Leukocytoclastic Vasculitis Associated with Ciprofloxacin

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INTRODUCTION

Since its introduction on the Canadian market in 1989, ciprofloxacin has been generally well tolerated by patients. The most common side effects are gastrointestinal in nature (e.g., nausea, vomiting, and diarrhea), and some central nervous system effects, such as dizziness, have also been reported.[1] These side effects are dose-dependent, occurring more frequently at higher doses. Despite its popularity and wide applicability, ciprofloxacin is rarely associated with hypersensitivity reactions (rash, pruritus, or photosensitivity occurs in less than 2% of cases), and severe anaphylactic or anaphylactoid reactions are even less frequent.[2]

This case report describes a patient who experienced a rare skin reaction with systemic involvement. Because there was a probable association with ciprofloxacin therapy, a brief review of the relevant literature for ciprofloxacin-induced vasculitis is also presented.

CASE REPORT

A 65-year-old woman (167 cm, 100 kg) with no known drug allergies was admitted to hospital on March 10, 2001, with a 2-week history of pain and swelling in her right foot. Ulcers had also developed on the dorsal aspect of her second and fourth toes 2 days before admission. Upon admission, her blood pressure was 160/90 mm Hg, and her temperature was 37.4°C. The patient's calculated creatinine clearance was approximately 30 mL/min (serum creatinine 184 µmol/L, blood urea nitrogen 19 mmol/L) according to the method of Cockcroft and Gault.[3] Electrolyte values were normal, hemoglobin was 94 g/L, the platelet count was 346 x 109/L, and the white blood cell count was 16 x 109/L.

The patient's medical history was significant for type 2 diabetes mellitus (diagnosed in 1997), which was controlled with insulin. She had experienced various complications of diabetes including retinopathy, neuropathy, and previous diabetic foot ulcers. In the previous year, she had been admitted to hospital for myocardial infarction, congestive heart failure, and complicated urinary tract infections.

On March 10, the day of admission, ciprofloxacin (500 mg bid PO) and clindamycin (600 mg IV q8h) were started as empiric antibiotic therapy for the patient's diabetic foot infection. A gallium scan performed on March 15 and a bone scan performed 2 days later showed signs of osteomyelitis in the fourth toe of the right foot.

After 5 days of antibiotic therapy, on March 15, the patient exhibited petechiae and a palpable purpuric rash described as "reddish purple nonblanchable papules", which appeared bilaterally on her legs and spread to her arms and face. Patches and plaques with central ulceration developed on the distal areas of her arms and legs. Her legs were swollen, warm to the touch, red, painful, and pruritic. Her renal function had declined acutely, and on March 16 her creatinine clearance was 13 mL/min (serum creatinine 408 µmol/L, blood urea nitrogen 40.9 mmol/L). Urinalysis results at this time did not show any evidence of eosinophils.

Ciprofloxacin and clindamycin were the patient's only new medications during this admission. However, she had used both of these antibiotics without complications in the past for treatment of infections. Both antibiotics were stopped immediately upon development of petechiae and other associated

symptoms on March 15. Nevertheless, the patient's serum creatinine continued to climb to a peak of 570 µmol/L on March 19, and her blood urea nitrogen level also rose, reaching 56.1 mmol/L on March 20. Consequently, her creatinine clearance declined to 9 mL/min on March 19, after which renal function gradually began to recover.

On the basis of the patient's newly developed signs and symptoms of vasculitis, additional laboratory tests were ordered to look for evidence of systemic disease, to identify any potential underlying disorders, and to determine the patient's prognosis.[4] Specifically, the presence of serologic markers such as antinuclear antibodies, antineutrophil cytoplasmic antibodies, and rheumatoid factor may indicate an underlying autoimmune disease component of the presenting vasculitis. Extractable nuclear antigen (ENA) antibodies may be present in Raynaud's disease and mixed connective tissue disease.[5] As well, anti-ENA antibodies are present in systemic lupus erythematosus. Abnormalities in complement levels may be observed in patients with suspected lupus erythematosus or urticarial vasculitis. Furthermore, cryoglobulinemia is associated with inflammation of blood vessels and with infections such as hepatitis C and bacterial endocarditis. Hepatitis B was previously thought to be associated with vasculitis, but this association is now considered more likely a result of hepatitis C coinfection in these patients.[4]

For the patient described here, laboratory tests for hepatitis B and C antigens and antibodies, antinuclear antibodies, anti-ENA antibodies, and cryoglobulins were negative. There was no evidence of eosinophilia or C3 or C4 (complement) abnormalities. However, her platelet count was elevated (above 450 x 109/L) for approximately 8 days (until March 24). Consultation with dermatology staff, combined with histological evidence from a skin biopsy performed on March 17, confirmed this to be a case of leukocytoclastic vasculitis (LCV).

In addition to immediate discontinuation of ciprofloxacin and clindamycin, the patient was managed in hospital with a 5-day course of prednisone (75 mg PO daily). Her skin rash improved significantly in 7 days (by March 21), and her renal function continued to improve after March 20.

The patient was subsequently started on a 6-week course of cloxacillin (2 g IV q4h), ceftriaxone (1 g IV q24h), and metronidazole (500 mg PO q12h) for adequate antimicrobial coverage to treat her diabetic foot infection and osteomyelitis.

DISCUSSION

The challenge of evaluating an adverse drug event lies in establishing a causal relationship between the drug and the event. A number of tools have been developed to aid the clinician in this respect, including an adverse reactions scoring system,[6] an adverse drug reactions probability scale,[7] and the Bayesian adverse reaction diagnostic instrument.[8] These tools have been described and discussed extensively elsewhere.[9,10] Although rating scales may increase the precision of assessing causality and increase standardization, they are not without limitations.[10] Nevertheless, the Naranjo adverse drug reactions probability scale (APS)[7] was applied in this case because it has been shown to have comparable reliability and validity without the complexity of other methods.[10]

The answer to each of the 10 close-ended questions of the APS contribute points to a total score ranging from –2 to 13.[7] The higher the APS score, the greater the likelihood of causality. This patient scored 7 on the APS, which suggested "probable" causality between her skin reaction and at least one of the antibiotics started in hospital. A probable causality implies that the reaction followed a temporal sequence after the drug was administered, possibly followed a recognized pattern for the suspected drug, was confirmed by withdrawal but not re-exposure to the drug, and could not be reasonably explained by the known characteristics of the patient's clinical state.[7] Nevertheless, the results from this scale must be interpreted within the context of similar reactions associated with drug therapy that have previously been reported.

LCV is a small-vessel vasculitis characterized clinically by purpuric, palpable papules, most commonly on the lower part of the legs.[11,12] Nodules, ulcerations, and urticaria may also be present.[12] Systemic involvement of the kidneys is frequently seen.[11] The reaction is fatal in less than 5% of cases, with increased risk if there is gastrointestinal involvement or glomerulonephritis.[12] The hypersensitivity response diminishes when the drug is stopped, but some patients may require corticosteroid treatment for severe disease.[13] Histological evidence of LCV from skin biopsy shows small dermal vessels with fibrinoid necrosis, infiltration by polymorphonuclear leukocytes, and nuclear debris.[12]

Approximately one-third to one-half of cutaneous vasculitis cases are idiopathic.[4] The remainder are associated with a variety of causes. More specifically, associated infections include upper respiratory tract

infections (especially with ß-hemolytic streptococci), viral hepatitis (hepatitis C), human immunodeficiency virus infection, and bacterial endocarditis.[4] Also, 10% to 15% of vasculitis cases can be attributed to collagen vascular diseases such as rheumatoid arthritis, Sjögren's syndrome, and lupus erythematosus.[4] In addition, inflammatory bowel disease, ulcerative colitis, and Crohn's disease have been associated with cutaneous vasculitis.[4] Similarly, foods and food additives may cause cutaneous vasculitis.[4] Furthermore, large-vessel vasculitis such as Wegener's granulomatosis, polyarteritis nodosa, and Churg-Strauss syndrome may present with a cutaneous component.[4] Less than 1% of cutaneous vasculitis cases are attributed to malignancy; these cases usually involve hairy-cell leukemia, and effective tumour therapy has shown corresponding resolution of the vasculitis.[4]

Drugs cause approximately 10% of cases of acute cutaneous vasculitis, and clinical symptoms are typically seen 1 to 3 weeks after drug exposure.[12,14] Commonly associated drugs include allopurinol, penicillin, aminopenicillins, sulfonamides, thiazides, pyrazolones, hydantoins, and propylthiouracil.[12] Recent reports have also implicated retinoids, quinolones, and agents used in immunotherapy.[12] Foreign proteins including streptokinase, vaccines, and monoclonal antibodies may be associated with serum sickness syndrome accompanied by an LCV component.[11] Immune complexes and autoantibodies are believed to be involved in the pathogenesis of LCV.[4] However, the exact mechanisms have yet to be elucidated.

The patient described here was receiving the following medications on admission: atorvastatin, metoprolol, ramipril, folic acid, omeprazole, enteric-coated acetylsalicylic acid, nitroglycerin patch (and nitroglycerin spray as needed), furosemide, insulin, and vitamins B, C, and E. Although she had been using the cardiovascular medications beyond the typical 1- to 3-week time frame for manifestation of drug-induced LCV, a MEDLINE search was performed for the period January 1966 to mid-December 2001 for case reports of LCV and hypersensitivity vasculitis associated with any of the patient's medications on admission. The only finding was a case report of furosemide-induced hypersensitivity vasculitis.[15] However, Hendricks and Ader[15] reported that the rash resolved without discontinuation of furosemide, and doses of the drug were even increased for management of edema; thus, the drug was an unlikely culprit in this case.

For the patient described here, ciprofloxacin and clindamycin were started simultaneously in hospital. To date, only one case report of clindamycin-induced LCV has been published.[16] In that case, the patient experienced generalized arthralgias on the fifth day of clindamycin treatment, and a diffuse, palpable, purpuric rash developed the next day.

In contrast, 8 case reports of ciprofloxacin-induced LCV have been published to date.[17-23] These reports originated from Spain, Singapore, and Belgium and described cutaneous reactions with or without fever, arthralgia, arthritis, and renal involvement. The onset of the adverse reactions ranged from 3 days to 5 weeks from the start of antibiotic therapy, and the reactions reversed within 1 week of drug withdrawal. Skin biopsies were performed in 6 cases,[17,21] with histological evidence of LCV in 4 of these. Oral rechallenge with ciprofloxacin was performed in 2 cases,[21,23] and the results were positive in both. The affected individuals included ciprofloxacin-naive patients as well as those who had previously used ciprofloxacin without known reactions. The patients ranged in age from 18 years to 79 years, and no difference in incidence was noted between men and women. These case reports support the likelihood that the hypersensitivity reaction reported here might have been induced by ciprofloxacin.

The clinical picture and results of laboratory investigations in this case are consistent with other case reports of LCV caused by ciprofloxacin. The purpuric rash, the onset of the rash on the fifth day of antibiotic treatment, the location of the rash on the patient's legs and arms, the positive result on skin biopsy, and the resolution of the rash within 7 days after discontinuing the antibiotics all match the descriptions in previously published case reports. Corresponding renal involvement and subsequent renal failure further support a strong association between this patient's antibiotic therapy and the adverse reaction. In addition, laboratory investigations that were negative for hepatitis B and hepatitis C antigens and antibodies, cryoglobulins, and hypocomplementemia ruled out potential nondrug causes of the vasculitis.

However, this patient was receiving ciprofloxacin and clindamycin simultaneously. Because rechallenge was not considered ethical in this situation, the cause of her LCV cannot be definitively determined. Nevertheless, appropriate alternatives should be considered for future antibiotic use. The patient was advised to avoid ciprofloxacin and clindamycin in the future unless safer alternatives do not exist, in which case the medication should be administered and used only while she is under direct medical supervision.

Moreover, cross-reactivity with other fluoroquinolones is likely to occur because of their similar chemical structures. In fact, cross-reactivity between ciprofloxacin and ofloxacin has been demonstrated *in vitro* through the use of a lymphocyte transformation test.[24] Three case reports of ofloxacin-induced hypersensitivity vasculitis have been published.[25-27] One of these patients died,[26] and rechallenge was positive in another case.[25] Thus, the patient described here was also cautioned about using other fluoroquinolones because of potential cross-reactivity with ciprofloxacin.

In conclusion, this case report presents a rare but serious reaction most likely due to ciprofloxacin therapy. Because ciprofloxacin is a commonly prescribed medication that is generally well tolerated, physicians and other health care workers should maintain a high index of suspicion to detect clinical and histological manifestations of LCV in patients receiving ciprofloxacin therapy. Furthermore, the potential for cross-reactivity with other fluoroquinolones has significant implications for patients who have experienced this reaction while taking ciprofloxacin and who require treatment of bacterial infections in the future.

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