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Case Report

A Pediatric Case of Trimethoprim/ Sulfamethoxazole Associated Aseptic Meningitis

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Introduction

Aseptic meningitis (AM) is a condition of meningeal irritation evidenced by headache, nuchal rigidity, and cerebrospinal fluid (CSF) changes in the absence of viral, bacterial, fungal, or autoimmune causes. Diagnosis is usually made by cessation of the suspected drug followed by resolution of symptoms and normalization of CSF cell counts in 48 to 72 hours. With prompt diagnosis and discontinuation of the offending drug, complete recovery is expected [4,5]. We present a case of an immunocompetent 14-year-old female who developed AM following treatment with Trimethoprim/Sulfamethoxazole (TMP-SMX).

Keywords: Aseptic meningitis; Bactrim; Drug-induced aseptic meningitis

Case Presentation

A 14-year-old female presented to the emergency department with complaints of fever (103F), nausea, vomiting, neck pain, and pruritic rash over bilateral upper and lower extremities, abdomen, chest, and bilateral palms. She had just returned from Rocky Mountain National Park in Colorado where she had been hiking. Her lodging had alpacas and chickens. She initially felt sick five days before admission, while in Colorado, with headache, fever, nausea, and vomiting (Day 0-4, Fig. 1). She was seen at an emergency room where an ultrasound ruled out appendicitis and she was discharged (Day 4). The next day (day 5), she woke up with a generalized, pruritic rash so she returned to the emergency department. On arrival, she was afebrile, tachycardic to 111 BPM with a BP of 100/55. Physical exam disclosed mild nuchal rigidity with negative Brudzinski sign and a non-petechial rash on the chest, face, and bilateral arms. CBC showed a WBC of 6.1 and segmented neutrophils of 87.7%. Her procalcitonin was 0.19 (0-0.10). CSF showed glucose of 63 (45-80), protein of 74 (15-45), RBC of 6,400 (0), nucleated cells of 11 (0-5), neutrophils of 82 (0-6) (Table 1), concerning for aseptic meningitis. Urinalysis was within normal limits, influenza A, influenza B, COVID, and an extended respiratory virus panel were negative. Her chest X-ray and CT Head without contrast were unremarkable. She was started on Ceftriaxone 2000mg q12h IV (50mg/kg/dose), Vancomycin 660mg q6h IV (15mg/kg/dose), and Acyclovir 440mg q8h IV (10mg/kg/dose). CSF HSV PCR and bio-FIRE panel were reported negative. Blood cultures were drawn before treatment and did not grow any organisms. Her CSF culture with gram stain was negative. Her rash self-resolved by the second day of admission. The infectious disease (ID) team was consulted (Day 6). Further questioning revealed she recently had an infection of the right big toe for which she had been taking TMP-SMX for 4 days. She stopped taking the TMP-SMX on arrival at the hospital when her inpatient antimicrobials were started (Day 5). Rocky Mountain Spotted Fever (RMSF), Colorado tick fever, West Nile, Ehrlichia, Murine Typhus, Kawasaki disease, and drug-induced aseptic meningitis were considered. At ID evaluation the patient was clinically normal, feeling well, and wishing to go home. We collected samples for laboratory tests, prescribed a 5-day course of doxycycline 100mg BID PO, and the patient was discharged.

A negative infectious work-up and resolution of all symptoms 48 hours after discontinuation of TMP-SMX meet the definition for a likely case of drug-induced aseptic meningitis from TMP-SMX.

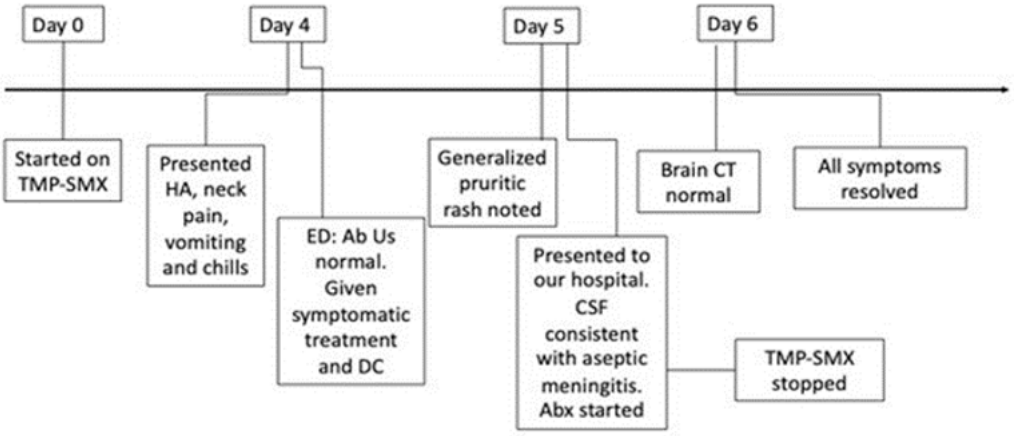

Figure 1: timeline of symptoms.

CSF Findings		Normal Range
Glucose	63	45-80
Protein	74	15-45
RBC	6,400	0
Nucleated cells	11	0-5
Neutrophils	82	0-6
Lymphocytes	16	40-80
Monocytes	2	15-45

Table 1: CSF findings.

Discussion

Drug induced septic meningitis (DIAM) was first reported in 1978 in an adult woman with a history of systemic lupus erythematosus (SLE) after using non-steroidal anti-inflammatory drugs (NSAIDs) [9]. From 1995 until 2017, only 151 cases of drug-induced aseptic meningitis were reported in the literature. Of those, 46 were attributed to antibiotics [4]. Literature reporting pediatric cases of drug-induced AM is even more rare, emphasizing the infrequency of the diagnosis in this population. In addition, AM symptoms with an unknown source may be more commonly ascribed to a virus in the pediatric population than the adult population due to the higher prevalence of viral illnesses in children, leading to under-reporting of drug-induced AM [2]. While the presentation of AM varies, the most common symptoms are fever and headache, with about half of the patients presenting with neck stiffness, and one-quarter with encephalitis, photophobia, or phonophobia [2,4]. A recent literature review recorded the median age of presentation to be 40 years old and found that 40% of patients with AM had an underlying autoimmune disease [2,4]. Timing of symptom onset relative to drug exposure varies from an immediate reaction to up to one year, with slight variance based on the type of drug [2,4,6]. In a review by Morris and Garcia-Monco of drug-induced aseptic meningitis [6], 39 patients had antibiotic-related aseptic meningitis; thirty-one of thirty-nine were due to sulfamethoxazole. The median range of latency was 10 minutes to 10 days. In our patient, latency was 4 days. It seems there is a relationship between prior exposure to the drug and faster development of ASM [5,6]. Diagnosis is generally accepted when there is complete recovery of all symptoms within 2 – 14 days of discontinuation of the suspected drug [1,4]. Other proposed diagnostic methods include controlled re-exposure to the drug in a medical setting [1], but there are potentially fatal consequences to this. Overall, complete recovery is expected with severe illness, coma, or hypotension occurring in <10% of patients [1,4,5]. There is no clear mechanism for AM; NSAIDs are the most common offending agent, and antibiotics are the

second most common [4]. Of all antibiotics, TMP-SMX is the most commonly reported antibiotic associated with AM [1]. TMP-SMX was originally approved by the United States Food and Drug Administration in 1973, as a synergistic combination of trimethoprim and sulfamethoxazole which works via blockade of microbial dihydrofolate reductase [8]. The most common side effects of TMP-SMX are gastrointestinal upset and skin rashes [3]. Although it is the most common antibiotic associated with DIAM, no pathophysiology has been identified. The leading theories include type III and type IV hypersensitivity reactions theorized to cause a small vessel vasculitis or delayed T-cell reaction leading to meningeal irritation [1,4,7]. This theory has been supported by reports of immune complexes identified in serum and CSF in patients with AM induced by a variety of antibiotics [6]. The exact reason why TMP-SMX is commonly implicated in DIAM is unclear. While it could be due to a property of the drug itself, it could also be due to the low cost and subsequent high usage of TMP-SMX for everything from urinary tract infections to soft tissue skin infections [1].

Our patient demonstrates the variability in presentation of DIAM with her being well below the median age and lacking an underlying autoimmune disease. In addition, her rash is an unusual presentation, demonstrating the need for high suspicion of DIAM in patients with no other identifiable condition.

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