CASE REPORT

Flucytosine-induced colitis

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SUMMARY

A 52-year-old man with a history of HIV (CD4 count 155, and viral load 154 K), who is on antiretroviral treatment presented in the emergency room with acute onset of headache. The patient had lumbar puncture and found to have elevated intracranial pressure and cryptococcal antigen was positive. The patient was started on flucytosine. After 10 days of treatment, the patient developed watery diarrhoea. An extensive infectious workup was carried out, which did not reveal any infectious aetiology. A colonoscopy was carried out which revealed acute colitis in the colon and the pathology confirmed the colonoscopic findings with severe colitis in the colon. At this time, the patient's diarrhoea was attributed to flucytosine and it was stopped. The patient's diarrhoea improved after 5 days of stopping flucytosine.

BACKGROUND

Immunocompromised patients are prone to have diarrhoeal illness. Patients with HIV and AIDS can develop severe infectious diarrhoea and colitis due to infections. Along with common infectious pathogens, atypical infections such as cytomegalovirus (CMV), herpes virus, *clostridium difficile* and *mycobacterium avium-complex*, *cryptosporidium*, *isospora belli* and histoplasma are also prevalent in the population with HIV. We present this unique case of diarrhoea and colitis in a patient with HIV, who was started on flucytosine (5-FC) for cryptococcal meningitis. We did an exhaustive infection work which was unrevealing. Finally, we attributed the patient's diarrhoea to 5-FC and by stopping this medication, diarrhoea resolved. We are presenting this rare case of 5-FC-induced colitis.

CASE PRESENTATION

This is a 52-year-old Caucasian man with a history of HIV, who presented with a 4-day history of headache. It was associated with photophobia. The headache was throbbing in nature and is generalised radiating to the neck. The patient also reported some nausea but no vomiting. The patient was on antiretroviral treatment with emtricitabine-tenofovir 200–300 mg/day, darunavir 800 mg/day and dolutravir 100 mg/day for the past 3 years but was not very compliant with the treatment.

A lumbar puncture was performed given the high suspicion of meningitis and the patient was found to have elevated opening pressure and cryptococcal antigen was positive. The patient was started on amphotericin and 5-FC. Amphotericin was stopped due to worsening of the renal function after 3 days. 5-FC dose was 2500 mg four times a day (25 mg/kg) but adjusted according to the drug level and

renal function. The patient also developed some alerted mental status after admission which was waxing and waning until day 8 and started improving steadily. On day 10 of hospitalisation, the patient developed diarrhoea which was loose and watery and reported some abdominal pain. He had about 6–8 watery bowel movement per day. There was no blood in stools. Physical examination revealed temperature of 98°F, pulse 80, blood pressure 110/80 and the oxygen saturation was 98% on room air. The patient was awake and alert. Abdomen was soft and non-tender. Heart was in regular rate and rhythm. Rectal examination revealed watery stools.

DIFFERENTIAL DIAGNOSIS

In the setting of HIV, infectious aetiologies are a common cause of diarrhoeal illness. CMV colitis, cryptospora, isospora and cryptococcal colitis can also be possible.¹ Drug-induced versus inflammatory bowel disease could be other possibilities although the later is less likely due to acuity of symptoms.

INVESTIGATION

White cell count was 4.2 ($4.0\text{--}10.0 \times 10^3/\text{mm}^3$), Hg 12.3 (13.7–17.5 g/dL), platelet 104 ($140\text{--}370 \times 10^3/\text{mm}^3$), sodium 133 (136–145 mmol/L), potassium 3.6 (3.5–5.1 mmol/L), chloride 100 (98–107 mmol/L), bicarbonate 23 (22–29), blood urea nitrogen 23 (6–20 mg/dL), creatinine 0.8 (0.67–1.17 mg/dL) at admission and worsened to 3.0 in 3 days, aspartate aminotransferase 34 (0–41 U/L), alanine aminotransferase 52 (0–40 U/L), alkaline phosphatase 206 (40–129 U/L), total bilirubin 0.6 (<1.2 mg/dL), albumin 2.8 (3.5–5.2 g/dL) and the total protein 8.2 (6.0–8.0 g/dL). Cerebrospinal fluid venereal disease research laboratory was negative. Serum cryptococcal antigen: positive (1:1028). Stool studies were carried out and *C difficile* was negative. There were no polymorphonuclear cells seen in stools. Stool for *microsporidium*, *cryptosporidium* and O&P was negative. Stool culture did not grow any pathogen. Plasma CMV PCR was negative. CT of the abdomen which was carried out for abdominal pain revealed fat stranding surrounding the descending colon from the splenic flexure distally most conspicuous at the rectosigmoid junction which suggested some inflammatory process. A colonoscopy was carried out and it showed normal terminal ileum.

Mild-to-moderate erythema with some petechiae-type lesions in caecum was seen. There were prominent blood vessels and some friability. Patchy area of erythema, friability and prominent vascularity was seen in the ascending colon (figure 1A) and

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Figure 1 Erythema, friability and prominent vasculature in the ascending colon (A) and transverse colon (B). Pathology infiltration of inflammatory cell consistent with acute colitis in (C) ($\times 20$) and (D) ($\times 40$).

transverse colon (figure 1B) and severe erythema, congestion, friability of the mucosa was seen in the descending and sigmoid colon and rectum. Mucosa was biopsied. Pathology results revealed benign small intestinal mucosa in the terminal ileum; mild acute colitis in the caecum; severe acute colitis in the transverse, descending and sigmoid colon and severe acute proctitis in the rectum (figure 1C, D). Detailed report showed severe colitis with acute inflammation and crypt abscesses, somewhat withered appearing crypts and markedly reactive nuclei with prominent

nucleoli and focal large smudgy nuclei. CMV and adenovirus immunostain are negative. The caecum is less affected.

OUTCOME AND FOLLOW-UP

On the basis of the above investigation, we diagnosed that the patient's diarrhoea and colitis was due to 5-FU as the infection workup was negative. The patient's diarrhoea improved after 5 days of stopping 5-FU. A repeat colonoscopy after 2 months showed normal colon mucosa.

DISCUSSION

It is common to have diarrhoea in patients infected with HIV. Most common aetiology of diarrhoea in immunocompromised patients is infectious in origin. Common pathogen includes microspora, cytospora and isospora. CMV colitis is also common in this population.² We initially thought that the patient's diarrhoea is infectious in origin. All the infection workup was negative. Colonoscopy finding revealed acute colitis. CMV PCR was negative and also we did not see any evidence of CMV in pathology. After excluding other aetiologies, we attributed the patient's colitis to 5-FU and diarrhoea improved after stopping the medication. 5-FU is a synthetic antimycotic compound which was synthesised in 1957.³ Once it is taken up by susceptible fungal cells, it is converted into 5-fluorouracil (5-FU), which is further converted to metabolites that inhibit fungal RNA and DNA synthesis.

It is absorbed very rapidly and has 85% bioavailability. It penetrates well into most body sites and renally cleared and half life is 3–4 h. Gastrointestinal side effects include nausea, vomiting and diarrhoea and rarely colitis,⁴ and bowel perforation has been reported.⁵ 5-FU-induced colitis due to its local cytotoxic effects on protein synthesis.⁶ There is case report of 5-FU enteritis. 5-FU can cause narrowing, ulceration and marked separation of small bowel loops. Biopsies of the small bowel reveal enteritis in that reports.⁷ In our patient, there was no evidence of small bowel involvement and the terminal ileum biopsy was normal. There were few case reports in the literature on 5-FU-induced colitis. 5-FU is directly used as a chemotherapeutic agent for various cancers.⁸ One can argue that it may be the metabolites of 5-FU which caused colitis but it is not very clear. The mainstay of treatment for 5-FU-induced colitis is to stop the drug. Few cases in the literature who has colitis due to 5-FU has also been treated with metronidazole, vancomycin and steroids,⁹ but the offending agent was also stopped in all the cases as well.

Although it is uncommon to have medication-induced colitis but when it happens, it is essential to recognise it early as culprit medication continuation can cause disease exacerbation.

Learning points

- It is important to remember the side effects of medications.
- After excluding the common causes of a disease presentation, we should think of atypical causes and atypical presentation of the disease.
- Discontinuing the offending medication is sometime the easiest treatment.

Competing interests None.

Patient consent Obtained.

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