Fatal Adenovirus Meningoencephalitis in a Bone Marrow Transplant Patient

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We describe a bone marrow transplant patient with fatal subacute adenovirus meningoencephalitis, the first such patient reported. Neuropathological examination revealed unique, bilaterally symmetrical degeneration in the inferomedial temporal cortex, amygdaloid nuclei, hippocampi, hypothalamus, and some brainstem nuclei. Viral intranuclear inclusions were noted in these areas by light microscopy and confirmed by electron microscopy. Identification was authenticated by viral culture and the isolation of adenovirus from cerebral cortical tissues, and further confirmed by immunofluorescence and serological methods.

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Approximately 48 to 70% of bone marrow transplant (BMT) patients develop CNS complications, about 6% of which are fatal [1, 2]. These deaths are most commonly due to infectious agents [2]. This report describes a BMT patient who developed a fatal subacute viral meningoencephalitis in which adenovirus was the pathogenic agent.

Case Report

A 17-year-old woman was initially diagnosed as having acute myelogenous leukemia in August 1983. After her fourth remission, she underwent high-dose chemotherapy and total body irradiation (14 Gy). In June 1985 she received a haploidentical marrow graft and cyclosporin for prophylaxis of graft-versus-host disease (GVHD). Her posttransplant course was complicated by acute and chronic GVHD, chronic headaches, and an episode of disseminated herpes virus infection. For control of GVHD, she received long-term combined immunosuppression including cyclosporin, prednisone, and azathioprine. For antimicrobial prophylaxis, she received trimethoprim-sulfamethoxazole, acyclovir, erythromycin, and intravenous immunoglobulins. Supplemental multivitamins and thiamine were also administered. She did relatively well until March 1986, when she was admitted for progressive GVHD. At that time a pleural effusion, abnormal liver function tests, urinary retention and incontinence, and polyarthritis were found. She also had episodes of fever without a known source of infection. Subsequently, serum titers of antibodies to hepatitis-B surface antigen and cytomegalovirus were elevated. Because of persistent diarrhea, she underwent flexible sigmoidoscopy, which showed findings consistent with GVHD. Microbiological stool studies were initially positive for adenovirus and *Clostridium difficile.* After a brief period of improvement, she developed a headache, became increasingly lethargic, experienced a seizure, became apneic and pulseless, and required resuscitation. Positive physical findings at that time included a rectal temperature of 38.0°C, cushingoid facies, truncal stria, bilateral diffuse rales, and abdominal distention. The neurological examination demonstrated disconjugate eye movement and hypoactive deep tendon reflexes but no other localizing signs. She was responsive to verbal commands. A chest x-ray film showed bilateral pleural effusions and infiltrates. A computed tomography scan of the head revealed mild cerebral atrophy. A lumbar puncture showed an opening pressure of 260 mm H_2O. Cerebrospinal fluid studies demonstrated 31 mononuclear leukocytes and 100 red blood cells/mm^3, 5.9 mmol/L glucose, and 0.21 gm/L protein. The concurrent serum glucose was 10.4 mmol/L. Latex agglutination and bacterial, fungal, and viral titers and cultures were negative. The patient's course was ingravescent, and she expired 13 days after the onset of neurological symptoms.

Pathological Findings

The autopsy was performed 6½ hours after death. General postmortem findings included an organizing interstitial pneumonia and moderate hepatic portal fibrosis. Engraftment of the donor marrow was noted and no residual leukemic infiltrates were identified. Adenovirus was isolated in culture from brain, liver, and lung tissue, as described below.

The brain weighed 1,200 gm and was externally unremarkable, except for mild sulcal widening and gyral narrowing in the posterolateral frontal region. Coronal sections of the cerebral hemispheres revealed distinctive, bilaterally symmetrical, dark, focal hemorrhages and softening in the anterior inferomedial temporal cortex, amygdalae, and anterior and middle hypothalamic areas (Fig 1). Posteriorly, these changes were limited to the fusiform gyri. The cortical mantle, centra semiovales, corpora striata, thalami, hippocampi, and mamillary bodies were unremarkable. Serial sections of the brainstem manifested a variegated gray discoloration with petechial hemorrhages and softening in the inferior colliculi (Fig 2). The superior colliculi appeared normal, as did the remainder of the midbrain, pons, and medulla. The cerebellum exhibited mild global atrophy.

Microscopically, the leptomeninges exhibited mononuclear inflammatory infiltrates, composed predominantly of lymphocytes and rare scattered macrophages.

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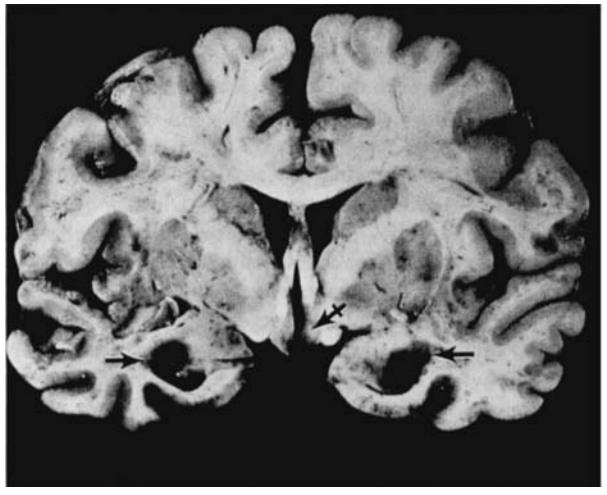

Fig 1. Brain coronal section showing bilaterally symmetrical softened and hemorrhagic lesions of the inferomedial temporal cortices, amygdaloid nuclei (arrows), *hypothalamus* (crossed arrow), *and septum pellucidum.*

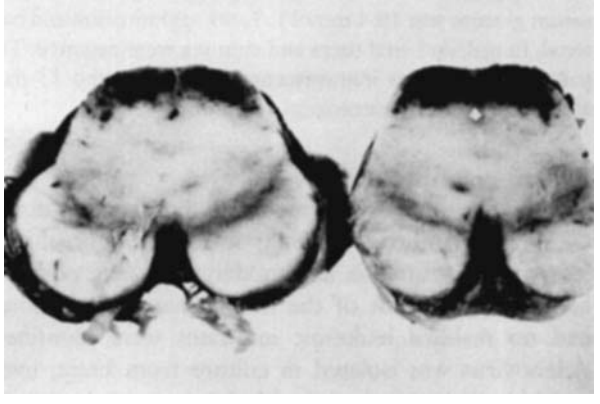

Fig 2. Midbrain coronal section demonstrating symmetrical hemorrhagic lesions of the inferior colliculi.

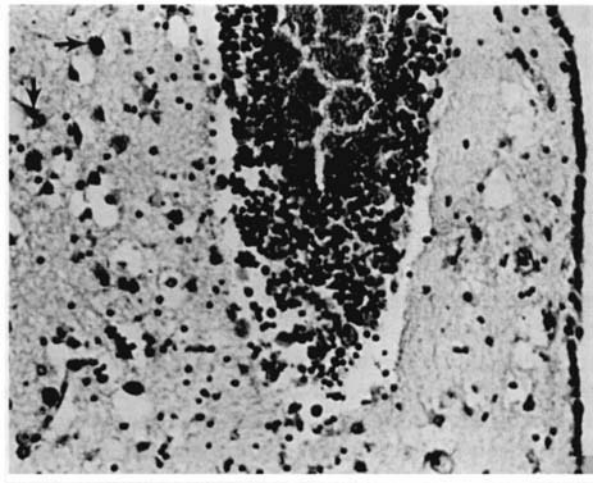

Fig 3. Marked perivascular and parenchymal mononuclear inflammation in the occipital periventricular region. Neurons demonstrate basophilic enlarged nuclei (arrows) *with intranuclear inclusions. (H&E, × 90 before 2% reduction.)*

Fig 4. High-magnification micrograph of neuronal intranuclear inclusions (arrows). *(H&E, × 320 before 2% reduction.)*

This was most striking in the areas overlying the infundibular region, inferomedial temporal cortices, and brainstem. In the most involved areas, there was lymphocytic infiltration along the Virchow-Robin spaces and into the adjacent parenchyma (Fig 3). Areas of the cerebral cortex and adjacent white matter that were normal by gross examination demonstrated diffuse edema. In the hypothalami, inferomedial temporal lobe, amygdalae, inferior colliculi, and a few other focal cortical areas there was lymphocytic infiltration, as well as scattered microhemorrhages that were often angiocentric. Reactive astrocytes, scattered microglial cells, and microglial nodules were also conspicuous. A striking finding was the presence of neuronal intranuclear inclusions (Fig 4), as well as occasional oligodendroglial inclusions. These basophilic inclusions produced considerable nuclear enlargement and usually manifested a hyaline, ground-glass, smudgy appearance or slightly granular quality. Nuclear debris was scattered widely in severely affected areas. Neurons of the supraoptic nuclei exhibited extensive ferrugination. Other nuclei that were affected bilaterally were the sensory nuclei of the trigeminal nerve, lateral vestibular nuclei, mesencephalic periaqueductal gray interpeduncular nuclei, superior colliculi, and the nuclei ambiguus. The changes in the nuclei ambiguus were vacuolar in nature. The neostriatal nuclei were relatively less affected. The cerebellum showed scattered microglial nodules and rare inclusions in neurons of the dentate nuclei.

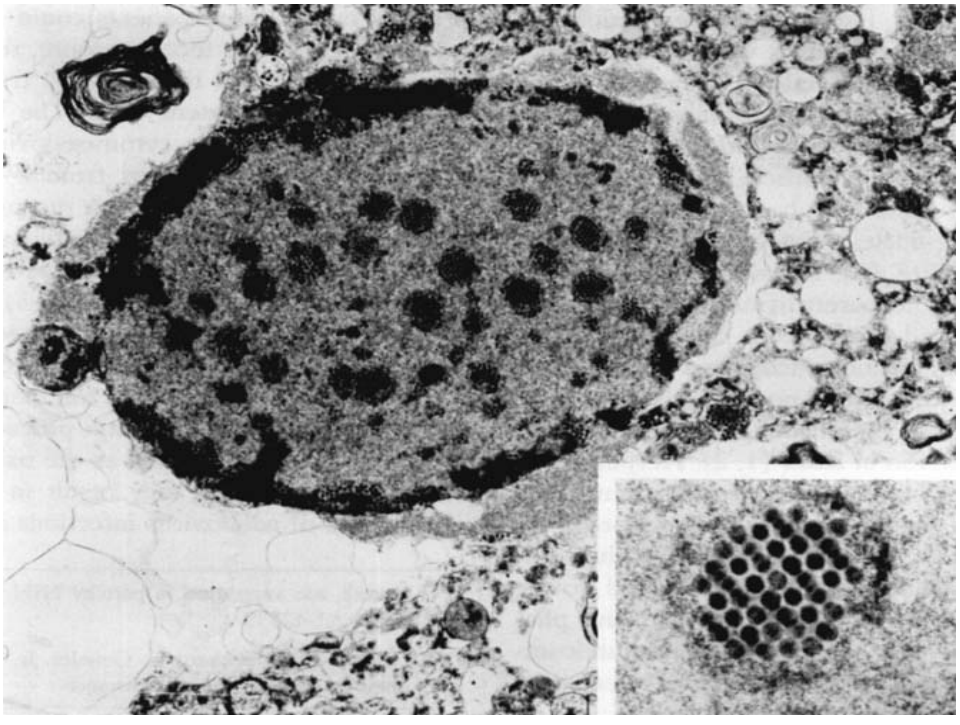

Fig 5. Electron micrograph demonstrating neuronal intranuclear and cytoplasmic arrays of viral aggregates. (Uranyl acetate and lead citrate, × 28,000 before 30% reduction.) Inset: *Hexagonal virions with alternating rows of light- and dark-staining viral particles. (× 148,500 before 30% reduction.)*

For ultrastructural examination, formalin-fixed specimens were taken from the right inferior temporal gyrus and left hippocampal presubiculum. These were fixed in 3% glutaraldehyde, rinsed with phosphate buffer, postfixed in 1% osmium tetroxide, and embedded in Epon 812. Thin sections were stained with uranyl acetate and lead citrate and examined in a Jeol JEM 100S electron microscope. Cells from each area demonstrated neuronal intranuclear viral inclusions (Fig 5). The viral particles were organized as symmetrical crystalline arrangements with alternating electron-dense and electron-light rows. The virions measured 80 nm in average diameter. Many of the viral particles appeared to have membrane-like materials enveloping the aggregated structures. The nuclear membranes of many of the cells were disrupted, and viral particles were seen in the cytoplasm.

Adenovirus was isolated from autopsy tissues removed from the left frontal cortex. Isolation was performed by a reference laboratory (Smith-Kline Bio-Science Laboratories, Tucker, GA) by inoculation of a suspension of tissue onto human foreskin, rhesus monkey kidney, and primary cynomolgus monkey kidney cell lines. The virus was isolated from only the human foreskin cell culture after 11 days of incubation. Confirmation was made by immunofluorescence using a commercially available antibody conjugate (M. A. Bioproducts, Walkersville, MD) directed against adenovirus. Concurring confirmatory tests were performed by the Centers for Disease Control in Atlanta, GA, where the virus was identified to be Group D. Further specific serotyping of the virus could not be carried out.

Discussion

This paper describes a patient in her fourth relapse of acute myelogenous leukemia who underwent a haploidentical, T cell–depleted BMT and subsequently developed a fatal adenovirus meningoencephalitis. The clinical picture of headache, lethargy, and a seizure were compatible with meningoencephalitis, but lacked specificity. The overall course of her illness was complicated by recurrent severe GVHD requiring increased immunosuppressive therapy, which further predisposed her to infection. This is the second case of meningoencephalitis with ultrastructurally identified and cultured adenovirus to be reported and it is the first to be morphologically documented in a BMT patient.

The neuropathological manifestations of this case are unique. The symmetrical hemorrhagic degeneration in the inferomedial temporal cortex, amygdalae, anterior hypothalamus, and inferior colliculi has not been described previously. Chou and associates [3] described inferomedial temporal hemorrhagic degen-

eration in the initial autopsy-verified case of adenovirus meningoencephalitis. However, in their patient, no other cortical or subcortical areas were affected, with the exception of microglial nodules identified in the temporal and parietal cortex. The findings in our patient are distinctive because not only were viral intranuclear inclusions seen in cortical neurons, but they were present in neurons of subcortical nuclei, brainstem, and cerebellar nuclei. In addition, in the report of Chou and associates [3], subcortical white matter changes were limited to parenchymal edema, perivascular hemorrhage, and lymphocytic infiltrates. White matter, in the present patient, exhibited similar alterations plus scattered microglial nodules.

The development of meningoencephalitis is not an uncommon complication in BMT [1, 2]. Herpes group viruses (including cytomegalovirus) are frequently the cause of meningoencephalitis in series reported by other investigators [1, 2]. Adenoviruses in the nonimmunocompromised host have been found to be responsible primarily for pulmonary [4–6] and pharyngoconjunctival infections [7]. In the immunocompromised host, including BMT patients, adenovirus has been shown to cause pneumonia, hepatitis, and renal dysfunction [8, 9]. Adenovirus in normal and immunosuppressed patients has only rarely been implicated as a pathogen in the CNS. Nine other cases of adenovirus encephalitis have been documented by culture of CSF or brain tissue [10–15] since the report by Chou and associates in 1973 [3]; however, no report has identified the histopathological changes in the CNS. The most recent reported cases have occurred in patients with the acquired immune deficiency syndrome (AIDS) [14, 15]. The patient described by Horoupian and associates [15] demonstrated symmetrical degeneration of the frontopontine and corticospinal fibers, and white matter changes in the cerebellar corpus medullare. Whether the changes in that patient were due to a previously undescribed morphological alteration caused by the human immunodeficiency virus or were possibly another symmetrical manifestation of adenovirus in the CNS is open to speculation.

A comparison between the localization of gross and microscopical lesions in the two cases of histologically documented adenovirus meningoencephalitis reveals many similarities and suggests a topographically restricted infection in the CNS. Topographically restricted lesions are seen in other meningoencephalitic processes, most notably herpes virus meningoencephalitis. Specifically why certain neuronal groups should demonstrate selective vulnerability to viral agents is unclear. Studies to date have not identified a specific membrane receptor or other surface structure that would preferentially allow the virus initially to attach and infect cells in the recognized areas of primary involvement [16, 17].

Transmission of adenovirus to BMT and other immunocompromised patients could occur via the nasopharyngeal or the fecooral route, reactivation of latent virus in lymphoid tissue, or by transfusion of leukocytes containing latent virus. The last mechanism has been postulated for cytomegalovirus [18]. Reactivation of latent adenovirus from a donor kidney in a renal transplant patient with the production of a fatal disseminated adenoviral infection has also been hypothesized [19]. Of the more recent proven cases of adenovirus meningoencephalitis, 3, including this case, have been in immunocompromised hosts. An awareness of this entity in the immunocompromised patient is essential. The increasing number of patients undergoing various transplantation procedures requiring immunosuppression, as well as the rising number of individuals with AIDS, may result in an increase in the incidence of adenovirus infections in the CNS.

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Central Pontine Myelinolysis after Rapid Correction of Hyponatremia: A Magnetic Resonance Imaging Study

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We describe a patient with severe hyponatremia (serum sodium 94 mmol/L) who developed encephalopathy and decorticate posturing after a 29 mmol/L rise in serum sodium concentration during the first 24 hours of correction. High-resolution computed tomography of the pons was normal during the first, second, and twelfth weeks of the illness. Subsequent magnetic resonance imaging revealed a pontine lesion consistent with central pontine myelinolysis.

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Central pontine myelinolysis (CPM) is a demyelinating process of the brain that has been associated with the rapid correction of hyponatremia [1–4]. In the past, the diagnosis has been made at autopsy; increasing awareness and availability of sophisticated imaging techniques has now made it possible to make the diagnosis before autopsy [5–9]. We describe a woman who developed a clinical picture of encephalopathy and decortication after rapid correction of symptomatic hyponatremia. High-resolution computed tomography (CT) of the brain was repeatedly normal. However, magnetic resonance imaging (MRI) demonstrated an unsuspected pontine lesion consistent with CPM.

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Case Report

A 37-year-old nonalcoholic woman was admitted to an outside hospital with a one-week history of nausea, lethargy, and polydipsia, and a two-day history of disorientation. She was taking a combination diuretic (triamterene 50 mg and hydrochlorothiazide 25 mg) for essential hypertension. Laboratory evaluation revealed a serum sodium of 94 mmol/L, chloride of less than 55 mmol/L, bicarbonate of 24 mmol/L, potassium of 2.8 mmol/L, and normal serum creatinine and blood urea nitrogen. The urine sodium was 19 mmol/L. Serum osmolarity was 214 mOsm/kg when the urine osmolarity was 382 mOsm/kg. The initial neurological examination was reported to be normal.

Therapy consisted of Ringer's lactate solution and intravenous 514 mmol/L sodium chloride solution. At 6 hours the serum sodium was 106 mmol/L and a brief generalized seizure occurred that ceased with intravenous diazepam and phenytoin. A high-resolution CT scan of the brain with contrast was normal. After 24 hours the serum sodium was 123 mmol/L and the patient was transferred to our institution. At 48 hours the serum sodium was 129 mmol/L and subsequently never exceeded 137 mmol/L.

With correction of hyponatremia, the patient's mental status improved and no more seizures occurred. At 120 hours the patient deteriorated and developed encephalopathy. There was generalized hypotonia but normal muscle strength and deep tendon reflexes. The gait was ataxic. Psychometric evaluation demonstrated impaired cortical capacities. By the ninth hospital day the patient was unresponsive, did not talk, and had decorticate posturing and frontal lobe release signs. Gag reflex was hypoactive and swallowing was impaired. A second high-resolution CT scan of the brain and pons was normal. Electroencephalography revealed a dominant rhythm of 4 to 5 Hz consistent with a diffuse encephalopathic process. Somatosensory evoked potentials showed dysfunction in somatosensory pathways rostral to the cervical cord. Brainstem auditory evoked potentials were normal. Cerebrospinal fluid protein was 50 g/L (normal, 15–45 g/L), and the myelin basic protein was 4.1 ng/ml (normal, 1–4 ng/ml). After five weeks the patient gradually regained speech, comprehension, and the ability to swallow. Her gait remained ataxic. Four months after presentation, repeat psychometric testing demonstrated a full-scale intelligence quotient of 82 (Wisconsin Adult Intelligence Scale). She has been unable to return to her position as a school teacher.

MRI utilizing a superconducting magnet operating at 1.5 Tesla was performed 12 weeks after presentation. Initial T1-weighted images (Fig 1) demonstrated a low signal focus occupying most of the pons, and T2-weighted images showed a corresponding high signal abnormality (Fig 2),

