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Herpetic Esophagitis: A Diagnostic Challenge in Immunocompromised Patients

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Viral esophageal infection is common in immunocompromised patients. Twelve patients with esophagitis secondary to herpes viruses are described. Odynophagia, dysphagia, and gastrointestinal bleeding were the most common symptoms. Multiple infections particularly with candida were present in three of the 12 cases (25%). Typical "volcano ulcers" at endoscopy and discrete diffusely scattered shallow ulcers seen on double contrast esophagram are highly suggestive of herpetic esophagitis. Single contrast esophagram plays no specific role in the diagnosis of herpetic esophagitis. An analysis of clinical, endoscopic, radiological, and pathological features is presented.

INTRODUCTION

The esophagus is the most common site of gastrointestinal infection in the immunocompromised patients (1, 2). *Candida albicans* and herpes simplex virus (HSV) are the most frequently found organisms (1–4). Other herpes viruses particularly cytomegalovirus (CMV) have been associated with ulcerations in other parts of the gastrointestinal tract (5–7), but only rarely cause esophageal disease (8–10). With the development of effective antifungal and antiviral treatment, discrimination between different infecting organisms has become essential. We report on a group of 12 immunocompromised patients with esophageal involvement by herpes viruses (HSV and CMV) and discuss the importance of and difficulties in diagnosing herpetic esophagitis.

MATERIALS AND METHODS

The medical, radiological, and pathological records of 12 patients with histopathologically proved herpetic esophagitis between 1979 and 1984 at the University of Michigan Hospital were reviewed.

RESULTS

Clinical findings

There were six men and six women aged 17 to 80 yr. The underlying pathological processes predisposing these patients to infections were: diffuse histiocytic lymphoma in three, chronic granulocytic leukemia in two, diabetes mellitus in three, prolonged steroid therapy in two, extensive burns in one, renal transplantation in two, diffuse carcinomatosis in one, and acquired immunedeficiency syndrome in one patient. All patients were immunosuppressed and usually multiple predisposing factors were responsible. All patients with hematological malignancy had received extensive chemotherapy before the onset of herpetic infection. The pertinent clinical data on these 12 patients are summarized in Table 1.

All patients were symptomatic at the time of diagnosis. Odynophagia was present in 10 of 12 patients and was the predominant symptom. A sensation of food slowly moving down the esophagus after swallowing was reported by all patients but dysphagia was the prime symptom in only two patients. Gastrointestinal blood loss was found in three patients. Nonspecific symptoms such as anorexia, early-satiety, and nausea with vomiting were also present in four patients. Follow-up data showed that five patients with herpes simplex esophagitis were treated with Acyclovir. All five patients experienced marked symptomatic improvement of odynophagia within 2 wk and had no evidence of recurrence for at least 1 yr. One of the five patients, however, died from metastatic carcinomatosis 1 yr after treatment. One patient with concomitant herpes and candida esophagitis experienced symptomatic improvement after Nystatin treatment. One patient with CMV esophagitis did not receive any antiviral treatment and died from complications of renal and pancreatic transplant rejections. Thus all five patients with herpes simplex virus esophagitis responded to Acyclovir therapy.

Endoscopic findings

Eight of the 12 patients underwent upper gastrointestinal endoscopy. All eight patients had extensive esophagitis predominantly involving the distal esophagus. The ulcerations were seen on a background of marked erythema and edema. Typical "volcano" or marginal ulcers were seen in six of eight patients (Fig. 1), while two patients had confluent ulcers at the gastroesopha-

TABLE 1
*Clinical Data on 12 Patients with Herpetic Esophagitis**

No./Patient/Age/Sex	Predisposing Factors	Symptoms	Esophagram Findings	Endoscopic Findings	Diagnostic Method	Treatment/ Outcome	Comment
1 (TL) 28 F	Bilateral renal transplants	Odynophagia	Discrete punctate ulcers	"Volcano" ulcers	Brush cytology culture +	Acyclovir recovered	HSV esophagitis
2 (PM) 23 M	Type I DM severe DKA	Odynophagia	Nonspecific	"Volcano" ulcers	Brush cytology	Acyclovir recovered	HSV esophagitis
3 (SM) 39 M	DM severe DKA	Odynophagia	Ulcers esophagitis	Discrete ulcers	Brush cytology culture +	Acyclovir recovered	HSV esophagitis
4 (MW) 80 M	Giant cell arteritis steroids therapy	Odynophagia	ND	Discrete "volcano" ulcers	Brush cytology culture +	Acyclovir recovered	HSV esophagitis
5 (RP) 50 M	Metastatic carcinomatosis from prostate chemotherapy hormone therapy radiation therapy	Odynophagia Ca	Nonspecific	Confluent ulcers	Brush cytology culture +	Acyclovir recovered from esophagitis and died 1 yr later	HSV esophagitis
6 (DA) 74 F	CLL gram negative sepsis chemotherapy steroids antibiotics	Odynophagia	ND	ND	Postmortem Dx herpetic esophagitis submucosal hemorrhage	Died	HSV esophagitis
7 (WC) 17 M	Extensive burns sepsis antibiotics	Odynophagia	ND	ND	Postmortem Dx herpetic ulcers	Died	HSV esophagitis
8 (MR) 55 M	DHL chemotherapy steroids	Odynophagia oral candidiasis	Plaques ulcers and esophagitis	Discrete ulcers and plaques	Culture candida herpes	Nystatin improved odynophagia	Concomitant herpes and candida esophagitis
9 (RP) 71 F	DHL chemotherapy steroids	Odynophagia	Nonspecific esophagitis	ND	Postmortem Dx herpetic ulcers superinfection with candida	Died	Concomitant herpes and candida esophagitis
10 (LV) 65 F	Rheumatoid arthritis agranulo-cytosis severe leucopenia steroid therapy	Odynophagia	Nonspecific esophagitis	ND	Postmortem Dx herpetic esophagitis disseminated candidiasis	Died	Herpes and candida esophagitis
11 (DR) 20 F	IDDM bilateral renal transplants	Dysphagia	Ulcers stricture	Ulcers plaques	Brush cytology CMV inclusions No herpes or candida found	Died	CMV esophagitis
12 (BR) 32 M	AIDS homosexual	Dysphagia	Nonspecific esophagitis	Ulcers plaques	Postmortem—Dx CMV esophagitis disseminated CMV infection	Died	CMV esophagitis disseminated CMV infection

* DM, diabetes mellitus; DKA, diabetes ketoacidosis; DHL, diffuse histiocytic lymphoma; IDDM, insulin-dependent diabetes mellitus; AIDS, acquired immunodeficiency syndrome; Dx, diagnosis; ND, not done; +, positive.

geal junction. Inflammatory exudates were seen in all patients. The typical "volcano ulcers" seen at endoscopy predicted herpetic esophagitis in six patients. Secondary candida infection was diagnosed in two patients and missed in one patient with coexistent herpes infection. In two patients who subsequently proved to have cytomegalovirus esophagitis, the endoscopic diagnosis was herpetic esophagitis.

Radiological findings

Nine patients had barium esophagrams. The majority of patients were too sick to undergo double contrast esophagram, thus only three had satifactory double contrast esophagrams and six had single contrast studies. One patient demonstrated diffusely scattered superficial tiny punctate ulcers throughout the esophagus (Fig. 2) and a diagnosis of herpetic esophagitis was suggested. The second patient who had double contrast esophagram showed plaques and ulcerations and the diagnosis of candida and or herpes esophagitis was made. The third patient showed typical plaques and the diagnosis of candida esophagitis was suggested. All six patients who had single contrast esophagrams demonstrated esophagitis with nonspecific ulcerations mostly in the distal third of the esophagus (Fig. 3*A* and *B*). One patient had a stricture in the distal esophagus secondary to Barrett's esophagus and developed a secondary HSV infection (Fig. 4*A* and *B*). A second patient had a distal stricture due to chronic gastroesophageal reflux with CMV esophagitis (Fig. 5*A* and *B*). The

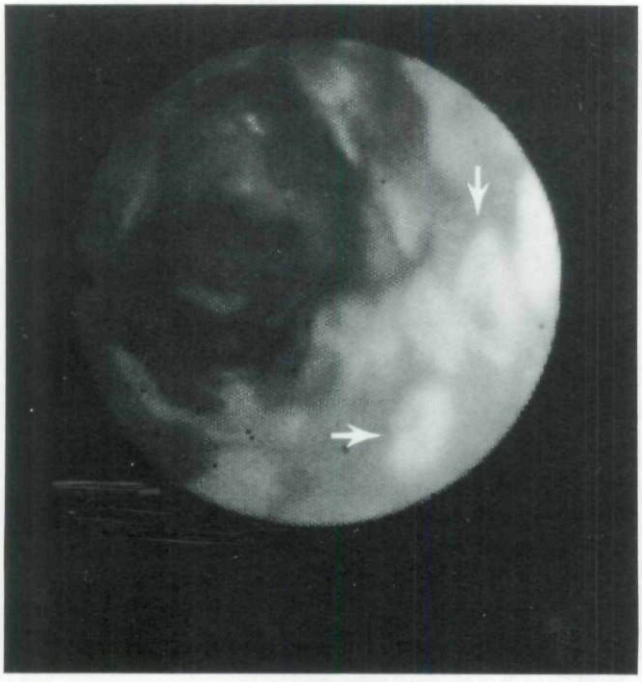

FIG. 1. Case 4. Endoscopic photograph of the esophagus shows several typical "volcano" ulcers (*arrows*) representing shallow ulcers with a yellow rim due to herpetic esophagitis (HSV).

diagnosis of herpes esophagitis was not considered in the six patients studied by conventional single contrast esophagrams.

Pathological findings

In six patients brush cytology was diagnostic of herpetic esophagitis. In one patient with concomitant HSV and candida infection, viral cultures established the diagnosis. In three patients a definitive diagnosis of HSV esophagitis was made at postmortem examination (Fig. 6). Of the two patients with CMV esophagitis, brush cytology was positive in one and the second patient with acquired immunodeficiency syndrome was found to have CMV esophagitis along with disseminated CMV infection at autopsy.

DISCUSSION

The first description of herpetic esophagitis was by Pearce and Dagradi in 1943 (11). Until recently herpetic esophagitis has been rarely diagnosed antemortem. Buss and Scharyj (1) found 56 cases among 39,111 consecutive autopsies (incidence: 1.4%). Nash and Ross (3) on the other hand, reported an incidence of herpes virus esophagitis at autopsy ranging from 1.4 to 25%. Recently with the increasing use of endoscopy and double contrast esophagraphy, herpetic esophagitis in an appropriate clinical setting is being seen more frequently.

There are approximately 70 known herpes viruses in nature but only five are recognized to cause infection in humans (12). These are herpes simplex virus I and

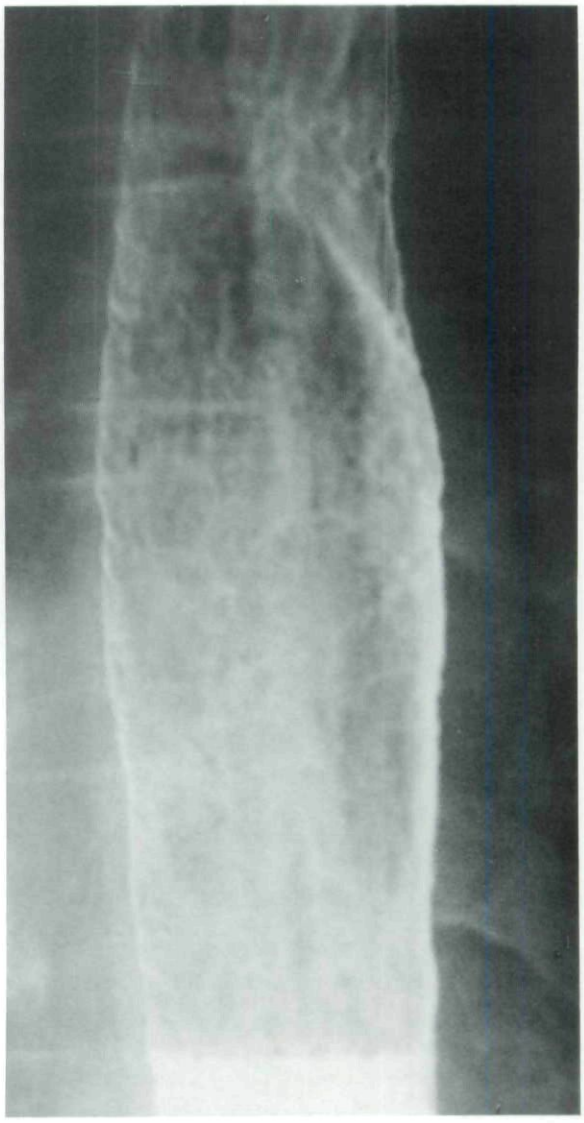

FIG. 2. Case 1. Double contrast esophagram shows several small discrete superficial ulcers due to HSV esophagitis.

II (HSV-I and HSV-II), herpes zoster virus (HZV), Epstein-Barr virus, and CMV (12). Herpes simplex virus and *C. albicans* infection in otherwise healthy adults may cause esophagitis (13–19), however, such infections are more common in immunocompromised patients (20–24). Fishbein *et al.* (25) have reported that HSV esophagitis is found with increasing frequency among patients with cancer, burns, and renal transplantation. Chemotherapy and prolonged steroid therapy are also frequently implicated as predisposing factors (25). The actual incidence figures for each of the specific causes of esophagitis in immunosuppressed patients are not known, although autopsy figures document that one-fourth of cases of esophagitis are due to HSV and one-third are due to *C. albicans* (3). The HSV infection is usually self-limited in healthy adults but in immunocompromised patients, it is progressive if unrecog-

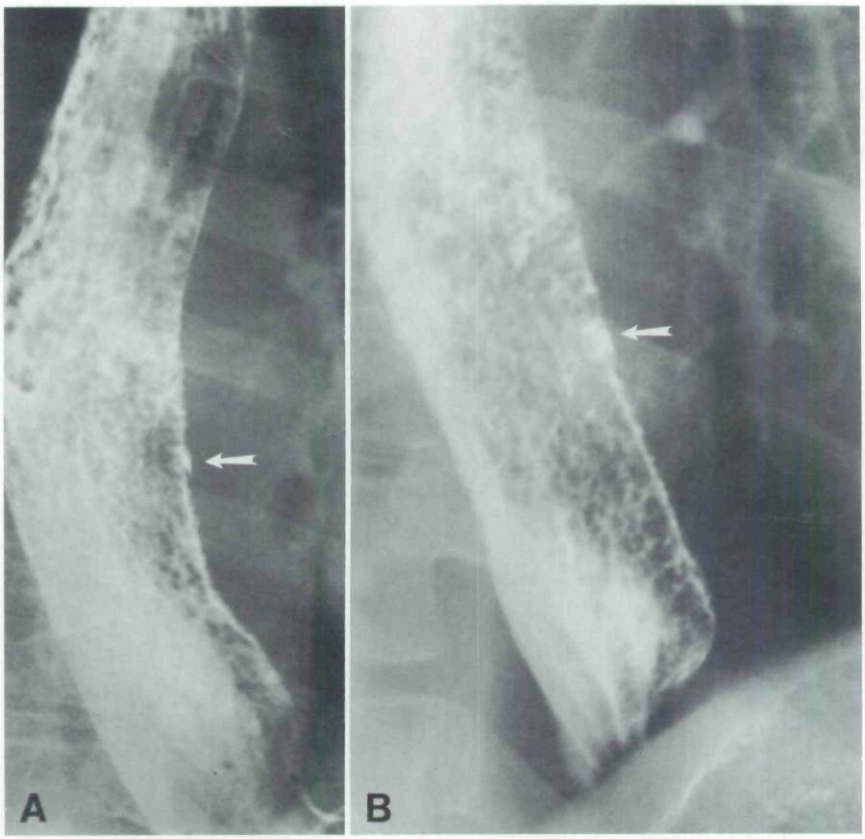

FIG. 3. *A* and *B*, double contrast esophagram shows that the esophagus is distensible and is studded with a combination of plaques and ulcers. Note one focally penetrating ulcer. Cultures revealed candida and herpes (HSV) infection.

nized. Fatal hemorrhage (3, 17, 25), esophageal perforation with tracheoesophageal fistula formation (26), and diffuse visceral dissemination (1) have been reported in herpes infection.

Clinically herpetic esophagitis presents as odynophagia in the majority of cases. The substernal pain after swallowing is often severe and sudden in onset. A small subset of young and otherwise healthy individuals may be asymptomatic and manifest acute self-limited HSV esophagitis. Herpes labialis may precede, be concomitant with, or follow herpetic esophagitis. Rarely hematemesis has been reported (25). These symptoms are indistinguishable from those of candidiasis and the presence of both infections concomitantly as noted in three of our patients has been reported previously (27, 28).

Herpes esophagitis is considered an opportunistic infection. The role of underlying malignancy, immunosuppression, chemotherapy, steroids, irradiation, and local trauma due to intubation are difficult to define in individual cases. In the largest series to date 35 of 56 cases were associated with malignancy, two-thirds of which were cases with leukemia or lymphoma (1). In another series of 31 cases with visceral herpetic infections and malignancy, the esophagus was the only organ involved in 21 cases (29). A significant number of cases without underlying malignancy may have immunosuppression due to a variety of causes including renal transplantation (25) and autoimmune disorders (1).

The endoscopic appearance of early HSV esophagitis is bullae (which are rarely seen) or discrete ulcers with a yellow rim of exudate or ulcer base, the so-called "volcano ulcers" (Fig. 1). These ulcers may vary in size from a few millimeters to 1 to 2 cm. Later the ulcers may coalesce and the mucosa may become friable with diffuse erosions and appear hemorrhagic. Exudates were seen in our eight patients with herpetic esophagitis examined endoscopically. Exudates on a background of nonerythematous mucosa are rarely seen in herpes esophagitis and may be more specific for candida infection.

The radiological features of herpetic esophagitis consist of discrete shallow ulcers, diffusely scattered and occasionally widely separated. These ulcers may be punctate, linear, or stellate in shape and are variable in size (30–33). Advanced cases may show plaques, a cobblestone appearance, or a shaggy ulcerative esophagitis indistinguishable from candidiasis. The discrete stellate ulcers on a background of normal mucosa are considered characteristic (33). Ulcers within plaques should suggest herpetic infection or concomitant herpes and candida esophagitis. When herpes and candida

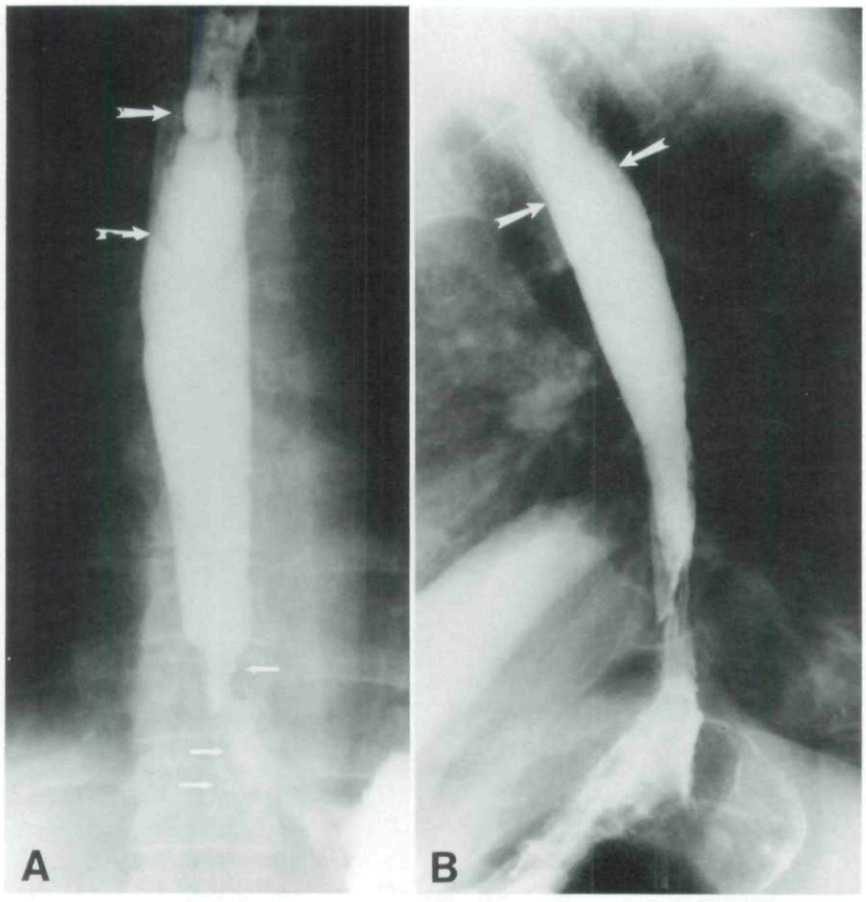

FIG. 4. Case 3. *A* and *B*, single contrast esophagram shows nonspecific ulcerations and stricture in the distal esophagus (*small arrows*) due to HSV infection. Note intraluminal flow artifacts in the proximal esophagus (*large arrows*) due to esophageal dysmotility.

infection are present concomitantly, the plaques of candida usually mask the herpetic ulcers (26, 27). HZV infection of esophagus (chicken pox or shingles of the esophagus) has only been reported in two cases previously (34, 35), one of those cases had a HZV-induced esophageal stricture. The radiological features of CMV esophagitis consist of nonspecific ulcerations in the distal esophagus (36, 37). Recent reports regarding graft *versus* host disease in patients after marrow transplantation have shown an increased incidence of esophageal infection by herpes viruses (HSV and CMV) (38, 39).

Pathologically three stages of mucosal damage by herpes simplex virus are recognized in the esophagus. Discrete raised vesicles in the distal esophagus are the first histological changes. The next stage is coalescence into larger 0.5–2 cm lesions with raised borders. The third stage is diffuse mucosal necrosis and ulcerative esophagitis. The second and third stages are commonly encountered findings at endoscopy or autopsy (Figs. 1 and 5). Nash *et al.* (3) have described typical "punched out" ulcers with raised yellowish granular margins. They vary in size, are superficial, and show a background of normal and slightly hyperemic mucosa. In autopsy cases the early vesicular stage may occasionally be seen. In late stages diffusely ulcerative and even hemorrhagic mucosa is seen. The mucosa may be completely denuded from the underlying submucosal layer. Larger plaques may show concomitant bacterial and fungal infection.

Histologically the diagnosis depends on the typical cellular changes of herpetic infection which consists of ballooning degeneration, ground glass nuclei with margination of chromatin (40) multinucleated giant cells, and Cowdry type-A intranuclear inclusions found in the ulcer margin. Rosen and Hajdu (29) have described the characteristic Cowdry type-A inclusion bodies and ideally the diagnosis should rest upon identifying these inclusion bodies. However, Burrig *et al.* (41) reported these findings to be less frequent at electron microscopy. Ground glass nuclei and multinucleated giant cells are characteristic changes of the late ulcerative stages. Since herpes virus rarely invade below the epithelial layer, therefore, cellular changes are mostly found at the ulcer edges and the characteristic inclusion bodies are frequently seen in sloughed squamous epithelium.

Lightdale *et al.* (21) have documented the usefulness of exfoliative cytology in the antemortem diagnosis of herpetic esophagitis. Biopsies and brushings should be

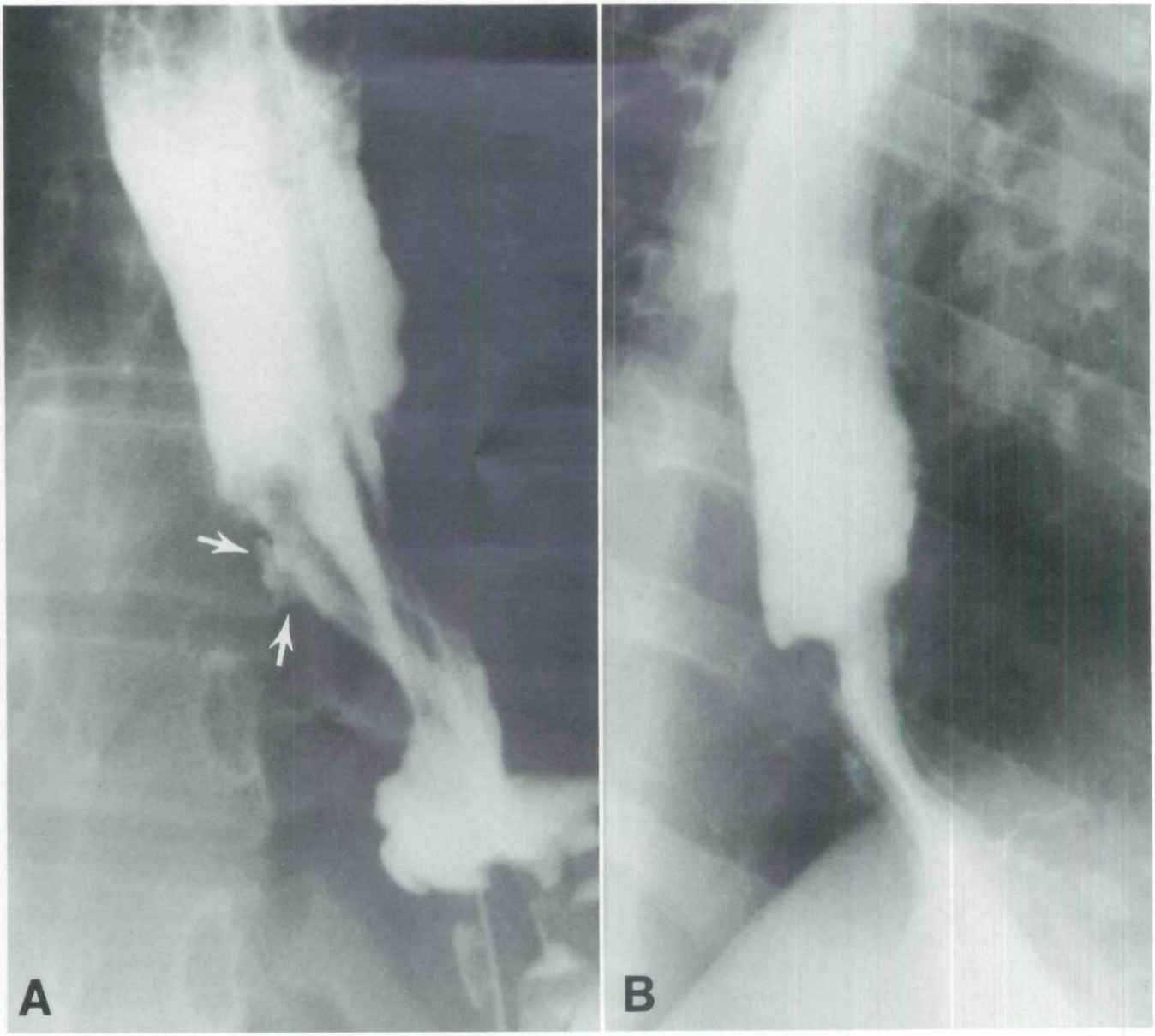

FIG. 5. Case 11. *A* and *B*, esophagram shows ulceration (*arrows*) and stricture in the distal esophagus. Biopsy and cultures showed CMV inclusions (CMV esophagitis).

obtained from the ulcer margins since herpes viruses are trophic for intact squamous epithelium. Both mucosal biopsy and brush cytology are equally effective in diagnosing HSV infection.

CMV infection can be localized to the submucosa and the vascular endothelium, therefore, biopsies and specific immunoperoxidase stains may be required for definitive diagnosis. CMV infection of the esophagus is usually associated with involvement of other sites particularly the lungs (42). Cases of concomitant infection with herpes simplex virus and CMV in the esophagus have been reported (43).

When esophageal symptoms develop in these patients an aggressive diagnostic approach should be taken to document a specific infecting organism so that appropriate antiviral and antifungal therapy can be instituted. Many patients may be asymptomatic or the esophageal symptoms may be overshadowed by symptoms related to other organ systems. Viral cultures are superior to cytological and histological examination in the detection of HSV. Differentiation between CMV and herpes simplex is especially important since potential treatment with Acyclovir has only been shown to be effective for herpes simplex virus (44).

In summary, our findings suggest that endoscopy and double contrast esophagraphy are relatively accurate techniques for diagnosing herpetic esophagitis. A single contrast esophagram plays no specific diagnostic role.

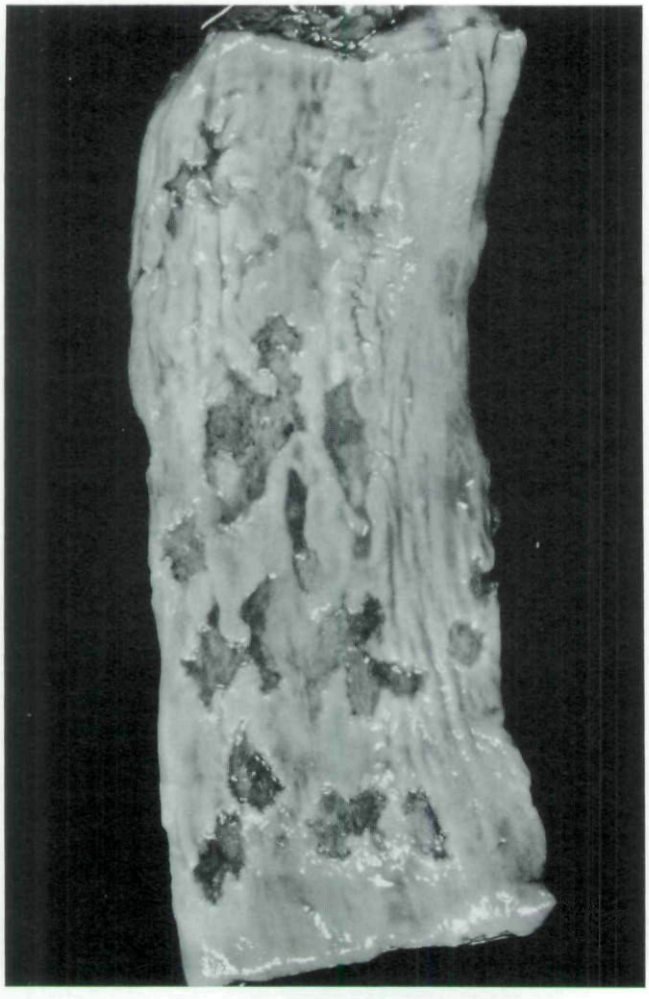

FIG. 6. Case 7. Photograph of an autopsy specimen of esophagus from a patient with severe herpetic esophagitis. Note discrete punched out ulcers and several coalescent ulcers with raised margins and yellowish base.

In immunocompromised patients, with esophageal symptoms, typical "volcano ulcers" at endoscopy and discrete shallow widely scattered ulcers and occasionally on a background of normal mucosa on double contrast esophagram should strongly suggest the diagnosis of herpes virus infection.

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