Part III: A. Cutaneous Hypersensitivity During Selective Serotonin Reuptake Inhibitor Therapy Resulting in Acquired Cutis Laxa

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CASE REPORT

A 44-year-old female presented with a two-year history of erythematous axillary and inframammary lesions, progressing to wrinkled, lax skin (Figures 1 and 2). Her symptoms were associated with a persistent cough, diagnosed as adult-onset asthma. Over the next six months, she experienced several flares of her symptoms, necessitating multiple courses of oral steroids and antibiotics. Her medications during this time included: fluticasone inhalant, azelastine nasal spray and oral escitalopram. As her skin lesions continued to increase in size and number, multiple skin biopsies were performed. Initial biopsies revealed superficial and deep dermal inflammation with eosinophils; subsequent biopsies revealed collagen degeneration, elastolysis and no evidence of vasculitis.

Her initial laboratory studies were notable for significant eosinophilia (16.5%, normal range 0–5%), and an elevated IgE level (258 IU/mL, normal 0–100 IU/mL). CT scan revealed pulmonary nodules with ground glass opacities. Patch testing was negative. ANA was positive at 1:80 in a speckled and homogeneous pattern. An initial diagnosis of atypical Churg-Strauss or hypereosinophilic syndrome was considered; however, sinus biopsy revealed no vasculitis and ANCA studies were repeatedly negative. Comprehensive workup, including stool studies, patch testing, bone marrow biopsy, tuberculin test, complement levels, serum copper levels, alpha-1 antitrypsin, troponins, ferritin, Lyme titers, thyroid stimulating hormone, SPEP/UPEP and erythrocyte sedimentation rate levels were all unremarkable.

The patient was initially treated with variable courses of prednisone, dapsone, cyclosporine and PUVA. The patient also discontinued all medications, except escitalopram, which she had taken at a stable dose for approximately five years. However, her skin disease continued to progress. Upon discontinuation of escitalopram, approximately 2.5 years after her skin lesions began, her disease stabilized and she was weaned from all immunosuppressive medications. Her eosinophilia, IgE level and CT findings all improved, as did her cutaneous disease. She has not developed any new lesions in the last year, though her cutis laxa persists.

DISCUSSION

Acquired cutis laxa is an uncommon condition characterized clinically by loose, wrinkled, pendulous skin that gives the appearance of premature aging. The features histologically are manifest by decreased or fragmented elastic fibers.[1] Cutis laxa is most often hereditary, resulting from mutations that cause decreased elastin production or function, or increased elastin degradation. Acquired cutis laxa is rare, and may be malignancy-related, post-inflammatory, or idiopathic.[1] At least one report suggests a mechanism of genetic susceptibility even for the acquired forms.[2] This patient's presentation is most consistent with acquired cutis laxa, likely related to escitalopram hypersensitivity, given that the remainder of her workup was negative. Moreover, she has remained free of active inflammatory lesions for over 1.5 years since discontinuing escitalopram.

This patient developed a significant hypersensitivity reaction to the escitalopram, as manifest by her eosinophilia, pulmonary infiltrates and robust eosinophilic infiltrates on skin biopsy. Post-inflammatory cutis laxa is thought to result from secretion of elastases by infiltrating neutrophils.[2] Some forms of cutis laxa affect internal organs in addition to skin, causing emphysema and pneumothorax, aneurysms, diverticuli and

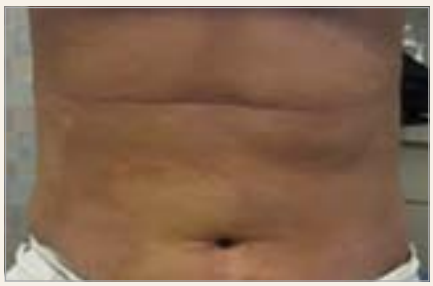

FIGURE 1. Initial examination revealed diffuse erythematous, indurated arcuate plaques and nodules on the trunk, extremi-

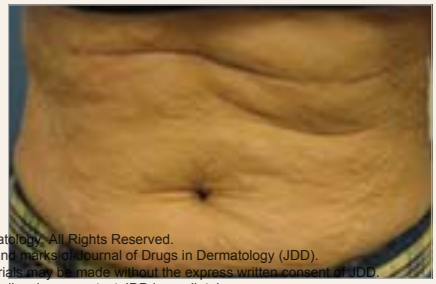

FIGURE 2. One year later (after discontinuing escitalopram), the erythema had subsided. However, she developed significant wrinkled, lax, and pendulous skin in areas of

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hernias. However, the post-inflammatory form of cutis laxa is less commonly associated with internal organ involvement.[1] The most common reported causes of post-inflammatory elastolysis include hypersensitivity reactions, as to medications or arthropods, systemic lupus erythematosus, rheumatoid arthritis, Lyme disease and parasitic infections.

Selective serotonin reuptake inhibitors (SSRI) are widely used medications for the treatment of depression, anxiety, obsessive compulsive disorder and related conditions. These medications are thought to have fewer side effects than other psychiatric treatments, and are therefore frequently prescribed.[3,4] Escitalopram (S-citalopram) is the S enantiomer of citalopram, a second generation SSRI with a higher affinity for the anti-serotoninergic receptor. Escitalopram is FDA-approved for the treatment of major depressive disorder and generalized anxiety disorder and has also been recently used in the treatment of dermatologic conditions with psychiatric features, including delusions of parasitosis, neurotic excoriations and chronic skin picking.[5–7]

Prior to onset of skin lesions, the patient had been on escitalopram for approximately five years. Though there are no reported cases of escitalopram-induced cutis laxa, the class of SSRI's has been noted to cause hypersensitivity eruptions. In a recent large German study assessing severe adverse drug reactions of antidepressants, SSRI's were found to be associated with a 5 percent incidence of severe dermatologic adverse reactions, including allergic exanthema.[8] Specifically, SSRI's have produced bruising, acneiform eruptions, alopecia, urticaria, erythema nodosum, erythema multiforme and Stevens Johnson-Syndrome.[9] Escitalopram has been reported to cause leukocytoclastic cutaneous vasculitis.[10] The authors believe this patient's systemic hypersensitivity and resultant cutis laxa developed due to escitalopram therapy; diagnosis was delayed in part because she had been on the medication for over two years prior to the onset of symptoms. The authors report this case to notify clinicians of this rare but serious delayed complication of SSRI therapy.

DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

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Part III: B. Levamisole-Induced Retiform Purpura

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CASE REPORT

A This 29-year-old female presented to the authors with bilateral calf ulcerations (Figure 1). Rheumatologic evaluation revealed a positive ANA, as well as PR3 and MPO ANCA positivity. Further laboratory investigations for vasculitis were unremarkable. Skin biopsy showed a subepidermal bullous dermatitis, with a sparse lymphocytic perivascular infiltrate and vascular occlusion. Immunoflourescent staining showed focal IgG deposition along some of the superficial dermal vessels. On examination the patient admitted to daily cocaine use. A presumptive diagnosis of levamisole toxicity was made. Cocaine use was stopped, skin grafts were applied and the patient's legs are now healing well four months later.

Levamsole is a medication that was formerly used as chemotherapy, and is still used by veterinarians as an inexpensive anti-helminth medication. Levamisole also has similar physical properties to cocaine, and is thought to possibly increase cocaine-induced euphoria. Because of levamisole's availability and favorable properties, it is used as a diluting agent for cocaine. This practice is also growing more frequent, and is thought to occur in the agrarian nations where cocaine is produced. Recent reports show that 70 percent of cocaine seized in the United States is mixed with levamisole.[1]

The side effects of levamisole use, including retiform purpura, have long been described. These purpura seem to favor symmetric involvement of the ears, as well as face, upper extremities, and lower extremities. The appearance of purpura is likely secondary to a PR3 ANCA positive vasculitis induced by levamisole. Biopsies of levamisole-induced purpura show features of thrombotic vasculititis, leukocytoclastic vasculitis, and/or vascular occlusion. Previous reports suggest that areas of new skin involvement usually cease within weeks of cocaine cessation, and serologies are reported to normalize in two to 14 months.

In conclusion, the constellation of retiform purpura, PR3 ANCA positivity, and agranulocytosis should lead the physician to consider levamisole toxicity. This is a rising, and potentially fatal, condition in cocaine users across the country.

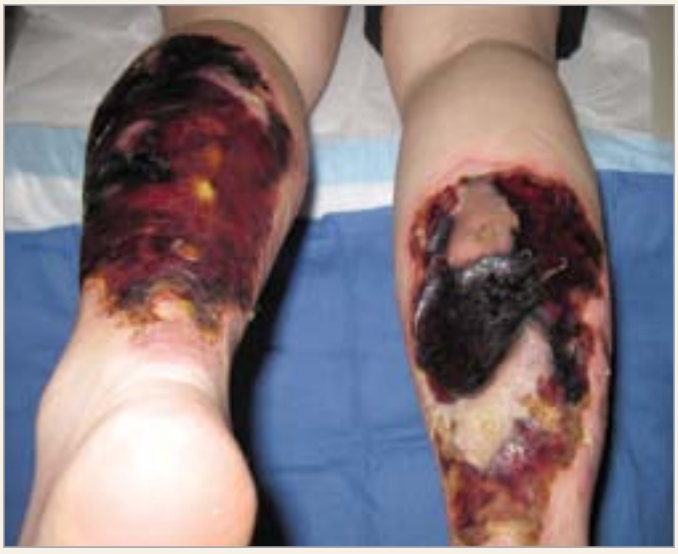

FIGURE 1. A 29-year-old female with bilateral calf ulcerations.

DISCLOSURES

The author has no relevant conflicts of interest to disclose.

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