Skin Manifestations Associated with Fatal Cytomegalic Inclusion Disease in a Renal Transplant Patient

Cytomegalovirus Skin Ulcers

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Abstract

A case of cytomegalovirus-induced vasculitis leading to skin ulcerations in a renal transplant patient is reported. Light and electron microscopy revealed inclusion bodies and viral particles, respectively, characteristic of cytomegalovirus. To our knowledge, this is the first report of cytomegalovirus-induced vasculitis producing skin ulcerations, and it illustrates another of the protean manifestations of cytomegalovirus inclusion disease which may have important clinical implications.

Cytomegalovirus (CMV) is now considered as a member of the herpesvirus family which includes agents that are remarkable for their capacity to persist in a latent state, possibly from the time of conception to the time of death. In the general population, from 0.5 to 2.0% of newborn infants may be infected with CMV depending on the socioeconomic level.[1] On the other hand, Cytomegalic Inclusion Disease (CMID) in adults often becomes manifest in chronic debilitating conditions and frequently in immunosuppressed individuals, such as cancer patients and recipients of organ transplants. Of these, up to 91% may show evidence of CMV infection.[2]

The clinical manifestations of CMID in the adult are often nonspecific and vary depending on the organ involved. In the localized form of infection, the lungs (pneumonia) and the gastrointestinal tract (ulcers) are commonly affected, whereas in the disseminated form most of the tissues may be compromised. Except for maculopapular or purpuric rash,[3] specific dermatological signs of CMID and the presence of the virus in the skin have not been documented in the literature. To our knowledge, this is the first report of CMV-induced vasculitis leading to skin ulcerations. This finding represents another manifestation of CMID which may have important clinical implications.

Report of a Case

This 24-year-old white female transplant patient had her last admission to the Medical College of Virginia for chief complaints of skin ulcers, fever of unknown origin, and decreased visual acuity. She was first diagnosed as having nephritis at the age of 7 which was well controlled by medical therapy. However, at the age of 21 she developed chronic uremia and renal tubular acidosis secondary to chronic pyelonephritis for which she was admitted to the Staten Island Hospital and treated by peritoneal dialysis. Subsequently, she had many hospital admissions there for hemodialysis. In August 1972, she had her first admission to the Medical College of Virginia, and in September of that year she underwent renal transplantation 2 weeks after bilateral nephrectomy, ureterectomy, splenectomy, and appendectomy. Her mother served as a kidney donor for this purpose. Subsequently, she was started on immunosuppressive therapy with azathioprine (Imuran) and steroids. Hepatitis B (HB_S) antigen was first detected in her serum by complement fixation approximately a month after transplantation, but a peak titer of 1:2,000,000 was detected at 2 1/2 months. The patient had two episodes of rejection at 37 and 104 days post-transplant for which alternate therapy with cyclophosphamide (Cytoxan), Imuran, prednisone as well as irradiation was instituted. Her subsequent course was complicated by

anemia; febrile urinary tract infections treated with gentamicin, nafcillin, and gantrisin; and hypertension followed by a seizure and hemiplegia of unknown etiology. She recovered from these problems and was discharged from the hospital 192 days post-transplant to remain under the care of her private physician.

The patient's condition was well under control until July 24, 1973 when she was readmitted to the Staten Island Hospital with a history of fever ranging from 101 to 106° C. At this time she had 3,400 WBC/cu mm, 100,000 platelets/cu mm, 8 g% hemoglobin, and 27% hematocrit. Escherichia coli was isolated from her blood culture, and she was then treated with ampicillin and chloromycetin. Two necrotic skin ulcers, one on her left elbow and the other on her right thigh, were noted for the first time but were not biopsied. She was discharged on September 8, 1973 with continuation of immunosuppressive therapy and Travase ointment for her skin lesions.

Despite intensive therapy, the patient continued to have symptoms and she was readmitted to the Medical College of Virginia Hospital on September 24, 1973 for the last time with complaints of necrotic skin ulcers (Fig 1), a chronic dry cough, fever of unknown origin, decreased visual acuity, and dysphagia. Physical findings on admission included oral candidiasis, skin ulcers, one on her left elbow and the other on her right thigh, Cushing's type of habitus, poor visualization

of fundi with narrowed vessels and scarring with waxy exudates in the left eye and failure to see the discs. Punch biopsies from the skin ulcers were performed shortly after admission. She progressively deteriorated during her hospitalization which was complicated by gastrointestinal bleeding for which she received multiple transfusions. During this admission she was diagnosed as having chorioidoretinitis of presumed viral etiology which progressed to blindness. Terminally, she developed diffuse pulmonary infiltrates bilaterally and her fever persisted despite broad spectrum antibiotic therapy. She expired approximately 7 weeks following this admission.

Materials and Methods

For light microscopy, punch biopsies from ulcers on the right elbow and the right leg and from nearby uninvolved skin were fixed in Zenker's solution and embedded in paraffin. Sections 6 μm in thickness were cut and stained with hematoxylin and eosin. At postmortem, specimens were submitted from the skin, lung, liver, kidney, breast, ovaries, adrenal, parathyroid, and eye tissues. Frozen sections from skin, kidney, liver, and lung tissues were prepared for indirect immunofluorescence using isothiocyanate-conjugated rabbit anti-human gammaglobulin (Microbiological Associates, Bethesda, Maryland) and

human antiserum to CMV (prepared at the Medical College of Virginia Virology Laboratory) free of antibody to herpes hominis and varicella-Zoster viruses according to complement fixation and immunofluorescence tests. Cell cultures of human embryonic lung (HEM Research, Inc., Rockville, Maryland) uninfected and infected with CMV were employed as negative and positive controls, respectively. Negative control serum (from and tested at the Medical College of Virginia Virology Laboratory) was also included. The technique used was originally described by Hanshaw.[4]

For electron microscopy, blocks of skin and subcutaneous tissue fixed in formalin and embedded in paraffin were used. Depending on previous histological examination the blocks containing more inclusion bodies were selected. The paraffin was removed and the tissue rehydrated; then the cubes were placed in 4% glutaraldehyde in cacodylate buffer, postfixed in 2% osmium tetroxide dissolved in cacodylate buffer, dehydrated, and embedded in Epon 812. One micron sections were cut with glass knives and stained with Paragon PS-1301 for a general survey. Thin sections were cut with a diamond knife, double stained with uranyl acetate and lead citrate and observed with the Hitachi HS-8-F-2 electron microscope.

Results

Microscopic examination from both skin ulcers demonstrated that the main pathologic change involved the small dermal vessels (Fig 2). CMV inclusions were present in the endothelial and perithelial cells of the small arterioles, venules, and capillaries. The affected cells were characteristically enlarged and showed large purplish intranuclear inclusions surrounded by a clear halo. Occasional cells had circumscribed granular pale eosinophilic intracytoplasmic inclusions (Fig 3). Rarely, large cells with two nuclei containing inclusions were seen. The lumen of the involved vessels was markedly narrowed by the swollen cells (Fig 4). There was a severe perivascular and interstitial infiltrate composed of polymorphonuclear neutrophils, histiocytes, and lymphocytes. The biopsy from the uninvolved skin revealed no CMID nor inflammation (Fig 5).

At autopsy, disseminated CMID was present with involvement of the skin, lungs, liver, kidneys, breasts, ovaries, adrenal and parathyroid glands, and eyes. The kidney, liver, and lung sections showed areas of specific immunofluorescence with anti-CMV rabbit antiserum. The ulcerated skin sections were unsatisfactory for immunofluorescense.

Electron microscopic study revealed numerous degenerating cells within the dermis containing intranuclear viral particles approximately

110 nm in diameter. Some of these particles were devoid of dense cores while others represented immature intranuclear forms of the virus (Fig 6 and 7).

Discussion

Cytomegalovirus inclusion disease may have protean clinical manifestations ranging from inapparent infection to widely disseminated disease with a fatal outcome, as in this case. The development of CMID in patients with underlying debilitating conditions is well documented, but whether CMV infection in organ-transplant or immunosuppressed individuals is primary or represents reactivation of a latent infection is unclear.[5] Approximately one year following renal transplantation and while she was under immunosuppressive therapy, this patient was readmitted to the hospital with chief complaints of skin ulcers, fever of unknown origin, and decreased visual acuity. To our knowledge, this is the first report of CMV-induced vasculitis presenting with skin ulcerations in a fatal case. The histologic changes in this case are similar to the ones described by Goodman and Porter[6] and Nakoneczna and Kay.[7] Both of these cases had GI tract ulceration secondary to CMV-induced vasculitis. We believe that the striking CMID vasculitis in the dermal vessel caused the skin ulceration in our case.

The pathologic and histologic findings described in this case as well as the demonstration by electron microscopy of intranuclear herpes-like viral particles in the ulcerated skin lesions of this patient confirm that CMV was associated with the pathogenesis of the skin lesions in this patient. We suggest that biopsy should be taken if immunosuppressed patients present with skin ulcers. This case is another example of the protean manifestations of CMID and should alert the clinician of the possible occurrence of skin ulceration induced by CMV.

References

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Figures

Fig 1. Three inch punched out ulcer of the skin with a clear base and subcutaneous tissue with slight erythema of the surrounding epidermis on the anterior lateral upper thigh.

Fig 2. Cytomegalic inclusion disease involving dermis and subcutaneous tissue. Dermal vessels markedly narrowed by the affected enlarged endothelial and perithelial cells with a surrounding perivascular and interstitial inflammatory infiltrate (hematoxylin-eosin, X 120).

Fig 3. Affected vessels revealing characteristically enlarged cells with large purplish intranuclear inclusion surrounded by a clear halo and occasional eosinophilic intracytoplasmic inclusions (hematoxylin-eosin, X 375).

Fig 4. Dermal arteriole markedly narrowed by swollen cells having characteristic large purplish intranuclear inclusion with surrounding halo (hematoxylin-eosin, X 920).

Fig 5. Low power view of clinically uninvolved skin revealing no cytomegalic inclusion disease (hematoxylin-eosin, X 52).

Fig 6. Electron micrograph revealing intranuclear spherical viral particles measuring 110 nm in average diameter containing either empty or dense cores (X 20, 000).

Fig 7. Collection of mature and immature viral particles within

nucleoplasm; some of them reveal dense cores while others are immature forms with single or double rings (X 45, 000).