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Short Communication

Cytomegalovirus colitis in immunocompetent critically ill patients☆

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SUMMARY

Objectives: Cytomegalovirus (CMV) is a ubiquitous virus and its reactivation may lead to CMV end-organ disease (CMV EOD) in immunocompromised patients and also in immunocompetent patients when they are critically ill. We aimed to investigate the frequency and the clinical features of proven CMV EOD in previously non-immunosuppressed patients admitted to our institution.
Methods: From January 2000 to March 2013, the records of all patients with a histopathological diagnosis of CMV EOD at our teaching hospital were reviewed retrospectively. CMV EOD was diagnosed histologically by the identification of true cytomegalic viral inclusion involving endothelial, stromal, and/or epithelial cells on hematoxylin and eosin staining, and was subsequently confirmed by immunohistochemistry using specific antibody against CMV antigens. Immunocompromised patients were excluded.
Results: CMV EOD manifesting as colitis was diagnosed in 14 previously immunocompetent intensive care unit (ICU) patients. The mean age of the patients was 64 years. All had co-morbidities and developed shock before CMV EOD. The major manifestation was gastrointestinal bleeding. The in-hospital mortality rate was 71.4% despite specific treatment with ganciclovir.
Conclusions: Despite being a rare condition, lower gastrointestinal bleeding in this profile of ICU patients could be the clinical manifestation of CMV colitis, and intensivists should be alert to this condition.

1. Introduction

Cytomegalovirus (CMV) is a ubiquitous virus and its serology is positive in over two-thirds of the healthy population.[1] Seroprevalence rates increase with age.[2] Like other herpes viruses, CMV stays in a dormant phase for the individual's entire life.[1–3] Therefore, CMV reactivation may lead to CMV end-organ disease (CMV EOD) in immunocompromised patients.[2] The most frequently involved organs are the retina, esophagus, lung, central nervous system, and colon.[3] Over the last decade, a few publications have reported CMV EOD in previously immunocompetent patients, mostly during a critical illness.[3–6] However, the clinical relevance and prevalence of CMV EOD in critically ill patients are not well understood. We aimed to investigate the frequency and the clinical features of proven CMV EOD in previously non-immunosuppressed patients admitted to our institution.

2. Materials and methods

From January 2000 to March 2013, the records of all patients with a histopathological diagnosis of CMV EOD at our teaching hospital were reviewed retrospectively. The Heart Institute (InCor) is a 500-bed tertiary care cardiology center in Sao Paulo, with 158 intensive care unit (ICU) beds. The SNOMED code and the terms 'cytomegalovirus' and 'CMV' were used to search for cases with a histological diagnosis of CMV EOD in the electronic medical records (biopsies and autopsies) of the pathology laboratory. CMV EOD was diagnosed histologically by the identification of true cytomegalic viral inclusion on hematoxylin and eosin staining and was subsequently confirmed by immunohistochemistry using specific antibody against CMV antigens (monoclonal mouse anti-cytomegalovirus, clone DDG9 + CCH2/DAKO). Solid organ or hematopoietic stem cell transplant recipients and patients with

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Table 1
Clinical data of 14 previously non-immunosuppressed patients from admission to the ICU to biopsy-proven CMV EOD at a cardiology hospital

Case	Patient age (years)/ sex	Comorbidities	Diagnosis at admission	Complications	Septic episodes (*n*)	Hospital length of stay/ICU (days)	MV/VA (days)	Transfusion of blood components (yes/ no)	CMV clinical manifestations	Diagnostic resource	Site of infection	In-hospital outcome
1	80/M	Hypertension + cardiomyopathy	Pneumonia	Septic + cardiogenic shock	2	50/50	25/–	No	Hematochezia	Colonoscopy	Rectum	Death
2	43/F	Cardiomyopathy + valvulopathy	CHF	Cardiogenic shock	–	23/0	–/–	No	Abdominal pain + nausea + vomiting	Colonoscopy	Cecum + left colon	Death
3	82/F	Pulmonary hypertension + cardiomyopathy	CHF	Septic + cardiogenic shock	1	35/13	7/6	Yes	Diarrhea + hematochezia	Colonoscopy	Rectum	Death
4	61/F	DM + cardiomyopathy	Elective myocardial revascularization	Septic shock + ventricular fibrillation	4	60/30	10/30	Yes	Hematochezia	Colonoscopy + left hemicolectomy	Rectum + sigmoid	Death
5	77/F	DM, cardiomyopathy + Alzheimer's disease	Myocardial infarct	Septic + cardiogenic shock	2	32/32	12/18	Yes	Melena	Colonoscopy	Rectum + left colon	Discharge
6	74/M	Dialytic CRF + cardiomyopathy + valvulopathy + hepatitis C	CHF	Septic shock + Clostridium colitis + UTI	3	23/6	0/2	No	Diarrhea	Colonoscopy	Terminal ileum	Discharge
7	66/F	DM + CRF + cardiomyopathy	CHF	Septic shock	3	48/34	0/34	Yes	Melena + hematochezia	Left hemicolectomy	Left colon	Death
8	38/F	Chronic aortic dissection	Surgical correction of aortic dissection	Septic shock + rhabdomyolysis + acute renal injury + surgical wound infection + VAP	2	50/45	18/15	No	Fever, diarrhea + hematochezia	Colonoscopy + autopsy	Left colon + sigmoid	Death
9	47/M	Hypertension + CRF + cardiomyopathy	Severe pneumonia	Septic shock	3	38/37	35/20	Yes	Diarrhea + abdominal distension + vomiting	Colonoscopy + autopsy	Cecum + left colon	Death
10	71/F	Cardiomyopathy + CRF + COPD	CHF + myocardial revascularization	Septic + cardiogenic shock	2	50/39	39/39	Yes	Melena	Upper endoscopy	Duodenum	Death
11	53/M	DM + previous myocardial revascularization	Myocardial revascularization	Septic + cardiogenic shock	2	35/15	5/2	Yes	Fever + hematochezia	Right hemicolectomy	Right colon + terminal ileum	Discharge
12	56/M	Polyglandular autoimmune disease type II + CRF	Ischemic colitis	Septic shock	1	41/13	0/0	No	Diarrhea + hematochezia	Colonoscopy + right hemicolectomy	Right colon	Death
13	73/F	CRF + hypertension + DM + cardiomyopathy	CHF	Septic shock	2	97/82	42/30	Yes	Melena + hematochezia	Colonoscopy	Left colon + sigmoid + rectum	Death
14	78/M	CRF + hypertension	Surgical correction of aortic dissection	Septic shock	1	30/8	1/5	Yes	Diarrhea	Colonoscopy	Sigmoid	Discharge

CHF, congestive heart failure; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; DM, diabetes mellitus; EOD, end-organ disease; F, female; ICU, intensive care unit; M, male; MV, mechanical ventilation; UTI, urinary tract infection; VA, vasopressin amines; VAP, ventilator-associated pneumonia.

evidence of an HIV infection, primary immunodeficiency, or use of immunosuppressive drugs, chemotherapeutic agents, or cancer treatment in the 6 months prior to the diagnosis of CMV EOD, were excluded.

3. Results

We identified 14 patients who were previously considered non-immunosuppressed and developed CMV EOD, all of them presenting colitis. Patient characteristics are shown in Table 1. The mean age of the patients was 64 years and all had co-morbidities such as cardiomyopathy (64.2%), chronic kidney disease (50%), and diabetes mellitus (35.7%). All developed septic or cardiogenic shock before CMV EOD. At least one episode of septic shock was seen in 13 patients (92.8%), with an average of two episodes per patient. The mean in-hospital stay was 44 days, with an average of 29 days in the ICU. In this series, 71.4% of patients needed mechanical ventilation, with an average of 20 days under ventilation. Eleven patients (78.5%) needed vasoactive drugs (mean 19 days of use). The in-hospital mortality rate was 71.4% despite specific treatment with ganciclovir. Only one patient (number 8) did not receive specific treatment.

4. Discussion

Critically ill patients frequently demonstrate a transient depression in immunity, predisposing them to viral reactivations, like CMV.[1,3] The detection of CMV in the blood in ICU patients leads to increased mortality and morbidity in terms of increased ICU stay, long-term mechanical ventilation, and higher rates of nosocomial infection.[1,2,7,8] A recent meta-analysis by Kalil and Florescu showed that ICU patients with positive CMV serology at admission, who stayed more than 5 days in the unit, or those who had severe sepsis, were significantly more prone to CMV EOD, with a prevalence of 36%. They also had a higher mortality than patients without CMV infection.[1]

CMV colitis in the immunocompetent host is an uncommon disease and is rarely considered in the differential diagnosis in patients who are not overtly immunocompromised.[9] As well as the patients described herein, CMV EOD has also been observed in other critically ill ICU patients with a long hospital stay and episodes of septic shock. A meta-analysis by Galiatsatos et al. found 44 cases of CMV colitis in immunocompetent patients over a 23-year period. Fourteen patients (31.8%) died.[3] In another study, critically ill immunocompetent patients with CMV colitis had a higher mortality rate and required a longer ICU stay.[7]

Similarly to our series, the major clinical manifestations of CMV colitis in the literature are lower gastrointestinal bleeding and abdominal pain.[6,8,9] Studies have shown a higher incidence of transfusions in patients with active CMV during critical illness.[3] In our series, blood component transfusions were needed in 64.2% due to bleeding related to CMV colitis. This suggests an aggressive disease due to CMV reactivation and rules out CMV infection related to blood transfusion.

There remains the dilemma of whether or not CMV viremia in critically ill patients should be treated with ganciclovir.[2] Although there are no clinical studies on critically ill patients, these patients would probably benefit from early initiation of therapy.[7,8] Histopathological evaluation of suspected patients should also be performed in search of CMV colitis.[8]

This case series was restricted to patients with histological evidence of CMV EOD and probably underestimates the prevalence in this population. Most cases diagnosed as 'probable' CMV EOD depend on diagnostic criteria that do not include histological examinations.[10]

Despite being a rare condition – we found only 14 cases over 13 years of a retrospective search – lower gastrointestinal bleeding in this profile of ICU patients could be the clinical manifestation of CMV colitis, and intensivists should be alert to this condition.

Conflict of interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

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