Clinical Case Report

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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 concerns 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.

Abbreviations: CNS = central nervous system, CSF = cerebrospinal fluid, GvHD = graft versus host disease, allo-HSCT = allogeneic hematopoietic stem cell transplantation, MAC = myeloablative conditioning, MRI = magnetic resonance imaging.

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

1. Introduction

Central nervous system (CNS) disorders are frequent complications after allogenic 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.[2–4] Indeed, some cases were initially misclassified as CNS GvHD and were later diagnosed as EBV-induced lympho-proliferation through progress in immunochemistry analytical techniques and the use of EBER probes.[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]

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In 2010, neurological manifestations of chronic GvHD were described as a distinct entity in the Consensus Conference on Clinical Practice in chronic GvHD.[6] 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.[6] The Consensus Conference delineated 3 types of chronic CNS GvHD: cerebrovascular disease, CNS demyelinating disease, and immune-mediated encephalitis.[6] 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 factor on brain biopsy.[6] 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 15[5,7–14] with histological analysis (brain biopsy, spine biopsy, or autopsy), from 20 articles published between 1990 and December 2016.[5,7–23] 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 AxioImager; 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 analyzes 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–I). Electroneuromyogram showed motor and sensitive neuronopathy. 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

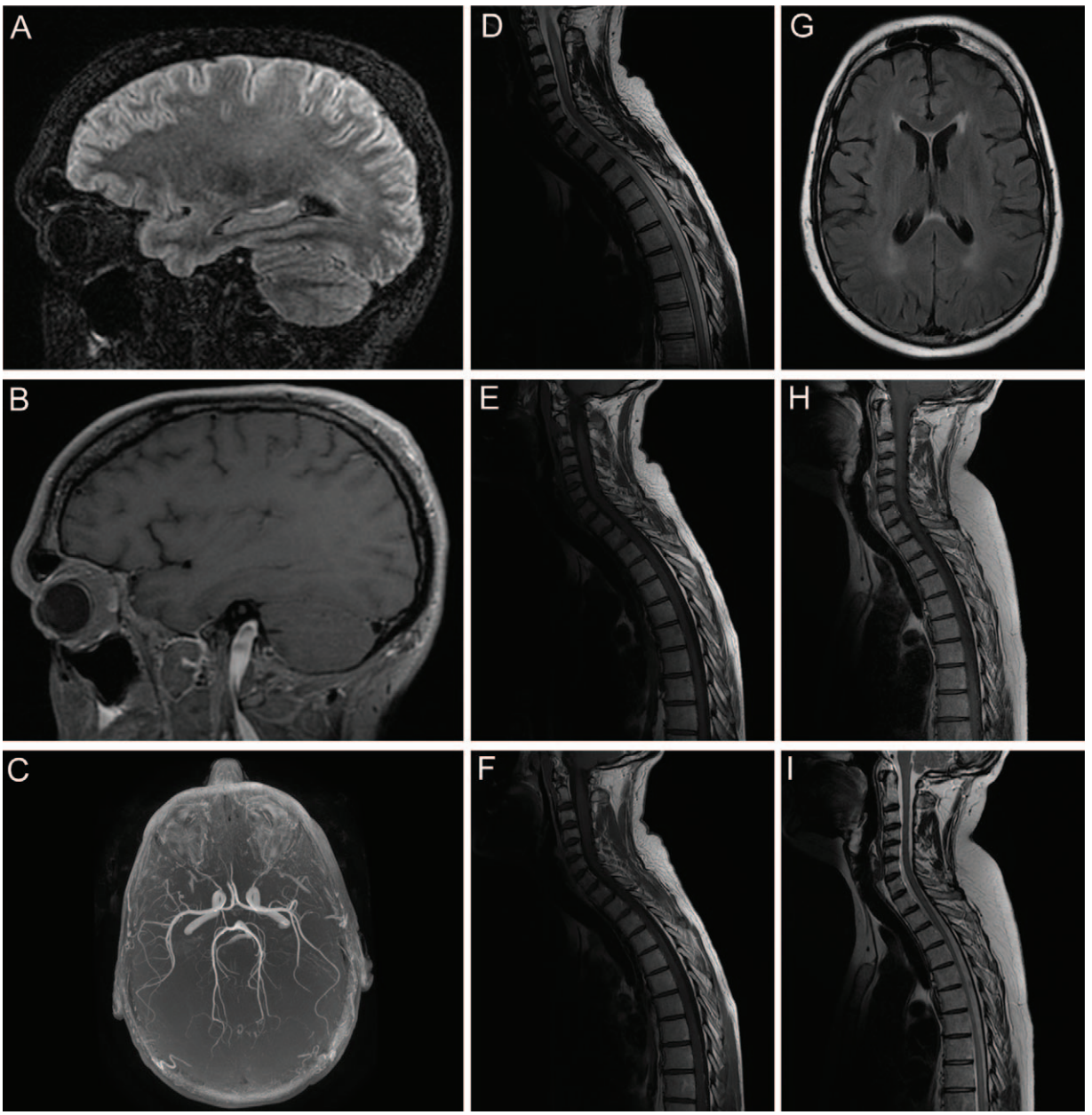

Figure 1. Head and medullary MRI show central nervous system lesions (case 1, Table 1). Head MRI showed a lepto-meningitis in sagittal cube-FLAIR sequences (A) and T1 FAT SAT sequences (B), with no vascular lesions in 3D TOF sequence (C). Medullary MRI revealed a centro-medullar pan-myelitis in sagittal T2 sequence (D), T1 FSE (E), and T1 FSE with gadolinium injection (F). After 1 year, a new head MRI uncovered an atypical leucopathy 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.

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 thrombocythemia. 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

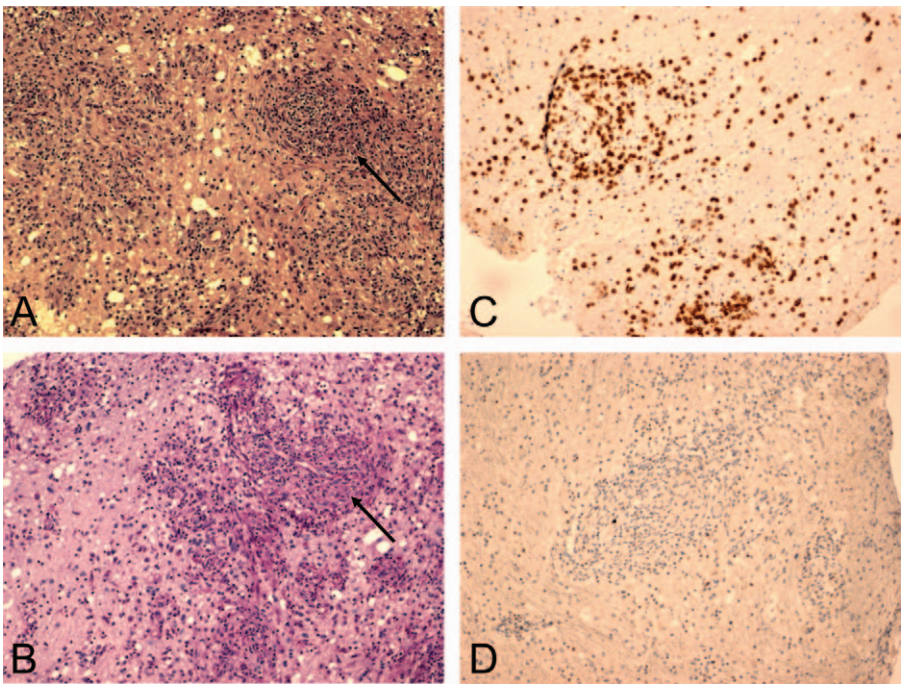

Figure 2. Brain biopsy reveals a cytotoxic T cells perivascular infiltration (case 1, Table 1). (A) Hematoxylin eosine staining reveals a lympho-histiocytic vasculitis with a perivascular infiltration around small and medium vessels in case 1 (black arrows, magnification ×400). (B) Periodic acid coloration 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.

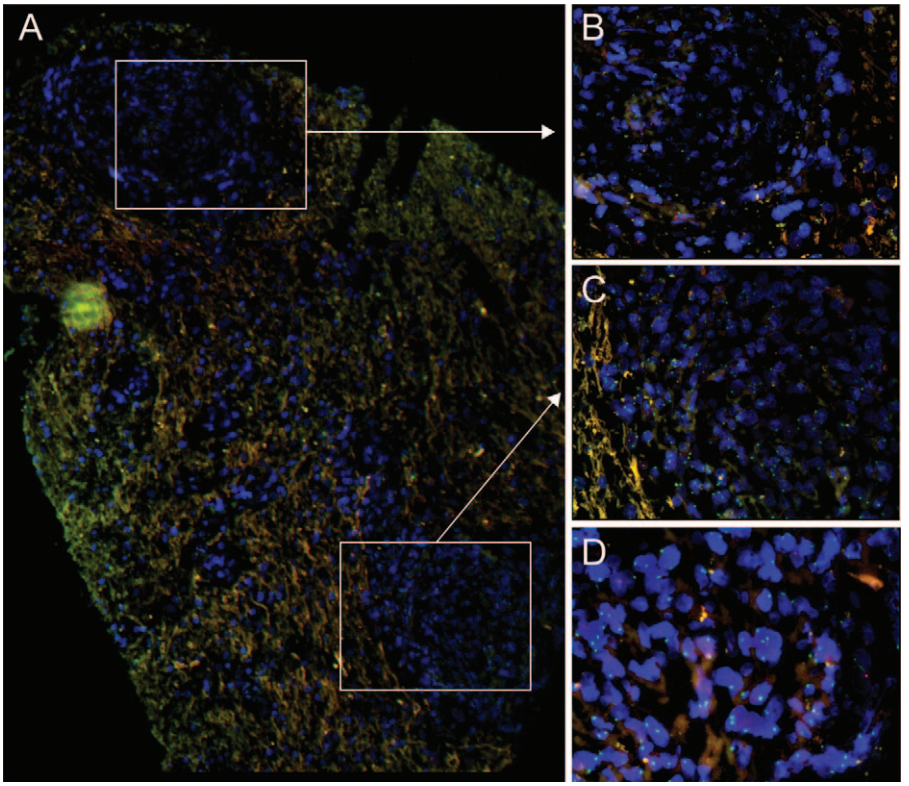

Figure 3. Fluorescent in situ hybridization (FISH) on brain biopsy confirms infiltration by donor T cells showing perivascular infiltration by female cells from donor origin (case 1, Table 1). (A) FISH with centromeric probes for X (green) and Y (red), and DAPI (blue) was performed on paraffin-embedded 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.

Table 1

Characteristics, CNS manifestation presentation, management, and follow-up of our series of patients.

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 + 308 Clinic: Myelitis with motor and sensitive neuronopathy and memory disorders MRI: Pan-myelitis and posterior lepto-meningitis EMG: Motor and sensitive neuronopathy 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	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 + 9 Clinic: encephalitis MRI: Hyper T2 focal lesion of the left hemisphere EEG: Encephalitis CSF: Lymphocytosis (100% of donor lymphocytes)	Corticosteroids (2 mg/kg) No response	Deceased5 d 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 + 378 Clinic: cerebellar syndrome, cranial nerves deficits and atypical poly-radiculonevritis MRI: normal EMG: Poly-radiculonevritis CSF: elevated protein (4.14 g/L) and no pleiocytosis	Corticosteroids (3 bolus then 1 mg/kg), plasmapheresis (5 courses), IV Ig (6 courses) Partial response	Deceased 30 m after CNS symptoms
5M/50	MPN	MAC MRD GvHD prophylaxis: CsA + MMF	No acute GvHD Moderate chronic GvHD (D + 250): polymyositis	Onset: D + 2590 Clinic: transient and focal deficits (right hemiparesis and paresthesia) MRI: T2 hyper-signals compatible with multiple sclerosis CSF: normal	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: peri-ventricular and posterior leuko-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 MRD GvHD prophylaxis: CsA + MTX	Grade I acute GvHD (D + 59): skin Severe chronic GvHD: cutaneous lichen, oral erosion, and fasciitis	Onset: D + 119 Clinic: cerebellar and vestibular syndromes, focal deficits (left hemiparesis and hypoesthesia), and cranial nerves deficits MRI: left internal capsule and thalamic lacunar infarct compatible with cerebral vasculopathy associated with cerebellar peduncle focal lesion and right mesencephalic focal lesion Angiography: normal AEP: unilateral cophosis CSF: Elevated protein (0.63 g/L) with IgG 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 = mycophénolate mofetil, MPN = myeloproliferative neoplasms, MRD = matched-related donor, MRI = magnetic resonance imaging, 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-HCST 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 posttransplantation. 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 the 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 MRI 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 ciclosporin A. Case 4 received additional courses of plasmapheresis and intraveinous 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),[7,10,12,13,18,19] myelodysplastic syndrome (n = 1),[17] acute lymphoblastic leukemia (n = 4),[5,8,12,24] myeloproliferative neoplasm (n = 3), chronic myelogenous leukemia (n = 6),[11–13] chronic myelomonocytic leukemia (n = 1),[19] lymphoma (n = 9),[5,9,14–16,20–22,25] chronic lymphoid leukemia (n = 1),[13] constitutional bone marrow failure (n = 3),[13] and aplastic anemia (n = 2).[8,23] Fourteen patients received MAC,[5,9,10,13,17,18,21] 7 reduced intensity conditioning,[5,14,16,19,22] 1 patient did not have any conditioning,[13] and 1 had sequential conditioning.[19] Donors were matched-related donor (n = 14),[5,7,9,15,17–19,21,23] matched-unrelated donor (n = 8),[8,13,16,19,22] mismatch-unrelated donor (n = 3),[10] cord blood (n = 2),[5] and haplo-identical T depleted cells (n = 1).[13] Acute GvHD history was reported for 26 cases, among them, 21 patients had at least 1 episode of acute GvHD.[5,10,12,16,18,20–22,26] Moreover, chronic GvHD episodes were reported before or during neurological symptoms in 25 patients[5,8,9,11–15,17,18,23,25] whereas 11 patients had no other cGvHD symptoms than those attributed to CNS GvHD[10,16,19–22,24] (Table 3).

4.2. Clinical features and histological results

Among the 39 patients with CNS GvHD, median symptoms onset was 385 days after HCST (7–7320). 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)[9,11,18] or discontinuation (8 patients from the literature)[5,12–14,17,22] 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.[7] Thirteen patients (cases 1, 3, 4, and 7, and 9 patients from the literature)[10,12,15,16,19–21,23] were already treated with immunosuppressive drugs at neurological symptoms onset.

Clinical features were heterogeneous: 7 patients developed stroke-like episodes (case 7 and 6 patients from the literature),[12,15,24,26] 3 patients developed lacunar syndrome,[12,13] 7 patients had multiple sclerosis-like presentation (cases 1, 4, and 5, and 4 patients from the literature),[17,19,25] 4 patients had acute demyelinating encephalomyelitis-like presentation,[7,16] 14 patients had an encephalitis (cases 2, 3, and 6, and 11 literature patients),[5,8,10,11,13,20–23] 1 patient had a mass syndrome,[9] and 3 had nonspecific clinical presentations.[13,14,18]

Histological data were available for 17 patients. According to the Conference Consensus 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.[9]

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

Table 2

Characteristics, CNS manifestation presentation, management, and outcome of 33 patients with CNS GvHD described in literature.

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	Clinic: encephalopathy, dysphagia, dysarthria CSF: normal	Perivascular infiltrates of CNS	NA	Deceased
Iwasaki (1993)	9/M	Posthepatitis aplastic anemia MRD	Chronic GvHD	Onset: 240 d after HSCT Clinic: seizure, encephalopathy, spasticity CSF: pleiocytosis, elevated protein MRI: cortical atrophy, ventricular dilatation	Diffuse infiltration of white matter with CD3 lymphocytes	NA	Deceased
	13/F	ALL MRD	Chronic GvHD	Clinic: encephalopathy MRI: white matter lesions in cerebelum	Diffuse CD3 lymphocytes infiltration and gliosis	NA	Deceased
Provenzale (1996)	14/F	Lymphoblastic lymphoma B MAC MRD	Grade III acute GvHD	Onset: 71 d after HSCT Clinic: disorientation and myoclonus CSF: elevated protein (0.9 g/L), elevated CSF Ig MRI: diffuse white matter lesions EEG: diffuse slowing	No	Corticosteroids	Clinical and MRI PR Deceased 123 d after HSCT of severe sepsis
Padovan (1999)	43/M	CML	Acute and chronic GvHD	Onset: 18 mo after HSCT Clinic: acute vertigo, hemiparesis, aphasia MRI: multiple hematoma CSF: elevated protein Angiography: normal	Angiitis and focal demyelinisation	Corticosteroids (1.5 mg/kg) and cyclophosphamide (bolus)	CR Deceased 5 mo after (pneumonia)
	32/F	AML	Acute and chronic GvHD	Onset: 28 mo after HSCT Clinic: vasospasm with aphasia and right hemiparesis then brutal left hemiparesis and seizure CT: several hypodensities in the left frontoparietal region MRI: ischemic areas, white matter lesion CSF: normal	No	Corticosteroids (1.5 mg/kg) and cyclophosphamide (bolus)	Progression with cerebral infarctions Deceased of tentorial herniation
	19/M	ALL	Acute and chronic GvHD	Onset: 31 mo after HSCT Clinic: sub-acute confusion, spastic right hemiparesis Perfusion CT: disseminated area with lower perfusion MRI: leukoencephalopathy CSF: normal Angiography: normal	No	Corticosteroids (1.5 mg/kg)	CR
	32/M	CML	Acute and chronic GvHD	Onset: 5 y after HSCT Clinic: aphasia, apraxia, dementia, tetraparesis MRI: leukoencephalopathy, hemorrhage CSF: normal Perfusion CT: multifocal cortical and white matter hypo- perfusion Angiography: normal	No	Corticosteroids (1.5 mg/kg) and cyclophosphamide (bolus)	Clinical and MRI stability
	53/M	CML	Acute and chronic GvHD	Onset: 30 mo after HSCT Clinic: acute aphasia and cognitive deficit MRI: periventricular white matter lesion, frontoparietal ischemia CSF: pleiocytosis Angiography: MCA branch occlusion	No	NA	Progression
Takastuka (2000)	22/F	ALL	No	Clinic: hemiparesis MRI: white matter lesions in frontal lobe Angiography: multiple stenosis and occlusions in the peripheral branches of the anterior and middle cerebral arteries	No	Corticosteroids	CR
Solaro (2001)	24/F	Lymphoblastic T-cells lymphoma	Chronic GvHD	Onset: 380 d after HSCT Clinic: cerebellar and pyramidal syndromes and peripheral neuropathy CSF: oligoclonal bands, lymphocytosis MRI: white matter lesions of cerebellum pons	No	Corticosteroids and plasmapheresis	Transient improvement
Ma (2002)	18/F	AML MAC Mismatch unrelated donor	Acute GvHD	Onset: 2 mo after HSCT Clinic: seizure encephalopathy MRI: diffuse atrophy EEG: bilateral slowing and voltage suppression over the left hemisphere CSF: elevated protein and lymphocytosis	Small and medium vessels vasculitis with meningo-encephalitis	Corticosteroids (bolus)	PR
Tomonari (2002)	48/F	AML MAC MRD	Acute and severe chronic GvHD	Onset: 10 mo after HSCT Clinic: diplopia, dysarthria, gait disturbance CSF: normal MRI: multifocal white matter lesions of both cerebral hemisphere, brainstem and cerebellum, evocative of demyelinating disease	No	No specific treatment described	CR Alive 15 mo after
Campbell (2005)	55/F	Non-Hodgkin lymphoma MRD	Chronic GvHD	Onset: 23 mo after HSCT Clinic: acute cerebellar syndrome CT: acute intra-parenchymal hemorrhage in left cerebellum MRI: white matter lesions peri-ventricular Angiography: aneurysm of the left posterior inferior cerebellar artery and dilated branches of cerebral arteries	No	Tacrolimus	PR
Shortt (2005)	47/M	Follicular lymphoma RIC MUD	Acute GvHD	Onset: 425 d after HSCT Clinic: personality changes, seizure, cognitive dysfunction CSF: elevated protein (0.73 g/L) and lymphocytosis EEG: slow wave activity MRI: diffuse white matter lesions	No	Corticosteroids (2 mg/kg)	CR
Delios (2007)	54/M	AML MRD		Onset: 390 d after HSCT Clinic: ADEM CSF: elevated protein (0.86 g/L) MRI: multiple sub-cortical lesions, one with a relatively open ring sign	Loss of myelin and axon preservation	Corticosteroids and IV Ig (5 courses)	PR Deceased 5 y later
	59/M	AML MRD		Onset: 240 d after HSCT Clinic: ADEM CSF: elevated protein (1.43 g/L), oligoclonal bands MRI: pontine white matter lesion	No	IV Ig (5 courses)	PR Alive 9 y later
	29/F	AML MRD		Onset: 63 d after HSCT Clinic: ADEM CSF: elevated protein (0.57 g/L), oligoclonal bands MRI: multiple white matter lesions of cervical spine and few in brain	Biopsy of spinal cord Loss of myelin and axon preservation	Corticosteroids, and IV Ig (5 courses)	Light clinical improvement Deceased 2 y later of severe chronic GvHD
Kamble (2007)	44/F	T-cell lymphoma MAC MRD	Acute and chronic GvHD	Onset: 18 mo after HSCT Clinic: right hemiparesis and seizure CSF: normal MRI: white matter lesions in fronto-parietal lobe	Perivascular inflammation mainly composed of CD3+/CD4+ T cells of the donor (FISH XY)	Corticosteroids (bolus)	Clinical then MRI CR Alive 8 y after HSCT
	58/F	Phi+ ALL RIC Cord blood	Acute and chronic GvHD	Onset: 178 d after HSCT Clinic: encephalopathy and seizure CSF: elevated protein (0.67 g/L) MRI: diffuse white matter lesions	Leptomeningeal perivascular infiltration of CD3+/CD8+ T cells	Corticosteroids	Transient improvement Deceased 184 d after HSCT

(*continued*)

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 MRD	Chronic GvHD	Onset: 18 mo after HSCT Clinic: progressive left hemiparesis CSF: normal MRI: large mass of right parietal lobe	Focal infiltration of lympho-histiocytic inflammatory cell and noncaseating granuloma with perivascular predominance IHC: CD3+ T cells	Corticosteroids and ciclosporin	Clinical and MRI PR
Matsuo (2009)	32/F	MDS MAC MRD	Chronic GvHD	Onset: 7 mo after HSCT Clinic: bilateral papillar edema 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 thorax 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 RIC	Severe chronic GvHD	Onset: 3 y after HSCT Clinic: dizziness, tinnitus, vertigo, and proximal weakness MRI: large lesion of the corpus callosum	Perivascular inflammation and scattered CD3+/CD8+ T cells associated with microglia activation and macrophages in brain parenchyma	Corticosteroids and mycophenolate mofetil	Progression Deceased 2 mo later
Yamamoto (2009)	40/F	Follicular lymphoma	Acute GvHD	Onset: 7 d after HSCT Clinic: encephalitis and seizure CSF: elevated protein (6.75 g/L), pleiocytosis (96.8% of donor cells) MRI: normal	No	Corticosteroids (3 bolus) followed by etoposide (50 mg/m^2) because of HLH evidence	Progression Deceased 32 d after HSCT
Sostak (2010)	35/M	CML MAC MUD	Acute and chronic GvHD	Onset: 4 y after HSCT Clinic: seizure MRI: cortical/sub cortical acute ischemic lesions in peri-insular region, left frontal and parietal lobe EEG: temporal slowing without epileptic discharges	Micro-angiopathy	Corticosteroids (3 bolus then 1 mg/kg) and cyclophosphamide (bolus) Then methotrexate (10 mg/week)	CR
	28/F	AML MAC MUD	Acute and chronic GvHD	Onset: 2 y after HSCT Clinic: progressive depression, cognitive deficits, cortical blindness, seizure, ataxia, tetraparesis CSF: elevated protein, oligo-clonal bands MRI: leukoencephalopathy then internal brain atrophy EEG: generalized slowing and epileptic discharges	Cerebral vasculitis with infiltration of donor lympho-monuclear cells (FISH XY)	Corticosteroids (5 bolus then 1 mg/kg) and cyclophosphamide (1 bolus then 100 mg/j)	CR
	8 mo/M	SCID No conditioning Haplo-identical T depleted HSCT (father)	Chronic GvHD	Onset: 20 y after HSCT Clinic: hemiparesis, ataxia, cortical blindness and deafness CSF: elevated protein, pleiocytosis MRI: multiple focal ischemic lesions and hemorrhage	Cerebral angiitis without argument for infection	Corticosteroids and cyclophosphamide (4 bolus)	PR Deceased 1 y later of severe sepsis
	33/M	CLL MAC MUD	Acute and chronic GvHD	Onset: 2 y after HSCT Clinic: ataxia, cortical blindness, spastic tetraparesis, acute pseudo-bulbar syndrome CSF: elevated protein, pleiocytosis, intrathecal IgG synthesis MRI: frontally accentuated brain atrophy	Cerebral and meningeal angiitis	Corticosteroids (3 bolus then 1.5 mg/kg) and cyclophosphamide (1 bolus)	Small improvement Deceased
Voß (2010)	57/M	CMML RIC MUD	No	Onset: 4 weeks after HSCT Clinic: 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) then cyclophosphamide (7 bolus)	CR but relapse of myelitis 1,5 y later. Treatment by cyclophosphamide with PR
	65/M	AML Sequential conditioning MRD	No	Onset: 3 y after HSCT Clinic: recurrent myelitis with mild paraparesis and lower limb hypoesthesia CSF: elevated protein (0.55 g/L) and oligoclonal bands MRI: multiple white matter lesion of spinal cord without cerebral abnormalities	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: 92 d after HSCT Clinic: dizziness, blunted mentation, vestibular syndrome and mild cognitive impairment CSF: elevated protein (1.1 g/L) MRI: multifocal subcortical and juxta-cortical white matter lesions evocative of ADEM	No	Corticosteroids	Clinical and MRI CR Alive 1 y after
Rathore (2015)	7/M	Idiopathic aplastic anemia MRD	Chronic GvHD	Onset: 15 mo after HSCT Clinic: depression and seizure CSF: normal MRI: bilateral uncus lesions EEG: slowing background and one epileptic focus VGKC and ILGI1 antibodies positives	No	Corticosteroids (5 bolus then 1 mg/kg) and IV Ig (5 courses)	Clinical PR

ADEM = 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.

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, CLL = chronic lymphocytic 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, MRD = matched related donor, MUD = matched unrelated donor, NA = not available, RIC = reduced intensity conditioning.

* No conditioning (n = 1) and sequential conditioning (n = 1).

† Cord blood (n = 2) and haplo-identical T depleted donor (n = 1).

published cases, 11 patients (28%), of whom 2 had a brain biopsy, did not have extra-CNS chronic GvHD. Interestingly, these patients had a different clinical presentation compared to patients with extra-CNS chronic GvHD history. First, CNS GvHD appeared earlier in this population: median neurological symptoms onset delay was 81.5 days (range 7–1095) versus 549 days (range 119–7300) for patients with extra-CNS chronic GvHD, $P = .001$. In the group of patients without chronic GvHD history, 8 patients out of 11 (73%) had an acute GvHD history and 3 patients had active acute GvHD at neurological symptoms onset (case 3 and 2 patients from the literature).[20,21] Moreover, clinical presentations seem to be different. Encephalitis was more frequent in the group of patients without chronic GvHD: 7/11 patients (64%, cases 2, 3, and 6, and 4 patients from the literature)[10,20–22] versus 7/25 patients (28%), $P = .07$. Conversely, stroke-like episodes and lacunar syndromes were less frequent: 1/11 (9%)[24] 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 corticosteroids[5,7,9,10,12–14,16,17,19–25] in combination with at least another immunosuppressive drug in 19 patients.[7,9,12–14,17,19,20,23,25] Other immunosuppressive treatments included intravenous immunoglobulin (IV Ig) (n = 6), plasmapheresis (n = 3),[25] cyclophosphamide (n = 9),[12,13,19,25] anticalcineurin inhibitors (n = 4),[9,15,17] mycophenolate mofetil (n = 3),[14] 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,[5,12,13,16,18,19,22,24] 15 had a partial response,[7,9,10,13,15,17,19,21,23] and 2 had a transient response[5,25] (TR). Disease remains stable for 2 patients[12] 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,[5,8,9,11,14,20–22] 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 4

Analysis of patients with or without history of extra-CNS chronic GvHD.

	No chronic GvHD history (n = 11)	Chronic GvHD history (n = 25)	*P*
CNS symptoms onset (median, d)	81.5 (7–1095)	549 (119–7300)	.001
Clinical features			
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	3	
Demyelinating lesions	–	–	
Vasculitis and demyelinating lesions	–	3	
Immune mediated encephalitis	1	6	
Other†	–	1	
NA	10	11	

ADEM = acute demyelinating encephalomyelitis, CNS = central nervous system, GvHD = graft versus host disease, NA = not available.
* Mass syndrome.
† Noncaseating-granuloma.

increased in piriform, occipital, visual, and prefrontal neurons 3 days after GvHD onset.[29] 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.[30] In rats, T cell infiltration of CNS was associated with increased expression of class I and class II major histocompatibility antigens.[31] In mouse models, cerebral endothelial adhesion molecule expression was modified: ICAM-1 and VCAM-1 expression were upregulated and could contribute to T cell infiltration in neural tissues.[26] Recently, it has been demonstrated in murine[32] and primate[33] models with acute GvHD, that neurological symptoms and behavior modifications were caused by alloreactive activated donor $CD8^+$ T cells.[32,33] T cell infiltration was prevented by immune prophylaxis.[33] 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).[5,8,9,14] 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)[5,14] whereas only 1 showed $CD3^+$/$CD4^+$ cells infiltration.[5] A recent paper demonstrated that this infiltration let to inflammatory cytokine production. IL-6 production together with indoleamine 2,3 deoxygenase upregulation played a central role in CNS GvHD by its action on host microglial cells.[34] In this model, IL-6 blockade could partially reversed neuroinflammation.

Table 5

Treatment and outcome of 39 patients with CNS GvHD.

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*	8 (21%)
Treatment response	
CR	10 (26%)
PR	15 (39%)
Transient response	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).

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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