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Severe Cytomegalovirus Gastritis During Natalizumab-Mediated Immunosuppression

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ABSTRACT
We report a 35-year-old female receiving natalizumab as monotherapy for multiple sclerosis who subsequently developed severe cytomegalovirus gastritis. As cytomegalovirus gastritis has not been previously described during natalizumab treatment, we discuss the biological plausibility of this potential association and avenues for further study.

INTRODUCTION
Gastrointestinal (GI) infection by cytomegalovirus (CMV) primarily afflicts patients who are immunosuppressed, occurring in association with transplantation, malignancy, human immunodeficiency virus (HIV) infection, and chronic steroid usage. T cell-mediated immunity is essential in restraining CMV replication and reactivation; thus, abnormalities of lymphocyte number, function, or tissue distribution may impact patient susceptibility to infection. Treatment with natalizumab, which binds α4-integrins, promotes such an immunocompromised state by blocking adhesion interactions required for lymphocyte trafficking, thus perturbing normal immunosurveillance. While numerous studies have discussed natalizumab-associated infections of the central nervous system, fewer studies have addressed infectious sequelae at other anatomic sites.

CASE REPORT
A 35-year-old woman presented in September 2015 with two weeks of nausea, vomiting, and epigastric pain, with no fevers, chills, or GI bleeding. Her past medical history was notable for multiple sclerosis (MS) diagnosed in 2012, no prior history of GI disease, and no history of recurrent or opportunistic infections that would suggest immunodeficiency. Her medications included ergocalciferol, dosed at 50,000 units per week since October 2013, and natalizumab, dosed at 300 mg every 4 weeks since February 2015; she denied use of alcohol and nonsteroidal anti-inflammatory drugs. The patient’s only prior MS therapy was a 6-month trial of dimethyl fumarate started December 2013, with no prior treatment with steroids.

On physical examination, the patient was in no apparent distress and exhibited normal vital signs. Abdominal exam showed a non-tender, non-distended abdomen with normal bowel sounds and no palpable masses. Complete blood count showed a white blood cell count of 4,900/μL (absolute neutrophil and lymphocyte counts were 1,700/μL and 2,710/μL, respectively), hemoglobin 10.5 g/dL, and platelet count 168,000/μL. Basic chemistry, hepatic function, lipase, and coagulation testing were normal. The patient was HIV-negative, and periodic John...
Cunningham (JC) virus serology testing since starting natalizumab was negative. Immunoglobulin and cortisol levels, as well as counts of CD4$^+$ and CD8$^+$ T lymphocytes, were not assessed. Barium upper GI fluoroscopy demonstrated no esophageal dilatation or stricture, hiatal hernia, reflux, or ulceration of the esophagus or duodenum. Helical computed tomography scans of abdomen and pelvis with intravenous contrast were unremarkable.

Upper GI endoscopy revealed severe inflammation of the entire examined stomach, with mucosal erosions and erythema and without ulceration or mass lesions (Figure 1). Cold forceps biopsies of the gastric antral mucosa were obtained for histopathologic analysis. Microscopic examination of hematoxylin and eosin-stained tissue showed a chronic inflammatory infiltrate and nuclear enlargement of the glandular epithelial cells consistent with reactive changes (Figure 2). Occasional epithelial cell nuclei showed prominent nucleoli and possible intranuclear inclusions. Immunostaining for CMV was positive, while it was negative for herpes simplex virus and Helicobacter pylori (Figure 3). Rapid urease testing of the biopsy tissue was negative. On the basis of these findings, a final diagnosis of severe chronic active CMV gastritis was rendered.

The patient completed a 3-week course of valganciclovir, dosed at 900 mg twice per day. She reported complete resolution of her symptoms on follow-up with her infectious disease physician 1 week after finishing treatment. Due to her clinical improvement, the patient declined repeat endoscopy. Natalizumab was continued as her MS symptoms were well-controlled; she has continued follow-up with her neurologist approximately every 3 months and has denied recurrence of her GI symptoms.

**DISCUSSION**

CMV has a broad cellular tropism and can cause disease in nearly any organ; within the GI tract, the colon and stomach are the most commonly affected sites.\(^1^,\,^4\) Definitive diagnosis of CMV gastritis relies on endoscopy and biopsy. Grossly, mucosal erosion and ulceration may be observed, with hemorrhage, obstruction, or perforation seen in more severe cases. Unusual tissue morphologies of CMV gastritis, with polypoid or pseudotumoral appearance on endoscopy, have been described.\(^5^,\,^6\) Microscopically, infected cells may show cytomegaly and intracellular viral inclusions with a surrounding clear zone ("owl's eye" inclusions).\(^2^,\,^7\)

CMV gastritis is a rare condition, with approximately 110 cases described in the literature. Presenting symptoms are generally nonspecific, including nausea, vomiting, and epigastric pain, although several unique presentations have been described, including protein-losing gastropathy with generalized edema, postural epigastric pain, chronic dysmotility, and
gastrocolic fistula formation.\textsuperscript{8,11} The majority of reported patients were immunocompromised, although several cases in immunocompetent patients have been described.\textsuperscript{8,12} CMV gastritis is typically self-limited and can be managed supportively in healthy patients, but antiviral treatment was frequently initiated in the reported cases if patients were immunosuppressed or had severe or persistent disease.\textsuperscript{2} Complete recovery was often achieved with resolution of the pathologic endoscopic findings, though notably adult cases of protein-losing gastropathy showed poorer prognosis than their pediatric counterparts.\textsuperscript{8}

Natalizumab has primarily been associated with progressive multifocal leukoencephalopathy secondary to JC virus reactivation.\textsuperscript{3} Consequently, clinical and laboratory assessment of patient immune status, including total leukocyte and T-lymphocyte counts, history of opportunistic infection and prior immunosuppressive therapy, and periodic JC virus serologic screening have been recommended for patients taking this medication.\textsuperscript{4,15} Other atypical infections, including herpes simplex and varicella zoster virus encephalitis and meningitis, as well as CMV colitis, have also been described.\textsuperscript{16,17} Notably, CMV colitis has also been reported with the use of vedolizumab, an \alpha\beta7-integrin specific antibody used to treat inflammatory bowel disease.\textsuperscript{18}

We hypothesize that CMV gastritis and colitis in patients taking natalizumab or vedolizumab share a common pathogenesis, whereby lymphocyte \alpha\beta7-integrin blockade disrupts normal mucosal immunosurveillance. Consistently, the cell adhesion molecule MAdCAM-1, which binds \alpha\beta7-integrins, is expressed by gut endothelial cells, particularly during inflammation.\textsuperscript{29} Human studies and mouse models of \textit{H. pylori} gastritis have demonstrated dense lymphocytic infiltration of MAdCAM-1-positive tissue foci, implicating this receptor in recruiting circulating lymphocytes into the gastric mucosa.\textsuperscript{19,20} More studies, however, are necessary to solidify the connection between CMV gastritis and natalizumab; given the rarity of this condition, accrual of greater numbers of natalizumab-treated patients will likely be necessary. Detailed immunologic workup will be particularly helpful in excluding other causes of immunodeficiency. Finally, animal models of viral GI infection in the setting of integrin blockade may provide important proof-of-principle and pathophysiologic insights to how natalizumab impacts susceptibility to CMV GI infection.

**DISCLOSURES**

Author contributions: SP Persaud wrote the manuscript and is the article guarantor. T. Hassan provided the images. All authors edited the manuscript and approved the final version.

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**Informed consent was obtained for this case report.**

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