Central nervous system graft-versus-host disease in a 68-year-old man presenting with myoclonus

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Cite as: CMAJ 2019 September 30;191:E1078-81. doi: 10.1503/cmaj.190216

A 68-year-old man presented to the emergency department with a 1-week history of sudden-onset myoclonus of his right leg. His medical history included allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome performed 742 days earlier, type 2 diabetes mellitus, hypertension and dyslipidemia. The patient had undergone a 9/10 unrelated human leukocyte antigen (HLA) donor transplantation, and after transplantation, his myelodysplastic syndrome was in complete remission and he had complete donor engraftment. On presentation, he was receiving methotrexate (10 mg by mouth weekly) for large granular lymphocytosis and acyclovir (400 mg by mouth twice daily) for herpes simplex virus prophylaxis. A detailed neurologic examination on presentation showed a right-sided pyramidal distribution of weakness and a stimulus-sensitive, spontaneous positive myoclonus, present in the right leg more than the arm, and absent in the face. Deep tendon reflexes were brisk on the right side.

Given this patient’s history of hematopoietic stem cell transplantation and relative immunosuppression with methotrexate, the differential diagnosis was broad and included central nervous system infections, central nervous system relapse of his primary malignancy, metabolic derangements, paraneoplastic process, microangiopathy, central nervous system vasculitis, toxicity related to immunosuppressive agents, and central nervous system graft-versus-host disease. On further history, it was noted that he received a reduced intensity conditioning transplantation with fludarabine, busulfan and total body irradiation of 200 Gy. His graft-versus-host disease prophylaxis was with antithymocyte globulin, and posttransplantation cyclophosphamide and cyclosporine.1

The patient was admitted to the internal medicine service, and neurology was consulted, given his neurologic findings. Magnetic resonance imaging (MRI) of the brain showed multiple scattered T2-weighted fluid-attenuated inversion recovery hyperintense, non-enhancing, mildly expansile, cortical and subcortical lesions in both cerebral hemispheres, with no associated restricted diffusion (Figure 1A–D).

Over the following days, the patient had a rapid neurologic deterioration. He became nonverbal, and his only preserved motor function was smooth pursuit eye movements. Given this rapid progressive encephalopathy, the patient was treated empirically for viral encephalitis with acyclovir (800 mg intravenously every 8 hours). Despite this treatment, the patient’s clinical condition did not improve. Lumbar puncture showed a protein level of 0.53 (normal 0.2–0.45) g/L, a glucose level of 3.7 (normal 2.5–4.5) mmol/L and no pleocytosis. Microbiological and molecular analysis did not show any evidence of causative infectious pathogens; the analysis included an extensive panel of bacterial, viral (Epstein–Barr virus, cytomegalovirus, polyomavirus, varicella zoster, herpes simplex, human herpesvirus 6, rubella, measles, West Nile virus and arbovirus), parasitic (toxoplasmosis), prion (Creutzfeldt–Jakob disease) and fungal (Cryptococcus) infections. Electroencephalography showed diffuse slow wave activity corresponding to nonspecific encephalopathy but did not show any epileptogenic focus. There was no evidence of malignant cells on cerebrospinal fluid cytopathology and flow cytometry. A vasculitis panel including cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA), perinuclear ANCA (p-ANCA), antinuclear antibodies, anti-double stranded DNA, C3, and C4 was negative. Testing for antibodies for paraneoplastic syndrome was negative. Methotrexate-induced leukoencephalopathy, classically seen in patients receiving high-dose methotrexate,
especially intrathecally, was included in the differential diagnosis. However, the patient’s MRI findings were inconsistent owing to sparing of the centrum semiovale, as well as a lack of restricted diffusion. Furthermore, his symptoms persisted despite discontinuation of methotrexate.

Given worsening of the patient’s clinical condition and radiographic findings despite 10 days of treatment with intravenous acyclovir, a brain biopsy of the left frontal parietal cortical lesion involving both grey and white matter was performed. This showed perivascular lymphocytic infiltrate (Figure 2A). Luxol fast blue stains showed the absence of demyelination (Figure 2B). There was evidence of microglial activation involving the neuropil and perivascular spaces, highlighted by CD163 immunostains (Figure 2C). A sparse CD3 positive T lymphocyte perivascular infiltrate was present, without direct infiltration of the vessel wall (Figure 2D). There were no CD20 positive B lymphocytes. The pathologic findings of perivascular infiltrate were consistent with literature reports of central nervous system graft-versus-host disease. Investigations looking for other sites of involvement including liver enzymes, cutaneous examination and endoscopy, although not exhaustive, did not show graft-versus-host disease of other organs.

Even with this extensive workup, the patient’s diagnosis was unclear. It was imperative that infectious causes were considered and ruled out, which we had done. Given the patient’s clinical deterioration, a presumptive diagnosis of central nervous system graft-versus-host disease was made, and an empirical course of corticosteroid pulse was started (methylprednisolone 150 mg/d intravenously). Clinical improvement was rapid, and by day 3 of corticosteroid therapy, the patient was able to move his limbs and vocalize. He continued to improve and was ambulatory within 2 weeks of treatment. Repeat MRI showed resolution of many of the lesions (Figure 1E–H). The patient’s dosage was subsequently tapered, and he was transitioned to maintenance prednisone (60 mg/d by mouth) and azathioprine (75 mg/d by mouth).

Unfortunately, recurrent infections developed while the patient was receiving immunosuppressive treatment. Three months later, as his prednisone was tapered, he again had a flare of neurologic symptoms, and MRI showed worsening of the lesions. The patient’s goals of care were changed to comfort measures, and he died 927 days after the transplantation and around 195 days after onset of the central nervous system symptoms.

**Discussion**

Allogeneic hematopoietic stem cell transplantation is a life-saving treatment for many hematologic diseases. Graft-versus-host disease is a leading cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation. Between 30% and 50% of patients will develop graft-versus-host disease, whereby the donated tissue (the graft) recognizes the recipient (the host) as foreign and mounts a T cell–mediated immune response. The clinical manifestations vary, as multiple organs can be affected.

Classification of graft-versus-host disease has traditionally been divided into acute and chronic, depending on the onset of...
symptoms within or beyond 100 days, respectively. However, recent criteria consider overlap syndromes with increased emphasis on clinical features rather than timing of symptom onset alone.\textsuperscript{5,6} Central nervous system graft-versus-host disease is a rare but emerging entity after allogeneic hematopoietic stem cell transplantation, probably in part because the number of hematopoietic stem cell transplantations has risen.\textsuperscript{7–9}

**Clinical features**

Although chronic graft-versus-host disease can affect any organ, the skin, gastrointestinal tract, liver, joints, fascia and lungs are most frequently affected. Signs and symptoms of graft-versus-host disease relate to the organs of involvement, including maculopapular rash, hyperbilirubinemia with jaundice, and abdominal pain with either nausea and vomiting or diarrhea.\textsuperscript{4} With such broad-ranging clinical features, diagnosis relies on the assessment of target organs by means of clinical, laboratory and pathological findings. Important risk factors include compatibility of recipient and donor, including degree of HLA mismatch, sex of donor and recipient, use of peripheral-blood stem cell grafts and the conditioning regimen used. Criteria from the National Institutes of Health (NIH) help in defining and stratifying chronic graft-versus-host disease.\textsuperscript{10} Because of the rarity of cases, central nervous system graft-versus-host disease is not defined in the NIH criteria.

Neurologic involvement (first documented nearly 3 decades ago\textsuperscript{11}) is rare, and graft-versus-host disease afflicting both the central and peripheral nervous system has been described in the literature.\textsuperscript{7–9} Symptoms involving the central nervous system are often nonspecific and can include headaches, altered mental status, seizures and paresis.

In a recent case report and review, Ruggiu and colleagues reported a total of 39 presumed cases of central nervous system graft-versus-host disease, with a median patient age of 35 (range 0.67–68) years and a median duration of symptomatic presentation of 385 (range 7–7320) days after transplant.\textsuperscript{8} In this case series, which is limited by a lack of histopathology in more than half of the patients, those presenting with central nervous system disease without other chronic features of graft-versus-host disease presented earlier and in most cases had a history of acute graft-versus-host disease.\textsuperscript{8}

Our patient did not present with evidence of extracentral nervous system graft-versus-host disease. This may be owing to the newer conditioning regimen he was given, immunosuppression, or other underlying medical diagnoses and comorbidities. Our current lack of understanding of the clinical course of patients with central nervous system graft-versus-host disease is not defined in the NIH criteria.

**Figure 2:** Histopathologic images of the patient’s frontal cortex biopsy. (A) Hematoxylin and eosin staining showing sparse perivascular lymphocytic infiltrate in the white matter (arrowheads). (B) Luxol fast blue staining showing the absence of demyelination. (C) Perivascular activated microglia as shown by CD163 staining (arrowheads). (D) T lymphocytes infiltrating perivascular spaces (black arrowhead) and the neuropil (green arrowhead) as shown by CD3 staining. Scale bar = 200 µm.
nervous system graft-versus-host disease highlights the importance of further research into identifying risk factors, developing better diagnostic tools and finding new strategies for prevention.

**Diagnostic criteria**

The diagnosis of central nervous system graft-versus-host disease is complicated by conflicting differential diagnoses that can be challenging to exclude, such as infection, drug and radiation toxicity, and primary disease metastasis. As such, a combination of microbiologic and laboratory studies, and radiographic and histopathologic findings are required for the workup.

Given these diagnostic challenges, the 2009 Consensus Conference on Clinical Practice in chronic graft-versus-host disease defined the neurologic manifestations of the disease. This definition included the following criteria: 1) occurrence with chronic graft-versus-host disease affecting other organs, 2) neurologic signs of central nervous system involvement without other explanation, 3) corresponding MRI brain abnormality, 4) abnormal cerebrospinal fluid findings, 5) brain biopsy or postmortem examination confirming graft-versus-host disease and 6) response to immunosuppressive therapy. Criteria 1 and 2 are considered mandatory requirements in the diagnosis of central nervous system graft-versus-host disease, whereas criteria 3–6 are facultative requirements. A definitive diagnosis can be made when all 6 criteria are met, and a possible diagnosis can be made when both mandatory criteria and at least 2 facultative requirements are met.

Our patient met all the criteria according to this consensus definition except the first (occurrence with chronic graft-versus-host disease affecting other organs). Interestingly, the case series by Ruggiu and colleagues showed that 28% of patients did not have extracranial nervous system features of chronic graft-versus-host disease, although most of these patients did have a history of extracranial nervous system acute graft-versus-host disease.

Despite immunosuppressive treatment, central nervous system graft-versus-host disease portends a poor prognosis. Prior case series show that even though 70% of patients who received treatment with corticosteroids showed at least a partial response, only 18% of patients were alive at last follow-up.

This case highlights the importance of the late central nervous system complications of hematopoietic stem cell transplantation, the challenges with diagnosis and the role of timely immunosuppressive therapy. Though concepts regarding central nervous system graft-versus-host disease continue to evolve, it is important to keep as a differential diagnosis in patients with noninfectious neurologic complications who have undergone hematopoietic stem cell transplantation.

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