Viral and Fungal Infectious Colitides

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ABSTRACT

Viral and fungal colitides are rare in the immunocompetent host but are most clinically significant in populations with compromised immune function. They may be associated with high mortality, particularly when treatment is delayed. It is important to be aware of these diseases when treating patients with colitis to allow early diagnosis and treatment, which will improve outcome.

KEYWORDS: Colitis, cytomegalovirus, histoplasmosis, candidiasis, AIDS

Objectives: On completion of this article, the reader should be able to summarize the presentation and treatment strategy for the most common viral and fungal colitides.

Viral and fungal colitides rarely become clinically apparent in the immunocompetent host. However, in the evaluation of colitis in patients with known alteration in immune function, many of these entities need to be considered. Patients with acquired immunodeficiency syndrome (AIDS), a transplant history, and even processes resulting in more subtle alterations in immune function such as chronic liver and renal disease, diabetes, and older age may be predisposed to developing these infections. Patients with a history of inflammatory bowel disease (IBD), with or without oral steroid therapy, may also be particularly susceptible to viral colitides. Even when treating colitis in a patient with presumably normal immune function, it is helpful to have an excellent understanding of these disease possibilities because all of them have been reported to occur, albeit rarely, in immunocompetent hosts as well. This article provides a discussion of the most frequently encountered viral colitides including cytomegalovirus and evaluation of colitis in the patient with AIDS. Fungal colitides including histoplasmosis, aspergillosis, and candidiasis are also reviewed. A diagnostic approach and treatment strategy are outlined for each of the pathogens.

VIRAL COLITIDES

Cytomegalovirus

Cytomegalovirus (CMV) is a member of the Herpesvirus family and is a double-stranded DNA virus. It is an extremely common pathogen, and it is estimated that the majority of people have had an asymptomatic infection with a lifetime prevalence between 60% and 90%. When CMV colitis occurs, it is generally believed to be most commonly due to a reactivation of a latent infection secondary to an alteration in immune function of the host, specifically T lymphocyte immunity. This type of infection is termed a secondary infection. Less commonly, initial exposure to CMV in an immunocompromised host may also produce a symptomatic primary infection. CMV viremia results in deposition of CMV in endothelial cells, which serves as a foci for inflammation, causing vasculitis and the development of erosions in the colon. Although our article focuses specifically on CMV colitis, CMV infection can occur anywhere throughout the entire gastrointestinal tract. Three groups of patients are especially susceptible to CMV infection and they are

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Miscellaneous Colitides; Guest Editor, Judith L. Trudel, M.D.

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addressed separately in this article: patients with AIDS, transplant recipients, and patients with IBD.

Patients with CMV colitis present clinically with abdominal pain, fever, and bloody or watery diarrhea. Patients may also have tenesmus, hematochezia, and smaller volume stools. Endoscopic findings typically show friability of the involved mucosa and may be segmental.¹ CMV has also been described as mimicking colon cancer by appearing as a polypoid mass,^{2,3} clinically mimicking ischemic colitis⁴ or arising with megacolon. Given the ubiquity of seropositivity of this virus in the general population, distinguishing between colitis from CMV infection and diarrhea from another etiology in a seropositive patient can be challenging. Biopsies of the colon should be obtained and may be analyzed in several ways. Microscopic examination of infected tissues may demonstrate CMV inclusions surrounded by a clear halo, termed Cowdry "owl's eye" inclusions. The identification of these inclusion bodies among inflamed cells is considered pathognomonic for CMV colitis. Inclusion bodies surrounded by normal-appearing cells may represent colonization. Immunohistochemistry and polymerase chain reaction may also be performed on biopsy specimens. These are more sensitive testing modalities but also produce more false positives secondary to identifying viremia from blood in the biopsy that may not necessarily indicate cellular infection.

When CMV colitis is identified, it should be treated promptly with parenteral ganciclovir (5 mg/kg intravenously every 12 hours) or foscarnet (60 mg/kg every 8 hours) followed by oral treatment. Surgery is reserved for patients who do not improve with medical management or those presenting with perforation, megacolon, and uncontrolled bleeding.⁵ This represents a minority of cases. When surgical treatment is undertaken, the goal is resection of the diseased area without anastomosis because of the seriousness of the disease process. A meta-analysis reported on 44 immunocompetent patients and identified a mortality rate of 31% for the group.⁶ Advanced age, male gender, comorbidities, and need for surgical intervention were associated with higher mortality rates.

CMV INFECTION IN THE PATIENT WITH AIDS

CMV is the most common gastrointestinal infection in patients with AIDS, and its development often leads to the diagnosis of AIDS in patients not previously diagnosed. Although the most common form of CMV infection in patients with AIDS is retinitis, colitis is the second most common CMV infection.⁷ CMV colitis is usually uncommon in patients with CD4 counts greater than 100/mm³ but has been described in patients with moderate immune deficiency⁸ and higher CD4 counts. It should be considered a possibility in any patient with AIDS and significant abdominal examination findings. Some have suggested that with increased prophylaxis of

other infection and success of antiretrovirals, the incidence of CMV colitis may be increasing.⁹

Principles of management include early colonoscopy with biopsies. Patient should also undergo routine ophthalmologic examination to look for retinitis, which could be a possible sequela of disseminated CMV infection. Patients with severe symptoms should be treated with ganciclovir or foscarnet. Current practice parameters from the Infectious Diseases Society of America suggest a 21- to 28-day course of treatment with these antivirals.⁷ If symptoms are mild, some specialists recommend withholding specific therapy while initiating or optimizing highly active antiretroviral therapy (HAART). Oral valganciclovir may also be considered as a treatment modality if symptoms are not interfering with oral absorption. Chronic maintenance therapy is no longer recommended routinely for gastrointestinal disease but may be considered when recurrent cases of colitis develop.

CMV IN THE TRANSPLANT PATIENT

CMV infections are overall the most common viral infections among solid organ transplant recipients.¹⁰ Untreated CMV colitis is associated with an extremely high mortality rate, and the clinical presentation may be subtle in this group of patients. CMV infections have also been demonstrated to be related to an increased incidence in graft rejection. There is a relationship between CMV infection in the endothelium and subsequent vascular damage, which is the likely etiology of the increased rejection.¹¹ In a study of transplant patients, early colonoscopy was advocated whenever the diagnosis of CMV colitis is considered.¹² In this group's series, several of the patients had very mild clinical symptoms and colonoscopy expedited initiation of appropriate treatment. Early colonoscopy and prompt treatment of CMV colitis in the transplant patient may minimize mortality and maximize graft survival.

CMV AND IBD

An understanding of the relationship between CMV infection and IBD is evolving and becoming clearer as more literature is available regarding this topic. It is known that patients with IBD treated with immunosuppressive agents are at risk for CMV colitis. Patients with ulcerative colitis (UC) appear to be more at risk than those with Crohn's disease, but CMV infections have been reported in patients with Crohn's disease as well.¹³ It has been reported that simultaneous CMV infection may exacerbate IBD and cause medical treatment failures or increase the need for colectomy. Differentiating between symptoms related to IBD and those resulting from CMV infection can be especially difficult because the symptoms can be very similar. A group from Japan performed a thorough pathologic analysis of all specimens after colectomy

for UC.¹⁴ Patients were divided into three groups: severe UC, refractory UC, and those undergoing surgery for dysplasia and cancer. The authors found that 25% of those with severe UC had evidence of CMV infection compared with 8.3% in the steroid-refractory group and 0% in the group undergoing surgery for dysplasia. The authors suggested that CMV infection should be ruled out in UC patients requiring higher doses of steroid and immunomodulator therapy.

Evaluating Other Viral Colitides in the AIDS Patient

Although CMV colitis is the most common viral colitis in AIDS patients, several other viral pathogens have been described in AIDS patients. Herpes simplex virus (HSV) most commonly causes proctitis and perianal disease but has been described as also causing colitis in patients with AIDS. Adenovirus colitis may mimic CMV colitis, and coinfection with adenovirus and CMV has also been described.¹⁵ Norwalk virus and rotavirus may cause colitis in AIDS patients as well as immunocompetent hosts. Picobirnavirus and astrovirus are additional potential pathogens leading to colitis in the AIDS patient.¹⁶

AIDS enteropathy has been used as a general term to describe chronic diarrhea occurring in a patient with AIDS when a specific cause cannot be identified despite an extensive work-up. Histologic changes have been described in patients with AIDS, and these include mucosal hypoproliferation. The theory is that enteric human immunodeficiency virus (HIV) infection may cause mucosal atrophy, which would diminish the absorptive capacity of the bowel and lead to diarrhea and weight loss.¹⁷ Although it is possible that these pathologic changes associated with AIDS infection may result in diarrhea, it is more likely that most cases of AIDS enteropathy are due to a pathogen that was not diagnosed. It is suggested that with an extensive work-up the precise cause may be found in more than 90% of cases.¹⁸

The current management recommended for working up diarrhea in a patient with AIDS¹⁴ includes a stool specimen for bacterial culture (salmonella, shigella, campylobacter) and a stool smear (fecal leukocytes, ova and parasites with three to six specimens, acid-fast stains, *Clostridium difficile* toxin). Patients with rectal bleeding, tenesmus, or fecal leukocytes should undergo lower endoscopy and biopsies for pathology, viruses, and protozoa. Whenever CMV is suspected, complete colonoscopy should be performed given the possibility of isolated right-sided lesions with CMV colitis. Upper endoscopy and small bowel mucosal biopsy are recommended if diarrhea and weight loss persist. It is important to remember that AIDS patients receiving treatment with antiretroviral medication may also develop a drug-induced diarrhea, which should be included

in the differential diagnosis, particularly when the infectious work-up is negative.¹⁹

FUNGAL COLITIDES

Histoplasmosis

Histoplasmosis is caused by the fungus *Histoplasma capsulatum*. The majority of clinical histoplasmosis infections occur among immunocompromised patients. It is the most common fungal gastrointestinal infection among AIDS patients. The organism is widely distributed throughout the United States but particularly prevalent in the Ohio and Mississippi River valleys. The general mode of transmission of histoplasmosis is inhalation of spores followed by a self-limited pulmonary infection and dissemination of fungus hematogenously in the immunocompetent individual. Patients with immune system defects are likely to develop more serious infections when exposed to histoplasmosis because of the possibility of disseminated disease after hematogenous exposure.²⁰ These patients may develop gastrointestinal infections as a part of a disseminated disease process, although the gastrointestinal symptoms may be most prominent during the initial clinical presentation. Symptoms can vary and may involve abdominal pain, anorexia, and diarrhea. In the largest published series, a constellation of symptoms including fever, diarrhea, weight loss, and abdominal pain was particularly common in patients with AIDS who develop gastrointestinal histoplasmosis.²¹ Endoscopic findings usually include some hyperemia and friability, although larger ulcerations and pseudopolyps have been described as well. The presence of particularly deep central ulcers on top of pseudopolyps may be one manifestation of histoplasmosis in the colon. It should be noted that the presentation of histoplasmosis has been reported to mimic that of colon cancer with constricting mass lesions²² and has been mistaken for IBD in some reports.²³ Although histoplasmosis is most commonly associated with immunocompromised patients, particularly those with AIDS, there are reports in the literature of patients with normal immune function experiencing colonic histoplasmosis.²²

When colonic histoplasmosis is suspected, colonoscopy with multiple biopsies should be performed. Diagnosis of histoplasmosis may be based on the tissue culture or examination of the histology. Histoplasmosis characteristically can be identified by the presence of granulomas, but this finding may be reduced in severely immunocompromised patients.²⁴ A combination of fungal stains and cultures should be added to histologic examination. In some cases, diagnosis may not be made until after surgical resection for presumed malignancy has been performed.

The primary treatment of colonic histoplasmosis is medical. The most commonly used agent in published

case series has been amphotericin B (0.6 mg/kg/day). The use of liposomal amphotericin B should be the first-line treatment now, particularly in patients who are immunocompromised. Intravenous itraconazole at a dose of 200 mg/day is another option for patients who are unable to tolerate amphotericin. Surgical therapy may be required in some cases, with 28% of patients requiring surgery in one series.²¹ Surgery is often performed when the diagnosis is not known or suspected preoperatively, such as when patients develop strictures or masses or present with acute abdominal findings. Surgery may also be required when medical therapy is not successful and patients progress to a more fulminant form. Mortality is especially high in these circumstances.

Candidiasis

Candida is a saprophytic yeast with several forms. The most common form is *Candida albicans*, but increasing numbers of infections with *Candida glabrata* have been reported, particularly in immunocompromised patients. Candidal infections of the gastrointestinal tract have been recognized in immunocompromised patients for many years, particularly of the oral cavity and esophagus. In cases of disseminated disease the lower gastrointestinal tract may also be involved. *Candida* is a component of normal colonic flora, but pathologic colitic processes have been described in patients with HIV and transplant patients.²⁵

Treatment of candidal colitis is initially with oral antifungal agents. If patients fail to improve with medical management, surgical resection of the involved segment may be required. One recent case series documented fatal cerebral hemorrhage following right hemicolectomy in two patients with candidal colitis.²⁶ Although the available literature regarding the prognosis of candidal colitis is sparse, the case reports that exist suggest the potential for a serious infection with a high mortality rate.

Another possible manifestation of candidal involvement of the colon is the phenomenon of secretory diarrhea and histological evidence of infection without grossly visible inflammatory findings on endoscopy. This has been reported as a possibility for many years and was first suggested in 1936.²⁷ Supporting this hypothesis has been the observation that in the patients included in these case series, a prompt resolution of symptoms was observed after the initiation of oral antifungal therapy, usually with nystatin. The mechanism suggested has been an overgrowth of *Candida*.²⁸

Additional Fungal Infections

Several other fungal pathogens have also been described to result in colitis. *Aspergillus* is a saprophytic mold found worldwide that is characterized by aggressive and highly

lethal infections in the immunocompromised host.²⁹ Although the most frequent manifestations of aspergillosis involve pulmonary infection such as aspergilloma and allergic bronchopulmonary aspergillosis, the disease may become disseminated and affect the colon. Aggressive medical treatment with antifungals is required whenever it is identified.

Cryptococcus neoformans is a fungus that affects immunocompromised patients. It most commonly involves the pulmonary or central nervous system, and patients often present with meningitis. There are cases reported in the literature, however, of gastrointestinal cryptococcal infection. These have been reported in HIV-negative patients³⁰ as well as those with definite immunocompromising diseases. One series that studied autopsy specimens of patients with a history of disseminated cryptococcal infection found that the colon was the most common site of gastrointestinal infection when identified.³¹ The use of an antigen test may be helpful in establishing the diagnosis; perforation has been noted following colonoscopy and biopsy in one case report.³⁰ Medical treatment includes amphotericin B followed by fluconazole.

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