Case report: Central nervous system involvement of human graft versus host disease

Report of 7 cases and a review of literature

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Abstract

Rationale: Central nervous system (CNS) involvement of graft versus host disease (GvHD) is a rare cause of CNS disorders after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Chronic CNS GvHD symptoms are heterogeneous and include cerebrovascular manifestations, demyelinating disease and immune-mediated encephalitis. CNS-Acute GvHD is not formally defined in literature.

Patients and diagnoses: We report 7 cases of CNS-GvHD among which two had histological-proven disease. We reviewed 32 additional cases of CNS GvHD published in literature since 1990. In this cohort, 34 patients were transplanted for hematologic malignancies, and 5 for non-malignant hematopoiesis disorders. Of these patients, 25 had a history of chronic GvHD and immunosuppressive treatment had been decreased or discontinued in 14 patients before neurological symptoms onset. Median neurological disorder onset was 385 days [7-7320]. Patients had stroke-like episodes (n=7), lacunar syndromes (n=3), multiple sclerosis-like presentations (n=7), acute demyelinating encephalomyelitis-like symptoms (n=4), encephalitis (n=14), mass syndrome (n=1), and 3 had non-specific symptoms. Median neurological symptoms onset was 81.5 days [7-1095] for patients without chronic GvHD history versus 549 days [11-7300] for patients with chronic GvHD (P=0.001). Patients with early involvement of CNS after allo-HSCT and no chronic GvHD symptoms were more frequently suffering from encephalitis (64% versus 28%, P=0.07), whereas stroke-like episodes and lacunar symptoms were less frequent (9% versus 36%, P=0.13).

Interventions: 34 patients with CNS-GvHD were treated with immunosuppressive therapy, including corticosteroids for 31 of them. Other treatments were intravenous immunoglobulin, plasmapheresis, cyclophosphamide, calcineurin inhibitors, mycophenolic acid, methotrexate and etoposide.

Outcomes: 27 patients achieved a response: 10 complete responses, 15 partial responses and 2 transient responses. Of 25 patients with sufficient follow-up, 7 were alive and 18 patients deceased after CNS-GvHD diagnosis.

Lessons: CNS-related GvHD is a rare cause of CNS disorders after allo-HSCT and is associated with a poor prognosis.

Keywords: allogeneic hematopoietic stem cell transplantation, graft versus host disease, neurological disorders

1. Introduction

Central nervous system (CNS) disorders are frequent complications after allogeneic hematopoietic stem cell transplantation (allo-HSCT) occurring in 9% to 14% of patients.[1] CNS involvements are mainly due to infectious complications, stroke, drug toxicity, Epstein–Barr virus (EBV)-related posttransplantation lympho-proliferations, and metabolic disorders.[1] Graft versus host disease (GvHD) is one of the most severe complications after allo-HSCT and occurs when donor T cells recognize and target allo-antigens on healthy recipient tissues. Acute GvHD mainly targets skin, gut, and liver, whereas chronic GvHD can affect most of the organs. However, CNS lesions during GvHD are rarely described and remains controversial.[1,2,3] Indeed, some cases were initially misclassified as CNS GvHD and were later diagnosed as EBV-induced lympho-proliferation through progress in immunohistological and metabolic techniques and the use of EBER probes.[1,2,3] Moreover, Santa Chiara[4] described JC virus-associated progressive multifocal leukoencephalopathy (PML) as a differential diagnosis of CNS GvHD. Indeed, white-matter lesions described by magnetic resonance imaging (MRI) in several CNS GvHD cases could also be described in PML.[5]
In 2010, neurological manifestations of chronic GvHD were described as a distinct entity in the Consensus Conference on Clinical Practice in chronic GvHD. The authors proposed the following mandatory criteria for CNS manifestations of chronic GvHD: occurrence of neurological symptoms with chronic GvHD affecting other organs and CNS involvement without other explanations (ie, without any infectious, vascular, drug toxicity, or metabolic etiologies). Other criteria were facultative: paraclinic investigations showing MRI or cerebrospinal fluid (CSF) abnormalities, pathological brain biopsy or postmortem examination revealing GvHD lesions, and response to immunosuppressive therapy. The diagnosis of chronic CNS GvHD can be made when both mandatory and 2 facultative criteria are met. The Consensus Conference delineated 3 types of chronic CNS GvHD: cerebrovascular disease, CNS demyelinating disease, and immune-mediated encephalitis. Cerebrovascular disease can affect medium and large vessels causing stroke-like episodes or involve CNS small vessels to induce vasculitis. CNS demyelination disease is described as a relapsing-remitting course resembling multiple sclerosis. Diagnosis is based on association of white-matter lesions with gadolinium enhancement in MRI and CSF abnormalities. Immune-mediated encephalitis is more difficult to diagnose and it is characterized by infiltration of immune cells or humoral factors on brain biopsy. Between 1990 and 2015, only 32 cases of CNS chronic GvHD were reported in literature, among which only 15 were histologically proven. Furthermore, there is no formal definition of acute CNS GvHD in the literature.

Herein, we report 7 cases of CNS GvHD, of which 2 had a biopsy or a postmortem examination. We further describe 32 reported cases of CNS GvHD following a systematic PubMed database literature review.

2. Methods

2.1. Patients

Between 1998 and 2016, 7 patients had been diagnosed with CNS GvHD at Saint-Louis Hospital (France). All patients had received an allo-HSCT and developed CNS symptoms associated with biological or imaging abnormalities, in the absence of other possible etiological causes for CNS abnormalities, such as infection, autoimmune disease, relapse, and lympho-proliferation. Histology was available in 2 cases.

We searched via PubMed in the National Center for Biotechnology Information (NCBI) database for relevant articles using the keywords “allo-HSCT” together with “central nervous system GvHD”. References of all selected articles were reviewed for research of additional case reports. We selected 32 patients, including 13 with histological analysis (brain biopsy, spine biopsy, or autopsy), from 20 articles published between 1990 and December 2016. Patients were selected if they had received an allo-HSCT for hematological pathology and had CNS abnormalities without another diagnosis (infectious diseases, autoimmune disease, hematologic malignancies relapse, or posttransplantation lymphoproliferative disorders). All patients signed a consent for registration and use of clinical and biological data (CNIL number 1238249).

2.2. Histology and FISH assay

Paraffin-embedded sections were stained with hematoxylin and eosin or periodic acid-Schiff stain, for histopathological analysis. FISH analyses were performed on 2 to 3 μm paraffin of sections biopsies. The paraffin-embedded tissue section slides were processed using the Histology FISH Accessory Kit (Dako, Denmark) according to the manufacturer’s recommendations. The slide was hybridized overnight with specific probes CEP X (FITC) and Y(SPO) (Vysis Abbott, according to manufacturer’s recommendations. Samples were analyzed with an AxiolImager; M1 epifluorescence microscope (Carl Zeiss, Hamburg, Germany). Images were captured with a ×63, ×40, or ×16 oil immersion objective and were analyzed by using the Isis software (METAsystems, Altlussheim, Germany) or with Fiji software (ImageJ 1.49m).

2.3. Statistical analysis

Data are described as median for quantitative variables, and frequency and percentage for qualitative variables. Percentages were compared using Fisher exact test. All statistical tests were 2-tailed with a significance level of 0.05. Analyses were performed with R v3.2.4. Data collection and analyses were conducted in accordance with French national guidelines.

3. Results

3.1. Case 1

The 1st patient was a 33-years-old male who received an allo-HSCT from an HLA-matched unrelated donor for advanced Fanconi anemia associated with myelodysplastic syndrome. He received a reduced intensity conditioning with a total body irradiation of 2 gray, cyclophosphamide and fludarabine. He received cyclosporine A (CsA) and mycophenolate mofetil (MMF) as GvHD prophylaxis. Acute skin GvHD (grade I from Glucksberg classification) was diagnosed at day 12 after transplantation. Five months after transplantation, he developed chronic GvHD with lichen planus-like changes of mouth mucosa. Eleven months after transplantation, the patient described 4-limb paresthesia associated with inferior limb motor deficit and abnormal deglutition. CSF analysis revealed a lymphocytic meningitis associated with motor and sensitive neuropathy confirmed with an electromyogram. The patient was treated with 3 courses of intravenous immunoglobulin infusion, corticosteroid therapy (1 mg/kg), and CsA (6 mg/kg), with a good response. CSF analysis showed remaining lymphocytic meningitis 4 and 10 months later. Between 2 and 4 years after transplantation, the patient developed 3 neurological outbreaks, partially remitting, with pyramidal syndrome, posterior cordonal track syndrome, and eventually memory disorders and cranial nerves deficits. Multiple CSF analysis revealed lymphocytic meningitis with CD4+ and CD8+ T cells, absence of bacterial, viral and fungal infection in direct examination, culture and PCR, and absence of autoantibodies in CSF and blood samples. Three years after transplantation, MRI showed a lepto-meningitis and a cervical centro-medullar pan-myelitis (Fig. 1A–F). One year later, MRI uncovered an atypical leucopathy affecting the fornix, the corpus callosum, and centrum semiovale (Fig. 1G–L). Electromyogram showed motor and sensitive neuromopathy. Ten courses of plasmapheresis failed to improve the patient’s medical condition. High-dose methylprednisolone (5 bolus followed by oral corticosteroid 1 mg/kg) stabilized symptoms. Finally, a pathological brain biopsy was performed and showed lympho-histiocytic vasculitis without necrosis, perivascular infiltration with CD3+ CD8+ T cells surrounding small and medium vessels, confirming...
the hypothesis of chronic GvHD of the CNS (Fig. 2). Fluorescent in situ hybridization with centromeric probes X and Y confirmed that perivascular infiltration was composed by donor cells of female origin (Fig. 3). The patient received a 5 bolus of high-dose methylprednisolone followed by oral corticosteroid (1 mg/kg) in combination with mycophenolic acid (30 mg/kg). Immunosuppressive drugs stopped disease progression and improved the patient’s quality of life (Table 1).

3.2. Case 2

The 2nd patient was a 62-years-old male who received an allo-HSCT from an HLA-mismatched unrelated donor (HLA-A mismatch) for a myelofibrosis after an essential thrombocytopenia. He was treated with ruxolitinib, which was discontinued before allo-HSCT (JAK ALLO study, clinical trial registration number NCT01795677). He received a myeloablative conditioning (MAC) regimen with fludarabine, melphalan, and antithymocyte globulins. He was then treated with cyclosporine A (CsA) and mycophenolate mofetil (MMF) as prophylaxis of GvHD. He developed skin, gut, and liver acute GvHD (grade III) at day 101 posttransplantation. He was treated with intravenous methylprednisolone at 2 mg/kg and reached complete remission at day 3 of treatment. At day 13, after a reduction in corticosteroid therapy, a new gut acute GvHD outbreak was successfully treated with tacrolimus and sirolimus. Five months

Figure 1. Head and medullary MRI show central nervous system lesions (case 1, Table 1). Head MRI showed a lepto-meningitis in sagittal cube-FLAIR sequences (A) and T1 FAT SAT sequences (B), with no vascular lesions in 3D TOF sequence (C). Medullary MRI revealed a centro-medullar pan-myelitis in sagittal T2 sequence (D), T1 FSE (E), and T1 FSE with gadolinium injection (F). After 1 year, a new head MRI uncovered an atypical leukoapathy affecting the fornix, the corpus callosum, and centrum semiovale in axial T2 FLAIR sequence (G) and persistence of a pan-myelitis in sagittal T1 FSE (H) and T2 sequence (I). MRI = magnetic resonance imaging; FAT SAT = fat saturation; FLAIR = fluid attenuated inversion recovery; FSE = fast spin echo; TOF = time of flight.
Figure 2. Brain biopsy reveals a cytotoxic T cells perivascular infiltration (case 1, Table 1). (A) Hematoxylin eosine staining reveals a lympho-histiocytic vasculitis with a perivascular infiltration around small and medium vessels in case 1 (black arrows, magnification ×400). (B) Periodic acid coloration shows that vasculitis is not associated with necrosis (black arrows, magnification ×400). Immunohistochemistry for CD3 (C) and granzyme B (D) confirmed that cellular infiltration is mainly composed of cytotoxic T cells.

Figure 3. Fluorescent in situ hybridization (FISH) on brain biopsy confirms infiltration by donor T cells showing perivascular infiltration by female cells from donor origin (case 1, Table 1). (A) FISH with centromeric probes for X (green) and Y (red), and DAPI (blue) was performed on paraffin-embedded brain biopsy in case 1. Mosaic of 2 adjacent acquisitions shows cellular infiltration surrounding vessels (DAPI signal in blue, magnification ×160). (B, C) Cellular infiltration is mainly composed of female cells from donor origin, revealed by a double green signal at magnifications ×400 and (D) ×630.
| Sex/age | Initial disease | Allo-HSCT characteristics | GvHD history | Clinical characteristics, imaging, and biological abnormalities | Immunosuppressive therapy | Follow-up |
|---------|----------------|--------------------------|--------------|---------------------------------------------------------------|---------------------------|-----------|
| 1M/33   | Fanconi disease | RIC MRD GvHD prophylaxis: CsA + MMF | Grade I acute GvHD: skin (D + 12); Severe chronic GvHD (D + 30): cutaneous and oral | Onset: D + 309 Clinic: Myelitis with motor and sensitive neuropathy and memory disorders MRI: Pan-myelitis and posterior表白-white matter injury EMG: Motor and sensitive neuropathy and muscular junction damage CSF: Lymphocytosis with majority of T cells, elevated protein (1.33 g/L) and oligoclonal bands Histology: lymphohistiocytic vasculitis without necrosis | Corticosteroids (10 bolus then 1 mg/kg), IV Ig (3 courses), plasmapheresis (10 courses), MMF (30 mg/kg) Partial response | Quality of life improvement |
|         |                |                          |              | CSF: Lymphocytosis with majority of T cells, elevated protein (1.33 g/L) and oligoclonal bands Histology: lymphohistiocytic vasculitis without necrosis | Alive 37 m after CNS symptoms |
| 2M/61   | MPN            | MAC Mismatch unrelated donor GvHD prophylaxis: CsA + MMF | Grade III acute GvHD: skin, GIT and liver (D + 103); No chronic GvHD | Onset: D + 152 Clinic: Encephalitis MRI: Normal EEG: Diffuse brain suffering and frontal peak-waves discharges CSF: Lymphocytosis and elevated protein (1.6 g/L) Histology: Diffuse lymphocyte T infiltrate with small perivascular predominance and diffuse gliosis | Corticosteroids (1 mg/kg) No response | Deceased 17 d after CNS symptoms |
| 3F/68   | MPN            | MAC MUD GvHD prophylaxis: CsA + MMF | Grade III acute GvHD: skin, GIT and liver (D + 7); No chronic GvHD | Onset: D + 378 Clinic: cerebellar syndrome, cranial nerves deficits and atypical poly-radiculoneuropathy MRI: Normal EMG: Poly-radiculoneuromyopathy CSF: Elevated protein (4.14 g/L) and no pleocytosis | Corticosteroids (2 mg/kg) No response | Deceased 30. m after CNS symptoms |
| 4F/29   | Fanconi disease | RIC Cord blood GvHD prophylaxis: CsA + MMF | No acute GvHD; Severe chronic GvHD; Cutaneous and oral lichen and liver GvHD | Onset: D + 9 Clinic: Encephalitis MRI: Hyper T2 focal lesion of the left hemisphere EEG: Encephalitis CSF: Lymphocytosis (100% of donor lymphocytes) | Corticosteroids (3 bolus then 1 mg/kg), plasmapheresis (5 courses), IV Ig (6 courses) Partial response | Deceased 5 d after CNS symptoms |
| 5M/50   | MPN            | MAC MUD GvHD prophylaxis: CsA + MMF | No acute GvHD; Moderate chronic GvHD (D + 250): polynymylitis | Onset: D + 2590 Clinic: transient and focal deficits (right hemiparesis and paresis) MRI: T2 hyper-signal in the left hemisphere EEG: Normal CSF: Elevated protein (0.63 g/L) and no pleocytosis | Ciclosporin A (6 mg/kg) Complete response | Alive 8, 3 mo after CNS symptoms |
| 6F/16   | AML            | MAC Mismatch unrelated donor GvHD prophylaxis: CsA + MTX | Grade I acute GvHD (D + 110): skin; No chronic GvHD | Onset: D + 255 Clinic: progressive encephalitis with extra-pyramidal syndrome MRI: Periventricular and posterior leuко-encephalopathy associated with hemispheric cerebellar lesions with contrast enhancement EEG: Global and diffuse slowing – EMG: Normal CSF: Normal | Corticosteroid (1 mg/kg) No response | Deceased 4, 2 mo after CNS symptoms |
| 7M/36   | CML            | MAC MUD GvHD prophylaxis: CsA + MTX | Grade I acute GvHD (D + 59): skin; Severe chronic GvHD: cutaneous lichen, oral erosion, and faciitis | Onset: D + 119 Clinic: cerebellar and vestibular syndromes, focal deficits (left hemiparesis and hypoaesthesia), and cranial nerves deficits MRI: left internal capsule and thalamo-thalamic lacunar infarct compatible with cerebral vasculopathy associated with cerebellar peduncle focal lesion and right mesencephalic focal lesion Angiography: normal AEP: Unrelated cisternitis CSF: Elevated protein (0.63 g/L) with IgY polyclonal | Corticosteroids (1 mg/kg) Partial response then secondary aggravation | Deceased 29, 8 mo after CNS symptoms |

AEP = acoustic evoked potential, AML = acute myelogenous leukemia, CNS = central nervous system, CsA = ciclosporine A, CSF = cerebrospinal fluid, EEG = electroencephalogram, EMG = electromyogram, GvHD = graft versus host disease, HSCT = hematopoietic stem cell transplantation, IV Ig = intravenous immunoglobulin, MAC = myeloablative conditioning, MMF = mycophenolate mofetil, MPN = myeloproliferative neoplasms, MRD = matched-related donor, MTX = methotrexate, MUD = matched-unrelated donor, RIC = reduced intensity conditioning.
after transplantation, the patient exhibited confusion with a rapid progression to coma. Electroencephalogram revealed an encephalopathy. CSF analysis showed elevated protein (1.6 g/L) and lymphocytosis. CNS screening by both MRI and scanner were normal. No evidence for infection, metabolic, or autoimmune diseases were found. The patient’s neurological state did not improve after large spectrum antibiotic, antiviral, and antiepileptic treatment. Finally, due to difficulty with swallowing, he was transferred to an intensive care unit for tracheal intubation. He developed a Pseudomonas aeruginosa pneumonia and died of acute respiratory distress syndrome and septic shock. Brain postmortem examination uncovered a perivascular T cell infiltrate with diffuse gliosis and was considered as a GVHD of CNS (Table 1).

3.3. Case 3

The 3rd patient was a 65-years-old woman who received an allo-HSCT from an unrelated HLA-matched donor for a myeloproliferative neoplasm with JAK2 V617F and SRSF2 mutations. She received ruxolitinib, which was discontinued before allo-HSCT. She had a MAC regimen with fludarabine and melphalan. She was treated with CsA and MMF as GVHD prophylaxis. She developed skin, gut, and liver acute GVHD (grade III according Glucksberg classification) at day 7 after transplantation. At day 9, she presented an encephalitis confirmed with an electroencephalogram. MRI showed a hyper-T2 focal lesion of the left hemisphere, and CSF analysis revealed lymphocytosis with 100% of cells from donor origin confirmed with molecular chimerism. CSF and blood analysis showed absence of bacterial, viral and fungal infection by direct examination, and culture and PCR. She was treated with methylprednisolone (2 mg/kg) without response. Despite treatment, the patient’s neurological symptoms worsened, resulting in coma. Eventually, she developed pneumonia and multivisceral failures and deceased at day 14 (Table 1). The chronology of CNS alteration, the donor lymphocytosis in CSF, and the absence of toxic or infectious diagnosis suggested that the patient developed acute GVHD-related encephalitis.

3.4. Others cases

Four other patients with GVHD-related CNS involvement were identified during this period. Patients’ characteristics are summarized in Table 1. Clinical presentation was polymorph but always characterized by neurological symptoms associated with CNS lesions. Most patients had MIR or CSF abnormalities, with a constant cerebellum involvement. Case 4 and 5 had multiple sclerosis-like presentations with a remission-remittent course. Case 6 developed progressive encephalitis. Case 7 had a stroke-like presentation. Cases 4, 6, and 7 were treated with corticosteroids, whereas case 5 was treated with cyclosporin A. Case 4 received additional courses of plasmapheresis and intravenous immunoglobulin. Only 2 patients are still alive at the end of follow-up and only 1 patient reached complete response with immunosuppressive drugs.

4. Discussion and literature review

Between 1990 and December 2016, 7 cases of CNS GVHD (Table 1) were diagnosed in Saint-Louis Hospital, France, and 32 cases were reported in literature (Table 2).

4.1. Patients’ characteristics

In our cohort and in literature, sex ratio was 1.3 and median age at HSCT was 35 years old (0.67–68). Allogeneic stem cell transplantations were performed for acute myelogenous leukemia (n = 9), myelodysplastic syndrome (n = 1), acute lymphoblastic leukemia (n = 4), myeloproliferative neoplasm (n = 3), chronic myelogenous leukemia (n = 6), chronic myelomonocytic leukemia (n = 1), lymphoma (n = 9), chronic lymphoid leukemia (n = 1), constitutional bone marrow failure (n = 3), aplastic anemia (n = 2). Fourteen patients received MAC, 7 had reduced intensity conditioning, 7 had sequential conditioning, 1 patient did not have any conditioning, and 1 had sequential conditioning.

Donors were matched-related donor (n = 14), mismatch-unrelated donor (n = 3), cord blood (n = 2), and haplo-identical T depleted cells (n = 1). Acute GVHD history was reported for 26 cases, among them, 21 patients had at least 1 episode of acute GVHD. Moreover, chronic GVHD episodes were reported before or during neurological symptoms in 25 patients (10, 12, 15, 17, 18, 22, 23) whereas 11 patients had no other cGVHD symptoms than those attributed to CNS GVHD (10, 16, 19, 22, 23) (Table 3).

4.2. Clinical features and histological results

Among the 39 patients with CNS GVHD, median symptoms onset was 385 days after HSCT (7–7230). In our cohort and in literature, only immunosuppression modulations were found as triggering factor. Fourteen patients developed their neurological symptoms after decreased (cases 2, 5, and 6, and 3 patients from the literature) or discontinuation (8 patients from the literature) of immunosuppressive therapy after a median delay of 124.5 days (14–549). Interestingly, 1 patient received donor lymphocyte infusion for malignancy relapse and developed neurological symptoms 3 days later.

Thirteen patients (cases 1, 3, 4, and 7, and 9 patients from the literature) were already treated with immunosuppressive drugs at neurological symptoms onset. Clinical features were heterogeneous: 7 patients developed stroke-like episodes (cases 7 and 6 patients from the literature), 3 patients developed lacunar syndrome, whereas 11 patients had no other CNS lesions (Table 3). Cases 2, 3, and 6 presented both vasculitis and demyelinating lesions, 1 patient had a mass syndrome, and 3 had nonspecific clinical presentations.

Histological data were available for 17 patients. According to the Consensus Conference definition of CNS GVHD histological classification, 6 neurological vasculitis was founded in 7 biopsies (case 1 and 6 patients from the literature) (10, 12, 13) demyelinating lesions in 5 biopsies (7, 12, 13) (3 patients presented both vasculitis and demyelinating lesions) (12, 13) immune-mediated encephalitis in 5 biopsies (case 2 and 6 patients from the literature) (5, 8, 11, 14) and 1 patient had noncaseating granuloma.

4.3. CNS GVHD diagnosis

In the Consensus Conference, occurrence of chronic GVHD affecting other organs is one of mandatory criteria to diagnose chronic CNS GVHD. [6] No diagnosis criteria for acute GVHD were defined in literature. In our cohort and in previously
| Patient | Age/sex | Initial disease and allo-HSCT characteristics | GvHD history | Clinical characteristics, imaging, and biological abnormalities | Histology | Immunosuppressive therapy | Outcome |
|---------|---------|-----------------------------------------------|--------------|---------------------------------------------------------------|----------|--------------------------|---------|
| Marosi (1990) | 32/M | CML | Chronic GvHD | Onset: 240 d after HSCT; Clin: encephalopathy, dysphagia, dysarthria; CSF: periventricular, elevated protein; MRI: cortical, ventricular dilatation | Perivascular infiltration of CNS; Diffuse infiltration of white matter with CD3 lymphocytes; Diffuse CD3 lymphocytes infiltration and gliosis | NA | Decayed |
| Iwasaki (1993) | 9/M | Posthepatitis aplastic anemia | Chronic GvHD | Onset: 240 d after HSCT; Clin: encephalopathy, dysphagia, dysarthria; CSF: normal | Perivascular infiltration of CNS; Diffuse infiltration of white matter with CD3 lymphocytes; Diffuse CD3 lymphocytes infiltration and gliosis | NA | Decayed |
| Provan et al. (1996) | 14/F | Lymphoblastic lymphoma | Grade III acute GvHD | Onset: 71 d after HSCT; Clin: encephalopathy, dysphagia, dysarthria; CSF: normal | Perivascular infiltration of CNS; Diffuse infiltration of white matter with CD3 lymphocytes; Diffuse CD3 lymphocytes infiltration and gliosis | NA | Decayed |
| Padovan et al. (1999) | 35/F | ALL | Acute and chronic GvHD | Onset: 18 mo after HSCT; Clin: encephalopathy, dysphagia, dysarthria; CSF: normal | Perivascular infiltration of CNS; Diffuse infiltration of white matter with CD3 lymphocytes; Diffuse CD3 lymphocytes infiltration and gliosis | NA | Decayed |
| Provan et al. (1996) | 14/F | Lymphoblastic lymphoma | Grade III acute GvHD | Onset: 71 d after HSCT; Clin: encephalopathy, dysphagia, dysarthria; CSF: normal | Perivascular infiltration of CNS; Diffuse infiltration of white matter with CD3 lymphocytes; Diffuse CD3 lymphocytes infiltration and gliosis | NA | Decayed |
Table 2 (continued).

| Patient | Age/sex | Initial disease and allo-HSCT characteristics | GvHD history | Clinical characteristics, imaging, and biological abnormalities | Histology | Immunosuppressive therapy | Outcome |
|---------|---------|-----------------------------------------------|--------------|---------------------------------------------------------------|-----------|--------------------------|---------|
| Kew (2007) | 41/M | Follicular lymphoma, MAC | Chronic GvHD | Onset: 18 mo after HSCT; GvHD: progressive left hemiparesis; CSF: normal | Focal infiltration of lymphohistiocytic inflammatory cell and necrosing granuloma with perivascular predominance (H. CO3+ T cells) | Corticosteroids and ciclosporin | Clinical and MRI PR |
| Matsuo (2009) | 32/F | MDS, MAC | Chronic GvHD | Onset: 7 mo after HSCT; bilateral papular exema with almost blindness, weakness of lower limbs, urinary retention, evolution by remission and relapse; CSF: normal; MRI: multiple white matter lesions mainly in internal capsule, thalamus and thalamus spine, evocative of multiple sclerosis | No | Corticosteroids (bolus then 0.5 mg/kg) and ciclosporin | Clinical and MRI PR Alive 2 y after HSCT |
| Saad (2009) | 56/M | Non-Hodgkin lymphoma | Severe chronic GvHD | Onset: 3 y after HSCT; dizziness, tinnitus, vertigo, and proximal weakness; MRI: large lesion of the corpus callosum; CSF: normal | Perivascular inflammation and scattered CO3+CD8+ T cells associated with microglia activation and macrophages in brain parenchyma | Corticosteroids and myophosphatidic acid | Progression | Deceased 2 mo later |
| Yamamoto (2009) | 40/F | Follicular lymphoma | Acute GvHD | Onset: 7 d after HSCT; encephalitis and seizures; CSF: elevated protein (6.75 g/L), pleiocytosis (96.8% of donor cells) | MR: large mass of right parietal lobe | No | Corticosteroids (bolus then 0.5 mg/kg) and ciclosporin | Alive 2 mo after HSCT |
| Sostak (2010) | 35/M | CML | Acute and chronic GvHD | Onset: 4 y after HSCT; cortical/subcortical acute ischaemic lesions in peri-insular region, left frontal and parietal lobe; EEG: temporal slowing without epileptic discharges | T cells | Corticosteroids (3 bolus) followed by etoposide (50 mg/m2) | CR |
| 28/F | AML, MAC MUD | Chronic GvHD | Onset: 2 y after HSCT; GvHD: progressive depression, cognitive deficits, cortical blindness, seizure, ataxia, tetraparesis; CSF: elevated protein, oligoclonal bands | Cerebral vasculitis with infiltration of donor lympho-mononuclear cells (FRH IV) | Corticosteroids (5 bolus then 1 mg/kg) and cyclophosphamide (1 bolus then 100 mg/week) | CR |
| 8 mo/M | SCD No conditioning | Chronic GvHD | Onset: 20 y after HSCT; homopaire, ataxia, cortical blindness and deafness; MRI: elevated protein, pleocytosis; MRI: multiple focal ischaemic lesions and hemorrhage | Central ganglios with argument for infection | Corticosteroids and cyclophosphamide (4 bolus) | PR | Deceased 1 y later of severe sepsis |
| 33/M | CLL, MUD | Chronic GvHD | Onset: 2 y after HSCT; ataxia, cortical blindness, spinal tetraparesis, acute pseudo-bulbar syndrome; CSF: elevated protein, pleoocytosis; intrathecal IgG synthesis | Cerebral and meningeal angiitis | Corticosteroids (bolus then 1.5 mg/kg) and cyclophosphamide (1 bolus) | Small improvement | Decayed | |
| 57/M | OMML, RIC MUD | No | Onset: 4 weeks after HSCT; recurrent myelitis with mild paraparesis, urinary difficulty; CSF: elevated protein; MRI: multiple white matter lesion of spinal cord without cerebral anomalies | No | Corticosteroids (5 bolus then 1 mg/kg) and cyclophosphamide (1 bolus) | CR but relapse of myelitis 1.5 y later. Treatment by cyclophosphamide with PR |
| 65/M | AML, Sequential conditioning | No | Onset: 3 y after HSCT; recurrent myelitis with mild paraparesis and lower limbs hypoeesthesia; CSF: elevated protein (0.55 g/L) and oligoclonal bands; MRI: multiple white matter lesion of spinal cord without cerebral anomalies | No | Corticosteroids (5 bolus) | CR but relapse of myelitis 1 mo after Treatment by corticosteroids with CR |
| Harvey (2014) | 63/M | CLL and Richter syndrome, RIC MUD | Acute GvHD | Onset: 10 d after HSCT; GvHD: dizziness, blurred vision, vestibular syndrome and mild cognitive impairment; CSF: elevated protein (1.14 g/L) MRI: multifocal subcortical and juxta-cortical white matter lesions | No | No | Clinical and MRI CR Alive 1 y after |
| Rathore (2015) | 7/M | Idiopathic aplastic anemia | Chronic GvHD | Onset: 15 mo after HSCT; GvHD: depression and seizure; CSF: normal; MRI: bilateral uncus lesions; EEG: slowing background and one epileptic focus | No | No | Clinical PR |

ADAM = acute demyelinating encephalomyelitis, ALL = acute lymphoblastic leukemia, AML = acute myelogenous leukemia, CLL = chronic lymphocytic leukemia, CML = chronic myelogenous leukemia, CNS = central nervous system, CR = complete response, CSF = cerebrospinal fluid, DLI = donor lymphocyte infusion, EMG = electromyogram, EEG = electroencephalogram, GvHD = graft versus host disease, HLH = hemophagocytic lymphohistiocytosis, HSCT = hematopoietic stem cell transplantation, MAC = myeloablative conditioning, MDS = myelodysplastic syndrome, MPN = myeloproliferative neoplasms, MRD = matched related donor, MRI = magnetic resonance imaging, MUD = matched unrelated donor, NA = not available, PR = partial response, RIC = reduced intensity conditioning.
MUD = myelodysplastic syndrome, MPN = myeloproliferative neoplasms, GvHD = graft versus host disease, CNS = central nervous system.

Frequent in the group of patients without chronic GvHD: 7/11 clinical presentations seem to be different. Encephalitis was more frequent: 1/11 (9%) versus 9/25 patients (36%), \( P = .07 \). Conversely, stroke-like episodes and lacunar syndromes were less frequent: 1/11 (9%) versus 9/25 patients (36%), \( P = .13 \). This suggests that early encephalitis after allo-HSCT may be a clinical presentation of CNS involvement during acute GvHD (Table 4). However, due to the rarity of this complication, we were not able to identify in our series or in literature, patients at risk to develop CNS GvHD.

Consensus conference distinguishes 3 presentations of GvHD: cerebrovascular disease, demyelinating disease, and immune-mediated encephalitis.\(^{[6]}\) This study highlights the link between clinical presentation and histological lesions. Large and medium vessels vasculitis can be revealed by stroke-like episode or lacunar syndrome. Demyelinating disease can arise as acute demyelinating encephalomyelitis or as multiple sclerosis-like episodes. Both of these histological forms can be diagnosed by the association of specific clinical, biological, and imaging evidences (Table 2). However, histological sampling and analysis remains the only way to formally distinguish small vessel vasculitis and immune-mediated encephalitis, as both lesions might induce encephalitis symptoms (Table 2). Moreover, the biopsy may also help to exclude differential diagnoses such as EBV-related lymphoproliferative disorders. Interestingly, we were able to confirm in 2 cases that immune infiltration was of donor origin. In case of sex mismatch, centromeric XY FISH assay is an easy way to determine the origin of infiltrating immune cells. Molecular chimerism can also be used when FISH cannot be performed and can also be applied to lymphocytes detected in CSF.

### 4.4. Treatment and outcome

Of 35 patients with available data, 34\(^{[5,7,9,10,12–17,19–23,25]}\) received immunosuppressive therapy: 31 patients had been treated with corticosteroid,\(^{[5,7,9,10,12–14,16–17,19–25]}\) in combination with at least another immunosuppressive drug in 19 patients.\(^{[7,9,12–14,17,19–23,25]}\) Other immunosuppressive treatments included intravenous immunoglobulin (IV Ig) \( (n = 6) \), plasmapheresis \( (n = 3) \), cyclophosphamide \( (n = 3) \), anticalcineurin inhibitors \( (n = 4) \), mycophenolate mofetil \( (n = 3) \), and methotrexate \( (n = 1) \), and 1 patient was also treated with etoposide because of secondary hemophagocytic lymphohistiocytosis\(^{[20]}\) (Table 5).

With immunosuppressive therapy, 10 patients reached complete response,\(^{[5,7,9,10,13,16,18,19,22,24]}\) 15 had a partial response,\(^{[5,7,9,10,13,15,17,19,21,23]}\) and 2 had a transient response\(^{[5,23]}\). Disease remains stable for 2 patients\(^{[5,23]}\) and 7 patients had progressive disease.\(^{[12,14,20]}\) Data were not available for 3 patients (Table 5).

At last follow-up, 7 patients (18%) were alive\(^{[5,7,16–18]}\) and 18 patients (46%) were deceased\(^{[5,7,8,11–14,20,21]}\). Data were not available for 14 patients (Table 5).

### 4.5. Pathophysiology of CNS GvHD

CNS involvement of GvHD is controversial, especially since clinical manifestations of CNS GvHD are heterogeneous: cerebrovascular manifestations,\(^{[12,15,24,26]}\) encephalitis\(^{[5,8,9,11,14,20–23]}\) or myelitis.\(^{[7,16–19]}\) Interestingly, some human cases were histologically proven and revealed frequent T cell infiltration, supporting the hypothesis of an immune-mediated CNS disease after allo-HSCT. Furthermore, several animal models, including primate models, bring some evidence of CNS targeting by donor T cells during GvHD. In rat disease models, it has been demonstrated that GvHD was associated with diminished cerebellar RNA synthesis and transcription, and with ectopic protein and change in protein expression profile compared to syngeneic controls.\(^{[27]}\) In addition, immunosuppressive treatment of GvHD was able to restore cerebellar RNA synthesis and protein expression.\(^{[28]}\) In rat models of allo-HSCT, expression of c-Fos, a neural activation marker,

#### Table 3

Clinical feature of 39 patients with possible CNS GvHD.

| Feature | Patients, n, % |
|---------|----------------|
| Sex     |                |
| M       | 22 (56%)       |
| F       | 17 (44%)       |
| Age, y, median (range) | 35 (0.67–68) |
| Initial disease |                |
| Constitutional bone marrow failure | 3 (8%) |
| MPN    | 3 (8%)         |
| CML    | 6 (14%)        |
| CMML   | 1 (3%)         |
| MDS    | 1 (3%)         |
| AML    | 9 (23%)        |
| ALL    | 4 (10%)        |
| Lymphoma | 9 (23%)       |
| CLL    | 1 (3%)         |
| Aplastic anemia | 2 (5%)   |
| Conditioning regimen |            |
| MAC    | 14 (36%)       |
| RIC    | 7 (18%)        |
| Other  | 2 (5%)         |
| NA     | 16 (41%)       |
| Donor characteristics |        |
| MRD    | 14 (36%)       |
| MUD    | 8 (21%)        |
| Mismatch unrelated donor | 3 (8%) |
| Other† | 3 (8%)         |
| NA     | 11 (28%)       |
| Acute GvHD history |            |
| Yes    | 21 (54%)       |
| No     | 5 (13%)        |
| NA     | 13 (33%)       |
| Chronic GvHD History |        |
| Yes    | 25 (64%)       |
| No     | 11 (28%)       |
| NA     | 3 (8%)         |

AML = acute myelogenous leukemia, ALL = acute lymphoblastic leukemia, CML = chronic myelogenous leukemia, CMML = chronic myelomonocytic leukemia, CNS = central nervous system, GvHD = graft versus host disease, MAC = myeloablative conditioning, MDS = myelodysplastic syndrome, MPN = myeloproliferative neoplasms, RIC = matched related donor, MUD = matched unrelated donor, NA = not available, RIC = reduced intensity conditioning.

* No conditioning (\( n = 1 \)) and sequential conditioning (\( n = 1 \)).
† Card blood (\( n = 2 \)) and haplo-identical T depleted donor (\( n = 1 \)).
increased in piriform, occipital, visual, and prefrontal neurons 3 days after GvHD onset. In murine models, allogeneic HSCT was also associated with a donor T cells-mediated alloimmune response in brain. Compared to syngeneic control, brain necropsies of transplanted mice revealed T cell infiltration, microglia activation, and angiitis-like abnormalities. In rats, T cell infiltration of CNS was associated with increased expression of class I and class II major histocompatibility antigens. In mouse models, cerebral endothelial adhesion molecule expression was modified: ICAM-1 and VCAM-I expression were upregulated and could contribute to T cell infiltration in neural tissues. Recently, it has been demonstrated in murine and primate models with acute GvHD, that neurological symptoms and behavior modifications were caused by alloreactive activated donor CD8+ T cells. T cell infiltration was prevented by immune prophylaxis. Few data are available about human CNS GvHD pathophysiology. Infiltration of T cells was described in 8 biopsies (case 1 and 2, and 6 patients from literature). Consistently with data obtained in animal models, this infiltration was mainly composed of CD3+CD8+ cytotoxic T cells in 3 brain biopsies (case 1 and 2 biopsies from literature) whereas only 1 showed CD3+/CD4+ cells infiltration. A recent paper demonstrated that this infiltration led to inflammatory cytokine production. IL-6 production together with indoleamine 2,3 deoxygenase upregulation played a central role in CNS GvHD pathophysiolog. Infiltration let to inflammatory cytokine production. IL-6 production together with indoleamine 2,3 deoxygenase upregulation played a central role in CNS GvHD pathophysiolog.

To conclude, despite the paucity of human CNS GvHD described in the literature, analysis of CNS clinical biopsies and necropsies suggests that the CNS may be a target of GvHD. CNS GvHD is a rare and severe complication after allo-HSCT that can be difficult to diagnose. MRI and CSF analysis should be performed to eliminate all other etiology of CNS disorders, especially infections, drug toxicity, or relapses of underlying malignancies. Although brain biopsy may be difficult to achieve, histological analysis is useful to eliminate other diagnoses. CNS GvHD treatment is not consensual and mainly based on immunosuppressive drugs, especially high-dose corticosteroids. However, despite a frequent response to treatment, CNS GvHD remains associated with a dismal prognosis.

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### Table 4

| Clinical features | No chronic GvHD history (n = 11) | Chronic GvHD history (n = 25) | P |
|------------------|---------------------------------|-----------------------------|---|
| Stroke-like episode and lacunar syndrome | 1 (9%) | 9 (36%) | .13 |
| ADEM and multiple sclerosis-like presentation | 3 (27%) | 5 (20%) | 1 |
| Encephalitis | 7 (64%) | 7 (28%) | .07 |
| Other† | 0 | 1 (4%) | – |
| NA | 0 | 3 (12%) | – |

Histological features

- Vasculitis: 1
- Demyelinating lesions: –
- Vasculitis and demyelinating lesions: –
- Immune mediated encephalitis | 1 | 6 |
- Other† NA | 10 | 11 |

ADEM = acute demyelinating encephalomyelitis. CNS = central nervous system. GvHD = graft versus host disease. NA = not available.

†Mass syndrome.

### Table 5

| Feature | Patients, n, % |
|---------|---------------|
| Immunosuppressive therapy | |
| Yes | 34 (87%) |
| No | 1 (3%) |
| NA | 4 (10%) |
| Immunosuppressive treatment details | |
| Corticosteroids | 31 (80%) |
| IV Ig | 6 (15%) |
| Plasmapheresis | 3 (8%) |
| Cyclophosphamide | 9 (23%) |
| Other‡ | 6 (15%) |
| Treatment response | |
| CR | 10 (26%) |
| PR | 15 (39%) |
| Toxicity | 2 (5%) |
| Disease stability | 2 (5%) |
| Disease progression | 7 (18%) |
| NA | 3 (8%) |
| Last follow-up | |
| Alive | 7 (18%) |
| Deceased | 18 (46%) |
| NA | 14 (36%) |

CNS = central nervous system, CR = complete response, GvHD = graft versus host disease, IV Ig = intravenous immunoglobulin, MMF = mycophenolate mofetil, NA = not available, PR = partial response.

‡Tacrolimus (n = 1), cyclosporine A (n = 2), MMF (n = 2), cyclosporine A and MMF (1) methotrexate (n = 1), and etoposide (n = 1).
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