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Letter to the Editor

CLOSTRIDIUM DIFFICILE AND CYTOMEGALOVIRUS COLITIS COINFECTION AFTER BARIATRIC SURGERY: CASE REPORT

Colite por Clostridium difficile e Citomegalovirus após cirurgia báriatrica: relato de caso

Ana Carolina Peçanha **ANTONIO**, Juçara Gasparetto **MACCARI**, Arthur **SEABRA**, Tulio Frederico **TONIETTO**

From Hospital Moinhos de Vento, Porto Alegre, RS, Brazil

Correspondence:
Ana Carolina Peçanha Antonio
E-mail: ana.carolina.antonio@gmail.com

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INTRODUCTION

Although controversial, chronic critical illness may be best defined as prolonged dependence of intensive care unit and/or mechanical ventilation, carrying on not well-understood physiopathological processes that affect individual consciousness, respiration, nutrition, neuromuscular and hormonal function. It is becoming a large and growing issue in worldwide health systems, counting for excessive costs and caregivers burden[15]. *Clostridium difficile* associated to diarrhea has become one of the most common healthcare infections[4]. Cytomegalovirus infection is an important cause of morbidity and mortality among immunosuppressed patients in contexts such as organ transplantation, malignant hematologic disease, Aids and complicated inflammatory bowel disease[21]. Colitis co-infection by *Clostridium difficile* and Cytomegalovirus has been reported especially in those scenarios as well. Here is described a unique case of concomitant infection in a chronic critically ill patient with no other previous immunosuppressive condition.

CASE REPORT

A 37-year-old morbid obese female patient, without any other baseline comorbidity, was admitted to the intensive care unit in the immediate postoperative period after laparoscopic Roux-en-Y gastric bypass. On the 4th postoperative day, she was submitted to urgent exploratory laparotomy and repair due to small bowel anastomotic dehiscence, resulting in septic shock and multiple organ dysfunctions, which were rapidly reverted. Tracheostomy was performed after ten days of mechanical ventilation. Patient evolved with prolonged stay and intensive care, demanding long lasting parenteral nutrition, renal replacement therapy, stress doses of corticosteroids and multiple antibiotic regimens as a consequence of several infectious complications – intra-abdominal abscesses, ventilation associated pneumonia and bloodstream/catheter related infection -, not to mention a short course of parenteral high-dose steroids for drug rash with eosinophilia and systemic symptoms syndrome management. After all, she was successfully cared with vacuum assisted devices for enterocutaneous fistula. About two months after intensive care admission, the patient started presenting high volume, watery diarrhea – around four liters a day -, which worsened during enteral feeding. She also complained of nearly constant abdominal pain. She became febrile and hemodynamically unstable. Laboratory tests showed leukocytosis and elevated C-reactive protein levels. A stool specimen contained white cells and a test for *Clostridium difficile* toxin was positive. Given the severity of clinical manifestations, vancomycin was administered orally and metronidazole intravenously. The patient's condition was unimproved after two weeks of treatment: profuse liquid stools continued as well as inflammatory systemic signals. Total parenteral nutrition had already been reinstituted. Abdominopelvic computed tomography findings were inexpressive. On account of this, she underwent colonoscopy, which revealed diffuse colitis and terminal ileitis and no pseudomembranes. Anatomopathological examination showed innumerous ulcers and crypt microabscesses, in addition to nuclear inclusions in endothelial and mucosal cells suggestive of cytopathic effect of viral infection (Figure 1). A blood test for Cytomegalovirus antigen was positive (57 white cells per 200,000). She had high Cytomegalovirus immunoglobulin G (IgG) antibodies titers (1:800). Hepatitis B and C and HIV serologies were repeatedly negative. Ganciclovir therapy was begun; nevertheless it had to be replaced by foscarnet after development of agranulocytosis. Patient condition improved progressively and it was completely solved after six weeks of treatment. She was discharged from intensive care unit a week later and ultimately recovered physical, respiratory and mental states within two months at ward level.

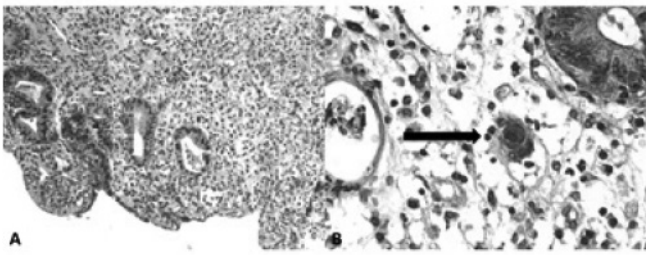

FIGURE 1 - A) Photomicrograph of bowel biopsy stained with H&E, 100x: note the chronic ulcerative ileitis, with areas of necrosis, gland regeneration and high neutrophil activity; B) nuclear inclusions in endothelial cell (arrow) suggestive of cytopathic effect of viral infection (H&E, 400x)

DISCUSSION

It was performed a review for other case reports describing simultaneous infection with *Clostridium difficile* and Cytomegalovirus in the PubMed/Medline, Lilacs and Embase as showed in Table 1.

TABLE 1 - Search strategies performed and results from each database

Eletronic databases	Search databases	Results	
		Found	Related
Medline	((“*Clostridium difficile*”[Mesh]) AND “Coinfection”[Mesh]) AND “Cytomegalovirus Infections”[Mesh]	1	19
Lilacs	(tw:(*Clostridium difficile*)) AND (tw:(Cytomegalovirus Infections)) (tw:(*Clostridium difficile*)) AND (tw:(Infecções por Citomegalovirus)) (tw:(*Clostridium difficile*)) AND (tw:(Infecciones por Citomegalovirus))	1	0
Embase	‘*clostridium difficile* infection’/exp AND ‘cytomegalovirus infection’/exp AND ‘diarrhea’/exp AND [humans]/lim AND [embase]/lim	38	5

Chronic critical illness consumes a great percentage of intensive care unit resources and its society costs are expected to climb with increases in the incidence of this syndrome and in overall expenditures for critical care. Those patients represent a singular group constantly exposed to barrier breaches, such as intravenous catheterization and skin breakdown, and to virulent and resistant pathogens in intensive environment. Moreover, it has been postulated development of “immune exhaustion” as consequence of functional dependence, poor nutritional status and multiple infections[15,20]. *Clostridium difficile* is a major cause of nosocomial diarrhea and an increasing problem particularly in hospitalized patients receiving antibacterial therapy. Advanced age and presence of comorbidities with functional impairment are well-known hosts risk factors, and the most important modifiable risk factor is exposure to antimicrobial agents, once it suppresses the normal bowel flora. Gastrointestinal surgery is also a recognized hazard[4]. Cytomegalovirus colitis is not a common clinical presentation and a result of reactivation of the virus and not primary infection, Cytomegalovirus specific IgG antibodies will be present[9]. The precise role of Cytomegalovirus infection in contributing to outcomes in critically ill immunocompetent patients has not been fully defined. As a feared threat in transplant centers and a classic opportunistic infection in HIV-hosts, It has been associated to worse outcomes in non-immunosuppressed intensive care population as well[3,8,10,21]. A case-control study found a Cytomegalovirus antigenemia prevalence of 17% among 237 critical patients, and linked this disease to renal failure and steroid use[8]. Another observational study detected its DNA in 35% of patients staying at least 14 days in the intensive care and active Cytomegalovirus infection occurred in 56% in the subgroup of seropositive individuals[21]. There is correlation between it and longer permanence in intensive care, longer duration of mechanical ventilation, higher rate of nosocomial infection and higher mortality[3,8]. Two systematic reviews about the role of active Cytomegalovirus infection in critically ill patients could not establish a cause-effect relationship between virus and mortality rate[10,17]. Nonetheless, accumulating data really suggest its frequent occurrence in that setting and, considering a large number of people requiring intensive level of care, the impact of this infection in these patients may be equally or potentially wider than in other immunocompromised hosts traditionally recognized to be at risk for it. Cytomegalovirus infection also has immunomodulatory effects and it has been described as an independent risk factor for development of post-transplant lymph proliferative disorder, invasive fungal disease, and bacteremia, but not particularly for *Clostridium difficile* associated diarrhea. Risk factors partially overlap for both infections. It was found 11 clinical reports about simultaneous occurrence of *Clostridium difficile* and Cytomegalovirus colitis, all but two in severe immunosupressed patients (Table 2)[2,5-7,10,12-14,16,18,19]. Authors invariably described a scenario with refractory diarrhea and persistent sepsis after appropriate initial management. Among the 12 patients included in this review, only two were previously higid and had not passed through the intensive care unit until diagnosis. Three of four individuals who died were transplant hosts. All cases were published after 2000, probably reflecting higher success rates of organ transplantation, the emergency of a more virulent strain of *Clostridium difficile* after 2001[11] and increasing diagnostic suspicious for both infection. Many clinicians stop looking, once a diagnosis has been made, and forget that immune suppression is a common risk factor for multiple infections. It has been

suggested performing colonic biopsies in patients with refractory *Clostridium difficile* colitis. Of the two diagnoses, Cytomegalovirus likely missed more often because a biopsy is required to confirm the intestinal source of infection[6].

TABLE 2 - Case reports of simultaneous *Clostridium difficile* and Cytomegalovirus colitis published in medical literature

Reference	Age/ gender	Underlying medical condition	First organism diagnosed	Outcome
Kottaridis et al.[12]	57/M	Autologous bone marrow transplantation (BMT)	CD	Recovery
Nichols et al.[16]	52/M	Lung transplantation	CMV	Death
Riva et al.[18]	39/M	Induction chemotherapy for acute lymphoblastic leukemia (ALL)	CMV	Recovery
Garcia et al.[7]	30/M	AIDS	CD	Death
Veroux et al.[19]	42/F	Kidney transplantation	CMV	Death
Arnold et al.[2]	61/M	Severe flare of ulcerative colitis treated with corticosteroids, immunomodulators and infliximab.	CD	Recovery
Alkhatib et al.[10]	81/M	- -	CD	Recovery
Dahman et al.[5]	73/F	Kidney transplantation	CMV	Death
Florescu et al.[6]	35/M	Pancreatic transplantation	CMV	Recovery
	55/F	Kidney transplantation	CD	Recovery
Kurtz et al.[13]	78/F	- -	CD	Recovery
Nannegari et al.[14]	65/M	Ulcerative colitis treated with corticosteroids	CD	Recovery
Antonio et al.,(present report)	37/F	Chronic critical illness	CD	Recovery

CD=*Clostridium difficile*; CMV=Cytomegalovirus

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