

Amoxicillin-Induced Aseptic Meningitis

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ABSTRACT

Amoxicillin is a semi-synthetic beta-lactam antibiotic that belongs to the penicillin family. It is the most prescribed antibiotic in the world. It has few side effects, even though hypersensitivity reactions may occur, with potential life-threatening effects. The authors present the case of a 63-year-old male admitted to the emergency department with a 2-week history of fever and occipital headache. The symptoms began after he started antibiotic prophylaxis with amoxicillin for a dental procedure. Cerebrospinal fluid analysis was suggestive of aseptic meningitis and the patient improved quickly after discontinuation of the drug. The patient's previous medical history highlighted a similar episode after he had started taking amoxicillin as part of a scheme for the treatment of a *Helicobacter pylori* infection. Aseptic meningitis is an extremely rare adverse reaction of amoxicillin, with only 16 cases reported in the literature.

LEARNING POINTS

- Aseptic meningitis is a rare side effect of amoxicillin.
- It is a diagnosis of exclusion and establishing a chronological relationship between the administration of amoxicillin and the onset of clinical symptoms is a key element for the diagnosis.
- The physiopathology is not well defined, but the consensus is that it is most probably the result of an immunologic hypersensitivity reaction.

KEYWORDS

Aseptic meningitis, drug-induced aseptic meningitis, amoxicillin

CASE DESCRIPTION

We present the case of a 63-year-old man with no significant past medical history admitted to the emergency department with a 2-week history of fever, with multiple daily spikes, and occipital headache. The fever had a poor response to antipyretics and the headaches got progressively worse. The patient reported that the symptoms began after he started taking amoxicillin as a prophylactic antibiotic 3 days before a dental implant surgery. After the procedure, he kept taking amoxicillin as indicated by his dental surgeon, and the symptoms continued as described.

On examination, the patient was alert and coherent but febrile (tympanic temperature of 38.5°C). The neurological examination was negative for neck stiffness and Brudzinski and Kernig signs were absent.

Admission blood tests revealed a neutrophilic leucocytosis (white blood cell count of 12,200 μ l, absolute neutrophil count of 10,990 μ l) and a C-reactive protein level of 3.05 mg/dl. Blood cultures and urine culture were all negative. Serologies for the human immunodeficiency virus and nontreponemal tests for syphilis were negative.

Cranial computed tomography (CT) and cranial magnetic resonance imaging were unrevealing.

Due to the recent history of an invasive dental procedure, a transthoracic echocardiogram was performed, followed by a transoesophageal echocardiogram, and both showed no evidence of valve vegetations. Thoracic and abdominal CT was also unremarkable.

A lumbar puncture was then performed, which revealed a clear and colourless cerebrospinal fluid (CSF). The cytochemistry study showed mild pleocytosis (white blood cell count of 25/ μ l), with a lymphocytic predominance, moderate protein elevation (100 mg/dl) and a normal glucose value (54 mg/dl). The microbiological examination (direct and culture) was negative. Taken as a whole, the CSF was suggestive of aseptic meningitis. The CSF viral panel was negative for enteroviruses, herpes simplex virus (HSV) type 1 and type 2, varicella-zoster virus, Epstein-Barr virus and cytomegalovirus. The CSF cytology assessment showed no evidence of malignant cells.

The investigation performed showed evidence of aseptic meningitis, but was not favourable to an infectious cause. Furthermore, the patient showed no evidence of systemic and neoplastic diseases.

The patient's medical history highlighted a previous episode suggestive of meningitis. He reported a similar episode of headache and fever, that had motivated a previous admission to the hospital, after he had started *Helicobacter pylori* eradication therapy, which included amoxicillin. At that time, there was no clear conclusion on the cause of the patient's symptoms, but he improved with interruption of the medication.

We considered Mollaret's meningitis as a possible diagnosis. However, the CSF was negative for HSV type 2 and the temporal relationship between the administration of amoxicillin and the symptoms was an element in favour of drug-induced aseptic meningitis (DIAM)^[1,2].

Keeping in mind the clinical evidence, the previous medical history and the positive correlation between the timing of the amoxicillin administrations and the onset of the symptoms, after the exclusion of more frequent aetiologies, amoxicillin-induced aseptic meningitis (AIAM) was then established as the most probable diagnosis.

Our patient had fast clinical and analytical improvement after the suspension of amoxicillin. He was discharged after 4 days and at 3 years follow-up he was doing well, without recurrence of the symptoms.

DISCUSSION

The diagnosis of DIAM is a clinical dilemma, since it can present as any other type of meningitis. In addition, sometimes the antibiotics used to treat the meningitis can be the offending agent, further confusing the diagnosis^[3].

DIAM on the whole is an uncommon diagnosis and its physiopathology is not well defined. It is believed to be the result of an idiosyncratic immunologic hypersensitivity reaction and, due to the erratic nature of these, it is statistically challenging to review their incidence^[2].

Aseptic meningitis is a rare side effect of amoxicillin. A review of the recent literature revealed only 16 reported cases of AIAM. The patients presented with similar symptoms to those we report, and the majority had pleocytosis and hyperproteinorrachia in the CSF analysis. Just like our patient, most had previous episodes suggestive of meningitis after exposure to amoxicillin^[4].

The diagnosis of AIAM requires a high degree of suspicion. Considering the use of amoxicillin worldwide, it is important to be aware of it as a possible cause of DIAM. It is also important to document and report these cases, since generally there is a recurrence after re-challenge with the suspected drug^[2].

A detailed anamnesis with a thorough drug history was essential for establishing the temporal relationship between the use of amoxicillin and the symptoms in our patient, and therefore vital for the diagnosis.

AIAM is a diagnosis of exclusion and should only be proposed after infectious meningitis and meningeal involvement of other diseases (mainly neoplasms and autoimmune disorders) have been ruled out^[5].

AIAM is a rare but recognized complication of treatment with amoxicillin. We report this case in the hope of contributing to a better understanding of this disorder.

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