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A Case Report of Antibiotic-Induced Aseptic Meningitis in Psoriasis

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Abstract

Although frequently prescribed, certain antibiotics such as trimethoprim-sulfamethoxazole carry the risk of a rare yet life-threatening adverse effect, termed drug-induced aseptic meningitis. Morbidity can be avoided if the medication is identified and discontinued. Patients in reported cases tend to be female and have an autoimmune disease or prior adverse reaction to the offending agent. As a rare and poorly characterized condition, the subset of patients using antibiotics at risk for aseptic meningitis remains unclear; hence, cataloging these adverse events remains critical for better elucidating the disease. Here, we report a 62-year-old man with psoriasis and no prior history of sulfa allergy, who presented with a sudden onset of fever, chills, vomiting, and muscle aches 5 hours after taking single doses of trimethoprim-sulfamethoxazole and ciprofloxacin. Common infectious causes were ruled out, and his medications were discontinued. Despite initial symptom resolution with discontinuation, the patient neurologically deteriorated over the next two days before eventually recovering with supportive care. This case highlights the variable presentation of drug-induced aseptic meningitis. In contrast to previous reports of drug-induced aseptic meningitis, our patient was male, older than the median age of 40 years, and did not have a prior adverse reaction to the antibiotic. Furthermore, to the best of our knowledge, we report a possible case of antibiotic-induced aseptic meningitis in a patient with psoriasis. Lastly, the case emphasizes not only the value of a thorough medication history but also the importance of recognizing that patients may deteriorate in the first 48 hours before resolution.

Keywords

Trimethoprim, sulfamethoxazole, aseptic meningitis, drug-induced, adverse effect, TMP-SMX, meningitis, drug reaction

Abbreviations and Acronyms

ADR = adverse drug reaction
CIAM = ciprofloxacin-induced aseptic meningitis
CSF = cerebrospinal fluid
DIAM = drug-induced aseptic meningitis
ED = emergency department
HIV = human immunodeficiency virus
IQR = interquartile range
NSAID = nonsteroidal anti-inflammatory drugs
PCR = polymerase chain reaction
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
SLE = systemic lupus erythematosus
TMP-SMX = trimethoprim-sulfamethoxazole
TNFα = tumor necrosis factor α
TSIAM = trimethoprim-sulfamethoxazole-induced aseptic meningitis

Introduction

First recorded in 1925 as a syndrome involving the acute onset of meningeal irritation, abnormal cerebrospinal fluid content with absence of bacterial involvement, and a brief clinical course, aseptic meningitis has since become recognized as an all-encompassing term for non-pyogenic meningitides.[1,2] Aseptic meningitis can be further stratified as infectious (often viral) or non-infectious, with non-viral etiologies including drugs, neoplasms, and autoimmune diseases.[1-6] Drug-induced aseptic meningitis (DIAM) is a rare condition that disproportionately affects females. It is most commonly documented as secondary to nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, intravenous immunoglobulins, monoclonal antibodies, and intrathecal agents.[3-7] The median age of presentation is 40 years (interquartile range [IQR], 28–58 years).[7] In particular, NSAID- and antibiotic-induced DIAM have been strongly associated with specific autoimmune and connective tissue diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis, Crohn's disease, and Sjogren's syndrome.[8-16] Of the antibiotics, trimethoprim-sulfamethoxazole (TMP-SMX) is the most frequently reported agent associated with DIAM.[4,5] The median age of those affected is 41 years (IQR, 24.5–61 years), and, consistent with DIAM, females are disproportionately affected. Patients tend to have an autoimmune disease, previous exposure to the precipitating agent, or immunocompromise.[4,5,7] Ciprofloxacin-induced aseptic meningitis (CIAM) is an even rarer condition with few recorded cases to draw significant epidemiological trends.[6,7] Notably, in a series of 192 cases of DIAM, 36% were antibiotic-induced, and, of these, 3% were associated with ciprofloxacin. In contrast, 46% were associated with TMP-SMX.[6] In another series of 329 cases of DIAM, 11% were antibiotic-induced, of which 16% were associated with TMP-SMX and none were associated with ciprofloxacin.[7]

Case Report

A 62-year-old Japanese American man with a history of psoriasis and benign prostatic hyperplasia was brought by his wife to the emergency department (ED) with fever, chills, vomiting, and muscle aches. One day prior, he visited his urologist and received a prostate massage as part of the examination. Five hours prior to his presentation, he took his first doses of ciprofloxacin 500 mg and TMP-SMX 800–160 mg orally as prophylaxis for an upcoming prostate biopsy. Over several hours, he developed fever, chills, vomiting, dizziness, and muscle aches.

He denied having headache, neck stiffness, visual symptoms, focal neurologic symptoms, ataxia, abdominal pain, or sore throat. No seizures were noted by family members. Aside from ciprofloxacin and TMP-SMX, he did not take any other of his medications that day.

The patient's medical history was significant for psoriasis, hypertension, hyperlipidemia, and benign prostatic hyperplasia. His medications included amlodipine, losartan, atorvastatin, coenzyme Q10 supplements, calcipotriene, betamethasone, and triamcinolone ointments. He took these medications for several years without adverse reactions. Although he reported mild muscle aches with atorvastatin, it was resolved with coenzyme Q10 supplementation. Of note, he was not taking any tumor necrosis factor α inhibitors at this time. Medication allergies included erythromycin, from which he experienced a rash and low-grade fever, and penicillin and ampicillin, from which he experienced hives. His immunizations were up-to-date. He did not travel recently and did not have any sick contacts. The patient worked in his garden and water lily pond daily but does not recall mosquito bites and has not had significant exposure to fresh water.

His vitals in the ED were as follows: temperature 39.4°C, blood pressure of 136/91 mm Hg, heart rate of 111, and respiratory rate of 22 per minute. The patient was only noted to have mild tenderness in the left lower back to palpation on physical examination. Initial laboratory included a complete blood count notable for leukocytosis of $10.5 \times 10^3/\mu L$ with a neutrophil predominance at 82% and lactic acid elevated to 3.3 mmol/L. The differential diagnosis at this time included gastroenteritis, sepsis secondary to his recent prostate massage, pyelonephritis, and discitis and osteomyelitis. Blood cultures and a urinalysis were obtained along with severe acute respiratory syndrome coronavirus 2, better known as SARS-CoV-2, and influenza polymerase chain reaction (PCR) tests. A chest x-ray, computed tomography of the abdomen and pelvis, and magnetic resonance imaging of the brain and thoracic spine were obtained. His daily medications and antibiotics were held, and he was empirically treated with cefepime and acetaminophen. His urinalysis, influenza, and imaging results returned negative and, after seven hours, his fever resolved, thus he was discharged home with ondansetron. He received a discharge diagnosis of back pain, nausea and vomiting, and fever, unspecified. His SARS-CoV-2 test was negative.

The next morning, he was found in a confused state upon awakening, along with fever, chills, nausea, vomiting, and muscle aches. He was again brought to the ED. A review of symptoms in the emergency department was negative for focal weakness, numbness, seizures, visual loss, dizziness, and difficulty walking. The patient did not restart any of his antibiotics. He had a fever of 39.6°C and was given acetaminophen. A lumbar puncture was then performed. Cerebrospinal fluid (CSF) analysis revealed a pleocytosis of $63/mm^3$ with polymorphic neutrophils at 28%, monocytes at 60%, red blood cell count of $468/mm^3$, elevated total protein at 76 mg/dL, and normal glucose levels at 58 mg/dL, which was consistent with meningitis. CSF cultures and gram stain were obtained, along with a meningitis/encephalitis PCR panel for *Escherichia coli*, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, enterovirus, herpes simplex viruses 1 and 2, human herpesvirus 6, human parechovirus, varicella zoster virus, cytomegalovirus, and *Cryptococcus neoformans/gattii*. Also, separate rapid plasma reagin, herpes simplex viruses, and cryptococcal antigen tests were obtained. Blood cultures were again drawn, and computed tomography of the head was obtained, which was shown to be unremarkable. Because the patient had a known allergy to ampicillin, empiric treatment with vancomycin, meropenem, and acyclovir was started, and the patient was admitted for meningitis.

On hospitalization day 1, he developed a headache and continued to have altered mental status, fever, nausea, and myalgia. Both infectious disease and neurology teams were consulted for further management of meningitis. On hospitalization day 2, symptoms persisted, and an electroencephalography revealed mild global dysfunction suggestive of encephalopathy but no seizures or epileptic abnormalities. His symptoms and neurologic status started to improve on hospitalization day 3, and empiric antibiotics were discontinued after cultures, rapid plasma reagin, PCR, and antigen tests were shown to be negative. At this time, the neurology team suggested DIAM as a possible diagnosis. On hospitalization day 4, the patient markedly improved and was discharged with a diagnosis of aseptic meningitis. Two weeks after discharge, he continued to have fatigue, but his cognition returned to baseline, and he denied having any other symptoms from his initial presentation. Two months since admission, the patient has not experienced any recurrence of symptoms or adverse effects from the disease; he returned to baseline and resumed his normal daily activities. Although an outpatient follow-up for a drug rechallenge was scheduled, the patient eventually decided not to undergo the test.

Discussion

Epidemiology

DIAM is predominantly observed in women and those with comorbid autoimmune disease.[3-7] TSIAM is additionally associated with previous TMP-SMX exposure and functional immunocompromise, such as human immunodeficiency virus (HIV) infection.[3-6] In TSIAM, the more frequent observation in female patients is thought to be due to higher rates of urinary tract infection, which is commonly treated with TMP-SMX, while the more frequent observation in HIV-infected patients is thought to be due to the use of TMP-SMX for prophylaxis against opportunistic infections.[5] In addition, one series of 41 TSIAM cases identified 20% having comorbid autoimmune disease.[5]

The patient in our case is notable in that he is a male, older than the typical age of most DIAM patients, and has a history of psoriasis. Although comorbidity with psoriasis is consistent with the association between DIAM and autoimmune disease in general, the association between any antibiotic-induced aseptic meningitis and psoriasis, in particular, has not been reported in the literature to the best of our knowledge.

Etiology

NSAIDs are the most commonly documented cause of DIAM, followed by antibiotics, of which TMP-SMX is most frequently described.[3-5,7] Other commonly reported causes of DIAM include intravenous immunoglobulins, monoclonal antibodies, intrathecal agents, and vaccines.[3-6] Monoclonal antibodies that inhibit tumor necrosis factor α (TNFα) may be used to treat severe psoriasis.[17] Several cases have documented an association between TNFα inhibitors and severe psoriasis or psoriatic arthritis, leading to the entity termed TNFα inhibitor-associated aseptic meningitis.[18-20] Of note, while there was no prior history of TNFα inhibitor use, our patient was exposed to several antibiotics during his clinical course.

As symptoms are initiated upon taking TMP-SMX and ciprofloxacin, these medications are implicated as the causative agents by temporal association. A series of 329 cases reported that, of antibiotic-induced cases of aseptic meningitis, 16% were associated with TMP-SMX, while none were associated with ciprofloxacin.[7] Another series of 192 cases of DIAM showed that, of all those involving antibiotics, 46% involved TMP-SMX, while only 3% involved ciprofloxacin.[6] By extrapolation, TMP-SMX would be the most likely cause of aseptic meningitis in our patient. Notably, the series further identified 16% of cases to involve trimethoprim alone, with 1% sulfamethoxazole only, suggesting that trimethoprim may be the more common cause of TSIAM.[4,6] However, as clinical interests precluded the ability to conduct confirmatory tests, we cannot definitively exclude other administered antibiotics for contributing to the patient's disorder (ie, the aseptic meningitis in this case). While thought to be likely due to TMP-SMX, this reaction could have also been caused by ciprofloxacin, trimethoprim alone, sulfamethoxazole alone, or even another unidentified trigger.

As the definitive diagnosis of adverse drug reactions (ADRs) remains challenging, several semi-quantitative measures of causality have been developed.[21-28] Utilizing a ten-question survey published in 1981 by Naranjo et al, our patient was deemed to have had a *possible ADR*.[22] While useful for reducing inter-rater disagreements and categorizing the probability of ADRs, ultimately, these algorithms do not confirm causality nor accurately measure the likelihood of an ADR.[22,28] Moreover, many questions in these algorithms rely on a drug rechallenge test, which is usually clinically impractical and often unethical.[21] Hence, by nature of the questions (ie, use of arbitrary weights per question and requirement of a drug rechallenge), the causality grades of these algorithms are practically limited to no higher than *possible ADR*.[22,28]

Pathophysiology

The two commonly hypothesized mechanisms of DIAM include either a direct irritation of the meninges, particularly with intrathecal administration of drugs, or an immunologic hypersensitivity reaction with systemic administration.[3,4] The association of DIAM with autoimmune disease favors an immune-mediated mechanism, especially in our patient, as intrathecal drugs were not administered. Sulfonamide antibiotics such as TMP-SMX are commonly associated with hypersensitivity reactions.[20] Hypersensitivity reactions to TMP-SMX are generally not mediated by type I hypersensitivity and tend to be non-immediate in presentation.[4,5,29] In addition, type II hypersensitivity only would occur if the drug or metabolites are introduced into the CSF.[3-5] Therefore, in our patient, a type III or IV hypersensitivity mechanism is most likely. A series of 41 cases of TSIAM showed that the onset of symptoms generally occurred in the order of hours to days, consistent with type III or IV.[5] In addition to hypersensitivity, the recently described concept of p-i interactions may also have a role in TSIAM.[5,29] In this concept, drugs may bind directly to receptors on T cells, activating them.[5,29] As psoriasis is also a T cell-mediated disease, the meningitis in our patient may have been T cell-mediated as well.[30] T cells are also the major mediator of cutaneous manifestations of TMP-SMX hypersensitivity, such as Stevens-Johnson syndrome and toxic epidermal necrolysis.[29]

While the relation between psoriasis and DIAM is only a conjecture, other studies have linked DIAM with other autoimmune diseases.[4] Moreover, autoimmune diseases are often are comorbid with each other—psoriasis, in particular, has been found to be associated with SLE, rheumatoid arthritis, Crohn's disease, celiac disease, multiple sclerosis, and autoimmune thyroid disease.[31,32] By extension, DIAM—an immune-mediated inflammation of the meninges—may potentially also be linked to psoriasis. Indeed, psoriasis has been found to be associated with increased odds of meningitis.[33]

Clinical Manifestations

Previous reports of TSIAM have shown that the onset of symptoms generally occurs within hours to days after TMP-SMX ingestion; however, a few reported cases have an onset after 3 months.[5,6] The presentation is similar to that of other meningitides: fever, headache, altered mental status, nausea, vomiting, and signs of meningismus, though many other manifestations may occur.[1-6] Alarming manifestations such as hypotension, seizures, and coma have also been reported.[4,5] However, initial presentations can be vague, as in the patient in our case, who presented with flu-like symptoms without headache. Even with discontinuation of the offending agent, patients may continue

to deteriorate clinically as the drug continues to be absorbed.[5] A series of 41 cases of TSIAM noted patients that deteriorated within the first 24 hours after discontinuation and recovered within 3 days.[4] This is highlighted in our case, in which our patient was initially stabilized in the ED, sent home, only to present once more with deteriorating clinical status. This potential to worsen is hypothesized to be due to accumulation of the drug in body tissues, while resolution represents clearance of the drug.[5] The observed recovery time within 3 days may be explained by the pharmacokinetics of TMP-SMX. As the half-life of TMP-SMX is 10 hours, recovery within 3 days correlates with 5 to 7 half-lives, which correlates to 95% to 99% of drug clearance.[4] Our patient was noted to improve on hospital day 3 and markedly improved on day 4, which is in concordance with the pattern suggested by TMP-SMX's pharmacokinetics.

Diagnosis

DIAM is a diagnosis of exclusion.[3-5] Patients present with aseptic meningitis characterized by pleocytosis, elevated proteinorrhachia, and normal glycorrhachia in the CSF, though these findings are nonspecific.[3-5] Importantly, routine cultures will be negative.[3-5] However, the differential diagnosis of potential pathogens causing aseptic meningitis is extensive.[34] A limitation of our case is that, while workup for viral pathogens was performed, only pathogens specifically included in the panel tests were excluded. However, the meningitis panel used in this case was relatively sensitive, with a very high negative predictive value.[35] Thus, the most common viral causes were most likely ruled out, and viral meningitis was thought to be less likely. In practice, a detailed history of medications, onset of symptoms, and observing recovery after discontinuation are key components of the diagnosis.[3-6]

The most reliable method of diagnosing DIAM is by drug rechallenge.[3-6] However, this may be unethical or impractical for many patients, particularly in this case's patient, in whom the neurologic manifestations were severe and distressing. In addition, empiric antibiotics are often started after obtaining cultures and CSF samples in patients presenting with meningitis.[4,5,36-39] While the patient's CSF findings of mild pleocytosis with a monocytic predominance, normal glucose, and mildly elevated protein rule against bacterial meningitis, it should be noted that a limitation of our study is that the patient took ciprofloxacin, TMP-SMX, and cefepime upon presenting for his first ED visit. This may have caused the sterile CSF cultures collected during his second ED visit and may have also dampened potentially markedly abnormal CSF findings that would have been present before antibiotic use. Thus, the collection of CSF before empiric antibiotic therapy is essential, as it can be difficult to distinguish DIAM from an incompletely treated bacterial meningitis.[3-5,40] However, given that TSIAM is more common, in addition to the overall presentation of recent TMP-SMX use in a patient with autoimmune disease, negative tests for common infectious causes, CSF findings suggestive of aseptic meningitis, the improvement after discontinuation, TSIAM was thought to be the most likely cause of the patient's aseptic meningitis.

Management and Prognosis

Discontinuation of the offending drug is the mainstay of treatment for DIAM.[3,5,6] In practice, many patients with suspected meningitis are treated with empiric antimicrobial agents, as in this case.[5,36-39] Otherwise, management is primarily supportive.[3,5] With discontinuation of the offending drug, resolution of both symptoms and CSF abnormalities typically occurs within days.[3] In TSIAM, symptoms resolve within 2–3 days, which correlates with enough half-lives of TMP-SMX for near-complete drug elimination.[5] Ultimately, full recovery is expected for most patients, though many patients will experience a recurrence if re-administered TMP-SMX, and thus should be advised to avoid TMP-SMX.[5] In this case, the patient, began improving on day 3, with discharge by day 4, which generally agrees with the concept of drug elimination as the mechanism of recovery. The patient was fully recovered within 2 months. The delay in complete recovery may be caused by residual inflammation from the acute phase of the condition.

Conclusion

In summary, we report a possible case of antibiotic-induced aseptic meningitis in a patient with psoriasis. As our patient diverged from the common epidemiologic trends, this case highlights the variable presentation of DIAM. Despite antibiotic discontinuation, the patient neurologically deteriorated over 48 hours before eventually recovering with supportive care. Furthermore, while autoimmune disease has been observed to increase risk, aseptic meningitis caused by antibiotics in patients with psoriasis, in particular, has yet to be reported in the literature. Lastly, in patients presenting with aseptic meningitis, this case emphasizes the value of a thorough medication history. When DIAM is suspected, clinicians should remain aware that patients may experience an initial period deterioration, depending on the implicated drug's pharmacokinetics.

Conflict of Interest

None of the authors identify any conflict of interest.

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