Leuprolide Acetate–Induced Dermatitis Herpetiformis

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Dermatitis herpetiformis (DH) is a chronic, pruritic, papulovesicular dermatosis on extensor surfaces that is characterized by a neutrophilic infiltrate and granular immunoglobulin A deposition at the dermal papillae. Although the presence of immunoglobulin A in the skin and the severity of DH are known to be associated with gluten intake, few drugs have been implicated in the induction of DH. We report a case of DH triggered by intramuscular injections of leuprolide acetate, a gonadotropin-releasing hormone analog, in a patient with a history of prostate cancer.
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Dermatitis herpetiformis (DH) was first described by Duhring[1] in 1884 as a relapsing, polymorphic, pruritic disorder. Over time, the defining criteria of the disease have evolved to encompass clinical, histologic, and immunopathologic characteristics. Overall, DH is slightly more common in male patients than in female patients. Onset may occur as early as childhood, although most cases begin in the second to fifth decades.[2] On clinical examination, DH appears as polymorphic lesions with papulovesicular, bullous, and urticarial patterns, usually on a background of erythema and intense pruritus.

DH and celiac disease (CD) are closely linked to gluten sensitivity and immunogenetics. Although gastrointestinal symptoms are rarely reported in DH patients, histologic changes identical to those of varying stages of CD are common findings. Results of serologic assays often demonstrate HLA-B8, HLA-DR3, and HLA-DQw2 antigens in both DH and CD patients. In addition, DH and CD patients respond to a gluten-free diet.[3]

DH is known to be associated with other autoimmune diseases, cancer, pernicious anemia, and thyroid disease.[4] Lymphomas, particularly non-Hodgkin lymphoma, are the most common cancer in patients with DH.[5]

Other than gluten, various factors can affect the severity of DH. Iodide, both topical and oral, has long been known to exacerbate DH, and thyroid hormone replacement therapy has been implicated in both improving and exacerbating DH.[6,7] Contraceptive hormones[7] and chemotherapeutic drugs[8] have been reported to aggravate DH. Indomethacin was studied in DH patients and shown to exacerbate skin manifestations of the disease.[9] In contrast, another study found no effect of the anti-inflammatory ibuprofen on disease activity.[10]

Case Report

A 68-year-old white man presented with a history of a recurrent vesicular eruption. He denied the presence of any systemic symptoms. The patient's medical history included bilateral carpal tunnel syndrome, osteoarthritis, hyperlipidemia treated with pravastatin, and adenocarcinoma of the prostate with a Gleason score of 9 out of 10. The patient's surgical history included vasectomy, pilonidal cystectomy, rectal fistulectomy, right total hip arthroplasty, and radical prostatectomy with pelvic lymph node dissection. After cancer surgery, the patient was randomized to receive an intramuscular injection of leuprolide acetate every 3 months and oral bicalutamide daily for one year.

Within 2 to 3 weeks after his initial injection of leuprolide, the patient developed highly pruritic and erythematous papules and tense vesicles on his knees, elbows, and left thumb (Figure 1). The lesions decreased in intensity toward the end of each 3-month therapeutic cycle, only to flare within 1 to 3 days after the subsequent injection. When the patient was examined by our team, he was 2 months into his third cycle of treatment. The differential diagnosis included drug eruption and DH. The

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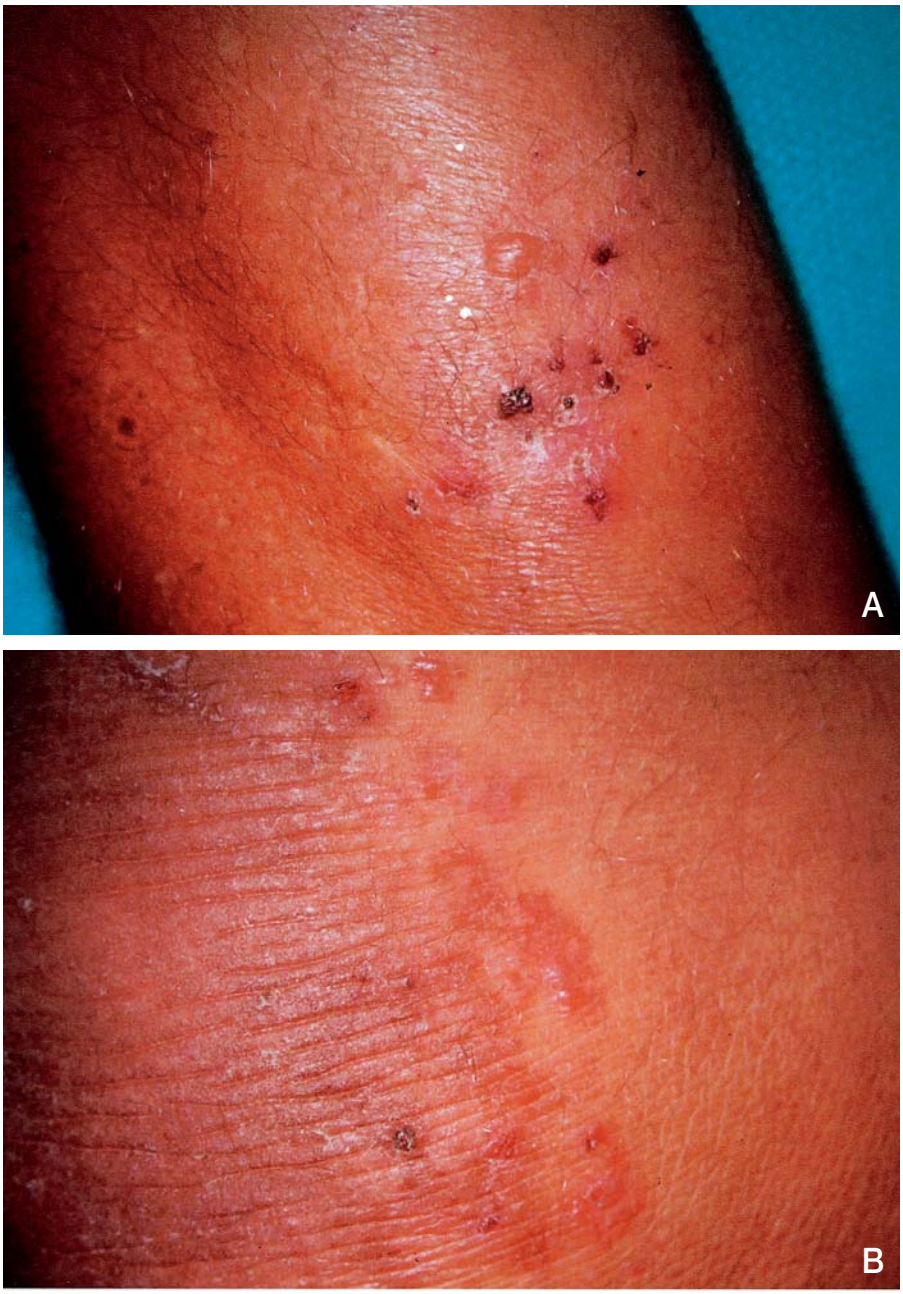

Figure 1. Grouped vesicular lesions on the left elbow (A) and scattered vesicular lesions around the knee (B).

patient had discontinued the bicalutamide 6 weeks prior to being seen by our team. However, owing to the long-acting depot nature of leuprolide, it could not be discontinued during this period.

The diagnosis of DH was confirmed by the results of hematoxylin and eosin staining and immunofluorescence assays of 4-mm biopsy samples of lesions and perilesional tissue (Figures 2 and 3). The patient later underwent rechallenge with the last of the series of leuprolide injections, and the papulovesicular eruption flared within 3 days. The patient declined systemic therapy; therefore, treatment was confined to application of topical emollients. Over the subsequent 9 months, the skin lesions steadily improved. However, symptoms persisted, tiny vesicles occasionally developed, and results of direct immunofluorescence remained positive for DH.

Comment

This case illustrates the classic histologic and immunofluorescent findings of DH. Results of

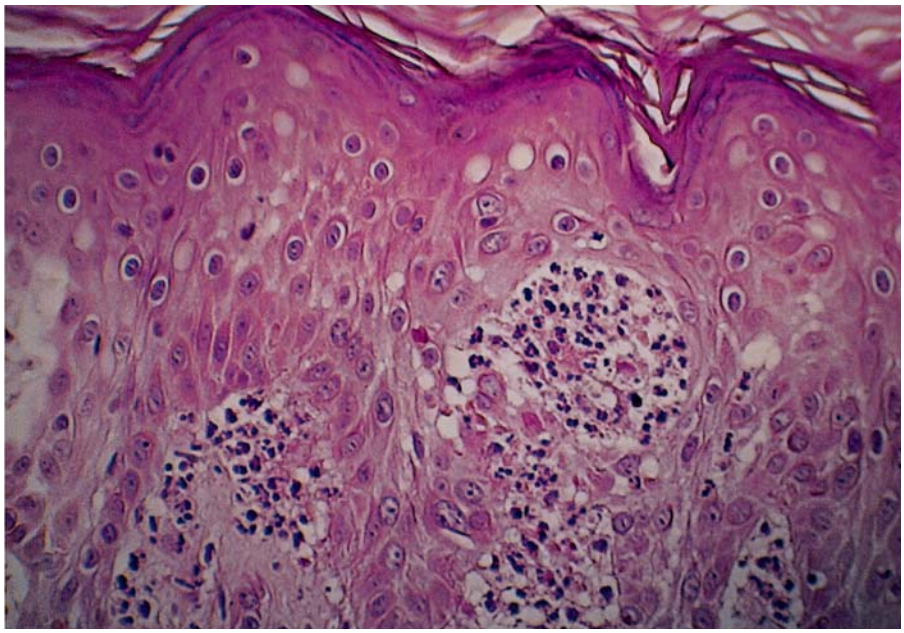

Figure 2. Lesional skin demonstrating a neutrophilic infiltrate concentrated in the dermal papillae (H&E, original magnification ×20).

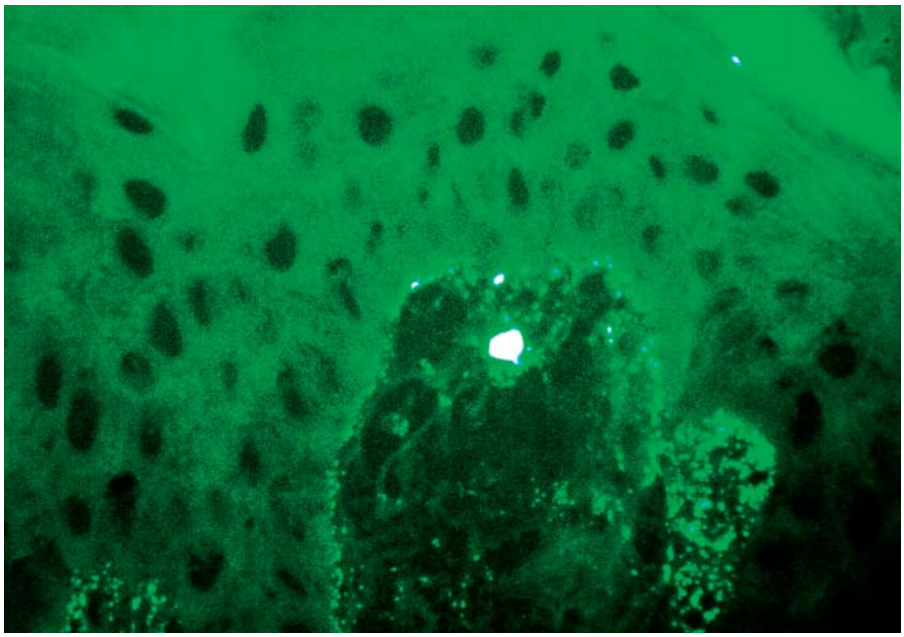

Figure 3. Granular immunoglobulin A at dermal-epidermal junction accentuated in dermal papillae (immunofluorescence, original magnification ×20).

histologic examination showed a neutrophilic infiltration into the dermal papillae, followed by fibrin deposition, localized necrosis, and microabscess formation. In DH, microabscesses often coalesce and form tense vesicles at the dermal-epidermal junction (DEJ). Results of immunofluorescence assays demonstrate granular deposits of immunoglobulin A at the DEJ.[11] Serologic studies in DH have failed to reveal immunoglobulin A antibody that binds to the DEJ. However, antigliadin, antireticulin, and antiendomysial antibodies, as well as circulating immune complexes, have been reported.[12]

Treatment for DH includes a gluten-free diet and medications. A gluten-free diet involves meticulous avoidance of the gliadin fraction of gluten that wheat, barley, rye, and other grains contain. Because of the difficulty associated with gluten avoidance, the mainstays of therapy are dapsone and sulfapyridine. Dapsone, considered the first-line therapy, usually reduces symptoms within days. The initial dose of dapsone is typically 50 to

100 mg/d; the dose is then titrated to the lowest dose that controls symptoms. Sulfapyridine is used when reactions to dapsone necessitate dose reduction or drug discontinuation.

Although various factors have been shown to worsen preexisting DH, to our knowledge, few drugs have been implicated in inducing DH de novo. Ibuprofen and flurbiprofen each have been reported to provoke an individual case of DH.[13] In the case reported here, the start of treatment with leuprolide acetate and bicalutamide initiated the emergence of DH, and each flare was temporally related to a leuprolide injection. Leuprolide alone was responsible for the last exacerbation. The persistence of the disease for months after the last dose was likely due to the depot nature of the drug (trace levels are still detectable by company assays 5–6 months after administration)(TAP Pharmaceutical Inc representative, oral communication, 2000) and the continued immune response against antigens in the drug. Therefore, we suggest that leuprolide be added to the list of drugs that have induced DH.

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