Dapsone as a Potential Treatment for Cutaneous Rosai-Dorfman Disease With Neutrophilic Predominance

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 31-year-old Taiwanese woman, who from her medical history was generally well, presented with 1 slowly enlarging elevated plaque on the posterior aspect of her right shoulder. This had first been detected 3 months before the visit to our clinic. The lesion had originated as a small, tender, erythematous papule and had since grown into a large confluent plaque with satellite papules. She claimed that the lesion was increasing in size, and this was accompanied by intense itching and fever. On physical examination, there was 1 palm-sized, dusky red, elastic firm plaque on the right shoulder. The main lesion was surrounded by multiple 2- to 8-mm erythematous satellite papules (Figure 1). There were no palpable cervical, supraclavicular, axillary, or inguinal lymph nodes. A systemic workup that included head, neck, and chest computed tomographic scans showed no involvement of other organs. Workups done to determine the source of her febrile episodes yielded no evidence of active infection. The only abnormal laboratory finding was polyclonal hypergammaglobulinemia found on serum protein electrophoresis. An incisional biopsy was performed. Microscopically, a dense dermal infiltrate extended from the upper dermis deep to the subcutis (Figure 2). The infiltrating cells were mainly composed of histiocytes with large vesicular nuclei. They also had abundant cytoplasm with spindly borders. Neutrophils, lymphocytes, and plasma cells were scattered between the histiocytes, and the presence of lymphocytes engulfed within the histiocytic cytoplasm, a feature called emperipolesis, was also noted. The mixed infiltration was neutrophil predominant. Immunohistochemical studies revealed histiocytes that stained positively for S100 protein and CD-68. Notably, the dermis surrounding the histiocytes was infiltrated by numerous neutrophils. Clinically and histologically, she was diagnosed as having cutaneous Rosai-Dorfman disease (CRD).

Before visiting our hospital, she had been treated at a dermatologic clinic for 2 months, first with topical triamcinolone, oral prednisolone (30 mg/d), and then with oral isotretinoin (100 mg/d). However, the lesion had continued to worsen and the symptoms of pruritus and intermittent episodes of fever had progressed during the treatments. Superficial irradiation was suggested, but the patient refused owing to its potential hazards.

THERAPEUTIC CHALLENGE

The patient was treated unsuccessfully with a variety of therapeutic modalities, including topical and systemic corticosteroids just noted, as well as oral isotretinoin. She refused superficial radiation treatment and the large size of the lesion prevented the tumor from being simply excised. A safe and effective alternative treatment was needed.
We administered oral dapsone, 100 mg daily, to treat the patient since the skin biopsy findings revealed profuse neutrophilic infiltration, which clinically corresponded to an inflamed component of the disease. Ten days after starting dapsone therapy, the patient felt an obvious improvement in the itching and local erythema. Within 3 months, the extensive and disfiguring skin lesion had undergone significant regression (Figure 3). After 3 months of treatment, the histologic characteristics of a skin biopsy specimen taken from the right shoulder showed only residual scar tissue; dapsone therapy was therefore discontinued. No recurrence of the skin lesion was noted during the year that followed the discontinuation of dapsone therapy.

**COMMENT**

In 1969, Rosai and Dorfman first described the disease of sinus histiocytosis with massive lymphadenopathy (SHML), a histiocytosis syndrome that usually presents with cervical lymphadenopathy. Extranodal involvement is frequently seen and the skin is the most common organ of involvement. The pure cutaneous form of this histiocytosis without involvement of the lymph nodes or other organs is known as CRD. The pathogenesis of SHML and CRD remains unclear. Most cases of CRD have a limited distribution and are self-limiting, requiring no treatment. However, the disease has an unpredictable duration before reaching spontaneous remission. Patients who have extensive cutaneous involvement may be subjected to intolerable disfigurement and mental stress. In addition, some patients are significantly disturbed by the symptoms and need careful evaluation and active treatment. Various treatment modalities for localized CRD have been introduced including superficial radiation treatments, surgical excision, intralesional or systemic corticosteroids, retinoids, and thalidomide. In our patient, the previous treatments included systemic and topical corticosteroids as well as oral isotretinoin, but these drug regimens failed to relieve her symptoms. We tried dapsone therapy because we noticed clinically severe inflammation of the skin lesion with the microscopic finding of profuse neutrophilic infiltration within the lesion. The skin lesions of CRD in the presenting case regressed after 2 months of dapsone treatment alone. The regression of her cutaneous lesion could have been related to the incisional biopsy, but progression of the skin lesions after she underwent the first incisional biopsy for diagnosis at another dermatology clinic makes the beneficial effect of surgical intervention unlikely.

Dapsone (4,4'-diaminodiphenylsulfone) is an antimicrobial substance that has anti-inflammatory activity, which has been attributed to its ability to inhibit myeloperoxidase (MPO), a human enzyme in the azurophilic granules of neutrophils and in the lysosomes of monocytes. During the process of neutrophilic inflammation, MPO catalyzes the conversion of hydrogen peroxide and chloride ions into hypochlorous acid, a potent oxidant that causes cell damage, thus forming a killing zone around activated neutrophils. Successful dapsone treatment, which targets the neutrophilic component by inhibiting the MPO–hydrogen peroxide–chloride system, may have brought about the surprising regression of the major histiocytic component of the lesion in our case. Therefore, dapsone may be a useful treatment for neutrophilic CRD. Dapsone has been found to be metabolized to hydroxylamine in neutrophils, monocytes, and activated mononuclear leukocytes. Since monocytes and their derivatives, tissue macrophages and histiocytes, also have MPO, dapsone may change their inflammatory response too and it has been reported to be a successful treatment for lymphohistiocyte-predominant diseases such as erosive lichen planus. We surmise that similar effects should also contribute.
to the regression of the histiocytic component of CRD, which was supported by the positive reaction of both histiocytes and neutrophils to an MPO immunohistochemical study in our presenting case (Figure 4). Though the precise mechanisms of pathogenesis and treatment response in CRD remain unknown, the significance of our finding allows for an alternative therapeutic option when treating CRD, especially in those cases where there is dense neutrophilic infiltration.

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REFERENCES


Submissions

Clinicians, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Manuscripts should be prepared double-spaced with right margins nonjustified. Pages should be numbered consecutively with the title page separated from the text (see Instructions for Authors for information about preparation of the title page). Clinical photographs, photomicrographs, and illustrations must be sharply focused and submitted as separate JPG files with each file numbered with the figure number. Material must be accompanied by the required copyright transfer statement (see Instructions for Authors). Preliminary inquiries regarding submissions for this feature may be submitted to George J. Hruza, MD (ghruza@aol.com). Manuscripts should be submitted via our online manuscript submission and review system (http://manuscripts.archdermatol.com).