

HIV infection and the esophagus

LINDA RABENECK, MD

ABSTRACT: The esophagus can be involved in human immune deficiency virus (HIV) infection. Esophageal ulcers can occur as part of an acute (primary) HIV infection syndrome. In addition, the esophagus can be involved with the neoplasms associated with acquired immune deficiency syndrome (AIDS) — both Kaposi's sarcoma and non-Hodgkin's lymphoma. Opportunistic infections may also involve the esophagus, most commonly candida and cytomegalovirus infection. It is important for gastroenterologists to be aware of the clinical features of these lesions and to be ready to carry out endoscopy to diagnose these lesions correctly. *Can J Gastroenterol* 1989;3(1):1-6

Key Words: *Acquired immune deficiency syndrome (AIDS), Esophageal ulcers, Esophagus, Human immunodeficiency virus (HIV)*

L'infection à VIH et l'oesophage

RESUME: L'oesophage de l'être humain infecté par le virus d'immunodéficience humaine (VIH) peut aussi être touché. Des ulcères de l'oesophage peuvent se produire dans le cadre du syndrome aigu (primaire) d'infection à VIH. De plus, il peut être atteint de néoplasmes secondaires au syndrome d'immunodéficience acquise (SIDA), tels le sarcome de Kaposi et les lymphomes non-Hodgkin. Les germes opportunistes peuvent également attaquer l'oesophage — les candida et le virus cytomégalytique surtout. Il est important que les gastroentérologues reconnaissent les caractéristiques cliniques de ces lésions et soient prêts à pratiquer une endoscopie afin de les diagnostiquer correctement.

University of British Columbia, St Paul's Hospital, Vancouver, British Columbia

Correspondence and reprints: Dr Linda Rabeneck, Yale University School of Medicine, Clinical Scholars Program, Room 1E, SHM, 333 Cedar Street, New Haven, CT 06510-8025, USA

Received for publication May 16, 1988. Accepted May 19, 1988

THE CENTER FOR DISEASE CONTROL (CDC) first reported cases of the acquired immune deficiency syndrome (AIDS) in 1981 (1,2). The cause of AIDS is a human retrovirus, first named human T-cell lymphotropic virus (HTLV-III) (3,4) or lymphadenopathy associated virus (LAV) (5), subsequently renamed human immunodeficiency virus (HIV) (6).

Infection with HIV over a period of time results in a variety of immunologic defects, the most critical of which is depletion of T-helper cells, which in turn leads to the development of opportunistic infections, Kaposi's sarcoma and lymphoid malignancies (7). It is the presence of these specific opportunistic infections and malignancies in an HIV infected individual which establishes a diagnosis of AIDS, as defined by the CDC (8,9).

The gastrointestinal tract is a major target organ for involvement in AIDS (10). The esophagus is of particular interest as it can be involved not only with a number of the opportunistic infections and malignancies of AIDS but also at the

onset of HIV infection. This paper reviews the clinical features of the esophageal lesions associated with HIV infection.

ACUTE (PRIMARY) HIV INFECTION

Current evidence suggests that, following exposure to HIV, most individuals who seroconvert (ie, who develop antibodies to HIV) experience no symptoms (11). However, a number of individuals do experience a clinical illness; certain specific clinical syndromes have been described. The first of these syndromes to be recognized was that of an acute mononucleosis-like illness. The clinical features of this illness include fever, chills, night sweats, malaise, myalgia, arthralgia, sore throat, lymphadenopathy and skin rash (12,13). Other syndromes subsequently recognized to occur in association with acute HIV infection include acute meningitis (14), acute encephalitis (15), acute polyneuropathy (16) and acute brachial neuritis (17).

It is now clear that acute HIV infection may cause an illness characterized by the presence of unusual esophageal ulcers. The features of this illness, occurring in a series of homosexual men, seen

TABLE 1

Classification system for human T-lymphotropic virus type III/lymphadenopathy associated virus infection

Group I	Acute infection
Group II	Asymptomatic infection
Group III	Persistent generalized lymphadenopathy
Group IV	Other disease
Subgroup A	Constitutional disease
Subgroup B	Neurologic disease
Subgroup C	Secondary infectious diseases
Category C-1	Specified secondary infectious diseases listed in the CDC surveillance definition for AIDS*
Category C-2	Other specified secondary infectious diseases
Subgroup D	Secondary cancers*
Subgroup E	Other conditions

* Includes those patients whose clinical presentation fulfills the definition of the acquired immune deficiency syndrome (AIDS) used by CDC for national reporting

in Vancouver between 1982 and 1984, were described at the Canadian Society for Clinical Investigation meeting in September 1987 (18). Thirteen homosexual men presented with odynophagia, 11 also had a maculopapular skin rash and three had ulcers on the hard palate. Esophagogastroduodenoscopy revealed the presence of multiple discrete ulcers measuring 0.3 to 1.5 cm in diameter in the esophagus (Figures 1,2). HIV serology carried out by Western blot technique demonstrated seroconversion.

Electron microscopic examination of biopsy specimens taken from the margins of the esophageal ulcers revealed the presence of virus-like particles 120 to 160 nm in diameter, with morphologic features consistent with retroviruses. In all men the acute illness was self-limited; the rash cleared and the esophageal ulcers healed.

Proof of the presence of HIV in the esophageal tissue requires further study. However, the description of this syndrome extends knowledge of acute HIV

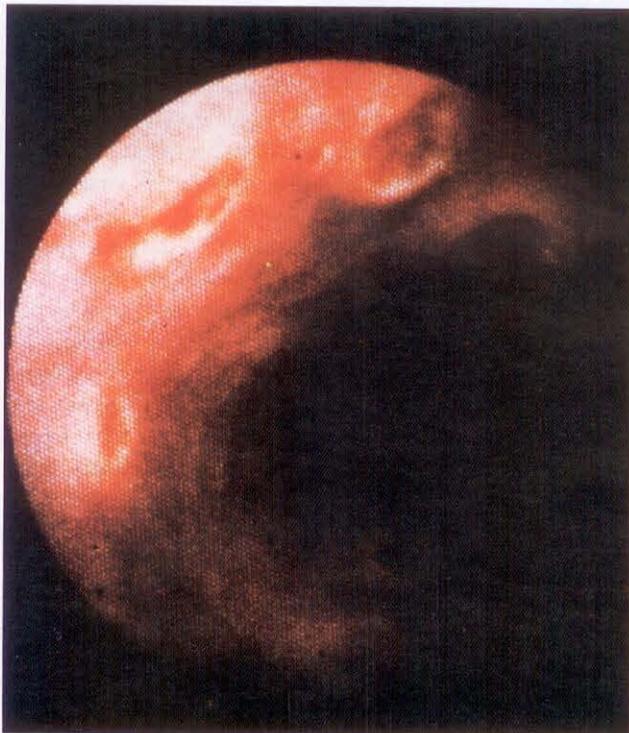


Figure 1) Multiple esophageal ulcers measuring 0.5 to 1 cm in diameter in an individual with primary HIV infection

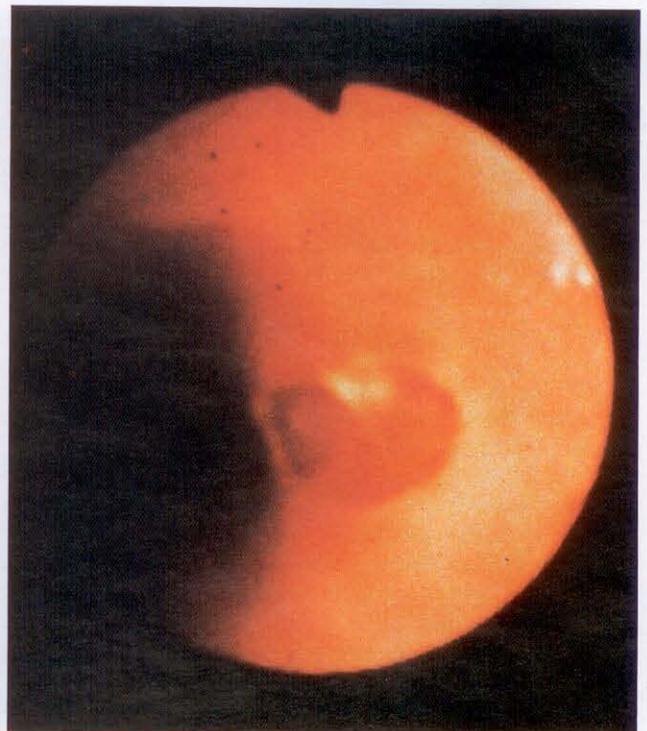


Figure 2) Discrete single esophageal ulcer, 1.5 cm long and 1 cm wide in an individual with primary HIV infection

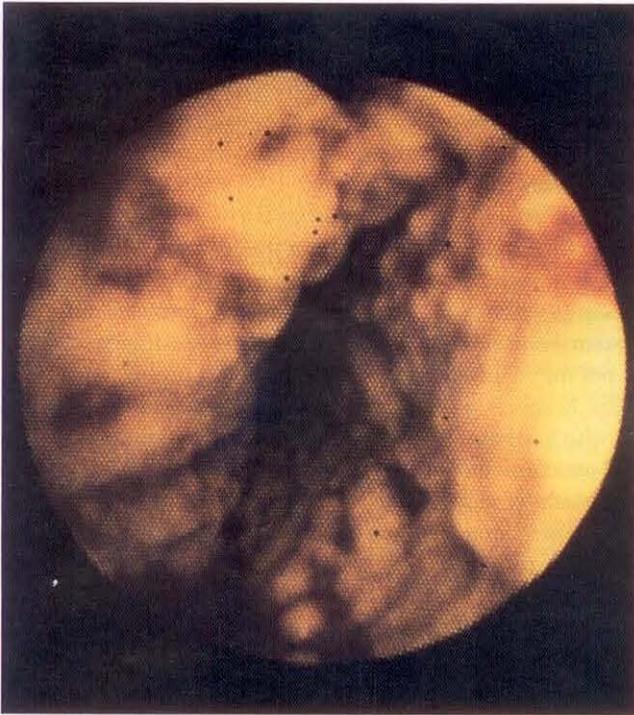


Figure 3) Esophageal candida in a man with AIDS: Confluent raised white plaques in the esophagus



Figure 4) CMV associated esophageal ulcer with irregular margins, measuring 3 cm in length and 1.5 cm in width in an individual with AIDS

syndromes and suggests that esophageal cells may be a target for HIV infection.

ESOPHAGEAL LESIONS IN AIDS

AIDS can be considered one of the chronic sequelae of HIV infection. As discussed previously the CDC has defined and classified AIDS (Table 1) (9). As far as the gastrointestinal tract is concerned, the CDC has defined specific opportunistic infections (group IV, category C-1) and specific neoplasms (group IV, category C-2) which fulfill the definition of AIDS.

Esophageal candida: Esophageal candida is one of the most common opportunistic infections in AIDS (10,19). A patient with esophageal candida may complain of dysphagia or, less commonly, odynophagia. Some complain only of heartburn or of anorexia, while others report no symptoms. While some observers have argued that the presence of oral candida is predictive of the presence of esophageal candida (20), this is not necessarily so; in HIV infected individuals, esophageal candida can be present in the absence of oral candida and vice versa.

It is important to endoscope individuals at risk for AIDS who present with

symptoms suggestive of esophageal candida. The reasons for this are: there are other possible causes of dysphagia and odynophagia in such persons besides esophageal candida; and the finding of esophageal candida in an HIV infected individual establishes a diagnosis of AIDS. The latter is crucial information which the individual and the physician deserve to know.

At endoscopy the lesion is characterized by the presence of raised white plaques which may be confluent (Figure 3). Endoscopic biopsies reveal the presence of budding particles and hyphae; findings which are consistent with the diagnosis. Fungal cultures can be obtained if positive identification of the fungus is desired. A recent report of white plaques and esophageal ulcers in an AIDS patient was attributed to *Torulopsis glabrata*, a related fungus (21).

While mycostatin oral solution controls oral candida, often it is ineffective therapy for esophageal candida. Ketoconazole at a dose of 200 mg by mouth once daily can be effective (22), although there are reports of esophageal candida refractory to this therapy (23) and the agent can cause hepatocellular necrosis

(24). In addition, of importance to those patients receiving antimycobacterial therapy, ketoconazole can interact with rifampin and isoniazid (25). Amphotericin B therapy has been advised by many (26-32). Clotrimazole, however, is effective therapy and avoids the risk of toxicity with amphotericin B as well as the need for parenteral administration. The drug is given as a suppository at a dose of 100 mg by mouth to suck three times daily. The esophageal candida clears in seven to 10 days. Thereafter, the drug can be given in a dose of 100 mg once or twice daily to prevent recurrences (33).

Cytomegalovirus infection (CMV): CMV infection of the esophagus can cause esophageal ulcers. Individuals with CMV-associated esophageal ulcers usually present with odynophagia or constant retrosternal pain. The ulcers may be single and discrete or multiple with normal appearing intervening esophageal mucosa (Figure 4). The ulceration may also be confluent and can mimic peptic esophagitis due to gastroesophageal reflux disease (34,35). A case of a giant CMV-associated esophageal ulcer with extension to the adventitia has been described (36).

Light microscopic examination of endoscopic mucosal biopsy specimens reveals the presence of characteristic intranuclear and intracytoplasmic inclusion bodies. Viral culture of the inflamed tissue will grow the virus. Since CMV can often be documented in uninflamed gastrointestinal mucosa of patients with AIDS, it can be difficult to be certain the CMV is the cause of the mucosal ulceration. If other causes of mucosal ulceration can be ruled out, a stronger case for CMV as the causative agent can be put forward.

The natural history of CMV esophageal ulcers is not clear. Ganciclovir (9-[1,3-dihydroxy-2-propoxymethyl] guanine) therapy of CMV infection has been attempted (37). Of a series of 41 patients treated with this agent, five had esophageal involvement. Evaluation of the response to therapy was inconclusive in these patients as follow-up endoscopy was not carried out. Therapy with Foscarnet (phosphonoformate) has also been reported (38).

Herpes simplex virus: Herpes simplex virus can cause chronic perianal ulceration in individuals with AIDS (39). However, there is little published regarding herpes simplex infection of the esophagus in AIDS patients.

Cryptosporidia: *Cryptosporidium* is the most common protozoan to infect the gastrointestinal tract in AIDS patients. It commonly affects the small bowel or colon and causes diarrhea, which may be secretory in type (10,40). *Cryptosporidia* have also been observed in gastric mucosa and more recently a case of esophageal cryptosporidiosis was described (41). The patient was a two-year-old girl with AIDS. The patient developed dysphagia; endoscopy showed 'areas of inflammation in the distal esophagus'. Pathological examination of mucosal biopsy tissue revealed the presence of *cryptosporidium*.

A diagnosis of cryptosporidiosis can be established by demonstrating the presence of the organism in stool using an acid fast stain. Light microscopic examination of mucosal biopsy specimens demonstrating the presence of the organism may also be used to establish the diagnosis. Spiramycin has been reported to be effective therapy for

cryptosporidiosis (42); however, this observation requires confirmation.

Mycobacteria: Mycobacterial infection is common in AIDS patients. Overall, the most common mycobacterial isolate is *Mycobacterium avium-intracellulare* complex (MAIC). However, in AIDS patients from ethnic groups in which tuberculosis is highly prevalent, infection with *M tuberculosis* is more common (43). Both organisms involve the gastrointestinal tract, although generally not the esophagus. The author has seen, however, a patient with odynophagia who had large hilar lymph nodes and a 2 cm diameter deep ulcer of the esophagus which was due to MAIC. At post mortem examination, it was established that the patient had a fistula between the esophagus and the mediastinum.

The diagnosis of mycobacterial infection may be established by tissue biopsy. Since granuloma formation has been described as poor and acid fast stains may be negative, culture of tissue specimens is of greatest importance (44,45). When the gastrointestinal tract is involved, stool samples stained with acid fast stain may be positive.

The CDC has issued guidelines for the treatment of mycobacterial diseases in individuals with HIV infection (46). Chemotherapy is advised whenever acid fast bacilli are found in a tissue or fluid specimen. The initial drug regimen should be effective against tuberculosis, eg, isoniazid, rifampin and either ethambutol or pyrazinamide. If the isolate proves to be MAIC, the regimen is switched to isoniazid, ethambutol, ansanmycin and clofazimine. It is recognized that the appropriate duration of therapy for tuberculosis in HIV infection is unknown, in addition, optimal therapy for MAIC is not known. Patients with *M tuberculosis* and HIV infection tend to respond to therapy whereas those with MAIC do not.

Kaposi's sarcoma: Kaposi's sarcoma is a malignancy which can involve the skin, lymph nodes and other organs in AIDS patients. Approximately 50% of AIDS patients with skin involvement have visceral involvement with Kaposi's sarcoma (47). The lesions may involve any portion of the gastrointestinal tract from the oral cavity to the anus. Usually Kaposi's

sarcoma involving the gastrointestinal tract does not cause symptoms or complications such as bleeding or obstruction (47). Kaposi's sarcoma involving the esophagus, however, may cause dysphagia.

Endoscopy is a more sensitive method than barium studies for documenting the presence of the lesions. The endoscopic appearance is characteristic. The lesions are macules or sessile nodules. The latter may have central umbilication. The colour is usually a red or red-purple and the size varies from several millimetres in width to several centimetres. Because the lesions are submucosal, endoscopic biopsies taken in the usual manner with biopsy forceps may not reach the lesions, hence in practice the diagnosis is often established on the basis of the gross appearance alone.

In patients with Kaposi's sarcoma involving the skin, the finding of gastrointestinal Kaposi's sarcoma is associated with a poorer prognosis. There are chemotherapy regimens for the treatment of Kaposi's sarcoma. The decision to treat is usually left with the oncologist.

Lymphoma: Lymphomas occur less commonly than Kaposi's sarcoma in AIDS patients. Although both non-Hodgkin's lymphoma and Hodgkin's lymphoma are reported to occur in association with HIV infection, only non-Hodgkin's lymphoma fulfills the CDC criteria for the diagnosis of AIDS (9). In AIDS patients, lymphomas have been reported to occur throughout the gastrointestinal tract. Bernai and del Junco (49) reported the clinical features of four cases of esophageal lymphoma occurring in AIDS patients. Three of the patients reported dysphagia. Endoscopic biopsy of the lesion established the diagnosis, which in each case was a non-Hodgkin's lymphoma.

Esophageal ulcers: Lastly, there may be an additional esophageal lesion in AIDS patients. Such patients present with odynophagia and are found to have discrete esophageal ulcers at endoscopy. In these cases a search for an underlying infectious agent or neoplasm has failed to reveal the cause of the lesions (50). It is possible that these esophageal ulcers are in some way related to those of the acute (primary) HIV infection.

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