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Case Report
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Case of Antibiotic Associated Hemorrhagic Colitis in a Burn Patient by *Klebsiella oxytoca*

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Abstract

Antibiotic Associated Hemorrhagic Colitis (AAHC) is the bloody diarrhea caused after recent initiation of antibiotic therapy and its association with *Klebsiella oxytoca (K. oxytoca)* has been proved recently. Antibiotics, especially the penicillins have been found to cause AAHC. Antimicrobials alter the gut microflora eventually leading to mucosal damage. Painkillers such as NSAIDs also play a role in antibiotic associated colitis and diarrhea. This case report is about a burn patient with AAHC and the role of microbiology in its diagnosis. It was evident in this case that immediate discontinuation of antibiotics caused rapid recovery of the patient.

Introduction

Antibiotic Associated Hemorrhagic Colitis (AAHC) cases are on a rise and evidence of *Klebsiella oxytoca* (*K. oxytoca*) contributing to it are being observed recently. AAHC are the cases of Antibiotic Associated Diarrhea (AAD) with causative agent other than *Clostridium difficile* (*C. difficile*) [1]. AAD is a complication of the gastrointestinal tract of hospitalized patients due to antibiotic use, with being *C. difficile* the most common cause [2]. Gram negative bacilli such as *Klebsiella* spp. are prevalent ubiquitously and also in the gut microflora of humans [3]. It is important to note the relation of gut microflora with antibiotics as they are constantly evolving [4]. Here, we discuss the case AAHC by *K. oxytoca* due to penicillin derived antibiotics in burn inflicted adult patient.

Case Presentation

A 24-year-old female was admitted to the burn unit after sustaining burns on 60% of her body. She was treated empirically with piperacillin/tazobactam and vancomycin along with the routine management of burns with silver sulphadiazine cream and fluid reconstruction. The patient was on Non-Steroidal Anti-Inflammatory Drugs (NSAIDS). Five days after antimicrobial therapy was introduced, patient reported moderate abdominal pain around umbilical region and bloody diarrhea 7 to 8 times/day. It was associated with high-grade fever (temperature 103.6°F). Per abdomen palpation was not done because of abdominal burn wounds. However, there were no signs of any septicemia or bacteremia. Complete Blood Count (CBC) showed hemoglobin of 8 g/dL, White Blood Cell (WBC) count of 14,900/mm^3 and platelet count was 1,00,000/ul. CRP was raised to 63.3 mg/dl. Other laboratory findings, including a battery of chemistry tests, prothrombin time and activated partial thromboplastin time, were within the normal range. Stool routine examination showed plenty Red Blood Cells (RBCs) and WBCs. An X-ray of the abdomen revealed distension of the small intestine. Capsule colonoscopy was performed which showed ascending and transverse colon being affected with mucosal edema and hemorrhage. There was no obstruction, perforation of bowel or abscess in colon. The *C. difficile* toxin A and B were not detected by the cytotoxin assay. The BioFire FilmArray (bioMérieux, France) gastrointestinal panel tested negative for all diarrhoeagenic pathogens. A stool sample was sent to the laboratory for fecal culture. It showed the growth of large, mucoid colonies suggestive of *Klebsiella* spp. It was identified as *K. oxytoca*, by Matrix-Assisted Laser Desorption/Ionization-Time of Flight Mass Spectrometry (MALDI TOF MS) (bioMérieux, France) with 99.9% confidence value. Antibiotic sensitivity was done with VITEK 2 (bioMérieux, France) automated system. Isolate was found to be ESBL producer. Cessation of the antibiotic therapy led to resolution of the bloody diarrhea and improvement of symptoms within three days. Colonoscopy was performed four weeks later to rule out chronic inflammatory bowel disease. Histologic analysis of gastric and colonic biopsies showed no signs of chronic bowel disease, but submucosal hemorrhagic residues in the cecum and ascending colon consistent with resolving hemorrhagic inflammation were found. Six weeks after discharge from the hospital, *K. oxytoca* could not be cultured from subsequent stool samples.

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Discussion

K. oxytoca is the Gram-negative bacilli under genus *Klebsiella* and is found ubiquitously in environment and also in humans as commensal microbiota in various sites such as gut, skin, oropharynx, etc. [5]. *K. oxytoca* is known for many infections ranging from mild diarrhea to bacteremia, meningitis and even hospital acquired infections [5]. AAHC is among the recent, most discussed infections due to rise in antimicrobial usage, especially penicillin group of antibiotics. AAHC is a type of AAD presumed to be caused by many factors such as mucosal allergic reaction, mucosal ischemia, and cytotoxin of *K. oxytoca* [6,7]. Few cases of AAHC by *K. oxytoca* are reported both in children and adults with varied geographical distribution [1,6,8-11]. Most cases have been reported in France, followed by Japan and Austria and one case was reported in the United States [1]. The onset is sudden, with moderate - severe lower abdominal pain with or without cramping, and up to 15 to 20 loose stools in 20 hours. These clinical findings are not specific for AAHC and may exist in the presentation of any form of colitis [11]. Previously published case reports and series have demonstrated that *K. oxytoca* was present in the stool of most patients with AAHC. However, two case reports, in which *K. oxytoca* was the presumed cause of colitis in patients who had not received antibiotic therapy deserve special attention, as they suggest that *K. oxytoca* may be pathogenic even in the absence of antibiotics under certain circumstances [12,13].

Several studies have documented a strong association between *K. oxytoca* in stool and AAHC in *C. difficile*-negative patients [8,14]. Hogenauer et al. developed a rat model to establish that *K. oxytoca* follows the Koch's postulates of relation between microbe and disease, to be called as a pathogen for AAHC [9]. Certain key pathogenic factors associated with *K. oxytoca* being causative agent for AAHC have been identified. First is an inherent resistance of *K. oxytoca* to penicillin and its derivatives due to the production of enzyme B-lactamase. When penicillin derivatives are given to patients who harbor *K. oxytoca* in their gut microflora, it leads to growth of only *K. oxytoca* causing the damage [1]. In the present case, the use of piperacillin/tazobactam was the culprit. Additionally, cytotoxin released by *K. oxytoca* leads to epithelial death, mucosal damage and thus hemorrhagic diarrhea [10]. The gut microflora of humans is essential for maintaining the gastrointestinal intactness, the immune system balance and the energy metabolic pathway of the host. Any modification in this complex network can cause pathological changes in the gut including inflammation [4]. Although, antimicrobials have been one of the paramount discoveries in the world, their widespread use for a particular infectious disease does not necessarily eliminate the specific pathogens targeted but also affect the beneficial commensal microbiota [15]. As the antibiotics become more and more broad spectrum, a whole lot of host microbiota is affected including those in gut. Thus, the complex network of host microbe interaction and immune homeostasis is compromised [15]. The host defense mechanism of colonization resistance against the pathogen is also affected [16]. Antibiotics use thus can cause osmotic, functional or secretory diarrhea by impairing the metabolism, excretion of bile acids or increasing gut motility [2].

AAD caused by *C. difficile* and by *K. oxytoca* vary in clinical history and also in clinical presentation. It is observed that AAHC by *K. oxytoca* usually occurs in young individuals after brief treatment with penicillin derivatives such as amoxicillin-clavulanate, amoxicillin, ampicillin and piperacillin combinations like in our case. Whereas, AAD by *C. difficile* occurs mostly in old, hospitalized patients [6,17]. AAHC cases present with diffuse mucosal oedema and hemorrhagic lesions in the segments of ascending colon as observed in the colonoscopy findings. Thus, giving clinical picture of hemorrhagic diarrhea. However, the commonly notified AAD caused by toxin producing *C. difficile* presents differently causing watery diarrhea in mild to moderate conditions [9,17]. Furthermore, the differential diagnosis of enteropathogenic diarrhea from other bacteria such as *Shigella*, *Salmonella*, *Aeromonas*, *Plesiomonas*, EHEC was be ruled out by the fecal culture test, toxin assay. Ischemic colitis can be ruled out by colonoscopy, CT scan or even by the mere fact that patient improved after stopping antibiotics. Diagnosis of the *K. oxytoca* cytotoxin can be done by using Hep-2 cell culture assay which is impractical as it has a very long turn-around time [10]. The role of clinical microbiologist is instrumental in diagnosing this unusual cause of diarrhea.

In the present case, cytotoxin production of the isolated *K. oxytoca* strain was not verified. Four findings support our diagnosis of *K. oxytoca* –induced AAHC in the present case. Short treatment with piperacillin/tazobactam was followed by acute onset of abdominal pain and bloody diarrhea. Additionally, our patient had right-sided colonic inflammation which was in contrast to colitis caused by *C. difficile* where left colon is mainly affected. Furthermore, *K. oxytoca* could be isolated from our patient's stool, whereas results from analysis for other known intestinal pathogens were negative. Our patient had received concomitant NSAIDS before the onset of bloody diarrhea which is believed to contribute to AAHC caused by *K. oxytoca* and was noted in two thirds of the patients in a recent series [9]. Withdrawal of the causative antibiotic treatment resulted in the spontaneous resolution of symptoms. This course is consistent with findings in adults in whom symptoms resolved within 3 to 7 days after cessation of therapy [9]. The AAHC usually resolves immediately with discontinuation of antibiotics and the NSAIDs. However, some cases turn serious and should be managed accordingly. Similar case where the first burn patient who developed AAHC by *K. oxytoca* was notified in USA in 2009. This patient also responded rapidly to discontinuation of piperacillin/tazobactam therapy and improved by alternative management with meropenem and levofloxacin [1]. AAHC following antibiotic therapy with cephalosporins and quinolones has also been observed in certain studies [18]. Several studies have shown that NSAIDs exaggerate the colitis and diarrhea of various causes including pathogenic bacteria such as *K. oxytoca* [9,19,20].

We suggest that *K. oxytoca* should be considered in the differential diagnosis of potential intestinal pathogens. Best diagnostic method for AAHC is debatable. In resource limited country such as India, basis of diagnosis for AAHC by *K. oxytoca* can be clinical symptom of bloody diarrhea, negative Clostridial toxin A/B test, fecal culture on a differential culture media positive for *K. oxytoca* only, evidence of segmental or ascending colon thickening and improvement of clinical condition by ceasing the use of penicillin derivatives. We consider it important to draw attention to toxigenic *K. oxytoca*, since patients may have received a misdiagnosis of ischemic colitis with spontaneous resolution in the past, and since the diagnosis of antibiotic-associated hemorrhagic colitis has consequences for the care of such patients, who could be harmed by unnecessary treatment with drugs.

Conclusion

We describe here the classic presentation of AAHC caused by *K. oxytoca*. For patients with blood diarrhea after antibiotic treatment, *K. oxytoca* should be considered. Basis high clinical suspicion by physician and clinical correlation with microbiological findings diagnosis of AAHC secondary to *K. oxytoca* can be made.

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