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Review Article

Pseudomembranous colitis

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ABSTRACT

Pseudomembranous colitis is an inflammatory condition of the colon that is most often a manifestation of Clostridium difficile infection. If laboratory testing and endoscopic finding for Clostridium difficile infection is negative, then other less common etiologies should be sought for to identify the correct diagnosis. Ischemic colitis, inflammatory bowel disease, medications, chemicals, vasculitis, and multiple infectious pathogens are responsible for non-clostridium difficile Pseudomembranous colitis. Exposure history, chronic medical problems and a current medication list will aid in narrowing the differential diagnosis. Histology varies significantly with underlying etiology and can establish the diagnosis. Treatment is specific to the underlying etiology. The purpose of this review article is to aware clinicians and other healthcare professionals about various etiologies of pseudo membranous colitis along with its histological finding and treatment.

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INTRODUCTION

Clostridium difficile (CD) was first described in 1935, but its association with antibiotics and Pseudomembranous colitis (PMC) was not described until the 1970s, corresponding with an increased use of broad-spectrum antibiotics.[1,2] Clostridium difficile is an obligate anaerobic organism and toxin-producing gram-positive rod with the ability to form spores.[3,4] Pseudo membranous colitis is a manifestation of severe colonic disease associated with CD, which is transmitted among humans through feco oral route. The relationship between the bacillus and humans was once thought to be commensal but CD has emerged as a major enteric pathogen globally. In Nepal, Clostridium difficile infection (CDI) is diagnosed by high index of clinical suspicion in patient with immunocompromised status or in patients with abdominal symptoms in whom there is a prior history of antibiotics use.

PATHOGENESIS

Most disease-causing strains produce two large protein exotoxins, toxin A and toxin B. Once released in the colon,

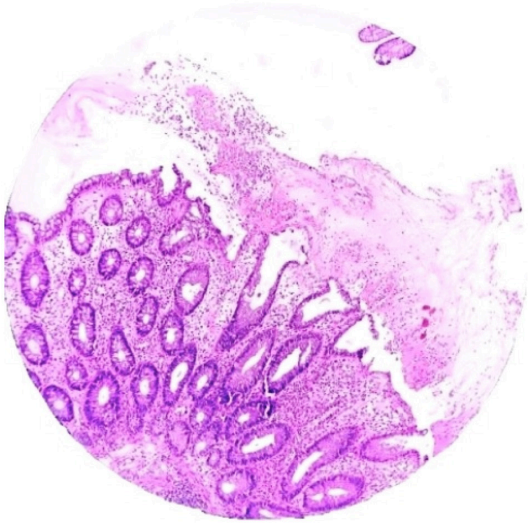

Figure 1: *Photomicrograph showing typical volcanic eruption with exudates (HE stain; X100).*

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.[5] Pseudomembranes form via this influx of neutrophils into the mucosa and further activation of the native immune system by the toxins occur. Activation of macrophages and monocytes causes the release of pro-inflammatory cytokines like interleukin (IL)-1, IL-8, tumor necrosis factor, and Leukotriene-B4, which lead to additional mucosal injury and focal microabscess and pseudomembrane formation.

On endoscopic examination, PMC is characterized by elevated yellow-white nodules or plaques that form pseudomembranes on the mucosal surfaces of the colon.

RISK FACTORS

Antibiotics like clindamycin, penicillin, fluoroquinolones and cephalosporins are typically associated with Clostridium infection, but the disease can occur with almost any antibacterial agents including vancomycin and metronidazole. The risk of CD infection and the severity of infection increases with the age.[6,7] The age is an important non modifiable risk factor. During an outbreak, risk of contracting CD is 10 times as high among persons older than 65 years, as among younger inpatients.[8] Most CD infections are hospital acquired but community acquired infection has increased dramatically in the past decade.[9] Community acquired CD infection occurs in patients who are younger and more often have had no clear exposure to antibiotics or other known risk factors. Antineoplastic chemotherapy and severe underlying disease contribute to susceptibility. Symptoms of colitis do not develop in all colonized persons, majority of infants are colonized with CD but are asymptomatic possibly owing to the lack of toxin binding receptors in infant gut.[10-12]

SIGNS AND SYMPTOMS

Accompanying signs and symptoms include fever, leukocytosis and abdominal cramping.

Severe cases can present with profound leukocytosis, hypovolemia, hypotension, hypoalbuminemia, renal dysfunction, and reactive arthritis. It is estimated that 3–8% of patients with CD infection develop fulminant infection including severe ileus, toxic megacolon, colonic perforation with subsequent peritonitis, and septic shock; many of these patients require colectomy and have an overall high mortality.[13] These symptoms are usually precipitated by using antibiotics but can also follow the use of chemotherapeutic drugs and immunosuppressive therapy.[14] Leukocytosis is a prominent feature of CDI. A retrospective study of 70 hospitalized patients found a significant difference in the white blood cell (WBC) counts of C. difficile-positive and C. difficile-negative patients (15,800/mm^3 vs. 7700/mm^3), demonstrating the utility of a frequently obtained lab marker in initial suspicion and subsequent diagnosis of CDI.[15,16] Newer advances in the diagnosis of CDI include nucleic acid amplification tests (NAAT) such as polymerase chain reaction (PCR), and stool testing for glutamate dehydrogenase (GDH).

HISTOPATHOLOGICAL FINDING AND DIFFERENTIAL DIAGNOSIS

Figure 1 shows the histopathological findings in a 74 year male patient whose tissue sample was sent to our centre, who has history of diarrhea and use of antibiotics. On colonoscopy, colon was poorly visualized and there was pseudmembrane with raised yellow white plaques. On histologic examination, PMC caused by CD include volcanic eruptions with superficial exudates as shown in figure 1.

The exudate consists of mucin, necrotic material and other inflammatory elements from the lamina propria on to the epithelium leading to pseudomembrane formation. The intervening mucosa may be slightly edematous to unremarkable. In fulminant cases there is transmural involvement.

The most common histological differential diagnosis is ischemic colitis, where watershed area is seen mostly in ssigmoid colon. Of all the findings, hyalinization of the lamina propria is the most specific finding for ischemic colitis.[17] Mucosal atrophy with occasional pseudo membranes and pseudo polyps are seen in more severe ischemia.[18] Chronic

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ischemic colitis is typically characterized by preserved crypt architecture, a mixed inflammatory infiltrate extending into the lamina propria, and deposition of collagen in a band-like or irregular distribution below the epithelium.[19] Similarly, inflammatory bowel disease is characterized by the presence of lymphoplasmacytosis, cryptitis and crypt abscess which is easily distinguished from the PMC.

Medications and chemicals can cause pseudomembranous colitis by localized ischemia and/or inflammation. Alosetron, cocaine, dextroamphetamine, gold, and glutaraldehyde are notorious agent for PMC.[20-24] Glutaraldehyde, used to disinfect endoscopes after use, and its association with PMC is a well-described phenomenon that occurs after inadequate rinsing of the solution from cleaned endoscopes. Presenting symptoms often occur within 48 hours of initial colonoscopy, and include abdominal pain, tenesmus, mucoid or bloody diarrhea, and fever.[16] Histological examination reveals depletion of the protective mucin layer in the colon, breakdown of the epithelium extending into the luminal surface of the mucosa and glands, neutrophilic exudate, hyperemia and edema within the lamina propria, and mucosal erosions and ulcerations. Non steroidal anti-inflammatory drugs involve the right side of the colon and cause mucosal damage, most commonly manifesting as inflammation, stricturing disease, or ulcers.

Cytomegalovirus (CMV) is a common human herpes viral pathogen. CMV colitis is an important gastointestinal manifestation of this viral infection histologically characterized by large basophilic inclusion bodies (Owl's Eye) in the nuclei along with Ischemic ulcers. Pathophysiology of pseudomembrane formation in CMV colitis is unclear, although poor tissue perfusion and anoxia, similar to ischemic colitis, have been suggested.[26]

Pseudomembranous colitis caused by Escherichia coli O157:H7 strain has also been reported. Pseudomembrane formation in these patients is postulated to occur from the innate ability of Shiga toxins to cause microvascular changes and endothelial damage in the colon.[27-29] Acute Shigella infection, also known as shigellosis, continues to cause severe disease and death in developing countries. Infection usually presents with fever, followed by a watery secretory diarrhea that progresses to invasive and hemorrhagic colitis, mediated by Shiga toxins.

Pathology findings of Staphylacoccus aureus enterocolitis show pseudo membranes characterized by fibrin, necrotic areas with polymorphonuclear cells, and clusters of gram-positive cocci in the luminal border. Necrotizing disease of the bowel, including complete bowel necrosis and gangrene, has also been reported.[30]

Entamoeba histolytica is caused by trophozoite invasion of the intestinal mucosa through the protective mucous layer of the colon. Amoebic colitis is characterized by mucosal thickening, edema, inflammation, ulcerations (classically flask-shaped), necrosis, and in severe cases, intestinal perforation.[31,32] Strongyloides stercoralis is a human parasitic roundworm. Immunosuppressed individuals are at highest risk for these forms of infection. Strongyloides appears to promote edema and inflammatory changes in the colon which might trigger pseudo membrane formation.

MANAGEMENT OF CASES OF CLOSTRIDIUM DIFFICILE INFECTION

Numerous studies have demonstrated equal or near-equal efficacy of vancomycin and metronidazole when treating initial and/or mild-to-moderate episodes of CDI. For the correct choice of treatment, knowing the severity of disease is important. For mild-to-moderate disease, recommended treatment is oral metronidazole for 10–14 days or oral vancomycin for 10–14 days, if the patient cannot tolerate or does not improve significantly while on metronidazole.[14] Fidaxomicin was approved for the treatment for CD infection in 2011 by the FDA; it was superior to Vancomycin as the recurrence rate was low. Despite its superiority to vancomycin, its higher cost limited its use.

Severe and complicated CDI are admitted to an intensive care unit and monitored for hypotension that may or may not require vasopressors, fever greater than 38.5°C, ileus, megacolon, altered mental status, severe leukocytosis (WBC > 35,000/mm^3) or leukopenia (WBC< 2000/mm^3), elevated serum lactate, and/or end-organ damage. Recommended treatment is oral vancomycin (500 mg X 4 times OD) in conjunction with intravenous metronidazole and rectal vancomycin enemas in cases of severe ileus.[14] In fulminant CDI refractory to medical therapy or with complications (toxic megacolon, perforation with peritonitis, or septic shock), surgical intervention, including hemicolectomy or subtotal colectomy, may be necessary.

RECURRENT CLOSTRIDIUM DIFFICILE INFECTION

Recurrent CDI is defined by the complete resolution of presenting symptoms on appropriate therapy, with subsequent relapse and return of symptoms after completion of treatment. Risk factors for recurrent disease include advanced age, female gender, additional courses of antibiotics and/or chemotherapy, the use of GI medications or procedures, prolonged hospital stays, and prior episodes of recurrent CDI. In patients with a history of one recurrence, the rate of additional recurrences increases to 40–65% percent.[14]

FECAL MICROBIAL TRANSPLANTATION

First reported in 1958 fecal transplantation has emerged as a safe and effective treatment for recurrent CDI.[34] The oral and rectal transplantation of feces from a healthy donor and simultaneous cessation of all antibiotics use in the recipient

are successful in treating more than 90% patients with recurrent infection.[35]

IMMUNIZATION

Passive immunization with monoclonal antibodies to CD toxins also provides substantial protection from recurrence after acute infection and may be cost effective in patients who are at high risk of recurrence.[36]

CONCLUSION

Pseudomembranous colitis and Clostridium difficile are synonymous; however there are several other mimics that need to be addressed before coming to the conclusion. Bacterial, viral, parasitic infection and drug have also been implicated for the formation of pseudo membranes. Hence a complete history including prior use of antibiotics along with the endoscopic findings is necessary for definitive diagnosis. Pathological diagnosis is usually confirmatory.

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Conflict of Interest: **None**

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