

Cytomegalovirus Infection of the Uterine Cervix: Histologic Findings in 3 HIV-Seropositive Patients

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ABSTRACT

Histologic findings of cytomegalovirus (CMV) infection of the uterine cervix in three HIV-seropositive patients are reported. The first case showed only few CMV-infected endocervical cells accompanied by minimal chronic inflammation. In the second case, many infected endocervical cells were associated with marked chronic inflammatory response. The third case was presented by a tumor-like lesion composed of marked acute and chronic inflammatory infiltration. Many infected endothelial and stromal cells were observed. There was no case of histologically diagnosed CMV infection of the cervix in HIV-seronegative patients in our hospital. Detection of CMV infection in cervical biopsy should necessitate further investigations to rule out underlying immunologic abnormality.

Key words: cytomegalovirus, uterine cervix, histopathology, HIV

Histopathologic detection of cytomegalovirus (CMV) infection of the uterine cervix was rare. To our knowledge, approximately 15 cases of histologically documented CMV infection of the cervix have been reported to the literature including one HIV-infected patient with AIDS.⁽¹⁻⁵⁾ We present the histologic findings of CMV infection of the cervix in additional three patients who also had positive serology for HIV.

Case reports

Case 1

A 29-year-old woman with a 5-year history of positive HIV serology presented with bleeding per gum and hypermenorrhea for 5 days. She had pneumocystis carinii pneumonia and disseminated tuberculosis with bone marrow involvement diagnosed

8 months before and still received anti-tuberculous drug treatment. Laboratory investigations revealed hemoglobin 7.2g%, hematocrit 23%, leukocyte count 2200/mm³ (lymphocytes 37%), and platelet count 47,000/mm³. Gynecologic examination revealed a cervical lesion which was diagnosed clinically as condyloma acuminata. The cervical biopsy and fractional curettage were performed. The hematologic work-up revealed erythroid hyperplasia with megaloblastic change of the bone marrow. On admission, she developed drug-induced hepatitis and died after 8 weeks of hospitalization.

Histologically, the cervical biopsy showed typical condyloma acuminata as well as mild lymphoplasmacytic infiltrate of the endocervix. Only few endocervical cells exhibited cytomegaly and

protruded into the luminal surface. These cells showed characteristic features of CMV infection including single large amphophilic or eosinophilic intranuclear inclusion surrounded by a halo and multiple small basophilic intracytoplasmic inclusions (Fig. 1). There was only scanty plasma cell infiltration in the surrounding stroma. The endometrial specimen showed only glandular-stromal dissociation with no infected cells. The histologic diagnosis of CMV infection was confirmed by immunohistochemical stain for CMV antigen (monoclonal mouse anti-CMV, DAKO, at dilution of 1:50).



Fig. 1. Two CMV-infected cells (arrowheads) in the endocervical epithelium (case 1). One showed characteristic intranuclear and intracytoplasmic inclusions. (H&E, original magnification $\times 1000$)

Case 2

A 36-year-old woman with a 4-year history of positive HIV serology presented with abnormal vaginal discharge for one month. On physical examination, two ulcers (size 3 cm each) were detected at the right

side of clitoris and the left labium minor. A condyloma-like lesion was noted at the cervix and biopsy was undertaken. The patient received antibiotic treatment for the vulvar ulcer with the clinical impression of chancroid. She was lost to follow.

The tissue biopsy consisted of an endocervical polyp showing marked chronic inflammatory reaction in the stroma. The endocervical epithelium contained many CMV-infected cells protruding into the lumina (Fig. 2). The intranuclear and intracytoplasmic inclusion bodies were also observed in metaplastic squamous cells, reserve cells, and endothelial or stromal cells (Fig. 3). The diagnosis of CMV infection was confirmed by immunohistochemical stain. The non-infected neighboring endocervical cells displayed cytoplasmic basophilia and mucin depletion. Neither squamous nor glandular intraepithelial lesion was observed.

Case 3

A 23-year-old hilltribe woman with a known HIV seropositive history presented with abnormal vaginal bleeding. Gynecologic examination revealed an infiltrative yellowish white mass involving the entire upper lip of the cervix. The cervical biopsy showed condyloma acuminata. Cold knife conization was done to exclude invasive carcinoma. The patient was lost to follow.

The cone specimen showed ulcerative mucosal surface with marked acute and chronic inflammation of the entire cervical stroma. There were scattered large cells that contained single large intranuclear inclusions and multiple intracytoplasmic inclusions characteristic of CMV infection. Most of the infected cells were endothelial cells while the rest were of stromal origin (Fig. 4). There was no viral inclusion in the adjacent endocervical and ectocervical epithelium. Histochemical stains including acid fast, methenamine silver, PAS, and Warthin-Starry stains showed negative results. The diagnosis of CMV infection was confirmed by immunohistochemical study.

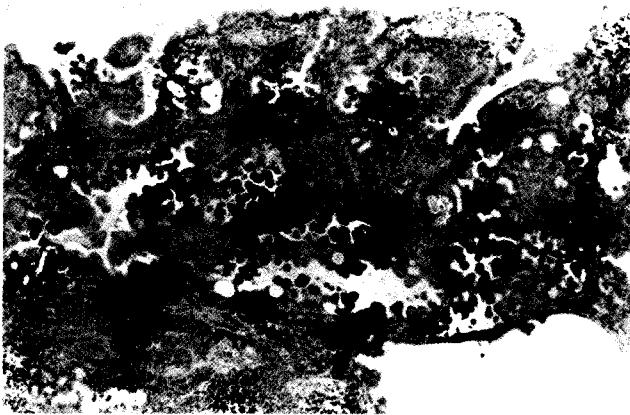


Fig. 2. Endocervical polyp with numerous CMV-infected cells (case 2). Note protrusion of infected endocervical cells into the lumens. (H&E, original magnification x 100)

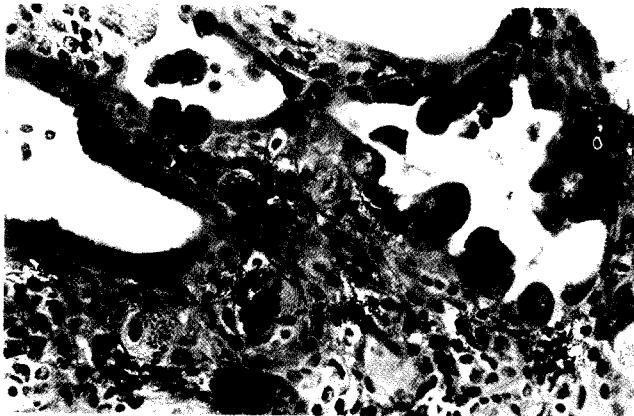


Fig. 3. CMV-infected cells were seen within the endocervical epithelium and the stroma (case 2). Marked lymphocytic and plasma cell infiltrate was observed. (H&E, original magnification x 400)

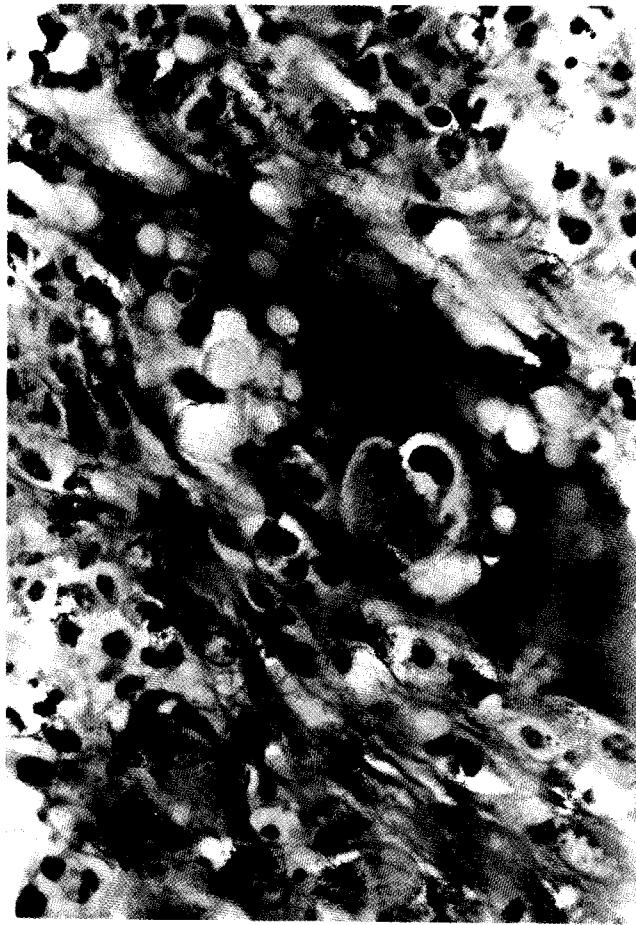


Fig. 4. CMV inclusions (arrowheads) in endothelial cell (center) and stromal cell (lower left) of case 3. An acute inflammatory response in the cervical stroma was noted. (H&E, original magnification x 400)

Discussion

CMV infection of the female genital tract is not uncommon as the reported rate of detection of genital CMV on culture was 4-12% of women.⁽¹⁾ The reported prevalence of CMV detection was variable and dependent on the population tested and the techniques applied.⁽⁶⁾ It was reported that the smears obtained from the cervix had the highest rate of CMV detection by polymerase chain reaction method (PCR) compared

to the other specimens from kidney, lung, liver, spleen, adrenal gland, and blood vessel.⁽⁷⁾ The examination of the hysterectomy specimens also revealed CMV transcripts and antigens in endocervical cells and other cells of the cervix, which supported the hypothesis that this organ may be the site of productive CMV infection.⁽⁷⁾

Histologic or cytologic examination is not a sensitive method for detection of CMV infection

because CMV genomes could be demonstrated by PCR in the absence of typical cytopathic change.⁽⁷⁾ The rarity of histologic demonstration of CMV infection was probably explained by sampling errors or failure to diagnosis.⁽¹⁾ In most reported cases, CMV infection was an incidental histologic finding in non-immunocompromised hosts who presented with vaginal bleeding or discharge. Only three were reported to have immunosuppression, the first was associated with systemic lupus erythematosus and steroid therapy, the second with bone marrow transplantation, and the third with AIDS.^(3, 5) Histologic detection of CMV in the female genital tract is still rare even after the epidemic spread of HIV infection. This may be associated with the relatively low proportion of female HIV-infected patients in Western countries. In this report, all three patients acquired HIV infection through heterosexual transmission. The first patient already had AIDS while the others were otherwise asymptomatic.

In most cases, CMV infection was associated with marked chronic cervicitis with or without acute inflammation.⁽¹⁻⁴⁾ The severity of inflammatory reaction in each specimen in this report was variable and ranged from minor alteration with few infected cells (case 1) to florid infection associated with marked chronic inflammatory response (case 2) and enlarged cervix due to severe inflammation that appeared clinically as a tumor-like lesion (case 3). Unfortunately, the complete clinical and laboratory investigations were not available for comparison between the morphologic change and the immunologic status of the patients. In case 1, it was not certain whether the observed minimal inflammation reflected a correlation between the number of infected cells and the degree of inflammatory response or reflected marked immunosuppression of the patient. Human papillomavirus-related lesions including condyloma acuminata and cervical intraepithelial neoplasia were additional findings in only few reported cases of cervical CMV infection.^(1, 2) Although two of our patients also had

condyloma acuminata of the cervix, the relation of these lesions to CMV infection was not clear because these patients had a high risk for sexually transmitted diseases.

In our hospital, there was no case of CMV infection detected by cervical biopsy in HIV-seronegative patients. Although most reported cases of histologically detected CMV infection of the cervix in the literature tended to be incidental and not apparently associated with any clinical significance,^(1, 4) the finding that all our three cases were HIV-infected patients indicated that detection of CMV in cervical biopsy may be significant and necessitate further investigations to rule out underlying immunologic abnormality.

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