Interstitial Nephritis, Thrombocytopenia, Hepatitis, and Elevated Serum Amylase Levels in a Patient Receiving Clarithromycin Therapy

We describe a patient who developed acute interstitial nephritis shortly after starting treatment with clarithromycin (Biaxin; Abbott Laboratories, Chicago, IL). It was accompanied by thrombocytopenia, hepatitis, and an elevated amylase level. Nephritis cleared with administration of prednisolone. This may be the first case of combined interstitial nephritis, thrombocytopenia, hepatitis, and elevated amylase levels after use of clarithromycin. These features point to an allergic reaction.

A 77-year-old man presented on 7 January 1997 with a 2-week history of cough, sputum production, and nasal stuffiness. He had been seen on 30 December 1996 for similar symptoms and had been prescribed trimethoprim-sulfamethoxazole (80/400 mg b.i.d.) without significant improvement in his condition. Physical examination revealed the following: temperature, 37.1°C (98.9°F); pulse rate, 81; blood pressure, 182/98 mm Hg; and respiratory rate, 12. Expiratory wheezes were heard over the chest. A clinical diagnosis of sinusitis and bronchitis was made (no laboratory studies were done), and the patient was prescribed clarithromycin (250 mg b.i.d.) on 7 January 1997.

Five days later, he presented again with a 24-h history of abdominal pain and intermittent fever. The patient had a history of hypertension for which he was receiving treatment with captopril (50 mg t.i.d.) and furosemide (40 mg q.d.); he was also being treated with an albuterol inhaler (p.r.n.), vitamin C (1,000 mg/d), nasal inhalation of beclomethasone dipropionate, and Actifed (Warner-Lambert, Morris Plains, NJ). He appeared acutely ill. His temperature was 36°C (96.8°F) (later rising to 37.6°C [99.7°F]); pulse rate, 110; respiratory rate, 22; and blood pressure, 129/77 mm Hg. He had cracbles at the base of the left lung and diffuse abdominal tenderness.

Laboratory studies disclosed the following values: hemoglobin, 15.2 g/dL; WBCs, 11.2/mm³ (37% segmented neutrophils, 48% band forms, 3% lymphocytes; vacuolization of neutrophils was present); blood urea nitrogen, 30 mg/dL; and creatinine, 3.4 mg/dL. Urinalysis revealed the following: SG, 1.025; blood, 2+; bilirubin, 2+; protein level, >300 mg/dL; ketones and glucose, negative; casts, negative; WBCs, 25 per high-power field; red blood cells, too numerous to count; bacteria, negative; nitrite, positive; and leukocyte esterase, 1+. Other laboratory studies revealed the following values: amylase, 324 U/L (normal range, 25–125 U/L); aspartate aminotransferase, 109 U/L (10–42 U/L); lactate dehydrogenase, 431 U/L (91–180 U/L); creatine kinase, 410 U/L (22–240 U/L); creatine kinase MB isoenzyme, 6.3 ng/mL (0–7.5 ng/mL); bilirubin, 1.7 mg/dL; albumin, 3.1 g/dL (3.5–5.0 g/dL); alkaline phosphatase, 76 U/L (32–92 U/L); total protein, 7.2 g/dL (6.7–8.6 g/dL); calcium, 8.9 mg/dL; and phosphate, 2.2 mg/dL (2.5–4.6 mg/dL). Chest radiography did not reveal any infiltrates. Blood cultures were sterile.

Therapy with ampicillin (2 g intravenously b.i.d.) and gentamicin (150 mg intravenous dose) was started. He continued treatment with the albuterol inhaler and was given 10 mg of oral vitamin K. Captopril administration was discontinued, and hydralazine therapy was started (25 mg q.i.d.; this dosage was later increased to 50 mg q.i.d.). He was also treated with diltiazem (30 mg q.i.d., which was later changed to 180 mg q.d.), furosemide (80 mg t.i.d.), and metolazone (5 mg/d). Cimetidine (400 mg h.s.) was also administered.

The following day (13 January 1997), cefuroxime (2 g intravenously b.i.d.) was substituted for ampicillin and gentamicin. Urine examination revealed 35% eosinophiluria. Results of laboratory studies over subsequent days are shown in table 1. Antibiotic therapy was discontinued 3 days after admission. Treatment with prednisolone (60 mg/d) was started 4 days after admission. Renal biopsy 9 days after admission confirmed the diagnosis of interstitial nephritis with eosinophilic infiltration. Bone marrow biopsy revealed an increase in the number of eosinophils and precursors. The patient recovered completely and was discharged; medications at this time were the albuterol inhaler, diltiazem (180 mg q.d.), and one aspirin daily.

When the patient was seen 6 months later, laboratory studies disclosed the following values: hemoglobin, 13.8 g/dL; WBCs, 6.6/mm³ (37.8% segmented neutrophils, 43.6% lymphocytes, 13.1% monocytes, 4.6% eosinophils, 0.9% basophils); blood urea nitrogen, 19 mg/dL; and creatinine, 1.3 mg/dL. He was receiving the following medications: atenolol, hydrochlorothiazide/triamterene, and naproxen. We chose not to rechallenge the patient. It is interesting that the patient received a 10-day course of clarithromycin starting on 22 May 1996.

The findings of this case are consistent with sensitization occurring with the first course of clarithromycin and an allergic or hypersensitivity reaction occurring rapidly during re-exposure. The patient had acute interstitial nephritis with nonoliguric renal failure. There was no radiological evidence of pancreatitis, although the amylase level was elevated to almost 3× the upper limit of normal. Thrombocytopenia, hepatitis, and elevated amylase levels resolved with nephritis. Pancreatitis has been reported as a complication of clarithromycin treatment [1]. Erythromycin, also a macrolide, has been reported to cause interstitial nephritis [2]. Thrombocytopenia has been associated with clarithromycin [3]; hepatitis has also been associated with clarithromycin [4].

Our case is unusual since it caused combined interstitial nephritis, thrombocytopenia, pancreatitis, and hepatitis in the same patient; to our knowledge, this is the first such case. The
findings are very similar to the “allopurinol hypersensitivity syndrome” [5] or phenytoin hypersensitivity [6] except for the absence of skin rash. Although it is possible that any of the drugs administered to the patient may have caused this reaction, the temporal relationship between clarithromycin administration and subsequent problems suggests that clarithromycin is the most likely culprit. The patient had been receiving treatment with furosemide since 1993 and captopril since September 1996.

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Table 1. Laboratory findings for a patient receiving clarithromycin treatment that resulted in acute interstitial nephritis and thrombocytopenia.

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<tr>
<td>Total WBCs/mm³</td>
<td>5.6</td>
<td>11.2</td>
<td>19.6</td>
<td>17.1</td>
<td>18.6</td>
<td>17.9</td>
<td>20.1</td>
<td>23.2</td>
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<td>Eosinophils (%)</td>
<td>9.2</td>
<td>10.7</td>
<td>11.7</td>
<td>12.7</td>
<td>14.2</td>
<td>12.8</td>
<td>13.2</td>
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<td>12.7</td>
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<td>Creatinine level (mg/dL)</td>
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<td>3.9</td>
<td>4.9</td>
<td>6.5</td>
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<td>BUN level (mg/dL)</td>
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<td>Eosinophils in urine (%)</td>
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<td>Platelets/mm³</td>
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<td>206</td>
<td>154</td>
<td>153</td>
<td>83</td>
<td>71</td>
<td>45</td>
<td>67</td>
<td>81</td>
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NOTE: BUN, blood urea nitrogen.

References

Valvular and Myocardial Abscesses Due to Erysipelothrix rhusiopathiae

In humans, Erysipelothrix rhusiopathiae infection manifests primarily as a skin disease. Systemic infection with E. rhusiopathiae is uncommon, and <1% of all cases of E. rhusiopathiae infection results in bacteremia and endocarditis [1, 2]. We describe a case of E. rhusiopathiae bacteremia and subsequent development of valvular and myocardial abscesses in a patient with a history of consumption of undercooked pork.

A 78-year-old man with a history of chronic alcohol abuse was admitted to the hospital with chills, weakness, fatigue, and poor appetite 3 weeks after noticing streaks of blood in his stools. He had consumed a batch of partially cooked pork over a 1-week period before the episode of blood in his stools. Blood cultures yielded non–spore-forming gram-positive bacilli consistent with Lactobacillus species. Therapy with intravenous penicillin G was initiated, but the patient left the hospital the next day and stopped receiving penicillin G therapy. One week later, he was readmitted with shortness of breath on exertion, and a transesophageal echocardiogram revealed vegetations on the mitral valve with mild mitral regurgitation. Intravenous penicillin G therapy was restarted, but over the next few days, he developed acute congestive heart failure and was transferred to our institution.

Physical examination was remarkable for heart failure, and cardiac examination revealed a grade 5/6 pansystolic murmur in the mitral area and a grade 4/6 early diastolic murmur in the aortic area. A transthoracic echocardiogram revealed severe aortic and mitral regurgitation, as well as vegetations on the aortic and mitral valves. On the same day, organisms recovered in previous blood cultures were reidentified as E. rhusiopathiae by the state public health laboratory. The dosage of intravenous penicillin G was increased to 4 million IU every 4 hr, and the patient underwent replacement of the mitral and aortic valves on the following day. During surgery, he was found to have a large abscess on the aortic valve with disruption of the entire valve. The abscess extended to the anterior leaflet of the mitral valve and the septum. A second abscess was identified; this abscess involved the posterior leaflet of the mitral valve and extended to the posterior wall of left ventricle.

Histopathologic examination of the heart valves showed findings consistent with infective endocarditis. Subsequent blood cultures were all negative. The patient did well postoperatively and was discharged to home; medication at the time of discharge was intravenous penicillin G to be continued for a total of 6 weeks.

Domestic swine is the major reservoir of E. rhusiopathiae [3].