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Case Presentation

Stasis Dermatitis as a Complication of Recurrent Levofloxacin-Associated Bilateral Leg Edema

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Abstract

Introduction: Several drugs have been associated with the development of peripheral edema. Leg edema can result in dermatitis of the lower extremities. We describe levofloxacin-induced peripheral leg edema, which progressed to stasis dermatitis.

Methods: A 76-year-old man with a history of esophageal adenocarcinoma was administered intravenous vancomycin and a combination of piperacillin and tazobactam by injection for treatment of aspiration pneumonia. Prior to discharge, the patient's antibiotic therapy was switched to oral levofloxacin. The patient developed drug-associated bilateral peripheral leg edema and stasis dermatitis. Both the dermatitis and leg edema resolved after withdrawal of levofloxacin and administration of topical corticosteroid therapy. The patient had a similar reaction to levofloxacin one year prior, which had subsided with discontinuation of the drug.

Results: Several medications have been documented to cause leg edema and secondary stasis dermatitis. The timing, recurrence, and resolution of edema and stasis dermatitis with respect to the administration and termination of levofloxacin suggest that the leg edema and stasis dermatitis occurred secondary to levofloxacin administration.

Discussions: Levofloxacin can be added to the list of drugs associated with the development of peripheral leg edema. Stasis dermatitis proceeded by lower extremity edema can be added to the list of adverse events associated with levofloxacin.

Keywords: adverse, dermatitis, drug, effect, leg, levofloxacin, peripheral edema, reaction, side, stasis

Introduction

Stasis dermatitis is an inflammatory skin condition that may result from venous hypertension and subsequent pooling of interstitial fluid secondary to venous valve incompetence; it typically occurs in both lower extremities [1]. The acute phase of stasis dermatitis presents with erythema and crusting, whereas its chronic phase it is characterized by hemosiderin hyperpigmentation and potential development of lipodermatosclerosis [1,2]. Levofloxacin is a renally excreted fluoroquinolone antibiotic with

activity against a wide range of microbes [3]. We describe a man with pneumonia who developed levofloxacin-induced leg edema that progressed to stasis dermatitis and summarize the other medications associated with leg edema.

Case Report

A 76-year-old man with a history of esophageal adenocarcinoma that was successfully treated with chemotherapy, radiation, and esophagectomy was hospitalized for gram-positive aspiration pneumonia and partial small bowel obstruction. He was initially treated with intravenous vancomycin and a combination of piperacillin and tazobactam by injection. Prior to discharge his antibiotics were changed to orally administered levofloxacin. Within two days after starting levofloxacin, his legs began to swell. The leg swelling continued after he left the hospital.

Eleven days after starting levofloxacin, the man presented to a dermatology clinic for evaluation of his enlarged, nonpruritic, lower extremities, particularly the medial distal right foot and left leg (Figure 1). Edema was noted bilaterally from the great toes to the calves and the erythematous skin was warm and tender to palpation (Figure 2). Doppler studies ruled out deep vein thrombosis.

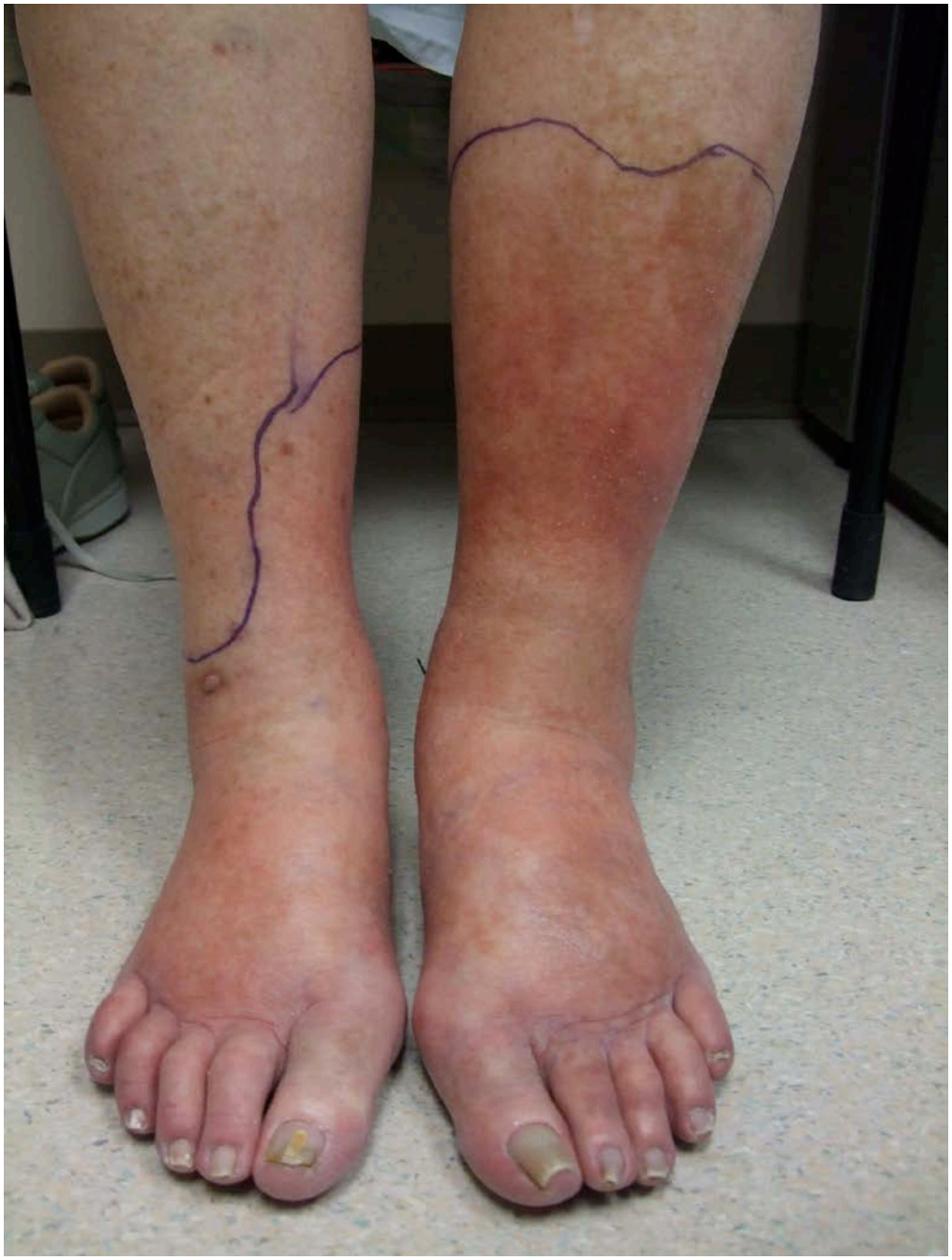

Figure 1. Bilateral acute stasis dermatitis secondary to levofloxacin-induced leg edema. The frontal view shows the markedly enlarged, red, and tender lower extremities of a 76-year-old man. The pen marking delineates the superior border of the erythema.

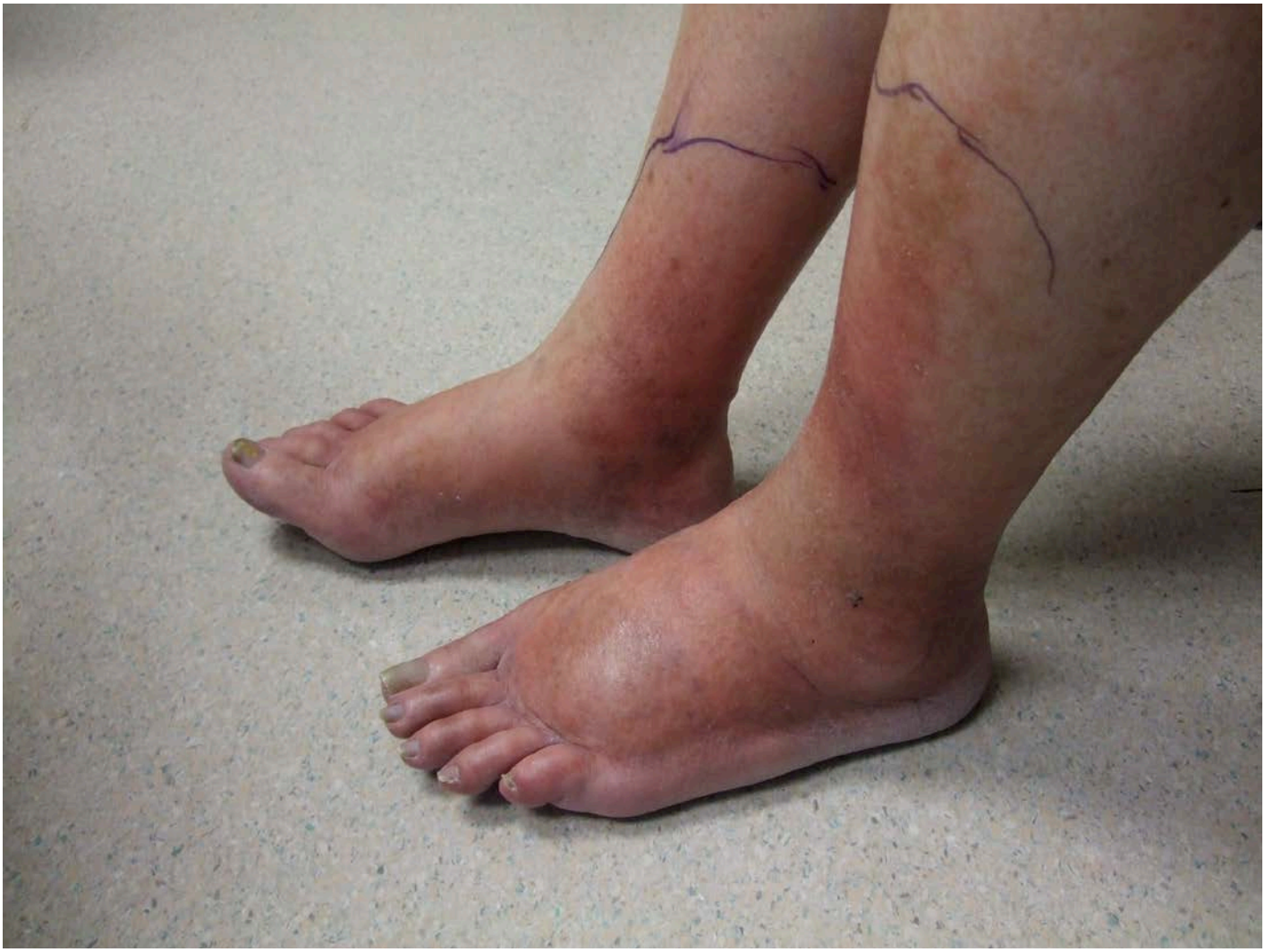

Figure 2. A side view of the medial right leg and lateral left leg shows bilateral stasis dermatitis secondary to levofloxacin-induced edema. Post inflammatory hyperpigmentation from a similar episode 1 year earlier is also noted outside the demarcated area of erythema.

Based on the correlation of the clinical presentation and skin lesions, a diagnosis of levofloxacin-induced bilateral leg edema and consequent stasis dermatitis was made. Levofloxacin was discontinued and the patient's legs were treated twice daily with clobetasol propionate 0.05% ointment for three weeks. The potency of the corticosteroid was subsequently lowered to topical fluocinolone 0.05% cream twice daily and then tapered to once daily for two weeks and one week, respectively. At three weeks follow up, there was improvement with markedly reduced edema and dermatitis; erythema was limited to the left lower leg. Complete resolution of the leg swelling and skin changes was observed within the next two months.

The diagnosis of levofloxacin-associated leg edema and subsequent stasis dermatitis was reinforced by the patient's history. One year previously he had similar symptoms, consistent with the diagnosis of stasis dermatitis secondary to edema, while on a 90-day course of levofloxacin. Similar to his current drug-induced bilateral lower extremity swelling and dermatitis, both the symptoms and clinical changes had eventually subsided after levofloxacin was discontinued. Unfortunately, neither the patient nor his wife had remembered the medication that had resulted in his earlier episode of leg edema when the intravenous and injection antibiotic treatment of his pneumonia was changed to oral levofloxacin therapy and he was discharged from the hospital.

Discussion

Our patient received levofloxacin treatment and developed stasis dermatitis secondary to drug-induced leg edema. Edema is defined as an increase in volume in extracellular fluid within interstitial space. There are many potential causes for edema including congestive heart failure, decreased oncotic pressure, drug interaction, Graves' disease, increased peripheral venous pressure, infection, liver disease, or pelvic tumors [4]. In patients over 50 years of age, the most common cause is venous insufficiency, which affects 30% of the population [5]. Medications that have been reported to cause leg edema are listed in Table 1 [6]. To the best of our knowledge, levofloxacin-induced leg edema has not been previously described.

Table 1: Medications associated with leg edema [6]

Alpha-Adrenergic antagonists
Antidepressants
    Monoamine oxidase inhibitors
Antihypertensive medications
    Calcium channel blockers [a]
    Direct vasodilators [b]
    Beta-Blockers
    Clonidine
    Methyldopa
    Antisympathetic agents [c]
Antirheumatic drugs
Chemotherapeutic agents
Endothelin receptor antagonists [d]
Erythropoietic agents
Hormones
    Corticosteroids
    Estrogens/progesterones
    Testosterone
Levofloxacin [e]
Nonsteroidal anti-inflammatory agents [f]
Pregabalin
Thiazolidinediones [g]

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a. Benzothiazepines, dihydropyridines, phenylalkylamines
b. Diazoxide, hydralazine, minoxidil
c. Guanethidine, reserpine
d. Ambrisentan, bosentan
e. Current case report
f. Nonselective cyclooxygenase-2 inhibitors, phenylbutazone, selective cyclooxygenase-2 inhibitors
g. Pioglitazone, rosiglitazone, troglitazone

Edema may be classified according to fluid content into the categories of venous edema and lymphedema. In venous edema, interstitial fluid has low protein content and viscosity; it is the result of increased fluid flux through the capillaries beyond the capacity of lymphatic drainage [5]. In lymphedema, interstitial fluid has high protein content, which builds up as a result of diminished lymphatic drainage [5].

Acute edema begins hours to a day after the cause of its etiology and rapidly progresses within the next few days; it is more likely to be venous edema. Etiologies of acute edema include abscess, cellulitis, compartment syndrome secondary to arterial bypass, deep vein thrombosis, and gastrocnemius muscle rupture [4]. Conversely chronic leg edema may begin within days after the associated cause and subsequently continues to slowly develop over weeks to months; it is more characteristic of chronic venous insufficiency or lymphedema. Etiologies of chronic edema may be systemic and include advanced prostatic carcinoma, benign prostatic enlargement, drug interaction, or ovarian carcinoma [4].

Similar to our patient's symptoms, the bilateral distribution of lower extremity edema is consistent with a more systemic etiology as opposed to bilateral local etiologies. Moreover, the temporal relationship between drug administration and bilateral edema presentation suggests the etiology of this edema to have resulted from the systemic effects of a drug interaction [4]. Hence, in our patient, the painless, chronic bilateral leg edema post levofloxacin administration-after ruling out of deep vein thrombosis-is strongly suggestive of a drug-related edema.

Stasis dermatitis is an inflammation of the dermis owing to venous insufficiency. Indeed, stasis dermatitis affects 7% of individuals over the age of 50 and is the cause of nearly half of chronic leg ulcers [2,7]. Similar to acute edema blisters of the lower extremities, the development of which correlates with the onset and speed of leg swelling, stasis dermatitis can occur following edema [8].

In stasis dermatitis related to venous insufficiency, edema occurs first. Subsequently, plasma, proteins, extracellular fluid, erythrocytes, and macrophages pass into the interstitial space, resulting in hemosiderin deposition and purpura [9]. Stasis dermatitis presents with erythema and crusting with pruritic, scaly erythematous papules and plaques in the acute phase [1,2,7]. Hemosiderin hyperpigmentation and possibly lipodermatosclerosis develops in the chronic phase [1,2,7].

Stasis dermatitis can morphologically mimic cellulitis. However, there are several clinical features that can differentiate the two conditions. Peripheral stasis dermatitis usually has bilateral involvement and post inflammatory hyperpigmentation. The patient is generally afebrile. In addition, swelling may be present over the medial malleoli. Associated symptoms may include itching, restlessness, and limb heaviness and aching [10]. In contrast to cellulitis, stasis dermatitis frequently improves with local compression, limb elevation, and topical application of corticosteroids [10].

A lesional biopsy of chronic stasis dermatitis shows hemosiderin laden macrophages, fibrosis, and thickened blood vessels in the papillary dermis [7]. Acute stasis dermatitis may only demonstrate reactive erythema with a sparse perivascular lymphocyte infiltrate and minimal epidermal changes. Reactive inflammation may occur secondary to increased hemosiderin as macrophages break down extravasated erythrocytes in the skin [11]. Clinically, these microscopic changes present as post inflammatory hyperpigmentation, as noted in our patient form his initial episode of stasis dermatitis.

Treatment for stasis dermatitis traditionally includes some of the following interventions: compression, elevation, occlusive dressings, and topical therapy including corticosteroids [2]. Middle to higher potency topical corticosteroid preparations such as betamethasone valerate 0.12% have been shown to reduce erythema and petechiae and improve the Dermatology Life Quality Index at two weeks and four weeks of treatment when compared to placebo [2]. Unna paste boots have also been reported to eliminate patient non-compliance and yield positive outcomes [11].

Levofloxacin is a third generation fluoroquinolone antibiotic. It has a broad spectrum of efficacy in the treatment of infections of the respiratory tract, urinary tract, skin and soft tissue, bones and joints, gastrointestinal tract, and in some sexually transmitted diseases [12]. Indeed, the antibiotic is particularly effective against gram positive bacteria, such as *Streptococcus pneumoniae* and *Enterococcus*, and atypical pathogens, such as *Mycoplasma* and *Chlamydia* [12].

The most common adverse events associated with the fluoroquinolone class of drugs are headache and dizziness, electrocardiogram abnormalities, disrupted glucose metabolism, phototoxicity, tendon and joint disorders, hypersensitivity skin disorders, and hepatic toxicity [12]. Adverse cutaneous reactions are rare amongst the adverse side effects of fluoroquinolones. In comparison to other fluoroquinolones, levofloxacin has a lower incidence of phototoxicity because it is more stable following ultraviolet radiation exposure than other drugs in its class [3].

The most common levofloxacin-related reactions are diarrhea, headache, insomnia, and nausea; discontinuation owing to adverse drug reactions occurs in 4.3% of patients [12]. However, as of July 2008, levofloxacin specifically carries a black-box warning regarding increased likelihood of tendonitis and tendon rupture [12]. To the best of our knowledge, this is the first observation of stasis dermatitis occurring as the result of levofloxacin-associated bilateral edema of the lower extremities.

Conclusion

Stasis dermatitis may be associated with prior swelling of the lower extremities caused by bilateral peripheral edema of the legs. We describe a 76-year-old man with a history of esophageal adenocarcinoma who developed stasis dermatitis following oral levofloxacin treatment. Following each episode of levofloxacin therapy, the patient developed peripheral edema of both lower extremities, which progressed to bilateral stasis dermatitis. This subsequently subsided after discontinuation of levofloxacin treatment. The occurrence of painless bilateral leg edema post levofloxacin administration supports our clinical hypothesis of levofloxacin induced leg edema with secondary stasis dermatitis. In conclusion, levofloxacin should be added to the list of medications associated with the potential development of peripheral edema and subsequent stasis dermatitis.

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