Probable Cerebral Mycobacterium Avium Complex-Related Immune Reconstitution Inflammatory Syndrome in an HIV-Infected Patient

Shuji Kishida¹ and Atsushi Ajisawa²

Abstract

The advent of highly active anti-retroviral therapy (HAART) has reduced both the morbidity and incidence of acquired immunodeficiency syndrome (AIDS)-related central nervous system (CNS) diseases. However, some patients seem to suffer paradoxical clinical deterioration after starting HAART, known as immune reconstitution inflammatory syndrome (IRIS). We report a rare case of probable Mycobacterium avium complex (MAC) infection of the brain in a patient with AIDS who had been treated effectively for probable pulmonary and cerebral MAC infection, with both lesions recurring after significant decreases in plasma human immunodeficiency virus type-1 viral load following initiation of HAART. This case appears to represent the first precise clinicopathological description of severe ventriculo-encephalitis in CNS MAC-related IRIS.

Key words: Mycobacterium avium complex, immune reconstitution inflammatory syndrome, central nervous system, acquired immunodeficiency syndrome


Introduction

While disseminated Mycobacterium avium complex (MAC) infection is the most common bacterial infection in patients with AIDS, relatively few cases of MAC infection involving the central nervous system (CNS) have been described. In most reported cases of MAC involvement in the CNS, infection has been an incidental finding at autopsy in patients with the disseminated disease. Clinicopathological manifestations of MAC infection in the CNS, particularly MAC-related immune reconstitution inflammatory syndrome (IRIS), have only rarely been described (1, 2). We report herein an interesting case of probable MAC-related IRIS of the brain in a patient who had been treated effectively for probable pulmonary and CNS MAC infection, with both lesions recurring after significant decreases in plasma human immunodeficiency virus type-1 (HIV) viral load (VL) following initiation of highly active antiretroviral therapy (HAART).

Case Report

A 51-year-old homeless man was discovered with disturbance of consciousness after a fall on August 2, 2004. Infectious subcutaneous abscess of the face with chronic hepatitis and diabetes mellitus were diagnosed. Seropositivity for HIV was discovered with an absolute CD4 cell count of 26/µL and he was also hepatitis C virus (HCV)-positive. Antibiotics for the abscess and insulin therapy for diabetes mellitus were administered, and his condition improved. Two months later, he became febrile and computed tomography (CT) of the chest demonstrated multiple disseminated pulmonary nodular lesions in both lung fields. Gastric juices were positive for acid-fast bacilli (AFB) on smears. Treatment was started using isoniazid (INH), rifampicin (RFP) and ethambutol (EB), under a presumptive diagnosis of pulmonary Mycobacterium tuberculosis (MTB). This regimen was changed to kanamycin (KM), clarithromycin, RFP and EB after MAC was isolated from a culture of gastric juice.

¹Divisions of Neurology, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo and ²Divisions of Infectious Diseases, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo

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Correspondence to Dr. Shuji Kishida, s-kisida@cick.jp
The patient became lethargic and developed asymmetrical quadriparesis status at the end of November 2004. Brain CT showed multiple enhanced lesions (Fig. 1a, b) in the left frontal and parietal lobes and the right temporal lobe. Cerebrospinal fluid (CSF) analysis yielded no significant results, with negative results for AFB on smears. While treatment for MAC was continued without definite diagnosis of cerebral lesions, the patient showed improvement of clinical symptoms with mild right hemiparesis and cognitive deficits. In addition, repeated brain CT showed marked improvements with only non-enhancing low-density lesions of the left parietal and frontal lobes, and chest CT showed no nodular lesions in January 2005.

He was transferred to our hospital for HIV treatment on February 7, 2005. On initial evaluation, general physical features were unremarkable, with no fever and normal chest and abdominal findings. Neurological examination showed disorientation, impairment of short-term and remote memory, dysarthria, spastic right hemiparesis with pyramidal signs and gait disturbance. Laboratory studies showed mild anemia (hemoglobin, 9.3 g/dL) and mild thrombocytopenia (platelet count, 11.0×10^5/μL). Alkaline phosphatase 883 IU/L (normal, 115-359 IU/L), γ-glutamyltranspeptidase 151 IU/L (normal, 9-70 IU/L) and HbA1C 6.7% (normal, 4.2-5.6%) were elevated, but results were otherwise normal. C-reactive protein level was normal. Immunological study showed: HCV-antibody (+); HCV-polymerase chain reaction (PCR), 816 kUI/mL; HIV-VL, 170,000 copies/mL; and CD4 cell count, 20 cells/μL. Blood and sputum culture for AFB yielded negative results, as did nested PCR for MAC in sputum. CSF examination showed: white cells, 3/mm³; protein, 42 mg/dL; and glucose, 85 mg/dL. CSF PCR for varicella-zoster virus, Epstein-Barr virus (EBV) and cytomegalovirus were all negative. T2-weighted and fluid attenuated inversion recovery (FLAIR) imaging revealed small residual signal hyperintensities without mass effect and without gadolinium (Gd) enhancement in the left frontal white matter and left parietal cortex, along with small signal hyperintensities in the right cerebellum. Chest and abdominal CT showed small multiple lymphadenopathies in bilateral axillae and supraclavicular regions and the retroperitoneum, but no nodular or infiltrative lesions in the lung nor hepatosplenomegaly were apparent.

HAART was started on February 15, 2005, with administration of sanilvudine, lamivudine and atazanavir/ritonavir in addition to azithromycin, EB, INH and levofloxacin for possible MAC or MTB. The patient began to display continuous fever 4 weeks after initiating antiretroviral therapy. Absolute number of CD4 cells was 26 cells/μL, but HIV-VL decreased significantly (to <400 copies/mL) within 1 month after initiating antiretroviral therapy. Follow-up brain MRI in mid-March 2005 revealed no changes in previous findings (Fig. 2a, b). Chest CT at the beginning of May demonstrated multiple small nodular lesions and infiltrative lesions with cavitation up to 3.0×2.0×2.0 cm in both lung fields. Repeated blood cultures for AFB yielded negative results. MAC-related IRIS was suspected and amikacin was added for additional anti-MAC therapy. Follow-up chest CT showed decrements in lesion size. The patient became lethargic at the beginning of June 2005. Repeated brain MRI showed new abnormalities, including a confluent ring-like Gd-enhanced mass lesion with mass effect in the left periventricular area of the inferior horn of the lateral ventricle, subependymal linear enhancement of left and right lateral ventricles (Fig. 3), and slight enlargement of the cerebellar lesion on T2/FLAIR imaging. Treatment with dexamethasone and trimethoprim/sulfamethoxazole was initiated for suspected toxoplasmosis and primary CNS lymphoma, but the condition of the patient deteriorated acutely and he died of renal failure soon after onset of neurological symptoms, with an absolute CD4 cell count of 10 cells/μL and HIV-VL <50 copies/mL.

Full post-mortem examination was performed. Granulomatous ventriculo-encephalitis, lymphoma in the cerebellum and pulmonary granuloma were the major findings. The brain weighed 1,400 g. Coronal section revealed a mass lesion measuring 2.0×1.3×2.0 cm, containing necrotic material inside in the medial part of the left temporal lobe (Fig. 4). The lesion extended from the inferior horn to the foramen of Monro along the left lateral ventricular wall. Microscopic examination revealed that the wall of the mass lesion comprised granulomatous reaction, including lymphocytes, histi-
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**Figure 2.** a, b) Gadolinium-enhanced MRI obtained in mid-March 2005. Enhanced lesions disappeared after anti-MAC therapy.

**Figure 3.** No enhanced lesions were observed on gadolinium-enhanced MRI obtained in mid-March 2005 (a). On gadolinium-enhanced MRI at the beginning of June 2005 (b), confluent ring-like enhanced lesions with surrounding marked edema are present in the left temporal lobe along with periventricular enhancement.

**Figure 4.** Coronal section of cerebral hemispheres through the mamillary bodies, showing subependymal yellowish discoloration of lateral ventricles (white arrows) and a mass lesion in the medial part of the left temporal lobe (black arrow).

**Figure 5.** a: Histopathology of the mass lesion in the medial temporal lobe. Original magnification ×5. b: The wall of the mass lesion showing granulomatous reaction. Original magnification ×100.

ocytes and fibrous tissue (Fig. 5). The necrotic center was filled with a mass of ghost pleomorphic cells. Periventricular parenchymal tissue showed a chronic granulomatous lesion associated with lymphocytes, epithelioid cells, a few multinucleated giant cells and increased collagen fibers (Fig. 6). Ventriculitis extended to the right lateral ventricle and third ventricle. Stains for AFB yielded negative results. Nested PCR analysis using oligonucleotide primers specific for MAC and MTB gene fragments in formalin-fixed depa-
Figure 6. a: The ventricular ependymal lining has been lost and the subependymal regions show granulomatous inflammation comprising lymphocytes, plasma cells and epithelioid cells with a few scattered multinucleated giant cells. Original magnification ×40. b: High-power view of (a), showing a readily identifiable multinucleated giant cell. Original magnification ×400.

Figure 7. Histopathology of the lung showing nodular lesions with cavitation (a; original magnification ×5) and granulomatous lesions comprising lymphocytes, plasma cells, histiocytes and a few multinucleated giant cells (b; original magnification ×40). c) High-power view of (b). A Langhans-type multinucleated giant cell is seen in the granulomatous inflammatory reaction. Original magnification ×400.

Discussion

The present patient initially presented with probable CNS lesions associated with pulmonary MAC infection in the context of profound cellular immunodeficiency. Subsequent presentations a few weeks after initiating of HAART are likely explained by MAC-related IRIS, which resulted in pulmonary disease followed by cerebral lesions. Primary CNS lymphoma developed as a complication.

The causative agents in this case were not identified on ante- or postmortem examinations from lung- or brain-derived microbiological specimens or blood, with the exception of MAC isolated from the culture of the gastric juice. This case was unusual, since MAC disease in patients with AIDS generally causes disseminated multi-organ infection with high MAC-bacteremia, and parenchymal lung and brain involvements have rarely been described (3, 4). However, in this case MAC disease is likely, as anti-MAC therapy including clarithromycin resulted in almost complete resolution of the lesions in the lung and brain before starting HAART in the absence of other pathogens except MAC isolated from the gastric juice, and because postmortem histopathology of the lesions showed granulomatous inflammation with caseous necrosis. It is reported that some patients may have fluctuating low levels of mycobacteremia and intermittently negative blood cultures in spite of disseminated MAC infection (3). This may have been such a case.

MAC infection has infrequently been reported to involve the CNS, despite a high incidence of disseminated MAC disease among AIDS patients (5). Few clinical and histopathological descriptions in association with CNS MAC have been described. Previously reported CNS signs and symptoms in patients with MAC infection include meningitis, encephalitis/encephalopathy, seizures, organic brain syndrome, headache, altered mentation/impaired cognition, nuchal ri-
gidity, lethargy, cranial nerve palsies, progressive neurological deterioration, hydrocephalus and abscess formation (1). According to the rare descriptions of histopathology associated with CNS MAC, lesions consist of small perivascular aggregates of lymphocytes and macrophages or granulomatous inflammation (1). In the present case, CNS findings on first presentation were non-diagnostic, but suggestive of multiple brain abscesses. Clinical diagnosis of CNS MAC infection is difficult, and most cases of cerebral MAC infection are diagnosed by biopsy or on autopsy (1, 2).

The second CNS presentation of this case occurred in association with pulmonary lesions a few weeks after the start of HAART. This was after the lesions were almost resolved as a result of anti-MAC therapy. While HAART had not brought about significant increases in CD4 T-cell count despite virological response, the clinical course in this case was thought to be complicated by IRIS, because the increase in CD4 T-cell count sometimes might be a delayed response in spite of recovery of other immune function following initiation of HAART and because postmortem pathological findings included granulomatous inflammation which developed at the original organs of infection with symptoms recurring after initiation of HAART (6-8).

The introduction of HAART for HIV infection has prolonged the lives of patients with AIDS. However, a subgroup of HAART-treated patients is increasingly being recognized that can develop paradoxical clinical, laboratory or radiological deterioration, despite satisfactory control of viral replication and improvements in CD4 T-lymphocyte counts. This phenomenon has been called IRIS. Consistent diagnostic criteria and standards of therapy are yet to be defined, but this condition results from an exuberant inflammatory response towards previously diagnosed or incubating opportunistic pathogens, as well as responses towards other as-yet-undefined antigens due to restored immune function by HAART (6-8).

MAC is frequently reported as a causative pathogen in IRIS. MAC-related IRIS most commonly presents with localized lymphadenitis/lymphadenopathy or pulmonary disease. Localized involvements of the musculoskeletal system, intra-abdominal organs and CNS are less frequently described. Histopathological examination of the lesions often reveals granulomatous inflammation. MAC is usually cultured from granulomatous and/or necrotizing lesions, and the organisms are surrounded by intense inflammatory response in these lesions on pathological examination (2, 7, 9). However, the presumed organisms could not be identified by culture or other diagnostic methods in some cases due to the pathogen-specific intense inflammation rather than actual reactivation of the infection. Most cases display generally favorable outcomes without any additional treatment other than anti-mycobacterial drugs, and when inflammation threatens significant morbidity or mortality, anti-inflammatory measures are considered (7, 9).

The present case was peculiar in that findings of MAC were not demonstrated by morphological, microbiological or nested PCR DNA amplification approaches from lesions, and clinicopathological features showed granulomatous ventriculo-encephalitis with necrosis. The pathogenesis of this case was likely the result of an exuberant inflammatory response toward dead or dying organisms or residual antigen in the original infected organs.

MAC-related IRIS may be clinically indistinguishable from active infection, and might be benign and self-limiting, or severe as in this case. While immune reconstitution remains a therapeutic goal in patients with HIV infection, the very same phenomenon can ironically result in a heightened immune response, causing tissue destruction and subsequent exacerbation of the disease. This may be more apparent in the brain, where the phenomenon can be fatal. The significance of positive EBV PCR in CSF obtained at autopsy in the present patient was probably an incidental pathological finding related to primary CNS lymphoma. IRIS plays a role in several AIDS-related CNS disorders, such as tuberculosis, cryptococcal disease, HIV encephalitis and progressive multifocal leucoencephalopathy (10). Proper recognition of this syndrome is essential, as antiretroviral therapy is increasingly being used worldwide, and IRIS may thus emerge as an important neurological complication of HIV and HAART.

References