Abstract

We report a patient with acquired immunodeficiency syndrome dementia complex (ADC) that presented human immunodeficiency virus infection as an initial manifestation. A 34-year-old man developed disturbance of consciousness and severe abulia over 3 months. The CD4 lymphocyte count was 7.9/μl, while human immunodeficiency virus RNA in blood amounted to 4.2×10⁴ copies/ml. T2-weighted magnetic resonance imaging showed diffusely high signal intensity in the deep white matter of both cerebral hemispheres. On the 20th hospital day, the patient died of sepsis caused by methicillin-resistant Staphylococcus aureus. Autopsy findings in the brain included increased glial cells and multinucleated giant cells in cerebral white matter and subcortical gray matter. These features were compatible with ADC.

Key words: acquired immunodeficiency syndrome dementia complex, magnetic resonance imaging, post-mortem examination

Introduction

Acquired immunodeficiency syndrome dementia complex (ADC), also called human immunodeficiency virus (HIV) encephalitis or HIV-associated dementia complex, is one of the most important central nervous system manifestations of the syndrome. As some of these terms suggest, this dementia is generally thought to be caused by the virus itself, rather than secondarily by opportunistic infection or neoplasia (1). In most cases, the dementia complex develops as a terminal event, or developed after the patient had succumbed to various characteristic opportunistic infections or malignant disease. Here, we describe a patient with advanced acquired immunodeficiency syndrome (AIDS) who developed the dementia complex as an initial manifestation.

Case Presentation

A 34-year-old man developed fever and general malaise in May 2003. Periodic medical check-ups at several hospitals did not provide a definite diagnosis. Fever subsided spontaneously in June, but the patient’s general status deteriorated gradually until he became disoriented to time and place. Having stopped working, he was diagnosed with depression at a local clinic. Oral intake decreased, and he became bedridden. When he was admitted to a local hospital because of high fever, anti-human immunodeficiency virus antibody was detected. He was referred to our department in August 2003.

On admission, the patient was drowsy and apathetic. He barely nodded in response to some questions and seldom spoke, but he could clumsily carry out some movements. No abnormal findings were observed on chest or abdominal physical examination. Oral candidiasis was not observed. Neurologic examination disclosed no nuchal rigidity or paralysis. Deep tendon reflexes were slightly increased, and pathologic reflexes (Babinski and Chaddock) were observed on the right side. He was barely able to take food orally even with assistance.

Complete blood counts showed pancytopenia: red blood cell count, 231×10⁴/μl, hemoglobin, 9.9 g/dl, white blood cell count, 2,400/μl (36% of neutrophils and 33% of lymphocytes); and platelet count, 9.9×10⁴/μl. Mild liver damage was evident: alanine aminotransferase, 66 IU/l; aspartate aminotransferase, 96 IU/l; and lactate dehydrogenase, 394 (normal range, 120 to 240). The serum albumin concentration was 3.8 g/dl; thyroid hormones, within normal limits, immunodeficiency.
globulin G, 1,943 mg/dl; immunoglobulin A, 1,186 mg/dl; immunoglobulin M, 104 mg/dl; C-reactive protein 0.05 mg/dl; CD4 lymphocyte count, 7.9/µl; and human immunodeficiency virus RNA, 4.2×10⁴ copies/ml. Examination of cerebrospinal fluid showed a nucleated cell count of 0.3/µl. Total protein was 71.1 mg/dl, and glucose was 57.9 mg/dl; polymerase chain reaction (PCR) to detect JC virus was negative. T2-weighted and fluid-attenuated inversion-recovery magnetic resonance images of the brain bilaterally showed diffusely high signal intensity in the deep white matter of the cerebral hemispheres. Brain atrophy was not conspicuous (Fig. 1).

After admission, high fever exceeding 38°C occurred every day despite antibiotic therapy. No positive findings were detected by laboratory test for opportunistic infections (Table 1). The patient’s general condition gradually deteriorated. He was diagnosed with acquired immunodeficiency syndrome dementia complex (ADC), and received highly active antiretroviral therapy (HAART) consisting of lamivudine, stavudine, and nelfinavir beginning on hospital day 4. However, he developed methicillin-resistant *Staphylococcus aureus* sepsis on hospital day 13. Nasal colonization by the organism had been detected at the time of admission, while the central venous catheter considered related to development of sepsis had been inserted on hospital day 4. Despite catheter removal and antibiotic therapy, multiorgan failure developed and the patient died on hospital day 20.

**Pathologic Findings**

Autopsy examination of the brain was performed (Fig. 2). The weight of the brain was 1,210 g. No brain atrophy or atherosclerosis was observed. Abnormalities were predominantly in the cerebral white matter and subcortical gray matter; the cerebral cortex appeared essentially intact. In the lesions, numbers of glial cells were increased and multinucleated giant cells were present surrounding vessels. Spongy change resulting from demyelination in the white matter was seen anteriorly and laterally but was less evident in posterior regions. Lymphocytic infiltration and inclusion bodies were not seen. An excess of glial cells also was observed in the basal ganglia. The hypothalamus was essentially intact. PCR assay to detect JC virus in the specimen of white matter of anterior and temporal lobe was negative. The findings were compatible with ADC.

**Discussion**

The pathogenesis of ADC remains incompletely understood. Some investigators maintain that increased proliferation of HIV in the brain is necessary for the development of the dementia complex (2, 3). Others propose that a macrophage-initiated cascade of events can lead to brain dysfunction and clinical dementia, even in the absence of a high viral load in the brain. Activated macrophages, whether infected with the virus or not, are capable of secreting potent neurotoxins, including proinflammatory cytokines, and also can generate oxygen free radicals likely to damage cells and lead to neuronal dysfunction or death (4–6).

In general, ADC is an insidiously progressive subcortical dementia. Early symptoms include apathy, social withdrawal, diminished libido, slowness in thinking, poor concentration, and forgetfulness. Psychiatric syndromes some-
times are profound, and may be the first manifestation of infection of the virus; this may take the form of psychosis, depression, or mania. Motor signs include slowness in movement, leg weakness, and gait ataxia. Headache, tremor, seizures, Parkinsonian features, or frontal release signs may be prominent. When progressive, the dementia complex culminates in akinetic mutism, an immobile, bedridden state characterized by global cognitive impairment and urinary incontinence (7).

Pathologically, the dementia complex is characterized macroscopically by brain atrophy and diffuse white matter pallor. Microscopic abnormalities include microglial nodules, giant cells, focal perivascular demyelination and gliosis, and neuronal loss in the frontal cortex. However, a clear correlation often is lacking between severity of pathologic changes and severity of dementia (5–7).

Although the incidence of all opportunistic infections has declined dramatically in the era of potent antiretroviral therapy, the prevalence of HIV-associated brain disease or encephalopathy is rising despite supportive antiretroviral therapy (8). On the other hand, marked improvement in survival following onset of ADC in the era of potential antiviral therapy also has been reported (9). This increased survival has contributed to the increased prevalence of ADC, even though incidence of the ADC has declined or remained stable.

### Table 1. Laboratory Findings for Opportunistic Infection

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Sample</th>
<th>Method</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria (aerobic, anaerobic)</td>
<td>blood</td>
<td>culture</td>
<td>negative</td>
</tr>
<tr>
<td><em>Mycobacterium</em></td>
<td>blood</td>
<td>PCR (M. tuberculosis, M. avium complex)</td>
<td>negative</td>
</tr>
<tr>
<td>Fungus</td>
<td>blood</td>
<td>culture</td>
<td>negative</td>
</tr>
<tr>
<td><em>Cytomegalovirus</em></td>
<td>blood</td>
<td>beta-D-glucan antigenemia</td>
<td>negative</td>
</tr>
<tr>
<td><em>Herpes simplex virus</em></td>
<td>liquor</td>
<td>IgM (EIA)</td>
<td>negative</td>
</tr>
<tr>
<td><em>JC virus</em></td>
<td>liquor</td>
<td>IgG (EIA)</td>
<td>negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PCR</td>
<td>negative</td>
</tr>
</tbody>
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PCR: polymerase chain reaction, EIA: enzyme immunoassay.

Figure 2. In the white matter and subcortical gray matter of the cerebrum, glial cells were increased, and multinucleated giant cells were seen surrounding vessels. Neither lymphocytic infiltration nor inclusion bodies were observed. A: temporal lobe (HE stain, ×100), B: frontal lobe (HE stain, ×400).
Poor penetration of the blood-brain barrier by many antiretroviral drugs, particularly protease inhibitors, has been suggested as a reason of continued occurrence of ADC (10). Yet some evidence suggests that despite poor CNS penetration of most antiretrovirals, effective antiretroviral therapy still may attenuate neurotoxicity from circulating monocytes and their tissue counterparts, macrophages (11). Concerning the efficacy of antiretroviral therapy against the dementia complex, Schmitt et al reported that high-dose zidovudine had a favorable effect on test results in a placebo-controlled randomized trial (12). Several subsequent reports also have supported the efficacy of high-dose zidovudine for ADC (13, 14). Some recent investigators have demonstrated the efficacy of potent antiretroviral combinations in the improvement of neurologic dysfunction and even neuroimaging findings, indicating that ADC may be at least partly reversible (15, 16). Where antiretroviral therapy is available, ADC typically shows milder, more slowly progressive deterioration in mental function as compared with the severe, rapidly progressive dementia seen among untreated individuals. Unfortunately, the intensive antiretroviral therapy in the present patient was interrupted by early death from catheter-related sepsis, so a benefit could not be observed.

In the present patient, several unusual clinical features were present. First, CD4 cells were severely decreased at the time of referral. Despite this, the patient had not experienced AIDS-specific complications except for an attack of Herpes-zoster that subsided spontaneously. ADC was the first manifestation of AIDS. A Japanese surveillance group has reported that ADC is 1.2% of the opportunistic infections as an initial manifestation (17). Second, symptoms compatible with ADC progressed rapidly over about 3 months, resulting in the bedridden state. Third, unexplained high fever persisted without C-reactive protein elevation during the early part of the hospital course. In general, ADC is not complicated by fever. Finally, although pathologic findings were compatible with ADC, brain atrophy, the frequent finding of ADC, was not observed.

Several instructive cases, where atrophy was seen only after several months of antiretroviral therapy and occurred despite clinical improvement, have been reported (18, 19). Considering such chronologies, rapid progression of ADC associated with severe immunosuppression, and early death may have precluded development of atrophy in our patient, as considerable time may be required for appearance of brain atrophy. Several unusual clinical aspects of our patient may be characterized by the rapid progress of ADC.

Although we cannot definitely explain some unusual aspects of the present case, most clinical and microscopic features were characteristic. Thus, ADC apparently can occur as an initial manifestation, and then can progress rapidly.

References


