with nodules on her left leg for seven months. She reported no systemic symptoms, and had no lymphadenopathy. The initial biopsy was interpreted as an eruptive xanthoma, but, given the clinical history, further testing was performed. Further evaluation revealed aggregates of large pale to eosinophilic histiocytes with large round or oval nuclei with dispersed chromatin and prominent nucleoli in areas showing emperipolesis of other inflammatory cells. There was also an associated neutrophilic and lymphoplasmacytic infiltrate, and surrounding vascular proliferation and fibrosis (Figure 2). The histiocytes were diffusely positive for S100 protein (Figure 3), and there was no light chain restriction with kappa and lambda light chains. Based on these findings she was diagnose with CRDD.

The patient reported mild headaches since the onset of CRDD, and eye examinations revealed anterior bilateral uveitis. The patient was treated with intralesional corticosteroid to the CRDD and intraocular corticosteroids for the uveitis, with clearing of the uveitis and CRDD.

Case 2. A 54-year-old female presented with seven reddish-brown 3-12cm diameter plaques that started on the left leg six months earlier, and had enlarged, and were now also on the right buttock. She developed dull eye pain with photophobia.

Recognition of cutaneous Rosai-Dorfman disease and the possibility of associated uveitis is important so that patients can be referred for appropriate ophthalmologic evaluation.

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at about the same time. A biopsy was performed and showed histologic features identical to those seen in Case 1. IHC showed diffuse staining of histiocytes for S-100 protein, MAC-387, CD4, CD68, CD74, and negative staining for CD1a.

Laboratory results showed an elevated C-reactive protein 44.7 and viral titers for Epstein-Barr virus, Human Herpes Virus (HHV)-6, HHV-7, and parvovirus B19 were negative. Serum protein electrophoresis showed no evidence of a polyclonal gammopathy.

Ophthalmologic examination revealed bilateral anterior uveitis that responded two weeks course of prednisone ½ mg/kg/day follow by topical corticosteroid. The patient’s cutaneous lesions also showed some clearing with the oral steroid, but remained stable after discontinuation of the oral steroid. The patient was started on methotrexate a month later increasing to 10 mg/weekly with progressive clearing of the skin lesions. The methotrexate was discontinued after two months, and she had no recurrence three months later.

Histiocytes in RDD express S-100, CD4, CD68, CD74, MAC387 (S100A9), and often CD30 consistent with an activated phenotype, but not CD1a. The disease usually has an indolent, self-limiting course. However, in some patients the disease may be persistent, but stable; and rarely, the disease may be progressive and fatal. Progressive disease usually occurs in patients with an underlying primary immune deficiency.5

Uveitis in association with RDD has been reported in seven previous cases; five with associated lymphadenopathy, and two others with only CRDD.2,3,6,7

**DISCUSSION**

The underlying cause of RDD is unclear. Regarding the underlying cause of RDD, some reports have suggested the possibility of a reaction to a herpes virus including Epstein-Barr virus, HHV6 and HHV7, but this has been documented in minority of cases.1-4

Other associations include underlying autoimmune disease, inherited immune deficiency, i.e. Wiskott Aldrich syndrome and more commonly autoimmune lymphoproliferative syndrome (ALPS), immune stimulation with vaccination, and other benign and malignant lymphoproliferative disorders including Polycythemia Vera and non-Hodgkin’s B cell lymphoma.1-3,8

Thus, RDD appears to be a lymphoproliferative process that may arise secondary to a number of different stimuli or underlying inherited or acquired genetic of epigenetic defects. Of these, the significant association with ALPS 1a (affecting the Fas gene with dysregulation of lymphoreticular cell apoptosis) may give the best clue to the pathogenesis.8 Defects in apoptosis could explain the histiocytic proliferation and cytokine dysregulation RDD, and acquired Fas defect may occur due to somatic mutation but more commonly due epigenetic hypermethylation. Methotrexate can be used as a demethylating agent as well as an immune modulator.

We present two additional cases in which CRDD disease was associated with uveitis, and suggest that patients with CRDD should have ophthalmologic examinations.  

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