Journal of Neuroimmunology 307 (2017) 74–81

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

# Central and peripheral nervous system immune-mediated demyelinating disease after allogeneic hematopoietic stem cell transplantation

M.I. Stefanou*, F. Bischof

*Department of Neurology & Stroke, and Hertie Institute for Clinical Brain Research, Eberhard Karls University of Tübingen, Tübingen, Germany*

ARTICLE INFO

*Keywords:*
Neuroopthalmology
All demyelinating diseases
Autoimmune diseases
All clinical neurology
Hematologic diseases

ABSTRACT

*Objective:* We aimed to evaluate clinical and diagnostic features of central and peripheral immune-mediated demyelinating disease (CPID) in allogeneic hematopoietic stem cell transplantation (aHSCT) recipients.

*Background:* CPID refers to the late-onset, immune-mediated neurological complications following aHSCT, when other frequent differential diagnoses have been ruled out, and when symptoms and signs of systemic GvHD manifestations are absent.

*Methods:* Case records at the University of Tuebingen, between 2001 and 2015, were screened to identify patients with CPID after aHSCT.

*Results:* Seven patients who developed CPID after aHSCT were identified. The average time interval from aHSCT until onset of CPID was 2.6 ( ± 2.8) years (mean ± SD). The most prevalent manifestations of CPID were optic neuritis and/or myelitis and polyneuropathy. Cerebrospinal fluid analyses involved elevated protein concentration and lymphocytic pleocytosis, while oligoclonal bands in CSF, but not in serum, were detected in 28% of cases. Aquaporin-4-antibodies were consistently absent. MRI studies showed features suggestive of demyelination processes, with cerebral and/or spinal cord white-matter involvement, and features compatible with cerebral vasculitis. Corticosteroids, Immunoglobulins, Cyclophosphamide, Rituximab and Interferon beta-1a showed marginal treatment responses, whereas plasma exchange resulted in marked clinical improvement in two treated patients. A chronic disease-course with persisting neurological deficits was prevalent.

*Conclusions:* CPID may comprise a rare complication of aHSCT, which manifests as optic neuritis and/or myelitis and is accompanied by sensorimotor polyneuropathy. A concomitant systemic manifestation of GvHD is not mandatory for CPID diagnosis. Usually, CPID exhibits a chronic, persisting disease course. Thus, clinical awareness is required, as early diagnosis and aggressive treatment may be prognostically advantageous.

## 1. Introduction

Allogeneic hematopoietic stem cell transplantation (aHSCT) is an effective treatment for a variety of hematologic malignancies and nonmalignant disorders (Saiz and Graus, 2004). The procedure consists of a myeloablative preparatory regimen, followed by intravenous infusion of hematopoietic stem cells of an HLA-matched family member or non-related donor (Padovan et al., 1998). It has been shown, that neurological complications occur in 14–45% of aHSCT recipients and vary, depending on the underlying disease, the immunomodulatory agents used, and the time relevant to transplantation (Table 1) (Delios et al., 2012). In particular, during the initial conditioning phase, when high-dose chemotherapy, radiotherapy or both, are used to destroy the patient's defective bone marrow, peripheral nervous system (PNS) complications or drug-related encephalopathies are frequent. In the following phase of bone marrow depletion, metabolic encephalopathies, septic cerebral infarctions and hemorrhages are common, while central nervous system (CNS) dysfunction due to failure of other organ systems may also be noted (Saiz and Graus, 2004). Subsequently, during the phase of chronic immunosuppression after aHSCT, opportunistic infections and neurotoxic side effects of the potent immunosuppressants are observed (Saiz and Graus, 2004). Months to years after transplantation, late-onset events may arise, usually involving relapses of the original disease, occurrence of secondary malignancies, and rarely, immune-mediated neurological disorders (Delios et al., 2012) (Baumer et al., 2015). In respect to the latter, it remains to date a matter of ongoing controversy, whether the late-onset, immune-mediated neurological sequelae - indicated by the term ‘central and peripheral immune-mediated demyelinating disease’ (CPID) adopted herein - actually constitute a form of autoimmunity or a form of alloreactive immune disorder, in the spectrum of graft-versus-host disease (GvHD) (Delios et al., 2012). In fact, although many recent studies have dealt

* Corresponding author at: Dept. of Neurovascular Diseases, Hertie Institute for Clinical Brain Research, & Centre of Neurology, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany.
*E-mail addresses:* maria-ioanna.stefanou@med.uni-tuebingen.de (M.I. Stefanou), felix.bischof@uni-tuebingen.de (F. Bischof).

http://dx.doi.org/10.1016/j.jneuroim.2017.04.005
Received 10 January 2017; Received in revised form 8 April 2017; Accepted 8 April 2017

**Table 1**
CNS Complications following allogeneic HSCT, classified according to the time relevant to transplantation. During the conditioning phase, the preparatory regimens may cause severe cytotoxic damages to the CNS. During the phase of bone marrow depletion, delayed engraftment has been associated with prolonged thrombopenic states and platelet dysfunction, thereby exacerbating the risk of cerebrovascular events. Failure of other organ systems may also cause CNS disorders, while nutritional imbalances during phases of intense regenerative cell proliferation and metabolic stresses may account for injury to the susceptible CNS tissue. Moreover, the effects of prolonged post-transplant immunosuppression, in combination with prolonged leukopenic states, predispose to opportunistic CNS infections and post-transplant lymphoproliferative disorders. Immune reconstitution inflammatory syndrome may also occur due to immunological regeneration. Furthermore, underlying malignant disease may not be fully eradicated and may recur despite engraftment of the new marrow. Months to years after transplantation, secondary malignancies may occur. Lastly, immune-mediated complications, albeit rare, should be considered in the differential diagnosis of late-onset neurological complications following aHSCT.

Abbreviations: aHSCT: allogeneic hematopoietic stem cell transplantation, CNS: Central nervous system, CPID: Central and peripheral immune-mediated demyelinating disease after aHSCT, NMOSD: Neuromyelitis optica spectrum disorders, ADEM: Acute disseminated encephalomyelitis.

| | | |
|---|---|---|
| Conditioning phase | Encephalopathies or leukoencephalopathies (i.e. due to microvascular dysfunction, irradiation, chemotherapy and/or drug toxicity) | |
| Phase of bone marrow depletion | Metabolic encephalopathies | |
| | Cerebrovascular events | - Ischemia or septic cerebral infarctions<br>- Hemorrhages<br>- Vasculitis (i.e. drug-induced, infectious, post-infectious) |
| | CNS dysfunction due to other organ system failure | |
| Phase of chronic immunosuppression | Opportunistic infections (i.e. bacterial, fungal, parasitic, viral) and associated encephalopathies (i.e. progressive multifocal leukoencephalopathy) | |
| | Neurotoxic effects of potent immunosuppressants | |
| | Post-transplant lymphoproliferative disorders | |
| | Immune reconstitution inflammatory syndrome | |
| Months to years after transplantation | Relapse of original disease | |
| | Secondary malignancies | |
| | Late-onset immune-mediated disorders | - CNS Graft-versus-host disease<br>- CPID<br>- NMOSD<br>- Multiple Sclerosis/ ADEM<br>- Vasculitis |

with the early neurological complications of aHSCT, there is still limited evidence regarding the late-onset, immune-mediated neurological disorders in long-term aHSCT survivors (Solaro et al., 2001). This study focuses on the analysis of clinical features of patients, who presented neurological symptoms suggestive of CPID, discusses the relation of CPID to CNS-GvHD and other neuroimmunological disorders, and presents current diagnostic and treatment options.

## 2. Materials and methods

We conducted a retrospective study based on an electronic database of adult patients, who underwent aHSCT at the University Hospital of Tuebingen, between 2001 and 2015, and had one of the following diagnoses: “malignant disease of the hematopoietic or lymphoid system” (ICD10 C81-C96), “graft versus host disease” (ICD10 D89.811) or “agranulocytosis secondary to cancer chemotherapy” (ICD10 D70.1). Among them, patients who additionally had the diagnoses “inflammatory disease of the CNS – encephalitis, myelitis and encephalomyelitis” (ICD10 G04.8-G04.9), “unspecified demyelinating disease of the CNS” (ICD10 G37.9) or “inflammatory polyneuropathy” (ICD10 G61.8-G61.9) were identified. The case records of the identified patients were further reviewed to investigate the clinical syndromes, radiological findings, applied treatments and outcome. Diagnosis of CPID was critically assigned to these patients who met the selection criteria, and also fulfilled all of the following conditions: a) no alternative etiology of the neurological pathology was suspected, b) no neurologic disorder preceded aHSCT, c) treatment with aHSCT was documented, d) treatment with immunosuppressants followed aHSCT, and e) no systemic GvHD manifestation, determined according to the National Institutes of Health criteria for chronic GvHD (Jagasia et al., 2015), was recorded. Finally, patients, who based on their clinical or paraclinical records, presented: signs of CNS infection, serious neurological adverse events, according to the international guidelines for good clinical trial practice, within the first 3 months after transplantation, signs of neurotoxicity according to the National Cancer Institute common toxicity criteria (Trotti et al., 2003), or disease relapse were excluded. Clinical and demographic features, brain imaging, laboratory findings, treatment effects and long-term neurological outcomes of the identified patient group were evaluated.

## 3. Results

Sixty-one patients, who had one of the diagnoses: “malignant disease of the hematopoietic or lymphoid system” (ICD10 C81-C96), “graft versus host disease” (ICD10 D89.811) or “agranulocytosis secondary to cancer chemotherapy” (ICD10 D70.1) and, additionally, one of the diagnoses “inflammatory disease of the CNS – encephalitis, myelitis and encephalomyelitis” (ICD10 G04.8-G04.9), “unspecified demyelinating disease of the CNS” (ICD10 G37.9) or “inflammatory polyneuropathy” (ICD10 G61.8-G61.9) were identified. The case records of these 61 patients were further reviewed and eventually, 7 patients who fulfilled all the aforementioned criteria and developed CPID were further examined.

The average time interval between aHSCT until onset of CPID was 2.6 ( ± 2.8) years (mean ± SD) with a median onset of CPID manifestation 1.5 (and range 0.25–8.0) years after aHSCT. Of the investigated group, 3 patients received aHSCT from matched related- and 4 from matched unrelated donors. Diverse combined protocols of chemotherapy, total body irradiation and GvHD-prophylaxis were applied (Table 2). Among the identified CPID patients, only 2 developed acute systemic manifestations of GvHD. None of the identified patients exhibited chronic GvHD (as already specified in the inclusion criteria).

The most prevalent neurological manifestations of CPID were optic neuritis (ON) ($n = 3$), myelitis ($n = 7$) or a combination of the above ($n = 3$) (Table 2). In the identified cases, where both ON and myelitis occurred, the time-span between the two manifestations varied from 1 to 12 months (Patient 3 in Table 2 presented with myelitis followed by ON after 1 month, Patient 1 presented with ON followed by myelitis after 6 months, and Patient 6 presented with myelitis followed by ON after 12 months). Notably, the diagnostic criteria for neuromyelitis optica spectrum disorders (NMOSD) with negative Aquaporin-4-antibodies (AQP4-Ab) status were fulfilled in one patient (Wingerchuk et al., 2015), while the other two patients, that presented with both ON and myelitis, did not fulfill the criteria for NMOSD diagnosis, as they harbored no typical spinal MRI findings of longitudinally extensive transverse myelitis (LETM) (Table 2). Additionally, one patient fulfilled the diagnostic criteria of multiple sclerosis (MS) (Patient 2 in Table 2) (Polman et al., 2011), yet, was included in the CPID cohort due to ‘red flag’ features in the clinical course and his radiological findings. In particular, the patient presented with fulminant myelitis, unresponsive to steroids, showed no treatment effect to Interferon beta-1a therapy, while his brain MRI revealed few MS-typical neuroradiological features (i.e. no evidence of callosal lesions, no Dawson's fingers, few periventricular and no juxtacortical lesions). Furthermore, concurrent sensorimotor polyneuropathy was common among patients ($n = 6$). A chronic disease course with persisting neurological deficits in the follow-up was prevalent in all cases. Visual impairment, movement disorders, spasticity and sensory deficits were noted in the patient group.

The paraclinical parameters associated with CPID arose mainly from