Case Report

A CASE REPORT OF PSEUDOMEMBRANOUS COLITIS, NOT ASSOCIATED WITH PRIOR ANTIMICROBIAL DRUGS TREATMENT

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ABSTRACT

Clostridium difficile associated colitis /CDAC/ is an inflammatory bowel disease with infectious etiology and specific endoscopic and histological data. It is the most common cause of acute diarrhea syndrome, occurring during hospitalization. CDAC usually appears after treatment with antimicrobial agents, such as Clindamycin, Glycopeptides, Fluoroquinolones, II-nd and III-rd gen. Cephalosporins. Sometimes CDAC is triggered by other factors – nonsteroid anti – inflammatory drugs (NSAIDs), chemotherapy drugs, ulcerative colitis, Crohn’s disease and others. The typical complaints of the patients with CDAC are: abdominal pain, diarrhea, fever, and leukocytosis. Since pseudomembranous colitis is associated with C. difficile infection, stool testing and empirical antibiotic treatment should be initiated when suspected.

The case report is about 83 years old woman with clinically, laboratory, endoscopic and histological data typical for pseudomembranous colitis, without a history of previous antibiotic therapy. The case shows that CDAC may be atypical and the disease should be well-known and expected, especially in immunocompromised or comorbid people over 65 years old with history for NSAIDs or chemotherapy drugs treatment, with acute diarrhea.

Key words: Clostridium difficile, pseudomembranous colitis, antimicrobial therapy

INTRODUCTION

Clostridium difficile – associated colitis (CDAC) is an inflammatory bowel disease with infectious etiology, acquired most often after antimicrobial therapy (Clindamycin, Glycopeptides, Fluoroquinolones, Cephalosporins second and third generation) and associated imbalance of normal intestinal flora. CDAC is the most common cause of diarrhea syndrome that developed during hospital treatment.

C. difficile infection is the result of ingesting the spores of the microorganism, which vegetative forms multiply in the body and produce toxins causing diarrhea and pseudomembranous colitis (PMC) (1).

C. difficile are an obligate anaerobic, spore forming Gram-positive and toxin-producing rods. Spores of bacteria are widespread in nature. In 1935 C. difficile were discovered by Hall and O’Toole as commensal microorganisms, part of the normal flora in neonates.

In 1978 they were identified as the toxin-producing which are the major cause of pseudomembranous colitis (2, 3).

The pathogenesis of CD infection consists of the ingestion of spores of toxigenic clostridia, some of which survive in gastric acidity, reach the small intestine where they become vegetative, toxin-producing forms that multiply and colonize the lower gastrointestinal tract. C. difficile produce two
types of exotoxins – Toxin A (enterotoxin) and Toxin B (cytotoxin). Some strains (BI / NAP1 / 027) also produce a third exotoxin - a binary toxin that potentiates the action of Toxin A and B, and determines the severe course of the infection (4, 5). As a result of these toxins, a barrier dysfunction of epithelial cells, diarrhea, and pseudomembrane formation in the colon are observed. Once released in the colon, the toxins bind to cell-surface receptors and are internalized within the targeted cells.

Inside the cell, they cause glycosylation of small proteins involved in cell signaling and regulating pathways. This, in turn, leads to cytoskeleton disruption, causing cell morphologic changes, cytokine activation, and eventual cell death. In addition, tight junctions between neighboring colonic cells are affected, allowing infiltration by neutrophils and causing an inflammatory response characteristic of colitis. Pseudomembranes form via this influx of neutrophils into the mucosa and further activation of the native immune system by the toxins. Activation of macrophages and monocytes causes the release of pro-inflammatory cytokines like interleukin (IL)-1, IL-8, tumor necrosis factor (TNF), and leukotriene B4, which lead to additional mucosal injury and focal microabscesses and pseudomembranes formation.

**Risk factors** for PMC development are: previous antibiotic therapy (2-4 weeks prior to the first symptoms), treatment with proton pump inhibitors (PPIs), nonsteroid anti-inflammatory drugs (NSAIDs), corticosteroids, cytostatics, antidepressants, females, Caucasian white race, body mass index (BMI) > 35, immunocompromised patients, comorbidities /autoimmune inflammatory bowel disease (IBD), chronic kidney disease/, long hospital stay and frequent hospitalizations in the last 3 months (6, 7).

**Macroscopically** PMC is characterized by so-called pseudomembranes, which are usually confined to the mucosa of the large intestine and are initially manifested as white-yellowish plaques with a diameter of 1-2 mm. As the disease progresses, pseudomembranes merge to form larger, confluent plaques that engage the entire circumference of the colon. Typically, the entire colon is affected, but 10% of patients have recta sparing.

**Microscopically**, the pseudomembranes have an attachment zone to the underlying mucosa and consists of necrotic polymorphonuclear leukocytes, fibrin, mucin and detritus. The epithelium is eroded with focal necrosis and neutrophil infiltration of the mucosa (8, 9).

Diarrhea is the most common manifestation of PMC. Stools are almost never grossly bloody and range from soft and unformed to watery or mucoid in consistency, with a characteristic odor. Patients may have as many as 20 bowel movements per day. Abdominal pain, fever, asthenia, and weight loss were also observed. In severe forms, pronounced leukocytosis and hypoalbuminemia may occur.

**Complications** include fulminant colitis, intestinal perforation, toxic megacolon, severe dehydration and electrolyte disorders, intestinal obstruction (ileus) and even death.

**The diagnosis** of CDAC is based on a combination of clinical criteria: (1) diarrhea (≥3 unformed stools per 24 h for ≥2 days), with no other recognized cause; plus (2) toxin A or B detected in the stool, toxin-producing **C. difficile** detected by stool culture, or pseudomembranes seen in the colon. Typical endoscopic changes are visualized only at 50% of patients with diarrhea who have a positive stool culture and toxin assay for **C. difficile**. The Lower GI endoscopy is a rapid diagnostic tool in severely ill patients suspected for PMC. The negative result in this examination does not rule out infection with **C. difficile**.

**Treatment recommendations** of CDAC include: discontinuance of antibiotic treatment (if present), adequate parenteral rehydration, avoiding application of antiperistalsis agents and opioid analgesics, which may mask symptoms and possibly worsen disease. It is recommended that all medications be administered orally (incl. vancomycin and metronidazole). The usual dose of metronidazole in patients with mild to moderate pseudomembranous colitis is 1500 mg / daily, divided into three intakes for at least 10 days. In the absence of treatment with metronidazole, the agent of choice is vancomycin at a dose of 125 mg orally four times a day. It is also appropriate to administer Saccharomyces boulardii at a dose of 500 mg / daily [1,9,10].

**Case report**

An 83-years-old woman, admitted at the emergency department with diarrhea of 48 hours, with 4-5 defecations/24 h of watery, slime-bloody stools, diffuse abdominal pain,
dyspeptic symptoms, progressive asthenia and weight loss. No recent antibiotic treatment was reported in a targeted questioning. Reports of regular NSAIDs (acetylsalicylic acid in anti-aggregate dose).

**Comorbidities:** Hypertension and Cerebrovascular disease. From a past history: data on ischemic stroke and surgical intervention for endometrial cancer with subsequent chemotherapy and radiotherapy. From the family history - no data on the family burden of gastrointestinal tract disease.

**Clinical examination** – the patient is in impaired general condition, with pale skin and mucous membranes with reduced turgidity and elasticity, dry and flat tongue, subfebrile to 37.5 °C. Respiratory system – in the age limit. Cardiovascular system – rhythmic, high frequency heartbeat up to 95 bpm, weakened heart tones, no murmurs. Registered hypotension up to 100/60 mmHg at hospitalization. Abdominal status – soft - elastic abdominal wall allowing deep palpation, without clinical evidence of muscular defence, with palpatory tenderness in the left abdomen, accelerated peristalsis, no manifest hepatosplenomegaly. Rectal digital examination showed no evidence of palpable tumor formations in the rectum, only the presence of large quantity of bloody-slime stools in the rectal ampulla.

**Laboratory tests** showed leukocytosis up to 12.18 x 10^9 / l. with neutrophilia / St - 9; Sg - 76) and lymphopenia (Lym - 11), as well as elevated CRP (90 mmol/l) and normal serum creatinine, urea, total protein and serum albumin. The abdominal ultrasound showed no abnormalities.

The patient was given parenteral Ringer infusion therapy in adequate volume and symptomatic spasmolytic therapy. Since diverticulitis was included in the differential diagnosis in the patient, a parenteral antibiotic (Ciprofloxacin) was also empirically included in the treatment. Due to clinical evidence of acute bleeding from the lower gastrointestinal tract, parenteral hemostatics (Etamsylate, Ca gluconate, Phytomanadion, Vit. C) were also administered. In parallel with the therapy, on the second day of the hospitalization the bowel preparation with solution of Endofalk® was performed.

**Colonoscopy** revealed a diffuse hyperemic, contact and spontaneous sanguinous mucosa with a reduced, partially obscured vascular pattern and glare, dotted with multiple flat erosions, single superficial, linear ulcerations covered with dense, hardly separable dirty white membranes (Figure 1).

![Figure 1. The Lower GI endoscopy reveals diffuse hyperemic, contact and spontaneous sanguinous mucosa with a reduced, partially obscured vascular pattern and glare, dotted with multiple flat erosions, single superficial, linear ulcerations covered with dense, hardly separable dirty white membranes](image-url)

These changes were visualized in all sections of the colon, with the exception of ascending colon and caecum, and the most manifest were in the area of descending and transverse colon.

Of the affected areas, twenty biopcies were taken, which were fixed in a 10% formalin solution and sent for pathological examination. A sample for microbiology testing was also
sent. The lower GI endoscopy also visualized single, inflamed diverticula in the sigmoid colon, as well as a sessile polyp with 6 mm in diameter, which was resected and sent for histological analysis. Following the colonoscopy, intravenous administration of Ciprofloxacin was discontinued due to the high-grade endoscopic data for pseudomembranous colitis, and metronidazole 1500 mg / daily and Saccharomyces boulardii (Enterol®) 500 mg / daily were added to the therapy.

**The C. difficile Toxin A / B test** showed a positive result, and pathogenic and conditionally pathogenic intestinal bacteria (Salmonella, Shigella, Klebsiella, E. coli, Yersinia and Candida) were excluded from the stool culture.

The histopathological analysis of the biopsy specimen showed hyperplasia, swollen mucous membrane, destructed basal epithelium and the presence of a mononuclear inflammatory infiltrate presented by lymphocytes, plasmatic cells and single eosinophils. The crypts visualized highly deformed, filled with mucus, cellular debris and multiple neutrophilic leukocytes – pathohistological data characteristic of pseudomembranous colitis (Figure 2).

As a result of the treatment, on the fifth day of therapy, the patient experienced a significant improvement in the general condition, a significant decrease of the acute phase proteins (CRP - 60 mmol/l) and the leukocytes (5.7x10^9/l) and the patient was dehospitalised with one bowel movement for 24 hours with no impurities), without abdominal pain and dyspeptic symptoms. The patient was given detailed dietetic guidance compliance and recommendation for continuation of treatment with Metronidazole 500 mg, three times per day for another 10 days and Enterol® 250 mg, two times per day for a further 14 days at home, as well as recommendations for discontinuation of acetylsalicylic acid and NSAIDs.

**CONCLUSION**

It is a case report of a C. difficile associated colitis in a patient without a history of prior antibiotic therapy. Cases such this are rare in the clinical practice and indicate that pseudomembranous colitis not associated with antibiotic therapy may develop. Knowledge of the disease and the options for its therapy as well as its inclusion in the differential diagnosis in patients with acute diarrhea, especially in immunocompromised patients over the 65 years of age and a history of long-term NSAIDs or chemotherapeutics is rarely important.

**REFERENCES**

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