CASE REPORT

Central nervous system graft-versus-host disease (CNS-GvHD) after allogeneic haematopoietic stem cell transplantation

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SUMMARY

A 60-year-old man presented with impaired consciousness and psychomotor agitation after a second allogeneic haematopoietic stem cell transplantation (HSCT) from a matched unrelated donor for acute myeloid leukaemia. Clinical, biological and radiological evidence suggested a diagnosis of central nervous system graft-versus-host disease (CNS-GvHD). After intrathecal infusion of methylprednisolone, the clinical symptoms as well as the radiological abnormalities disappeared. The present report illustrates the difficulties in the diagnosis and the management of CNS-GvHD, a very rare and still challenging neurological complication that can occur after allogeneic HSCT.

BACKGROUND

Graft-versus-host disease (GvHD) is one of the major complications of allogeneic haematopoietic stem cell transplantation (HSCT) associated with a very high mortality and morbidity. Recently, it has been shown that the central nervous system (CNS) can be a target for GvHD.^{1,2} However, CNS-GvHD remains very rare with only few cases reported.^{3–7}

Clinical diagnosis of CNS-GvHD is challenging as many other and more frequent aetiologies need to be excluded before establishing the diagnosis of CNS-GvHD.⁸ CNS-GvHD neurological presentation is pleomorphic,^{3,6} and no uniform diagnostic criteria exist. Similarly, no standard treatment option for CNS-GvHD is established. We present here a case of acute demyelinating encephalomyelitis with a relapsing–remitting course and MRI findings consistent with a diagnosis of CNS-GvHD.

CASE PRESENTATION

A 60-year-old male patient in good general condition (Eastern Cooperative Oncology Group (ECOG) 0–1), with a history of acute myeloid leukaemia with recurrent genetic abnormalities, originally diagnosed at the end of 2013 and treated with a cytarabine-based chemotherapy regimen including CNS prophylaxis by three doses of intrathecal chemotherapy [methotrexate (total dose 45 mg), cytarabine and steroids], underwent a first allogeneic HSCT from a 10/10 human leucocyte antigen (HLA)-matched unrelated donor in October 2014 in first haematological and molecular complete

remission, after reduced intensity conditioning (RIC) with fludarabine (150 mg/m²), melphalan (140 mg/m²) and antithymocyte globulin (25 mg/kg). Neutrophil engraftment occurred on day 15 with 100% donor chimerism at day 30.

Approximately 3 months after transplantation, we detected mixed chimerism in the bone marrow (82% of donor cells among granulocytes) associated with pancytopenia pointing to a diagnosis of secondary graft failure. He received a donor lymphocyte infusion (DLI) containing 6 × 10⁶ CD3 cells/kg. One month later, he developed a grade II cutaneous acute GvHD that was initially treated with systemic immunosuppression, including ciclosporin (replaced by tacrolimus 6 days later because of insufficient response) and methylprednisolone. Two months later, 3 months since the DLI administration, the patient developed a grade III intestinal acute GvHD. Mycophenolate mofetil was added to his immunosuppressive therapy leading to the control of the GvHD. Despite full donor chimerism being obtained, severe pancytopenia persisted in the context of poor graft function. At 5 months post-transplantation, the patient was diagnosed with *Candida glabrata* fungemia, most likely central venous catheter related and without evidence of embolisation. He was treated initially with caspofungin for 2 weeks, thereafter combined with amphotericin B because of recurrent fungemia. The caspofungin was next replaced with voriconazole because of *C. glabrata* resistance to echinocandins on the fungigram.

Because of the poor graft function complicated by recurrent fungal infection, the patient underwent a second allogeneic HSCT from the same 10/10 HLA-matched unrelated donor following RIC with fludarabine (90 mg/m²) and total body irradiation (2 Gy), at 6 months since the first transplant. GvHD prophylaxis consisted of in vitro T cell depletion with alemtuzumab⁹ and continuation of methylprednisolone, tacrolimus and mycophenolate mofetil.

On day 3 after the second allogeneic HSCT, at 1 week since voriconazole treatment initiation, the patient reported temporary visual hallucinations, which were initially attributed to the antifungal treatment. Voriconazole was stopped and replaced by high dose caspofungin (1.3 mg/kg) with complete resolution of visual hallucinations. On day 7, 4 days

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after voriconazole discontinuation and with tacrolimus levels within the therapeutic range, the patient presented with temporary impaired consciousness, agitation and aggressive behaviour towards the care workers. Importantly, starting from day 9 post-transplantation, we had no evidence of recurrent fungemia under amphotericin B and caspofungin that were continued for 1 and 2 months, respectively. At day 10, the patient presented with psychomotor agitation and delusion of persecution. Neurological examination revealed a progressive decrease of strength in both legs.

INVESTIGATIONS

Laboratory evaluation at the onset of symptoms showed no toxic-metabolic abnormalities. The cerebrospinal fluid (CSF) examination revealed no pleocytosis (leucocytes $110 \times 10^6/L$ (normal range $0-5 \times 10^6/L$) and erythrocytes $<1 \times 10^6/L$ (normal range $0-10 \times 10^6/L$)) nor oligoclonal band but slight protein elevation (0.51 g/L (normal range 0.15–0.45 g/L)). Microbiological and molecular analysis by PCR showed no evidence of bacterial, viral (cytomegalovirus, polyomavirus, varicella zoster, herpes simplex, human herpesvirus 6 and Epstein-Barr virus), parasitic (toxoplasmosis) or fungal infections. There was no evidence of relapse of the underlying haematological disease. Electroencephalography showed only non-specific signs of moderate diffuse encephalopathy without epileptic discharge. MRI of the brain revealed multiple hyperintense lesions on T2 and fluid-attenuated inversion recovery sequences of the deep white matter in the supratentorial, subcortical and paraventricular (frontal, parietal, temporal and occipital) regions as well as on the splenium of the corpus callosum, the posterior limb of the internal capsule on both sides, the putamen and also the thalamic lobes. These lesions did not show restricted diffusion, contrast enhancement or significant mass effect (figure 1).

DIFFERENTIAL DIAGNOSIS

A variety of neurological complications can appear after HSCT. Besides metabolically driven neurological symptoms, HSCT recipients are at risk to present other potential complications, which may vary depending on the time since transplantation. In the first 30 days after transplantation, calcineurin inhibitor (CNI)-related complications are the most common iatrogenic cause. Because of thrombocytopenia, CNS haemorrhage can also occur. During the prolonged neutropenic period, graft

recipients have increased risk of developing bacterial, viral or fungal CNS infections. From the second month, the risks of bacterial infection decrease because of engraftment; however, the risk of opportunistic infections increases. Microangiopathy with CNS involvement either associated with GvHD or secondary to CNI's toxicity can appear during the first 6 months after transplantation. CNS relapse of the underlying haematological malignancy or secondary CNS tumour are considered as late neurological complications.⁸ In our case, CSF microbiological and virological results were negative. CNI serum levels were within the normal therapeutic range. We had no biological criteria of haemolysis pointing to ongoing microangiopathy. Brain MRI sequences showed no bleeding complication nor images suggesting post-transplantation lymphoproliferative disorder or fungal embolisation. Nor was evidence of CNS disease relapse found by flow cytometry analysis of the CSF. No hyponatraemia, hypercalcaemia, hypomagnesaemia or other major metabolic abnormalities were detected. Similarly, no severe renal or hepatic impairments were present.

MRI abnormalities shown above can be observed in patients with ciclosporin or methotrexate toxicity as well as following radiotherapy. Ciclosporin-induced white matter signal abnormalities are mainly localised in the occipital region and are reversible after the drug is withdrawn.¹⁰ Ciclosporin had been ceased in our patient before clinical signs and MRI abnormalities developed. Methotrexate-related changes typically develop within 10 days after methotrexate intrathecal treatment.¹¹ Our patient received this drug 1 year before the transplantation when no clinical signs or MRI abnormalities were present. A diagnosis of infectious encephalitis or the presence of a neoplastic process seem unlikely due to the absence of enhancement and to the reversibility of abnormalities following the corticosteroids treatment.¹²

TREATMENT

In addition to the already ongoing systemic immunosuppression, including methylprednisolone 2 mg/kg/day, tacrolimus and mycophenolate mofetil, the patient received empiric therapy with intrathecal methylprednisolone (40 mg) once a week for 3 weeks, resulting in rapid clinical improvement of the neurological symptoms within 24 hours from the first dose.

Figure 1 MRI shows multiple hyperintense lesions on T2 and fluid-attenuated inversion recovery of the deep white matter in frontal (arrows in B) as well as on the splenium of the corpus callosum (asterisk in C), the posterior limb of the internal capsule on both sides, the putamen and thalamic (arrows in C) and in cerebellar lobes (arrows in A).

Figure 2 (A–C) MRI done 1 month after intrathecal therapy with methylprednisolone shows the disappearance of the lesions.

OUTCOME AND FOLLOW-UP

MRI repeated 4 weeks after the diagnosis of CNS-GvHD revealed the disappearance of the white matter lesions (figure 2). The patient remained free of symptoms for about 3 months, when the symptoms recurred. Thereafter, the neurological disorder displayed a relapsing–remitting course, with periodic reappearance, every 5–6 weeks, of clinical manifestations very similar to the ones present at the time of initial diagnosis. At every symptom relapse, we administered one intrathecal dose of methylprednisolone (40mg) for a total of six doses with complete clinical response. New MRI studies failed to show any new white matter lesions. The CSF remained negative for signs of bacterial, viral or fungal infections and showed no evidence of leukaemia relapse. More than 4 months after the second HSCT, the patient developed neutropenic fever. Probable invasive pulmonary aspergillosis was diagnosed based on CT scan findings and two consecutive samples positive for serum galactomannan antigen. Intravenous voriconazole was initiated. Forty-eight hours later, the patient developed neurological symptoms with confusion and visual hallucinations. His symptoms were considered drug related due to supratherapeutic blood levels of voriconazole and tacrolimus. Voriconazole was stopped and replaced by amphotericin B. However, despite the normalisation of both voriconazole and tacrolimus levels, absence of significant metabolic abnormalities and radiological and biological responses to anti-fungal treatments, the patient failed to completely recover and presented transient impaired consciousness, psychomotor slowing persistence of fluctuating visual hallucinations and progressive paresis of lower limbs. The performance status in accordance with the ECOG score dropped to 4. A new MRI did not reveal any new white matter lesions displaying only the appearance of a hard convexities dura mater thickening with contrast enhancement, which could correspond to a subdural haematoma. We administered a new dose of intrathecal methylprednisolone to treat a possible relapse of CNS-GvHD without any significant improvement. The patient died suddenly 5 months after the diagnosis of CNS-GvHD and 6 months after the second HSCT. The comprehensive autopsy examination identified proven invasive bronchopulmonary aspergillosis as the cause of death and found no evidence of relapse of the underlying haematological malignancy. Interestingly, histological analysis did not reveal any lymphocytic infiltration in the CNS or in the skin, in accordance with the complete remission of acute GvHD.

DISCUSSION

CNS-GvHD remains a very rare entity after allogeneic HSCT that should be taken into consideration in the absence of evidence of other diseases representing alternative explanations for neurological symptoms.⁸ The pathophysiology of CNS-GvHD is pleomorphic, and underlying pathological processes include cerebrovascular disease,^{13 14} demyelinating disease of the CNS¹⁵ and immune-mediated encephalitis.^{6 13–20} Patients with biopsy-proven CNS-GvHD⁶ present with a variety of clinical symptoms including, seizures,³ confusion, progressive spasticity,²¹ irritability, proximal muscular lower extremity weakness,⁶ dysphagia, dysarthria, hemianopsia, aphasia, paresis,¹⁴ progressive clouding of consciousness and coma.²² Risk factors for CNS-GvHD are prior intense neurotoxic treatments by intrathecal chemotherapy and irradiation of the CNS, both present in our case. Other probable risk factors are disorders with increased risk for neurotoxicity including long-lasting diabetes and pre-existing neurological disorders.²³ In order to diagnose this entity, a number of criteria, reported by Openshaw in 2009,²⁴ can be used including occurrence concomitant with chronic GvHD affecting other organs, neurological signs of CNS involvement without other explanation, consistent brain MRI abnormalities, abnormal CSF studies (pleocytosis, elevated protein or IgG oligoclonal bands), pathological brain biopsy and response to immunosuppressive therapy.

All six criteria must be met to formally establish a diagnosis of CNS-GvHD. More recently, adapted criteria were reported,²³ these permit a diagnosis of ‘possible’ CNS-GvHD when the two first, mandatory criteria are fulfilled and a minimum of two out of the other four are present, as in the case of our patient. Although our patient had no evidence of chronic GvHD at the time of symptoms onset, he was still on systemic immunosuppression with high doses of steroids, tacrolimus and mycophenolate mofetil for the recent acute GvHD. Notably, the CNS has been recently identified as a potential target of acute GvHD,¹ and systemic chronic GvHD is not always present at the time of CNS manifestations.⁸ Neurological symptoms had no other clear explanation in our patient, and he met at least two CNS-GvHD facultative criteria including consistent brain MRI abnormalities, abnormal CSF studies with elevated protein with no pleocytosis or oligoclonal bands and very rapid response to local immunosuppressive therapy. Given the favourable response to treatment after the diagnosis of possible CNS-GvHD, we renounced to obtain a diagnostic brain biopsy.

The postmortem histological examination confirmed our expectations and failed to uncover any T cell infiltrates, highly likely as the result of treatment response with the resolution of brain lesions on MRI. Previous cases reported in the literature were most often treated by corticosteroid pulses⁶ or by intrathecal corticosteroid therapy⁵ with, in most cases, favourable response to the treatment. In progressive cases, an increase in systemic immunosuppressive therapy or rituximab treatment may be beneficial.²³ In our case, we observed a rapid response to intrathecal steroids, acting through their local anti-inflammatory effect and allowing us to avoid higher doses of systemic steroids. A better understanding of both clinical and pathological bases of CNS-GvHD is needed, and we believe that each experience, including possible CNS-GvHD cases, should be reported in order to improve our knowledge of this rare, although potentially devastating complication after allogeneic HSCT.

Learning points

- Central nervous system graft-versus-host disease (CNS-GvHD) is a rare neurological complication after allogeneic haematopoietic stem cell transplantation (HSCT), whose clinical presentation is pleomorphic and whose diagnosis is still challenging.
- In most cases, the symptoms resolve after corticosteroid pulse or, as in our case, by intrathecal corticosteroid therapy.
- In the case of neurological symptoms after allogeneic HSCT, other more frequent aetiologies must be excluded including metabolic, drug related, microangiopathic or infectious complications.
- Our case represents another rare example of CNS-GvHD, an entity still incompletely described. We believe that all cases should be documented in order to better define this entity.

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