PSEUDOMEMBRANOUS COLITIS: A BIBLIOGRAPHIC REVIEW

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ABSTRACT

The aim of this study is to describe through literary findings pseudomembranous colitis and its main characteristics, diagnoses and treatments. It was performed by searching the Virtual Health Library (VHL), using mainly the databases: Latin American and Caribbean Health Sciences Literature (LILACS), Scientific Electronic Library Online (SciELO), Medical Literature Analysis and Retrieval System Online (Medline) and PubMed. Pseudomembranous colitis is a nonspecific pattern of injury resulting from decreased oxygenation, endothelial damage, and mucosal-impaired blood flow, which can be triggered by various disease states, is caused by the gram-positive anaerobic bacterium Clostridium difficile (C.difficile). For the diagnosis a careful and complete history is crucial; quality and duration of symptoms, exposure history, chronic medical conditions (including conditions that cause an immunosuppressed state) and a list of medications will help narrow the differential diagnosis. Treatment is specific to the underlying etiology and will be individualized. Consultation with a gastroenterologist should be considered early in the course of the disease. As there is no vaccine available yet preventive measures are advocated such as strict hand washing, enteric precautions and careful use of antibiotics are imperative and remain the most effective means of preventing the spread of the body and disease.

KEYWORDS: PSEUDOMEMBRANOUS COLITIS. CLOSTRIDIUM DIFFICILE. DIAGNOSIS. TREATMENT.

INTRODUCTION

Pseudomembranous colitis is a nonspecific pattern of lesion resulting from decreased oxygenation, endothelial damage and impaired mucosal blood flow, which can be triggered by various disease states. Chemicals, drugs, ischemia, microscopic colitis, other infectious organisms and inflammatory conditions can predispose to the formation of pseudomembranes and must be included in the differential diagnosis[1].

Since most patients with pseudomembranous colitis have C. difficile infection, it must be ruled out first. The most common predisposing factor is the previous use of antibiotics, including vancomycin and metronidazole, which are therapy for C. difficile colitis[2].

Pseudomembranous colitis is rare but catastrophic in C. Difficile infection and may occur in less than 25% of other bacterial, viral and toxic causes of diarrhea, gastroenteritis and anorectal fistulas[3].

This study aims to describe, through literary findings, pseudomembranous colitis and its main characteristics, diagnoses and treatments.

It was carried out by searching the Virtual Health Library (VHL), using mainly the databases: Latin American and Caribbean Literature in Health Sciences (LILACS), Scientific Electronic Library Online (SciELO), Medical Literature Analysis and Retrieval System Online (Medline) and PubMed.

LITERATURE REVIEW

2.1. HISTORY OF PSEUDOMEMBRANOUS COLITIS

A colite pseudomembranosa foi descrita em 1893 nos estudos de Finney4. O Clostridium difficile foi descrito pela primeira vez em 1935, mas sua associação com antibióticos e PMC não foi descrita até a década de 19705.

Pseudomembranous colitis was described in 1893 in Finney's studies[4]. Clostridium difficile was first described in 1935, but its association with antibiotics and PMC was not described until the 1970s[5].

Only in 1977 was that Larson described the association with the use of antibiotics, more precisely oral penicillin[6].

In 1978 Larson describes that Clostridium difficile was identified as a source of the toxin in the feces of patients with pseudomembranous colitis[7].

C. difficile is a gram-positive anaerobic toxin-pro-

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ducing organism with the ability to form spores. This last characteristic lends itself to the acquisition of the environment, particularly in nosocomial contexts. It has been identified as the causative agent in 15 to 30% of diarrhea associated with antibiotics and as the main cause of colitis associated with antibiotics[6].

2.2. DEFINITIONS ABOUT PSEUDOMEMBRANOUS COLITIS

Pseudomembranous colitis, also called antibiotic-associated colitis, is caused by the gram-positive anaerobic bacteria Clostridium difficile (C.difficile) (Figure 1). Infection is common in elderly patients on chronic antibiotic use and in immunosuppressed patients[8].

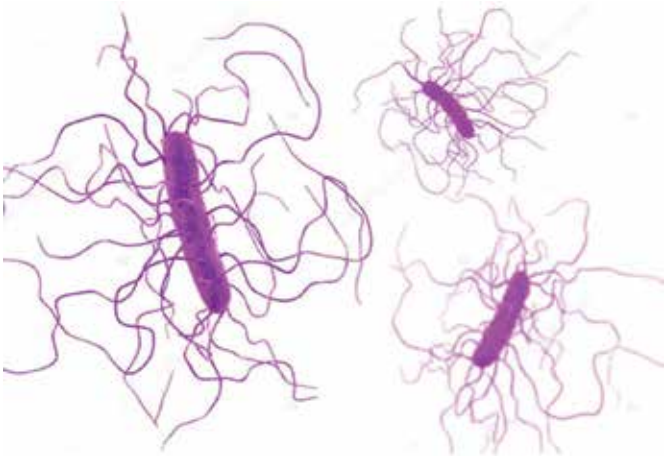

Figure 1 –Clostridium difficile (C.difficile)
Source: LabNetwork, 2019[9].

Pseudomembranous colitis, caused by Clostridium difficile, has increased its incidence in recent years, driven mainly by the indiscriminate use of antibiotics[10].

It is an inflammatory condition of the colon and rectum characterized by elevated yellowish-white plaques that fuse to form pseudomembranes in the mucosa. Patients with the condition usually have abdominal pain, diarrhea, fever and leukocytosis[6].

The mortality rate is high in debilitated patients and when not properly diagnosed and treated. Occasionally, emergency surgery is required due to complications, including perforation of the colon and toxic colitis[11].

Typical symptoms of C. difficile infection include bloodless diarrhea or colitis associated with severe abdominal pain, fever and/or apparent or occult blood in the stool. The most severe form of this disease occurs as a result of a severe inflammatory response to C. Difficile toxins[12]. Toxic megacolon and acute peritonitis secondary to colon perforation are the most serious complications[13].

Pensa-se que a antibioticoterapia possa alterar a flora entérica, permitindo que C. difficile prolifere e produza toxinas com efeitos citopáticos (toxina B ou citotoxina) e hipersecretores (toxina A ou enterotoxina) na mucosa. Os maiores efeitos das toxinas A e B são a ruptura do citoesqueleto de actina. As células intoxicadas por estas proteínas demonstram uma retração do processo celular e uma circularização do corpo celular. Isso ocorre devido a desmontagem dos filamentos F de actina e um aumento de actina-G antes da circularização da célula. Poucas moléculas de toxina são necessárias para produzir esta circularização. No estado de doença ativa, o epitélio do cólon é o maior alvo das toxinas do C. difficile. Elas causam a ruptura da barreira celular abrindo as junções intercelulares. Este efeito aumenta a permeabilidade do cólon, levando a diarreia aquosa, a qual é um sintoma característico da diarreia associada a C. difficile (figura 2)[14].

Antibiotic therapy is thought to alter the enteric flora, allowing C. difficile to proliferate and produce toxins with cytopathic effects (toxin B or cytotoxin) and hypersecretors (toxin A or enterotoxin) in the mucosa. The greatest effects of toxins A and B are the disruption of the actin cytoskeleton. The cells intoxicated by these proteins demonstrate a retraction of the cell process and a circularization of the cell body. This occurs because of the disassembly of the actin F filaments and an increase in actin-G before the cell is circularized. Few toxin molecules are needed to produce this circularization. In the active disease state, the colon epithelium is the major target for C. difficile toxins. They cause the cell barrier to rupture by opening the intercellular junctions. This effect increases the permeability of the colon, leading to watery diarrhea, which is a characteristic symptom of diarrhea associated with C. difficile (figure 2)[14].

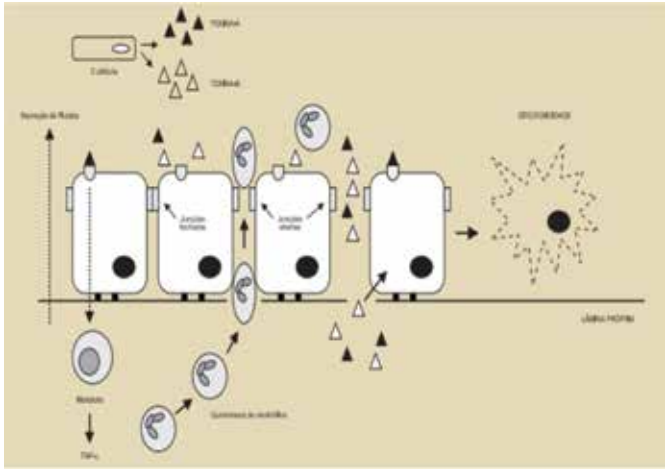

Figure 2 - Actions of toxins A and B of C.difficile in th intestina epithelium
Source: SILVA, SALVINO, 2003[14].

In addition to clindamycin, the first antibiotic recognized for being clearly associated with pseudomembranous colitis, the most commonly responsible antimicrobial agents are cephalosporins and ampicillin (or amoxicillin). However, practically all antibiotics, except parenterally administered aminoglycosides, can cause the disease[13].

The disease has gained importance in recent years due to the occurrence of serious epidemics in several advanced countries[15].

When analyzing 80 patients (43-GES; 37-MS) the profile found was: average age - 68.6 ± 17.7 years; male gender - 52.5%; Antibiotic therapy in the previous 3 months - 85%; average AB time 10.5 ± 6.1 days. The most implicated antibiotics were: cephalosporins, amoxicillin / clavulanic acid and quinolones. Associated Risk Factors: renal failure (22.5%), heart failure (22.5%); previously bedridden patient (36.3%). Diagnostic Methods: toxin search-58 patients (out of 36); colonoscopy - 62 (out of 53); culture - 23 (out of 16). Mortality was 18.8% (n=15); recurrences - 10% (n=8). Therapy: metronidazole - 37 patients (46.3%); vancomycin - 24 (30%); metronidazole + vancomycin - 12 (15%) [16].

2.3. DIAGNOSTIC METHODS OF PSEUDOMEMBRANOUS COLITIS

Pseudomembranes are generally seen during endoscopic procedures, sigmoidoscopy or, if possible, colonoscopy; the most useful microbiological tests for confirming the diagnosis include cultures of cefoxitin fructose-agar with cycloserine and AGFA and fecal toxin assays in tissues or by immunological techniques[13].

The diagnosis is based on the detection of C. difficile in feces, either by culture, tissue culture assay for cytotoxin B or detection of antigens in feces by rapid enzyme immunoassays[12].

Laboratory tests cannot distinguish between asymptomatic colonization and symptomatic infection by C. difficile. Diagnostic approaches are complex due to the availability of several testing strategies. Multi-step algorithms using the polymerase chain reaction (PCR) for the toxin gene (s) or single-step PCR in liquid stool samples have the best test performance characteristics (multiple step: sensitivity 0 , 68 to 1.00 / specificity 0.92 to 1.00; single step: sensitivity 0.86-0.92 / specificity 0.94-0.97)[17].

Although Clostridium difficile infection is the cause of most cases of pseudomembranous colitis, physicians should consider less common causes, especially if pseudomembranes are seen at endoscopy, but tests remain negative for C. difficile or if the presumed C. difficile infection does not respond to treatment[1].

Ultrasonography can be used as an early screening for pseudomembranous colitis and the main findings are: Diffuse colon thickening of less than 10 mm, often more prominent on the left; Extensive submucosal edema; Free pericolic fluid; intramural gas[18].

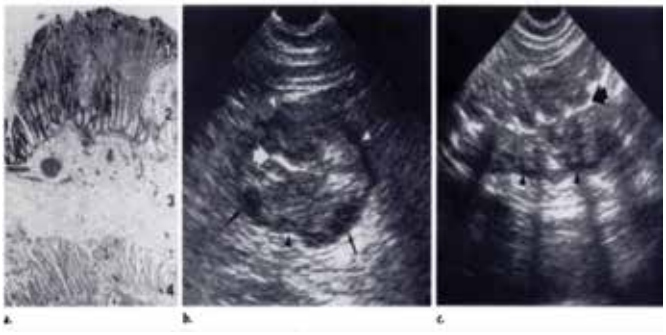

Figure 3 – Pseudomembranous Colitis USG
Images of a 54-year-old man with severe PMC undergoing colectomy because of severe fluid and electrolyte imbalances. (a) Photomicrography of the ascending colon wall shows four distinct layers, histologically discernible. Layer I shows a classic pseudomembranous plaque consisting of inflammatory cells and debris. Layer 2 contains partially ruptured mucous glands distended by mucin and a marked inflammatory infiltration. Layer 3 demonstrates the grossly edematous submucosa. Layer 4 shows moderate edema of the muscle itself. (Hematoxylin-eosin stain; low power magnification.) Transverse (b) and sagittal (c) ultrasound images of the ascending colon demonstrate gross thickening of the intestinal wall with removal of the lumen (thick arrow). The pseudomembranous plaque, mucosal and submucosal layers are not resolved individually, but are collectively represented by a heterogeneous zone of medium echogenicity. The focal expansions in this layer (thin arrows) are the taeniae coli muscles.
Source: DOWNEY, WILSON 1991[18].

Tomographic changes are present in the colon in 88% of cases of pseudomembranous colitis. In a study with 26 patients, 23 demonstrated an intestinal wall abnormality, with a medium wall thickness of 14.7 mm (range, 3-32 mm); in three patients, intestinal wall thickness was normal. Pancolonic involvement was observed in 13 cases, while seven patients had only involvement on the right side; three patients presented thickening of the intestinal wall limited to the rectosigmoid only, there is no high specificity for the isolated exam[19].

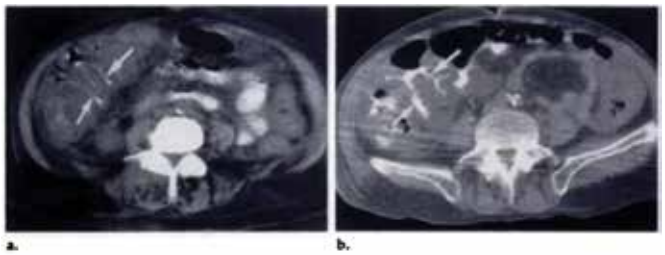

Figure 4 – CT of Pseudomembranous colitis
Marked thickening of the right side of the colon with tracking of contrast material (arrows) between the thickened folds. Thickening of pericolonic tissues is perceived. (b) Extensive inflammation of the right side of the colon with layers of contrast material between inflamed mucous folds (arrows). (FISHMAN, 1991)[19].

2.4. PSEUDOMEMBRANOUS COLITIS TREATMENT

Clostridium difficile is a pathogen known to cause diarrhea and colitis. If not treated properly, it can repeat itself and progress to life-threatening conditions, such as toxic megacolon and multiple organ failure. The updates to the guidelines launched in 2018 reflect notable changes in the treatment of C. difficile infection. Metronidazole is no longer recommended as a first-line therapy for adults; oral vancomycin and fidaxomycin are now recommended[20].

Vancomycin is also effective, but its use should be limited to decrease the development of organisms resistant to vancomycin, such as enterococci. Vancomycin (125-500 mg 4 times daily for 10 days) should be limited to those who cannot tolerate or respond to metronidazole, or when the use of metronidazole is contraindicated, as in the first trimester of pregnancy. A therapeutic response within a few days is usual. The recurrence of symptoms after antibiotics occurs in 20% of cases and is associated with the persistence of C. difficile in the stool. Additional recurrences become more likely. Antibiotic therapy in a pulsed or conical regimen is often effective, as are efforts to normalize faecal flora. The yeast Saccharomyces boulardii has been proven in controlled trials to reduce recurrences when administered as an adjunct to antibiotic therapy. Careful hand washing and environmental decontamination are necessary to prevent epidemics[12].

Recent data demonstrates clinical success rates of 66.3% for metronidazole versus 78.5% for vancomycin for severe CDI. The latest therapies show promising results, including fidaxomycin (clinical cure rates similar to vancomycin, with lower recurrence rates for fidaxomycin, 15.4% vs. vancomycin, 25.3%, P = 0.005) and fecal microbiota transplantation (response rates from 83% to 94% for recurrent CDI) [17].

O transplante de microbiota fecal está associado à resolução dos sintomas de CDI recorrente, mas seu papel no CDI primário e grave não está estabelecido[17].

Fecal microbiota transplantation is associated with the resolution of symptoms of recurrent CDI, but its role in primary and severe CDI has not been established[17].

Relapses are seen in 5 to 50% of treated patients. Antibiotic treatment should avoid sporulation, leading to other relapses. 'Biotherapy' (lactobacilli, Saccharomyces) has also been proposed[13].

The pharmacist's involvement in antibiotic administration programs optimizes the treatment of infections by selecting appropriate antibiotics, decreasing therapy when applicable, reducing hospitalizations and still providing patient education to prevent spread such as washing hands with soap and water every time that the bathroom is used and always before eating and still by recommending that patients with diarrhea use a separate bathroom at home, if possible and all surfaces are be cleaned with a mixture of bleach and water[20].

CONCLUSION

Clostridium difficile is the most common hospital infection of the gastrointestinal tract and is mainly caused by C. difficile infection but there are other risk factors besides antibiotics and C. difficile.

A careful and thorough history is crucial; quality and duration of symptoms, history of exposure, chronic medical problems (including conditions that cause an immunosuppressed state) and a list of medications will help narrow the differential diagnosis.

Treatment is specific to the underlying etiology and will be individualized. Consultation with a gastroenterologist should be considered early in the course of the disease.

As there is no vaccine available yet, preventive measures are recommended, such as strict hand washing, enteric precautions and the careful use of antibiotics are imperative and remain the most effective means of preventing the spread of the organism and disease.

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