Case Reports

Cytomegalovirus Encephalitis in Acquired Immunodeficiency Syndrome

DEAN A. HAWLEY, M.D., JOHN F. SCHAEFER, M.D., DALE M. SCHULZ, M.D., AND JANS MULLER, M.D.

A 38-year-old black man died from acquired immunodeficiency syndrome (AIDS) after a 15-month course. The autopsy revealed a pancolitis and a pneumonia caused by cytomegalovirus (CMV). Exceptionally, there also was a periventricular encephalitis caused by the same organism. Identification of the virus was aided by immunoperoxidase methods. (Key words: Acquired immunodeficiency syndrome; Cytomegalovirus; Cytomegalovirus encephalitis; Cytomegalovirus pneumonia; Cytomegalovirus colitis) Am J Clin Pathol 1983; 80: 874-877

Report of a Case

A 37-year-old black, homosexual man first came to medical attention in August 1981, complaining of diarrhea with eight to ten loose watery stools per day. The only significant medical history was an episode of acute viral hepatitis (hepatitis B) eight months before. Despite determined attempts to culture the agent of the diarrhea, nothing was recovered until six months later, when Shigella was isolated. He was treated with ampicillin, but there was little change in the diarrhea.

Two months later, two papular lesions were noted on the patient's right forearm. A VDRL was positive (titer 1:256). A biopsy of one of the skin lesions was consistent with secondary syphilis; he was treated with a course of penicillin.

Three months later, 11 months after the onset of the diarrhea, a duodenal aspirate revealed Giardia lamblia. The diarrhea, however, did not respond completely to treatment with metronidazole. Fourteen months after the onset of the diarrhea, he was producing 1½–2½ L of watery stool per day; he had lost a total of 60 pounds in weight since the beginning of the illness. A white blood cell count at this time (previous counts were normal) was 4,000/µL with an absolute lymphopenia (600/µL). Of the lymphocytes, 54% were T cells. The ratio of the helper/inducer T cell subset to the suppressor/cytotoxic subset was 0.2 (normal 1.6). Serum IgG was elevated slightly, but IgA and IgM were normal. A titer for cytomegalovirus (CMV) was positive but only 1:64. At sigmoidoscopy, a rectal biopsy was performed. The biopsy showed inclusions characteristic of CMV, and the culture revealed cytomegalovirus. The inflammatory process could be followed on colonoscopy through much of the colon.

At this time, the patient had high spiking fever develop, and a pulmonary infiltrate became evident with subsequent respiratory failure. The patient required mechanical ventilation. A transbronchial biopsy was positive for CMV. He was treated empirically with trimethoprim-

Departments of Pathology and Internal Medicine, Methodist Hospital of Indiana, Inc. and Division of Neuropathology, Indiana University School of Medicine, Indianapolis, Indiana

sulfamethoxazole even though Pneumocystis infection could not be documented. Therapy for the disseminated CMV infection also was instituted with intravenous acyclovir.

The patient developed severe gastrointestinal hemorrhages that required multiple daily transfusions to maintain a hematocrit above 30. His clinical condition deteriorated. On the 56th day of his last hospitalization, 15 months after the onset of the diarrhea, he suddenly became unresponsive and completely flaccid. A CAT scan of the head revealed a subarachnoid hemorrhage. Clinical brain death took place within the next 24 hours; the patient died on November 10, 1982.

Pathologic Findings

The autopsy was started 2½ hours after death. The major gross pathologic findings were left ventricular hypertrophy, confluent bronchopneumonia, hepatomegaly, generalized lymphadenopathy, large swollen kidneys, and hemorrhagic ulcers of the stomach and colon. The brain showed some subarachnoid hemorrhage with massive swelling, softening, and transforaminal herniation ("respirator brain"). Peripheral blood cultures were obtained, but neither bacteria nor fungi could be isolated. Lung cultures did yield Candida albicans, however. Viral cultures were not obtained.

Histologically, the lungs showed bronchopneumonia with considerable aspiration of gastric contents. Candida albicans were present in the bronchi. There was an interstitial pneumonitis with typical inclusions of CMV22: large, granular, intranuclear inclusions separated from the nuclear membrane by a prominent clear halo and smaller basophilic cytoplasmic inclusions (Fig. 1). Staining with the immunoperoxidase technic15 with goat antibody to CMV (Dynatech Laboratories, Inc., Alexandria, VA) showed positive staining of the cytoplasmic inclusions. There was no evidence of hepatitis. There was a Kupffer cell hyperplasia; many of the Kupffer cells contained irregularly shaped, finely granular, birefringent material,
perhaps related to intravenous drug abuse. In the colonic ulcers many CMV inclusions were present, particularly in the submucosa (Fig. 2).

The enlarged lymph nodes in all areas sampled, both above and below the diaphragm, showed almost no remaining follicles and no germinal centers at all (Fig. 3). Instead, there was paracortical hyperplasia of small, somewhat variable lymphocytes, by far the dominant cell populating these nodes. In deeper areas there were some scattered larger, less basophilic immunoblasts. The vessels were prominent.

Sections of the brain demonstrated extensive respirator effect with much nuclear karyorrhexis and liquefactive change, particularly of the cortex and the deeper gray
matter. There were also scattered fresh hemorrhages, both intraparenchymal and subarachnoid. There were some fairly well preserved areas adjacent to the lateral ventricles, and here foci of necrosis (Fig. 4) with intense leukocytoclastic vasculitis (Fig. 5) were observed. Both in and around these blood vessels numerous giant cells with characteristic intranuclear inclusions were found (Fig. 6). The immunoperoxidase method showed a positive reaction for CMV (Fig. 7)—this reaction was also positive in sections from the colon and the lung.

Discussion

CMV encephalitis is of course well known in newborns and small infants (the first of many reports was by Diezel in 1956), infection taking place in utero. Typically, this is a ventriculitis with periventricular destruction. Involvement of the adult central nervous system with CMV also has been reported, although it is quite rare. Four clinical cases have been reported, although it is quite rare. Four clinical cases have been reported. Four additional cases have had histologic confirmation, with cerebral involvement in three and involvement of the pituitary alone in one. Four of these seven cerebral cases occurred in "immunologically normal" adults. The distribution was periventricular in one case and was not specified in the other six. In the case that we present, there is a typical periventricular distribution, much as in the newborn.

The pathology of the acquired immunodeficiency syndrome (AIDS) still is poorly known, although a number of cases now have been reported. Among the homosexual population, disturbances of the alimentary tract with diarrhea (the "gay bowel syndrome") are common; surely few of these patients go on to have the AIDS syndrome develop. More than 20 causative agents have been listed. Enteritis caused by CMV is not on this list and represents perhaps a more ominous development: gastrointestinal tract biopsies in 18 patients with AIDS yielded CMV in seven cases. There was clinical suspicion of CMV encephalitis in one reported patient with AIDS, but no such cases have been documented morphologically.

AIDS is defined by the presence of opportunistic infections, with or without malignancies such as Kaposi's sarcoma, Hodgkin's disease or non-Hodgkin's lymphoma. The opportunistic infections are not a random collection; Cytomegalovirus and Pneumocystic carinii, alone or in combination, figure heavily. Others include Candida albicans, Toxoplasma gondii, Mycobacterium avium-intracellulare, Herpes simplex, Hepatitis B, Cryptococcus neoformans, Entameba histolytica, various gram-negative organisms, and doubtless others.

The significance of disseminated infection with CMV has been acknowledged by many, and there are those who believe that the entire AIDS phenomenon does represent the outcome of a CMV infection with particular damage to the helper T cell subset of the lymphocyte population. There is by no means unanimity concerning this particular hypothesis on the pathogenesis of the AIDS syndrome.

The histopathologic features of lymph nodes in the AIDS syndrome are presented in several recent abstracts. The lymph node architecture that we
describe, with depletion of follicles and replacement with a population of small lymphocytes, is similar to the lymphoid-depleted patterns recently reported.5,12,13,34 We can only concur that, in the clinical setting of AIDS, this lymph node architecture may imply a grave prognosis.

References
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