Annals of Medicine Research and Public Health
Case Series (ISSN: 2995-5955)

Fluoroquinolone Induced Ischemic Colitis: A Case Series and Review of Literature

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Citation: *Abdullah Aleem, Blake Purtle, Keith Garrison, Suhair Al Salihi, Andrew Dupont. Fluoroquinolone Induced Ischemic Colitis: A Case Series and Review of Literature. Ann Med Res Pub Health. 2024;3(1):1-7.*

Received Date: 11 June, 2024; **Accepted Date:** 17 June, 2024; **Published Date:** 19 June, 2024

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ABSTRACT

Ischemic colitis (IC) occurs when blood flow to the colon is compromised, typically appearing at the splenic flexure or rectosigmoid junction, known as 'watershed' areas. Various pharmacological agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, phentermine, antipsychotics, and certain antibiotics (notably penicillin derivatives) have been implicated in IC pathogenesis. Although fluoroquinolones have been associated with pseudomembranous colitis in Clostridioides difficile infection (CDI), culture-negative colitis following fluoroquinolones is extremely rare. We report two cases of ciprofloxacin-induced IC. The first case was that of a 38-year-old woman who developed symptoms on day 4 of ciprofloxacin use. The second case involved a 68-year-old woman who developed symptoms one week after completing a 10-day course of ciprofloxacin. Colonoscopy and histopathology confirmed the presence of IC in both cases.

Keywords: Ischemic colitis; Fluoroquinolones; Antibiotics; Infectious colitis; Hemorrhagic colitis; Klebsiella oxytoca; Clostridioides difficile.

INTRODUCTION

Ischemic colitis (IC) occurs when blood flow to the colon is compromised and typically appears at the splenic flexure or rectosigmoid junction, the so-called watershed areas. There are many causes and associations, but they commonly include thromboembolic events, trauma, mechanical obstruction, and sequelae of hemodynamic compromise.[1] IC cases have increased over the past three decades, and a population-based study showed that the incidence of IC quadrupled from 1976 to 2009. Increasing age and cardiac comorbidities put patients at high risk for developing IC; the incidence of IC for those older than 80 years is 107 per 100,000 compared to only 1.1 per 100,000 for those under 40.[2] Although IC can be misdiagnosed for conditions that have a similar presentation such as infectious colitis and inflammatory bowel disease, the hallmark symptoms of IC include sudden onset abdominal pain, bowel urgency, and hematochezia.[3] Severity and management vary significantly, ranging from transient ischemia, which is often self-limiting, to fulminant colitis, necessitating surgical

intervention. IC carries a high in-hospital overall mortality rate of 11.5%; therefore, it is important to identify high-risk patients and make an early diagnosis.[2]

Several pharmacological agents, including non-steroidal anti-inflammatory agents (NSAIDs), oral contraceptives, phentermine, antipsychotics, and certain antibiotics, notably penicillin derivatives, have been implicated in the pathogenesis of IC.[4] Antibiotics have a long history of being harmful to the gastrointestinal system, most notably multiple antibiotic classes are associated with Clostridioides difficile infection (CDI), which can range in severity. [5] However, cases of antibiotic-induced colitis without isolation of C. difficile are rare. There are several cases in the literature that implicate penicillin derivative antibiotics, such as amoxicillin-clavulanate, as a culprit for antibiotic-associated hemorrhagic colitis.[6,7] In most of these cases, the pathogen Klebsiella oxytoca was isolated from stool cultures. Similar to the pathogenesis of CDI, K. oxytoca is a gram-negative organism that proliferates when there are alterations in the gut microbiome and produces the cytotoxin tilivalline, which induces apoptosis and localized inflammation.[8] Although fluoroquinolones have been reported to cause pseudomembranous colitis in the setting of CDI, C. difficile negative colitis following fluoroquinolone administration is extremely rare, with four documented cases of which one was culture-negative.[9,10] In fact, current guideline recommendations suggest the use of fluoroquinolones for the treatment of moderate-to-severe ischemic colitis, although the supporting evidence is controversial.[3]

We report two cases of ciprofloxacin-associatec IC. The first case involved a 38-year-old woman who developed symptoms on day 4 of ciprofloxacin treatment. The second case involved a 68-year-old woman who developed symptoms one week after completing a 10-day course of antibiotics. Colonoscopy and subsequent histopathology confirmed the presence of IC in both cases.

CASE DESCRIPTION

Patient 1:

A 38-year-old female with a history of GERD and hypothyroidism was prescribed ciprofloxacin for a urinary tract infection, and on day 7 of antibiotic treatment, she developed acute onset abdominal pain with bloody mucoid diarrhea. She was seen in the gastroenterology clinic and did not report any fever, night sweats, recent travel, hypotensive episodes, or any sick contacts. Her labs were notable for fecal calprotectin <5 µg/g, negative C. difficile PCR, and negative enteric pathogen panel. Abdominal CT angiography revealed colonic wall thickening in the transverse colon without any vascular abnormalities. Her symptoms resolved approximately 48-72 hours after the cessation of ciprofloxacin. Colonoscopy performed 10 days after symptom resolution showed subepithelial hemorrhage, erythema, and several small erosions in the transverse colon (Figure 1). Subsequent histopathology examination (Figures 2 and 3) showed colonic mucosa with focal crypt atrophy, rare intraepithelial neutrophils, and mild eosinophilic collapse of the lamina propria, consistent with a diagnosis of focal ischemic colitis. She was examined for routine follow-up 1 month later and returned to baseline without any recurrence of the initial symptoms.

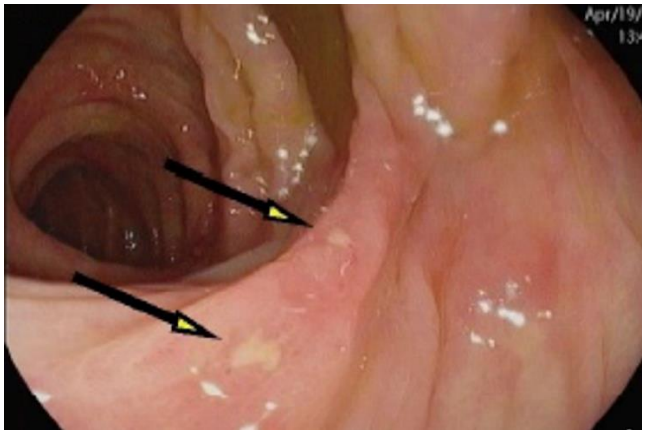

Figure 1: Inflammation and scattered erosions seen in the transverse colon for patient 1

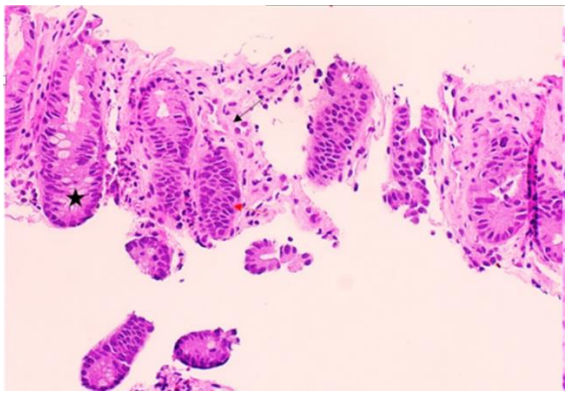

Figure 2: Microscopic changes that are characterized by increased fibrosis shown by dense eosinophilia of the lamina propria with acute inflammatory cells (black arrow), smaller crypts, loss of goblet cells (red arrow), compared to the more normal crypt with intact goblet cells (star) (x200 magnification).

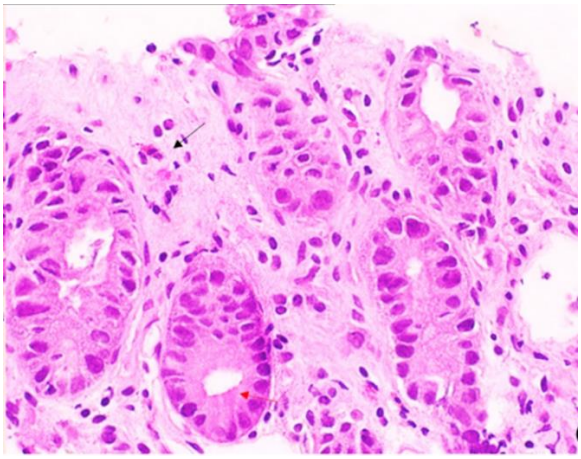

Figure 3: Microscopic changes showing a higher magnification (x400 magnificaiton) of the smaller crypts without goblet cells (red arrow) and increased fibrosis shown by dense eosinophilia of the lamina propia with acute inflammatory cells (black arrow).

Patient 2:

A 68-year-old female with a history of hypertension and hypothyroidism presented to the emergency department with a 2-day history of sudden onset right lower quadrant abdominal pain and tenesmus without diarrhea or hematochezia. One week prior to the onset of symptoms, she had completed a 10-day course of ciprofloxacin for an ear infection. Her labs were notable for WBC (5.8 x10^9/L and hemoglobin 11.9 g/dL, stool studies were not conducted due to the absence of diarrhea on presentation. CT abdomen and pelvis showed diffuse mild circumferential wall thickening of the terminal ileum and cecum, with reactive right lower quadrant mesenteric lymphadenopathy. She was admitted to the hospital and a colonoscopy performed the following day showed superficial ulceration with exudate noted throughout the cecum due to ischemic colitis, and the terminal ileum appeared edematous without ulcerations**.** Histopathological examination of the cecal biopsies revealed fibrinopurulent exudate, necrotic colonic mucosa, surface epithelial denudation, submucosal fibrosis, lamina propria hyalinization, focal crypt withering, and dropout (Figure 4A and 4B). Although these findings were strongly suggestive of ischemic colitis, similar histological patterns can also be seen in infectious colitis; therefore, CMV and HSV stains were requested, which were negative. There was no evidence of granulomas, viral inclusions, or dysplasia. Given the onset of symptoms within one week of completing ciprofloxacin therapy, it was suspected that the etiology of focal ischemic colitis was induced by ciprofloxacin. The patient was treated conservatively and advised to avoid further use of fluoroquinolones. She was followed up in the gastroenterology clinic three weeks later and had resolution of symptoms. A repeat colonoscopy two months after the initial episode showed complete healing of the cecal mucosa.

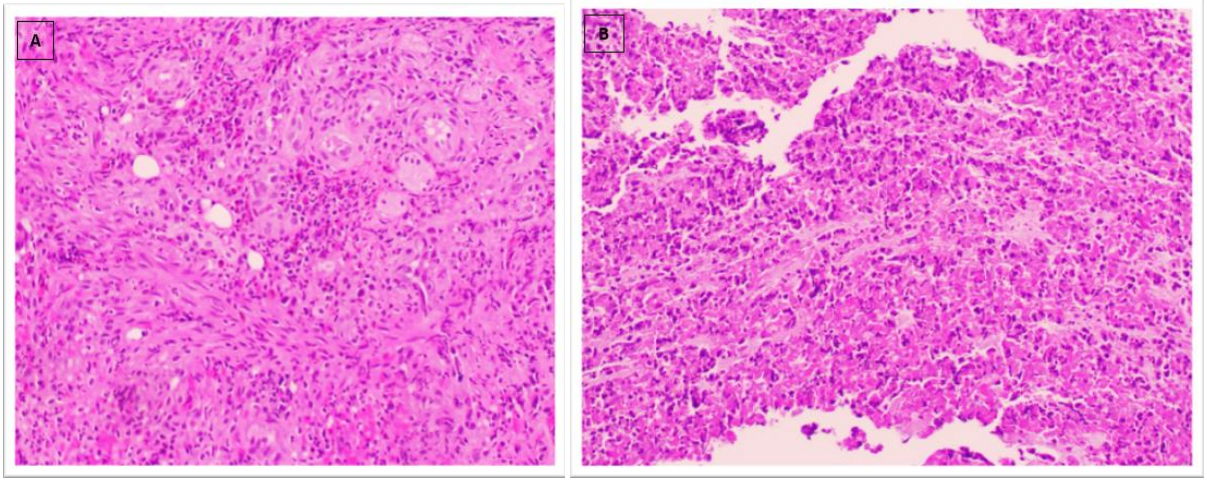

Figure 4: Histopathology of biopsies from patient 2; (A) cecal biopsy shows ulcerated mucosa with severe epithelial denudation, submucosa fibrosis, lamina propria hyalinization, focal crypt withering and drop-out (H&E x200). (B) cecal biopsy shows ulcerated mucosa with fibrinopurulent exudate and necrosis. Fig C (H&E x200).

DISCUSSION

Ischemic colitis following antibiotic use is rare, with most documented cases involving penicillin derivatives rather than fluoroquinolones.[11] Typically, antibiotic-associated colitis is reported to be hemorrhagic due to the isolation of an infectious pathogen that triggers inflammation.[12] To our knowledge, there have been only four previously reported cases of fluoroquinolone-induced hemorrhagic colitis, and none of them showed focal ischemic colitis.[9,10] In this case series, we describe two cases of ischemic colitis following a short course of fluoroquinolones prescribed for routine infections in an outpatient setting. Patient 1 was unique in that she was relatively young, had no cardiovascular risk factors, and developed symptoms while actively taking the antibiotic. The second patient experienced a delayed onset of symptoms, occurring one week after completing the antibiotic course, and her condition was severe enough to necessitate hospitalization. Both patients underwent colonoscopy and histopathological evaluation, which confirmed features of ischemic colitis. Patient 1 had a negative enteric pathogen panel, helping to rule out infectious colitis. Patient 2 did not undergo initial stool studies due to the absence of diarrhea, but her histopathological findings were strongly suggestive of ischemic sequelae and negative for potential infectious etiology. Remarkably, both patients experienced resolution of symptoms within 48–72 hours and had complete remission on routine follow-up with avoidance of further fluoroquinolone use.

Beyond fluoroquinolone antimicrobial activity, they have been implicated in the modulation of collagen metabolism, a feature that has been associated with a constellation of adverse effects such as tendon rupture, aortic dissection, and retinal detachment.[13] While the link between fluoroquinolones and IC induction remains ambiguous, evidence points to their role in triggering conditions with ischemic underpinnings, such as pseudomembranous and hemorrhagic colitis. Pseudomembranous colitis, often a prelude to CDI, and hemorrhagic colitis, typically precipitated by the overgrowth of an infectious pathogen such as Klebsiella oxytoca or Escherichia coli, suggest an ischemic insult to the colon given their histopathological similarities to ischemic colitis.[6,13,14] The occurrence of fluoroquinolone-induced ischemic colitis, devoid of an underlying bacterial toxin involvement, appears to be exceedingly uncommon. From the previously reported cases of fluoroquinolone-induced hemorrhagic colitis, three had isolation of Klebsiella oxytoca, and only one was culture-negative. We suspect that dysregulation of collagen metabolism in the local vasculature compounded by colonic dysbiosis caused by fluoroquinolones may have a role in transiently restricting blood flow and inducing focal ischemic damage, particularly in patients in whom a causative organism is not identified.

The variability in presentation makes the diagnosis of fluoroquinolone-induced IC difficult. Boelser reported the onset of symptoms only a few hours after the first dose.[10] This contrasts with the three cases from Japan reported by Koga, which had late onset of symptoms, with all three patients developing symptoms after 1 month.[9] Our 2 cases ranged in onset of symptoms from 4 to 17 days after the first dose of ciprofloxacin. Although limited by the small sample size, delayed symptom onset, often after completing the antibiotic course, is more common.

CONCLUSION

Although fluoroquinolone-induced ischemic colitis is rare, its increasing incidence has been noted, and this case series provides further evidence of this association. Clinicians should exercise caution when prescribing

fluoroquinolones, given their serious side effects in children, the elderly, and, as highlighted by our first case, the middle-aged population. Current guidelines suggest fluoroquinolones as a treatment option for ischemic colitis. However, our findings underscore the complexity of their use and the need for careful patient evaluation to assess the overall net benefit. These cases highlight the importance of a thorough patient history, particularly in individuals presenting with abdominal pain, hematochezia, or diarrhea. Early recognition of antibiotic-induced colitis is crucial to promptly discontinue the offending agent and to avoid unnecessary further workup. We recommend that all patients suspected of having antibiotic-associated colitis undergo a comprehensive infectious workup, including evaluation for C. difficile and other enteric pathogens, potentially including testing for Klebsiella oxytoca. Previous cases and our cases demonstrate that fluoroquinolone-induced colitis in Clostridium difficile-negative patients tends to be self-limited, and complete recovery can be expected with discontinuation of the antibiotic, thereby highlighting the importance of prompt diagnosis.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Abdullah Aleem], [Blake Purtle] and [Keith Garrison]. The first draft of the manuscript was written by [Abdullah Aleem] and [Blake Purtle], all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST AND FUNDING

All authors of this study declare that there were no conflict of interests. There were no sources of funding used for this project.

HUMAN/ANIMAL RIGHTS

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008(5).

CONSENT

All subjects in this study provided informed consent

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