

CASE REPORTS

Severe ischemic colitis following olanzapine use - A case report

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ABSTRACT

Ischemic colitis is the most common subtype of intestinal ischemia usually resulting from vasospasm, vessel occlusion or mesenteric hypoperfusion. Neuroleptics have seldom been linked to ischemic colitis by blocking peripheral anticholinergic and antiserotonergic receptors inducing severe gastrointestinal paresis. We report a young patient with severe ischemic colitis requiring surgery due to necrosis of the bowel. After exclusion of other potential causes, olanzapine was admitted as the cause of ischemia. Clinicians should be aware of how to recognize and treat the potentially life-threatening effects of neuroleptics.

Key words: Neuroleptics. Olanzapine. Ischemic colitis.

INTRODUCTION

Ischemic colitis represents the most common form of intestinal ischemia with an incidence estimated between 4.5 and 44 cases per 100,000 person-years (1). Age represents an important risk factor as up to 90% of ischemic colitis occurs in patients over 60 years of age (2). Rarely, ischemic colitis has been reported in young and otherwise healthy individuals with no known risk factors (3). Many drugs have been associated with ischemic colitis including antibiotics, anti-inflammatory drugs, vasopressors, cytotoxic agents, and neuroleptics (4). Clozapine, an atypical antipsychotic commonly prescribed for the treatment of schizophrenia and manic episodes, has been linked to several reports of ischemic colitis (5-7). The underlying mechanism is believed to involve blockage of peripheral anticholinergic and antiserotonergic receptors leading to severe gastrointestinal hypomotility (8). Olanzapine, an atypical antipsychotic with a similar pharmacological profile to clozapine (9), has recently been associated with ischemic colitis (2). A study from the French Pharmacovigilance database also linked olanzapine to at least 4 potential

cases of ischemic colitis (10). In this paper, we report the second case of ischemic colitis associated with olanzapine. We discuss clinical, endoscopic and histological findings and review the existent literature.

CASE REPORT

A 38-year-old male was admitted to our institution following a course of constipation, abdominal pain, and proctalgia. His medical history was significant for autism and systemic hypertension. Five years earlier, the patient had started olanzapine (15 mg/day), melperone (25 mg/day), carbamazepine (400 mg/day) and biperiden (4 mg/day) which he maintained in stable doses. He did not drink, smoke or consume recreational drugs. There was no history of recent travel or unprotected sexual intercourse. Two months prior to admission, he started complaining of low grade fever, abdominal pain, constipation and worsening tenesmus, mucorrhea and proctalgia. He was sequentially prescribed ciprofloxacin, cotrimoxazol and metronidazole by his attending physician, without significant clinical improvement. In the following month, he was admitted 2 times to an outside clinic with worsening of complaints. His investigation included an abdominal computed tomography (CT), showing thickening of the rectum and sigmoid with fat stranding, and a colonoscopy revealing hyperemia, edema, erosions and ulceration continuously involving the rectum and proximal sigmoid. The anatomopathologic examination showed epithelium erosion, hemorrhage and atrophy, as well as a decrease in the number of crypts and goblet-cells, and no significant inflammation. A diagnosis of inflammatory bowel disease (IBD) was considered and the patient was started on mesalamine and prednisolone (90 mg/day) without clinical and endoscopic improvement. Follow-up biopsies showed nuclear and cytoplasmic inclu-

Received: 28/07/2015

Accepted: 07/08/2015

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Fernandes SR, Alves R, Araújo Correia L, Gonçalves AR, Malaquias J, Oliveira E, Velosa J. Severe ischemic colitis following olanzapine use - A case report. *Rev Esp Enferm Dig* 2016;108(9):595-598.

DOI: 10.17235/reed.2015.3944/2015

sions compatible with cytomegalovirus (CMV). Nevertheless, there was no improvement after intravenous ganciclovir and immunocytochemistry and antigenemia were both negative. One week later, the patient was admitted to our institution. At admission, his physical examination was relevant for diffuse abdominal distention and tenderness. Blood work showed mild leukocytosis and elevated CRP. On contrast-enhanced CT the colon upstream the sigmoid was dilated and filled with feces. There were no signs of vascular thrombosis. After careful bowel preparation, colonoscopy was repeated showing severe ulceration of the rectum and distal sigmoid (Fig. 1). Again, histological examination revealed severe erosion and ulceration of the epithelium without significant inflammation, compatible with an ischemic event (Fig. 2). There were no granulomas or signs of infectious disease, and immunocytochemistry for CMV and herpes simplex virus were negative. After exclusion of infectious, autoimmune and thrombophilic

diseases, we assumed a presumptive diagnosis of ischemic colitis secondary to neuroleptics. The patient's therapeutic regimen was adjusted with discontinuing of olanzapine, gradual tapering of steroids, wide spectrum antibiotics and intestinal decompression with rectal enemas. Despite an initial laboratory improvement, there was persistence of abdominal pain and constipation. Given the failure of conservative management, we decided it was best to intervene surgically while the patient remained stable. On laparoscopy, while the sigmoid appeared unaffected, the rectum showed signs of severe ischemia. Fecal stream derivation with proximal colostomy resulted in rapid clinical and symptomatic improvement. After 21 days of hospitalization, the patient was discharged with overall resolution of clinical symptoms. Five months later we confirmed complete endoscopic healing. One year later, segmental resection of distal sigmoid and rectum with end-to-end anastomosis was performed. Anatomopathologic examination was consistent with ischemic colitis (Fig. 3).

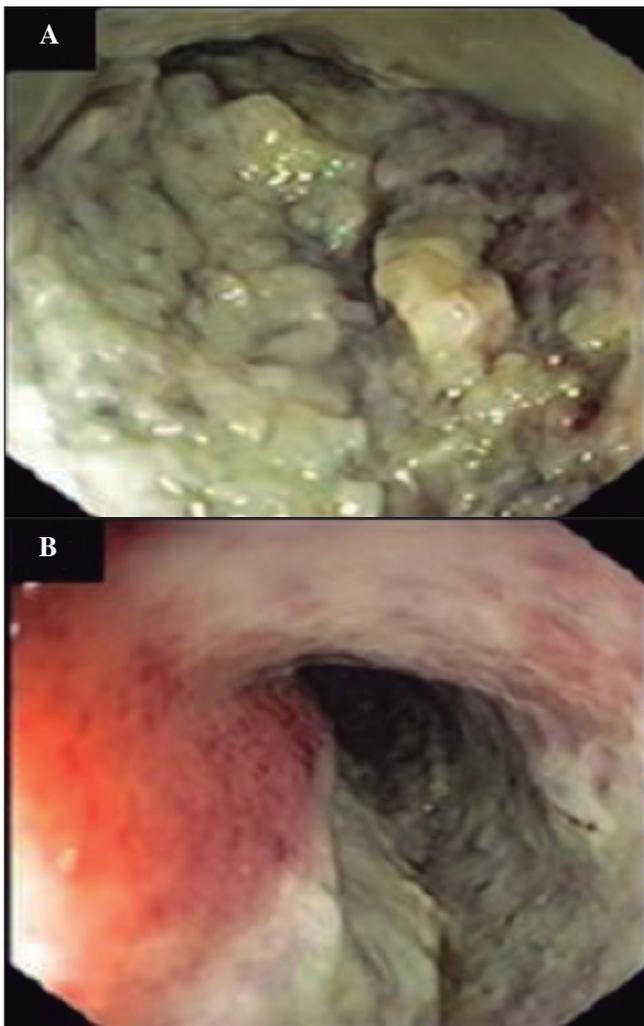


Fig. 1. Findings at sigmoidoscopy. Continuously from the anal verge there is severe inflammation and ulceration with areas of purplish mucosa suggesting necrosis.

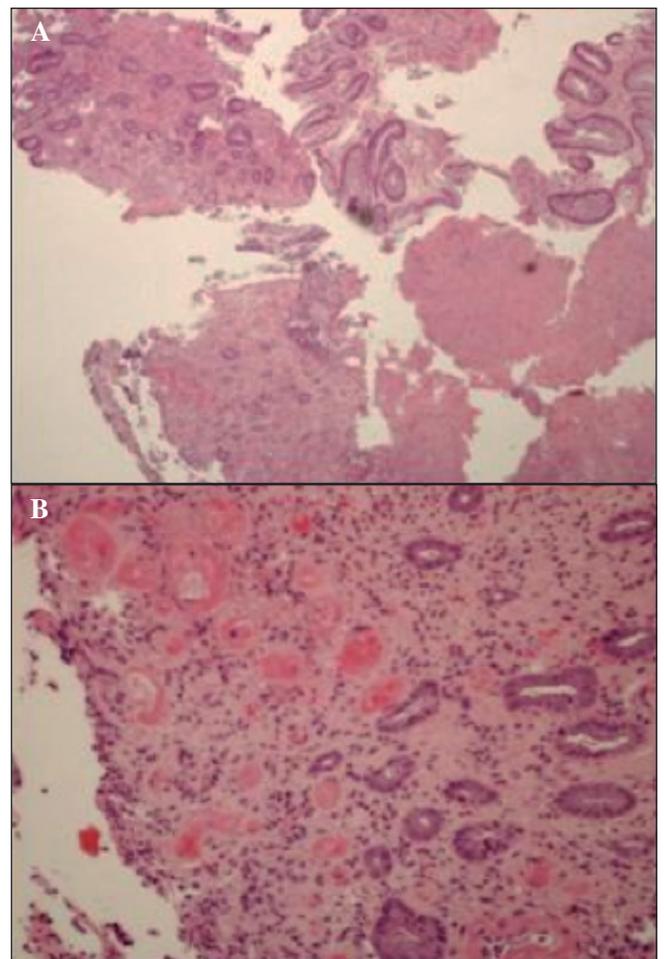


Fig. 2. Anatomopathologic examination of colonoscopy biopsies (hematoxylin-eosin staining). A. Extensive fibrinoid necrosis with exuberant deposition of granulation tissue. B. Necrosis of the ischemic type with focal erosions, ulcerations and fibrinoid necrosis of small blood vessels.

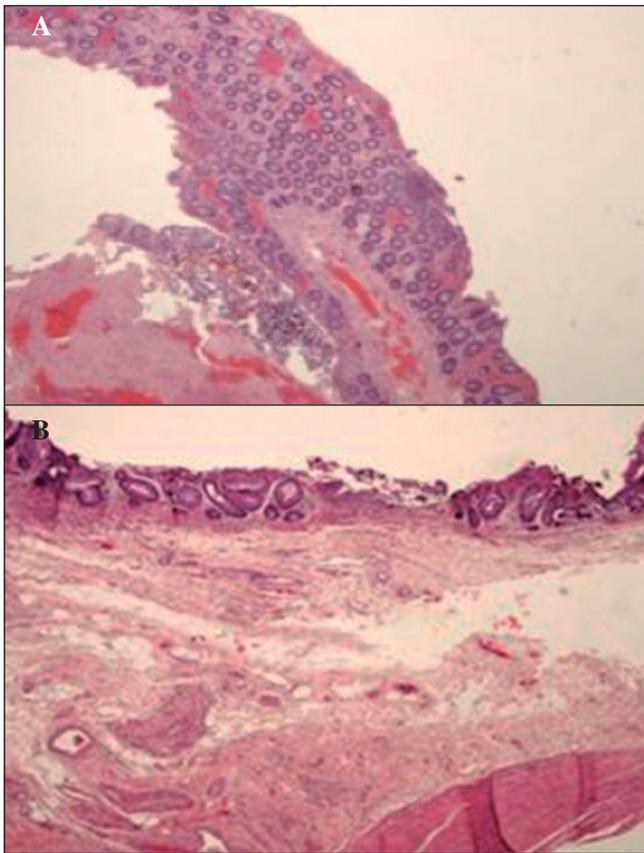


Fig. 3. A. Histologic examination of resected colon (hematoxylin-eosin staining). Epithelium shows areas of hemorrhage. B. Loss of superficial epithelium and crypts suggesting ischemia.

DISCUSSION

The spectrum of altered intestinal motility induced by neuroleptics includes constipation, gastric outlet obstruction, paralytic ileus, intestinal obstruction, ischemia, necrosis and perforation (11,12). Despite general practitioner unawareness, neuroleptic induced constipation is a very common and potentially severe event. Hayes and Gibler documented constipation in up to 60% of hospitalized patients using clozapine. Although most cases responded to laxatives, stool softeners and fecal volume expanders, up to 12% required repeated enemas for relief of constipation (6). Mortality of clozapine-induced constipation is estimated to be 3 times higher than that of agranulocytosis (13). Although severe, ischemic colitis has been infrequently linked to neuroleptics, occurring in only 0.3% of patients exposed to clozapine (5). The exact mechanism by which antipsychotics lead to ischemia is not yet fully understood. Inhibition of peripheral anticholinergic and antiserotonergic receptors has been proposed as the leading mechanism (9). This may in part explain why the incidence is higher for clozapine than for olanzapine, whose affinity for cholinergic and serotonergic

receptors is higher (9). Antagonism of these receptors has shown to limit gastrointestinal smooth muscle contraction leading to a delay in intestinal transit and constipation (14). Blockage of gastrointestinal 5-HT₃ receptors also reduces gastrointestinal autonomic reflexes and sensitivity to distention leading to increased compliance of the colon, favoring gastrointestinal hypomotility and constipation (5). Slow transit and progressive fecal accumulation lead to increased intraluminal pressure, reduced intestinal blood flow and subsequent tissue ischemia (15). A third plausible mechanism may involve a complex interaction between intestinal dopamine receptors inhibiting mesenteric vasodilation (4). Finally, inflammation and thrombotic phenomena at the level of submucosal capillaries may worsen intestinal ischemia. Secondary bacteria translocation due to impairment in mucosal integrity may lead to severe sepsis and necrotizing colitis (10). Concomitant administration of other drugs with anticholinergic and antiserotonergic effects, such as tricyclic antidepressants and antiparkinsonians, may potentiate the side effects of neuroleptics (10,11). Psychiatric patients, usually sedentary, polymedicated and with low-fiber, low fluid diets, may be more susceptible to the severe side effects of neuroleptics. Early recognition and treatment of antipsychotic-induced constipation is of particular importance. Adoption of a high fiber diet, increased fluid intake and regular physical exercise should be maintained during psychiatric treatment. In patients not responsive to these general measures, osmotic laxatives or stool softeners should be prescribed. Treatment of ischemic colitis usually involves conservative measures (intestinal decompression through nasogastric tube placement or enemas), bowel rest, intravenous fluids and broad-spectrum antibiotics to reduce bacterial translocation. Suspension of any drugs associated with ischemic colitis has been suggested to be beneficial (12). In the absence of response to conservative treatment or when evidence of intestinal infarction or perforation exists, early surgical consultation with resection of the diseased bowel should be undertaken (5,15). In conclusion, ischemic colitis associated with neuroleptics is an unusual but potential severe disease. Efforts should be aimed at prevention with early recognition and treatment of constipation. Alternatively, monitoring or switching to other antipsychotics may be an option.

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