

Amoxicillin-Induced Meningoencephalitis: Case Report and Review of the Literature

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Abstract: Amoxicillin is one of the most frequently prescribed antibiotics for common bacterial infections in the primary care setting. Although being considered one of the safest drugs, amoxicillin can induce a rare hypersensitivity reaction with direct leptomeningeal irritation leading to drug-induced aseptic meningoencephalitis (DIAM). Given its rare incidence and poorly elucidated risk factors, amoxicillin-induced aseptic meningoencephalitis remains a diagnostic challenge. We report here the case of an 82-year-old male who presented to our emergency department with fever and cellulitis on the left foot. Antibiotic therapy with amoxicillin-clavulanate was established. Two days after admission, the patient developed frontal headaches, nausea, photophobia, and nuchal rigidity, while remaining febrile. In addition, intermittent episodes of amnesic aphasia, confusion, and agitation were observed. Cerebrospinal fluid (CSF) analysis revealed mononuclear-predominant pleocytosis, without detecting a causative pathogen by culture or PCR screening. Repeated and focused exploration of the patient's medical history unraveled a similar episode of severe cephalgia with mononuclear-predominant pleocytosis on CSF analysis after the intake of amoxicillin-clavulanate 15 years before the current presentation. The combination of clinical signs for leptomeningeal irritation following ingestion of a distinct medication and the lack of evidence for a causative pathogen on CSF analysis, were suggestive of DIAM. DIAM is most commonly caused by nonsteroidal anti-inflammatory drugs, antibiotics and intravenous immunoglobulins. DIAM remains a diagnosis of exclusion. Its pathomechanism is still not completely understood. Our illustrative case emphasizes the key points of this rare but important diagnosis. In the context of our report, we review all published cases of amoxicillin-induced meningoencephalitis. Our case report may increase the awareness of this challenging diagnosis.

Keywords: Amoxicillin, Drug-Induced Meningoencephalitis, DIAM, Aseptic Meningitis, Amoxicillin-Induced Meningitis

1. Introduction

Aseptic meningoencephalitis is defined as the clinical presentation of leptomeningeal inflammation with an undeterminable causative pathogen [1]. The estimated incidence of aseptic meningitis in the United States is as high as 11 per 100,000 person-years and leads to approximately 26,000-42,000 hospitalizations yearly [2]. The differential diagnosis includes mycobacteria, fungi, parasites, connective tissues disorders, malignancies, autoimmune diseases, parameningeal infections,

and drugs [2-4].

Drug-induced aseptic meningoencephalitis (DIAM) is considered to be rare, although probably underreported [5]. DIAM might be induced by nonsteroidal anti-inflammatory drugs, antibiotics, intravenous immunoglobulins and OKT3 monoclonal antibodies [3]. Pleocytosis in the cerebrospinal fluid (CSF) often represents the only laboratory indicator of meningeal irritation [3]. Patients may exhibit a broad spectrum of neurologic symptoms: DIAM typically presents with meningitis-like symptoms such as fever, nuchal rigidity, headache, photophobia and phonophobia. Symptoms

indicating encephalitis such as cognitive impairment, mental status changes, impaired consciousness, focal neurologic deficits, and seizures have also been described [3, 5]. The pathomechanism behind the development of DIAM is considered to represent delayed immunological hypersensitivity reaction to the drug (type III or IV) and/or direct leptomeningeal irritation [6, 7]. Due to its low incidence, poorly understood pathogenesis and diverse clinical presentation, DIAM remains a diagnosis of exclusion. It is supported by a close temporal relationship between drug ingestion and meningeal inflammation, in the absence of any causative pathogens [6].

Our case aims to increase the awareness for amoxicillin, the most prescribed antibiotic in the world, as a potent trigger of DIAM [8]. Thorough exploration of the drug reaction history is key to prevent unfavorable outcomes following treatment of common bacterial infections. By reviewing the published cases of amoxicillin-induced aseptic meningoencephalitis, we aim to provide an overview of common clinical presentations and discuss the characteristic features of DIAM.

2. Case Description

An 82-year-old male presented to our emergency department with fever and a painful, sharply demarcated skin lesion with explicit swelling on his left forefoot. The patient was admitted for cellulitis. Antibiotic therapy (intravenous amoxicillin-clavulanate, 2.2g tid) was started.

Two days after initiating the antibiotic treatment, the patient developed frontal headaches, nausea, photophobia and nuchal rigidity, while remaining febrile. In addition, the patient exhibited intermittent episodes of amnesic aphasia, confusion and agitation.

Due to suspected meningoencephalitis the antibiotic therapy was escalated to high-dose ceftriaxone and acyclovir. A CT scan of the head was unremarkable. Lumbar puncture showed clear liquor and CSF analysis yielded a mononuclear-predominant pleocytosis with a total cell count of 66 cells/uL (normal range: 0-5 cells/uL; mononuclear, 58 cells/uL and polynuclear, 8 cells/uL) with a differential of 54% lymphocytes and 2% neutrophils. Protein and lactate levels were elevated with 1450 mg/L (normal range: 200-400 mg/L) and 2.8 mmol/L (normal range: 1.2-2.1 mmol/L), respectively. Glucose levels were normal with 2.2 mmol/L (normal range: 2.2-3.9 mmol/L). No malignant cells were present. Blood and CSF cultures remained sterile. Polymerase chain reaction was negative for HSV1/2, VZV, EBV, CMV and enteroviruses. Tick borne encephalitis (TBE) antibody profile was consistent with a post-vaccination status and anti-Borrelia-IgM were undetectable. Levels of CXCL13 were low (3.9 pg/mL, normal range: < 20 pg/mL) in the CSF.

Contrast-enhanced magnetic resonance imaging of the head showed no signs of inflammation or structural lesions. Electroencephalography revealed no significant pathologies. Chest radiographs showed no pneumonic infiltrates, a SARS-CoV-2 PCR was negative. Urinalysis was unremarkable. A repeated lumbar puncture revealed a further increase in cell

count by 86% (total cell count 123/uL; mononuclear, 120/uL and polynuclear, 3/uL) with elevation of lymphocytes up to 70% but remained negative for bacterial or viral pathogens. The systemic inflammatory markers peaked on the second day after admission (CRP 45,9 mg/l, normal range < 5,0 mg/l). However, the leukocyte count in the blood was always in the normal range.

During the further course, fever and headaches resolved completely, but the patient exhibited a prolonged delirium with confusion, agitation and disorientation.

Repeated exploration of the patient's history revealed a similar episode of severe cephalgia and a mononuclear-predominant pleocytosis on CSF analysis without detecting a causative pathogen after the intake of amoxicillin-clavulanate 15 years before the current presentation.

In light of this finding a diagnosis of aseptic meningoencephalitis, probably induced by amoxicillin was made. The patient's neurological status improved gradually, with remaining features of amnesic aphasia. He was discharged to a geriatric rehabilitation unit for further functional improvement.

3. Discussion

Although rare, drugs represent a relevant cause of aseptic meningoencephalitis and the list of potential agents is growing [2]. The first case of DIAM was described in 1963 and occurred following ingestion of sulfamethizole [9]. Antibiotics, particularly trimethoprim-sulfamethoxazole, ciprofloxacin, cephalexin, metronidazole, amoxicillin, penicillin, and isoniazid have been added to the list of DIAM-inducing medications [2]. In a recent study, Bihan and coworkers analyzed 329 cases of DIAM from a French pharmacovigilance database, and confirmed nonsteroidal anti-inflammatory drugs, intravenous immunoglobulins, and antibiotics as the main suspected drug classes provoking DIAM [10].

The delay of symptom onset in our patient is in line with the published literature [12]. Furthermore, it is described that the onset of symptoms may vary from days to months, but most commonly symptoms emerge within a week [11, 12]. This latency period might be found reduced to a few hours in case of re-exposition to a drug [13]. A complete recovery is mostly observed several days after discontinuing the offending drug [12].

CSF analysis in DIAM does not reveal pathognomonic characteristics [10]. Pleocytosis and elevated protein levels are the most common findings [10, 11, 14]. Pleocytosis shows lymphocytic or neutrophilic predominance, however, no particular CSF profile could be identified in DIAM to date [10].

The pathomechanism of DIAM is poorly understood. Possible mechanisms include direct meningeal irritation by the drug via the intrathecal route [13] and an immunological hypersensitivity reaction [13]. While some authors, supported by the presence of immune complexes in the serum and CSF [15, 16], suggest that a type III reaction may be the

underlying pathomechanism, others were unable to find such evidence [17]. More recently, a cytotoxic T-cell-mediated delayed hypersensitivity reaction (Type IV) has been suspected [7].

DIAM is a diagnostic challenge, which is particularly true in the case of DIAM induced by antibiotics. Since withholding the suspected agent may result in fatal deterioration of the patient's condition, switching to a different antibiotic drug class is usually the preferred approach, at least until an infectious etiology is excluded. Upon switching the antibiotic regimen in our patient to a third-generation cephalosporin, which is rarely associated with the development of DIAM [12], most of the symptoms resolved within a few days.

Amoxicillin is a beta-lactamase antibiotic and represents one of the most commonly prescribed antibiotics in the world. Amoxicillin is a generally well tolerated antibiotic, with gastrointestinal disturbances being its most common adverse effects [18]. In susceptible individuals, this drug potentially leads to meningoencephalitis.

Based on a global database of case safety reports, Chandler and coworkers reported 47 cases with suspected meningitis due to amoxicillin and 26 cases due to amoxicillin-clavulanate up to 2018 [5]. The increasing caseload over the past years highlights the emerging role of amoxicillin-clavulanate as a trigger of DIAM. Fever and headaches are

the two most common presenting symptoms in amoxicillin-induced meningoencephalitis and are observed in almost all cases (Table 1). Of note, the patient described in our vignette exhibited amnesic aphasia and prolonged delirium, indicating a cerebral involvement.

Dittrich et al. observed the coexistence of delirium and meningitis in every fifth patient and found an association with longer hospitalization, higher complication rates, and incomplete recovery. In this patient, the concurrent inattention, disorientation, restlessness, and agitation were highly suggestive for delirium [19], albeit the differentiation of altered mental status changes between delirium and inflammatory CNS diseases remains difficult.

Previous studies assessed a greater susceptibility of DIAM in individuals with autoimmune conditions, particularly systemic lupus erythematosus (SLE) [5]. However, this was not observed in our patient.

For differential diagnosis, we considered the syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis (HaNDL syndrome). This rare syndrome is a benign and self-limiting neurological condition, that is diagnosed clinically by exclusion of other causes [20, 21]. In the light of the patient's history with a previous episode of DIAM and significant improvement after switching the antibiotic regimen, HaNDL syndrome was considered unlikely in our case.

Table 1. Published cases of amoxicillin-induced meningoencephalitis.

Author	Year	Main Symptoms	Indication for Amoxicillin
Czerwenka et al. [22]	1999	Fever, headache, neck stiffness	Pretibial Wound
Jacobsson et al. [23]	1999	*	*
Mateos et al. [24]	2000	*	*
Wittmann et al. [25]	2001	Photophobia, AMS, difficulty reading, difficulty finding things	Sore throat
Thaunat et al. [26]	2003	Fever, extrapyramidal stiffness, confusion, coma	Skin grafting for varicose ulcers
Whyte et al. [27]	2008	Fever, headache, chills, phonophobia	Dental surgery
Shahien et al. [2]	2010	Fever, headache, chills, nuchal rigidity, phonophobia	Dental and gingival inflammation
Pietro-González et al. [28]	2011	Fever, headache, photophobia	Skin infection
Leung et al. [29]	2012	Fever, headache, nausea, vomiting	Dental surgery
Türk et al. [6]	2016	Fever, headache, nuchal rigidity, myalgias, phonophobia, photophobia	Genital infection
Chu et al. [30]	2018	Fever, headache, nausea, confusion	Otitis media
El Sheikh et al. [31]	2018	Fluctuating consciousness, headache, blurry vision, skin rash	Superinfection of chicken pox
Alarcón et al. [32]	2019	Fever, headache (2 cases)	Dental infection, herpetic whitlow
Sousa et al. [8]	2020	Fever, headache	Dental surgery

* Article not available in English; AMS=altered mental status

4. Conclusion

Amoxicillin-induced meningoencephalitis represents a key differential diagnosis that should be considered in every patient with aseptic meningitis. The clinical picture of meningitis or meningoencephalitis with pleocytosis on CSF analysis after exclusion of an infectious cause, should lead to thorough and focused medical history and consideration of DIAM. Early recognition and exploration of this rare drug adverse reaction improves patient safety and care. Our case emphasizes the importance to obtain a complete medical history with a focus on similar clinical events and drug exposition.

The most frequent drugs associated with DIAM are nonsteroidal anti-inflammatory drugs, intravenous immunoglobulins, and antibiotics [10]. The pathomechanism of DIAM is not completely understood. However, a delayed T cell-mediated hypersensitivity reaction seems possible [7].

Upon withholding the offending agent, complete clinical recovery is seen within several days in most cases [12].

Subsequent encephalopathy caused by either delirium or encephalitis is a common finding in patients with meningitis and is associated with longer hospitalization, higher complication rates and prolonged recovery [19].

Conflict of Interest Disclosure

The authors declare that they have no competing interests.

Patient Consent

Patient consent was obtained in written form.

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