Erythema Dyschromicum Perstans: Successful Treatment With Clofazimine Under a Single-Patient Investigational New Drug Study

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Erythema dyschromicum perstans (EDP), or ashy dermatosis, is a relatively rare condition clinically characterized by slate gray to blue-brown macules often with some degree of initial inflammation. This condition has been described more commonly in Fitzpatrick skin types III and IV and does not appear to have an age or gender predilection. The diagnosis is essentially made clinically, as histopathology is relatively nonspecific. To date, there is no consistent treatment of choice. The use of several therapies has been reported, including topical keratinolytics, corticosteroids, chloroquine diphosphate, sunscreens, dapsone, UV light, and Q-switched ruby laser treatments, but few have been effective. Clofazimine has shown to be successful in the treatment of EDP in smaller studies. However, commercial distribution of clofazimine was discontinued in November 2004. We report a case of EDP in which the patient was enrolled in an Investigational New Drug study for clofazimine and responded well to this treatment.

Erythema dyschromicum perstans (EDP) is a chronic, insidiously developing disorder of the skin characterized by ashy gray macules typically found symmetrically on the face, neck, trunk, and upper extremities. Mucous membranes are spared. Its etiology remains unknown, although many ideas have been proposed. While there is compelling evidence that this condition is closely related to lichen planus, especially histologically,[1,2] other reports show that they are, in fact, separate clinical entities.[1]

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CASE REPORT

A 34-year-old female initially presented with pruritic, inflamed, gray macules on her bilateral arms. These lesions were present for approximately one month. She had a past medical history of EDP, which was diagnosed 8 years prior to her presenting. Dermatological examination revealed several round, gray macules on both arms, which had progressed to the neck, chest, and legs (Figure 1). All laboratory tests were within normal limits, including liver function, electrolytes, thyroid function, and urinalysis, except for the complete blood count showing an increased number of eosinophils. Biopsy at the time of initial diagnosis revealed basal hypermelanosis with

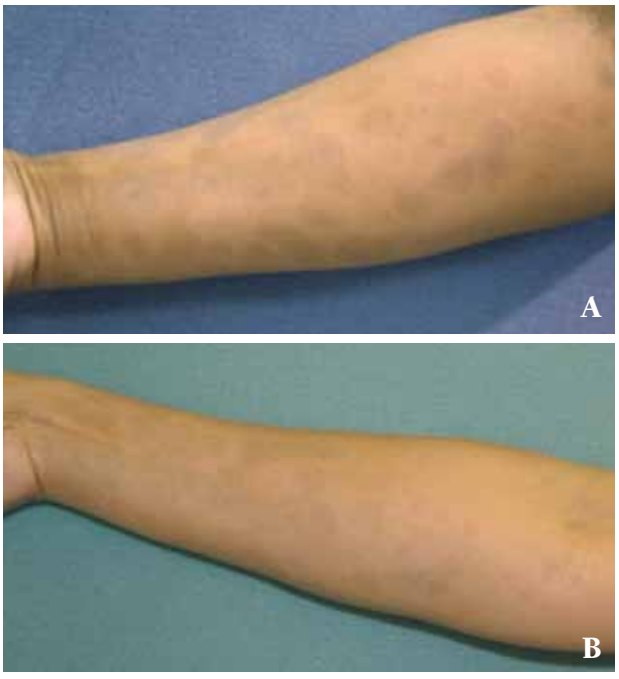

Figure 1. Female patient with erythema dyschromicum perstans, exhibiting several round, gray macules on the arm (A, B).

scattered pigmented macrophages in the superficial dermis and perivascular infiltrate (Figure 2).

Eight years prior, the patient had initially received PUVA treatment with no improvement. At that time, she was subsequently treated with 50 mg of oral clofazimine once daily, with complete resolution within 3 months. Since clofazimine was no longer available through prescription, the patient was started on a trial of 50 mg of dapsone daily. Consequently, she developed severe abdominal discomfort and diarrhea and discontinued dapsone therapy.

Because of this patient's previous success with clofazimine and intolerance to other treatment, a single-patient Investigational New Drug Study (IND) was submitted to the US Food and Drug Administration. Certain protocol was proposed as per the study requirements. Eventually, this patient was approved for the single-patient IND and was started on 50 mg of oral clofazimine daily, to be changed to 50 mg twice weekly for maintenance once the lesions resolved. After 2 to 3 months of therapy, the patient's pruritis and inflammation completely cleared and the gray macules on the arms (Figure 3), chest, neck, and leg improved with no appearance of new lesions.

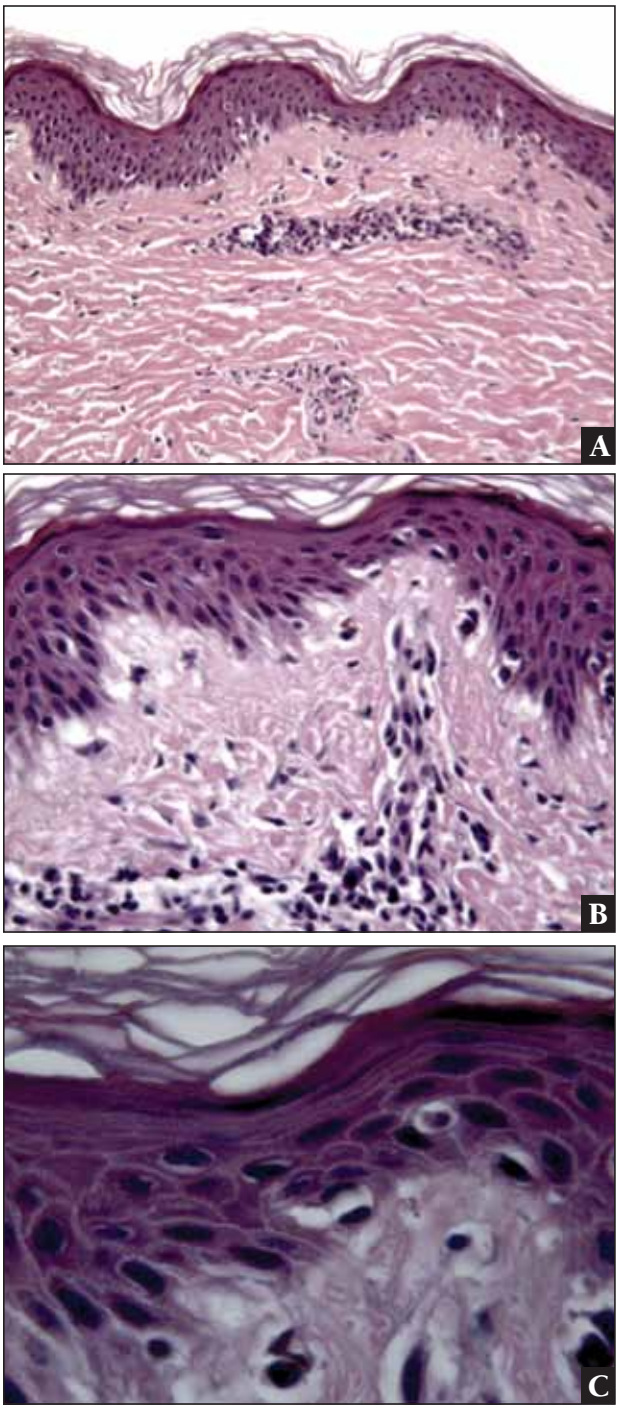

Figure 2. Biopsy of erythema dyschromicum perstans, revealing basal hypermelanosis with scattered pigmented macrophages in the superficial dermis and perivascular infiltrate (A-C).

DISCUSSION

A chronic disorder of the skin, EDP is characterized by ashy gray macules usually seen on the face, neck, chest, trunk, and extremities. While the etiology of this condition is unknown, many causative factors have been mentioned, including chlorothalonil,[3] cobalt allergy,[4] ingestion of ammonium nitrate,[5] fungicides,[6] endocrinopathies,[7] penicillin,[8] and oral radiographic contrast media.[9] There are 2 stages of EDP, with earlier lesions described as having raised, erythematous borders, while later, the borders can become ill-defined.[10]

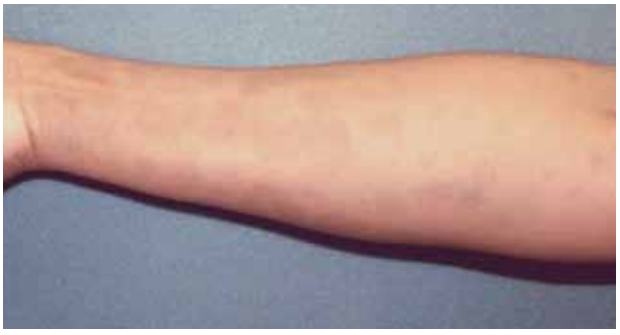

Figure 3. Female patient with erythema dyschromicum perstans after 2 to 3 months of treatment with 50 mg of oral clofazimine daily, exhibiting no pruritis or inflammation, with visible improvement of gray macules.

The histological features of EDP are relatively nonspecific. They may include a thinned epidermis, basal cell damage and vacuolization, perivascular infiltrate, and variable inflammatory infiltrate. An increase in melanin can be found in the epidermis with increased dermal melanophages, causing the blue-gray discoloration of the skin.[11] Histologically distinguishing between EDP and lichen planus has proven to be somewhat difficult. Similar findings consist of hyperkeratosis and basal vacuolization in the epidermis with the presence of melanin containing macrophages in the dermis.[1] A difference in cellular infiltration is worth noting, but may be dependent upon the stage of the disorder. While there seems to be a predominant perivascular infiltrate in EDP throughout its course, dermal cellular infiltrate in lichen planus can characteristically be found in a bandlike pattern or a variation thereof depending upon its stage.[12,13] It is also important to note that clinical distinctions can be made to differentiate between these 2 conditions in the areas of lesion morphology, distribution pattern, and clinical course.[1]

Immunopathologic examination has shed some light on the inflammatory process involved in EDP and has also been useful in determining the effectiveness of certain treatment. Immune cell involvement in the pathogenesis of EDP has been implicated due to the accumulation of several cellular markers and selective immune cells.[14] It has been shown that epidermal keratinocytes in active EDP lesions express ICAM1 (CD54) and HLA-DR, specifically in the basal layer.[13,15] Importantly, ICAM1 seems to be expressed only in keratinocytes involved in inflammatory processes, confirming the nature of EDP.[13] These cell adhesion molecules, as well as certain activation molecules, which have been found in the dermal cell infiltrate in EDP lesions, disappeared after 3 months of treatment with clofazimine.[15] Clofazimine has also been shown to decrease the CD4/CD8 ratio on immunocytochemical analysis, further reinforcing its role in cell-mediated immunity as it is related to EDP while providing clinically favorable results.[16] Clofazimine is indicated primarily for multibacillary leprosy, but has also been used for other infectious and noninfectious diseases, such as other mycobacterial infections and erythema nodosum. Even though the exact mechanism of action is unknown, it is known to have antimicrobial effects via binding directly to guanine residues of microbial DNA.

Furthermore, clofazimine exerts its action on neutrophils and monocytes, thus explaining its effects on inflammation and cellular response.[17] Since its discontinuation in 2004, clofazimine has only been available through a single-patient IND study through the US Food and Drug Administration, as it is now considered experimental. As part of the application process, study parameters must be specified, including treatment plan; study end points; study duration; laboratory evaluation parameters; methods of assessment for improvement/worsening of the patient's condition; stopping dose/reduction criteria dependent upon adverse effects; contraception methods (necessary specifically for clofazimine); and posttreatment follow-up. Once the patient's physician is approved as an investigator, the drug is distributed directly to the prescriber. While this method of treatment is not readily available, its previous success in this patient along with compelling study data prompted the single-patient IND study. This patient's success with clofazimine suggests its usefulness in the treatment of EDP.

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