

Herpetic Esophagitis Mimicking Carcinoma *In Situ*

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Summary

Herpes Simplex virus (HSV) type I is a common infectious agent of nongenital areas and has been diagnosed most frequently in esophagitis even in otherwise healthy subjects. Although some mild cellular alterations are commonly seen in this disease they can hardly be so intense as to simulate a carcinoma in situ of squamous epithelium. We report such a case and call attention to the possibility of an overdiagnosis of cancer. Some observations in literature relating HSV infection to cancer are also made.

Uniterms: *herpetic esophagitis; carcinoma in situ; esophagus*

Case report

A 65-year-old white man suffering from chronic obstructive pulmonary disease was admitted to the University Hospital because of a right femoral fracture. During hospitalization he presented frequent episodes of dyspnea and developed bilateral bronchopneumonia. Clinical evolution was bad with respiratory complications and death.

The autopsy revealed extensive bilateral bronchopneumonia associated with multiple pulmonary infarctions, irregular emphysema and bronchiectasis. There was also a decompensated chronic *cor pulmonale*, centrilobular hemorrhagic necrosis of the liver and deep right leg vein thrombosis. The middle and lower thirds of the esophagus showed multiple superficial longitudinal ulcerations with a granular yellow necrotic material covering their bases. Histologically, the ulcerations showed sloughing of the squamous epithelium, necrotic material and massive acute inflammatory infiltrate (Figures 1-3). The borders of one of the lesions exhibited well oriented and stratified cells which presented many nuclear alterations: nuclear irregularities, multinucleation and nuclear molding as well as eosinophilic intranuclear bodies (Cowdry type A). With a PAP staining for HSV-I and II¹³ many of the cells stained positively (Figure 4). In the center of this lesion and with a gradu-

al transition with the borders there were more marked cytologic and structural atypias characterized by hyperchromasia, irregularities of the nuclear contour, alteration of the nucleus/cytoplasmic *ratio* in favor to the first and voluminous bizarre *nuclei*. There was also loss of cell polarity and superficial maturation involving the full thickness of the epithelium, thus resembling a severe dysplasia/carcinoma *in situ* (Figure 3).

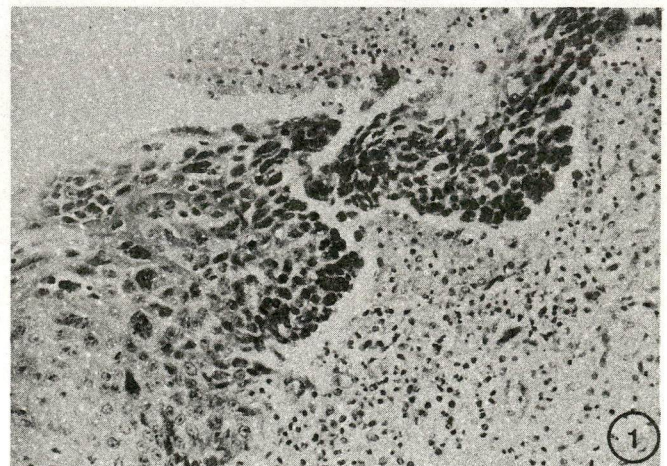


Figure 1 — Photomicrograph showing an acute ulcerated esophagitis (HE, x 600).

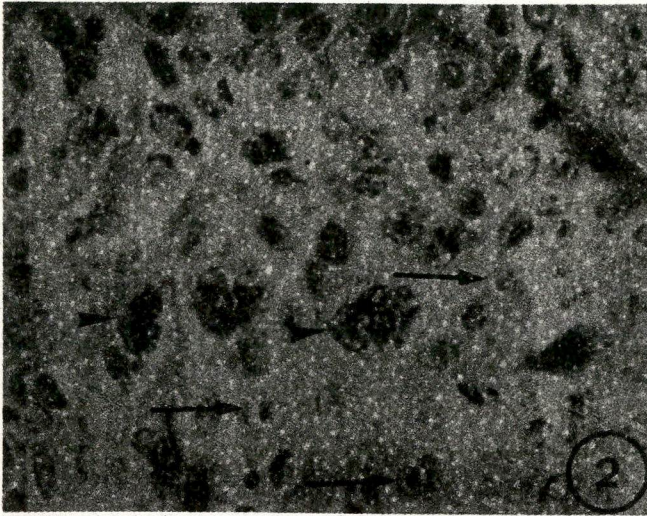


Figure 2 — Border of the lesion seen in Figure 1. There are cytologic alterations consistent with herpesvirus infection: multinucleation with a nuclear molding (arrowhead), large eosinophilic inclusions (long arrows) and mild cellular atypias (HE, x 1200).

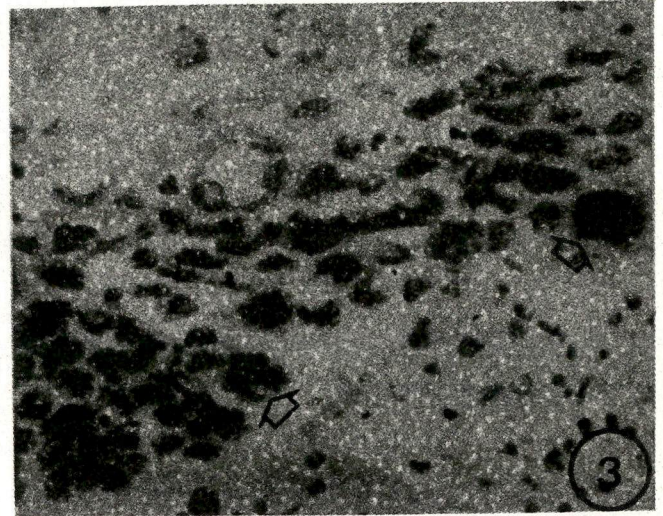


Figure 3 — Center of the lesion seen in Figure 1 showing both loss of superficial maturation and cell orientation. The cells are irregular and exhibit hyperchromatic and sometimes bizarre nuclei (open arrows), resembling a carcinoma *in situ* (HE, x 1200).



Figure 4 — PAP staining for HSV I and II (Dako Corporation). Note positively stained intranuclear inclusion bodies (arrows) that could be seen in the border of the ulceration seen in Figure 1 (x 1300).

Discussion

The main interest of the present case is to report the presence of cytologic and structural alterations in a proved herpesvirus infection that could be interpreted as a carcinoma *in situ*. This is important to be known by the pathologist as it may induce the less experienced to overdiagnose a neoplastic lesion. This could particularly happen in the observation of small endoscopic biopsies.

The usual herpesvirus lesion is characterized by nuclear alterations such as multinucleation with nuclear

molding, hyperchromasia and the presence of eosinophilic intranuclear inclusions (Cowdry type A). It evolves to blister formation with subsequent ulceration. Generally there is no structural alterations of the epithelium. Even in the bottom of these lesions there are usually characteristic infected cells making the diagnosis of herpesvirus infection easy. As a matter of fact, mild atypias are not absent in such lesions but severe cytologic and structural alterations represented by loss of polarity and of superficial maturation is infrequent. Eventually an overdiagnosis of severe dysplasia/carcinoma *in situ* could be stated if the characteristic herpesvirus infection changes were not so clearly represented in this case.

Much has been said about the association of herpesvirus type II (HSV-II), a common genital infectious agent, to cervical squamous cell carcinoma. Although there are many serological^{2,3,13} assays supporting this observation, true evidence of the oncogenic potential of this virus is not proved. Experimentally, HSV-II can induce transformation of cells of both human and animal origin⁵, although oncogenic transformation has been seen only in cultures of hamster cells⁸. Studies *in vivo* with nonhuman primates have shown that herpetic infection is associated with the production of mild to moderate dysplasia of the cervical epithelium¹⁴.

Herpes simplex virus type I (HSV-I) is responsible for the lesions present in nongenital areas. Unlike HSV-II, the oncogenic potential of HSV-I has not been investigated. There are only a few reports in the literature, usually as observations of single cases, reporting the occurrence of squamous cell carcinoma at the site of previous herpetic infection^{6,11}.

HSV-I esophagitis is being more and more recognized. It was usually seen as an incidental finding in autopsy, generally observed in immunodepressed subjects^{1,4,10,12}. Presently it has now been diagnosed in otherwise healthy subjects^{7,9}. This is probably due to a better understanding of this disease and to the routine use of fiberoptic instruments in symptomatic subjects followed by histologic and cytologic studies. So it is important to call attention to the fact that occasionally a HSV-I lesion may present changes resembling severe dysplasia/carcinoma *in situ*. If such alterations represent real transformed cells able to progress to a frank invasive carcinoma it is a question to be solved in the light of new evidences.

Resumo

O vírus do herpes simplex (HSV) tipo I é um agente infeccioso comum de áreas não-genitais e tem sido diagnosticado mais freqüentemente em esofagites em pacientes pelo demais saudáveis. Embora discretas alterações celulares sejam freqüentemente observadas, nesta doença raramente são tão intensas a ponto de simular carcinoma in situ do epitélio escamoso. Relatamos um destes casos e chamamos a atenção para a possibilidade de um diagnóstico errado de câncer. Algumas observações da literatura relacionando o HSV com câncer são também discutidas.

Unitermos: *esofagite herpética; carcinoma in situ; esôfago*

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