CASE REPORT

Clozapine-induced ischaemic colitis

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SUMMARY

Ischaemic colitis is a rare side effect of antipsychotics, especially phenothiazines and atypical antipsychotics. The colitis may be precipitated secondary to the anticholinergic effects of such medication rather than a direct cytotoxic effect of the drugs themselves.

A 32-year-old man with a history of schizophrenia was admitted to the hospital with a history of diffuse abdominal pain and vomiting. His bloods showed leucocytosis. Sigmoidoscopy demonstrated rectal sparing acute colitis, confirmed on biopsy findings. A CT scan also showed similar findings. After careful drug review, it was decided that clozapine was the cause of colitis and promptly stopped. The patient was managed conservatively on intravenous fluids and antibiotics and made a full recovery. Any patient starting antipsychotics should be counselled on their anticholinergic side effects. Drugs should always be considered as a cause of ischaemic colitis; although an uncommon complication of antipsychotics, it can have a potentially fatal outcome.

BACKGROUND

Ischaemic colitis represents a spectrum of pathologies that results in the insufficient supply of blood to a segment of colon. This disease results in ischaemic necrosis of varying severity that can range from superficial mucosal involvement to full-thickness transmural necrosis.[1]

About 10% of patients will present to the hospital with acute colitis that will fulfil the criteria for a severe attack,[2] which includes bowel opening more than six times in 24 h, and at least one of (a) haemoglobin <10.5, (b) erythrocyte sedimentation rate >30, (c) pulse >90 and (d) temperature >37.5°C. For these patients, especially, it is important to consider a differential diagnosis which includes infective, ischaemic, drug-induced and other inflammatory causes of colitis.[3] Here, we report on a patient with an unusual cause of necrotising colitis.

CASE PRESENTATION

A 32-year-old man with a history of chronic schizophrenia and learning difficulties was admitted to the hospital with a 5 day history of diarrhoea, vomiting and abdominal pain. He had seen his general practitioner 3 days earlier, who had prescribed loperamide, domperidone and hyoscine butylbromide. His diarrhoea had settled, but his vomiting and abdominal pain continued. He had also not passed flatus or moved his bowels in 2 days. There was no history of haematemesis, bleeding per rectum, fever, weight loss, foreign travel or illicit drug use. The only regular medication that the patient had been prescribed was 700 mg of clozapine, which the patient had been on for 15 years.

INVESTIGATIONS

On admission to the hospital, patient's abdomen was soft and non-distended, but diffusely tender. Bloods showed: white cell count 13.5, C reactive protein 198, aspartate aminotransferase 94, alanine aminotransferase 102 and γ-glutamyltransferase 370. Haemoglobin, platelets, urea, creatinine and electrolytes were normal. An abdominal film showed a dilated large bowel and he was initially managed with intravenous fluids, intravenous antibiotics and nasogastric suction.

After worsening of blood results and increasing intensity of symptoms, the patient underwent an urgent sigmoidoscopy, which demonstrated rectal sparing acute colitis. The pathology report from sigmoid biopsies noted ulcer slough and infarcted looking mucosa, consistent with a diagnosis of necrotising colitis. A subsequent abdominal CT again demonstrated an acute left-sided severe colitis with dilatation of the transverse colon to 8 cm.

A gastroenterology review suggested that the necrotising colitis was secondary to the anticholinergic activity of clozapine and subsequent diffuse gastric hypomotility. This was promptly stopped after discussion with the patient's psychiatrist.

TREATMENT

Intravenous hydrocortisone was suggested, but was not initiated due to an increased risk of psychosis with high-dose steroid therapy in this patient. Owing to ongoing clinical deterioration, the need for a laparotomy and colonic resection with stoma formation was discussed with the patient's mother, who had a guardianship order over the patient. She was unhappy with this course of action and the patient was managed conservatively with intravenous fluids, intravenous antibiotics and a rectal catheter to improve mucosal circulation and decrease colonic dilatation.

OUTCOME AND FOLLOW-UP

The patient made a full recovery and was discharged home on aripiprazole. Although the patient's mental state did initially deteriorate on discontinuation of clozapine for a few weeks, this gradually improved on titration of aripiprazole. The patient subsequently had a relapse of psychotic symptoms and is now requiring inpatient treatment in the hospital. As he has been refusing oral medication, he is currently prescribed an intramuscular antipsychotic and while assessing its efficacy, we are also considering whether it would be safe to restart clozapine.

DISCUSSION

Several drugs have been known to cause ischaemic colitis. These include chemotherapeutic agents,

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antibiotics, hyperosmolar laxatives,[4] vasopressor drugs, ergotamines, psychotropic drugs, cocaine, digitalis, oestrogens, nonsteroidal anti-inflammatory drugs (NSAID) and diuretics.[5] For example, studies have shown that up to two-thirds of NSAID users may demonstrate intestinal inflammation distal to the duodenum on radionuclide scans.[6] However, mechanism of injury for different drugs may vary from increased intestinal permeability, localised mucosal toxicity and significant anticholinergic effects to mesenteric vascular insufficiency.

Clozapine is an atypical antipsychotic licensed for the treatment of refractory schizophrenia after other antipsychotics have proved ineffective or have intolerable side effects. Clozapine is generally reserved for secondary use due to its propensity to cause serious side effects, such as life-threatening agranulocytosis and the necessity for life-long blood monitoring.[7] Other common side effects that have been reported include weight gain, dyslipidaemia, myocarditis, cardiomyopathy and hepatic impairment.[8]

Gastrointestinal side effects associated with clozapine include constipation, gastric outlet obstruction, prolonged postoperative ileus and peritonitis with bowel perforation. The prevalence of developing intestinal side effects, while a patient is on clozapine has been reported to be as high as 33%.[9]

It is believed that clozapine's marked anticholinergic and antiserotonergic activity is a key to potentiating constipation. This action is exacerbated by coprescription of anticholinergic agents such as benztropine and tricyclic antidepressants.[10] Prolonged gastrointestinal hypomotility and constipation is believed to promote ischaemia by increasing intraluminal pressure and compression of mucosal vessels. As a sequelae, bacterial translocation, inflammation and ischaemia of the segment of bowel proximal to the obstruction. This was thought to be the mechanism of action causing colitis in this patient. In addition, although this patient was initially presented with diarrhoea, the prescription of hyoscine may have contributed to a general decline in intestinal motility and prolonged colonic ileus.

This case also highlights the importance of asking patients about their bowel function, and incorporating dietary advice and the prescription of laxatives prior to the initiation of medication, likely to have significant anticholinergic effects. In this instance, the patient did admit to having chronic constipation prior to his admission. His psychiatrist had attempted to give him a laxative, but compliance was a problem with the patient. His mother, who was his guardian, had attempted to manage this with dietary measures that included fresh fruits and vegetables, and an adequate fluid intake, although the patient's nutritional intake was variable.

Learning points

- Causes of bowel infarction include (but are not limited to) arterial and venous thrombus and emboli, mucosal toxicity, non-occlusive and occlusive mesenteric ischemia and splanchnic vasoconstrictive agents.
- Drugs are an important, but often missed cause of inflammation of the colon and subsequent infarction.
- Psychiatrists and general practitioners working with patients on atypical antipsychotics, especially clozapine, should be vigilant to the possibility of constipation and should counsel patients appropriately on its complications.
- The coprescription of laxatives should be considered prior to the initiation of drugs likely to have a significant anticholinergic effect.

Competing interests None.

Patient consent Obtained.

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