LETTERS TO THE EDITOR

Erythema Nodosum Associated With Inflammatory Tinea Capitis (Kerion Celsi)

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To the Editor:

Erythema nodosum is the most common form of panniculitis. The wide variety of processes with which it may be associated includes dermatophytes, particularly inflammatory forms such as kerion celsi. The pathogenesis of erythema nodosum in such cases has not been fully elucidated. Traditionally, it has been considered, together with dyshidrotic reactions and follicular rashes, to be an id reaction, in other words, a hypersensitivity reaction to various fungal antigens at a site distant from the primary lesion.

We describe the cases of 2 patients, aged 9 and 11 years, with inflammatory tinea of the scalp due to Trichophyton mentagrophytes, who developed erythema nodosum subsequent (16 and 26 days afterwards, respectively) to the initiation of treatment with griseofulvin (Figures 1 and 2). Relative rest was prescribed for both patients and the second patient also received ibuprofen (100 mg/5 mL) at a dose of 15 mL every 8 hours. In both patients the lesions resolved without sequelae in the following weeks.

The pathogenetic mechanism underlying erythema nodosum has not been fully elucidated. It is considered a hypersensitivity reaction to a broad group of trigger factors. This wide variety of antigenic stimuli giving rise to a single process can be explained by the limited ways in which the skin can respond to different etiologic agents. One theory suggests that the mechanism is an antigen-antibody reaction, as immune complex deposits have been found around the venules of the septa of the hypodermis. This theory has been supported by the detection of circulating immune complexes and complement activation in patients with erythema nodosum. Direct immunofluorescence studies have also shown immunoglobulin deposits on the vascular walls of the septa. However, such findings are not constant, and other types of hypersensitivity, such as type IV hypersensitivity, may play an important role in the development of the condition. Llorente et al. used semi-quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) to study the messenger RNA (mRNA) expression of T helper (Th) 1 (interleukin [IL] 2 and interferon γ [IFN-γ]) and Th2 (IL-4 and IL-10) cytokines in skin biopsies and peripheral blood of 11 patients with erythema nodosum and 9 healthy control subjects. They found increased Th1 cytokine expression in the skin lesions and peripheral blood of most of the patients with erythema nodosum, while no expression of either Th1 or Th2 cytokines was observed in the skin or peripheral blood of the control subjects.

The number of cases of erythema nodosum associated with dermatophyte infections described in the literature is extremely limited. MEDLINE has only 8 indexed citations in Spanish or English, with a total of only 14 patients. Of these 14 cases, 9 were cases of inflammatory dermatophytosis caused by T. mentagrophytes (Table). There have been immunologic studies of patients with skin infections due to T. mentagrophytes that can explain this causal coincidence. These studies demonstrated the presence of a considerable cellular immune response both in vivo (showing the appearance of delayed hypersensitivity to the intradermal injection of trichophyitin), and in vitro (using leukocyte migration inhibition and lymphocyte transformation tests). In another study, Koga found increased IFN-γ synthesis by peripheral blood mononuclear cells in response to stimulation with trichophyitin, and by RT-PCR detected IFN-γ mRNA in tinea lesions. All of these findings tend to support the hypothesis that skin lesions produced by dermatophytic infections of zoophilic origin, specifically those produced by T. mentagrophytes, are caused by a Th1 response involved in the host defense against the dermatophytoesis. This response may be responsible for both the associated erythema nodosum, as mentioned, and the spontaneous regression of most such infections.

It has been observed, on the other hand, that anthropophilic species such as Trichophyton rubrum can more frequently trigger a low-intensity humoral immune response that is unable to destroy the fungus. For this reason, infections by such species resolve more...
slowly and are less frequently associated with the appearance of erythema nodosum.\textsuperscript{12,13,15}

Other authors have linked the origin of erythema nodosum to the administration of griseofulvin, perhaps due to the release of fungal antigens as a result of antifungal therapy.\textsuperscript{5} This mechanism has been seen to operate with other antifungal agents, such as terbinafine, in which the release of fungal antigens as a consequence of therapy causes an increase in immunoreactivity to intradermal trichophytin antigen.\textsuperscript{16} In our patients, as in 6 of the 14 other patients reported in the literature (Table), the appearance of erythema nodosum was preceded by the administration of griseofulvin.

Finally, we must consider the possibility of a direct relationship between griseofulvin and the appearance of erythema nodosum. To the best of our knowledge, there are no studies that either demonstrate or rule out such a causal relation. Nonetheless, we believe that it is a possibility that must be taken into account, as erythema nodosum has been associated with the administration of several other drugs.

REFERENCES

Table. Summary of the Cases of Erythema Nodosum Associated with Dermatophytosis Indexed in MEDLINE in Spanish or in English

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Age, y</th>
<th>Type of Tinea</th>
<th>Microbiology Findings</th>
<th>Antifungal Treatment</th>
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<td>5</td>
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<tr>
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<tr>
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<tr>
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<td>Onychomycosis, tinea pedis, and inflammatory tinea cruris</td>
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<td>Terbinafine (erythema nodosum and inflammatory tinea cruris prior to treatment)</td>
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<td>Hicks\textsuperscript{11}</td>
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<td>58</td>
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<td>Griseofulvin (erythema nodosum prior to treatment)</td>
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Indapamide-Associated Stevens-Johnson Syndrome

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To the Editor:

Indapamide is a non-thiazide sulfonamide derivative with an indole ring. It belongs to the diuretic group of drugs and is widely used in antihypertensive therapy. The most frequent side effects are electrolyte imbalances and prerenal acute renal failure. Several types of occupational cutaneous exanthemas have also been described, among which Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis stand out due to their severity.

We present the case of a 62-year-old man, with no known drug allergies, admitted with a fever of 39°C, acute renal failure with oliguria/anuria, anasarca, and cutaneous lesions.

Physical examination showed erythematous maculopapular lesions, some of which had a ring-like shape and a tendency to merge. They were located on the trunk, head, palms, and soles, as well as the oral, nasal, and genital mucosa (Figures 1 and 2).

Seven days before admission he had begun treatment with indapamide for recently diagnosed hypertension; he did not report taking any other medication.

Skin biopsy showed a lymphohistiocytic perivascular infiltrate in the superficial dermis, along with eosinophils, foci of lymphocytic exocytosis, vacuolation of basal cells, and cellular necrosis in the epidermis and hair follicles.

Treatment was begun with intravenous corticosteroids (methylprednisolone 60 mg every 6 hours) and topical corticosteroids, and indapamide was withdrawn. The cutaneous lesions completely resolved, without scarring, and renal function returned to normal. Three months later he underwent patch tests using the Spanish Contact Dermatitis Research Group (Grupo Español de Investigación en Dermatitis de Contacto) standard battery, with negative results at 48 hours and 96 hours. Patch tests with indapamide (1:1000 in petrolatum) produced a positive reaction (+++) at 48 hours and 96 hours.

The incidence of SJS is estimated to be between 1 and 3 cases per million inhabitants per year, and mortality among those affected is approximately 5%. In the case series analyzed by Laguna et al, mortality due to SJS was 0%. It is clinically characterized by erythematous or purpuric macular target lesions and vesiculobullous lesions—either disseminated or predominating on the trunk—that lead to detachment affecting less than 10% of the body surface, and it is frequently associated with mucosal and visceral lesions.

It is currently thought that SJS is unrelated to exudative erythema multiforme from a clinical, etiologic, or histopathologic standpoint. The mechanism by which a drug is capable of inducing epidermal necrosis is partly understood. First, there seems to be individual susceptibility to develop this type of cutaneous drug reaction. It has also been suggested that these patients metabolize the drug in an anomalous way, giving rise to the active metabolites...