Challenges in the Diagnosis of Cytomegalovirus Colitis in a Presumed Immunocompetent Patient: Interpretation of Clinical Condition, Tissue, and Serum Cytomegalovirus Polymerase Chain Reaction Findings

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Cytomegalovirus (CMV) is a double-stranded DNA classified as part of the *Herpesviridae* family. The prevalence of exposure and becoming seropositive in the general population varies between 60–100%. Primary CMV infection is usually asymptomatic, but it can be associated with mononucleosis. Secondary infection is usually seen in immunosuppressed patients with impaired T-cell immunity.

Symptomatic secondary CMV infection in immunocompetent patients is rare, but when present can cause severe morbidity and mortality [1-3]. In such patients the gastrointestinal tract seems to be the most prevalent site of CMV involvement [3,4]. Few subgroups of patients with no known impaired cellular immunity are prone to develop CMV colitis. These groups include the elderly, patients with diabetes mellitus, and patients with chronic renal failure [3,4].

Practitioners involved in the evaluation and treatment of immunocompetent patients presenting symptomatic colitis may miss the diagnosis if the initial wide differential diagnosis does not include the possibility of CMV colitis and if specific diagnostic tests are not requested by the medical team.

In this case report, we describe a case of CMV colitis in an 85 year old woman with diabetes mellitus and chronic renal failure.

PATIENT DESCRIPTION

An 85 year old female patient was admitted to our hospital with abdominal pain, watery diarrhea, vomiting, and fatigue. Significant medical history included diabetes mellitus, hypertension, chronic renal failure (pre-dialysis GFR < 10 ml/hr), and s/p cerebrovascular accident. The patient had no known history of immunodeficiency and had not received any immunosuppressive medications.

Clinical examination revealed a diffuse abdominal tenderness but no signs of peritoneal irritation.

Routine blood tests results showed leukocytosis (24×10^3, normal range [NR] $4–10 \times 10^3$) with neutrophilia (90%, NR 40–70%), thrombocytosis (869×10^3, NR $140–400 \times 10^3$), metabolic acidosis (pH 7.24, NR 7.38–7.42) with high anion gap (18.1, NR 8–16), normal lactate levels (1.38 mmol/L, NR 0.5–2.4), and high creatinine (520 micromol/L, NR 46–92).

A computed tomography scan without intravenous contrast product showed notable thickening of the rectum to 2.5 cm, diffuse para-rectal fat blurring, and cecal thickening [Figure 1A].

Blood, urine, and stool cultures as well as polymerase chain reaction (PCR) for *Clostridium difficile* were taken. Empirical treatment with intravenous ceftriaxone and metronidazole was initiated for 7 days.

Under this regimen the patient's condition improved and leukocytosis normalized. Kidney function deteriorated and hemodialysis was started. Blood and stool cultures were sterile, but the diarrhea persisted.

Further evaluation included sigmoidoscopy, which demonstrated large ulcers in the rectum and sigmoid, with extensive mucosal necrosis and inflammatory pseudopolyps [Figure 1B].

Histological examination of a specimen taken from a colonic ulcer demonstrated occasional bi/multinucleate cells. Immunohistochemical staining for CMV was negative. Serum CMV-PCR was also negative. However, tissue CMV-PCR was positive (2785 copies/ml).

At this point, the patient's condition slightly improved and diarrhea lessened. Based on the clinical improvement under antibacterial therapy and the negative serum CMV-PCR and immunohistochemical staining, and despite the positive tissue CMV-PCR (with relatively low number of copies), no antiviral therapy was started. It was decided to continue in-hospital follow-up and repeat sigmoidoscopy, if necessary.

However, during the following week, the patient's condition deteriorated and diarrhea resumed. Repeat sigmoidoscopy disclosed the known colitis and pseudopolyps [Figure 1C]. Biopsies were obtained. On biopsy, immunohistochemical staining was now positive for CMV [Figure 1D] with nuclear inclusion bodies, and serum CMV-PCR became positive and tissue CMV-PCR increased dramatically (2415 and 754,884 copies/ml, respectively). Anti-viral therapy

Figure 1. Cytomegalovirus colitis imaging on a computed tomography scan, macroscopic aspect on colonoscopy, and immunohistochemic staining: [A] Rectal thickening on computed tomography, [B] Mucosal sloughing, [C] Pseudopolyps, [D] Positive staining with inclusion bodies (arrows)
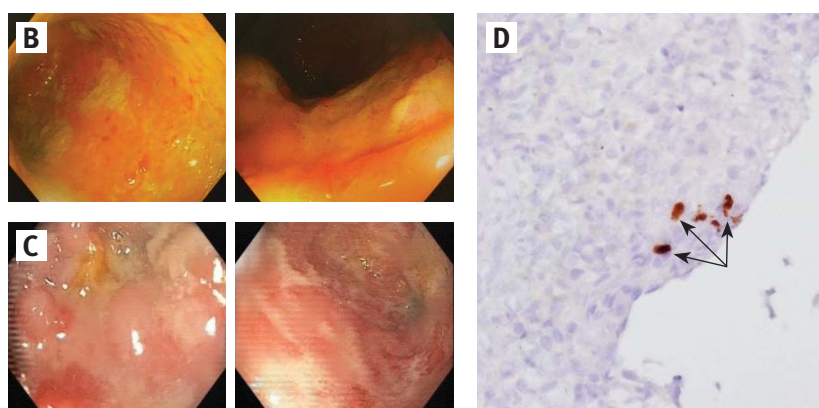
with ganciclovir was initiated for 6 weeks.

Under this regimen, the patient's condition improved and the diarrhea diminished in frequency and volume. The patient was discharged to continue ganciclovir treatment and hemodialysis at a geriatric hospital. Serum CMV-PCR became negative after the conclusion of anti-viral therapy. Four months later, the patient was re-hospitalized with severe septic shock. Despite comprehensive medical support, the patient died. Serum CMV-PCR that was obtained on arrival was negative.

COMMENT

The diagnosis of CMV colitis in immunocompetent patients is challenging for several reasons. First, due to its low incidence, the index of clinical suspicious is usually low. Second, the presentation of CMV colitis is non-specific and can mimic other diarrheal diseases, which can delay the diagnosis or lead to misdiagnosis [1]. Last, the relative role of the various diagnostic tests, including serum CMV-PCR, tissue immunohistochemical staining, and tissue

CMV-PCR has not been determined.

In the presented case, only the tissue CMV-PCR was positive at the initial evaluation. Other diagnostic methods such as immunohistochemical staining, which is considered the most acceptable method of diagnosis [5], were negative. Since the patient's condition improved with anti-bacterial therapy, it was decided not to initiate antiviral therapy and to continue follow-up.

However, the re-appearance of diarrhea and the changes in the results of repeated serum CMV-PCR and immunohistochemical staining underscore the significance of tissue CMV-PCR, even with a relatively low number of copies and when other diagnostic tests are negative.

The mortality of immunocompetent patients with CMV colitis is high. In the most comprehensive study, Galiatsatos and co-authors [2] reviewed 44 cases with a mortality rate of 32%. Another series of 19 patients reviewed by Einbinder and colleagues [5] reported a mortality rate of 26% in elderly patient with multiple co-morbidities. Another study [4] reported a mortality rate of 35.7% among 14 chronic

kidney disease patients with CMV colitis.

There are a few conditions that contribute to a higher rate of CMV colitis in patients even without immunodeficiency.

Chen et al. [4] found that most of the patients, with a medical history of chronic kidney disease and a low GFR (< 60 ml/min, stage III–V), who presented with CMV infection that involved the gastrointestinal tract (92%) (mainly colitis) frequently were affected by diabetes mellitus (50%) and hypertension (57.1%).

In addition, advanced age (above 55 years) was reported to be a risk factor for CMV colitis [1].

Our patient had a few co-morbidities, which put her at risk for CMV colitis. She was above the age of 55 years and had a medical history of diabetes mellitus, hypertension, and chronic renal failure, which caused her to be more susceptible to the occurrence of CMV colitis.

Her symptoms and laboratory results suggested bacterial or pseudomembranous colitis as the most probable diagnosis rather than CMV colitis, which was not initially suspected. The quick response to a short course of antibiotics at the beginning of the hospitalization suggested that the patient had a preliminary bacterial infection in addition to CMV colitis

CONCLUSIONS

CMV colitis in immunocompetent patients without an overt state of impaired cellular immunity is a rare but potentially severe disease associated with a high rate of mortality. It should be considered as part of the differential diagnosis of patients with colitis without formal immunodeficiency but with risk factors such as old age, diabetes mellitus, chronic kidney disease, and hypertension.

Physicians evaluating such symptomatic patients must be aware of this possible diagnosis, and specifically request CMV staining on pathology samples and tissue CMV-PCR, which are not routinely performed. The diagnosis requires consideration of the various diagnostic tests so that treatment is initiated early, thus modifying the course of the disease and reducing mortality and morbidity [1,5].

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Capsule

High-dimensional single-cell analysis predicts response to anti-PD-1 immunotherapy

Immune-checkpoint blockade has revolutionized cancer therapy. In particular, inhibition of programmed cell death protein 1 (PD-1) has been found to be effective for the treatment of metastatic melanoma and other cancers. Despite a dramatic increase in progression-free survival, a large proportion of patients do not show durable responses. Therefore, predictive biomarkers of a clinical response are urgently needed. **Krieg** and colleagues used high-dimensional single-cell mass cytometry and a bioinformatics pipeline for the in-depth characterization of the immune cell subsets in the peripheral blood of patients with stage IV melanoma before and after 12 weeks of anti-PD-1 immunotherapy. During therapy, the authors observed a clear response to immunotherapy in the T cell compartment. However, before commencing therapy, a strong predictor of progression-free and overall survival in response to anti-PD-1 immunotherapy was the frequency of CD14+CD16−HLA-DRhi monocytes. They confirmed this by conventional flow cytometry in an independent, blinded validation cohort, and proposed that the frequency of monocytes in PBMCs may serve in clinical decision support.

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Capsule

Tackling the mechanisms behind depression

The anaesthetic drug ketamine also has a rapid antidepressant effect. Although ketamine is known to block *N*-methyl-D-aspartate (NMDA) receptors, its exact target—which brain region and which cell groups—has remained elusive. **Yang** et al. found that neuronal burst firing in a single brain region called the lateral habenula drove robust depressive-like behaviors. These behaviors could be rapidly blocked by local ketamine infusion. Instead of acting on GABAergic neurons as previously suggested, ketamine blocked glutamatergic neurons in the "anti-reward center" lateral habenula to disinhibit downstream dopaminergic and serotonergic neurons. Lateral habenula bursting strongly required the synergistic action of NMDA receptors and voltage-sensitive T-type calcium channels. The latter may therefore be another promising target for the development of new rapid-acting antidepressants.

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Capsule

Innate receptor sees cancer growth factor

Innate lymphoid cells (ILCs) and natural killer (NK) cells express receptors that recognize ligands associated with pathogens and cellular stress. One such human receptor, NKp44, has been implicated in recognizing transformed cells, but its actual target has remained elusive. **Barrow** and colleagues reported that a member of the platelet-derived growth factor (PDGF) family, PDGF-DD, is a ligand for NKp44. Notably, cancer cells use PDGFs to promote their survival, growth, and dissemination. PDGF-DD induced ILC and NK cell cytokine secretion in vitro. Furthermore, the expression of PDGF-DD in tumors promoted increased rejection in NKp44-expressing transgenic mice. This effect was further enhanced by anti-CD96 checkpoint blockade. A meta-analysis of human cancer data hints that NKp44–PDGF-DD interactions may have positive clinical outcomes for certain cancers, such as glioblastoma.

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