

Trimethoprim-Induced Aseptic Meningitis in an Adolescent Male

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ABSTRACT. Drug-induced aseptic meningitis attributable to trimethoprim alone has only rarely been documented in the literature. A previously healthy adolescent male presented to our hospital with recurrent headaches, photophobia, and meningismus after serially starting and stopping trimethoprim. Cerebrospinal fluid studies revealed elevated white blood cell counts with a polymorphonuclear predominance. This case is the second documented report of trimethoprim-induced aseptic meningitis in a pediatric patient. *Pediatrics* 2002;110(2). URL: <http://www.pediatrics.org/cgi/content/full/110/2/e26>; aseptic meningitis, trimethoprim.

ABBREVIATIONS. LP, lumbar puncture; WBC, white blood cell; PMN, polymorphonuclear leukocytes; CSF, cerebrospinal fluid.

Aseptic meningitis is associated with a wide variety of infectious and noninfectious processes. Adverse drug reactions presenting as aseptic meningitis have been well documented and pose a considerable diagnostic challenge to the clinician.¹ The most common medications associated with this syndrome include nonsteroidal antiinflammatory drugs, intravenous immunoglobulin, muromonab-CD3 (OKT3), and numerous antibiotics.²

Aseptic meningitis attributable to trimethoprim alone has been described in the adult population.³⁻⁵ A careful search of the literature, however, revealed only 1 documented pediatric case.⁴ We report a case of trimethoprim-induced aseptic meningitis in an adolescent male.

CASE REPORT

A 15-year-old male was prescribed trimethoprim, 200 mg in the morning and 100 mg in the evening, for acne. After 1 month, he discontinued the medication for no apparent reason. At that time the patient was asymptomatic. One month later the patient resumed the medication. Within 2 days, he noted headache, nausea, neck pain, numbness in his extremities, photophobia, subjective fever, and red eyes. The patient discontinued his trimethoprim again, this time because of the above noted adverse reaction. His symptoms resolved within 24 hours without his seeking medical assistance.

One week later, the patient resumed the trimethoprim, starting with the evening dose. By the next morning, before taking a second dose of trimethoprim, the patient's previously described

symptoms had recurred. These symptoms were described as more severe than the initial episode.

The patient's primary care physician referred him to the local emergency department for a lumbar puncture (LP). The LP revealed glucose of 62 mg/dL, protein of 85 mg/dL, and 38 white blood cells (WBCs) with a differential of 99% polymorphonuclear leukocytes (PMNs) and 1% lymphocytes. Gram-stain and culture of the cerebrospinal fluid (CSF) were negative.

The patient discontinued the trimethoprim again. However, his headache persisted for 3 days, necessitating a second emergency department visit. A second LP was not performed at this time, but CSF cultures from the previous visit remained negative. Tylenol #3 was prescribed, the patient returned home, and his symptoms resolved.

Twelve days later, the patient felt well and again resumed his trimethoprim with his morning dose of 200 mg. Within 15 minutes of taking the medication, he experienced severe headache, neck stiffness, nausea, and numbness in his extremities. The patient presented to the emergency department with a temperature of 100.9°F. On physical examination he had a stiff neck and marked conjunctival injection. His complete blood count showed 20 800 WBCs with a differential of 75% PMNs, 20% bands, and 3% lymphocytes. A repeat LP revealed glucose of 64 mg/dL, protein of 56 mg/dL, and 210 WBCs with a differential of 98% PMNs and 2% monocytes. Direct antigen screening for bacteria, Gram-stain, and culture of the CSF were negative.

The patient was admitted to the hospital and started on toradol, vancomycin, and ceftriaxone. After careful elaboration of his history, the diagnosis of trimethoprim-induced aseptic meningitis was considered the most likely cause of his recurrent symptoms. Antibiotics were stopped. By hospital day 2, the patient's complete blood count showed 7900 WBCs with a differential of 56% PMNs, 31% lymphocytes, and 6.5% eosinophils. Blood and CSF cultures remained negative. His condition improved; only mild back pain and slight nuchal rigidity remained 1 day after stopping the trimethoprim. The patient was advised to avoid all trimethoprim-containing medication and was discharged on hospital day 3.

DISCUSSION

Drug-induced aseptic meningitis is uncommon in the pediatric population. Only 4 pediatric cases of trimethoprim-sulfamethoxazole-induced aseptic meningitis have been described in the literature.⁶⁻⁹ These patients ranged between 4 and 16 years of age. We were able to identify only 1 pediatric case attributable to trimethoprim alone.

The previously documented case of trimethoprim-induced aseptic meningitis in the pediatric population occurred in a 17-year-old female.⁴ Her symptoms occurred within 1 hour of ingestion of the drug and consisted of headache, nausea, vomiting, nuchal rigidity, and low-grade fever. An LP after her first exposure revealed mild pleocytosis with 50% lymphocytes and 50% PMNs. She was exposed to the drug again 1 month later, which produced similar symptoms, but an LP did not reveal pleocytosis. Although the 2 cases had many similar symptoms, our patient demonstrated symptoms and a leukocytosis on LP that are more consistent with the docu-

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mented findings in drug-induced aseptic meningitis.¹

Most patients with drug-induced aseptic meningitis experience headache, mental status changes, fever, nausea, and nuchal rigidity.¹ Because this process is an adverse drug reaction, other systemic symptoms, such as rash, arthralgias, myalgias, facial edema, lymphadenopathy, and uveitis, may be prominent features of the initial presentation. Our patient experienced photophobia and marked conjunctival injection. Photophobia has not previously been noted in aseptic meningitis attributed to antibiotics.¹ Although formal ophthalmologic consultation was not obtained because of cost consideration, this patient may have had concomitant conjunctivitis or uveitis.⁵

CSF findings have varied widely between cases of drug-induced aseptic meningitis.¹ The CSF protein may be elevated; however, the glucose level is nearly always normal. The CSF WBC count has ranged between 8 and several thousand. Most patients have a predominance of PMNs in the CSF that may falsely raise concerns about bacterial meningitis. Morris and Garcia-Monco¹ note that with each successive exposure to an offending agent, the CSF protein concentration tends to increase and the PMN pleocytosis tends to become more pronounced. In contrast, the glucose concentration and differential cell count tend not to change. As in our case, the severity and rapidity of onset of symptoms increased with each successive drug exposure.

Migraine headaches have been associated with an increased risk of developing drug-induced aseptic meningitis.¹ Our patient had a previous history of intermittent migraine headaches. However, his migraines had not been active during the several months before his presentation to our hospital.

The pathophysiology of drug-induced aseptic meningitis is poorly understood. In the adult population, trimethoprim-sulfamethoxazole is one of the antibiotics most commonly associated with aseptic meningitis. Both trimethoprim and sulfamethoxazole can cause aseptic meningitis when taken alone.^{2,10} It is not known which compound is responsible for the majority of cases resulting from the medications being taken together. A disproportionate number of cases occur in patients with collagen vascular diseases.² Our patient had no findings consistent with collagen vascular disease at the time of his presentation.

Aseptic meningitis has been associated with an abnormal upregulation of interleukin 6 in both CSF and plasma.^{11,12} IL-1 β and tumor necrosis factor- α levels have been normal in those patients studied. The high levels of interleukin 6 seen in aseptic meningitis are most likely a marker of immune dysregulation. Unfortunately, the exact mechanism of this dysregulation is poorly understood.

Blumenfeld et al¹³ documented abnormal magnetic resonance imaging findings in 2 patients with aseptic meningitis. Both patients had supratentorial white-matter T₂-signal abnormalities that resolved after discontinuing the agent suspected of causing aseptic meningitis. These findings suggest that "aseptic meningitis" is actually "aseptic meningoencephalitis." The clinical utility of magnetic resonance imaging in differentiating drug-induced meningitis from other causes is unclear at this time.

Drug-induced aseptic meningitis seems to best explain this patient's presentation. The 3 separate recurrences of symptoms were closely timed to restarting trimethoprim, and the time between exposure and development of symptoms decreased with each subsequent exposure. Symptoms resolved with removal of the drug after each episode. Both lumbar punctures failed to reveal a bacterial cause. Viral, mycobacterial, and fungal studies were not performed on this patient because of the rapid response to removal of the offending agent.

Trimethoprim-induced aseptic meningitis has only rarely been described in the adult literature. This patient is the second and youngest documented case of trimethoprim-induced aseptic meningitis in a pediatric patient. This provides additional evidence that trimethoprim alone should be considered a possible cause of drug-induced aseptic meningitis in the pediatric population.

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