CASE IN POINT

Agranulocytosis and Aseptic Meningitis Induced by Sulfamethoxazole-Trimethoprim

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Background: Sulfamethoxazole-trimethoprim is an antibiotic that can cause rare and potentially life-threatening adverse effects. This case describes an immunocompetent patient who developed acute agranulocytosis complicated with aseptic meningitis after being prescribed sulfamethoxazole-trimethoprim.
Case Presentation: A healthy 39-year-old male veteran presented to the emergency department with worsening left testicular pain and increased urinary urgency and frequency. The patient was diagnosed with left epididymo-orchitis and prescribed oral sulfamethoxazole-trimethoprim 800-160 mg every 12 hours for 30 days. Two weeks later, the patient returned to the emergency department with fever, headache, chills, and generalized body aches that led to hospitalization. It was discovered that he had not finished the full course of antibiotics due to symptoms resolution and had restarted the medication to finish the course of therapy. The patient was diagnosed with agranulocytosis and aseptic meningitis secondary to sulfamethoxazole-trimethoprim.
Conclusions: This case highlights the rare potential for acute agranulocytosis in combination with aseptic meningitis following the use of sulfamethoxazole-trimethoprim in an immunocompetent patient.

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Acute agranulocytosis and aseptic meningitis are serious adverse effects (AEs) associated with sulfamethoxazole-trimethoprim. Acute agranulocytosis is a rare, potentially life-threatening blood dyscrasia characterized by a neutrophil count of < 500 cells per µL, with no relevant decrease in hemoglobin or platelet levels.[1] Patients with agranulocytosis may be asymptomatic or experience severe sore throat, pharyngitis, or tonsillitis in combination with high fever, rigors, headaches, or malaise. These AEs are commonly classified as idiosyncratic and, in most cases, attributable to medications. If drug-induced agranulocytosis is suspected, the patient should discontinue the medication immediately.[1]

Meningitis is an inflammatory disease typically caused by viral or bacterial infections; however, it may also be attributed to medications or malignancy. Inflammation of the meninges with a negative bacterial cerebrospinal fluid culture is classified as aseptic meningitis. Distinguishing between aseptic and bacterial meningitis is crucial due to differences in illness severity, treatment options, and prognosis.[2] Symptoms of meningitis may include fever, headache, nuchal rigidity, nausea, or vomiting.[3] Several classes of medications can cause drug-induced aseptic meningitis (DIAM), but the most commonly reported antibiotic is sulfamethoxazole-trimethoprim.[4]

DIAM is more prevalent in immunocompromised patients, such as those with a history of HIV/AIDS, organ transplant, collagen vascular disease, or malignancy, who may be prescribed sulfamethoxazole-trimethoprim for prophylaxis or treatment of infection.[2] The case described in this article serves as a distinctive example of acute agranulocytosis complicated with aseptic meningitis caused by sulfamethoxazole-trimethoprim in an immunocompetent patient.

CASE PRESENTATION

A healthy male veteran aged 39 years presented to the Fargo Veterans Affairs Medical Center emergency department (ED) for worsening left testicular pain and increased urinary urgency and frequency for about 48 hours. The patient had no known medication allergies, was current on vaccinations, and his only relevant prescription was valacyclovir for herpes labialis. The evaluation included urinalysis, blood tests, and scrotal ultrasound. The urinalysis, blood tests, and vitals were unremarkable for any signs of systemic infection. The scrotal ultrasound was significant for left focal area of abnormal echogenicity with absent blood flow in the superior left testicle and a significant increase in blood flow around the left epididymis. Mild swelling in the left epididymis was present, with no significant testicular or scrotal swelling or skin changes observed. Urology was consulted and prescribed oral sulfamethoxazole-trimethoprim 800-160 mg every

TABLE 1. Blood Test Results

Tests	ED visit	Admission[a]	Day 2	Discharge	Follow-up[b]	Reference range
WBC, cells/μL	7100	2300	16,300	6900	5300	4800-10,800
ANC, cells/μL	5100	900	15,100	4800	2500	1500-8000
AL, cells/μL	1200	1300	400	1200	1700	1000-4000
IG, cells/μL	0	0	100	0	0	0-70

Abbreviations: AL, absolute lymphocyte count; ANC, absolute neutrophil count; ED, emergency department; IG, absolute immature granulocyte count; WBC, white blood cell count.
[a]13 d after initial ED visit; agranulocytosis noted.
[b]17 d after discharge.

12 hours for 30 days for the treatment of left epididymo-orchitis.

The patient returned to the ED 2 weeks later with fever, chills, headache, generalized body aches, urinary retention, loose stools, and nonspecific chest pressure. A serum blood test revealed significant neutropenia and leukopenia. The patient was admitted for observation, and sulfamethoxazole-trimethoprim was discontinued. The patient received sodium chloride intravenous (IV) fluid, oral potassium chloride supplementation, IV ondansetron, and analgesics, including oral acetaminophen, oral ibuprofen, and IV hydromorphone as needed. Repeated laboratory tests were completed with no specific findings; serum laboratory work, urinalysis, chest and abdominal X-rays, and echocardiogram were all unremarkable. The patient's neutrophil count dropped from 5100 cells/μL at the initial ED presentation to 900 cells/μL (reference range, 1500-8000 cells/μL) (Table 1). Agranulocytosis quickly resolved after antibiotic discontinuation.

Upon further investigation, the patient took the prescribed sulfamethoxazole-trimethoprim for 10 days before stopping due to the resolution of testicular pain and epididymal swelling. The patient reported initial AEs of loose stools and generalized myalgias when first taking the medication. The patient restarted the antibiotic to complete the course of therapy after not taking it for 2 days. Within 20 minutes of restarting the medication, he experienced myalgias with pruritus, prompting him to return to the ED. Agranulocytosis and aseptic meningitis developed within 12 days after he was prescribed sulfamethoxazole-trimethoprim, though the exact timeframe is unknown.

The patient's symptoms, except for a persistent headache, resolved during hospitalization. Infectious disease was consulted, and a lumbar puncture was performed due to prior fever and ongoing headaches to rule out a treatable cause of meningitis. The lumbar puncture showed clear spinal fluid, an elevated white blood cell count with neutrophil predominance, and normal protein and glucose levels. Cultures showed no aerobic, anaerobic, or fungal organisms. Herpes virus simplex and Lyme disease testing was not completed during hospitalization. Respiratory panel, legionella, and hepatitis A, B, and C tests were negative (Table 2). The negative laboratory test results strengthened the suspicion of aseptic meningitis caused by sulfamethoxazole-trimethoprim. The neurology consult recommended no additional treatments or tests.

The patient spontaneously recovered 2 days later, with a normalized complete blood count and resolution of headache. Repeat scrotal ultrasounds showed resolution of the left testicle findings. The patient was discharged and seen for a follow-up 14 days later. The final diagnosis requiring hospitalization was aseptic meningitis secondary to a sulfamethoxazole-trimethoprim.

DISCUSSION

Sulfamethoxazole-trimethoprim is a commonly prescribed antibiotic for urinary tract infections, pneumocystis pneumonia, pneumocystis pneumonia prophylaxis, and methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections. Empiric antibiotics for epididymo-orchitis caused by enteric organisms include levofloxacin or ofloxacin; however sulfamethoxazole-trimethoprim may be

TABLE 2. Cerebrospinal Fluid Tests

Test	Result
Appearance	Clear, colorless
Protein, mg/dL	45
Glucose mg/dL	67
Gram stain	No organisms; no epithelial cells; high white blood cell count
Mycology culture	Negative
Anaerobic/aerobic/fungal cultures	Negative
White blood cells	44
Monocytes, %	33
Neutrophil, %	60
Lymphocytes, %	6
Basophils, %	1
Red blood cells, × 10^6/μL	1

considered as alternative.[5,6] Agranulocytosis induced by sulfamethoxazole-trimethoprim may occur due to the inhibition on folic acid metabolism, which makes the highly proliferating cells of the hematopoietic system more susceptible to neutropenia. Agranulocytosis typically occurs within 7 days of treatment initiation and generally resolves within a month after discontinuation of the offending agent.[7] In this case, agranulocytosis resolved overnight, resulting in leukocytosis. One explanation for the rapid increase in white blood cell count may be the concurrent diagnosis of aseptic meningitis. Alternatively, the patient's health and immunocompetence may have helped generate an adequate immune response. Medication-induced agranulocytosis is often a diagnosis of exclusion because it is typically difficult to diagnose.[7] In more severe or complicated cases of agranulocytosis, filgrastim may be indicated.[1]

Sulfamethoxazole-trimethoprim is a lipophilic small-molecule medication that can cross the blood-brain barrier and penetrate the tissues of the bone, prostate, and central nervous system.[8] Specifically, the medication can pass into the cerebrospinal fluid regardless of meningeal inflammation.[9] The exact mechanism for aseptic meningitis caused by sulfamethoxazole-trimethoprim is unknown; however, it may accumulate in the choroid plexus, causing destructive inflammation of small blood vessels and resulting in aseptic meningitis.[10] The onset of aseptic meningitis can vary from 10 minutes to 10 days after initiation of the medication. Pre-exposure to the medication typically results in earlier onset of symptoms, though patients do not need to have previously taken the medication to develop aseptic meningitis. Patients generally become afebrile with resolution of headache and mental status changes within 48 to 72 hours after stopping the medication or after about 5 to 7 half-lives of the medication are eliminated.[11] Some patients may continue to experience worsening symptoms after discontinuation because the medication is already absorbed into the serum and tissues.

DIAM is an uncommon drug-induced hypersensitivity AE of the central nervous system. Diagnosing aseptic meningitis caused by sulfamethoxazole-trimethoprim can be challenging, as antibiotics are given to treat suspected infections, and the symptoms of aseptic meningitis can be hard to differentiate from those of infectious meningitis.[11] Close monitoring between the initiation of the medication and the onset of clinical symptoms is necessary to assist in distinguishing between aseptic and infectious meningitis.[3] If the causative agent is not discontinued, symptoms can quickly worsen, progressing from fever and headache to confusion, coma, and respiratory depression. A DIAM diagnosis can only be made with resolution of aseptic meningitis after stopping the contributory agent. If appropriate, this can be proven by rechallenging the medication in a controlled setting. The usual treatment for aseptic meningitis is supportive care, including hydration, antiemetics, electrolyte supplementation, and adequate analgesia.[3]

Differential diagnoses in this case included viral infection, meningitis, and allergic reaction to sulfamethoxazole-trimethoprim. The patient reported history of experiencing symptoms after restarting his antibiotic, raising strong suspicion for DIAM. Initiation of this antibiotic was the only recent medication change noted. Laboratory testing for

infectious agents yielded negative results, including tests for aerobic and anaerobic bacteria as well as viral and fungal infections. A lumbar puncture and cerebrospinal fluid culture was clear, with no organisms shown on gram stain. Bacterial or viral meningitis was presumed less likely due to the duration of symptoms, correlation of symptoms coinciding with restarting the antibiotic, and negative cerebrospinal fluid culture results.

It was concluded that agranulocytosis and aseptic meningitis were likely induced by sulfamethoxazole-trimethoprim as supported by the improvement upon discontinuing the medication and subsequent worsening upon restarting it. Concurrent agranulocytosis and aseptic meningitis is rare, and there is typically no correlation between the 2 reactions. Since agranulocytosis may be asymptomatic, this case highlights the need to monitor blood cell counts in patients using sulfamethoxazole-trimethoprim. The possibility of DIAM should be considered in patients presenting with flu-like symptoms, and a lumbar puncture may be collected to rule out aseptic meningitis if the patient's AEs are severe following the initiation of an antibiotic, particularly in immunosuppressed patients taking sulfamethoxazole-trimethoprim. This case is unusual because the patient was healthy and immunocompetent.

This case may not be generalizable and may be difficult to compare to other cases. Every case has patient-specific factors affecting subjective information, including the patient's baseline, severity of symptoms, and treatment options. This report was based on a single patient case and corresponding results may be found in similar patient cases.

CONCLUSIONS

This case emphasizes the rare but serious AEs of acute agranulocytosis complicated with aseptic meningitis after prescribed sulfamethoxazole-trimethoprim. This is a unique case of an immunocompetent patient developing both agranulocytosis and aseptic meningitis after restarting the antibiotic to complete therapy. This case highlights the importance of monitoring blood cell counts and monitoring for signs and symptoms of aseptic meningitis, even during short courses of therapy. Further research is needed to recognize characteristics that may increase the risk for these AEs and to develop strategies for their prevention.

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Ethics and consent

The authors did not receive verbal or written informed consent from the patient. Details have been omitted to avoid identification will not be included in the entirely of this manuscript.

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