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Case report

TMP-SMX induced type 4 hypersensitivity with multi-organ involvement

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ABSTRACT

Trimethoprim-sulfamethoxazole (TMP-SMX), also referred to as co-trimazole, is a common antibiotic used to treat a wide range of infections ranging from simple skin and soft tissue infections to opportunistic infections such as Pneumocystis jirovecii. Generally, this medication is well-tolerated, but severe adverse reactions, such as myelosuppression and hepatitis, can occur, albeit rarely. In this case report, we describe a patient who presented to the hospital with symptoms of rash, elevated liver enzymes, thrombocytopenia, and acute kidney injury 2 weeks after completing a course of TMP-SMX for a skin infection. We highlight the difficulties in diagnosing adverse events associated with this drug due to the variability in its presentation and the unpredictable onset of symptoms. By excluding common differential diagnoses including thrombotic thrombocytopenic purpura (TTP) and glucose-6-phosphate- dehydrogenase (G6PD) deficiency, we concluded that the patient was suffering from TMP-SMX-induced multi-organ dysfunction and treated him supportively. Through this case report, we aim to elucidate the importance of early recognition and treatment of the adverse effects of TMP-SMX.

Introduction

Trimethoprim-sulfamethoxazole (TMP-SMX) is a combination of two antimicrobial agents: a diaminopyrimidine (trimethoprim) and a sulfonamide (sulfamethoxazole) and acts through synergistic inhibition of tetrahydrofolic acid synthesis in bacteria [1]. It is effective against a wide variety of gram-positive and gram-negative bacteria and some opportunistic infections. It is widely used to treat urinary tract infections, pneumonia and skin and soft tissue infections [2]. Several formulations are available but the most frequently used is a double-strength tablet of 160 mg TMP/800 mg SMX. Some common and mild side effects include GI disturbances which can be alleviated by stopping the drug, whereas serious adverse effects such as hepatitis or acute liver failure, acute kidney injury, and myelosuppression require that patients receive supportive care to ensure resolution of their illness. In this case report, we discuss a patient who presented with delayed onset of multi-organ failure secondary to TMP-SMX use.

Case presentation

The patient presented is a 61-year-old male with a past medical history significant for hypertension and squamous cell carcinoma of the skin who presented to the hospital with altered mental status, fevers, and a rash for several days. The patient was alert and oriented x1 (to self), so most of the history was obtained from the wife at the bedside. Approximately 2 months before admission, the patient underwent a cyst removal from his upper middle back at his primary care physician's office. The cyst removal was unsuccessful and the patient was referred to a general surgeon who performed the excision under general anesthesia about 4 weeks later. The preliminary reports from this surgery stated the wound was "infected". During this time, he also underwent the removal of two squamous cell skin lesions on his left upper arm and central chest. He was prescribed a seven-day course of TMP-SMX double strength twice a day, which he completed two weeks before presenting to the emergency room. Three days prior to admission, the patient began having fevers (Tmax 102 F), as well as confusion, which prompted him to come to the hospital. The patient had no additional surgical history and denied any alcohol use or illicit drug use. The patient has a twenty-pack-year history of tobacco use and continues to smoke daily. He has no known drug allergies and takes no medications daily. Vital signs on admission were a temperature of 101.7 F, blood pressure(BP) of 120/56 mmHg, heart rate(HR) of 120 beats /minute, respiratory rate(RR) of 22 breaths/ minute, and O2 saturation of 94 % on room air.

Physical exam was significant for an ill-appearing middle-aged male with altered mental status (alert and oriented x1), sinus tachycardia, mild tenderness in the right upper quadrant with no distention or

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guarding, healing excisions on the left forearm and central chest, sutured wound on the upper middle back and diffuse petechiae and maculopapular rash isolated to the back, chest, and abdomen; no mucosal/oral involvement was noted and the rash was not present on soles/palms, no bullae or pustules noted. No gross motor or sensory deficits were noted.

Labs on admission were significant for white blood cell count of 5.1 $\times$ 10^3 /uL, there were no eosinophils or monocytes identified in the differential, platelet count of 13 $\times$ 10^3 /uL, sodium of 122 mmol/L, creatinine of 2.77 mg/dL, blood urea nitrogen of 50 mg/dL, Aspartate aminotransferase of 238 units/L, Alanine aminotransferase of 79 units/L, Prothrombin time (PT) of 12.4 s, International normalized ratio (INR) of 1.1, and Partial thromboplastin time of 65 s(Table 1). Of note, the patient's pre-op labs 4 weeks before admission were normal. Non-contrast Computed Tomography (CT) of the head was negative for any acute processes. Chest x-ray was negative for any acute cardiopulmonary issues. Right upper quadrant ultrasound revealed a diffuse nonspecific gallbladder wall thickening without stones or other acute findings.

The patient met sepsis criteria on admission (temperature of 101.7 F, RR of 22 breaths/min, and HR of 120 beats/min) with the skin being the presumed source of infection. Lactic acid was 1.8 mmol/L. Following the sepsis guidelines, the patient was fluid resuscitated, blood cultures were drawn and he was started on empiric antibiotics, vancomycin, and piperacillin/tazobactam. He was also transfused 1 unit of platelets.

Given the fever, acute renal injury, confusion, and severe thrombocytopenia, the patient was emergently transferred to the ICU for possible plasmapheresis for presumed thrombotic thrombocytopenic purpura (TTP). Additionally, Infectious Disease, Nephrology, and Hematology/Oncology were consulted.

A detailed investigation was performed including a review of the patient's peripheral smear which failed to show evidence of schistocytes. These findings accompanied by elevated fibrinogen and D-dimer ruled out TTP. In addition, disseminated intravascular coagulation (DIC) was also ruled out secondary to the normal PT/INR and the absence of schistocytes on peripheral smear. His ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity was slightly decreased at 34.9 %, G6PD (glucose-6-phosphate-dehydrogenase) value was within normal limits. Renal studies performed showed evidence for 2+ hemoglobin, trace RBC's and FeNA of 2.79 mEq/L in the urine consistent with intrinsic renal injury, but further studies were not done to stratify the type of intrinsic injury (ie: acute interstitial nephritis vs acute tubular necrosis).

Through a diagnosis of exclusion, the Infectious Disease specialist concluded that these constellations of symptoms were a result of a delayed hypersensitivity reaction to TMP-SMX.

From day 1 of admission to day 3, the patient's creatinine, transaminitis, and hyponatremia continued to worsen. The patient was monitored closely in the intensive care unit and treated with supportive care. The patient's blood culture showed no growth for 4 days, and antibiotic treatment was stopped due to the low probability of infection.

Slowly, his mentation returned to baseline and the maculopapular rash disappeared by day 3; there was no scarring noted. By day 4, the patient's lab values began to correct (Table 1). He was able to be transferred out of the intensive care unit to the medical floor. He was finally discharged on day 5 and advised to never re-challenge TMP-SMX again.

Table 1
Pertinent laboratory data.

Tests	Admission	Day 2	Day 3	Discharge	References (units)
White blood count	5.1	3.5	5.1	5.4	4.0–10.5 10^3 uL
Hemoglobin	13.5	11.3	11.4	11.2	11.2–17.5 g/dL
Hematocrit	38.2	30.6	32.3	29.7	40.1–51 %
Platelets	13, repeat 9	15	20	81	150–400 10^3 uL
Sodium	122	124	127	136	136–145 mmol/L
Potassium	4.8	4.6	4.3	4.4	3.5–5.1 mmol/L
Carbon dioxide	19	19	17	24	21–32 mmol/L
BUN	50	40	52	35	7–18 mg/dL
Creatinine	2.77	3.83	4.48	2.21	0.6–1.30 mg/dL
GFR	23	16	13	30	> 60
Total bilirubin	0.6	0.6	0.5	0.4	0.2–1.0 mg/dL
AST	238	428	676	362	15–37 units/L
ALT	79	108	214	171	13–56 units/L
PT	12.4	n/a	10.5	n/a	11–13.5 s
INR	1.1	n/a	0.9	n/a	0.8–1.1
APTT	65	n/a	42	n/a	30–40 s
Fibrinogen	125	n/a	102	n/a	200–400 mg/dL
D-dimer	52,292	n/a	n/a	n/a	0–529 ng/mLFEU

AST=aspartate aminotransferase; ALT=alanine aminotransferase; MCV=Mean corpuscular volume; BUN=Blood urea nitrogen; PT=Prothrombin time; APTT=Activated Prothrombin time; INR=International Normalized Ratio

Discussion

Trimethoprim/sulfamethoxazole (TMP-SMX) is a commonly used antimicrobial agent that is used to treat a variety of bacterial infections. It has been used to treat bronchitis, otitis media, Traveler's diarrhea, urinary tract infections, community-acquired pneumonia and opportunistic infections, just to name a few [3]. With the increase in MRSA-positive community acquired infections and the ability of this medication to adequately treat a multitude of MRSA infections, the usage of TMP-SMX has increased significantly. Because of the relatively cheap cost of this medication, it is used often in outpatient and inpatient clinical settings.

Folic acid is an enzyme that is needed to synthesize amino acids and DNA. Humans get folic acid through diet. But in bacteria, folic acid is made from other cellular components, including p-aminobenzoic acid (PABA). TMP-SMX is a combination medication with each component, trimethoprim, and sulfamethoxazole, working in different ways. Sulfamethoxazole, and other sulfonamides, are structurally similar to PABA and act as a competitive inhibitor to dihydropteroate synthetase, which is the first step in folic acid synthesis in bacteria. Trimethoprim inhibits dihydrofolate reductase (DHFR), which stops the production of tetrahydrofolate, which is necessary for DNA and protein synthesis. When used alone, they are bacteriostatic, suppressing the growth of the bacteria; in combination, they are bactericidal, effectively killing the bacteria [4].

As with any medication, TMP-SMX is not without side effects. TMP-SMX is generally well-tolerated with the most common side effects being rash, nausea, and vomiting [5]. Severe hypersensitivity reactions affecting the liver, kidney, skin and bone marrow can occur after the administration of TMP-SMX. Many case reports describe the adverse effects of TMP-SMX on specific organ systems in isolation, however, the combination of adverse effects on multi-organ systems is rarely seen in one patient [6].

Cutaneous and gastrointestinal symptoms are the most frequently encountered side effects of TMP-SMX, attributed largely to the sulfonamide portion of the drug. Dermatologic reactions occur in 3–4 % of patients taking this drug and can occur in the form of a maculopapular rash, urticaria, morbilliform lesions, erythema multiforme, purpura, etc [7,8]. It can also infrequently present in the form of Stevens-Johnson syndrome and toxic epidermal necrolysis [9]. TMP-SMX has also been noted to cause a Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), which is a T-cell mediated hypersensitivity reaction leading to an acute cutaneous eruption, fevers, lymphadenopathy,

eosinophilia and organ involvement [10]. Though the pathogenesis of DRESS is not completely understood, it is thought to have a genetic component thought HLA genes and polymorphisms in the cytochrome P-450 enzyme that allow of the accumulation of the drug and its metabolites, causing a delayed reaction [11]. Regardless of the pathogenesis of DRESS, it is important to recognize this as this condition can be fatal if not identified quickly. Most cases are associated with leukocytosis with eosinophilia and mononucleosis. The presence of a rash, fevers and multi-organ involvement (ie: hepatitis, myocarditis, nephritis, pneumonitis) can be cues that this reaction is DRESS, but there are have been rare cases where a rash and eosinophilia are not present [12]. In the case we presented, the patient did present with a mild rash after an exposure to an offending agent with multiple organ involvement, but there were no eosinophils or monocytes noted in the patient's complete blood count differential. Given this constellation of symptoms with delayed on-set after drug exposure and variability of symptoms, DRESS syndrome cannot be completely excluded from this patient's differential diagnosis.

Gastrointestinal side effects occur in 3–8 % of patients and frequently include nausea, vomiting, and loss of appetite [8]. Uncommon GI side effects include diarrhea, glossitis, and stomatitis [7]. Due to the benign and reversible nature of these side effects, they do not require discontinuation of this drug. However, a retrospective case series of seven patients showed the sudden onset of conjunctivitis, lymphopenia, and rash (generalized sunburn-erythema) combined with hemodynamic changes, such as shock, in the setting of recent TMP-SMX use [13].

A variety of serious adverse effects involving the bone marrow can occur in patients being treated with TMP-SMX. Myelosuppression caused by non-cytotoxic drugs, such as sulfonamides, can be associated with idiosyncratic reactions causing cytopenias that may arise days or weeks after the use of the inciting drug. Some of these hematologic disturbances include thrombocytopenia, leukopenia, agranulocytosis, and bone marrow aplasia. No clear causative associations have been determined and, unfortunately, deliberate re-exposure provides the strongest evidence for association [14]. The rates of these idiosyncratic reactions occurring in patients taking TMP-SMX have been reported to occur at rates similar to other sulfonamide drugs [2]. Megaloblastic changes of the marrow may occur in persons with underlying folate and B12 deficiencies who are receiving long-term treatment of TMP-SMX. In these patients, supplementation of folic acid can mitigate this effect [2].

This drug combination is also notorious for causing renal dysfunction. Trimethoprim is known to decrease tubular secretion of creatinine, interfering with serum creatinine assays and leading to mild, benign elevations of the serum creatinine without true reduction in the glomerular filtration rate (GFR) [15]. It also alters transepithelial voltage in the distal tubule leading to significant hyperkalemia, which can be more pronounced in patients with underlying renal disease and patients taking angiotensin-converting enzyme inhibitors (ACEi) and potassium-sparing diuretics [16]. The sulfamethoxazole component of this antibiotic is known to cause acute kidney injury (AKI), documented as early as day 2 of antibiotic use up to weeks after completion of antibiotic therapy. The original mechanism of AKI was thought to be secondary to acute interstitial nephritis (AIN) [17]. Diagnosis of AIN is made through the presence of eosinophils in the blood and urine, fevers, rash, and proteinuria, however, definitive diagnosis is made through a kidney biopsy. Fraser TN et. al. studied the incidence, extent, and severity of AKI associated with TMP-SMX in a middle-aged veteran population. Of this population, 11.2 % of patients had an AKI, regardless of the mechanism of this injury (ie: intrinsic injury, acute interstitial nephritis, or acute tubular necrosis). Of the 37 patients who had urine analysis, only 4 had hematuria and/or pyuria, none had eosinophils, rash, or fevers. Based on their research, intrinsic renal impairment better explained this mode of acute kidney injury [18]. However, other case reports have diagnosed acute tubular necrosis as the inciting cause of TMP-SMX-induced AKI following kidney biopsy [19]. Other case series also describe interstitial nephritis and acute tubular necrosis with TMP-SMX therapy [20–22]. Further research is necessary in determining the mechanism of action responsible for TMP-SMX-induced acute kidney injury.

There have been many case reports that have made significant associations between acute hepatitis and TMP-SMX use. Although rare and variable in severity, hepatotoxicity is a well-known and feared adverse reaction to TMP-SMX use [23]. This was originally thought to be secondary to the sulfonamide component of this drug which can cause life-threatening fulminant liver failure, but in recent case reports, it has been shown that trimethoprim can cause liver injury in the absence of the sulfonamide component. Some review articles suggest that TMP-SMX-induced liver injury was due to a hypersensitivity reaction, drug allergy, or toxic metabolites [24]. There may also be a genetic component at play increasing the risk of hepatic injury, specifically in European Americans, African Americans and Taiwanese [25]. In most cases, this injury pattern arises after 2–12 weeks of use and resolves after 2–3 days of cessation of the antibiotic, except for a few cases in which mild liver injury led to fulminant hepatic failure [24, 26–29]. In one case report, a patient developed significantly elevated liver enzymes after completing a course of TMP-SMX for 1 week. After a negative workup, he underwent a liver biopsy which showed "submassive necrosis and collapse with prominent inflammation and eosinophils, suggestive of drug-induced liver injury" leading to death (the case was modified from a case in the database of the Drug-Induced Liver Injury Network [24]).

In this case report, we discuss a 61-year-old male who presented to the hospital with a delayed hypersensitivity reaction to TMP-SMX resulting in multi-organ failure. Given the constellation of symptoms and the severity of illness on admission, multiple diseases which are known to cause global organ dysfunction were considered, including TTP, G6PD deficiency, DIC, malignancy, hepatitis B and C infections, and Human Immunodeficiency Virus (HIV). All of these were ruled out with appropriate testing. Through a diagnosis of exclusion and a literature review, we concluded that this patient was experiencing a severe adverse reaction from antibiotic use, however, the diagnosis of DRESS cannot be excluded.

We urge clinicians to cautiously prescribe this antibiotic in specific patient populations. In patients older than 65 years, it is recommended to find another alternative to TMP-SMX, as "deaths per million prescriptions are 15x higher in patients aged 65 and old compared to those under the age of 40" [19]. In patients with known folate deficiencies, folic acid, and leucovorin should be prescribed in conjunction with TMP-SMX to decrease the risk of worsening underlying folate deficiency [2,30]. Caution must be used when prescribing TMP-SMX to patients with chronic kidney disease, as the half-life increases from 8 to 14 h to greater than 30 h necessitating renal dosing of this medication [31]. In patients with marked hepatic damage (ie: parenchymal damage, jaundice, liver failure), TMP-SMX should be avoided [23]. Patients who have previous anaphylactic reactions, Stevens-Johnson Syndrome(SJS), and Toxic Epidermal Necrolysis (TEN) reactions from sulfa drugs should avoid TMP-SMX. History of sulfonamide or trimethoprim-induced Immune Thrombocytopenic Purpura (ITP) or TTP excludes patients from using TMP-SMX. Dofetilide use is also contraindicated with TMP- SMX use.

Conclusion

When prescribing TMP-SMX, physicians should exercise their expertise in selecting patients that may require a baseline serum creatinine and BUN ratio, frequent complete blood counts, and complete metabolic panels. Close monitoring is recommended in patients with multiple comorbidities such as older age (>65 years old), diabetes, vascular disease and renal and hepatic insufficiency. Our patient was generally healthy, with no risk factors that would predict a complicated clinical course despite which he developed significant multi-organ system failure. Henceforth, caution should also be exercised in all patients.

Ethical approval

Consent and case report manuscript was approved the UCF/HCA GME Research division.

Statement of consent

Appropriate informed consent was obtained.

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Author Statement

Samantha Sircar: Primary author, wrote the original draft and revisions. Melanie Rayan: Secondary author, wrote the original draft and edited revisions. Peters Okonoboh: Attending physician, guidance.

CRediT authorship contribution statement

Samantha Sircar, DO- writer and editor. Melanie Rayan, MD- writer and editor. Peters Okonoboh, MD- attending physician and editor.

Declaration of Competing Interest

No conflict of interests.

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