Published in final edited form as:

Inflamm Bowel Dis. 2013 October ; 19(11): 2394–2399. doi:10.1097/MIB.0b013e3182a52553.

Cytomegalovirus Infection of the Ileoanal Pouch: Clinical Characteristics and Outcomes

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Abstract

Background—Up to 30% of cases of pouchitis are felt to have a secondary cause.

Cytomegalovirus (CMV) may represent a possible etiopathological agent. Here, we report our experience with CMV involvement of the pouch, including risk factors, clinical features, and pouch outcomes in patients with inflammatory bowel disease after proctocolectomy with ileal pouch-anal anastomosis.

Methods—The pathology database at Mayo Clinic in Rochester was searched between January 1995 and October 2012 for patients with a tissue diagnosis of CMV of the pouch following ileal pouch-anal anastomosis.

Results—Seven patients with CMV inclusions of the pouch were identified. The median age was 35 (range, 10–53) years, and the majority were female (71%). Five patients (71%) were on immunosuppressive medications including 4 who had undergone orthotopic liver transplantation for primary sclerosing cholangitis. The clinical presentation was similar among all patients: the majority had diarrhea (86%), fever (71%), and abdominal pain (57%). All had mucosal inflammation, with 71% having focal ulcerations in the pouch and 60% having inflammatory changes in the prepouch ileum. All patients improved with ganciclovir. None required pouch excision or had recurrent CMV infection. Three patients had recurrent nonspecific pouchitis.

Conclusions—A high index of suspicion is needed to diagnose CMV of the pouch. An increase in stool frequency and fever in patients on immune suppression or in those who have failed empiric antibiotics should prompt assessment for CMV infection. Antiviral therapy seems to be effective, and postinfection pouch outcomes seem favorable, particularly in those presenting with their first episode of pouchitis.

Keywords

cytomegalovirus; pouchitis; ileal pouch-anal anastomosis

Arestorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the surgical procedure of choice for patients with ulcerative colitis (UC) who are refractory to medical therapy or who develop colorectal neoplasia.^{1,2} Up to 50% of the patients develop postoperative complications, most commonly pouchitis,²⁻⁵ which in rare instances may require pouch excision.^{6,7}

The pathophysiology of pouchitis is incompletely understood but may be related to alterations in the pouch microbiota as a result of fecal stasis in a genetically susceptible individual.^{5,8} In support of this concept, antibiotics and probiotics have been shown to play a therapeutic role.^{9,10} Although most cases are considered idiopathic and respond to antibiotics, a substantial minority have a secondary cause and do not respond to conventional therapy.¹¹ Infectious agents, medications, ischemia, and associated autoimmune disorders have all been described as potential secondary causes.¹¹

A number of case reports have identified cytomegalovirus (CMV) as a possible etiopathological agent in patients with antibiotic-refractory pouchitis.¹²⁻¹⁵ CMV is a member of the Herpesviridae family and is ubiquitous among the adult population. Primary infection occurs most commonly in childhood followed by an indefinite period of dormancy in endothelial cells, fibroblasts, and members of the myeloid cell lineage.¹⁶ The seroprevalence varies depending on age and ethnicity with levels approaching 90% in the elderly.¹⁷ Reactivation occurs most commonly in individuals with impaired cell-mediated immunity. In patients with inflammatory bowel disease (IBD), particularly steroid-dependent disease, CMV reactivation may be common.¹⁸⁻²¹ Risk factors for CMV reactivation may include advanced age, female gender, severe disease, and immunosuppression, particularly with chronic corticosteroid use.²²⁻²⁵ CMV-associated colitis has been shown in some studies to portend a poor prognosis, with an increased risk of colectomy and mortality.^{23,26} However, data from small prospective case series and a recent larger multicenter prospective study indicate that CMV-specific antiviral therapies may improve outcome.^{20,27}

The precise role of CMV in secondary pouchitis remains unclear. Here, we report our institution's experience with CMV involvement of the pouch including risk factors, clinical features, and postinfection pouch outcomes in 7 patients with IBD following an IPAA.

METHODS

The Mayo Clinic Rochester pathology database was searched between January 1995 and October 2012 using the key terms "cytomegalovirus" or "CMV" and "pouchitis" or "ileal pouch" or "ileal pouch-anal anastomosis" or "IPAA" or "J-pouch." Inclusion criteria included patients with a history of IBD, undergoing an endoscopic examination at Mayo Clinic in Rochester, with biopsies of the ileal pouch and a tissue diagnosis of CMV. A tissue diagnosis was made histologically from hematoxylin and eosin-stained biopsies or by immunohistochemistry. Seven patients matching the key terms and the inclusion criteria were identified, including 2 who have previously been described.¹⁵ No patients were excluded from the study. The medical records of these patients, including pathology reports, endoscopy records, and laboratory values, were abstracted for relevant demographics,

clinical features, and outcomes. A preoperative diagnosis of IBD and the subtype was made based on clinical, endoscopic, radiological, and/or histological findings based on the treating physicians assessment. The Institutional Review Board of Mayo Clinic approved the study.

RESULTS

Between 1995 and 2012, 7 patients from a total of 2559 patient encounters undergoing biopsies of the pouch (0.0027%) were identified with CMV involvement of the pouch. The baseline characteristics of these patients are outlined in Table 1. Their median age was 35 (range, 10-53) years, and the majority were female (5 of 7). The initial indication for colectomy was medically refractory UC in 5 patients. The remaining 2 had a preoperative diagnosis of IBD unclassified. There was no histological evidence of CMV colitis by hematoxylin and eosin stain from all the available colectomy specimens. The median interval between IPAA and CMV pouchitis diagnosis was 9 (range, 3-15) years. Preinfection pouchitis was rare in those who underwent colectomy for UC, with only 1 individual experiencing an episode. In contrast, both patients with IBD unclassified had recurrent episodes of pouchitis before developing CMV.

Five of the 7 individuals were receiving immunosuppressive therapy at the time of CMV pouchitis (Table 1). Four individuals had undergone an orthotopic liver transplant for primary sclerosing cholangitis and were receiving immunosuppression consisting of tacrolimus with or without additional immunosuppression. The levels of tacrolimus were within therapeutic range in all individuals (data not shown). Two liver transplants were CMV mismatched (donor CMV positive, recipient CMV negative), 1 was CMV matched (donor CMV positive, recipient CMV positive), and the other could not be determined. Of the 3 nonprimary sclerosing cholangitis patients, 1 was receiving azathioprine and prednisone for recurrent pouchitis, and the others were not receiving any immunosuppressive medication.

Clinical symptoms were similar among patients; all reported crampy abdominal pain and increased stool frequency (Table 2). Fevers were also reported in 5 of the 7 patients (71%). The endoscopic appearance of the pouch included erythema and friability in all individuals. Discrete ulcerations with similarities to Crohn's-type ulcerations were present in the pouch in 5 of the 7 patients (71%) (Fig. 1). The inflammation and/or ulceration extended into the prepouch ileum in 3 out of 5 of these patients (60%). The diagnosis of CMV pouchitis was made histologically from hematoxylin and eosin-stained tissue in all patients (Fig. 2). Additionally, CMV DNA PCR of serum samples and immunoglobulin M serology that were assessed in 4 and 2 patients, respectively, were positive. CMV inclusions were detected in the pouch of all individuals and in the prepouch ileum in 3 of 5 patients (60%). In the remaining 2, involvement of the prepouch ileum could not be determined.

All patients were treated with ganciclovir for variable time lengths (Table 2). Symptomatic clinical responses were noted in all individuals, mostly within 2 weeks of treatment initiation. CMV eradication was assessed by PCR of serum samples or histologically in 5 patients and was confirmed in all the 5. Recurrent episodes of pouchitis, all CMV negative, occurred in 3 of 6 patients (50%) between 12 and 19 months after antiviral treatment. Of

these patients, 2 were felt to have recurrent Crohn's disease (CD). Both of these patients had recurrent episodes of pouchitis that preceded the CMV infection. The remaining individual had normal pouch function before developing CMV pouchitis.

DISCUSSION

In our experience, CMV infection is rarely associated with pouchitis. This study and the limited number of published case reports support this observation. Although only 0.0027% of our patient encounters (those undergoing pouchoscopy with biopsy) were positive for CMV, not all patients underwent evaluation for pouchitis, and therefore this does not reflect the true incidence of CMV as a cause of secondary pouchitis. Most centers, including our own, rely on routine histology or immunohistochemistry instead of PCR, a more sensitive diagnostic technique in establishing a diagnosis of CMV pouchitis. Therefore, it is possible that CMV-associated pouchitis is underdiagnosed. A previous study demonstrated a high prevalence of CMV in patients with pouchitis using tissue PCR for diagnosis.²⁸ In this Japanese population, 41% of patients with pouchitis compared with 11% of asymptomatic controls were positive for CMV. Interestingly, a number of these patients improved clinically and spontaneously cleared their infection following treatment with conventional agents for pouchitis, without specific antiviral therapy. This brings to question the role of CMV as a pathogen in these cases. Moreover, it remains to be determined if highly sensitive diagnostic techniques such as tissue PCR will increase the yield of diagnosing clinically relevant infections. High viral loads²⁹ and increased density of CMV-infected cells³⁰ in colonic tissue correlated with poor clinical outcomes in patients with CMV colitis. Similar studies are required in patients with CMV pouchitis to determine if a specific threshold of virus is necessary for developing clinically relevant infections.

The clinical presentation and endoscopic features of CMV pouchitis are similar to idiopathic pouchitis with a few notable exceptions. Febrile episodes were more common than the reported prevalence in patients with idiopathic pouchitis.^{5,31} Ulcers were not universally detected; however, when present they were extensive and deep, in keeping with the appearance of ulcers that has been suggested for CMV colitis.^{21,32} Interestingly, several patients had extensive involvement of the prepouch ileum, including 2 patients without CD. Both patients had endoscopic healing of the prepouch ileum after treatment with ganciclovir, supporting a direct pathogenic role for CMV. Extensive involvement of the prepouch ileum is not a feature of idiopathic pouchitis in the absence of CD.³³ Therefore, when extensive inflammation of the prepouch ileum is encountered, particularly in febrile patients, CMV infection should be considered in the differential diagnosis. Moreover, in these situations, we recommend a repeat endoscopic examination after antiviral treatment to document endoscopic healing and exclude the diagnosis of CD.

In this study, we identified female gender and immunosuppressive treatments as potential risk factors for CMV pouchitis. This is in keeping with the risk factors that have been identified for CMV colitis.²¹⁻²⁴ Of interest, 4 of our 7 patients had undergone liver transplantation, and at least 2 of these were CMV mismatched (donor graft CMV positive, recipient negative). In both patients, CMV pouchitis occurred within 1 month of stopping valganciclovir prophylaxis, likely representing a vulnerable time for this population to

acquire CMV disease. A high incidence of CMV disease, within the first year after orthotopic liver transplant has also been reported in the transplant literature. In the largest series, 19% of high-risk patients (donor graft CMV positive, recipient negative) develop CMV disease, with 14% involving the gastrointestinal tract.³⁴ Transplantation for primary sclerosing cholangitis (12% of the patients) was not identified as an independent risk for the development of CMV disease. Given the high rates of CMV disease within the first year after transplantation, clinicians should have a low threshold for performing an endoscopic evaluation of the pouch in individuals who develop symptoms of pouchitis.

Impaired cell-mediated immunity, NK cell effector function, and dysregulated cytokine responses, particularly involving tumor necrosis factor alpha and interferon gamma, are important risks for reactivation of CMV in intestinal mucosa.³⁵ In the absence of these risks, CMV is rarely detected. Only a small number of cases have been described in immunocompetent individuals, and many had other risk factors such as advanced age, comorbidities, and/or chronic intestinal inflammation.²⁵ Interestingly, we describe 2 individuals without any identifiable risk factors, each presenting with their first episode of pouchitis. Two similar cases have also been reported in the literature.^{12,13} Chronic inflammatory changes including mononuclear cell infiltrates and altered cytokine responses occur in normal pouches, likely an adaptive response to fecal stasis in genetically susceptible individuals.^{36,37} It is possible that this subclinical chronic inflammation predisposes these individuals to reactivation of CMV in the presence of altered antiviral immunity as a result of immunosuppressive treatment.

The precise role of CMV in the pathogenesis of IBD exacerbations has been a topic of considerable debate.^{18,21} It remains unclear whether CMV plays an active role in colonic inflammation or simply acts as an innocent bystander. When therapy is considered, intravenous ganciclovir at a dose of 5 mg/kg every 12 hours for at least 2 to 3 weeks is the treatment of choice.^{38,39} Oral formulations are an attractive alternative for convenience of administration; however, concerns regarding their bioavailability, particularly in patients with intestinal inflammation have limited their use. Oral valganciclovir has significantly improved bioavailability compared with oral ganciclovir, with levels that approximate those achieved by intravenous ganciclovir.⁴⁰ Moreover, in a prospective study of solid organ transplant recipients with CMV disease, including 30% with gastrointestinal involvement, valganciclovir was noninferior to intravenous ganciclovir in reducing CMV viremia and improving symptoms.⁴¹ Additional studies are needed to confirm these findings, particularly in patients in whom drug intestinal absorption may be impaired. As a result, we routinely initiate therapy with intravenous ganciclovir. The duration of therapy and the utility of a stepdown approach to oral valganciclovir have not been well studied. Therefore, we routinely involve the expertise of our infectious disease colleagues for guidance with these decisions. In our series, all patients were treated with intravenous ganciclovir, the majority for 3 weeks. Valganciclovir was used for an additional 24 weeks in 1 patient due to persistent low-grade viremia. All patients improved clinically after treatment with ganciclovir, and the majority did not receive additional conventional treatments for idiopathic pouchitis. Therefore, it is reasonable to conclude that the clinical responses were related to the specific antiviral treatment.

There is sparse data in the literature to guide clinicians on how best to follow patients after antiviral therapy. A repeat endoscopic examination should be considered to confirm CMV eradication and to assess for mucosal healing, especially when features of CD such as deep mucosal ulcerations and/or inflammation of the prepouch ileum were present on the index examination. An alternate method of following patients would be to use CMV serum levels as a surrogate marker for colonic disease. However, studies in UC have shown that CMV viremia correlates poorly with tissue diagnosis and, therefore, is not used routinely.^{26,42,43} In our study, serum PCR correlated with the tissue diagnosis of CMV of the pouch. All the 4 patients assessed for CMV viremia by PCR were positive, including 3 patients who underwent an orthotopic liver transplant. A possible explanation for this discrepancy is that the majority of these patients were treated with tacrolimus, a calcineurin inhibitor that inhibits T-cell activation and may make patients more susceptible to systemic CMV infection. Further studies are required to confirm these findings. Until then, we feel it is reasonable to repeat the endoscopic examination after completion of antiviral therapy.

This study provides insights into the natural history of pouch function after CMV infection. The development of CMV-related pouchitis did not appear to alter the preinfection pouch function. Therefore, individuals without a history of recurrent pouchitis were likely to maintain a normal pouch function after treatment for CMV. These findings were surprising given that CMV colitis is often associated with poor outcomes, including increased rates of colectomy and mortality.^{23,26} Caution must be used when interpreting these data, given the small sample size and relatively short follow-up (median of 1 yr).

A high index of suspicion is needed to diagnose CMV pouchitis. The presence of symptoms in individuals who are immunosuppressed or have not responded to conventional therapies for pouchitis should prompt an assessment for CMV infection. Additional clues include the presence of fever or ulcerations in the prepouch ileum. Antiviral therapy seems to be effective, and the postinfection pouch outcomes seem to be favorable, particularly in those individuals presenting with their first episode of pouchitis.

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FIGURE 1.
Representative endoscopic image of a patient with CMV involving the ileal pouch demonstrating loss of vascularity, erythema, and ulcerations.

FIGURE 2. Representative hematoxylin and eosin-stained mucosal biopsy from an ileal pouch demonstrating CMV inclusion bodies. A, $\times 100$ magnification; B, $\times 400$ magnification.

TABLE 1

Patient Demographics, Disease Characteristics, and Immunosuppression

Patient	Gender	Age	IBD	PSC	Medications
1	F	46	UC	Yes (OLT)	Tacrolimus and prednisone
2	F	23	UC	Yes (OLT)	Tacrolimus, prednisone, and azathioprine
3	F	10	IBDU	Yes (OLT)	Tacrolimus, MMF, ciprofloxacin, and metronidazole
4	M	53	IBDU	No	Prednisone and azathioprine
5	M	48	UC	Yes (OLT)	Tacrolimus, MMF, ciprofloxacin, and metronidazole
6	F	29	UC	No	None
7	F	35	UC	No	None

F, female; IBDU, IBD unclassified; M, male; MMF, mycophenolate mofetil; OLT, orthotopic liver transplant.

TABLE 2
CMV Infection of the Pouch: Clinical Characteristics, Diagnosis, Treatment, and Outcome

Patient	Pouch History	Clinical Presentation	Pouch	Prepouch Ileum	Diagnosis	Treatment	Outcome and Timing (Post Treatment)
1	Pouchitis (single episode)	Acute onset fever, diarrhea, abdominal discomfort, and hypotension	Inflammation; Extensive ulcers	Inflammation; Ulcers (2-3 mm)	Tissue H&E positive; Serum PCR positive	GCV (8 wk); VGC (24 wk)	Gradual clinical response over 4 wk; Serum PCR: 60-fold decrease viral load; No pouch assessment; No clinical recurrence (up to 1 yr)
2	No pouchitis	Acute onset fever, mild increase in stool frequency; No abdominal pain	Inflammation; No ulcers	Inflammation; Ulcers (2.5 cm)	Tissue H&E positive; Tissue IHC positive; Serum PCR positive; IgM serology positive	GCV (3 wk); VGC (4 wk)	Clinical response within weeks; Serum PCR and tissue H&E negative for CMV (2 d after ganciclovir treatment); Pouchoscopy: normal endoscopically; No clinical recurrence (up to 2 yr)
3	Chronic pouchitis	Acute onset diarrhea, fecal incontinence, and abdominal pain; No fever	Inflammation; No ulcers	No inflammation; No ulcers	Tissue H&E positive; Serum PCR positive; IgM serology positive	GCV (3 wk)	Clinical response within weeks; Tissue H&E negative for CMV (2 wk); Pouchoscopy: inflammation; Recurrent episodes pouchitis (1 yr), diagnosed with CD
4	Chronic pouchitis (CD of the pouch)	Acute on chronic diarrhea and abdominal pain; Fever	Inflammation; Extensive ulcers "superficial and deep"	Inflammation; Extensive ulcers "superficial and deep"	Tissue H&E positive	GCV (3 wk)	Clinical response within weeks; Recurrent episodes pouchitis (1.5 yr); Tissue H&E negative for CMV; Pouchoscopy: inflammation and ulcers; Diagnosed with CD
5	No pouchitis	Acute on chronic diarrhea; No fever or abdominal pain	Inflammation; Extensive ulcers "large"	No inflammation; No ulcers	Tissue H&E positive; Tissue IHC positive	GCV (5 wk)	Clinical response within weeks; Serum PCR negative (1 wk); No pouch assessment; No clinical recurrence (up to 5 mo)
6	No pouchitis	Fever, abdominal pain, and diarrhea	Unknown	Unknown	Tissue H&E positive	GCV (10 d)	Clinical response (timing not clear); 3 recurrent episodes of pouchitis; Tissue H&E negative for CMV; Pouchoscopy findings unknown
7	No pouchitis	Fever, N/V, malaise, blood discharge from defunctioned pouch	Unknown	Unknown	Tissue H&E positive; Tissue IHC positive; Serum PCR positive	GCV (3 wk)	Clinical response (timing not clear); No clinical recurrence (follow-up unknown)

GCV, ganciclovir; H&E, hematoxylin and eosin; IgM, immunoglobulin M; IHC, immunohistochemistry; N/V, nausea and vomiting; PSC, primary sclerosing cholangitis; VGC valganciclovir.