Adenovirus Esophagitis in an HIV-Positive Patient

Extraordinary Presentation of a Common Viral Infection

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Abstract: Human adenovirus mostly causes self-limiting diseases but may also induce serious complications in healthy as well as immuno-compromised patients. We report a case of a 40-year-old homosexual man with chronic untreated human immunodeficiency virus infection, presenting with dysphagia because of an ulcerative esophagitis caused by human adenovirus. Adenovirus infection as a cause of esophagitis has not been reported before, so it should be considered in a differential diagnosis of dysphagia, especially in the context of human immunodeficiency virus.

Key Words: adenovirus, ulcerative, esophagitis, HIV, AIDS, immunocompromised

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Human immunodeficiency virus (HIV) type 1 infection is associated with gradual immune deterioration, and unless treated, patients may progress to acquired immune deficiency syndrome (AIDS)–defining major opportunistic diseases. Esophagitis caused by *Candida albicans*, cytomegalovirus (CMV), or Herpes simplex virus (HSV) may be AIDS defining, but the list of infectious causes is more extensive.[1–5] Although highly active antiretroviral therapy (HAART) reduced their frequency, infectious gastrointestinal tract (GI) disorders remain an important cause of morbidity and mortality in HIV-infected patients.[2,5,6]

Adenovirus (ADV) infections usually cause mild self-limiting disease, if at all, among immunocompetent patients but are also recognized to cause serious morbidity and mortality in immunocompromised hosts.[7–9] We describe a unique case with ulcerative esophagitis in a therapy-naive HIV patient caused by a common viral infection, that is, ADV.

CASE REPORT

A 40-year-old Dutch homosexual man with a known untreated asymptomatic HIV-1 infection and CMV carriership reported to our hospital with a 1-week history of progressive dysphagia. He denied having other gastrointestinal discomfort or using alcohol. Two weeks previously, he endured a 5-day period with transient fever, sore throat, muscular pain, and unproductive coughing. Physical examination on admission did not reveal any abnormalities besides a new-onset raised temperature (37.8°C) and swollen tonsils but no oral candidiasis. No further temperature increase was observed during his hospital stay. Routine laboratory results were within normal limits. An up-to-date CD4 count and HIV viral load at admittance were unknown, but a CD4 decline was assumed. Endoscopic evaluation showed extensively inflamed esophageal mucosa, with large ulcers covering the full length of the esophagus. There were no signs of *Candida* infection, so differential diagnostic considerations included a reactivation of endogenous CMV or HSV infection. The patient was treated with ganciclovir intravenously. Contrasting with expectations, the CD4 count during admittance was 440/mm^3. A raised viral load (VL) greater that 10^5 copies/mL HIV-RNA was found. Pathological investigation of endoscopic biopsies showed ulcerative inflammation and epithelial cells with viral inclusions in nuclei (Fig. 1). Grocott stain of the biopsies was negative for *Candida*, and immunohistochemistry did not reveal CMV antigens. The CMV-DNA, that is, viral load (polymerase chain reaction [PCR] of peripheral blood) was undetectable. Serological tests showed latent CMV infection (IgM antibody [ab] negative, IgG ab: 92 IU/mL), a low complement fixation test (CFT <1:4) for HSV, and in contrast, a high ADV ab titer (CFT 1:128). Biopsies showed a positive viral isolation with immunofluorescent confirmation of an ADV. The combination of histology, viral isolation, and a high specific ab titer pointed to ulcerative esophagitis caused by ADV. Antiviral therapy, that is, ganciclovir, was ceased. Complementary treatment was unnecessary because complaints vanished within several days and were not noted again during a follow-up period of more than 2 years. Unfortunately, the patient refused further endoscopy. At the time of esophagitis diagnosis, HAART was not initiated because the patient did not meet treatment criteria and symptoms had vanished. A year later, the patient was eventually started on HAART because the CD4 count decreased further. In consequence, after a few months of treatment, the HIV viral load was reduced to undetectable.

DISCUSSION

Human ADV belongs to a group of nonenveloped double-stranded DNA viruses, are classified within seven subgroups or species (A–G), and at least 52 serotypes are recognized, each related to its own preferred anatomical site of infection.[2–4,7,8] Dispersed through respiratory, fecal-oral, or ocular conjunctival routes, ADV have an incubation period of days up to 2 weeks. Adenovirus infections are ubiquitous, frequently occur subclinically in immunocompetent patients, and typically cause mild and self-limited respiratory, GI, or conjunctival disease in healthy young children.[2–4,7,9] Adenovirus-related illnesses can be either a primary infection or a latent virus reactivation. However rare in previously healthy people, ADVs may also be associated with morbidity and mortality.[2,4,7,9] Adenoviruses have been increasingly recognized as important opportunists in immunocompromised patients, including HIV/AIDS. Despite improved treatment, HIV-infected patients remain more susceptible to infections.[2–4,7,9]

Dysphagia, odynophagia, retrosternal pain, and fever are symptoms related to esophageal disease. Many esophageal
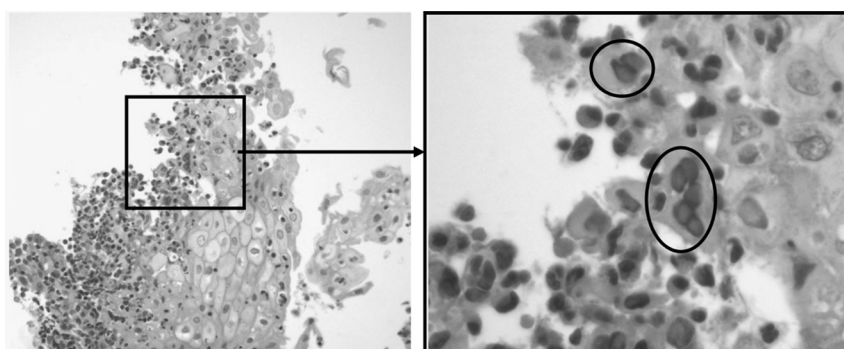
FIGURE 1. Ulcerative inflammation of esophageal epithelium and infected cells with viral inclusions in epithelial nuclei. Virus-infected cells were encircled.

disorders have been reported in up to 40% to 50% of the patients at a given moment in the course of HIV. Infectious esophagitis is one of the most frequently seen afflictions.[1,2,10–14] Infectious etiology occurs in 30% to 40% of HIV patients mostly if the CD4 count is less than 200/mm³. An extensive array of infectiousagents has been reported in reviews and case reports. Table 1 summarizes all reported common as well as most of the rare microorganisms causing infectious esophagitis in HIV/ AIDS.[1,2,4–6,10,11,14–20] Adenoviruses have not been added to this summary yet.

Identifying the cause of esophagitis in HIV is important for therapy, prognosis, and (nowadays of lesser importance) staging of HIV/AIDS, so it remains a diagnostic challenge regardless of the level of immunodeficiency. Inflammation or ulcers may be of various infectious or noninfectious origins, including HIV-associated idiopathic ulceration, which is diagnosed per exlusionem, and typically appearing at CD4 levels less than 50/mm³.[2,3,10,12] *Candida*

is the main cause reported in 50% to 79% of patients, and CMV is the most prominent viral pathogen, followed by HSV (Table 1).[1,10,14–18] Also, esophageal *Candida* may hide CMV and HSV ulcers, for instance, and concurrent CMV and HSV esophagitis is reported.[2,19,20] Specific symptoms are rarely helpful in determining the etiology.[20] However, in cases of oral *Candida* with suspected esophagitis, empiric antifungal treatment is warranted. Endoscopic evaluation with multiple biopsies of any lesion is recommended, regardless of the presence of fever, in all cases of severe odynophagia, weight loss, suspected upper GI bleeding, failure to eat and drink, and when empirical *Candida* therapy fails. In these cases, esophageal ulcerations, rather than candidiasis, are present.[1–5,10] At least 10 biopsies of lesions or nonlesional mucosa are recommended to enhance the diagnostic susceptibility and for reliable exclusion of a viral cause.[19] Besides diagnostic tests for microbes, histology with immunohistochemical staining is a reliable method to differentiate between common causes. Clues, like viral inclusions and smudge cell formation, are useful to detect viral infections. Microbial analyses, including viral cultures of biopsied materials, are recommended. Furthermore, repeated serological tests and tissue PCR, aimed at a diversity of potential pathogens, may be helpful in the workup.[1–5,10,12,17,19] However, the use of serology is limited because of the lack of sensitivity, especially in immunocompromised patients.[1,4] Despite the fact that PCR detects more etiologic and unusual pathogens, results should be interpreted with caution because several coinfections can be detected, leading to false-positive diagnoses.[10,12] Both remarks are also appropriate for ADV detection.[7–9]

If there is no evidence of a *Candida*, CMV, or HSV infection and before classifying ulcerative esophagitis as idiopathic HIV associated, ADV as well as other rare pathogens listed in Table 1 should be taken into account.

The diagnostic workup we performed (endoscopy, histology, viral isolation of lesions, and serology) pinpointed ADV infection reliably. Our case illustrates the association of a recent "possibly primary" ADV infection with ulcerative esophagitis in an HIV patient. Adenoviruses infecting the gut in HIV mostly belong to species D. We were regrettably unable to type the ADV because of lack of materials.

When immunity deteriorates, the risk of ADV acquisition increases. Most hosts remain asymptomatic, so the clinical relevance of subclinical infection and ADV shedding is not always clear.[3,4,8,10,11] Although GI infections can occur, to our knowledge, ADV as a cause of (ulcerative) esophagitis in HIV has not been reported before.

What could be learned in this case is a matter of cautious interpretation. Our patient endured a benign short course of disease possibly because of a relative preservation of immune capacity.

TABLE 1. Reported Microorganisms That Can Cause Infectious Esophagitis in HIV/AIDS

Frequency	Species	Infectious Agent	CD4, per mm³
Most common	Yeast	*Candida* species (most common *C. albicans*)	<200
	Virus	Cytomegalovirus	<100
		Herpes simplex virus	
Rare	Fungus	*Cryptococcus neoformans*	<100
		Exophiala jeanselmei	
		Histoplasma capsulatum	
		Penicillium chrysogenum	
	Virus	Epstein-Barr virus	
		Human Herpes virus type 6	
		Papovavirus	
		Varicella zoster virus	
	Bacteria	*Bartonella henselae*	
		β-Hemolytic streptococcus	
		Lactobacillus species	
		Mycobacterium tuberculosis	
		Mycobacterium avium intracellulaire complex	
		Nocardia	
	Protozoa/ parasite	*Cryptosporidium parvum*	
		Leishmania	
		Pneumocystis jirovecii	

The ADV esophagitis might otherwise have led to more serious disease in the presence of low CD4 levels. However, we cannot rule out a beneficial effect of ganciclovir in our case because moderate in-vitro activity against ADV infections and successful treatment have been reported.[21,22] The observations in an untreated and stable HIV patient might mirror a common transient presentation of ADV infection in immunocompetent individuals overlooked or missed if limited diagnostic testing would have been performed. Alternatively, ADV may only cause esophagitis in the context of subtle immunosuppression as in our HIV patient where lytic viral infection is temporarily ahead of the development of adequate immune defenses. So, in HIV-positive patients, ulcer formation may be caused by a longer ongoing lytic viral infection with more extensive tissue destruction, unbalanced aggressive local inflammatory responses, or both mechanisms.

The outcome of the ADV infection in immunodeficient hosts remains unclear because their natural course varies. It is questionable if and when ADV esophagitis should require antiviral treatment.[7,9,23,24] Several antivirals have been proposed, but to date, prospective randomized trials of potential agents are still lacking, and no drug has proven its clinical efficacy. Ribavirin and cidofovir may be useful in an early stage of ADV infection, that is, as prophylaxis or preemptive therapy in risk patients. However, patients generally present with already manifest disease. Results of new options like immunotherapy are promising, but reports are few, and more research is necessary to prove its effectiveness.[7–9,23,24]

In summary, we present a case of ulcerative esophagitis caused by ADV infection in an HIV patient, which may illustrate a thus far often missed affliction in normal as well as immunocompromised hosts. Both infectiologist as well as gastroenterologist should be aware of the wide spectrum of infectious agents, including ADV, causing esophagitis.

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