



A case of central nervous system graft-versus-host disease following allogeneic stem cell transplantation

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Abstract

Graft-versus-host disease (GVHD) is a serious complication of allogeneic stem cell transplantation (SCT). Here, we report a rare case of GVHD involving the central nervous system (CNS). A 35-year-old woman was diagnosed with myelodysplastic syndrome unclassifiable and underwent allogeneic peripheral blood SCT for disease progression to myelodysplastic syndrome with excess blasts-2. One year following SCT, she experienced chronic oral and hepatic GVHD symptoms, which were managed with oral steroids and tacrolimus. Sixteen months after SCT, she developed sudden-onset, generalized, tonic-clonic-type seizures. Magnetic resonance imaging and cerebrospinal fluid evaluation showed multiple discrete white lesions and elevated IgG levels. Brain biopsy revealed periventricular plaques with the destruction of axons, representing a demyelinating disease of the CNS. We diagnosed the case as CNS GVHD. Neurologic symptoms gradually improved with methylprednisolone pulse therapy and total plasma exchange combined with a calcineurin inhibitor; the brain lesions nearly disappeared after decreasing steroid maintenance dosage, and were completely resolved 1 year after the onset of CNS GVHD. The patient is CNS GVHD-symptom-free, 3-year post-transplantation. Thus, CNS GVHD should be considered in cases of newly developed neurologic symptoms in SCT recipients showing evidence of preceding chronic GVHD.

Keywords Central nervous system graft-versus-host disease · Allogeneic stem cell transplantation · Demyelination

Introduction

Allogeneic stem cell transplantation (SCT) is an important therapeutic option to treat hematologic diseases, but its use is limited by a wide spectrum of adverse events. Among them, graft-versus-host disease (GVHD) is a major serious complication contributing to patient morbidity and mortality. GVHD is a systemic syndrome mediated by immunocompetent donor CD3⁺ T cells, and its frequent targets are the mouth, eye, skin, gastrointestinal tract, and liver. However, only a few reports have described GVHD affecting the central nervous system (CNS). CNS GVHD

remains controversial because involvement of the CNS is less common and hard to distinguish from common neurological complications of SCT [1, 22]. The neurological complications observed in allogeneic SCT recipients are usually related to CNS infection, metabolic abnormalities, cerebrovascular events, drug toxicity, Epstein–Barr virus-associated lymphoproliferative disease, posterior reversible encephalopathy syndrome, and leptomeningeal relapse of malignancy [2]. In the present study, we report a case of alloimmune-mediated encephalomyelopathy considered to be chronic CNS GVHD with demyelinating features after receiving allogeneic SCT, which was successfully treated with steroid pulse therapy and an immunosuppressant.

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Case report

In October 2014, a 35-year-old woman visited the hospital with a complaint of moderate dyspnea and was diagnosed with myelodysplastic syndrome (MDS) unclassifiable. In 2015, she became transfusion-dependent, and bone marrow

aspiration revealed disease progression to MDS excess blasts-2. The patient underwent allogeneic SCT using HLA-identical unrelated donor peripheral blood, with a conditioning regimen of fludarabine (30 mg/m²/day for 5 days), anti-thymocyte globulin (ATG; 2.5 mg/kg/day for 4 days), and busulfan (3.2 mg/kg/day for 2 days). Tacrolimus plus a short course of methotrexate was administered for GVHD prophylaxis. Approximately 1 year after allogeneic SCT, the patient started to suffer from the dry mouth with lichen-type features and partial limitation of oral intake associated with mildly elevated bilirubin levels, but did not reach > 3 mg/dL. These overall mild-grade chronic GVHD (oral score 1, liver score 1, and overall score mild, because the patient had two organs' involvement with a maximum score of 1) symptoms were managed with oral steroids and tacrolimus.

The patient presented to the emergency department 12 months after chronic GVHD diagnosis with sudden-onset generalized tonic-clonic (GTC)-type seizures, with a duration of 30 s. A neurological examination revealed symmetrical lower leg weakness [Medical Research Council (MRC) grade 2] associated with hypoesthesia below T2 level and

increased knee- and ankle-deep tendon reflex. The patient also complained of a moderate headache and blurred vision in both eyes. However, there was no pathologic reflex, and following a mini-mental state examination, the cranial nerve and cerebellar function test results were normal. Brain magnetic resonance imaging (MRI) revealed T1 low, T2 high multifocal ring enhancement lesions in the left occipital, right frontal, and left-inferior frontal-subcortical periventricular area with mild perilesional edema, which is consistent with demyelinating features (Fig. 1a, b). A spine MRI showed multifocal nodular leptomeningeal enhancement and nodular intramedullary enhancing lesions along the spinal cord, predominantly at the mid-thoracic spine (Fig. 1c). Because these multifocal lesions in brain and spine MRI find highly suspicious of invasive fungal infection or disease relapse as Chloroma, we decided to stop oral steroids (prednisolone) 5 mg and tacrolimus 0.5 mg after reviewed imaging studies.

The cerebrospinal fluid (CSF) was clear, with normal pressure and white blood cell counts (1 cell/ μ L); total protein was 27.8 mg/dL, glucose 119 mg/dL, and LDH below

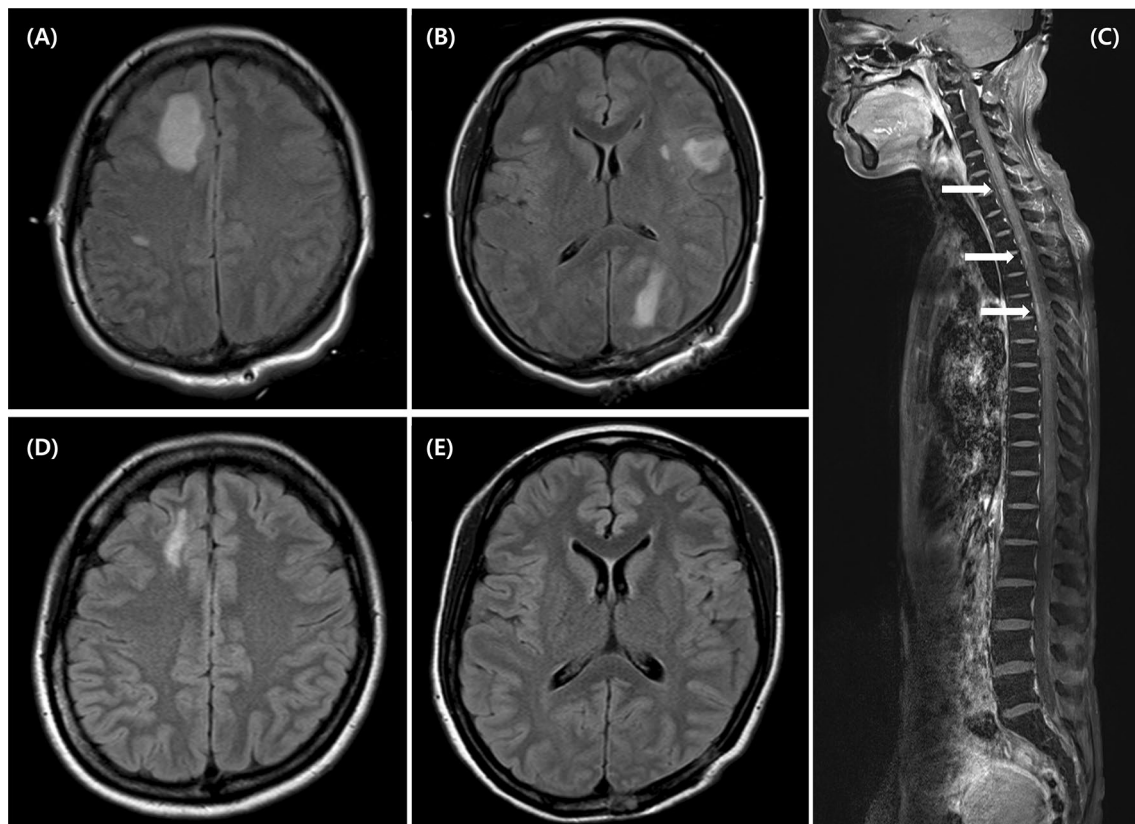


Fig. 1 A brain MRI revealed T2 FLAIR high multifocal ring enhancement lesions in the left occipital (a), right frontal (b), and left-inferior frontal-subcortical periventricular area (a), with mild perilesional edema, which is consistent with the demyelinating feature. A spine MRI showed multifocal nodular leptomeningeal

enhancement and nodular intramedullary enhancing nodules (indicated by arrows) along the spinal cord, predominantly at the mid-thoracic spine (c). A follow-up brain MRI showed interval improvement of multiple non-enhancing T2 and FLAIR hyperintensity lesions in the bilateral frontal and temporal lobes (d, e)

50 U/L. There was no evidence of malignancy and bacterial or fungal growth according to the cytology and culture results, respectively. The CSF tests for Acid-Fast Bacilli stain, culture, with *Mycobacterium tuberculosis* reverse transcription polymerase chain reaction (RT-PCR), cytomegalovirus RT-PCR, varicella zoster virus RT-PCR, herpes simplex virus culture with type I/II RT-PCR, enterovirus culture, toxoplasma IgM/IgG using enzyme-linked immunosorbent assay, cryptococcus antigen assay, treponema pallidum antibody, and CSF latex agglutination test for *Streptococcus pneumoniae*, *Streptococcus* Group B, *Haemophilus influenzae*, *Neisseria meningitidis* (A, B, C, W135, X, and Y), and *Escherichia coli* K1 species were negative. The oligoclonal band and anti-aquaporin4 IgG were not detected, but the IgG level was elevated to 3.69 mg/dL (reference range; 0.63–3.35 mg/dL) in the CSF sample. Levels

of serum autoimmune markers such as anti-SS-A/Ro, anti-SS-B/La, anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, rheumatoid factor, serum C3, C4, CH50, and IgG/A/M were all within normal limits. For diagnosis, the patient underwent a navigation-guided craniotomy, with brain mass excision biopsy using an ultrasonogram-guided trans-sulcus approach. The brain specimen revealed a loss of myelin fibers, perivascular T-cell infiltration (CD3⁺), and macrophage infiltration associated with reactive gliosis. Immunohistochemistry revealed infiltration of CD3, CD20, and CD68-expressing lymphocytes and monocytes associated with loss of myelin fiber shown by neurofilament and glial fibrillary acidic protein (GFAP) (Fig. 2a–f). Alpha thalassemia/mental retardation syndrome X-linked (ATRX) gene, isocitrate dehydrogenase 1 (IDH-1), and antigen Ki-67 staining were performed to rule out any possibilities of malignancy,

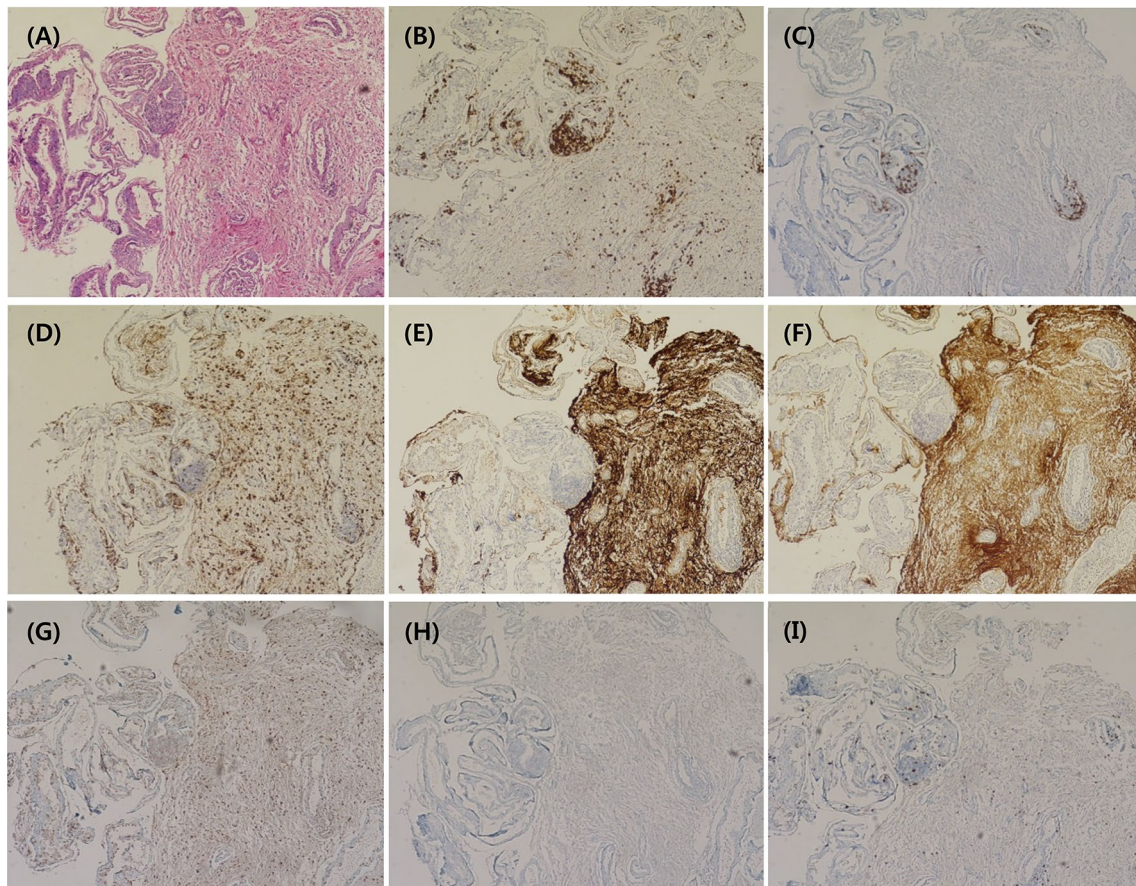


Fig. 2 The pathology sample of the cerebrum excision biopsy revealed the loss of myelin fibers, macrophage infiltration, and reactive gliosis, which is consistent with perivascular inflammation predominately located in brain parenchyma. Hematoxylin–eosin staining revealed lympho-histiocytic vasculitis with perivascular infiltration around small and medium vessels (magnification $\times 100$) (a). The inflammatory cells were T lymphocytes expressing CD3 (magnification $\times 100$) (b) moderate expression of CD20 (magnification $\times 100$) (c) and CD68 (magnification $\times 100$) (d) associated with loss of myelin

fiber shown by neurofilament (magnification $\times 100$) (e) and GFAP (magnification $\times 100$) (f) according to immunohistochemistry, but not ATRX (magnification $\times 100$) (g) IDH-1 (magnification $\times 100$) (h) and Ki-67 2% (magnification $\times 100$) (i). ATRX status is one of the critical markers that define the molecular classification of gliomas. IDH-1 immunohistochemistry reliably detects IDH-1 mutation in gliomas and other solid malignancies combined with Ki-67, which is strictly associated with cell proliferation and correlated with the clinical course of malignancy

especially gliomas or other CNS-origin tumors, and results showed negative findings (Fig. 2g–i).

Since there was no evidence of another disease, we diagnosed the condition as CNS GVHD with demyelinating features. The patient was treated with intravenous methylprednisolone pulse therapy (1 g/day for 7 days), subsequently tapered by 50% of the preceding dose every 3 days, total plasma exchange every other day for six times, in combination with tacrolimus, maintaining a therapeutic plasma level of 10–15 ng/mL. About 3 weeks after initiation of treatment, we changed intravenous methylprednisolone to an equivalent dose of oral prednisolone and tapered its dose by 10 mg every 3 days until reaching the maintenance dose of 0.1 mg/kg/day. The motor symptoms improved gradually after 4 weeks, and the patient could ambulate with minor support. The patient was discharged with strength in the lower extremities at MRC grade 4, steady improvement in sensory numbness, and improved vision, dry mouth, and bilirubin levels. A follow-up brain MRI, at 4 weeks from the start of methylprednisolone treatment, showed interval improvement of multiple non-enhancing T2 and FLAIR hyperintensity lesions in the bilateral frontal and temporal lobes (Fig. 1d, e).

The patient's improved neurological symptoms remained stable one and a half years after transplantation, despite the tapering of the oral prednisolone dose to 0.1 mg/kg/day, and a lower therapeutic range of oral tacrolimus. After the patient's motor and sensory functions were fully recovered (to MRC grade 5), steroid maintenance therapy was stopped 1 year after the onset of CNS GVHD, and there has been no evidence of relapse or newly developing neurologic symptoms since then.

Discussion

Following allogeneic SCT, patients are at risk of comorbidities due to acute or chronic GVHD and any organ systems can be involved in the latter [3]. However, there are only a few reports of patients with CNS manifestation as a feature of GVHD [1, 4–17]. A rodent study suggested that the brain and other CNS tissue can be a target for GVHD [18, 19], but it is not yet considered a typical feature in the NIH consensus 2014 [20], and the incidence or disease course of CNS GVHD remains controversial because of its rarity. There is a debate about whether CNS manifestations of chronic GVHD constitute an independent clinical entity, or they only result from complications of the cumulative effects of heavy treatments and procedures during allogeneic SCT [21].

Recently, the Openshaw group suggested helpful diagnostic guidelines for patients presenting both chronic GVHD and unexplained CNS signs and symptoms [22]. In following year, CNS manifestations of chronic GVHD were also

described as a distinct entity in the Consensus Conference on Clinical Practice in chronic GVHD [23]. There is a total of six diagnostic criteria, which include two mandatory features: (i) occurrence with chronic GVHD affecting other organs and (ii) neurological signs of CNS involvement without another explanation. The other four facultative features are: (i) corresponding brain MRI abnormality, (ii) abnormal CSF features (pleocytosis, elevated immunoglobulin G or protein level, and oligoclonal bands), (iii) pathological brain biopsy or post-mortem examination, and (iv) response to immunosuppressive therapy. In the present case, the patient met all six diagnostic criteria for CNS GVHD and responded well to steroid pulse therapy with maintenance immunosuppressive therapy without any evidence of relapse.

Myelin-specific antibodies or T lymphocytes are a major cause of demyelination, which coordinates an immune-mediated attack against the myelin sheath. There are a few case reports of demyelination during chronic GVHD affecting the optic nerve, cerebral white matter, spinal cord, or the CNS and peripheral nervous system simultaneously, but histology of patients with demyelinating CNS GVHD features is very rare [6, 10, 14, 16, 24]. We found increased numbers of diffusely infiltrating CD3⁺, CD20⁺, and CD68 cells with a loss of myelinated nerve fibers by Luxol fast blue staining, which is consistent with that observed in demyelinating disorders such as multiple sclerosis (MS) [25]. MRI imaging revealed multiple white matter lesions of the brain and spinal cord, also consistent with the findings of MS [25]. Distinguishing CNS GVHD with demyelinating features from other immune-mediated demyelinating disorders only by clinical findings might not be possible. Hence, patients should have at least one additional systemic sign of chronic GVHD before CNS GVHD is suspected, and like in this case, the patient should fulfill the proposed diagnostic criteria to make a definite (meeting all six criteria) or possible (meeting two mandatory and at least two facultative criteria) CNS GVHD diagnosis.

The treatment of CNS GVHD is not different from that of conventional chronic GVHD treatment and should include immunosuppression. This patient was treated with steroid pulse therapy combined with a therapeutic dose of tacrolimus. The short-term supportive total plasma exchange every other day was added, similar to MS treatment. Following steroid pulse therapy combined with calcineurin for chronic GVHD [2, 26], the patient's neurologic symptoms gradually improved. The patient's clinical course became temporarily worse during tapering of the dose of methylprednisolone without modifying the therapeutic dose of tacrolimus. However, unlike the typical clinical course of MS (wherein gradual deterioration is observed during the relapsing–remitting form of the disease), the patient's neurological symptoms finally improved after the steroid maintenance dose and did not relapse after discontinuation.

In conclusion, CNS GVHD should be considered in case of newly developed neurologic symptoms in SCT recipients who had evidence of preceding chronic GVHD. CNS GVHD is a rare and severe complication after allogeneic SCT that can be difficult to diagnose. Continued gathering, reporting, and work-up of similar cases remain important to develop accurate treatment strategies and differential diagnosis criteria.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this article.

Human/animal rights This study conducted according to the Declaration of Helsinki and the Institutional Review Board and Ethics Committee guidelines of the Seoul St. Mary's Hospital.

References

- Kamble RT, Chang CC, Sanchez S, Carrum G. Central nervous system graft-versus-host disease: report of two cases and literature review. *Bone Marrow Transplant*. 2007;39(1):49–52.
- Siegal D, Keller A, Xu W, Bhuta S, Kim DH, Kuruvilla J, et al. Central nervous system complications after allogeneic hematopoietic stem cell transplantation: incidence, manifestations, and clinical significance. *Biol Blood Marrow Transplant*. 2007;13(11):1369–79.
- Hymes SR, Alousi AM, Cowen EW. Graft-versus-host disease: part I. Pathogenesis and clinical manifestations of graft-versus-host disease. *J Am Acad Dermatol*. 2012;66(4):515.
- Marosi C, Budka H, Grimm G, Zeithofer J, Sluga E, Brunner C, et al. Fatal encephalitis in a patient with chronic graft-versus-host disease. *Bone Marrow Transplant*. 1990;6(1):53–7.
- Iwasaki Y, Sako K, Ohara Y, Miyazawa M, Minegishi M, Tsuchiya S, et al. Subacute panencephalitis associated with chronic graft-versus-host disease. *Acta Neuropathol*. 1993;85(5):566–72.
- Openshaw H, Slatkin NE, Parker PM, Forman SJ. Immune-mediated myelopathy after allogeneic marrow transplantation. *Bone Marrow Transplant*. 1995;15(4):633–6.
- Provenzale JM, Graham ML. Reversible leukoencephalopathy associated with graft-versus-host disease: MR findings. *AJNR Am J Neuroradiol*. 1996;17(7):1290–4.
- Padovan CS, Bise K, Hahn J, Sostak P, Holler E, Kolb HJ, et al. Angiitis of the central nervous system after allogeneic bone marrow transplantation? *Stroke*. 1999;30(8):1651–6.
- Takatsuka H, Okamoto T, Yamada S, Fujimori Y, Tamura S, Wada H, et al. New imaging findings in a patient with central nervous system dysfunction after bone marrow transplantation. *Acta Haematol*. 2000;103(4):203–5.
- Solaro C, Murialdo A, Giunti D, Mancardi G, Uccelli A. Central and peripheral nervous system complications following allogeneic bone marrow transplantation. *Eur J Neurol*. 2001;8(1):77–80.
- Ma M, Barnes G, Pulliam J, Jezek D, Baumann RJ, Berger JR. CNS angiitis in graft vs host disease. *Neurology*. 2002;59(12):1994–7.
- Nagashima T, Sato F, Chuma T, Mano Y, Sasaki I, Mori M, et al. Chronic demyelinating polyneuropathy in graft-versus-host disease following allogeneic bone marrow transplantation. *Neuropathology*. 2002;22(1):1–8.
- Campbell JN, Morris PP. Cerebral vasculitis in graft-versus-host disease: a case report. *AJNR Am J Neuroradiol*. 2005;26(3):654–6.
- Sakai M, Ohashi K, Ohta K, Yamashita T, Akiyama H, Kisida S, et al. Immune-mediated myelopathy following allogeneic stem cell transplantation. *Int J Hematol*. 2006;84(3):272–5.
- Shortt J, Hutton E, Faragher M, Spencer A. Central nervous system graft-versus-host disease post allogeneic stem cell transplant. *Br J Haematol*. 2006;132(2):245–7.
- Matsuo Y, Kamezaki K, Takeishi S, Takenaka K, Eto T, Nonami A, et al. Encephalomyelitis mimicking multiple sclerosis associated with chronic graft-versus-host disease after allogeneic bone marrow transplantation. *Intern Med*. 2009;48(16):1453–6.
- Yoon BN, Ha CK, Lee KW, Park SH, Sung JJ. A confusing case of multiple sclerosis and central nervous system graft versus host disease. *Korean J Intern Med*. 2016;31(5):995–8.
- Hickey WF, Kimura H. Graft-vs.-host disease elicits expression of class I and class II histocompatibility antigens and the presence of scattered T lymphocytes in rat central nervous system. *Proc Natl Acad Sci USA*. 1987;84(7):2082–6.
- Hartrampf S, Dudakov JA, Johnson LK, Smith OM, Tsai J, Singer NV, et al. The central nervous system is a target of acute graft versus host disease in mice. *Blood*. 2013;121(10):1906–10.
- Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. National Institutes of Health Consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2015;21(3):389–401.
- Rouah E, Gruber R, Shearer W, Armstrong D, Hawkins EP. Graft-versus-host disease in the central nervous system. A real entity? *Am J Clin Pathol*. 1988;89(4):543–6.
- Penshaw H. Neurological manifestations of chronic graft versus host disease. In: Vogelsang GB, Pavletic SZ, editors. *chronic graft versus host disease*. New York: Cambridge University Press; 2009. p. 243–51.
- Grauer O, Wolff D, et al. Neurological manifestations of chronic graft-versus-host disease after allogeneic haematopoietic stem cell transplantation: report from the Consensus Conference on Clinical Practice in chronic graft-versus-host disease. *Brain*. 2010;133:2852–65.
- Ruggiu M, Cuccuini W, Mokhtari K, Meignin V, de Latour RP, Robin M, et al. Case report: central nervous system involvement of human graft versus host disease: report of 7 cases and a review of literature. *Medicine*. 2017;96(42):e8303.
- Karussis D. The diagnosis of multiple sclerosis and the various related demyelinating syndromes: a critical review. *J Autoimmun*. 2014;48–49:134–42.
- Higman MA, Vogelsang GB. Chronic graft versus host disease. *Br J Haematol*. 2004;125(4):435–54.

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