

## Levofloxacin-Induced Interstitial Nephritis and Vasculitis in an Elderly Woman

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**Key words:** levofloxacin, vasculitis, acute renal failure, nephritis

*IMAJ 2006;8:726-727*

Quinolone antibiotics may sporadically induce vasculitis and nephrotoxicity [1]. Newer fluoroquinolone agents such as levofloxacin have been rarely implicated as the cause of either vasculitis or nephropathy [2,3]. We describe a patient who developed a palpable purpura, acute renal failure and eosinophiluria while receiving levofloxacin therapy. Withdrawing levofloxacin led to a rapid and complete recovery.

### Patient Description

An 80 year old woman was admitted to the medical ward with disseminated purpura and acute renal failure. Her history included colon carcinoma 13 years previously that necessitated a right hemicolectomy with no evidence of recurrence. Aortic valve replacement was performed 1 year later with insertion of a mechanical prosthetic valve, and myelodysplastic syndrome was diagnosed 2 years later, that is, 10 years before the present admission. For the past 2 years, she was regularly treated with warfarin, bezafibrate, pravastatin, carvedilol, erythropoietin, folic acid and famotidine. Ten days earlier she was admitted to our ward with bilateral pneumonia.

Laboratory tests showed hemoglobin 10.7 g/dl, white blood cells  $2310/\text{mm}^3$ , with 55% neutrophils, 3% band forms, 26% lymphocytes, 8% monocytes, 5% eosinophils 5% basophils and platelets  $278/\text{mm}^3$ . The serum creatinine level was 1.4 mg/dl and blood urea nitrogen 57 mg/dl. Urinalysis was unremarkable. Arterial oxygen pressure was 65 mmHg. The remaining routine laboratory tests were all within the normal range. Blood and urine cultures were negative. There was

a polyclonal increase in immune globulin levels. On chest X-ray, extensive alveolar infiltrates with air-bronchogram were seen in the right upper and left lower lobe. Treatment with tazobactam-piperacilline and azithromycin was initiated. One week later the patient's condition improved and she was discharged with levofloxacin treatment 500 mg once daily for 1 week. Serum creatinine was 1.1 mg/dl and the creatinine clearance according to the Cockcroft-Gault equation was 48 ml/min.

Five days after discharge, petechiae appeared over the lower limbs and abdomen while the patient was still on levofloxacin. She was readmitted to the medical ward. On examination, the body temperature was 36.8°C, blood pressure 140/70 mmHg, heart rate 72 beats/minute and respiratory rate 16/min. A palpable purpura was observed over both lower extremities, extending over the buttocks and trunk. Hemoglobin was 9.6 g/dl, no fragmented red blood cells were present, WBC count was  $2200/\text{mm}^3$  with the differential count essentially similar to the latest findings, and platelets  $320/\text{mm}^3$ . Erythrocyte sedimentation rate was 62 mm/hour. Blood urea nitrogen was 120 mg/dl and creatinine 3.3 mg/dl. Serum and urine protein electrophoresis, antinuclear antibodies, complement C3 and C4 fractions, cryoglobulin concentrations and anti-glomerular basement membrane antibodies were normal or negative. Serology, repeated 3 weeks apart, for hepatitis A, B and C, cytomegalovirus, Epstein-Barr virus and Toxoplasma was negative; human immunodeficiency virus enzyme-linked immunosorbent assay was

WBC = white blood cells

non-reactive. The urinary sediment showed 8-10 cells/high power field with 30% eosinophils (Hansel stain) and no casts. A 24 hour urine collection contained 0.8 g protein. Chest X-ray showed clear lung fields. Ultrasonography showed normal-sized kidneys with increased cortical echogenicity.

The diagnosis of leukocytoclastic vasculitis and interstitial nephritis was considered and ascribed to levofloxacin, which was the latest medication prescribed. Levofloxacin treatment was suspended and prednisone, 1 mg/kg body weight daily, was administered. The subsequent course was favorable, with progressive attenuation of the purpuric eruption and improvement of renal function. Five days after the second admission serum creatinine was 1.2 mg/dl and the patient was discharged. During follow-up there was no recurrence of vasculitis or renal failure; 16 months later the patient died of urosepsis.

### Comment

Acute interstitial nephritis is usually caused by drugs, infection, or is associated with immune or neoplastic disorders. The typical presentation of acute tubulointerstitial disease is that of a sudden decrement in renal function, most commonly in an asymptomatic patient who has experienced an intervening illness or who was given a new medication. With drug-induced acute tubulointerstitial disease, the patient commonly exhibits an allergic process, such as a maculopapular skin rash, fever or eosinophilia. Microscopic evaluation of the urine will reveal mild to moderate proteinuria and hematuria. The finding of eosinophils in the urine is suggestive of allergic intersti-

tial nephritis, although one study found a positive predictive value of eosinophiluria for interstitial nephritis of only 38%. Renal biopsy is the only definitive method of establishing the diagnosis of interstitial nephritis.

Arriving at a definite diagnosis in our patient would require tissue sampling for histologic evaluation. In this patient, a kidney biopsy would impose the risk of prosthetic valve obstruction if anticoagulation was to be discontinued. Additionally, a kidney biopsy appeared unwarranted. Indeed, acute renal failure with eosinophiluria that occurred shortly after initiating an antibiotic is consistent with allergic interstitial nephritis. The common practice does not require further evaluation or therapy if renal function begins to improve within 1 week after withdrawal of the drug [4]. Indications for biopsy generally include uncertainty as to the diagnosis, advanced renal failure, or lack of spontaneous recovery following cessation of drug therapy [4]. Most cases of acute interstitial nephritis resolve by withdrawing the offending drug or agent within several days to weeks. Such a favorable course was observed in our patient.

Palpable purpura is consistent with cutaneous vasculitis, usually the leukocytoclastic variant. The American College of Rheumatology in 1990 proposed the following five criteria for diagnosing hypersensitivity vasculitis: a) age above 16 years, b) use of a possible offending drug in temporal relation to the symptoms, c) palpable purpura, d) maculopapular rash, and e) biopsy of a skin lesion showing neutrophils around an arteriole or venule. The presence of three or more of these criteria has a reported sensitivity and specificity for the diagnosis of hypersensitivity vasculitis of 71% and 84% respectively. In the patient described here, three of the above criteria were satisfied, thus taking a skin biopsy seemed unnecessary.

A search of the literature revealed two reports [2,3] of acute renal failure occurring during levofloxacin therapy [Table].

The diagnosis of levofloxacin-induced allergic interstitial nephritis was assumed in each of these two patients on a clinical basis without the need to perform a renal biopsy. There is a strong similarity between the clinical and laboratory findings in our patient and those reported in the literature. All patients were elderly, had near normal

renal function at baseline, and received levofloxacin for 3–16 days prior to diagnosis of the adverse event. Palpable purpura occurred in the patient reported by Famularo and De Simone [3] and in our patient. Eosinophiluria was present in one patient [2] as well as in our patient. After withholding levofloxacin, renal function improved in all patients within 1 week and, finally, returned to baseline within 3–4 weeks. Treatment with prednisone was given to Famularo and De Simone's patient [3] and to our patient for the suspected allergic interstitial nephritis.

Are there alternative causes, other than levofloxacin, that could have caused the reaction on their own? On scrutiny of the literature, we did not find any report of interstitial nephritis caused by or associated with myelodysplastic syndrome. The possibility that former treatment with azithromycin and piperacilline-tazobactam was responsible for interstitial nephritis and vasculitis is less plausible than an adverse reaction to levofloxacin, in considering the close temporal association between levofloxacin treatment and subsequent nephritis and vasculitis.

It is biologically and temporally plausible that levofloxacin was responsible for

**Table.** Literature review of levofloxacin-induced renal failure with or without associated purpura

Author	Solomon and Moczzycki [2]	Famularo and De Simone [3]	Present patient
Age	68	73	80
Gender	Male	Male	Female
Lag time (days)*	16	3	5
Purpura	None	Yes	Yes
Serum creatinine (baseline)	2 mg/dl	1 mg/dl	1.4 mg/dl
Serum creatinine (at diagnosis of event)	6 mg/dl	6.4 mg/dl	3.3 mg/dl
Eosinophilia	Yes	None	None
Eosinophiluria	Yes	None	Yes
Prednisone treatment	None	Yes	Yes
Time to recovery (wks)	4	4	1

\* Days from the beginning of levofloxacin treatment to diagnosis of acute renal failure and/or onset of purpura.

the patient's renal and cutaneous disorder, consistent with an immune-vasculitic pathogenesis. In applying the Adverse Drug Reaction Probability Score [5] to our patient, the strength of a causal relationship between levofloxacin and the ensuing vasculitis and allergic interstitial nephritis scored 7 (i.e., 'probable') by this method. Awareness of this rare but important adverse reaction is warranted.

## References

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*Good deeds are the best prayer*

Serbian proverb