

Amoxicillin-induced aseptic meningoencephalitis

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Abstract: Meningitis is usually produced by an infectious agent, but there are multiple noninfectious causes. Drug-induced aseptic meningitis (DIAM) is an important entity and has been reported as an uncommon adverse reaction with numerous agents. Thus, DIAM constitutes a diagnostic and patient management challenge. We present a patient with three episodes of aseptic meningitis due to amoxicillin, and then review the literature on this rare idiosyncratic event which may occur after local or systemic drug administration. A 77-year-old man was admitted to our hospital with fever, headache, and neck stiffness. Seven days before admission he had a dental and gingival inflammation. He was treated with two oral doses of 500 mg daily of amoxicillin for one week. The seventh day he awoke with the complaints that prompted hospital admittance. Amoxicillin was stopped 1 day before his admission. From his history we knew of two similar episodes: The first episode was after a dental procedure 3 months before this incident. He had received a 1-week course of postprocedure amoxicillin of 500 mg daily and had similar headache, fever, and chills during the entire course of treatment. He wasn't admitted to the hospital, because he stopped taking amoxicillin and he felt spontaneous pain relief after taking symptomatic pain treatment. The second episodes was 6 months after his first admission, he had been admitted to our hospital with the same symptoms. Amoxicillin was stopped and changed with intravenous (IV) ceftriaxone (CTRX) for 10 days due to suspected partial untreated meningitis. The patient improved rapidly within 2 days and was discharged from the hospital. On the basis of these three confirmed episodes of meningitis after recurrent exposure to amoxicillin, with repetitive negative testing for viral, bacterial, and mycobacterial micro-organisms, we diagnosed aseptic meningitis induced by amoxicillin. To our knowledge, this is the seventh well documented publication of such a severe side effect of a commonly used antibiotic.

Keywords: drug induced aseptic meningitis, viral meningitis, meningoencephalitis, amoxicillin

Introduction

Aseptic meningitis is a central nervous system infection that encompasses all types of leptomeninges inflammation of the brain, characterized by fever and meningeal symptoms with moderate, predominantly lymphocytic cerebrospinal fluid (CSF) pleocytosis and with bacteriologically sterile cultures.^{1,2} Aseptic meningitis is not caused by pyogenic bacteria, but can be caused by various conditions including infectious viral and nonviral,²⁻⁷ drugs, malignancy, and systemic illnesses.⁸ Therefore, this term is no longer tantamount with viral meningitis, although the two often are used interchangeably.⁸

Largely, viral infection is the most common form of aseptic meningitis and enteroviruses are the most common causes of viral aseptic meningitis.^{2,9} Certain

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enteroviruses are more likely to cause meningitis outbreaks,¹⁰ while others are mostly endemic.⁹ Other viral agents include the herpesviruses;⁹ human immunodeficiency virus (HIV) which causes sterile meningitis;^{11,12} and mumps^{13,14} are sometimes involved.

However, aseptic meningitis occurs at all ages, especially during summer and early fall,^{15–17} without racial differences.³ The illness tends to occur three times more in males than in females.⁸ The incidence of aseptic meningitis in the US has been reported as 11 per 100,000 person-years, compared to 8.6 per 100,000 for bacterial meningitis.^{18,19} The illness is responsible for 26,000–42,000 hospitalizations each year in the US,^{20,21} and for 37 incidence cases per 10,000 hospital admissions among children in Singapore.²² The severity of the clinical picture can be divided according to the primary brain structure involved. When the infectious agent primarily attacks the brain parenchyma, the clinical picture of severe encephalitis will be encountered with seizures, loss of consciousness and obtundation. When the inflammation is primarily of the meninges, a relatively milder syndrome of viral or aseptic meningitis is performed. In this case it is usually considered a benign disease,²³ because of the low complications and complete recovery; most people exposed to these viruses experience either no symptoms or mild symptoms, and they usually experience full recovery in 5–14 days after onset of symptoms.⁸ However, fatigue and lightheadedness may persist longer in some people. Hence, there is a pathological and clinical linkage between the brain parenchyma and meninges and some degree of meningeal inflammation is found with encephalitis and vice versa. When the two structures are involved a mixed picture of meningoencephalitis is more appropriate and the prognosis is less encouraging. Diagnosis is by exclusion of an infectious agent and other noninfectious causes such as central nervous system tumors, metastatic carcinomas, sarcoidosis, systemic lupus erythematosus (SLE) and granulomatous angiitis, and by demonstrating a convincing temporal relationship between the time of ingestion of drugs and the onset of the patient's symptoms. The recurrence of symptoms after rechallenge strongly supports the diagnosis of drug-induced aseptic meningitis (DIAM). Our patient developed a nearly identical clinical picture consistent with DIAM on two separate occasions and a picture of meningoencephalitis on the third episode shortly after the consumption of amoxicillin. However, our case strongly suggests that the description of meningoencephalitis is more appropriate in view of the presence of confusion, unresponsiveness, psychomotor slowness, cognitive disturbances, nuchal rigidity and unilateral right

mild weakness of the limbs without pyramidal signs. Hence, a high index of suspicion is needed to make an accurate diagnosis of DIAM.

Description of our case report of amoxicillin-induced aseptic meningitis

DIAM is an important entity. This descriptive study comes to shed light on the literature reviews on this rare idiosyncratic event which may occur after local or systemic drug administration; and presents the seventh worldwide case report of amoxicillin-induced aseptic meningitis.

We describe a clinical case of a patient whom we believe to have had amoxicillin-induced aseptic meningitis after receiving informed written consent form and authorization for publication. A 77-year-old male was admitted to our hospital with a history of 7 days of headache, chills, fever, and nuchal rigidity. The headache was pressure-like, global, and progressive. There was associated mild phonophobia but no photophobia, vomiting, nausea, or other constitutional symptoms. He was treated before his admission by amoxicillin using two oral doses of 500 mg daily for 1 week following dental and gingival inflammation, the seventh day he awoke with the complaints that prompted hospital admittance. One day before his admission he stopped amoxicillin treatment.

At his admission, past clinical history, physical examination, laboratory, lumbar puncture, and computed tomography (CT) were performed. In his past history the patient had a similar syndrome after a dental procedure a 3 months before this incident. He had received a 1-week course of postprocedure amoxicillin of 500 mg daily and had similar headache, fever, and chills during the entire course of treatment. He wasn't admitted to the hospital, because he stopped taking amoxicillin and he felt spontaneous pain relief after taking symptomatic pain treatment.

On examination, the patient had an oral temperature of 38.1°C, with mild tachycardia (heart rate, 102 beats per min). Neurological examination revealed normal findings, including a normal mental status, supple neck, and absent Kernig's and Brudzinski's signs. Results of examinations of other systems (cardiac; respiratory; head, eyes, ears, nose, and throat; and skin) were all normal.

The patient's serum white blood cell (WBC) count was 11,900 cells/mL (normal range, 3600–11,200 cells/mL), with a differential of 79.6% neutrophils (normal range, 44%–88% neutrophils) and 11.4% lymphocytes (normal range, 12%–43% lymphocytes). Results of urinalysis were

within normal limits. Lumbar puncture revealed a pleocytosis with 20 cells (80% mononuclear), raised protein concentration of 91 mg/dL and glucose level was normal. No bacterial, fungal micro-organism or serological signs of viral infection had been found. Herpes simplex polymerase chain reaction and enterovirus CSF polymerase chain reaction (PCR) were negative. CT of the brain was normal and it was performed for excluding alternative diagnosis in certain situations. Amoxicillin was stopped and changed with intravenous (IV) ceftriaxone (CTRX) for 10 days due to suspected partial untreated meningitis. The patient improved rapidly within 2 days and was discharged from the hospital.

Six months after his first admission, he was admitted again with severe complaints of: headache, confusion, unresponsiveness, psychomotor slowness, cognitive disturbances, nuchal rigidity, and unilateral right mild weakness of the limbs without pyramidal signs and oral temperature of 38.3°C. The patient's son proclaimed that his father was under amoxicillin treatment for 4 days following a tooth problem, and had a fever 1 day after initiation the treatment.

On examination our patient showed psychomotor slowness, cognitive disturbances, nuchal rigidity and unilateral right mild weakness of the limbs without pyramidal signs. Lumbar puncture revealed a pleocytosis with 12 cells (70% mononuclear), raised protein concentration of 117 mg/dL, and normal range of glucose. CT of the brain was normal and electroencephalography (EEG) showed intermittent diffuse slow waves abnormality in the theta range. Laboratory examination showed no micro-organisms had been found. Drug-induced meningoencephalitis was considered and amoxicillin administration was stopped immediately. Control Lumbar puncture after 2 days of admission was performed and showed 80 WBC (86% mononuclears) and proteins level were 96 mcg/dL. The patient improved without any specific treatment, his general condition including mental status and a focal neurological sign improved significantly and after 6 days was discharged. Three weeks later the patient underwent complete medical examinations including CSF and cognitive exams, all the exams were normal.

According to these three repeated episodes, in which two were confirmed to be aseptic meningitis after repetitive negative culture results for viral, bacterial and fungal micro-organisms, and resolved with cessation of amoxicillin therapy, amoxicillin was the etiology of the two episodes of aseptic meningitis in this patient.

To our knowledge, amoxicillin-induced aseptic meningitis has been reported only six times in the literature; the last report was in 2008, and this will be the seventh well

documented case report dealing with such a severe side effect of a widely and popular antibiotic.

Methods, procedures and assays used for the diagnosis of aseptic meningitis

Several methods, procedures and assays are needed to establish fast and accurate diagnosis of aseptic meningitis. It is important to obtain a careful history of medical disorders such as systemic lupus erythematosus, the most frequent underlying condition associated with DIAM.³ In addition it is important to make inquiries about recent vaccinations that may be implicated in the development of aseptic meningitis.²⁴ It should take into account that patients who have DIAM, the typical CSF profile reveals a neutrophilic pleocytosis, with several hundred to several thousand white blood cells per microliter; normal glucose levels; and variably elevated protein levels.^{2,25} Results of CSF Gram stain and cultures are negative, and lymphocytic or eosinophilic pleocytosis may occur.

Different tests include: laboratory diagnosis; PCR assay and variants reverse transcription polymerase chain reaction (RT-PCR) and Multiplex PCR; procalcitonin (PCT); viral isolation; serology and sometimes imaging are needed for adequate diagnosis of aseptic meningitis.

Many studies demonstrate the convenience of the application of the molecular assays in the laboratory diagnosis of the meningoencephalitis of different etiology. Besides this, it is also a very valuable tool for the clinical management of the patients and for the execution of the epidemiological studies.^{26,27} Routine CSF enterovirus-specific polymerase chain reaction (EV-PCR) testing has been shown to reduce length of hospitalization in pediatric patients with suspected aseptic meningitis.²⁸⁻³⁰

Analysis of C-reactive protein (CRP) levels also may be helpful in distinguishing bacterial- from drug-induced aseptic meningitis because CRP levels are usually highly elevated in bacterial meningitis compared with DIAM.^{31,32}

In our case report different diagnostic studies were performed, in addition to complete medical history, physical examination and CT, the diagnostic work included blood and CSF examination and serology for infectious meningitis, viral culture of throat and rectal specimens was conducted in addition to serological tests for enteroviruses followed by herpes simplex PCR and enterovirus CSF PCR.

Discussion

DIAM still relatively infrequent but probably more frequent than the literature report; especially in our era where, the

usage of different antibiotics; the list of medications that cause DIAM continues to increase and currently includes a wide variety of medications.^{2,3,33–58}

DIAM continues to cause a clinical dilemma, because it can present as any other type of meningitis. Also, the empirical treatment may, in fact, be the offending agent; further confusing the physician involved in the care of the patient with DIAM.

Many classes of medications have been reported to cause DIAM, typically in patients known to have systemic lupus erythematosus.³ The most common drugs are nonsteroidal anti-inflammatory drugs, antibiotics, intravenous immunoglobulin, and muromonab-CD3 monoclonal antibodies^{4–6} of the antibiotics, the most commonly reported offending agents include many antimicrobials, such as trimethoprim-sulfamethoxazole, ciprofloxacin, cephalexin, metronidazole, amoxicillin, penicillin, and isoniazid, are causes of aseptic meningitis. In addition, the xanthine oxidase inhibitor allopurinol has been implicated in causing aseptic meningitis. DIAM is a complication in which numerous other drugs, namely ranitidine, carbamazepine, vaccines against hepatitis B and mumps and OKT3 monoclonal antibodies (ie, directed against the T3 receptor and, therefore, pan T-cell antibodies), co-trimoxazole, radiographic agents, and muromonab-CD3, also have been associated.^{2,3,33–40} Amoxicillin is a moderate-spectrum, bacteriolytic, β -lactam antibiotic used commonly to treat bacterial infections caused by susceptible micro-organisms. It is usually the drug of choice within the class because it is better absorbed, following oral administration, than other β -lactam antibiotics.

Notwithstanding the wide use of this antibiotic, side effects were reported. Indeed, amoxicillin-induced aseptic meningitis has been reported only six times in the literature; the latest report was in 2008.^{32,42,43,59–61}

Although there has been speculation of a type 3 hypersensitivity reaction as a possible mechanism of amoxicillin-induced aseptic meningitis, a study by Wittmann et al and Kastenbauer et al^{42,62} found no evidence of involvement of type 1 or type 3 reactions.

Regardless of its low frequency, aseptic meningitis is increasing and it can mimic an infectious process as well as meningitis that are secondary to systemic disorders for which these drugs are used. Therefore, it should be included in the differential diagnosis of aseptic meningitis, particularly if aseptic meningitis develops in association with the use of nonsteroidal anti-inflammatory drugs (NSAIDs)^{4,63} or other offending drugs and if clinical recovery is rapid following

cessation of the drug or if results of viral studies are negative. Indeed, the diagnosis of DIAM is made by establishing a chronological relationship with the administration of the drug, onset of clinical symptoms and rapid resolution of the syndrome after drug withdrawal.

The present case again helps shed some light on rare, morbid events that are attributable to commonly prescribed medications. Because clinical characteristics of DIAM mimic those of infectious or other types of meningitis, physicians must continue to take thorough histories and be aware of the various medications that could cause these illnesses.

Conclusion

We conclude that a thorough history on prior drug intake must be conducted in every case of meningitis, with special focus on those aforementioned drugs. If there is a suspicion of DIAM, a third-generation cephalosporin seems a reasonable treatment option until CSF cultures are available. We should keep in mind these recommendations:

1. Quick resolution of symptoms is an important sign that distinguishes DIAM from viral meningitis, in which recovery usually requires 10 to 14 days. The diagnosis of DIAM is made by establishing a temporal relationship with the administration of the drug and onset of clinical symptoms and rapid resolution of the syndrome after drug withdrawal.
2. CSF glucose levels are usually normal in DIAM, which may help in differentiating it from bacterial meningitis in which glucose levels usually are low.
3. Analysis of CRP levels also may be helpful in distinguishing bacterial from DIAM because CRP levels are usually highly elevated in bacterial meningitis compared with DIAM.

The clinical features of almost all cases of amoxicillin-induced aseptic meningitis reported in the Table 1 are similar. All patients who have amoxicillin-induced aseptic meningitis typically present with fever, headache, and stiff or rigid neck. The time between use of the amoxicillin and onset of the signs and symptoms ranged from 2 to 7 days after drug ingestion. DIAM has been reported as an uncommon adverse reaction. DIAM is a diagnosis of exclusion, and clinical signs and CSF findings vary greatly. Clinical symptoms and CSF findings in patients with DIAM were indistinguishable from the early stage of infections of the CNS. Detailed anamnesis was essential, particularly related to medication used immediately prior to the appearance of symptoms of CNS impairment. Hence, the diagnosis of DIAM was done by establishing a temporal relationship with the administration of the drug

Table I Cases of amoxicillin-induced aseptic meningitis reported previously in the medical literature

Authors and journals	Report titles
Czerwenka et al ³²	Aseptic meningitis after treatment with amoxicillin
Jacobson & Elowsson ⁵⁹	Amoxicillin caused aseptic meningoencephalitis
Mateos et al ⁴³	Recurrent aseptic meningitis associated with amoxicillin-clavulanic acid.
Wittmann & Wooten ⁴²	Amoxicillin-induced aseptic meningitis.
Thaunat et al ⁶⁰	Amoxicillin-induced aseptic meningoencephalitis.
Whyte et al ⁶¹	A case of amoxicillin-induced meningitis

and onset of clinical symptoms and rapid resolution of the syndrome after drug withdrawal.

In patients who have amoxicillin-induced aseptic meningitis, the typical CSF profile reveals a neutrophilic pleocytosis, with several hundred to several thousand white blood cells per microliter; normal glucose levels; and variably elevated protein levels. Results of CSF Gram stain and cultures were negative. Amoxicillin-induced aseptic meningitis was reversible, with most signs and symptoms resolving within 24 to 48 hours after the drug were discontinued.

Disclosures

The authors report no conflicts of interest in this work.

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