Case Report

A Case Report and Literature Review of Clostridium difficile Negative Antibiotic Associated Hemorrhagic Colitis Caused by Klebsiella oxytoca

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1. Introduction

Colitis can originate from a wide range of etiologies including ischemic, infectious, and inflammatory bowel disease. A thorough history is imperative to determine the causative nature of the patient’s presenting symptoms. Investigations range from observation and stool analysis, to endoscopy with biopsies, depending upon particular risk factors and severity of symptoms. A growing subset of colitis is antibiotic associated colitis. A majority of these cases are secondary to Clostridium difficile infection (CDI), with an estimated 453,000 cases of CDI throughout the United States in 2011 [1]. Within the most common antibiotics used, antibiotic associated diarrhea has been reported in 5-10% of patients taking ampicillin, 10 to 25% of those who are treated with amoxicillin–clavulanate, 15 to 20% of those who receive cefixime, and 2 to 5% of those who are treated with other cephalosporins, fluoroquinolones, azithromycin, clarithromycin, erythromycin, and tetracycline [2]. Yet, in cases of clostridium difficile-negative antibiotic associated hemorrhagic colitis (AAHC), Klebsiella oxytoca has been isolated at a significantly high rate [3]. In Hogenauer et al’s study, 385 healthy patients had stool testing for Klebsiella oxytoca and in 1.6% of the patients, the pathogen was isolated [4]. Interestingly, Klebsiella oxytoca is found mainly in young healthy individuals compared to patients with CDI who are generally older and with previous hospitalizations [4]. Here we present a case of Clostridium difficile-negative AAHC caused by K. oxytoca infection after taking ampicillin for a urinary tract infection.

2. Case Presentation

A 33-year-old Caucasian female with significant family history of inflammatory bowel disease (IBD) presents with profuse, bloody diarrhea for 5 days and associated tenesmus and urgency. One day prior to admission, she completed
a one-week course of ampicillin for a urinary tract infection and noted that her symptoms began three days after she had initiated treatment. On presentation, patient was hemodynamically stable, afebrile, with mild lower abdominal pain, and a positive guaiac exam. Laboratory findings showed WBC 12.4 bil/L (normal values 3.3–10.7 bil/L), neutrophils 11.0 bil/L (normal values 1.6–7.2 bil/L), Hgb 13.1 g/dL (normal values 12.1–15.0 g/dL), platelets 275 bil/L (normal values 150–400 bil/L), lactic acid 1.4 mmol/L (normal values 0.5–2.2 mmol/L), and liver function tests within normal limits. Initial stool studies that included stool culture, ova and parasite, and *Clostridium difficile* toxin PCR were negative. A colonoscopy was planned as the patient had an extensive family history of IBD and presented with bloody diarrhea. *Klebsiella oxytoca* testing was requested on the stool culture after *Clostridium difficile* PCR came back negative, given her previous use of penicillins. Colonoscopy was notable for ulcerated mucosa with erythema and easy friability, suggestive of moderate colitis throughout the colon with rectosigmoid sparing (Figure 1). Colonic biopsy was remarkable for mucosal congestion and ischemia suggestive of ischemic colitis (Figure 2). Subsequently, requested stool culture was positive for many *Klebsiella oxytoca*. The patient’s hematochezia resolved prior to discharge on day 3 of hospitalization, four days after cessation of ampicillin. She was advised to avoid future use of penicillins and minimize nonsteroidal anti-inflammatory drug (NSAID) use.

The patient has continued to follow with her gastroenterologist 10 months after her colonoscopy. She has had epigastric abdominal pain relieved by daily omeprazole. She no longer has documented hematochezia and there has been no repeat colonoscopy.

3. Discussion

Colitis is a well-known complication of treatment with antibiotic agents, yet the cause of antibiotic associated hemorrhagic colitis is not completely understood. Several mechanisms have been proposed including allergic reaction, mucosal ischemia, and *Klebsiella oxytoca* infection. *Klebsiella oxytoca* positive hemorrhagic colitis is a rare form of antibiotic associated hemorrhagic colitis that is *Clostridium difficile* negative [4]. In 1978, Toffler et al. were the first to describe AAHC [5]. It has been described that, in a majority of cases, penicillin and penicillin derivative administration typically precede AAHC; however, quinolones and cephalosporins have been described as well [6].

There appears to be a greater incidence of AAHC secondary to *K. oxytoca* in the Japanese population [13]. *K. oxytoca* has been reported in the United States as well, yet appears to be more rare. A PubMed literature review was conducted in order to consolidate all English written and adult population case reports on *K. oxytoca* hemorrhagic colitis. Search was conducted via the phrases “Klebsiella oxytoca AND colitis AND case report” and “colitis AND Klebsiella oxytoca.” A total of 74 articles resulted, 18 of which were case reports: 7 written in English, 8 written in French, and 3 written in Japanese. The English written cases range from the years 1999 to 2017 and total 9 cases. Five of the cases are reported from Japan and 4 from cities throughout the United States. Ages range from 37 years to 85 years with 4 males and 5 females. Eight of the 9 cases reported bloody diarrhea. The types of antibiotics reported were three penicillin derivatives (amoxicillin twice and amoxicillin-clavulanic acid once), one macrolide (clarithromycin), three fluoroquinolones (tosufloxacin, enoxacin, and levofloxacin), and one with metronidazole, and one case only reported perioperative antibiotics yet specifics were unknown. Two of the 9 cases noted prior use of a NSAID. Duration of antibiotic use ranged from 1 to 7 days. Interestingly, there was a delay of 3-4 weeks in symptomatology in patients who had taken fluoroquinolones compared to the other patients in which symptoms began closer to time of antibiotic use. Location of endoscopic findings varied throughout the 9 cases. Of the 9 cases, 2 cases were right sided only, 3 cases were from ascending to descending colon, 2 cases only involved the sigmoid colon, 1 case involved the transverse colon, and 1 patient declined colonoscopy. The duration of time for resolution of symptoms ranged from 4 days to 3 weeks. Seven of the 9 cases were treated supportively (one case was treated...
| Author | Year and Location | Patient Age and Gender | Presenting symptoms | Antibiotic prior to presentation | NSAID use prior to presentation | Duration of Abx prior to sx | Endoscopic location of disease | Time to resolution of sx | Treatment |
|--------|------------------|-----------------------|---------------------|---------------------------------|--------------------------------|----------------------------|-------------------------------|--------------------------|-----------|
| Koga et al. [6] | 1999 Japan | 37 y/o Female | Bloody diarrhea and abdominal pain | Tosu-floxacin tosylate 450 mg | none | 5 days* | Entire colon excluding rectum | 2 weeks | Hydration and Loperamide |
| Koga et al. [6] | 1999 Japan | 46 y/o Male | Bloody diarrhea and abdominal pain | Enoxacin | none | 7 days* | Right sided | 3 weeks | Supportive |
| Koga et al. [6] | 1999 Japan | 37 y/o Male | Bloody diarrhea | Levo-floxacin 300 mg | none | 7 days* | Transverse to sigmoid | 3 weeks | Supportive |
| Chen, Cachay, and Hunt [7] | 2004 San Diego, CA | 79 y/o Male | Diarrhea, abdominal pain, hematochezia | none | Aspirin | none | Sigmoid colon | 2 weeks | Cipro-floxacin |
| Philbrick, Ernst [8] | 2007 Iowa | 63 y/o Male | Watery diarrhea and BRBPR | Amoxicillin 500 mg q8h | Ibuprofen 800mg q8h | 5 days | Ascending to descending colon | 1 week | Metronidazole and Levo-floxacin |
| Miyachi, Kinoshita, Tokuda [9] | 2013 Japan | 67 y/o Female | Mucobloody diarrhea and abdominal pain | Clarithro-mycin 200 mg q12h | none | 5 days | Right sided | Not specified | Supportive |
| Sweetser, Schroede, Pardi [10] | 2009 Rochester, MN | 67 y/o Female | Watery diarrhea | Peri-operative abx | none | 3 days | Sigmoid colon | 4 days | Supportive |
| Kazuyuki et al. [11] | 2017 Japan | 65 y/o Female | Abdominal pain and hematochezia | Amoxicillin 1500 mg and Metronidazole 500 mg | none | 1 day | Transverse colon | 6 days | Bowel rest and prednisolone |
| Akanbi et al. [12] | 2017 Chicago, IL | 85 y/o Female | Abdominal pain and mucobloody diarrhea | Amoxicillin - clavulanic acid | none | 5 days | Declined colonoscopy | 5 days | Supportive care |

*Symptoms did not start until ~3-4 weeks after antibiotic cessation.*

Q8h, every 8 hours; q12h, every 12 hours; BRBPR, bright red blood per rectum; abx, antibiotics; ASA, aspirin; sx, symptoms; y/o, years old.
with prednisolone as well). Two of the 9 cases were treated with fluoroquinolones (one of the cases with metronidazole as well) with no reported recurrence of symptoms. In all cases, antibiotic course was either completed or terminated early prior to symptomatic improvement (Table 1). The diagnosis of K. oxytoca can be established by stool [6, 8–10, 12], tissue [7], or bacterial [11] culture. The priority of which culture is of highest yield is uncertain. Of the 9 cases, the most common past medical history was type 2 diabetes mellitus in 3 of the patients, hypertension in 2 of the patients, and systemic lupus erythematosus in 1 of the patients.

Our case is rare given her Caucasian ethnicity; however, as evident by Table 1, K. oxytoca in Caucasians have been reported in the past. The patient’s symptomatology, duration of symptoms, and time for resolution of symptoms are consistent with previous reported cases [8, 9, 14]. There have been reports of symptoms manifesting weeks after antibiotic course, yet these were reported after fluoroquinolone use [6]. Her age and lack of risk factors for hemorrhagic colitis are also consistent with previous described cases [4]. Colonic biopsies is generally misinterpreted as ischemic colitis [6–9], just as in this case. Diagnosis is made upon stool culture of K. oxytoca, which has to be specifically requested. Stool culture of K. oxytoca can result within 24 hours of testing. If suspicion is high enough, and physician is aware of such entity, diagnosis of AAHC secondary to K. oxytoca can be made and can possibly prevent unnecessary and risky diagnostic procedures. The disease course is generally self-limited with withdrawal of the offending penicillin. Avoidance of NSAIDs is recommended as well, as this can exacerbate the colitis in these patients [7, 14, 15]. It is unclear at this time if readministration of ampicillin would lead to a similar episode [16]; however, the patient has been advised to avoid all penicillins.

In conclusion, we presented a case of K. oxytoca colitis in order to raise awareness of the possible etiology of AAHC to be considered in young patients taking antibiotics in which the simple interruption of antibiotic should improve the symptomatology and potentially avoid unnecessary testing or invasive procedures like colonoscopy to be done.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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References

[1] F. C. Lessa et al., “Burden of clostridium difficile infection in the united states,” The New England Journal of Medicine, vol. 372, pp. 825–843, 2015.
[2] J. G. Bartlett, “Antibiotic-associated diarrhea,” Clinical Infectious Diseases, vol. 15, no. 4, pp. 573–581, 1992.
[3] L. Beaugerie, M. Metz, F. Barbut et al., “Klebsiella oxytoca as an agent of antibiotic-associated hemorrhagic colitis,” Clinical Gastroenterology and Hepatology, vol. 1, no. 5, pp. 370–376, 2003.
[4] C. Högenauer, C. Langner, and E. Beubler, “Klebsiella oxytoca as a causative organism of antibiotic-associated hemorrhagic colitis,” The New England Journal of Medicine, vol. 355, no. 23, pp. 2418–2426, 2006.
[5] R. Toffler et al., “Acute colitis related to penicillin and penicillin derivatives,” The Lancet, vol. 312, no. 8092, pp. 707–709, 1978.
[6] H. Koga et al., “Can quinolones cause hemorrhagic colitis of late onset?” Diseases of the Colon and Rectum, vol. 42, no. 11, pp. 1502–1504, 1999.
[7] J. Chen, E. R. Cachay, and G. C. Hunt, “Klebsiella oxytoca: A rare cause of severe infectious colitis: First North American case report,” Gastrointestinal Endoscopy, vol. 60, no. 1, pp. 142–145, 2004.
[8] A. M. Philbrick and M. E. Ernst, “Amoxicillin-associated hemorrhagic colitis in the presence of Klebsiella oxytoca,” Pharmacotherapy, vol. 27, no. 11, pp. 1603–1607, 2007.
[9] R. Miyauchi, K. Kinoshita, and Y. Tokuda, “Clarithromycin-induced haemorrhagic colitis,” BMJ Case Reports, 2013.
[10] S. Sweetser, K. W. Schroeder, and D. S. Pardi, “Pseudomembranous colitis secondary to klebsiella oxytoca,” American Journal of Gastroenterology, vol. 104, no. 9, pp. 2366–2368, 2009.
[11] K. Tanaka, M. Fujiya, A. Sakatani et al., “Second-line therapy for Helicobacter pylori eradication causing antibiotic-associated hemorrhagic colitis,” Annals of Clinical Microbiology and Antimicrobials, vol. 16, no. 1, 2017.
[12] O. Akanbi et al., “Antibiotic-associated haemorrhagic colitis: Not always Clostridium difficile,” BMJ Case Reports, 2017.
[13] A. M. Miller, M. L. Bassett, J. E. Dahlstrom, and W. F. Doe, “Case report: Antibiotic-associated haemorrhagic colitis,” Journal of Gastroenterology and Hepatology, vol. 13, no. 11, pp. 1115–1118, 1998.
[14] M. Yilmaz et al., “Prospective observational study on antibiotic-associated bloody diarrhea,” European Journal of Gastroenterology and Hepatology, vol. 24, no. 6, pp. 688–694, 2012.
[15] G. Gorkiewicz, “Nosocomial and antibiotic-associated diarrhoea caused by organisms other than Clostridium difficile,” International Journal of Antimicrobial Agents, vol. 33, no. 1, pp. S37–S41, 2009.
[16] H. Mouilis and R. J. Vender, “Antibiotic-associated hemorrhagic colitis,” Journal of Clinical Gastroenterology, vol. 18, no. 3, pp. 227–231, 1994.