DOUBLE VIRAL INFECTION OF THE MOUTH IN THE CANCER PATIENT

BY

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ABSTRACT

An autopsy case of renal cancer complicated with multiple oral ulcers is presented. Although serological tests were not available, double viral infection with herpes simplex virus and cytomegalovirus was suspected as causal agents in the retrospective examination. This infection may be a complication in the prolonged stage of cancer patients.

INTRODUCTION

Therapeutic progress has made prolonged survival possible in cancer patients associated with failure in hematopoiesis, reticuloendothelial system, and immunological function. Interference of the resistance in the host predisposes the patients to various infections, sometimes viral infection. Mucous membrane of the mouth is one of the easily affected organs for viral infection. In this report, we present an autopsy case of renal cancer complicated with multiple ulcers of the mouth, pharynx, and esophagus, cause of which was suspected to be double viral infection of herpes simplex virus and cytomegalovirus.

CASE REPORT

A 60-year-old man noted cough, rhinorrhea, anorexia, and dizziness in November, 1973. In January, 1974, an abnormal roentgenographic figure in the lung was pointed out in a hospital and he visited our University Hospital in February, 1974. Chest X-ray revealed an infiltrating tumor in the middle lobe and other multiple round lesions in the bilateral lungs. Hypercalcemia (12.5 mg/dl) was also noted. Primary renal tumor was diagnosed by biopsy from the cutaneous metastasis. Endoxan, 5-fluorouracil, mitomycin-C, and Toyomycin were given for tumor therapy. At the end of March, hypercalcemia syndrome such as anorexia, malaise, irritability, somnolence, and shortened QTC in electrocardiogram was apparent, which was controlled by administration of a large amount of prednisolone (40–80 mg/day). X-ray examination showed generalized osteolytic metastases in the scapula, tibia, skull, femur, sternum, ilium, and humerus. On March 8, oral pain appeared and eating was severely impaired. Fever rose to 37.5°C on March 13, which continued for 1 week. Towards the end of May, pleural effusion, general edema, and hypotension were observed and he died on May 28, 1974.

Laboratory data showed hypercalcemia (max. 12.5 mg/dl), hypophosphatemia (min. 2.0 mg/dl), hypochloremia (96 mEq/l), elevated alkaline phosphatase (159 mU/ml),

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and increased excretion of calcium (653 mg/day) and phosphorus (600 mg/day) in the urine. α-Fetoprotein increased to the value of 400 ng/ml. Australian antigen and antibody were negative. Immunoassay of the parathyroid hormone using the serum and tumor taken at autopsy showed no significantly elevated activity of the hormone.

**Autopsy Findings**

There was seen a tumor of 3×4 cm in size occupying upper half of the left kidney. Histologically, the tumor was renal cell carcinoma consisting mainly of clear cells arranged in solid alveoli and sheets interspersed by delicate stroma. Lymphogenous metastases were found in the retroperitoneal, lung hilar, bifurcation, and paratracheal lymph nodes. Hematogenous metastases were found in the kidney, lungs, adrenal glands, femur, and sternum. The same osteolytic metastases as those examined histologically in the femur and sternum were verified roentgenographically in the skull, scapula, humerus, ilium, and tibia.

There were multiple, irregular-shaped, shallow ulcers on the dorsal surface of the tongue, base of the tongue, soft palate, pharynx, and esophagus (Fig. 1). The margin of the ulcers was well-demarcated from the surrounding mucosa. The gingiva, buccal mucosa, floor of the mouth, and lip were not involved. The skin was free from the lesion. Histologically, the ulcers had shallow superficial necrotic zones with infiltration of leucocytes, lymphocytes, plasma cells, and histiocytes beneath. The epithelial changes at the edge of the ulcers were characteristic (Fig. 2). The epithelial cells were enlarged and contained evident nuclear membrane and faintly granular acidophilic particles that were frequently clumped. The intranuclear inclusion bodies were sometimes observed (Figs. 3 and 4). These epithelial changes were

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**Fig. 1.** Multiple shallow ulcers are seen on the dorsum of the tongue and soft palate (right side).

**Fig. 2.** The epithelium along the margin of ulcer shows intercellular dissociation, loss of cytoplasmic acidophilia, and ballooning degeneration. (Hematoxylin and Eosin stain. ×120)
found in every ulcer of the tongue, soft palate, tonsil, and esophagus.

There were relatively numerous typical cytomegalic inclusions below the ulcers (Fig. 5). The cytoplasm of these cells was abundant, pink or lavender, and occasionally small granular cytoplasmic inclusions were observed. The nuclei had large homogeneous, amphophilic intranuclear inclusion bodies and clear zones around them. The intranuclear inclusion bodies were stained red with Lendrum’s method for inclusion bodies. The giant cells were isolated singly in the connective tissue but more often found in the capillary endothelium.

Cytomegalic inclusion bodies were not identified in the submandibular gland.
Submandibular lymph node showed slight lymphadenitis with sinus histiocytosis and neutrophilic infiltration. The liver (960 g) was not remarkable except for congestion. Neither hyperplasia nor proliferation was found in the parathyroid gland. Other findings were atrophy of the heart (220 g) and congestion of the lung (l480 g, r610 g) and spleen (80 g).

DISCUSSION
In the present case, epithelial changes along the margin of the ulcers indicated these ulcers might be caused by viral infection. Of the known viral diseases found in the regions of the present case, herpes infection seems to be the most reasonably accepted. Microscopic features of the present case were consistent with herpes simplex virus infection described in the literature; ballooning degeneration, the so-called ground glass nuclei, Cowdry type A eosinophilic intranuclear inclusions, and herpetic giant cells.1,3,6,8,10) Herpes zoster was denied by the absence of distribution of the lesions and chicken pox by the absence of cutaneous involvement. Herpes simplex infection is classified into primary infection and recurrent manifestation, and distinction between the two groups has been well discussed. The most common lesion of the primary herpes infection is acute herpetic gingivostomatitis. According to Montgomery et al.,5) the possibility of the primary herpes simplex virus infection of their cases was excluded by the demonstration of complement-fixing antibodies to herpes simplex virus in the patients' blood before the development of esophageal lesions. The present case also might not be primary infection. Herpes infection usually has a tendency to involve anterior oral tissue. However, in the present case the lesions developed in the posterior mouth, pharynx, and esophagus. This altered localization might be attributed to the impaired immunological condition or general debilitation. It has been shown that herpetic esophagitis is not so uncommon. Berg11 reported 12 cases of esophageal herpes as a complication of cancer patients. Nash and Ross9) stated herpetic esophagitis is found
in approximately 25% of the cases of esophageal ulceration in a study of the autopsy cases.

Other interesting findings were simultaneous infection of herpes simplex virus and cytomegalovirus in the same location. In the morphological diagnosis of the cytomegalovirus infection, there is no difficulty in distinguishing it from other inclusion diseases. Cytomegalic inclusion disease is usually a disease of the infant but it is being observed with increasing frequency in adults as a complication of chronic debilitating systemic disease.\textsuperscript{5,6,7,9,11} Rosen and Hajdu\textsuperscript{3} reported 19 cases of cytomegalic inclusion disease in 5,788 conservative autopsies of cancer patients. In the literature some occurrences of double viral infection of herpes simplex virus and cytomegalovirus in the same location has been reported.\textsuperscript{8,9} Judging from the reported cases of the double infection of the herpes simplex virus and cytomegalovirus, this infection more often occurred in patients affected with renal diseases. It is not settled whether the infection of cytomegalovirus is focal or generalized. Montgomery et al.\textsuperscript{5} said cytomegalovirus is carried in circulating leucocytes. In the present case the distribution of inclusion bodies suggests exogenous infection of the cytomegalovirus through the ulcers caused by herpes simplex, though the possibility of activation of latent virus could not be excluded. Although cytomegalovirus did not involve the mucosa and did not cause ulceration, it probably aggravated the severity of the herpes simplex virus-induced ulceration.

In the present cancer patient, development of double viral infection might reflect impaired immunological responsiveness and/or general debilitation. As to both viruses, infection in the present case is thought either to be acquired during the terminal stage of the disease or to result from activation of virus latent since an earlier infection. Wide extension in the mouth, pharynx, and esophagus is probably due to epidermatropism of the herpes simplex virus, immunosuppression, and/or general debilitation. Usually esophageal herpes is of little clinical significance and most of the reported cases were diagnosed at autopsy. Recently antemortem diagnosis has been made in some cases.\textsuperscript{4,10} It is shown from the present case study that greater awareness of herpes simplex virus infection associated with cytomegalovirus is necessary in cancer patients.

\textbf{References}