Successful Use of Mizoribine in a Patient with Sarcoidosis and Cutaneous Vasculitis

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Sarcoidosis is a systemic disease of unknown aetiology that is thought to be the product of a combination of genetic, immunological, and environmental factors. It is characterized by non-caseating epithelioid granulomatous inflammation with tissue destruction in multiple organs. Approximately 25% of sarcoidosis patients have skin lesions (1).

Mizoribine is a purine synthesis inhibitor developed as a new immunosuppressant (2). It induces selective inhibition of inosine monophosphate dehydrogenase and guanosine monophosphate synthetase, which inhibits T-cell and B-cell proliferation (3). The pharmacological effects of mizoribine are the same as those of mycophenolate mofetil (MMF). In addition, mizoribine enhances some effects of glucocorticoids (4). We report here the first use of mizoribine in the treatment of a patient with sarcoidosis, which led to a satisfactory resolution of the skin eruptions and lung lesions.

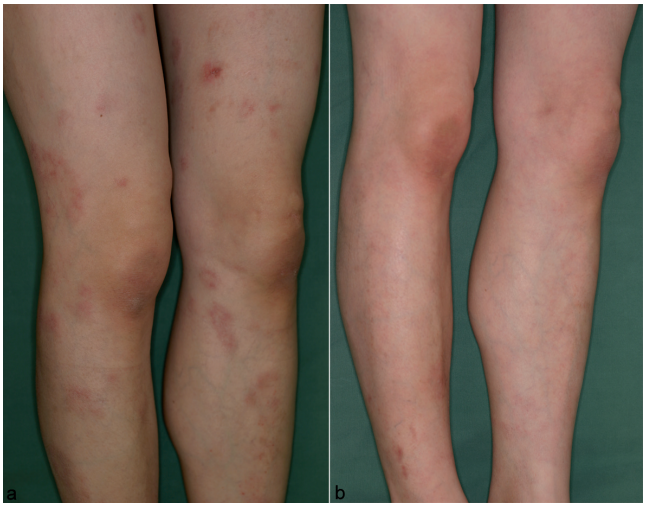

Fig. 1. (a) Multiple annular erythematous plaques, papules or nodules scattered over the lower extremities. (b) The cutaneous eruptions healed after one month of treatment with mizoribine (300 mg/day).

CASE REPORT

A 43-year-old woman was first admitted to our hospital with a 2-month history of cutaneous eruptions and mild oedema of her lower extremities. The patient reported having had backache for approximately one month prior to her visit. She reported no history of cough, myalgias, arthralgias or any other symptoms. Examination revealed multiple polymorphous erythematous plaques, papules, and nodules scattered over her lower extremities (Fig. 1a). Some of the larger plaques had an annular appearance with central clearing. Microscopic examination of the indurated erythematous lesions on her right leg revealed numerous non-caseating granulomatous inflammations throughout the dermis. The granulomas were well-circumscribed and consisted of epithelioid cells, multinucleate giant cells, and lymphocytes (Fig. 2a). Fibrinoid degeneration, nuclear dust, neutrophilic infiltration and erythrocyte extravasation, characteristic of necrotizing vasculitis in the dermis, were also found (Fig. 2b). Periodic acid-Schiff and Fite stains were negative.

Complete blood count and tests for blood urea nitrogen, creatinine, thyroid-stimulating hormone, and liver function tests were all within normal limits. Anti-streptolysin O (ASO) titre was elevated at 401 IU/ml (normal; 0–200 IU/ml). The patient had no serological evidence of hepatitis B or C. Results of the following laboratory investigations were negative or normal: serum angiotensin converting enzyme, calcium, cryoglobulins, urinalysis, tests for antineutrophil cytoplasmic antibodies, rheumatoid factor, antinuclear antibody, and anti-double-stranded DNA antibody. The serum level of complement (C3, C4, CH50), immunoglobulins (IgG, IgA, IgM), C-reactive protein, and angiotensin-converting enzyme was all within the normal range. The tuberculin (PPD) test was negative. Chest roentgenography and computed tomography of the lungs performed at the time of admission revealed bilateral hilar lymphadenopathy. No ophthalmological abnormalities were detected. Similarly electrocardiogram, abdominal and neurological examinations revealed no abnormalities. The findings from non-invasive vascular studies (venous and arterial Doppler studies) were also within normal limits.

Based on these findings, we diagnosed the patient as having sarcoidosis with cutaneous vasculitis. Oral administration of

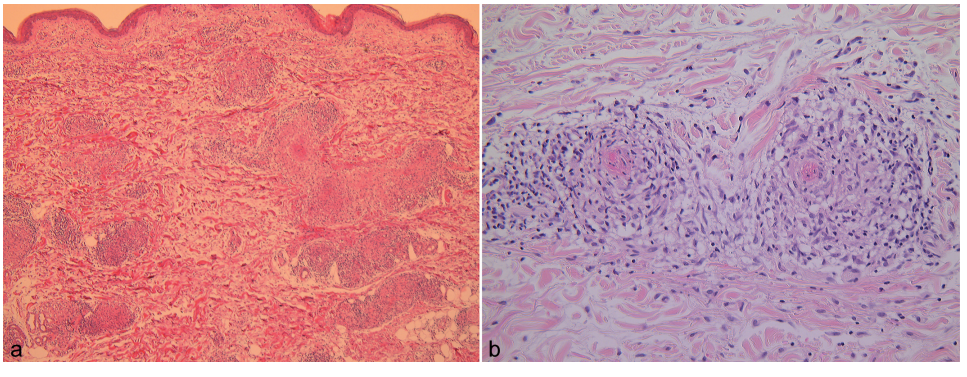

Fig. 2. (a) Microscopic examination of the erythematous plaques revealed multiple granulomas throughout the dermis (haematoxylin-eosin stain; original magnification ×40). (b) Necrotizing vasculitis in the dermis with focal involvement of the small blood vessel walls (haematoxylin-eosin stain; original magnification ×200).

mizoribine was commenced at a dose of 150 mg/day. She rejected prednisone therapy due to the various potential side-effects, including diabetes, osteoporosis and moon face. Mizoribine treatment led to mild improvement in her symptoms, including a slight reduction in skin eruptions. The serum mizoribine concentration 2 h after oral administration at this dose was 1.3 μg/ml. By increasing the oral dose to 300 mg/day, the serum mizoribine concentration was increased to 4.4 μg/ml. At this increased dosage, the patient's clinical condition gradually improved after one month of follow-up (Fig. 1b). In addition we noted that her chest roentgenograms and computed tomography of the lungs became normal. The patient has not experienced recurrence of the eruptions or significant adverse effects due to the drug.

DISCUSSION

Most patients with sarcoidosis respond well to corticosteroid therapy, but this treatment regimen can result in various side-effects, ranging from severe complications to cosmetic issues such as moon face. It has been reported that mizoribine-binding proteins enhance the transcriptional activity of glucocorticoid receptors, suggesting a steroid-sparing effect of mizoribine (4). Alternative treatments used in sarcoidosis include immunosuppressive agents, such as cyclosporine (5), chloroquine (6), methotrexate (7), cyclophosphamide (8), and tumour necrosis factor blockade (9). Compared with these immunosuppressive agents, mizoribine has fewer severe adverse effects, such as nephrotoxicity, gonadotoxicity and myelosuppression (2, 4). Previous authors (10, 11) have reported that MMF is also useful for sarcoidosis.

Monitoring mizoribine concentration is essential for a positive outcome (12). According to several studies, the peak blood concentration of mizoribine should be maintained at between 3.0 and 6.0 μg/ml 2 h after oral administration in order to inhibit human mixed-lymphocyte reaction (13). A mizoribine concentration over 2.6 μg/ml significantly enhances the interaction of the glucocorticoid receptor (14). When the concentration reached 4.4 μg/ml in the present patient, there was a marked improvement in symptomatology, with no apparent adverse side-effects.

In our patient, histopathological findings of the skin biopsy specimen from the cutaneous sarcoidosis lesion revealed necrotizing vasculitis. Sarcoidosis often exhibits a purely granulomatous vasculitis. The association between vasculitis and streptococcal infection has been reported (15) and was suggested in our patient by an increase in serum ASO.

Some observations suggest that the causes of sarcoidosis are environmental. The two common target organs, the skin and lungs, are in permanent contact with environmental agents. We propose that streptococcal antigens, could be implicated as environmental triggers in the development of vasculitis in sarcoidosis, knowing that mizoribine is effective for cutaneous vasculitis (12).

The authors declare no conflicts of interest.

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