Amoxicillin-Induced Aseptic Meningitis: 2 Case Reports and Appraisal of the Literature

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Drug-induced aseptic meningitis is an uncommon adverse reaction caused by different agents, particularly nonsteroidal anti-inflammatory drugs, antimicrobials, intravenous immunoglobulin, intrathecal agents, OKT3 monoclonal antibodies, and vaccines. The term aseptic meningitis refers to patients who have clinical and laboratory evidence of meningeal inflammation with negative routine bacterial cultures [1]. Amoxicillin-induced aseptic meningitis is an extremely rare adverse reaction, with only 14 reported cases [2-10]. We report 2 additional cases and review the literature.

Case 1. A 62-year-old man presented to the emergency department with fever and headache 48 hours after initiation of amoxicillin for dental pain. Physical examination, routine laboratory tests, and a computed tomography (CT) scan of the brain were unremarkable. Blood pressure was 160/105 mmHg, and body temperature was 37.7°C. The patient was discharged, although amoxicillin-clavulanic acid and analgesics (if needed) were prescribed. Four days later, the patient returned to the hospital with persistent headache and fever (37.8°C). Physical examination including detailed neurological examination, routine laboratory tests, and a cranial CT scan and magnetic resonance imaging (MRI) were unrevealing. Cerebrospinal fluid (CSF), which was obtained by lumbar puncture, showed lymphocytic pleocytosis (red blood cells, 5/µL; white blood cells [WBC], 44/µL; polymorphonucleocytes, 20%; mononuclear cells, 80%; glucose concentration, 50 mg/dL; and protein concentration, 80 mg/dL). Bacterial and fungal cultures of CSF were negative. Serology testing for herpes simplex virus type 1 and type 2 infection yielded negative results. The patient was diagnosed with acute viral meningitis and discharged from the hospital after 4 days. Two years later, he was seen at the Allergy Unit of our institution because of 2 similar episodes of fever, nausea, vomiting, and headache after taking amoxicillin for a dental procedure. The symptoms observed in both episodes resolved completely

after discontinuation of amoxicillin. In these episodes, a CSF analysis was not performed. Skin tests with penicilloyl-poly-L-lysine, minor determinant mixture, benzylpenicillin, and amoxicillin were performed according to the ENDA/EAACI Drug Allergy Interest Group protocol and yielded negative results. Rechallenge was not performed. The patient was diagnosed with amoxicillin-induced aseptic meningitis.

Case 2. A 58-year-old man was admitted to the emergency department with a 7-day history of fever (38°C) and headache that coincided with oral amoxicillin-clavulanic acid for whitlow on his toe. His blood pressure was 163/98 mmHg, and his body temperature was 37.6°C. The results of the physical and neurologic examination were normal, and routine laboratory tests, electrocardiogram, and cranial CT scan were unrevealing. Peripheral blood cultures were negative. CSF showed lymphocytic pleocytosis (red blood cells, 70/µL; WBC, 130/µL [100% lymphocytes]; glucose concentration, 48 mg/dL; protein concentration, 86 mg/dL; and adenosine deaminase activity, 9 IU/L). Bacterial and fungal cultures of CSF were negative. The patient reported 2 previous episodes of similar clinical symptoms during the previous year after taking amoxicillin-clavulanic acid for dental procedures, with lymphocytic pleocytosis documented in the CSF examination in both episodes. He was diagnosed with recurrent lymphocytic meningitis, probably due to the antibiotic agent. In one of these episodes, ampicillin, cefotaxime, and ceftibuten were administered for several days with good tolerance. The patient attended our Allergy Unit to confirm the diagnosis of amoxicillin-induced septic meningitis. Skin tests to penicilloyl-poly-L-lysine, minor determinant mixture, benzylpenicillin, and amoxicillin were performed according to the ENDA/EAACI Drug Allergy Interest Group protocol and yielded negative results for specific IgE to amoxicillin. Rechallenge was not performed. The patient was diagnosed with amoxicillin-clavulanic acid–induced aseptic meningitis.

Drug-induced aseptic meningitis secondary to amoxicillin is reported exceptionally and is not registered as a potential adverse effect on the package insert. The diagnosis is usually based on a temporal relationship with drug intake, CSF pleocytosis, negative microbiological tests, and rapid complete resolution after discontinuation. However, clinical signs and CSF findings may vary considerably. The exact pathogenesis is still unknown, but a delayed-type hypersensitivity reaction has been proposed. In the 2 cases reported here, an IgE-mediated mechanism could not be demonstrated because of the negative skin and serological test results. The literature contains no information on the underlying mechanism of this adverse reaction. Hypersensitivity syndrome related to amoxicillin is relatively frequent, although it typically includes gastrointestinal and dermatologic symptoms.

A review of the literature revealed 14 cases of amoxicillin-induced aseptic meningitis. The salient characteristics of these patients and of the 2 patients we report are summarized in the Supplementary Table. Ten of the 16 cases occurred in men, with a mean age of 64.4 years. Most patients reported 2 or 3 episodes of amoxicillin-induced aseptic meningitis, with symptoms of meningoencephalitis (cognitive disturbance, confusion, disorientation, and related neurological signs) in only 4 cases. Patients typically presented with fever and headache, which developed a few hours to 7 days after exposure to amoxicillin and mostly resolved within 2-4 days after discontinuation. Photophobia, nuchal rigidity, lethargy, myalgia, and general malaise were also present in some of the cases reported. Blood tests and brain CT or MRI scans were not diagnostic. Typical CSF findings consist of pleocytosis (lymphocytic or neutrophilic), which in some cases is accompanied by elevated protein and usually normal glucose levels. Normal CSF glucose levels may help to differentiate drug-induced aseptic meningitis from bacterial meningitis, in which glucose levels are usually low. CSF cultures are consistently negative. In some of the cases reported, treatment with other antimicrobials, including cefuroxime, ceftriaxone, cefotaxime, ampicillin, and ceftibuten was well tolerated.

Suggestive symptoms, a history of treatment with amoxicillin before appearance of clinical manifestations, a documented positive rechallenge result, CSF pleocytosis, and prompt resolution of symptoms, usually a few days after discontinuation of the drug, should alert clinicians to a diagnosis of amoxicillin-induced aseptic meningitis.

In the cases we report, allergy studies including skin tests and specific IgE levels to ß-lactam drugs were negative. However, allergy studies were not performed in previously published cases. Information about cross-reactivity with other penicillins or ß-lactams is lacking, although it seems reasonable to recommend avoidance of these agents in suspected cases of amoxicillin-induced aseptic meningitis. Clinicians should be aware that recognition and early diagnosis of amoxicillin-induced aseptic meningitis is very relevant in daily practice, since this condition is easily managed with discontinuation, thus obviating other, more aggressive diagnostic procedures and prolonged treatments, as well as the possibility of recurrent episodes related to the use of amoxicillin.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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