Pseudomembranous colitis related to valaciclovir: a clinical case

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Abstract

Clostridium difficile is a microbiological agent essentially nosocomial. In the last few years there have been important changes in its epidemiology. Nowadays Clostridium difficile associated disease is considered one of the most reported nosocomial diseases. There is also evidence of an increasing number of cases in the community, with data suggesting increasing pathogen's aggressiveness.

Antibiotics play a crucial role in the disease physiopathology. Clindamycin, cephalosporins and penicillins are the higher risk antibiotics, nevertheless, any antimicrobial agent can facilitate a Clostridium difficile infection.

Given the theme relevance, the authors present a clinical report of a case of pseudomembranous colitis secondary to valaciclovir, a rare association according to literature.

Key words: Clostridium difficile, colitis, diarrhoea, pseudomembranous colitis and valaciclovir.

INTRODUCTION

Clostridium difficile (CD) was identified for the first time in 1935, but it was not associated with the disease until 1978.[1] It is essentially a nosocomial agent, and the estimated incidence of *Clostridium difficile* associated diarrhea (CDAD) in the hospital environment varies from 5% to 39%.[2] In the community, its incidence is estimated at 7-12 cases per 100.000 people/year,[2] and there is evidence that the incidence of CDAD is increasing.[3] Of the nosocomial diseases reported to the Centers for Disease Control and Prevention, CDAD is currently the fourth most commonly reported.[2]

Antibiotics play a fundamental role in the pathogenesis of CDAD, and the ones traditionally considered to be associated with higher risk are clindamycin, cephalosporins and penicillins. However, any antimicrobial may potentially be involved, including metronidazole, vancomycin, antifungals and antivirals.[2]

Due to the importance and rarity of this disease, the authors present a clinical case of pseudomembranous colitis (PMC) secondary to Valaciclovir.

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CLINICAL CASE

Patient aged 75 years, male, Caucasian, retired, living in Germany. Admitted to the Hospital Garcia de Orta (HGO) with clinical symptoms of diarrhea over a period of three weeks, accompanied by vomiting, anorexia, colic pain in the lower abdominal quadrants, and edema of the lower limbs. The diarrhea was characterized by 8-10 bowel movements/day with yellowish, liquid feces containing no blood, mucus or pus. The diarrhea began 7 days after the start of therapy with Valaciclovir and Gabapentin, targeted at a Herpes zoster infection in the neck region, for which the patient completed 7 days of antiviral therapy. One week after the onset of the diarrhea, the patient was referred to the emergency service of the HGO with dysphagia for solids and retrosternal pain, aggravated by the ingestion of foods. Upper digestive endoscopy was carried out, obtaining images suggestive of Candida oesophagitis, and the patient was medicated with oral fluconazole. Personal history included partial sigmoid resection due to a benign bleeding polyp more than 20 years ago; type 2 diabetes mellitus medicated with Gliclazide; arterial hypertension controlled with Phosinopril and Indapamide; duodenal ulcer under chronic medication with Omeprazole, and total prostatectomy at the age of 69 due to benign prostate pathology. Patient also reported negative unprotected sexual behaviors and use of illicit substances: alcohol or other hepatotoxin. Patient denied previous transfusions of blood or hemoderivatives.

On objective examination, patient was alert, collaborative and oriented, but thin, dehydrated, and febrile

(37.5-38ºC) and with edema of the four limbs, face and abdominal wall. The abdomen was distended, with an increase in bowel sounds, and painful on touch of the lower abdominal quadrants, without defense. There were no stigmata of chronic liver disease.

The laboratory tests revealed neutrophils leukocytosis, C-reactive protein of 12.6 mg/dL and erythrocyte sedimentation rate of 53 mm in the 1st hour. The coagulation tests were altered (TP 66% and aPTT 48 seconds). The patient presented a cholestatic pattern (alkaline phosphatase 601 UI/L, gamma- glutamyl transpeptidase 322 UI/L, Total bilirubin 1.2 mg/dL, AST 65 UI/L and ALT 90 UI/L), total proteins 5 g/dL, albumin 1.5 g/dL, total cholesterol 90 mg/dL and normal immunoglobulins. Serologies for human immunodeficiency virus 1 and 2, antigen P24 and hepatotropic virus all negative. Renal function maintained, without evidence of proteinuria.

Abdominal echography did not reveal any structural alterations of the hepatic parenchyma or bile duct dilation; only biliary sludge was detected. Total colonoscopy identified pseudomembranes located in the sigmoid colon compatible with a diagnosis of CD-associated pseudomembranous colitis (PMC). Blood cultures were negative. Bacteriological and mycological exams of the feces were also negative. Study of lymphocyte populations was normal. No study of Clostridium difficile toxins was carried out due to logistical problems.

In view of the diagnosis of PMC, we decided to begin antibiotic therapy with Metronidazole, oral route. With the therapy instituted, a normalization of the intestinal transit and symptoms of abdominal pain was observed, but with persistence of slight edema of the lower limbs. The patient was discharged after fourteen days of antibiotic therapy. With regard to the laboratory tests, normalization of the PCR and transaminases was observed, together with a significant decrease in alkaline and gamma-glutamyl transpeptidase values. The total proteins, albumin and coagulation tests maintained similar values to those recorded at the start of hospitalization.

The patient remained in follow up at an Internal Medicine clinic, and was asymptomatic with normalization of the analytical parameters at the end of 2 months.

DISCUSSION

The occurrence of CDAD presupposes the existence of three events: Alteration of microbial colonic flora, colonization and proliferation of *Clostridium difficile* (CD), and the production of toxins. Microbial colonic flora inhibits the colonization and proliferation of CD, which means that any situations that alter its balance could increase the risk of CDAD.[4] Disruption of the microbial flora caused by antibiotics is the most consensual physiopathological mechanism for the emergence of CD infection.[3] The duration of therapy, use of multiple antibiotics, and broad-spectrum regimens increase the risk of CDAD.[3]

There are other factors that facilitate colonization by CD and increase the risk of associated disease, notably, the use of proton pump inhibitors (PPI), prokinetics, antiperistaltic agents, immunosuppressants, antineoplastics, gastrointestinal surgery, nasogastric probes and enemas.[4] After colonization, the risk of infection also depends on the immune response of the host. Individuals who produce less antibodies in response to toxin A have a higher risk of infection.[4] This fact may justify the role of some risk factors, like advanced age, the presence of severe underlying disease, and immunosuppression.

In general, the incidence of CDAD is increasing, even in the community and in individuals without traditional risk factors.[3] It is thought that this fact may be related to the large-scale use of PPI and increased virulence and alterations in patterns of resistance of some strains of Clostridium difficile.[3] Nowadays, fluoroquinolones are considered a risk factor for CDAD.[5] In epidemic outbreaks reported in the United States of America and Canada, a CD strain was identified which is resistant to Ciprofloxacin and has increased virulence factors.[5]

Valaciclovir is an antiviral used for the treatment of herpes infections, and does not present any antimicrobial activity on the colonic flora. The incidence of diarrhea associated with taking Valaciclovir is considered rare.[6] The association of Valaciclovir and CD-associated PMC is exceptional in the literature.[6] In the clinical case in question, there is a temporal relationship between the Valaciclovir therapy and the diagnosis of CPM. We believe Valaciclovir performs a pivotal role in CD infection, probably by inducing diarrhea and consequently, altering the microbial intestinal flora. We also suggest that other factors, like chronic PPI therapy, advanced age, and a transitory immune deficiency (evaluated by herpetic infection) may also have contributed to the patient's

pathogenesis.

The spectrum of the disease is variable, and may include mild diarrhea or may evolve to fulminant colitis. The temporal correlation between exposure to the antibiotic and the onset of CDAD may vary from 24h to 8 weeks.[7] Typical symptoms include watery diarrhea, abdominal pain, fever, anorexia, nausea and general malaise. Analytically, leukocytosis and Hypoalbuminaemia are common.[7] Hypoalbuminaemia, by exudative enteropathy, can lead to a decrease in oncotic pressure and the formation of edemas, as occurred in the present case.

Despite the clinical symptoms suggestive of CDAD, the fact that the patient had not been recently exposed to any antibacterial drugs led us to propose other possible diagnoses, and colonoscopy was requested. Although other, rare causes of PMC do exist, the identification of pseudomembranes by colonoscopy is, nowadays, practically pathognomonic of infection by CD.[7] However, not all patients present pseudomembranes, which makes sensitivity to the exam relatively low (51%).[7] Furthermore, in patients with abdominal distension, the risk of intestinal perforation is higher. For these reasons, in individuals with diarrhea associated with antibiotics, laboratory tests are advised for the diagnosis of CDAD (*Table I*).[7]

TABLE I

Laboratory diagnosis of CDAD

Laboratory diagnosis of CDAD	Advantages	Disadvantages
Cellular toxicity assay	High specificity High sensitivity	Expensive Results > 24h
Culture test	High sensitivity	Low specificity Results > 72h
EIA for toxins A or A + B	High specificity Low-cost Results in 2h	Low sensitivity

TABLE II

Antibiotic therapy with CDAD

	Therapeutic options
Mild to moderate disease	Metronidazole 500 mg, po, 8-8h, 10 days
Severe disease	Vancomicina 125 – 500 mg, po, 6-6h, 10 days Suspect intestinal obstruction (paralytic ileus) or toxic megacolon: Metronidazole (500 mg, iv, 6-6h) + Vancomicina via SNG (500 mg, 6-6h) or enema (500mg in 100 ml de SF every 4-12h), 10 days
	1st relapse: Same antibiotic as that used for the 1st episode ≥ 2nd relapse: • Vancomycin in high doses (1-2 g/day) • Vancomycin in titrated doses or in pulses • Immunoglobulin iv 400 mg/kg 1-2 doses

The first step in the treatment of CDAD (*Table II*) is to suspend the antibiotic therapy. Antiperistaltics and opiates are contraindicated. Metronidazole administered via oral is the therapy of choice for mild to moderate CDAD.[8] Vancomycin is the antibiotic of choice in cases of severe disease (doses up to 500mg every 6 hours, with the goal of achieving higher colonic concentrations).[2,8] A recent prospective, randomized trial supports this therapeutic approach. Comparing the two antibiotics in 172 patients with CDAD, the trial concluded that the therapeutic efficacy was similar in cases of mild disease, and that Vancomycin is more effective than Metronidazole in severe cases of the disease.[9] In cases of intestinal obstruction (paralytic ileus), or when the oral route is unavailable, intravenous Metronidazole associated with Vancomycin is recommended, administered via nasogastric probe or enema.[2,5]

The treatment of relapses is more controversial. Relapses occur in 22-26% of cases, generally 7-14 days after completion of the antibiotic therapy.[1] For the first relapse, treatment with the same antibiotic as that used for the first episode is recommended.[8] For patients with two or more relapses, it is essential to identify and correct the cause of the continuation of infection, and the need for a new antibiotic regimen should be considered. There are various therapeutic approaches with proven efficiency, notably, Vancomycin in high doses, pulses or titrated doses of Vancomycin and Vancomycin associated

with Rifampicin. However, there is no consensus as to the efficacy of any of these regimens.[8] Various studies have demonstrated the benefit of probiotics in the treatment of recurrent CDAD, but there has only been one prospective, randomized, controlled trial that has demonstrated the benefit of the association of Vancomycin with Saccharomyces boulardii.[10] Intravenous immunoglobulin is another therapeutic option for patients with frequent or severe relapses in which other therapeutic options are unfeasible.[8] Another therapeutic approach that does not involve antibiotics is fecal transplant, which consists of the administration of donor feces. Despite the controversy surrounding this procedure, and the potential risk of transmission of infectious diseases, the therapeutic response appears to be excellent.[8]

In the patient under study, two clinical situations are clarified; the fungal oesophagitis and the alterations in liver function tests. Fungal oesophagitis is considered rare in immunocompetent patients. Risks factors are identified, some of which were present in our patient, notably, advanced age, diabetes mellitus, and PPI therapy.[11,12] In relation to the liver disease, it was of multifactorial etiology (toxicity induced by Fluconazole and Gabapentin, with persistent infection and malnutrition). ■

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