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Case Report

Trimethoprim-sulfamethoxazole-induced aseptic meningitis: A rare presentation

Yash N. Panchal[1,*] and Mukund Kumar V. Patel[2]

[1]Department of Pharmacology, AMC MET Medical College, Ahmedabad, Gujarat, 38008, India;
[2]Department of Internal Medicine, Dr. Kiran C. Patel Medical College & Research Institute, Bharuch, Gujarat, 392001, India.

ABSTRACT

Aseptic meningitis is demonstrated by the negative bacterial culture in the cerebrospinal fluid (CSF). It is generally caused by autoimmune disorders, drugs, viral infection, and malignancy. Drug-induced aseptic meningitis is a rare disease. It is commonly caused by antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs). This case concerns a 30-year-old female patient with aseptic meningitis after intake of trimethoprim-sulfamethoxazole (TMP-SMX). The patient developed headache, fever, generalized weakness, stiffness of the neck, and vomiting after the 4th day of starting TMP-SMX treatment for urinary tract infection. Initial laboratory reports revealed normal blood chemistry and negative blood and urine culture. CSF examination showed neutrophilic pleocytosis (neutrophil count-62%), normal glucose level (58 mg/dl), elevated protein level (88 mg/dl), and negative CSF culture. The patient was admitted to our hospital, TMP-SMX was stopped, and was treated conservatively. Her symptoms resolved completely, and she was discharged on the 4th day in stable condition.

KEYWORDS: aseptic meningitis, drug-induced, trimethoprim-sulfamethoxazole.

INTRODUCTION

Meningitis refers to an inflammation of the meninges, which are a protective covering of the brain and spinal cord. It is one of the serious conditions due to its high mortality and morbidity. Meningitis is usually caused by infectious etiologies such as viral or bacterial infections and, less frequently by fungal and parasitic infections [1]. Coxsackievirus, in particular, is the most common cause of infectious meningitis [2].

However, non-infectious etiologies may also cause meningitis. Aseptic meningitis refers to meningeal inflammation which is not caused by bacterial infection and demonstrated by negative bacterial culture in the cerebrospinal fluid (CSF) [3]. Etiologies of aseptic meningitis include autoimmune disease with meningeal involvement, drug-induced meningitis, viral meningitis, and neoplastic meningitis. Drug-induced aseptic meningitis is a rare disease and is commonly caused by antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) [4]. Weidener and Littman initially discovered it in a young woman with systemic lupus erythematosus (SLE) who was taking NSAIDs [5]. Because of the differences in treatment approaches, the severity of the condition, and prognostic implications, it's necessary to distinguish the etiology of meningitis into bacterial and aseptic.

Trimethoprim-sulfamethoxazole (TMP-SMX) antibiotic combination is commonly used to treat various infections, including otitis media, urinary tract infections, bronchitis, and shigellosis. Commonly reported side effects with TMP-SMX are mouth sores, loss of appetite, black tarry stool, dizziness, headache, and skin color changes, while aseptic meningitis is rare. Drug-induced aseptic meningitis

*Corresponding author: dryashpanchal95@gmail.com

following treatment with TMP-SMX occurs predominantly in immunocompromised individuals [3]. Here, we present the case of drug-induced aseptic meningitis in a young female patient.

CASE REPORT

A 30-year-old female patient presented to the emergency department (ED) of our hospital with fever, headache, stiffness of the neck, generalized weakness, and vomiting for 3 days. There was no history of photophobia, difficulty in breathing, cough, and abdominal pain. Her family history and personal history were all insignificant.

On general examination, she was alert and oriented, had tachycardia with a heart rate of 111 beats/ minute, and had a fever with a body temperature of 101.5 °F. Her blood pressure was 128/69 mmHg, respiratory rate was 26 breaths/minute, and oxygen saturation was 98% on room air. The patient had nuchal rigidity, as well as Kernig's sign was also positive. No neurological, gastrointestinal, or lung abnormalities were noted.

For suspected meningoencephalitis, we started treatment with IV ceftriaxone, vancomycin, and acyclovir as empirical therapy, and did blood sampling. Laboratory reports showed a white blood cell (WBC) count of 7300 cells/mm^3, hematocrit value of 48.3%, and serum glucose of 112 mg/dl (Table 1). Blood culture and urine culture both came back negative. A chest X-ray, electrocardiography (ECG), and non-contrast computed tomography (CT) scan of the head did not reveal any abnormality. The patient was also tested for Covid-19 infection using real-time reverse transcriptase-polymerase chain reaction (RT-PCR), which was negative. The patient was subjected to lumbar puncture (LP) study. Cerebrospinal fluid (CSF) examination showed glucose-58 mg/dl, protein-88 mg/dl, red blood cell (RBC) counts-1/µl, WBC counts-19/µl, neutrophils-62%, and monocytes-14% (Table 1). CSF culture

Table 1. Laboratory findings of the patient with aseptic meningitis.

Laboratory test (Unit)	**Results**	**Reference Range**
Blood		
WBC (cells/mm^3)	7300	4000-10000
Hematocrit (%)	48.3	42-52
Glucose (mg/dl)	112	100-140
Blood culture	Negative	
Urine		
Urine culture	Negative	
CSF		
Color	Colorless	Colorless
WBC (/µl)	19	0-5
RBC (/µl)	1	<1
Neutrophils (%)	62	
Monocytes (%)	14	
Glucose (mg/dl)	58	50-75
Protein (mg/dl)	88	14-45
CSF Culture	Negative	
Test for SARS-CoV-2*		
RT-PCR (Nasopharyngeal swab specimen)	Negative	

*SARS-CoV-2-severe acute respiratory syndrome coronavirus-2

for bacterial growth and herpes simplex virus (HSV) polymerase chain reaction came negative. We did not perform fungal culture on CSF.

Her past medical history revealed treatment with trimethoprim-sulfamethoxazole (TMP-SMX) for urinary tract infection. The patient was started on TMP-SMX 800-160 mg tablet twice daily for 14 days. After the 4th day of starting TMP-SMX treatment, the patient developed headache and fever followed by stiffness of the neck, and generalized weakness. Based on her clinical symptoms, negative CSF and blood culture, and history of use of TMP-SMX, a presumptive diagnosis of trimethoprim-sulfamethoxazole-induced aseptic meningitis was made. The patient was admitted to our hospital, and the culprit drug and other antibiotics were stopped. The patient was treated conservatively, and all her clinical symptoms resolved completely. The patient was discharged on the 4th day in stable condition, and she was instructed to avoid the use of TMP-SMX in future. The patient was medically stable with no clinical symptoms during her one-week follow-up.

DISCUSSION

Trimethoprim-sulfamethoxazole (TMP-SMX) is a sulfonamides class of fixed-dose combination antibiotics that is widely used for the prophylaxis and treatment of various bacterial infections. It is one of the commonly prescribed antibiotics due to its cost-effectiveness [2]. Commonly reported side effects with this combination are gastrointestinal ones, while aseptic meningitis is rare. Aseptic meningitis is mainly caused by drugs, viral infection, neoplasm, and autoimmune disorders. Drug-induced aseptic meningitis (DIAM) is a rare clinical presentation. Since the diagnosis of DIAM is challenging, many of its cases remain undiagnosed [6]. The most common culprit drugs for DIAM are NSAIDs, while TMP-SMX is a common antimicrobial drug responsible for it [7]. Metronidazole, lamotrigine, carbamazepine, allopurinol, infliximab, and intravenous immunoglobulins are also responsible for causing DIAM [8].

In a recent literature review, Bruner *et al.* found 41 cases of TMP-SMX-induced aseptic meningitis [9]. The majority of patients developed the symptoms of aseptic meningitis within 24 hours of intake of the culprit drug [9]. In our case, the patient developed the symptoms after the 4th day of starting TMP-SMX treatment. The actual pathogenic mechanism is still not known. However, type II hypersensitivity reaction with the deposition of the immune complex is thought to be a possible mechanism [10]. Immune complexes have been detected in the plasma in some cases of TMP-SMX-induced aseptic meningitis [11]. Another possible mechanism is related to type IV hypersensitivity reaction. According to that mechanism, the culprit drug may bind to human leukocyte antigen (HLA) on the surface of the T-cell receptor reversibly, leading to type IV T-cell responses [12]. The commonly reported clinical symptoms of DIAM are headache, fever, the rigidity of the neck, and altered mental status [9]. Our patient also experienced the same clinical symptoms except for altered mental status. Rarely, in serious reaction, seizure, coma, and hypotension are also being reported [13].

The diagnosis of DIAM is mainly made by exclusion of other possible etiologies and causal relationship between the usage of culprit drug and onset of meningeal symptoms [6]. It was difficult to make a diagnosis of DIAM in our patient as she had no prior history of any drug allergy and was presented to our hospital just after 4 days of starting TMP-SMX treatment. But based on her clinical presentation, laboratory findings, and history of intake of TMP-SMX we made a presumptive diagnosis of DIAM. CSF examination in DIAM shows neutrophilic pleocytosis (neutrophil count > 50%), normal glucose level, elevated protein levels, and negative CSF culture [13], which was also observed in our case. Diagnosis of DIAM is mainly confirmed by drug challenge testing [9]. We did not perform drug challenge testing in our patient, as it is considered unethical due to reported worsening of the symptoms after re-exposure [6]. Following the discontinuation of the culprit drug, clinical symptoms normally resolve within 96 hours [13]. In our case, after the discontinuation of the culprit drug and with conservative treatment, all the clinical symptoms of the patient were resolved completely within 72 hours and the patient was discharged in stable condition.

CONCLUSION

Aseptic meningitis following treatment with trimethoprim-sulfamethoxazole (TMP-SMX) is a

rare presentation. It should be suspected in an individual presenting with typical symptoms of meningitis and negative blood and CSF culture and having a history of TMP-SMX intake. CSF neutrophilic pleocytosis (neutrophil count > 50%), and negative culture are suggestive of the diagnosis. The condition is self-limited, and it is treated conservatively. Once the culprit drug is discontinued, symptoms generally resolve quickly. We conclude that further studies are needed to identify the exact mechanism behind trimethoprim-sulfamethoxazole-induced aseptic meningitis.

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AUTHORS' CONTRIBUTIONS

All the authors have contributed equally to the data collection, its interpretation, and preparation of the manuscript.

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PATIENT'S CONSENT

For the publication of this case report, written informed consent was obtained from the patient.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest.

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