

## Ileitis: A Rare Side Effect of Trimethoprim/Sulfamethoxazole

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### Abstract

**Introduction:** Trimethoprim/Sulfamethoxazole (TMP/SMX), a commonly used antibiotic, is generally well tolerated, with adverse effects occurring in 6% to 8% of patients. Among the most common side effects are gastrointestinal and cutaneous reactions. Ileitis has rarely been associated with TMP/SMX use. We report a patient who developed DRESS syndrome with visceral involvement masquerading as ileitis.

**Case Report:** A 46 years old Hispanic male was treated with levofloxacin and then switched to TMP/SMX for urinary tract infection. The patient developed nausea, vomiting, diarrhea, arthralgias, myalgias and maculopapular rash. Colonoscopy showed ileitis and colitis confirmed by histopathology. Lab finding supported the diagnosis of drug rash with eosinophilia and systemic symptoms (DRESS syndrome). Other causes of ileitis such as infections, inflammatory bowel disease and ischemia were ruled out. Upon discontinuation of TMP/SMX and administering supportive therapy and steroids, the patient improved. Patient reported complete resolution of symptoms on follow up after four weeks.

**Conclusion:** In this patient, the timing of onset after initiation of TMP/SMX and the overall clinical picture is consistent with DRESS syndrome associated with ileitis. Gastrointestinal involvement in DRESS syndrome is uncommon. Differential diagnosis of ileitis is broad and the significance of drug induced ileitis is that diagnosis is by exclusion. Withdrawal of TMP/SMX with or without steroids and supportive care is mainstay of therapy. The role of steroids is considered beneficial when DRESS syndrome involves visceral organs.

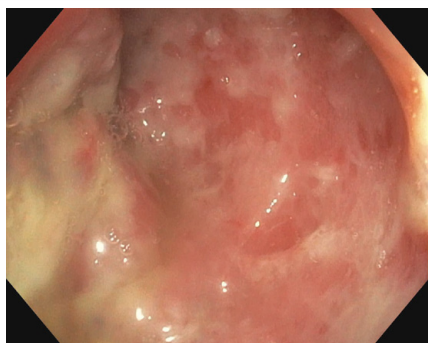
**Keywords:** DRESS syndrome; Ileitis; Rash

### Introduction

Trimethoprim/Sulfamethoxazole (TMP/SMX), is a widely used antibiotic due to its efficacy and low cost. TMP/SMX is used against a wide range of pathogens causing respiratory, gastrointestinal and urinary tract infections [1]. Although TMP/SMX is generally well-tolerated, it has many adverse effects, ranging from minimal to fatal reactions. Adverse effects occur in 6% to 8% of patients [2]. Gastrointestinal and cutaneous reactions are the most common side effects reported secondary to TMP/SMX [3]. TMP/SMX use may lead to allergic reactions, including DRESS Syndrome. Life threatening conditions like Toxic epidermal necrolysis, Steven Johnson Syndrome, neutropenia and exfoliative dermatitis have also been reported with TMP/SMX. A review of the literature identified few cases of TMP/SMX induced ileitis. We report a case of a 46 years old Hispanic male who developed drug rash with eosinophilia and systemic symptoms syndrome (DRESS Syndrome) including ileitis and colitis a few days after starting TMP/SMX.

### Case Report

A 47-year-old Hispanic man was in his usual state of health until five days prior to admission, when he noted burning micturition along



**Figure 1:** Colonoscopy shows erythematous mucosa with ulceration in terminal ileum.

with haematuria and was diagnosed with urinary tract infection. He was prescribed Levofloxacin by his physician. After the first dose of Levofloxacin, he developed tongue and lip swelling. Levofloxacin was switched by his physician to TMP/SMX along with Prednisone, Ranitidine and Benadryl [1]. The patient developed weakness with associated nausea and fluid retention. Three days prior to admission, he continued taking TMP/SMX, Ranitidine and Benadryl [1]. Prednisone was stopped due to development of fluid retention. Subsequently, his nausea worsened and he developed fever, myalgias, arthralgias, diffuse maculopapular rash and presented to the Emergency room. He denied any sick contacts, any recent travel within or outside USA or history of insect bites. His past medical history was significant for osteoarthritis and gastroesophageal reflux disease. Patient quit smoking one month ago. He denied alcohol and illicit drug use (Figures 1 and 2).

On admission to the hospital, vital signs were normal except for temperature of 99.8 Fahrenheit. Oral examination revealed dry tongue and mucous membranes. There were no mucosal ulcers. His cardiac, pulmonary and abdominal exams were normal. He had diffuse maculopapular erythematous rash.

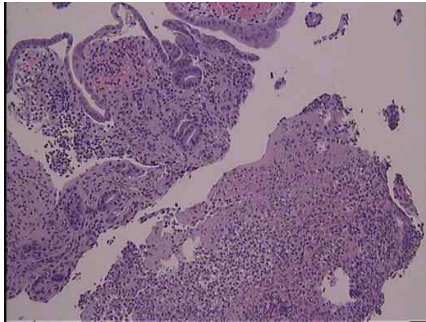
His labs showed a white blood cell count of  $10.1 \times 10^9$  /L, haemoglobin 15.1 g/dL, Haematocrit 44.3%, platelet  $192.0 \times 10^9$  /L, eosinophil 6.1%. Sodium 132 mmol/L, potassium 3.5 mmol/L, aspartate aminotransferase 222 U/L, alanine aminotransferase 609 U/L; alkaline phosphatase 254 U/L, total bilirubin 3.0 mg/dl, direct bilirubin 1.3 mg/dl, indirect bilirubin 1.7 mg/dl,  $\text{CO}_2$  19 mmol/L, total protein 5.4 g/dl,

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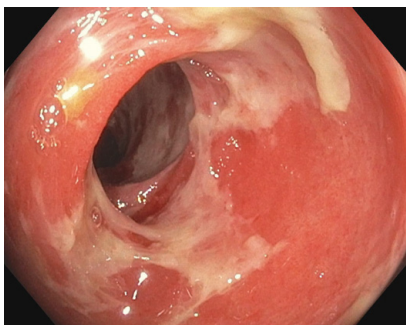
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**Figure 2:** Ileal biopsy shows ulceration with fibrinopurulent exudate and associated chronic active inflammation in the lamina propria.



**Figure 3:** Colonoscopy reveals erythematous mucosa with ulceration in colon.



**Figure 4:** Colonic biopsy reveals increased chronic inflammation in lamina propria; Glands show reactive change with scattered atrophic or attenuated crypts.

albumin 2.1 g/dl. Urinalysis showed ketones 3+ (80 mg/dl), RBCs 3-10/HP, urobilinogen 1+ (20 mg/dl) and bilirubin 1+ (0.5 mg/dl) (Figures 3 and 4).

Hepatitis A, B and C serology were negative. Patient developed abdominal cramps and profuse watery diarrhoea one day after admission. Stool lactoferrin was positive. Stool culture was negative for Salmonella, Shigella, *Campylobacter jejuni* and *Escherichia coli*. Stool antigen tests for Cryptosporidium, Giardia and Rota virus were negative. *Clostridium difficile* Toxin A and B were also negative. Anti-neutrophilic cytoplasmic antibodies were also negative. Colonoscopy showed erythematous mucosa with ulceration in terminal ileum (Figures 1-4). Pathology results showed acute ileitis with mucosal ulceration and fibrinopurulent exudate, and acute cryptitis representing chronic active colitis. Differentials according to the lab included drug induced versus ischemic bowel. Considering patients age, ischemia was very less likely.

Computed tomography scan (CT scan) of the abdomen and pelvis showed scattered retroperitoneal lymph nodes and focal fatty

infiltration of liver. CT scan was negative for masses, ascites or any process suggestive of sepsis or hepatic failure. Patient was started on IV Methylprednisolone 60 mg once a day (OD) for two days followed by 40 mg OD for one day, which was followed by oral prednisone 20 mg OD which was tapered over next 2 days. Mesalamine was also initiated before histopathology results as inflammatory bowel disease was considered one of the differential diagnosis. His clinical response was favourable after withdrawing TMP/SMX and steroid administration. Following this extensive workup, the acute ileitis was attributed to DRESS syndrome secondary to TMP/SMX use.

## Discussion

Differential diagnosis of ileitis is broad and includes inflammatory bowel disease. Infections such as Salmonella, Yersinia, mycobacterium and *Clostridium difficile* [4]. Other disorders such as Ischemia and small bowel neoplasm are also important to consider [4]. Additionally, use of some medications including non-steroidal anti-inflammatory agents, potassium chloride, parenteral gold therapy, oral contraceptive pills, digoxin have been associated with ileitis [4].

This patient's history of nausea, vomiting, rash, and fever and diarrhea after starting TMP/SMX suggests a causative role of TMP/SMX. Furthermore, the lab findings of abnormal LFTs, eosinophilia and lymphadenopathy are consistent with the diagnosis of DRESS syndrome. DRESS syndrome is a severe hypersensitivity syndrome which may cause multi-visceral involvement [5]. The incidence of DRESS syndrome is 0.001% to 0.0001% after drug administration, being potentially lethal in up to 10% of cases [6].

Involvement of gastrointestinal tract as part of DRESS syndrome is a rare occurrence [7]. Only a handful of cases of ileitis have been reported to be caused by TMP/SMX. While analyzing CT scan results; the pattern of attenuation and enhancement, symmetry and extent of bowel wall thickening can help narrow down differential diagnosis [8]. Histopathological findings along with clinical correlation suggest TMP/SMX induced ileitis. Colonoscopy with ileoscopy is indicated to assist with differential diagnosis of disorders of ileo-colonic regions and to obtain tissue for histopathology [9].

In our patient, timing of onset after initiation of TMP/SMX and the overall clinical picture along with histopathological findings are consistent with DRESS syndrome and ileitis.

Histological features from ileal biopsy included nonspecific mucosal ulceration with inflammatory exudate suggesting drug induced or ischemic cause. Absence of endoscopic appearance of IBD like granularity, cobblestone appearance, linear scars and absence of histological features like granulomas, crypt abscesses and chronicity of inflammation made IBD less likely. Additionally, ANCA in the patient was also negative, although it is not very useful in the diagnosis due to low sensitivity [10]. Infectious causes of ileitis were ruled out by negative stool cultures, serology and small bowel biopsy. Absence of risk factors for atherosclerotic disease and low perfusion states (shock, heart failure) made ischemic bowel disorder less likely in this patient [11].

The mainstay of treatment of DRESS syndrome is prompt withdrawal of the offending agent [12]. The use of steroids is controversial; however, some authors suggest their use when there is visceral involvement [12].

## Conclusion

Physician should consider the possibility of TMP/SMX as a cause when dealing with ileitis. Withdrawal of the offending agent with

steroid administration and supportive treatment is the mainstay of management.

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