Encephalitis with Antibodies Against Glial Fibrillary Acidic Protein (GFAP) After Allogeneic Hematopoietic Stem Cell Transplantation: A Rare Case Report and Literature Review

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Abstract: In this report, the patient was a 57-year-old woman who had been diagnosed with aplastic anemia for 3 years. This patient underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT). Twenty-four months after allo-HSCT, the patient experienced cognitive dysfunction, memory loss, and involuntary movements. Various central nervous system (CNS) complications may occur after allo-HSCT, which can lead to severe clinical problems. Diagnosis is often difficult because of the absence of distinctive clinical symptoms. In addition, different neurological disorders may show similar symptoms. Although antibodies in the CSF or serum have become well recognized in several CNS disorders, cases of autoimmune CNS disorders after allo-HSCT have rarely been reported. Here, we report the case of a patient who developed encephalitis associated with antibodies against glial fibrillary acidic protein (GFAP) after allo-HSCT. To the best of our knowledge, this is the first report of the involvement of antibodies against GFAP in post-transplantation encephalitis. Of course, all processes met the ethical and patient consents were obtained.

Keywords: glial fibrillary acidic protein, autoimmune encephalitis, allo-HSCT

Introduction

For various hematopoietic diseases, hematopoietic stem cell transplantation (HSCT) is a well-recognized treatment choice. After HSCT, infection, CNS complications, therapy-induced cytotoxicity, autoimmune diseases and graft versus-host disease (GVHD) are common complications. Calcineurin inhibitors-related neurological complications account for about 25–59%, and the neurotoxicity caused can be transient isolated symptoms or serious complications, such as Posterior reversible encephalopathy syndrome (PRES), thrombotic microangiopathy (TMA) etc. Post-transplantation complications are mainly related to hematopoietic and immune system hypoplasia. Because of the poor prognosis of CNS complications, early diagnosis and treatment are crucial to achieve a good prognosis. Encephalitis with antibodies against GFAP after allo-HSCT is extremely rare. Hence, its pathophysiology and treatment have not been elucidated. Here, we report the case of a patient who developed encephalitis associated with antibodies against GFAP after allo-HSCT.

Case Report

A 57-year-old woman was diagnosed with aplastic anemia (AA). She failed to respond to Cyclosporin A (CsA) combined with Stanozolol. She was then admitted to our institution to undergo allo-HSCT. The patient received an allogeneic bone marrow transplant from her daughter. The conditioning regimen consisted of antithymocyte globulin (ATG) 2.5 mg/kg on Days −12 to −9, busulfan 0.8 mg/kg on Days −7 to −6, fludarabine 30 mg/kg on Days −5 to −1, and cyclophosphamide 40 mg/m² on Days −5 to −4. Methotrexate (15 mg/m² on Day +1; 10 mg/m² on Days 3, 5 and 11) was administered, and
Tacrolimus was administered (1 mg/day) from Day 6 for graft-versus-host disease (GVHD) prophylaxis. Oral acyclovir (0.4 g/day) was administered for herpes simplex virus (HSV) prophylaxis starting on Day 1.

More than two years following transplantation, the patient developed a skin rash without fever, and she developed short-term memory dysfunction and emotional lability. Furthermore, she exhibited involuntary movements of her hands.

In the indirect immunofluorescence detection of the patient’s sample in brain tissue slices, there were fluorescence signals in the cerebellum and hippocampus regions. And the pattern was consistent with positive anti-GFAP antibodies. Anti-GFAP antibodies were detected in her cerebrospinal fluid (CSF) at a ratio of 1:320 by tissue-based assays (TBAs) and were positive by cell-based assays (CBAs) (Table 1). Protein levels were normal, and no viruses (HHV-6, cytomegalovirus, Epstein–Barr virus [EBV], herpes simplex virus [HSV], or varicella zoster virus) were detected in the CSF. No obvious abnormality was found in the electroencephalogram of the patient.

Brain magnetic resonance imaging (MRI) showed bilateral hyperintensity on T2-weighted and FLAIR images (Figure 1). Finally, we diagnosed her as having encephalitis with anti-GFAP antibodies. She received methylprednisolone in combination with FK-506, as it was unclear whether her encephalitis was due to GVHD or autoimmune encephalitis.

### Discussion

The patient’s main manifestations were cognitive and brain function impairment, short-term memory dysfunction, and drowsiness.

According to the literature reports, the reasons for central nervous system (CNS) complications include infection, immunological factors, transplant type, disease type, GVHD, CsA use, stem cell source and conditioning regimen.

In this study, we detected anti-GFAP antibodies in the patient’s CSF. Anti-GFAP antibodies is essential for diagnosis. However, there are also literature reports that GFAP is not a pathogenic antibody. The literature provides evidence for the possible mechanism of anti-GFAP antibody-associated encephalitis, including cytokines, viral infection, autoimmune factors, and GVHD. Concentrations of GFAP and IL-6 in CSF showed a good correlation during the onset

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<tr>
<td>GFAP</td>
<td>CBA</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>TBA detection of brain tissue slices</td>
<td>TBA</td>
<td>Positive</td>
<td>Negative</td>
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**Abbreviations:** GFAP, glial fibrillary acidic protein; TBA, tissue-based assays; CBA, cell-based assays; CSF, cerebrospinal fluid.

Figure 1 (A) MRI on FLAIR image shows well-demarcated bilateral hyperintensity (arrow) in insular. (B) MRI shows hyperintensity on T2-weighted and FLAIR images (arrow) in the limbic system.
of Neuromyelitis optica spectrum disorder. Reduced immune tolerance may promote the emergence of autoimmune diseases while waiting for immune reconstitution after transplantation. While waiting, autoimmune encephalitis with elevated anti-GFAP antibodies in the cerebrospinal fluid may have developed.

GFAP astrocytopathy is an autoimmune disease of the nervous system. Autoantibodies have been detected in the cerebrospinal fluid (CSF) and serum of GFAP astrocytopathy patients. Both tissue-based assays (TBAs) and cell-based assays (CBAs) are recommended methods to detect GFAP antibodies. Both methods confirmed GFAP antibody positivity in the patient whose case is reported here.

We completed cerebrospinal fluid and imaging examinations as well as electroencephalography. Infectious factors should be excluded, but the pathogenicity of autoimmunity or GVHD is still unclear. Brain tissue biopsy or invasive tissue examination may provide more evidence on pathogenicity. The etiology cannot be further demonstrated because of the limitations of the examination. Imaging examinations do a favor in differential diagnosis. Magnetic resonance (MRI) can display various lesions of central nervous system after HSCT. Nevertheless, we chose methylprednisolone in combination with FK-506, and the patient achieved a good response. The patient's cognitive function was restored. Methylprednisolone has been gradually reduced and has been stopped for more than a month. The patient has shown no signs of recurrence.

This may be the first case of anti-GFAP antibody-associated autoimmune encephalitis after allo-HSCT. Therefore, the accumulation of similar cases is necessary to elucidate the pathogenicity and disease specificity and to develop a treatment plan and prognosis.

**Patient’s Consent for Publication**
The current case report was published with informed consent of the patient, whose anonymity was preserved.

**Compliance with Ethical Standards**
The patient provided written informed consent for publication of the case report. Institutional approval was not required to publish the case details. The data that support the findings of this study are available on request from the corresponding author, Meng Hu, upon reasonable request.

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**Disclosure**
The authors declare no competing interests in this work.

**References**


