Case report

Acute disseminated encephalomyelitis (ADEM) after autologous peripheral blood stem cell transplant for non-Hodgkin's lymphoma

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Summary:

Acute disseminated encephalomyelitis (ADEM) is a demyelinating disorder of the central nervous system with an acute clinical onset and a wide variability in severity and outcome. It usually follows a viral infection or an immunization and is thought to be immunomediated. We report a case of ADEM with a dramatic clinical onset in an autologous peripheral blood stem cell transplant (PBSCT) recipient for non-Hodgkin's lymphoma who developed the neurologic syndrome 12 days after PBSC reinfusion. This is the first report of ADEM in the setting of autologous PBSCT, a therapeutic procedure performed with increasing frequency in a wide variety of hematologic and solid malignancies. Keywords: peripheral blood stem cell transplantation; high-dose chemotherapy; acute disseminated encephalomyelitis; neurologic complication

High-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (PBSCT) is a therapeutic intervention performed with increasing frequency for hematologic and solid malignancies.⁴ The widespread use of this procedure depends on its safety and easy feasibility. Mild organ toxicities and low incidence of life-threatening complications are usually reported. Neurologic events are frequently mild and reversible and usually secondary to injury to other organ systems.⁵

We report a case of ADEM in an autologous PBSCT recipient with non-Hodgkin's lymphoma (NHL) who developed the syndrome on day +12 after PBSC reinfusion, without any recognizable etiology. To our knowledge, this is the first report of ADEM developing after high-dose chemotherapy and PBSCT.

Case report

A 43-year-old man, was diagnosed as having anaplastic large cell lymphoma CD30⁺, stage III A, in January 1997. After 12 weeks of treatment with VACOP-B (etoposide, adriamycin, cyclophosphamide, vincristine and prednisone), partial remission was achieved. In July 1997 the patient underwent PBSC harvesting after priming with cyclophosphamide 7 g/m² and G-CSF 5 µg/kg. After treatment with etoposide 2 g/m², he was admitted in November 1997 to undergo PBSCT in complete remission. The conditioning regimen was: thiotepea 15 mg/kg on day -4 and melphalan 140 mg/m² on day -3. On day 0 the patient received 11.5×10^9 nucleated cells (14.7×10^6 CD34⁺ cells per kg body weight). On day +1 he was started on G-CSF 5 µg/kg/day. On day +11, after several days of fever of unknown origin, treated with vancomycin, imipenem-cylastatine and amphotericin-B, he developed mild drowsiness and attention defect with a negative neurologic examination. At that time he had already recovered from marrow aplasia. The WBC count was $5700 \times 10^6/l$ (neutrophils $4500 \times 10^6/l$), platelet count was $37 \times 10^9/l$, and Hb was 10 g/dl. Electrolyte levels, blood urea nitrogen, creatinine, glucose and liver function tests were normal. The next day he became confused and developed a generalized tonic-clonic seizure controlled with diazepam i.v. Vital signs were normal except for a cutaneous temperature of 38.5°C. No focal neurologic signs and no meningeal irritation were present. A brain CT scan showed only a small

Acute disseminated encephalomyelitis (ADEM) is a demyelinating disorder of the central nervous system (CNS), that presents with acute neurologic symptoms and seems to be immunomediated. It is usually preceded by a viral infection or vaccination. However, it may also occur without any recognizable preceding event. The illness is sudden in onset, with a wide spectrum of severity and clinical presentation (seizures, meningism, headache, hemi- or quadriplegia, sensory loss, optic neuritis, drowsiness evolving to coma), reflecting multifocal lesions involving the cerebral white matter, cerebellum, brain stem, optic nerve and spinal cord. Its pathologic hallmark is the presence of widely scattered small foci of perivenular inflammation and demyelination.¹ Computed tomography (CT) is often normal or shows nonspecific low density lesions in white matter. On magnetic resonance imaging (MRI) the lesions are seen as extensive white matter abnormalities, with no evidence of hemorrhage or mass effect.^{2,3} The clinical outcome of patients is variable, and recovery is often slow, but complete or near complete recovery is often achieved.

hypodense lesion without contrast enhancement located in the right coronae radiatae. He then became comatose and was transferred to intensive care. Soon after admission he developed repeated tonic-clonic seizures and was started on diazepam, phenobarbital and phenytoin. Cerebrospinal fluid (CSF) study showed: WBC 7/mm³, RBC 0, protein 52 mg/dl, glucose 159 mg/dl. CSF bacterial, fungal and viral cultures were negative and cryptococcal antigen was absent. CMV, EBV, HIV, Herpes simplex virus and toxoplasma serologic tests were negative or suggestive of prior infection. Electroencephalogram (EEG) disclosed generalized abnormalities suggesting diffuse and severe encephalopathy, as did sequential brain CT scans. For several days he was supported with artificial ventilation and parenteral nutrition. Fourteen days after the onset of symptoms he began regain consciousness and motility and he became completely alert 4 days later and was then readmitted to our department. A brain MRI performed at that time revealed diffuse abnormal signals in the cerebral white matter, with focal asymmetric lesions, suggestive of demyelination (Figure 1).

The radiological and CSF findings, together with the rapid clinical onset and monophasic course of the disease were consistent with a diagnosis of ADEM. Anti-myelin-associated glycoprotein (anti-MAG) and anti-myelin basic protein (anti-MBP) antibodies were detected in the CSF by peroxidase immunoassay and supported the diagnosis.

At discharge the patient showed major defects of motor coordination with an ataxic gait. His mental status was seriously compromised with memory and speech impairment. He was then started on a rehabilitation program and achieved some clinical improvement. A brain MRI performed 3 months after onset showed disappearance of the diffuse signal abnormality with persistence of focal lesions (Figure 2). As of December 1998, although there has been slight improvement, his mental status is still poor. However, there is no evidence of recurrent lymphoma.

Discussion

Eleven days after PBSCT for NHL our patient developed acute encephalopathy, presenting with confusion, disorientation and repeated generalized tonic-clonic seizures and evolving to coma. The rapid and dramatic clinical onset, multifocal central nervous system lesions with typical MRI findings, EEG showing diffuse cerebral abnormalities and failure to demonstrate an infectious origin of the disease all suggested a diagnosis of ADEM. The finding of anti-myelin antibodies in the CSF also supported the diagnosis. To make a diagnosis of ADEM, viral encephalitis or other CNS infections must be excluded, as must multiple sclerosis and cerebrovascular disorders. Clinical course, viral titres, EEG, CSF and MRI findings are useful for differentiating between these disorders.¹

ADEM is a demyelinating disorder of the CNS, believed to be immunomediated. Usually the disease is preceded by a viral infection or immunization. Smallpox, rabies, measles and Japanese B encephalitis vaccines and measles,

Figure 1 T2-weighted MR images performed 3 weeks after onset showed (a) diffuse abnormal hyperintense signal, suggestive for diffuse demyelination with (b) focal areas of abnormal high signal intensity in periventricular white matter.

varicella-chicken pox, rubella, mumps, influenza, parainfluenza, infectious mononucleosis virus infections have all been reported as possible causes of ADEM. Much less frequently, bacterial agents, such as mycoplasma pneumoniae, have been advocated as causative factors for the disease.¹ No virus has ever been recovered from affected brains and typical ADEM lesions have similarities to those of experimental allergic encephalomyelitis.⁶ The underlying pathogenic mechanism remains unknown. An autoimmune reaction against myelin components seems to be involved, resulting from cross-reactivity between external antigens and host determinants.

Human herpesvirus 6 (HHV-6), known to be detectable in the brain of many neurologically normal adults and demonstrated to have a regional localization to plaques of multiple sclerosis, has been recently reported as a possible etiologic agent in multifocal demyelinating fulminant encephalomyelitis in a young woman.⁷

Figure 2 T2-weighted MR images performed 4 months after onset showed (a) marked resolution of diffuse alteration of signal intensity with (b) persistence of focal white matter areas of high signal intensity.

Although in our case a specific viral or bacterial infection was not detectable by cultures and serologic studies, the history of several days of unexplained fever allows us to hypothesize an infective process provoking an immune response. The onset of the disease was after recovery of bone marrow aplasia with a WBC available to permit an immunologic and inflammatory response. The finding of antibodies to myelin protein in the CSF disclosed an auto-immune reaction against myelin within the blood-brain barrier. Thiopeta, an alkylating agent used in conditioning, has well-recognised neurotoxicity when used at high doses and has been reported to cause somnolence, confusion and seizures. Although we cannot firmly exclude a possible role of thiopeta or other antineoplastic and anti-infective agents as cofactors for the neurological damage in this case, there are no reports to our knowledge of demyelinating disorders

secondary to the drugs administered to our patient. The neurologic syndrome also seems unattributable to NHL because CNS involvement was never recognized during the course of the NHL and at the time of PBSCT the patient was in CR.

Our patient, as a recipient of high-dose chemotherapy was at increased risk of infections due to severe neutropenia and immunosuppression. The fever he developed suggests such a condition. Other authors have reported cases of ADEM in the setting of immunosuppression. A heart-lung transplant recipient developed ADEM while on immunosuppressive treatment, without any recognized preceding infectious process.⁸ An HIV-positive patient suffered this neurological disorder as the initial presentation of HIV infection, while the CD4⁺ lymphocytes were $600 \times 10^6/l$.⁹ In both cases a nonspecific and unrecognized viral infection in the setting of immunosuppression was presumed to be the primary event.

Even if there is no demonstrated evidence that corticosteroids improve outcome in ADEM, they are widely used and seem to be of some benefit. Dexamethasone, methylprednisolone or ACTH have been used with different schedules in the hope of preventing disease progression and speeding resolution of existing lesions.^{1,10} Some studies have also found plasmapheresis or IVIG to be of some benefit where steroids have failed.^{11,12} Unfortunately, the diagnosis of ADEM is usually made in retrospect, so that the active phase of the disease is already over. This was the case for our patient. A major role is also played by supportive care. Patients often require intensive care, with artificial nutrition and ventilation but the most dramatic clinical presentation can have a good outcome. Managing patients with ADEM involves rehabilitation, as many patients experience slow neurologic recovery.

Here, we report for the first time a case of ADEM in the PBSCT setting, a clinical entity that should be added to the list of complications of this therapeutic procedure and should be kept in mind while handling patients undergoing high-dose chemotherapy.

Further laboratory and clinical studies are necessary better to understand and recognize an entity which remains largely speculative.

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