

An Autopsy Case of Disseminated Cytomegalovirus Infection in a Classic Hemophiliac A with Acquired Immunodeficiency Syndrome

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SUMMARY : This is a case report of disseminated cytomegalovirus infection which occurred in 23-year-old male hemophiliac with AIDS. He has been receiving Factor VIII concentrate. Postmortem examination revealed generalized CMV infection in the lungs, the adrenal glands and the large intestine resulting in multiple organ system failure. These observations suggest that when Factor VIII concentrate used, careful evaluation of the pathogens such as ATL and HIV is essential.

INTRODUCTION

There have been increasing cases of acquired immunodeficiency syndrome (AIDS) since GOTTLEIB (1) reported the first case of AIDS in 1981. It is demonstrated that human T-lymphotropic virus, type III (HTLV) is the causative agent for AIDS (11). Recent studies (1, 7, 8) have also suggested that AIDS prevalently occurs in the people with various conditions such as homosexual life styles, drug abuse and Factor VIII deficiency. AIDS is one of the most devastating diseases of the immune system, with various abnormalities of humoral and cellular components of the host defense (16). Thereby, patients with AIDS are liable to opportunistic infections and neoplasms. Herein we report a case of hemophiliac A with AIDS who developed disseminated cytomegalovirus infection.

CASE REPORT

1. Clinical findings.

A 23-year-old man was admitted to our hospital for the fourth time because of dyspnea and diarrhea. He was diagnosed as having hemophilia A at the age of 5 years. He had been treated with Factor VIII concentrate since he was 8-year-old. His past history also included non-A non-B hepatitis at the age of 18 years. In February 1981, he entered our hospital with diagnoses of interstitial pneumonitis and esophageal candidiasis, and at that time he was diagnosed as having AIDS. Chemotherapy was effective and he was discharged. In May 1986, he was readmitted due to severe dyspnea and remarkable weight loss. There were candidiasis of oral cavity and pneumonia of both lungs. He was placed on ST drugs which was effective and was subsequently discharged in July 1986. In January 1987, he was readmitted because of cough and a high

fever which was treated with antibiotics, and was discharged in February 1987. In March 1987, he had frequent watery diarrhea and sensory loss of both lower extremities. His laboratory data on his final admission are shown in Table 1. Neither anemia nor thrombocytopenia was noted. Leukocyte count was 4000/mm³ with 29% lymphocytes, and no atypical lymphocytes were seen. Blood chemistry data indicated slightly increased levels of GOT, GPT and LDH suggesting chronic hepatitis. Serological tests revealed moderate increase in plasma polyclonal gammaglobulin, and plasma and urinal B2-MG. Both anti-ATLA and anti-HIV antibodies were positive. Examination of lymphocytes revealed the following values: T cell and B cell ratio, 82 to 6; OKT3, 75.5%; OKT 4, 1.6%; OKT 8, 71.6%; Ia1, 40.3%; IL-2R, 0.7%. Blastic transformation of lymphocytes was demonstrated to be diminished by spontaneous, PHA, and Con A tests. Multiple stool cultures and examinations revealed no intestinal pathogens for watery diarrhea. Routine peripheral blood studies showed that the white blood cell count and the platelet count were 600/mm³ and 2.8×10^4 /mm³, respectively. In April 1987, he developed a high fever, jaundice and bloody diarrhea. The results of liver function test gradually aggravated. The peak levels were as follows: GOT, 3070 IU/L; GPT, 1354 IU/L; ALP, 17.8 KA; LDH 5515 IU/L. Although serologic studies were carried out for viruses including measles, CMV, rubella and EB, only

CMV was positively detected with a titer of 1:16. Despite intensive care and chemotherapy, the patient developed respiratory failure and he died of shock in May 1987.

2. Autopsy findings

Gross Examination: The external examination of the body revealed marked scaphoid of the abdomen and moderate jaundice of the skin. In the body cavities, small volumes of brown serous fluid were present. The liver was moderately enlarged, descending approximately 2 cm below the right costal margin. The thymus was almost replaced by the fat tissue. Numerous petechiae were present on the peritoneum, the pleurae of both lungs, the epicardial and endocardial surface. The lungs were heavy and airless. The left and right lungs weighed 600 gm and 750 gm, respectively. The interstitium was evidently thickened. Scattered hemorrhagic areas were noted. Nodular or micronodular lesions were also noted here and there. In places, infiltrates were segmental or even lobar (Fig. 1). The tracheobronchial tree contained a slight amount of mucoid material. Cut section of the lung showed consolidation and necrosis. The liver weighed 1,400g. having a slightly granular capsule and dull edges. The consistency was increased and the color was icteric. Sections showed an alternating yellow-green mottled appearance. The gall bladder and the pancreas were normal. The spleen weighed 160g and was dark red. No swelling of the

Table 1. Laboratory Data

Peripheral Blood		Blood Chemistry		Serological Test	
RBC	534 × 10 ⁴ /mm ³	T. Prot.	8.4 gm./dl	CRP (+)	
Hb.	16.1 gm./dl	alb.	53.4%	RA (-)	
WBC	4,000/mm ³	r-glb.	22.2%	β ₂ -MG.	4.6mg/L
Baso	1%	T. Bil	0.8 mg/dl	IgG	3,200 mg/dl
Eo.	3%	GOT	531 U/L	IgA	930 mg/dl
St.	28%	GPT	591 U/L	IgM	210 mg/dl
Seg.	30%	AL-P	9.2 KA. L		
Ly.	29%	LDH	5391 U/L	HBsAg (-)	HBsAb (-)
Mono.	9%	BUN	15 mg/dl	anti-HTLV antibody (+)	
PLT.	16.9 × 10 ³ /mm ³	Creat.	0.8 mg/dl	anti-HIV antibody (+)	

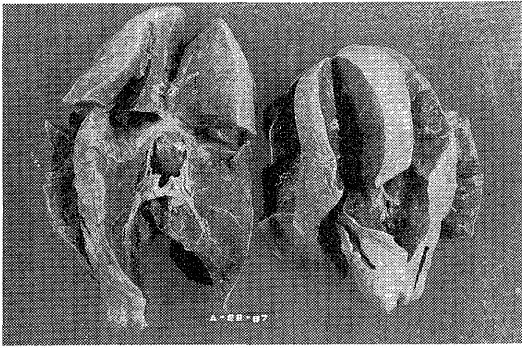


Fig. 1 Gross photograph of the lungs

lymphnodes was noted. The left adrenal gland weighed 4.5g and the right 5g. On cut section, the cortex was extensively necrotic and hemorrhagic. The kidneys were icteric. Considerable hemorrhage was noted in the soft tissues around the renal pelvis of each kidney. The esophagus was normal. The stomach was small and contracted. There were a few small mucosal hemorrhages in the mucosa of the stomach. The caecum had shallow irregular ulcer of 5×8 cm in the mucosa, which was coated with necrotic debris and coagulated blood (Fig. 2). Numerous eroded areas of about 1 cm in diameter were scattered in the large intestine. This necrotic change was accentuated by intense congestion of the underlying vessels and scattered hemorrhage. The left testis weighed 17g and the right 16g. The pelvic organs were normal. The bone marrow in the vertebral bodies was cellular and bright red in color. The brain weighed 1,350g and was slightly edematous. The spinal

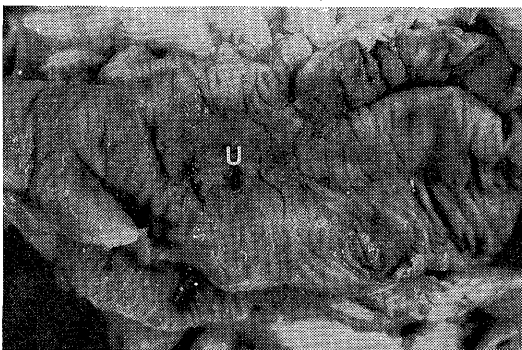


Fig. 2. Gross photograph of the ulcer (U) of the caecum.

cord was normal.

Microscopic Examination : Numerous cytomegalic cells were found in the alveolar epithelium with minimal evidence of inflammation and injury (Fig. 3). These cytomegalic cells were scattered throughout the lung. In these lesions, the pulmonary architecture was obliterated by an exudative inflammatory response in the interstitium and in the airspaces. The adrenal gland showed massive hemorrhagic necrosis. Cytomegalic inclusion cells were overwhelmingly seen in the necrotic areas (Fig. 4). There were frequent ulcerative lesions in the colon. The non-ulcerated areas showed crypt distortion, depletion of goblet cell mucin, and varying degrees of mucosal inflammation. The ulcerated areas contained large cells with large basophilic intranuclear inclusions which were characteristic of CMV

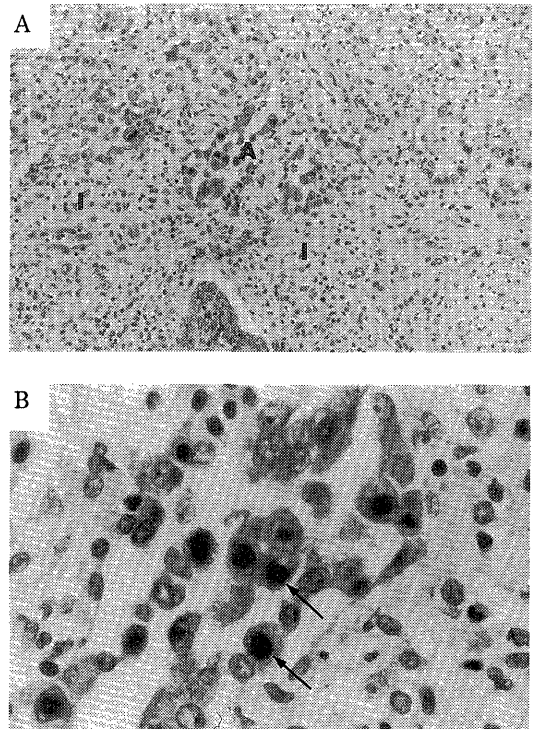


Fig. 3. Micrograph of the pulmonary lesions. A : The interstitium (I) is markedly thickened and infiltrated with mononuclear cells ($\times 170$). A : Alveolar space B : Higher magnification showing typical cytomegalic cells (arrow) in the alveolar epithelium ($\times 630$).

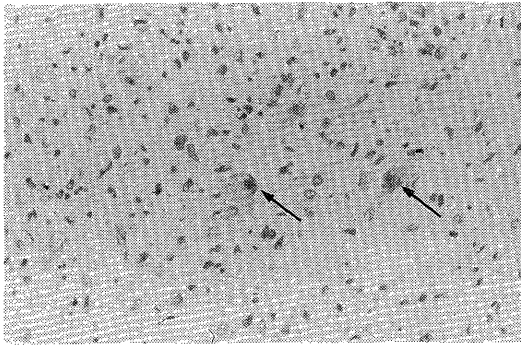


Fig. 4. Cytomegalic inclusion cells (arrow) are seen in the necrotic area of the adrenal ($\times 340$).

(Fig. 5). The hepatic lobular architecture was slightly distorted. Moderate intralobular cholestasis and fatty metamorphosis were noted. However, neither significant eosinophilic degenerate cells nor viral inclusions were noted. Portal areas were slightly widened, and had moderate amount of mononuclear cells (Fig. 6). The lymphnodes and the spleen had atrophic lymphfollicles. They contained hemosiderin-laden and erythrophagocytosed macrophages. The bone marrow showed hyperplasia with increased number of granulocytes and megakaryocytes, but decreased number of erythroblasts. In the testes, spermatogenesis was markedly depressed. The thymus contained occasional epithelial islands and calcified foci. Degenerate nerve cells with shrunken cytoplasm and pyknotic nuclei were occasionally seen in the thalamus, pons, and anterior horn of the spinal

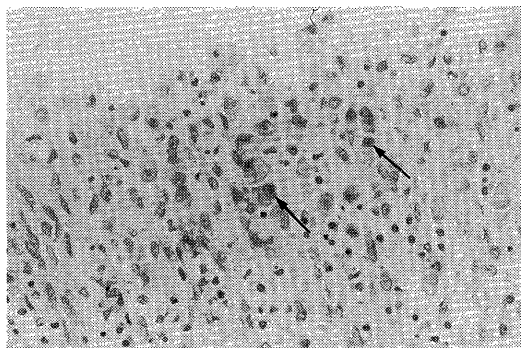


Fig. 5. The arrow points cytomegalic inclusion cells in the ulcerative lesions of the caecum ($\times 340$).

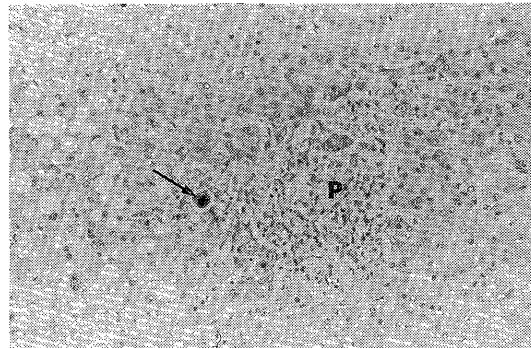


Fig. 6. Liver parenchyma displaying moderate fatty metamorphosis, inflammatory cell infiltration in the portal area and bile plugs (arrow) ($\times 170$). P : Portal area

cord (Fig. 7). Satellitosis was seen in the dorsal root ganglia of the spinal cord (Fig. 8).

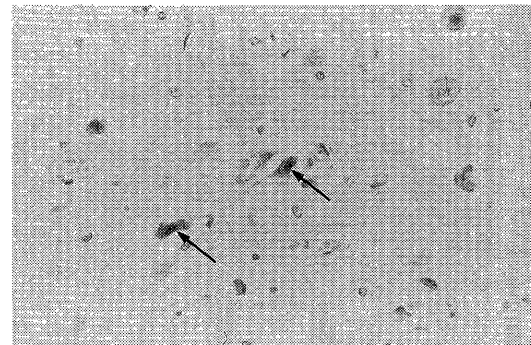


Fig. 7. Degenerate nerve cells (arrow) in the pons having cytoplasmic shrinkage and pyknosis of the nuclei ($\times 340$).

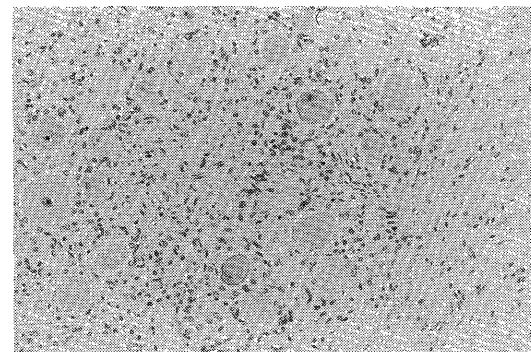


Fig. 8. Dorsal root ganglia showing satellitosis ($\times 170$).

DISCUSSION

Those patients receiving immunosuppressive agents (5) or those with debilitating diseases are at risk of developing clinically apparent CVM infection (3,4). The AIDS has been reported to be characterized by a severe disturbance of cell-mediated immunity that leads to opportunistic infections or development of unusual neoplasms (16). This hemophilic patient with AIDS showed a typical clinical course of generalized CMV infection resulting in multiple organ system failure. RINKER *et al.* (12) classified the mode of CMV infection into two types, a localized and a disseminated form. The localized form of cytomegalic inclusion disease is asymptomatic and clinically unimportant. The disseminated form commonly appears as a terminal complication of a severe debilitating disease. The clinical features are often obscured by the signs of the associated systemic disease (12). The major autopsy findings in this case showed generalized CVM infection involving mainly of the lungs, the adrenals and the large intestine.

The lungs were most severely affected, with a diffuse alveolar damage and hemorrhage. P. carinii and CMV have been reported to be the most common nonbacterial opportunistic invaders of the lungs in patients with AIDS (6, 8, 10). NASH *et al.* (9) also reported that cytomegalovirus was the most common pulmonary infection identified in 15 of 17 autopsy cases. We, therefore, should keep it in our mind that CMV can be a pathogen of pneumonia in the compromised hosts.

The adrenal glands are also known to be one of the most involved organs by CMV infection (13). GUARDA *et al.* (2) reported that involvement of the adrenal glands is generally mild and focal, and the viral inclusions are microscopically seen in the medulla or the perimedullary portion of the cortex. However, they noted one case with massive adrenal necrosis which was similar to our case. This lesion was thought to be clinically of importance, because it caused shock.

CVM infection involving the gastrointes-

tinal tract has been reported by various authors (4, 14). In opportunistic infections with ubiquitous organisms such as CMV it is difficult to prove that a given organism is responsible for symptoms and pathological changes. ROTTERDAM *et al.* (14) stated that the colon appears to be the organ most accessible for endoscopic examination and biopsy for the positive identification of CMV cells. Therefore, in order to prove the causative organisms, endoscopic examination and biopsy should be done.

As to the lesion of the nervous system in AIDS, it has been reported that marked gliosis is the main pathological features in AIDS (15). The present case had only occasional degeneration which suggests non-specific or beginning cellular changes specific for AIDS. However, it is of interest to note that peripheral neuritis was seen in the present case. GUARDA *et al.* (2) also found lesions in the peripheral nerve in one of the 17 cases.

Lastly, these findings clearly indicate that CMV is an important infection contributing to the death in an immunocompromised host. Since the severity of CMV infection depends upon the maturity and integrity of defense mechanism, it is urgent to establish the effective antiviral or immunochemotherapies.

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