Drug-induced aseptic meningitis secondary to trimethoprim/sulfamethoxazole: a headache to be aware of

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ABSTRACT

Trimethoprim/sulfamethoxazole (TMP/SMX), also known as Septra, is a commonly encountered and prescribed antibiotic in emergency department patients. The side effects associated with TMP/SMX are generally mild and self-limited, but serious side effects, including Stevens-Johnson syndrome and drug-induced aseptic meningitis, have been reported. We discuss the case of a 33-year-old woman who presented to our emergency department with the signs and symptoms of meningeal inflammation after being prescribed TMP/SMX 3 days earlier for an abscess with cellulitis.

RÉSUMÉ

Le triméthoprime-sulfaméthoxazole (TMP/SMX), aussi connu sous le nom de Septra, est un antibiotique d'usage courant, souvent prescrit aux patients traités au service des urgences. Les effets indésirables du TMP/SMX sont généralement bénins et spontanément résolutifs, mais des effets indésirables graves, notamment le syndrome de Stevens-Johnson et la méningite aseptique d'origine médicamenteuse, ont déjà été signalés. Il sera question ici du cas d'une femme de 33 ans, qui a consulté au service des urgences pour des signes et symptômes d'inflammation méningée 3 jours après avoir reçu du TMP/SMX pour un abcès accompagné de cellulite.

Keywords: aseptic meningitis, drug toxicity, emergency medicine, trimethoprim/sulfamethoxazole

Aseptic meningitis encompasses all nonbacterial etiologies of meningeal inflammation. Given the high morbidity and mortality of untreated bacterial meningitis, it is essential to rule out a bacterial source in any patient in whom meningitis is diagnosed or considered. Drug-induced aseptic meningitis (DIAM) is an underappreciated cause of aseptic meningitis. A number of different medication classes have been reported to cause DIAM, and treatment involves withdrawal of the offending agent and supportive care. Typically, patients make a complete recovery.

CASE REPORT

A 33-year-old woman presented to the emergency department (ED) with a left leg abscess and overlying cellulitis. The abscess had been incised and drained 10 days earlier, and initially the patient had been treated with outpatient intravenous (IV) cefazolin. Treatment was subsequently changed to oral trimethoprim/sulfamethoxazole (TMP/SMX) 3 days prior to ED presentation after culture of methicillin-resistant *Staphylococcus aureus* (MRSA) from wound swabs collected on the first visit. She returned to the ED with a 1-day history of gradual-onset, severe frontal headache, neck pain, nausea, vomiting, photophobia, fever, and chills.

The patient had a past medical history of iron deficiency anemia and was not taking any regular medications. She admitted to poor compliance with the prescribed TMP/SMX. Her last dose had been approximately 12 hours prior to presentation. She had not experienced similar symptoms previously and did not recall previous exposure to TMP/SMX. There was no history of recent travel, sick contacts, or IV drug use, and she denied risk factors for fungal, parasitic, or sexually transmitted infections.

Physical examination revealed an obese and unwell-appearing woman with a Glasgow Coma Scale score of 14 (eyes 3, verbal 5, motor 6) who was oriented to

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person, date, and place. Vital signs were all within normal limits at triage; however, in the ED, the patient was found to have a temperature of 38.4°C (101.1°F). Her respiratory, cardiovascular, and abdominal examinations were normal. Her neurologic examination showed no focal deficits, and her cranial nerves and fundoscopic examination were unremarkable. The patient had significant nuchal rigidity and jolt accentuation; however, both Kernig and Brudzinski signs were negative.

Laboratory analysis revealed the following: hemoglobin 89 g/L with a mean corpuscular volume of 59.2 fL, white blood cells (WBCs) 3.8×10^9 g/L, and platelets 189×10^9 g/L, with normal electrolytes, liver function tests, calcium, glucose, lactate, and creatinine. A nonenhanced computed tomographic (CT) scan of the brain was normal. The patient underwent a lumbar puncture revealing clear and colourless cerebrospinal fluid (CSF) containing red blood cells (RBCs) 2.0×10^6/L (2 cells/μL) and WBCs 25×10^6/L (25 cells/μL), with 7% neutrophils, 87% lymphocytes, 5% monocytes, and 1% eosinophils. Blood and CSF cultures, Gram stain, and viral polymerase chain reaction (PCR) were negative. Approximately 1 hour prior to her lumbar puncture and 45 minutes after ED presentation, the patient was administered vancomycin 1 g IV, ceftriaxone 2 g IV, and dexamethasone 10 mg IV. Her pain was managed with ketorolac 15 mg IV and additional IV morphine, as required.

The patient was admitted with the presumptive diagnosis of aseptic meningitis. TMP/SMX, the suspected culprit, was discontinued. Her symptoms rapidly improved and were completely resolved approximately 18 hours after she had taken her last dose of TMP/SMX. Blood and CSF cultures were normal, and she was discharged after a 48-hour admission. Given the rapid resolution of the patient's meningeal symptoms following cessation of TMP/SMX and the lack of evidence for bacterial, fungal, parasitic, or viral CSF infection, the patient was presumptively diagnosed with DIAM and advised to avoid TMP/SMX in the future. Confirmatory testing by drug re-exposure was not undertaken.

DISCUSSION

Meningitis is defined as an inflammation of the leptomeninges, the tissue membrane surrounding the brain and spinal cord. Bacterial meningitis is classically described as presenting with the clinical triad of fever, neck stiffness, and altered mental status. However, in reality, the findings are highly variable, and patients may exhibit any combination of fever, neck stiffness, headache, neurologic abnormalities, photophobia, seizures, malaise, nausea, and vomiting.[1]

Meningitis is a condition that includes infectious and noninfectious etiologies of meningeal inflammation (Table 1). ED recognition and treatment of bacterial meningitis are of paramount importance. Bacterial meningitis is a common worldwide disease associated with high morbidity and mortality when left untreated.[2,3] It is estimated that there are 1.2 million cases and 150,000 deaths annually worldwide from bacterial meningitis, with half of those affected suffering long-term sequelae.[4] Emergent antibiotic treatment has been shown to dramatically improve survival.[5]

Aseptic meningitis encompasses nonbacterial etiologies of meningeal inflammation and is characterized by CSF analysis that lacks signs of bacterial infection, including a negative Gram stain and culture. Although a misnomer, aseptic meningitis is classically defined as all causes of leptomeningeal inflammation that are not

Table 1. Infectious and noninfectious etiologies of meningitis

Etiology	Example
Infectious	
Bacterial	Bacterial infection
	Partially treated bacterial infection
	Parameningeal infection
	Mycobacterium tuberculosis
Viral	Echovirus
	Coxsackievirus
	Herpes simplex virus type 1, 2
	Human immunodeficiency virus (HIV)
Fungal	
Parasitic	
Noninfectious	
Drug induced	Nonsteroidal antiinflammatory drugs (NSAIDs)
	Antibiotics
	Immunomodulators
	Immunoglobulins
Malignancy	Lymphoma
	Leukemia
	Metastatic cancer
Autoimmune	Systemic lupus erythematosus (SLE)
	Sarcoid
	Behçet disease
Other	Vaccinations

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due to a bacterial source. This includes viral, fungal, and parasitic infections and meningeal inflammation from medications, malignancy, or neurosurgical procedures.[6] Incompletely treated bacterial meningitis may also produce aseptic CSF studies, thereby demonstrating the importance of elucidating a history of any recent antibiotic use in patients with suspected meningitis.

DIAM is a form of noninfectious aseptic meningitis that has been associated with a number of drugs, including antiinflammatory drugs, antimicrobial agents, IV immunoglobulins, immunomodulators, vaccines, and intrathecal agents (Table 2). Ibuprofen and TMP/SMX are the most commonly reported offending agents.[7] The signs and symptoms of DIAM are indistinguishable from other causes of meningitis, and no confirmatory radiographic or laboratory tests exist. CSF examination reveals a negative Gram stain and viral PCR, bacterial, and fungal cultures, and DIAM is usually indistinguishable from other nonbacterial meningitides. Diagnostic confirmation can be made through a controlled re-exposure to the suspected culprit agent, but this is rarely done and usually unnecessary.

The latent interval between drug exposure and onset of symptoms in DIAM is typically less than 48 hours but has been reported to range from a few minutes to 4 months.[7] Patients report previous exposure to the offending agent without incident in up to 45% of cases.[7] Repeated episodes of DIAM are possible and are characterized by a shorter latency period and increased severity of symptoms.[8] In previously reported cases, the acuity of symptoms varied greatly from weeks of mild headaches to rapid and severe onset, requiring intubation.[9,10] In all previously reported cases, symptoms completely resolved within 24 hours after therapy termination, without any long-term complications.[7,10]

Table 2. Potential causes of drug-induced aseptic meningitis

Class	Example
Nonsteroidal antiinflammatory drugs (NSAIDs)	Ibuprofen
	Naproxyn
	Diclofenac
	Cetuximab
	Celecoxib
Antibiotics	Trimethoprim/sulfamethoxazole
	Trimethoprim
	Ciprofloxacin
	Penicillin
	Metronidazole
	Penicillin
	Amoxicillin
	Cephalosporin
Immunomodulators	OKT-3 monoclonal antibodies
	Infliximab
	Methotrexate
Other	Intrathecal agents
	Lamotrigine
	Carbamazepine

The pathogenesis of DIAM is poorly understood. Some evidence indicates that DIAM may arise from a hypersensitivity mechanism localized to the CSF. Alternatively, it has been suggested that an accumulation of immune complexes in the choroid plexus may lead to small vessel vasculitis and resulting inflammatory changes associated with meningitis.[11,12]

TMP/SMX is a commonly used antimicrobial and the most widely reported antibiotic associated with DIAM. Amoxicillin, ciprofloxacin, and cephalosporins have also been implicated.[7] Of the reported cases associated with TMP/SMX use, most have been women. Evidence suggests that patients with systemic lupus erythematosus or human immunodeficiency virus (HIV) infection are at increased risk.[7]

DIAM should be suspected in cases of recurrant meningitis or when there has been a recent exposure to a culprit medication. If the diagnosis of DIAM is considered, the suspected agent should be immediately discontinued and while awaiting CSF culture to rule out partially treated bacterial meningitis. Cessation from the offending agent is the only required therapy, and complete reversal of symptoms can be expected within 24 hours.

As in previously reported cases, our patient presented with symptoms typical of meningitis and had unremarkable CSF studies, including negative bacterial cultures and viral PCR. It is possible that she had partially treated bacterial meningitis or a fungal or parasitic infection, thereby producing a falsely reassuring CSF analysis and a negative culture. However, such rapid improvement after TMP/SMX discontinuation is more suggestive of DIAM than an infectious etiology.

We suspect that DIAM is an underappreciated entity in emergency medicine. Unless emergency physicians are well versed in the differential of aseptic meningitis and causative etiologies of DIAM, the potential for a missed diagnosis in the ED is high. The increased use of TMP/SMX to treat MRSA and other emerging

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infections necessitates a thorough knowledge of the drug's side-effect profile.

CONCLUSION

DIAM is a rare, noninfectious source of meningeal inflammation that is initially clinically indistinguishable from bacterial or viral meningitis. Emergency physicians should entertain the possibility of DIAM in any patient who has a suggestive drug history after potentially dangerous etiologies have been excluded. A number of offending agents have been implicated, including commonly used antiinflammatory drugs, antibiotics, and immunomodulators. Cessation of the offending agent provides definitive therapy for DIAM and typically results in rapid and complete resolution of symptoms within 24 hours.

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REFERENCES

1. van de Beek D, de Gans J, Spanjaard L, et al. Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med* 2004;352:1849-59, doi:10.1056/NEJMoa040845.
2. Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998-2007. *N Engl J Med* 2011;364:2016-25, doi:10.1056/NEJMoa1005384.
3. Shears P. Emerging and reemerging infections in Africa: the need for improved laboratory services and disease surveillance. *Microbes Infect* 2000;2:489-95, doi:10.1016/S1286-4579(00)00309-9.
4. Scheld WM, Koedel U, Nathan B, et al. Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury. *J Infect Dis* 2002;186 Suppl 2:S225-33, doi:10.1086/344939.
5. Aronin SI, Peduzzi P, Quagliarello VJ. Community-acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. *Ann Intern Med* 1998;129:862-9, doi:10.7326/0003-4819-129-11_Part_1-199812010-00004.
6. Irani DN. Aseptic meningitis and viral myelitis. *Neurol Clin* 2008;26:635-55, vii-viii, doi:10.1016/j.ncl.2008.03.003.
7. Moris G, Garcia-Monco JC. The challenge of drug-induced aseptic meningitis. *Arch Intern Med* 1999;159:1185-94, doi:10.1001/archinte.159.11.1185.
8. Mifsud AJ. Drug-related recurrent meningitis. *J Infect* 1988;17:151-3, doi:10.1016/S0163-4453(88)91739-2.
9. Capra C, Monza GM, Meazza G, et al. Trimethoprim-sulfamethoxazole-induced aseptic meningitis: case report and literature review. *Intensive Care Med* 2000;26:212-4, doi:10.1007/s001340050048.
10. Harrison MS, Simonte SJ, Kauffman CA. Trimethoprim-induced aseptic meningitis in a patient with AIDS: case report and review. *Clin Infect Dis* 1994;19:431-4, doi:10.1093/clinids/19.3.431.
11. Gordon MF, Allon M, Coyle PK. Drug-induced meningitis. *Neurology* 1990;40:163-4, doi:10.1212/WNL.40.1.163.
12. Joffe AM, Farley JD, Linden D, et al. Trimethoprim-sulfamethoxazole-associated aseptic meningitis: case reports and review of the literature. *Am J Med* 1989;87:332-8, doi:10.1016/S0002-9343(89)80160-3.