BRIEF REPORTS

Azithromycin-Related Ototoxicity in Patients Infected with Human Immunodeficiency Virus

Azithromycin is increasingly being prescribed for human immunodeficiency virus (HIV)-related infections including *Mycobacterium avium* complex (MAC), toxoplasmosis, and cryptosporidiosis [1–3]. Ototoxicity has been reported in association with erythromycin [4, 5], clarithromycin [6], and azithromycin therapy [7]. We determined the prevalence and characteristics of azithromycin-related ototoxicity in patients who were seen at our HIV clinic.

We retrospectively reviewed the charts of all HIV clinic patients who received azithromycin via the Emergency Drug Release Program from September 1991 to September 1994. Demographic information as well as prior and concurrent therapy, illnesses that could cause ototoxicity, liver and renal function, azithromycin therapy, ototoxicity, audiograms, management of ototoxicity, and data on rechallenge with azithromycin were obtained. We used the World Health Organization's definitions for probable and possible adverse drug reactions [8].

Forty-six patients (43 male, 3 female) with a mean age of 41 years (range, 25–62 years) received azithromycin at a dosage of 600 mg/d (range, 300–1,500 mg/d) for a mean of 9.4 weeks (range, 0.5–46 weeks) as therapy for MAC infection or toxoplasmosis.

Eight (17%) of 46 patients experienced probable (n = 6) or possible (n = 2) azithromycin-related ototoxicity (table 1). Hearing loss (88%), tinnitus (37%), "plugged ears" (37%), and vertigo (25%) occurred after a mean of 7.6 weeks (range, 1.5–20 weeks), and were bilateral in 5 cases. Audiograms revealed mild-to-moderate sensorineural hearing loss (n = 4) and reflex decay (n = 1). After azithromycin was discontinued, symptoms resolved within a mean of 4.9 weeks (range, 2–11 weeks) in six cases. No patients were receiving concurrent ototoxic medications.

Confounding factors were present in two cases. Patient 7 had elevated baseline liver enzymes, borderline mild sensorineural loss, and an underlying unilateral moderate conductive defect. Follow-up data were unavailable in this patient's case. Patient 8 had an elevated baseline creatinine level, elevated liver enzymes, and a history of intermittent blocked ears. An audiogram revealed bilateral mild sensorineural hearing loss. Shortly after azithromycin was discontinued, the patient died of AIDS and renal failure.

Early phase 2-3 azithromycin safety reports suggested a low (<0.2%) rate of hearing-related adverse events [9]. However, Wallace et al. [7] reported ototoxicity in 14% (3 of 21) of patients who were receiving therapy with azithromycin (500 mg daily) for MAC infection. All patients had documented bilateral sensorineuronal hearing loss, and this loss occurred at conversational frequencies in two cases. Symptoms developed within 30–90 days and resolved 2–4 weeks after the drug was discontinued, and symptoms developed in one patient who was rechallenged. Similarly, 17% of our patients who received azithromycin (600 mg daily for 7.6 weeks) experienced ototoxicity, with resolution of symptoms by 4.9 weeks (mean) after the drug was discontinued.

Table 1. Clinical characteristics of eight patients who experienced ototoxicity while receiving azithromycin therapy.

Patient no.	Age (y)/ sex	Daily dose (mg)	Renal disease	Hepatic disease	Onset of otoxicity (w)	Management of ototoxicity	Time to recovery (w)	Audiogram performed	Underlying disease*	Concurrent therapy†
1	42/M	600	No	No	4	Discontinued drug	4	No	No	Fluconazole
2	38/M	600	No	No	1.5	Discontinued drug	2	Yes	No	
3	42/M	600	No	No	14	Discontinued drug	11	Yes	No	Ketoconazole
4	43/F	600	No	No	11	Discontinued drug	4	No	No	TMP-SMZ
5	40/M	600	No	No	4.5	Discontinued drug	4.5	Yes	No	Ciprofloxacin, fluconazole, TMP-SMZ
6	43/M	600	No	No	4	Discontinued drug	4	No	No	Fluconazole, TMP-SMZ
7	40/M	600	No	Yes	20	Discontinued drug	NA	Yes	Yes	Ketoconazole
8	58/M	600	Yes	Yes	2	Discontinued drug	NA	Yes	Yes	Diltiazem, ketoconazole

NOTE. Ototoxicity was probably related to azithromycin therapy for patients 1–6 and was possibly related to azithromycin therapy for patients 7 and 8. NA = not available; TMP-SMZ = trimethoprim-sulfamethoxazole.

* Prior or concurrent diseases that could cause ototoxicity.

† Potential ototoxic agents or potential inhibitors of drug metabolism.

The mechanism of dose-related macrolide otoxicity is unclear [4]. Patients who receive standard azithromycin dosages for respiratory infections (1.5 g over 5 days) have considerably less drug exposure than do those who receive regimens for HIV-associated indications. HIV-infected patients may also be at risk of developing hearing complications secondary to opportunistic infections or other potentially ototoxic drugs.

We were unable to eliminate many confounding factors in our review. Nevertheless, we had an accurate patient denominator, since all patients received azithromycin via the Emergency Drug

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Release Program. Ototoxicity was reported by the patients; while routine audiograms were not performed, macrolide-associated hearing loss is quickly noticed since it occurs at conversational frequencies [4]. Although many patients were receiving therapy with potential enzyme-inhibiting agents, such combinations have not been shown to affect azithromycin levels, and blood and otologic tissue drug concentrations were unavailable. Therefore, the clinical significance of receiving this therapy is unknown.

Patients who are receiving prolonged high-dose azithromycin therapy should be monitored for the development of ototoxicity; hearing loss has also been associated with erythromycin and clarithromycin therapy. If symptoms occur, they should abate after the drug is discontinued.

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Cat-Scratch Disease Mimicking Pancreatic Malignancy: Case Report

Bartonella henselae is a small gram-negative rod that causes cat-scratch disease (CSD) [1, 2]. Many cases of atypical CSD have been reported, including cases of CSD that presented as abdominal visceral granulomas [3, 4]. A case of CSD that presented as severe abdominal pain and biliary tract obstruction in an HIV-infected patient has also been reported [5]. We describe a patient with CSD that mimicked pancreatic cancer.

An immunocompetent, previously healthy 56-year-old male physician was admitted to our hospital with a 5-month history of abdominal distension and discomfort that was associated with progressive fatigue. He had lost 5 kg. One month before admission, he had treated himself for 1 week with metronidazole, tetracycline, bismuth subcitrate, and cimetidine for presumed *Helicobacter pylori* gastritis. Because he developed nausea, he discontinued therapy with metronidazole and tetracycline and instead took clarithromycin for 3 days. This treatment did not result in abatement of his abdominal complaints. One week before admission, he developed painless jaundice without fever. His stools were pale and clay-colored, and his urine was dark. He owned two adult cats but did not remember any recent scratches.

Physical examination revealed no abnormalities other than jaundice. Laboratory tests revealed the following values: plasma γ-glutamyltransferase, 401 U/L; alkaline phosphatase, 699 U/L; alanine aminotransferase, 120 U/L; and aspartate aminotransferase, 59 U/L. Unfortunately, the plasma bilirubin level was not measured. A CT scan and an ultrasonogram revealed a hypodense, 6-cm retroperitoneal mass in the area of the pancreatic head (figure 1) as well as near occlusion of the portal vein, with markedly decreased blood flow. The common bile duct (CBD) was dilated (diameter, 9 mm). Endoscopic retrograde cholangiopancreatography showed relative stenosis of the CBD (length, 4 cm) and no abnormalities of the pancreatic duct.

A stent was placed in the CBD. Examination of cells obtained by puncture of the mass was not diagnostic. Histological examination of a biopsy specimen obtained during laparotomy showed granulomatous necrotizing lymphadenopathy. Stains (hematoxylin-eosin, Grocott-Gomori methenamine silver nitrate, Ziehl-Neelsen, and Warthin-Starry silver stain) did not reveal any microorganisms. Titers of serum IgG antibody to *B. henselae,* measured with a whole-cell ELISA, were strongly positive (2,379 U/mL in a first sample obtained on admission, 6,004 U/mL at 4 weeks, and 412 U/mL at 11 months after admission [cutoff value for probable infection, >500 U/mL]), whereas titers of IgM antibody remained negative. A PCR assay for *B. henselae* with use of the primers p24E and p12B and appropriate negative and positive controls [1] was strongly positive.

On the basis of the positive results of serology and PCR, a diagnosis of CSD was made. The patient was treated with oral clarithromycin (500 mg twice daily) for 6 weeks as well as oral anticoagulants to prevent occlusion of the portal vein. After 3 weeks, the CBD stent was removed. A sonogram and a CT scan obtained 5 months after admission showed a marked decrease in the size of the retroperitoneal mass. Normal blood flow in the portal vein was restored, and there were no more signs of CBD compression.

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