A case of Rifampicin induced pseudomembraneous colitis

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ABSTRACT

We report a case pf pseudomembranous colitis that developed in a patient with tuberculous abdominal lymphadenopathy during treatment with rifampicin. The patient had delayed presentation (3 months) after the start of rifampicin. She had one relapse after 2 months that was successfully treated, and she finished her antituberculosis therapy without any further relapses. Awareness of this serious complication of rifampicin therapy should be encountered.

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Pseudomembraneous colitis (PMC) was first described in the 19th century and has subsequently been recognized with increasing frequency as a serious, sometimes lethal gastrointestinal disease. *Clostridium difficile (C.difficile)* was identified as a cause of antibiotic-associated PMC in 1978.[1] Clostridium difficile is a gram-positive spore-bearing anaerobic bacterium that was initially reported to be a component of the normal intestinal flora of newborn infants by Hall and O'Toole.[2] *Clostridium difficile* associated diarrhea is one of the leading causes of nosocomial enteric infections.[3,4] It can affect as many as 10% of patients hospitalized for more than 2 days.[5] The most common predisposing factor for *C.difficile* colitis is the use of antibiotics such as ampicillin, clindamycin, and cephalosporins. It has not been clearly established following aminoglycoside, sulfonamide and antimicrobial agents whose activity is restricted to fungi, mycobacteria, parasites or viruses.[4,6] Rifampicin is a pivotal antimicrobial in the treatment of tuberculosis; a large number of patients are exposed to its potential adverse effects each year. We are reporting a case of PMC following rifampicin treatment with a long latency period; one relapse and the patient was able to finish her course of anti-tuberculosis therapy successfully.

Case Report. A 43-years-old Saudi female came to our medical outpatient department for further evaluation of abdominal pain. The patient was complaining of epigastric pain for 2 years that was diagnosed as irritable bowel syndrome. The pain became more severe over the last 6 months, it is constricting in nature, radiating to the back, aggravated by spicy food, has no relieving factors and associated with loss of appetite and weight (patient does not know how much). There was no history of vomiting or changing bowel habit. She gave history of menorrhagia of 4 months duration for which she was followed by gynecologist. Her systemic review was irrelevant and apart from history of Bilharzias 15 years ago that was treated, no past history of significance was detected. She is a housewife, married with 3 children, and non-smoker. Her family and allergic history were irrelevant. She was not on any regular medications recently. On examination; she was pale but not jaundice. Her neck, chest and cardiovascular

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examinations were negative. Her abdominal examination revealed epigastric tenderness with no palpable masses or organomegaly. Bowel sounds were normal. Her initial investigations showed hemoglobin of 8.8 g/dl (microcytic hypochromic) with normal white blood cell and platelets. Her serum iron and ferettin were low. Her erythrocyte sedimentation rate was 118/first hr. Results of renal and liver functions were normal as well as stool analysis and chest x-ray. Gastro duodenal endoscopy was carried out for her and it did not reveal any abnormalities. Abdominal ultrasound was carried out and it showed a focal hypo echoic oval lesion at the pancreatic head measuring 3.5 x 0.7 cm, no calcification within the mass or within the rest of the pancreatic parenchyma. Liver, spleen, kidneys were normal and further evaluation was suggested by computed tomography (CT) guided biopsy. A CT scan of the abdomen was carried out and it showed a small well defined hypodense lesion below the left lobe of the liver, measuring 2x2.5x2.5 cm, which showed faint calcification and homogeneous enhancement after intravenous contrast media mainly located at the junction of the body and head of the pancrease. Findings were suggestive of pancreatic cyst adenoma. The patient was admitted, and on further questioning she did not give any history suggestive of endocrine pancreatic tumor. Laparotomy was carried out and it showed an enlarged prepyloric lymph node and another lymph node behind the head of the pancrease. Incisional biopsy was taken and caseating material came out. Histopathology showed chronic granuloma suggestive of tuberculosis. The patient was started on anti-tuberculosis treatment (rifampicin, isoniazide, pyridoxine, pyrazinamide, and ethambutol) and iron supplement. She showed remarkable clinical and laboratory improvement with gaining weight and drop in erythrocyte sedimentation rate to 2/first hour. Three months latter she presented to the medical clinic with history of watery diarrhea (15-20 times/day) and lower abdominal pain. There was no mucous or blood. Stool analysis and culture were normal. Complete blood count showed leuckocytosis of 14.2x103/mm^3. Colonoscopy was carried out, and it showed normal sigmoid and distal colon, in the cecum the mucosa up to 60 cm have multiple aphthus ulceration with cobble stoning appearance and pseudomembranes **(Figures 1 & 2)**. Histopathology showed moderately acute and chronic inflammation with ulceration and fibrin deposition highly suggestive of pseudomembranous colitis. Patient was started on metronidazole 500mg three times/day for 2 weeks. Her diarrhea improved within 2-days and repeated colonoscopy showed normal mucosa **(Figure 3)**. Eight weeks latter the patient presented again with history of watery diarrhea and lower abdominal pain with normal stool analysis and culture. Repeated colonoscopy showed inflammation in the cecum with edema and multiple aphthus ulceration. Patient was given another course of metronidazole 500mg 3 times/day for 2 weeks, and she showed remarkable improvement. She finished her anti-tuberculosis treatment without any further relapses.

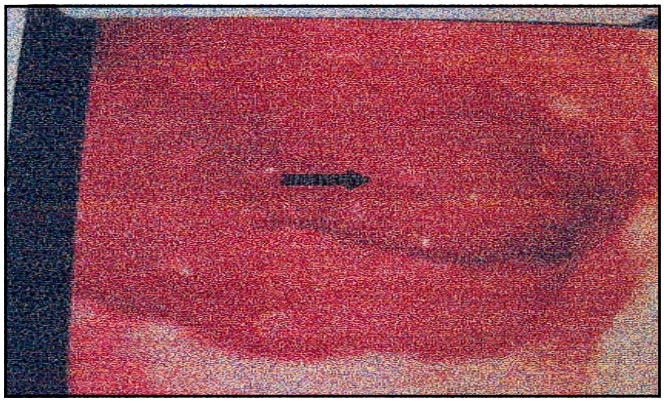

Figure 1 - Colonoscopy showing aphthus ulceration and pseudomembranes.

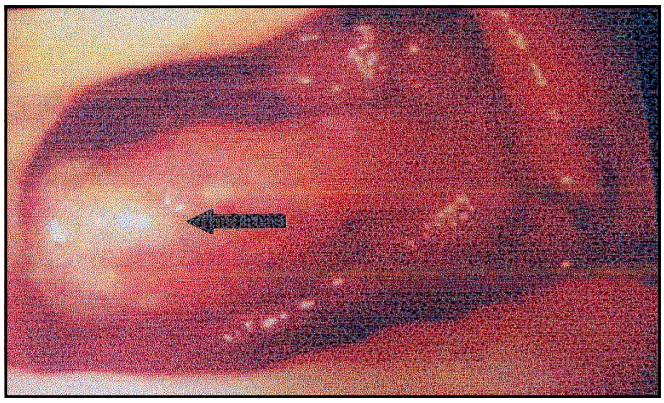

Figure 2 - Colonoscopy showing aphthus ulceration and pseudomembranes.

Discussion. Pseudomembraneous colitis following anti-tuberculosis therapy is an uncommon problem. Reports of rifampicin induced PMC began appearing in the literature as early as 1980. There has been a report of 11 cases only of antibiotic-associated colitis due to antituberculosis therapy, with equal sex distribution and mean age of 51 years at presentation.[7] Rifampicin was thought to be the responsible agent. Isoniazide, pyrazinamide and ethambutol have never been reported as a cause of PMC. This may be as their antibacterial spectrum of activity dose not significantly disturbs the intestinal flora. However, rifampicin has a broader antimicrobial spectrum of activity.[8] Two reports documented recurrence of PMC following readministration of rifampicin.[7,8] *Clostridium difficile* is one of the most common hospital acquired infections. It colonizes the human intestinal tract only after the normal gut flora has been altered by antibiotic therapy and is the causative organism of antibiotic associated

colitis. *Clostridium difficile* infection causes a spectrum of conditions in susceptible patients, ranging from the asymptomatic carrier state to severe fulminant disease with toxic mega colon.[9] The typical presentation is acute watery diarrhea with lower abdominal pain, starting during or shortly after antibiotic administration. Typical features of *C. difficile* associated colitis in advanced stages (10) include watery diarrhea with as many as 15-30 time stool/day, crampy abdominal pain, fever, leuckocytosis (ranging form 10 x103/mm^3- 20x103/mm^3, sometimes up to 40x103/mm^3). Our patient had diarrhea around 20 times/day with leucocytosis, and she presented 3 months after the start of rifampicin. This latency period, such as between rifampicin exposure and development of symptoms, is relatively long; there had been only one report of latency period of 4 months.[7] The diagnosis of *C.difficile* infection is established by the bioassay of stool for *C.difficile* cytotoxins or by immunoassay for toxins in stool.[10] However, sigmoidoscopy, colonoscopy or abdominal CT scan can provide useful diagnostic information. Several studies have documented the superiority of colonoscopy over sigmoidoscopy in detecting pseudomembranes[11] as one third of the patients may have lesions restricted only to the right colon without any significant diagnostic features in the recto sigmoid.[12] Our patient had changes only in the right colon without many changes in the recto sigmoid. For our patient immunoassay for *C.difficile* toxin in stool was not carried out as it is not available in our hospital and we made the diagnosis by colonoscopy. Therapy for PMC includes discontinuation of the implicated antimicrobial agents, non-specific support measures and in some cases with severe diarrhea or if you need to continue treating the original infection, oral antimicrobial agents as metronidazole or vancomycin can be used. Comparative clinical trials indicate that these drugs are therapeutically equivalent.[13] Approximately 15-20% of patients treated for PMC relapse following discontinuation of therapy.[9] Relapses do not appear to be related to persistence of resistant organisms.[14] The exact cause of relapses has not yet been known, but impairment of the host immune response to infection may be one contributing factor.[15] The timing of relapse of symptoms ranges from 2-30 days but typically occurs within few days after complete therapy. Our patient presented 8 weeks after discontinuation of metronidazole, and she was able to finish her anti-tuberculosis treatment without any further relapses.

In conclusion, rifampicin is a rare reported cause of PMC; awareness of this serious complication is warranted.

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