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TOPIC HIGHLIGHT

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Role of upper endoscopy in diagnosing opportunistic infections in human immunodeficiency virus-infected patients

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Abstract

Highly active antiretroviral therapy (HAART) has dramatically decreased opportunistic infections (OIs) in human immunodeficiency virus (HIV)-infected patients. However, gastrointestinal disease continues to account for a high proportion of presenting symptoms in these patients. Gastrointestinal symptoms in treated patients who respond to therapy are more likely to the result of drug-induced complications than OI. Endoscopic evaluation of the gastrointestinal tract remains a cornerstone of diagnosis, especially in patients with advanced immunodeficiency, who are at risk for OI. The peripheral blood CD4 lymphocyte count helps to predict the risk of an OI, with the highest risk seen in HIV-infected patients with low CD4 count (< 200 cells/mm^3). This review provides an update of the role of endoscopy in diagnosing OI in the upper gastrointestinal tract in HIV-infected patients in the era of HAART.

Key words: Human immunodeficiency virus; Opportunistic infections; Upper gastrointestinal tract; Gastrointestinal endoscopy; Highly active antiretroviral therapy

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INTRODUCTION

Highly active antiretroviral therapy (HAART) has dramatically reduced the incidence of opportunistic infections (OIs) in human immunodeficiency virus (HIV) disease. Different factors may be related to the decreasing prevalence of OI in the era of HAART. Besides restoring immune function[1], antiretroviral protease inhibitors have been reported to have a direct inhibitory effect on the proteases of certain pathogens, including the aspartyl proteases of some parasites[2,3].

Nevertheless, the gastrointestinal (GI) tract is still affected by OI in HIV-infected patients undergoing HAART, especially in those with severe immunosuppression[4]. Patients undergoing HAART may not have a sustained CD4 lymphocyte count increase for several reasons, including poor adherence to therapy, drug toxicity or interactions, acquisition of a drug-resistant strain of HIV, and/or the development of a discordant immunological response, which leads to low CD4 cell counts despite optimal suppression of plasma HIV viremia[5]. Whatever the reason, HIV-infected patients with a low CD4 cell count remain at high risk for OIs, including GI infections. Also, these patients may have an atypical presentation of OI, either early after the initiation of therapy or after prolonged treatment[6]. Hence, a CD4 count < 200 cells/mm^3 remains an important marker for those patients in whom OIs should be suspected as a cause of GI symptoms.

Nowadays, HAART-related GI adverse events have been recognized as a frequent cause of GI complaints[7]. When a physician is challenged with an HIV-infected patient with upper GI complaints undergoing HAART, his final diagnosis is usually unrelated to HIV-associated immunodeficiency. Therefore, careful evaluation is needed when considering GI symptoms in these patients, especially in those with advanced immunodeficiency.

The tropism of many pathogens for the squamous mucosa of the esophagus (*Candida*, herpesviruses), as well the appearance of new diseases (idiopathic esophageal ulceration) has established the upper GI tract as a common site for complications[8]. Upper endoscopy with mucosal biopsies is a standard part of the evaluation of upper GI symptoms in these cases, especially because the therapy will depend on the specific pathogen found. In this review, we discuss the role of endoscopy in diagnosing OIs in the upper GI tract, in the HAART era.

ESOPHAGUS

HAART has changed the epidemiology of esophageal infections in HIV disease. Mönkemüller *et al*[9] have evaluated the prevalence of GI OI in symptomatic HIV-infected patients undergoing endoscopic procedures from 1995 to 1998. They observed that the prevalence of OI fell from 69% to 13% coincident with the use of HAART. The number of patients identified with esophageal candidiasis or cytomegalovirus (CMV) infection fell by 80%, while the prevalence of gastroesophageal reflux disease rose eight-fold. In another more recent study[4], this same author observed GI OI in 9% of patients undergoing HAART. Those patients had a significantly decreased CD4 count (mean 23 cells/μL) despite HAART use.

There is not a close relationship between esophageal symptoms and OI. However, patients presenting with odynophagia are more prone to esophageal ulcers[10]. Biopsy is mandatory when finding esophageal ulcers upon endoscopy. Definitive differential diagnosis of esophageal ulcers can only be made by histological examination.

On the other hand, normal-appearing esophageal mucosa at endoscopy has a good correlation with the absence of OI. We have done a prospective study in a large cohort of dyspeptic and immunosuppressed HIV-infected patients (n = 1010), who underwent endoscopy with esophageal biopsies in order to evaluate the presence of OI in a normal-appearing esophagus. A pathogen was found in normal-appearing esophageal mucosa in only one patient (0.09%)[11]. We concluded that it is not necessary to perform biopsies in normal-appearing esophageal mucosa, even in patients with advanced immunosupression.

Candida spp.

Despite the decreasing prevalence of OI, *Candida* spp. continue to be the most common cause of OI in the esophagus, followed by viral infection, especially CMV. Patients often present with dysphagia, but may also develop odynophagia and/or acute retrosternal chest pain. The presence of oral candidiasis (thrush) suggests candidal esophagitis. On the other hand, the absence of thrush *per se* does not exclude it. Some authors recommend empirical antifungal therapy for HIV-infected patients who present with dysphagia, postponing endoscopy for those individuals in whom symptoms persist[12]. This approach seems to be a safe, efficacious, and cost-effective procedure.

At endoscopy, *Candida* esophagitis shows a characteristic superficial mucosal pattern: focal or confluent yellowish-white plaques that overlie an erythematous mucosa. It is seldom related to mucosal ulceration, which in general results from causes other than *Candida* infection[13].

Endoscopy has also been used to grade the severity of *Candida* infection. We have analyzed the relationship between *Candida* esophagitis severity and peripheral blood CD4 cell count in a prospective study of a large cohort of adult HIV-infected patients (n = 261, mean CD4 cell count = 78.8 cells/mm^3). Severity was graded I to IV[14] according to the extent of mucosal lesions. We have shown that the least severe disease (grade I) was related to the highest CD4 cell counts when compared to all others (P = 0.0003). Meanwhile, the progression of disease severity from grade II to IV was not related to a corresponding decrease in CD4 cell counts. These findings suggest that even in immunosuppressed HIV-infected patients, immunological status may play a role in limiting *Candida* disease in initial grades, but seems to be irrelevant in the following progression of the infection[15]. Other mechanisms, such as the local epithelial defenses, may be involved with the development of these OIs in the GI mucosa.

CMV

Patients that present with severe odynophagia or who fail empirical antifungal therapy usually have viral esophagitis or esophageal ulcers. These patients should be promptly referred for upper GI endoscopy, since they exhibit increased morbidity and may rapidly become malnourished[10].

The most common virus detected is CMV, which may cause erosive esophagitis or deep esophageal ulcers. Upon endoscopy, CMV esophagitis appears frequently as small, well-circumscribed ulcerations, with a normal appearance of the intervening mucosa[16]. This appearance is similar to herpes esophagitis, but it is usually distinguishable from esophageal candidiasis. CMV ulcers are usually located in the middle or distal esophagus and are characteristically deep, with a halo of edema. This appearance is identical to the large idiopathic esophageal ulcerations associated with HIV infection[17]. The former ulcers are believed to be secondary to CMV-induced vasculitis, with ischemic injury of the endothelium. The CMV viral cytopathic effect is rarely identified in squamous epithelial cells alone, and thus, biopsies of the ulcer base should be carried out. The diagnostic feature of CMV with hematoxylin-eosin (H&E) staining is a central dense eosinophilic inclusion with a surrounding halo, which leads to an owl's eye nuclear inclusion appearance. It may also show basophilic granular cytoplasmic inclusions[18].

Herpes simplex virus (HSV)

HSV type 1 or 2 infection is associated with small, superficial, scattered or coalescent shallow ulcers with

exudate, which are separated by normal-appearing mucosa[17]. It has also been associated with deep ulcers. Biopsies should be done at the edge of the ulceration, as the HSV viral cytopathic effect is more reliably found in squamous cells. Histological analysis reveals typical Cowdry type-A intranuclear inclusion bodies[19].

Mycobacterium

Esophageal tuberculosis is rare and is associated with direct extension of the disease from adjacent mediastinal lymph nodes or lung foci. The middle third of the esophagus is the typical site of tuberculous involvement. It may exhibit different endoscopic appearances. In the first form, deep single or multiple ulcerations of various sizes form, with shallow smooth edges and a gray-white base, and the surrounding mucosa may contain small nodules or ulcerations. The second form is characterized by a hypertrophic or a granular-appearing lesion. This form may produce granulomatous fibrosis in the esophageal wall with stricture of the lumen. The third form consists of a protruding subepithelial mass. Fistulas may develop, and it may be bronchoesophageal as well as esophagoesophageal[20]. Biopsies should be taken from the edge of the lesions. Histological findings infrequently show acid-fast bacilli and caseating granulomas[17].

Idiopathic ulceration

Idiopathic ulceration may develop at the time of initial HIV infection or may occur long after the initial seroconversion period. Endoscopy usually shows a large single or multiple deep ulcers in the mid or lower esophagus, with transverse ridges visible in the base, which represent circular muscle bundles of the esophageal muscularis propria. The margins show variable degrees of inflammation, are often irregular, and overhang into the central ulceration. Evidence indicates that these ulcers are caused by HIV[20]. These lesions are negative on biopsy for known viral and fungal agents. Electron microscopy can be used to confirm the presence of HIV-like viral particles in these ulcers[21].

STOMACH

Symptoms of dyspepsia, such as epigastric pain, fullness, nausea and vomiting, are frequently reported by HIV-infected patients, mainly those undergoing HAART[7]. These symptoms may have different etiologies, including any adverse drug effects (HAART or others), the HIV disease itself, and GI infections. It is still unknown whether GI OI may cause dyspepsia as the main symptom.

Under normal conditions, most organisms cannot thrive in the acidic gastric environment. A decrease in gastric acidity has been described in HIV-infected patients[22], possibly providing a more suitable environment for pathogen colonization. However, gastric OI seems to be an infrequent event even among HIV-infected patients[8].

We have performed upper GI endoscopy with biopsies of the stomach and duodenum in a large cohort of HIV-infected patients (n = 528) with dyspeptic symptoms undergoing HAART. We have shown a low prevalence (3.66%) of OI in these patients. It is noteworthy that the few cases of observed gastrointestinal OI were seen exclusively in HIV-infected patients with CD4 $\leqslant$ 200 cells/mm^3[23].

In order to look for a correlation between OI and dyspeptic symptoms, we have performed another prospective study in a large cohort of HIV-infected patients (n = 690) with advanced immunodeficiency (CD4 < 300 cells/mm^3; mean = 154.3 cells/mm^3), despite HAART. We have compared the prevalence of GI OI in dyspeptic (n = 500) *versus* non-dyspeptic (n = 190) patients. All patients underwent upper digestive endoscopy with tissue biopsies from stomach and duodenum. Although GI OI was detected exclusively in the dyspeptic patient group, we could not demonstrate a relationship between GI OI and dyspepsia, since it occurred in low numbers (just 1.6% of patients)[24].

Although not frequent, gastritis and/or gastric ulcers have been reported to be associated with some viral, helminthic, protozoan, and fungal pathogens[25-28].

CMV

Gastric CMV is the most common OI of the stomach[29]. It is commonly associated with non-specific symptoms such as epigastric pain, nausea and vomiting. Upon endoscopic examination, gastric CMV is usually associated with ulcerations, erosions and mucosal hemorrhage[25,30], although it may be present in a normal-appearing mucosa[31]. Less commonly seen lesions are thickened edematous folds[32], nodules[33], and masses[34]. CMV targets endothelial cells, and related injuries often induce epithelial and interstitial necrosis that resembles ischemic damage[30]. The presence of cytomegalic cells in tissue biopsies stained by H&E is considered the gold standard for establishing a diagnosis of CMV GI disease. When the diagnosis is uncertain, additional immunohistochemical methods may be useful in confirming the presence of CMV[35]. However, the number of tissue samples appears to be especially important for diagnosing CMV. Goodgame *et al*[31] have reported that even when immunoperoxidase staining was used to make a diagnosis of CMV, after routine histology failed to demonstrate cytomegalic cells, a positive result seemed equally dependent on the number of biopsies as on routine histopathology. When histology involved multiple sections of 8-10 biopsies, the frequency of diagnosing CMV by histology was greater than by culture.

Schistosoma mansoni

Gastric infection from *S. mansoni* is extremely rare, as this helminth usually infects the intestine and liver, which leads to portal hypertension[26]. In a large cohort of dyspeptic HIV-infected patients (n = 690), we have shown gastric *S. mansoni* (gastric ulcer) in just one

patient[24]. Reported endoscopic findings are gastric ulcers[36] and pseudopolypoid lesions[26]. Tissue biopsies reveal ova of *S. mansoni* stained by H&E, accompanied by little or no inflammatory or fibroblastic response.

Cryptosporidium

Cryptosporidium is a coccidian protozoan that more commonly affects the proximal small bowel. Gastric infection is considered a secondary localization. Parasites reach the stomach through duodenal backwash and localize mostly in the antrum because of its proximity[37]. There is no specific pathognomonic endoscopic appearance. Gastric hyperemia, edema and erosions, especially in the antrum, have all been reported[24,27]. Gastric cryptosporidiosis may also occur in normal-appearing mucosa[24]. Histological examination shows *Cryptosporidium* parasites mainly on epithelial cells covering gastric pits and stained by H&E[37]. Rivasi *et al*[38] have demonstrated a close relationship between the intensity of *Cryptosporidium parvum* infection and the degree of histological alterations. They did not find, however, a clear correlation between the endoscopic and histological alteration types found[38].

Strongyloides stercoralis

Str. stercoralis larvae infect the duodenum and the first part of the jejunum; it is considered an opportunistic agent when found in the gastric mucosa. There are remarkably few reports of gastric strongyloidiasis in HIV-infected patients. Among these reports, gastric ulcers[39], and edematous and thickened gastric folds have been reported[40]. Strongyloidiasis in normal-appearing gastric mucosa has also been reported by our group[24]. A true pathognomonic endoscopic finding does not exist, although a brownish mucosal discoloration of the gastric or duodenal mucosa is frequently observed[40]. The diagnosis is easily made by H&E tissue stained sections, identification of *Str. stercoralis* larvae and eggs, infiltration of eosinophilic cells into the lamina propria, and villous blunting.

Leishmania donovani

A few cases of gastric localization of *L. donovani* have been reported in severely immunosupressed HIV-infected patients. Endoscopy has shown gastric ulcers, erosions and a normal-appearing gastric mucosa as well[41,42]. Histological study has shown large macrophages, lymphoid cells and plasma cells infiltrating the lamina propria. Characteristically, macrophages are filled with round or oval nucleated complete microorganisms that contain kinetoplasts. Both the kinetoplasts and nuclei stain bright red with Giemsa staining and H&E[18].

SMALL INTESTINE

Chronic diarrhea is an important clinical problem in HIV-infected patients and is still a cause of morbidity and mortality in the HAART era[43]. Diarrhea in the setting of HIV infection may have many causes; it may be a consequence of HAART[44], the HIV infection itself or may result from any bacterial, viral or parasitic infection[45].

Currently, HAART-induced diarrhea is the primary reason for the continually high prevalence of diarrhea in HIV-infected patients, especially with the use of protease inhibitors[46]. The likelihood of an opportunistic process is linked to the severity of immunodeficiency. Therefore, the search for a typical HIV-associated process should be undertaken based on risk stratification of the patient. Patients with CD4 counts of < 100 cells are most at risk for *Cryptosporidium*, *Microsporidium* and CMV disease[8].

A consensus panel in 1999[47] recommended a stepwise approach to investigate diarrhea in HIV-infected patients at risk for OI: step 1, at least three sets of stool specimens for common enteric bacteria and parasites, including microsporidia and cryptosporidia; and step 2, colonic mucosal biopsies using flexible sigmoidoscopy or colonoscopy. Upper GI endoscopy with biopsy of the duodenum for light-microscopic examination, mycobacterial culture, and electron microscopy is considered the third recommendation if no pathogen is identified after performing steps 1 and 2. Duodenal aspirate seems to be of little value in the workup of these patients[48].

Cryptosporidium

Cryptosporidium is a protozoan that infects the small bowel mucosa and, in immunosuppressed persons, the large bowel and extraintestinal sites. Endoscopy may show fold thickening of the mucosa, with an erythematous and granular appearance that is most prominent in the duodenum[49]. In general, duodenal erosions or ulcers are not found. Histological study of duodenum samples shows a partial villus atrophy with crypt hypertrophy and increased chronic inflammatory cells, particularly eosinophils and plasma cells. The organisms are seen positioned along the brush border of the surface and crypt epithelium[37].

Microsporidia

Intestinal microsporidiosis is caused by *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*. The diagnosis is frequently established by examination of three stool samples with chromotrope and chemofluorescent stains. There is not a typical endoscopic appearance. A small bowel biopsy, especially in the jejunum may show microsporidium organisms in villus enterocytes by different stains such as H&E, Giemsa, Warthin-Starry silver staining, or Chromotrope 2A[50,51].

CMV

Isolated lesions caused by CMV in the duodenum may result in severe GI bleeding[52]. Also, diffuse mucosal involvement of the duodenum and jejunum may lead to malabsorption. Rare manifestations of CMV infection include isolated ulcers that may cause perforation, terminal ileitis mimicking Crohn's disease[53], and ileal

obstruction that results from a large inflammatory mass[54].

Mycobacterium avium complex (MAC)

MAC, commonly seen in the pre-HAART era, is now very rare and is most likely to be found in patients who first present with end-stage HIV infection. The most common site of MAC infection of the GI tract is the small bowel. The endoscopic appearance may mimic Whipple's disease with diffuse, scattered white nodules and plaques that may be yellow, white, yellow-whitish, or pink, located in the second portion of the duodenum. Therefore, it is often described as pseudo-Whipple disease[17]. Although nodular lesions are frequent, other endoscopic findings have also been described in the small bowel such as ulcerations, erythema, edema, friability, reduced mucosa vascular pattern, erosions, strictures and even normal-appearing mucosa[55]. Microscopically, the affected tissue is filled with large numbers of distended histiocytes that are packed with acid-fast organisms. Usually, granuloma formation or associate inflammatory response is minimal[56].

Mycobacterium tuberculosis

M. tuberculosis bowel infection is also rare. It usually involves the small bowel and ileocecal region. It may be associated with granulomatous reactions that lead to ulcers, fistulas and even perforations. Upon endoscopy, ulcers have a cratered appearance with mass-like edges. Upon histology, there are few acid-fast bacilli and usually they do not form well-developed non-caseating granulomas in HIV-infected patients[57].

Histoplasma capsulatum

Uncommonly, fungal organisms may cause disease in the small intestine in HIV-infected patients. H*istoplasma capsulatum* most commonly causes disease in the ileum, but may also cause disease in the jejunum. Ulcers are often found, but nodules, pseudopolyps or plaques caused by collections of infected macrophages have also been described[58]. Microscopic findings include lymphohistiocytic infiltration, infected macrophages within the lamina propria, and less commonly, granulomas[58].

The role of upper GI endoscopy in the diagnosis of OI in HIV-infected patients with GI complaints without diarrhea is still more controversial. We have done endoscopy with duodenal biopsies in a large cohort (n = 690) of HIV-infected patients that were severely immunosupressed (mean CD4 count 154.3 cells/mm^3), who were undergoing HAART and presented with GI complaints but without diarrhea, and we found a very low incidence of OI and non-opportunistic parasites in the tissue specimens (five patients, 1.0%). In 80% of these patients, the duodenum showed a normal-appearing mucosa upon endoscopy, which suggested the relevance of taking biopsies even from a normal-appearing mucosa when an OI diagnosis is suspected[24]. Our results seem to disagree with Olmos *et al*[59]. These authors observed a low prevalence of OI in HIV-infected patients without diarrhea when the duodenal mucosa was normal. They suggested that biopsies should not be taken from normal duodenal mucosa in patients without diarrhea. Pathogens found in biopsies of normal duodenum in our study (*Cryptosporidium* and *Giardia*), however, should also be detectable in stool samples. One possible option is that more stool tests should be performed prior to pursuing endoscopy in these patients.

CONCLUSION

Although there has been a decrease in the incidence of GI OI in the era of HAART, the gastroenterologist evaluating HIV-infected patients with GI symptoms should not discard this possibility. Since adverse events related to HAART are a frequent cause of GI complaints among HIV-infected patients, the approach for HIV-infected patient with CD4 counts > 200 cells/mm^3 and upper GI complaints should parallel those of any other patient when immunodeficiency is not advanced. Patients with CD4 $\leqslant$ 200 cells/mm^3, however, should be referred earlier for upper GI endoscopy, in order to diagnose OI early, especially because many of these infections are now treatable. Different pathogens can result in similar endoscopic findings. To correctly diagnose OIs, multiple biopsy specimens may be necessary even from normal-appearing mucosa.

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