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Neurologic Complications of Hematopoietic Stem Cell Transplantation

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Neurologic Complications of Hematopoietic Stem Cell Transplantation

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Abstract: Hematopoietic stem cell transplantation (HSCT) is a procedure that is used for the treatment of a number of haematological diseases, solid tumours, and autoimmune disorders. In this paper, the biological principles and stages of HSCT as well as the most common neuro-

logical complications are discussed. Special attention is paid to neurological disorders derived from toxicity of the treatment, infections, and graft-versus-host disease. A clinically oriented classification of these complications is provided, focusing on the most frequent disorders in

every step of the transplant. **EANO Mag 2012; 2 (2): 78–83.**

Key words: hematopoietic stem cell transplantation, neurological complications, graft-versus-host disease

■ Introduction: General Concepts

Hematopoietic stem cell transplantation (HSCT) is a complex procedure that in recent years has been increasingly used for a number of haematological and non-haematological diseases [1]. An international consortium estimated an annual worldwide number of approximately 60,000 procedures for 2009 (<http://www.ibtmr.org>).

In decreasing order of frequency, haematologic indications are: multiple myeloma, non-Hodgkin lymphoma, acute myeloid leukaemia, Hodgkin's disease, acute lymphoblastic leukaemia, myelodysplastic syndrome, aplastic anaemia, and other leukaemias. While mainly used for haematological malignancies, HSCT is also being used for solid tumours, such as breast cancer, and severe autoimmune diseases, including multiple sclerosis [2].

HSCT always includes several crucial steps (Figure 1), as dictated by the scientific principles underlying this therapy. The first step is to eliminate the patient's abnormal hematopoietic system. In order to do this, ablative chemotherapy regimes sometimes potentiated with total body irradiation are used ("conditioning regime"). This is the rationale for using HSCT in the treatment of haematological malignancies, other haematological disorders, such as aplastic anaemia, and autoimmune diseases. In the case of non-haematological malignancies, the objective is to use aggressive chemotherapy against the tumour and myeloablation is an unwanted "adverse event", which requires HSCT for rescue. The second step is to reconstitute a functioning hematopoietic system. This process starts with the infusion of hematopoietic stem cells ("the graft").

Hematopoietic stem cells have an extremely high regenerative capacity. It has been shown in animal experiments that it is possible to regenerate the whole hematopoietic system of a recipient after transplantation of a single hematopoietic stem cell. Also, hematopoietic stem cells can be cryopreserved, al-

lowing for donor and recipient to be temporally and geographically distant.

Depending on the source of "the graft" the transplant is classified as either autologous or autogenic, when the source is the patient himself, allogeneic transplant, when the source is a donor, be it related or unrelated, or syngeneic, in the rare event that the donor is a genetically identical twin. Allogeneic and autologous transplants differ in terms of outcome, frequency and type of complications. Allogeneic transplants are usually very effective in controlling the original disease but are associated with a high mortality rate (up to 40 %). Mortality is much lower in autologous transplants (< 10 %) but at the expense of a higher risk of relapse of the original disease. Both medical and neurological complications are more frequent in allogeneic transplants [3]. The most dreaded of these complications is the "graft-versus-host disease" (GVHD; for an example see Figure 2), which is difficult to treat and may be fatal. Here, immune cells developing from the donor's hematopoietic system react against host antigens, which they recognize as "foreign". In order to minimize the risk of this complication antigenic similarity between donor and recipient should be striven for by carefully matching them for the Human Leukocyte Antigen (HLA) system. Preferably, donor and recipient should be related and the closer their familial relation is, the less frequent and severe the GVHD will be. Also, potent immunosuppressive drugs are used to prevent GVHD, further increasing the risk of complications in allogeneic transplantation, either in the form of adverse medical reactions or through favouring opportunistic infections and secondary neoplasms.

It should be noted that, in some circumstances, the immunological reaction of the graft against host antigens might be beneficial when the target antigen is present in the malignant cell. This is known as the "graft-versus-leukaemia/tumour effect" and it is the rationale for "minitransplant" protocols. In these, less aggressive ablative regimes can be used with improved tolerance. The result is the co-existence of 2 different hematopoietic systems in the host, a situation known as chimerism, namely the host's original hematopoietic system, which will include some malignant cells, and the donor's hematopoietic system. It is expected that the immune system developing from the donor will eventually eliminate any residual malignant cells. Because the ablative regimes are less

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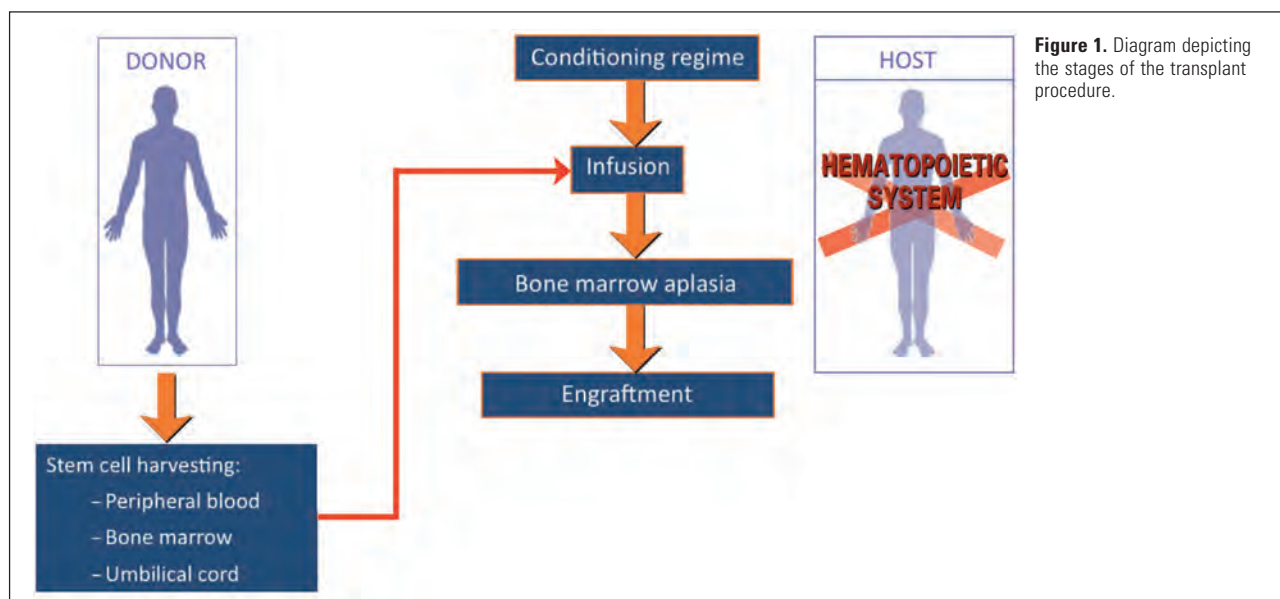


Figure 1. Diagram depicting the stages of the transplant procedure.

toxic in minitransplants, this procedure is suitable for elderly patients or those with poor pre-transplant general medical condition, be it from co-morbidities or from the disease. Medical and neurological complications are nevertheless frequent, given that patients are usually less fit [4].

Overall, neurological complications after HSCT are frequent, with estimates ranging from 8–42 % in the different series, depending on how strict the inclusion criteria are [5–14].

When seeing a patient with a suspected neurological complication from HSCT, it must be kept in mind that they have undergone a long and complicated process, including the use of several highly toxic drugs posing high demands on different metabolic systems. Thus, a thorough revision of medical records from the beginning of the haematological disease should be done to get a wider point of view. Particular attention should be paid to the following key points:

- Previously used treatments, including those for the haematological disease, but also the ones used for possible complications, such as infections. Pre-existing damage, due to toxicity from previous treatments, may be aggravated by the conditioning regimes used for HSCT.
- The moment of presentation of the complication in relation to the chronology of the transplant. This information can be very useful for narrowing down the differential diagnosis.
- Co-existent non-neurological complications and co-morbidities. On the one hand, these can have an impact or predispose to certain complications. For example, renal failure can predispose to posterior reversible encephalopathy syndrome in patients taking cyclosporine. On the other hand, systemic complications may help orienting the differential diagnosis. This is particularly relevant for infections, as a co-existent local infection may spread to the CNS. For example, in a patient with focal neurological symptoms and disseminated cortico-subcortical micro-abscesses, knowing that they are also being treated for pulmonary aspergillosis would suggest haematogenous spread.

Also, physicians dealing with these patients should become familiar with certain facts and general principles regarding HSCT, including:

- Neurological complications more commonly associated with the original disease. For example, one study suggested that patients with myeloblastic leukaemia have a higher risk of CNS subdural bleeding.
- Neurological complications more commonly associated with the drugs used.
- Atypical clinical and radiological presentations of neurological conditions, which are often seen in these patients. For example, cerebral toxoplasmosis may not present with the typical focal lesions surrounded by a contrast-enhancing ring, but rather with toxoplasmic encephalitis or lesions with a haemorrhagic component.
- The chronology and stages of the HSCT and the most common complications occurring at each stage. This is particularly relevant for infections. At each stage of the transplant different forms of immune response may be affected, resulting in a different propensity to infection from certain microorganisms. For example, bacterial infections are more common during the initial periods after myelo-ablation, due to neutropenia, whereas viral infections are more common later on, while cell-mediated immunity is still inefficient.

In the following section, we will discuss the different stages of the HSCT and the most common neurological complications seen at each of them.

■ Stages of the Transplant Procedure and Associated Neurological Complications

Pre-Transplantation Period

Stem Cell Harvesting

Hematopoietic stem cells may be harvested from different sources, including bone marrow, umbilical cord blood, and peripheral blood. The traditional source of hematopoietic stem cells is bone marrow, aspirated from posterior or anterior iliac crests. Complications of this procedure include local

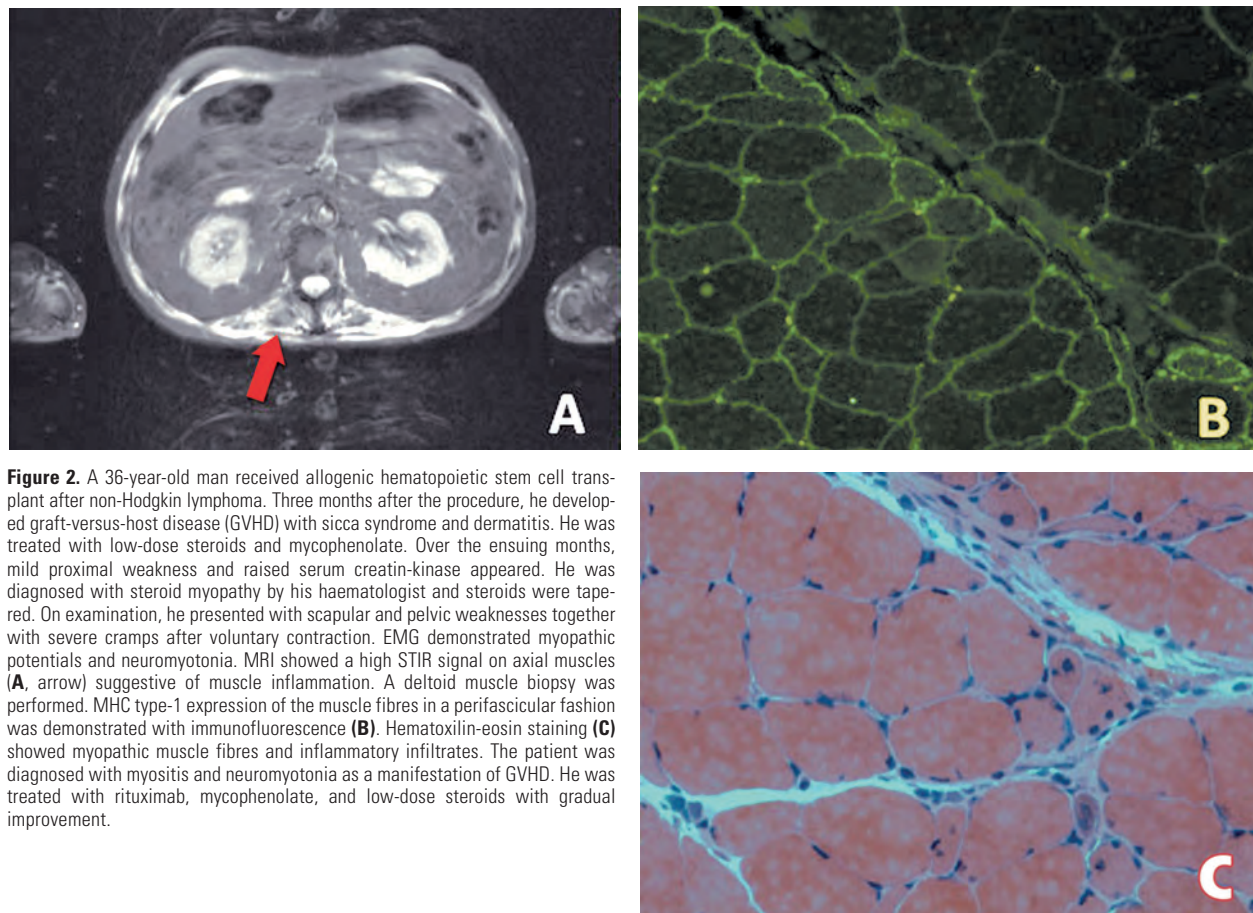


Figure 2. A 36-year-old man received allogeneic hematopoietic stem cell transplant after non-Hodgkin lymphoma. Three months after the procedure, he developed graft-versus-host disease (GVHD) with sicca syndrome and dermatitis. He was treated with low-dose steroids and mycophenolate. Over the ensuing months, mild proximal weakness and raised serum creatin-kinase appeared. He was diagnosed with steroid myopathy by his haematologist and steroids were tapered. On examination, he presented with scapular and pelvic weaknesses together with severe cramps after voluntary contraction. EMG demonstrated myopathic potentials and neuromyotonia. MRI showed a high STIR signal on axial muscles (A, arrow) suggestive of muscle inflammation. A deltoid muscle biopsy was performed. MHC type-1 expression of the muscle fibres in a perifascicular fashion was demonstrated with immunofluorescence (B). Hematoxylin-eosin staining (C) showed myopathic muscle fibres and inflammatory infiltrates. The patient was diagnosed with myositis and neuromyotonia as a manifestation of GVHD. He was treated with rituximab, mycophenolate, and low-dose steroids with gradual improvement.

haemorrhage, which may compress local nerves, such as the sciatic nerve, and accidental puncture of the subarachnoid space, which may cause intracranial hypotension [15].

Hematopoietic progenitors can also be recovered from peripheral blood, a method commonly used for autologous transplantation. In order to mobilize enough stem cells from the bone marrow to the peripheral blood, recombinant hematopoietic growth factors that reduce adhesion of stem cells are administered to the patient/donor (ie, Granulocyte-Colony Stimulating Factor [G-CSF], Granulocyte-Macrophage-CSF [GM-CSF]). Because these drugs are also cytokines they may induce hypercoagulability or exacerbate autoimmune disease. The progenitors are later collected through apheresis.

Myeloablation

Myeloablative conditioning regimes include high-dose chemotherapy, which can be combined with total body irradiation. This is more commonly done in allogeneic transplantation. Different chemotherapeutic agents can be used, depending on the original disease and the source of the graft. Many of these highly toxic drugs can potentially cause neurological complications. For example, ifosfamide and busulfan may cause encephalopathy, myoclonus, and seizures. Patients receiving treatment with busulfan are treated preemptively with antiepileptic drugs for this reason. Other commonly used chemotherapeutic agents which can be neurotoxic include cytarabine (cerebellar ataxia, peripheral neuropathy) and methotrexate (myeloradiculopathy).

Patients receiving allogeneic transplants will also be treated with immunosuppressant drugs, intended to reduce the risk of GVHD, further contributing to neurologic toxicity.

Pre-Engraftment Period

Day 0: Stem Cell Infusion

After myeloablation is completed, stem cells are infused intravenously to reconstitute the hematopoietic system. The day of infusion is customarily defined as “day 0”. Infusion of stem cells is a relatively simple procedure and complications are rare. Occasionally reported neurological problems include stroke and transient global amnesia. Dimethylsulfoxide, a chemical used for cryopreservation of hematopoietic stem cells, has been linked to rare cases of encephalopathy, seizures, and posterior reversible encephalopathy syndrome [16, 17].

Days 0–30: Bone Marrow Aplasia

As a consequence of myeloablation patients are left in a state of aplasia that will persist until the transplant engrafts in the bone marrow of the recipient. This process usually takes 2 weeks after stem cell infusion. Time to engraftment is usually longer in allogeneic transplantation and when stem cells are obtained from bone marrow. Any delay or failure of the transplant to engraft prolongs the period of pancytopenia, during which serious medical and neurological complications may ensue.

Commonly described medical complications in this period are mucositis, hepatic venoocclusive disease, and interstitial

pneumonitis. Mucositis facilitates access of resident microorganisms to the blood stream, favouring systemic infections, which may spread to the central nervous system (CNS). Dysfunction of vital organs, such as renal or hepatic failure, sometimes combined in acute multiorgan failure, may cause diffuse metabolic encephalopathy, presenting with altered levels of consciousness/delirium and/or seizures. Cytopenias may also contribute to specific neurologic complications. Thrombocytopenia predisposes to haemorrhagic events, such as subdural haematoma, anaemia contributes to encephalopathy, and neutropenia favours infections. Several factors further increase the risk of infection in this period: disruption of external barriers (mucositis, catheters), granulocytopenia, and impairment of cell-mediated and humoral immunity, related to chemotherapy and immunosuppressive drugs. The pathogens seen at this stage are similar to the ones seen in oncologic patients with profound neutropenia. They include mainly germs which colonize the skin, oral cavity, and gastrointestinal tract. Bacterial infections are the most frequent ones at this point and are most commonly caused by aerobic Gram-negative bacilli (*Escherichia coli*, *Pseudomonas* spp, and *Klebsiella* spp), Gram-positive cocci (*Staphylococcus* spp, which may colonize catheters, and *Streptococcus viridians*). Rarely, bacterial meningitis may result from haematogenous spread of these germs to the central nervous system. Whenever suspected, lumbar puncture is warranted, but before this some considerations must be taken into account. Because of the risk of bleeding due to severe thrombocytopenia (platelets < 40,000/ml), platelet transfusion should be considered. Caution is also advised when interpreting the results of the cytobiochemical analysis of the cerebrospinal fluid (CSF). This could be normal or show minor alterations despite infection, due to the inability of the immune system to mount an adequate inflammatory meningeal reaction in the context of immunosuppression. Diagnosis should be therefore based on microbiological studies, when in doubt. Other infections seen at this stage are candidemia with meningitis, often associated with endophthalmitis, and Herpes simplex virus (HSV) infections. These result most often from reactivation in seropositive patients and will usually present as herpetic gingivostomatitis, but may rarely cause encephalitis.

Drug toxicity from immunosuppressive drugs used to prevent GVHD is also a common cause of neurological symptoms. These regimes frequently include steroids and calcineurin inhibitors, such as cyclosporine or tacrolimus. Steroids may cause psychiatric symptoms, anxiety, insomnia, memory problems, myopathy, and epidural lipomatosis. Cyclosporine and tacrolimus frequently induce tremor, paraesthesias, and seizures. Isolated seizures may not require discontinuation of the drug, especially if these occur with toxic blood levels. Dose reduction may resolve the problem. Rarely, calcineurin inhibitors may induce posterior reversible encephalopathy syndrome (PRES), a very characteristic clinical and radiological entity [18]. Common clinical symptoms include headache, altered level of consciousness, seizures, and visual cortical dysfunction. Brain MRI typically shows bilateral hyperintense lesions in T2-weighted sequences involving the white matter of the posterior areas of the brain. It should be noted, however, that the cortex and more anterior areas of the brain may also be involved and that unilateral changes are also pos-

sible. Cortical enhancement has also been occasionally described. FLAIR sequences are more sensitive for detecting alterations. These lesions are thought to represent vasogenic oedema. It is important to recognize and treat other factors that may contribute to this syndrome: renal failure, sustained arterial hypertension, hypomagnesaemia, hyponatraemia, and simultaneous use of other drugs, such as chemotherapeutic agents (cyclophosphamide) and antibiotics (linezolid). Although PRES resolves without complications in most cases, if treated promptly, it must be emphasized that delay or inadequate treatment may result in permanent damage, related to brain haemorrhage, especially if thrombocytopenia co-exists, or atrophy of the involved cerebral areas. Unlike with isolated seizures, the offending drug should be discontinued. The occurrence of PRES seems to be of prognostic value. One study found that patients who developed this complication within the first 100 days after HSCT had a shorter survival time [7].

Developing neurologic complications with one calcineurin inhibitor does not necessarily imply that another will cause the same problem and, therefore, when neurologic complications occur with cyclosporine or tacrolimus, it is a reasonable first step to attempt switching to the alternative drug.

To summarize, the most frequent symptom leading to the consultation of a neurologist at this stage is acute diffuse encephalopathy with or without seizures. A careful clinical evaluation should be followed by brain neuroimaging (CT or preferably MRI) and lumbar puncture should be considered if CNS infection is suspected. Neuroimaging may disclose brain haemorrhage or PRES. If imaging is normal, the differential diagnosis includes organ failure, sepsis, or drug toxicity. Among the different drugs commonly used at this stage, cyclosporine is the most frequent offender. Other possibilities include steroids, amphotericin, acyclovir, and opioid drugs. Two treatable conditions in this setting that should not be missed are Wernicke encephalopathy and non-convulsive status epilepticus. Very often the aetiology will be multifactorial. Many episodes of post-transplant delirium may be transient and benign, but some patients may develop chronic cognitive deficits.

Post-Engraftment Period

Days 30–100: Engraftment

Once the hematopoietic stem cells have engrafted, the 2 main medical complications that may occur are infections and GVHD [19, 20].

At this stage, neutropenia has resolved and the external barriers should be healed, but the developing new immune system is still immature, and cell-mediated immunity, humoral immunity, and phagocytic function are not yet effective. For example, the engrafted immune system cannot mount an adequate immune response against polysaccharide-encapsulated bacteria, such as pneumococcus, haemophilus influenza, or meningococcus. Vaccination against these germs is thus recommended. Also, in allogeneic transplantation, the need for immunosuppressants to prevent GVHD will increase further the risk of infections.

For this reason, it is common practice to use prophylactic antimicrobial drugs. The choice of these drugs must be individualized for each patient. Immune status, for example, presence of antibodies against HSV, and history of previous infections, for example tuberculosis, are important considerations in this regard and should be carefully assessed before transplantation. Commonly used drugs include wide-spectrum antibiotics, fluconazol (*Candida* spp), acyclovir (*Herpes* virus), and co-trimoxazole (*Pneumocystis* spp). When dealing with a patient with a suspected infection, it is crucial to know their exact prophylactic regime, as this may alter the possible causative germs.

Bacterial infections at this stage are less frequent than in the pre-engraftment period. They are commonly caused by opportunistic bacteriae, such as *Listeria* spp, which may cause meningitis or rhombencephalitis (encephalitis involving brainstem and cerebellum), and filamentous bacteria, such as *Nocardia* spp.

Viral infections are more common at this stage, owing to the inefficient cellular and humoral immune response. This can lead to reactivation of latent viruses in seropositive patients or in the stem cells from the donor. Amongst these cytomegalovirus (CMV) infections are common and may involve the CNS, often with fatal consequences. Adenoviral infections are also frequent and may disseminate and cause meningoencephalitis [21]. Limbic encephalitis resulting from reactivation of Human-Herpes-virus type 6 (HHV6) is a characteristic infectious complication of patients with allogeneic HSCT at this stage [22]. Patients present with confusion, seizures, and anterograde amnesia. Brain MRI typically shows signal changes in the mesial temporal lobes. Again, FLAIR sequences are more sensitive. EEG may show epileptic discharges arising from the temporal lobe. CSF may show pleocytosis or raised protein, but it can be normal. CSF PCR for HHV6 confirms the diagnosis. Treatment with foscarnet may be effective, but cognitive sequelae are common.

A common fungal infection in this period is pulmonary aspergillosis, which may seed haematogenously to the CNS. Brain MRI may show multiple small cortico-subcortical abscesses. These fungi have a particular predilection for blood vessels, and the lesions may be associated with areas of ischemia or haemorrhage [23]. Others include *Cryptococcus* spp and *Candida* spp. The clinical syndrome can be helpful in establishing the aetiology of fungal infections. Filamentous fungi tend to cause brain abscesses (*Aspergillus*) whereas yeast fungi tend to cause meningitis (*Cryptococcus* spp, *Candida* spp).

Also arising at this stage, and from here onwards, 2 specific complications may occur, related to the development of a more effective cell-mediated and humoral immunity: immune reconstitution inflammatory syndrome (IRIS), also known as immune recovery syndrome, and GVHD. In IRIS, as the immune system matures and cell-mediated immunity recovers, an exaggerated inflammatory response against previously acquired infections may develop, which can either, paradoxically, worsen previous symptoms (paradoxical IRIS) or uncover a previously asymptomatic opportunistic infection (un-

masking IRIS) [24]. The optimal treatment for this condition is not well-established. In paradoxical IRIS, reactions causing spontaneous improvement are frequent and additional therapy is seldom needed. In unmasking IRIS, the most common approach is to administer antimicrobial drugs against the causative agent. In severe cases, immune-modulator agents, such as corticosteroids or non-steroidal anti-inflammatory drugs can be used to suppress inflammation until the infection has been controlled. CNS infections which are commonly associated with IRIS include viral encephalitis (CMV, Varicella-Zoster virus [VZV]), fungal CNS infections (*Cryptococcus* spp, *Aspergillus* spp, *Candida* spp), and progressive multifocal leukoencephalopathy (JC virus).

In GVHD, graft-derived allogeneic T-cells react against antigenic targets of the host cells, which they recognize as foreign. The incidence is higher in recipients of mismatched (non-identical HLA) or matched unrelated donors, in older patients, and in patients who have not received adequate immunosuppressive regimes [25]. There are 2 well-characterized clinical forms: acute and chronic GVHD. Acute GVHD develops within the first 100 days after transplantation and is a specific syndrome involving skin, liver, and the gastrointestinal system. It presents most commonly 4 weeks after transplantation with a pruritic erythematous rash. The liver is also often involved causing cholestasis, with raised levels of bilirubin, alanine amino-transferase (ALT), aspartate amino-transferase (AST), and alkaline phosphatase (AP). Intestinal involvement will manifest as diarrhoea and abdominal pain. Acute GVHD very rarely affects the nervous system and neurological complications are more often related to the treatments used for prevention and management of the condition: high doses of intravenous corticosteroids, antithymocyte globulin, and monoclonal antibodies targeting T-cells.

Late Post-Transplantation Period

Days > 100: Chronic Phase

Neurological complications arising at the chronic stage include infections, chronic GVHD, and secondary neoplasms.

The most common infections are again viral. VZV is the most frequent causative agent. This occurs most often through reactivation, which can be prevented with prophylaxis with acyclovir in seropositive patients. Most patients will present with shingles, which may result in severe post-herpetic neuralgia, but some may develop chickenpox. Disseminated VZV infection, which may involve the CNS, occurs more frequently in patients with chickenpox, but may also happen after shingles. Other relevant viral infections at this stage are those due to the Epstein-Barr virus (EBV) and JC virus. EBV infection can present with a wide range of severity, ranging from a benign febrile illness, resembling infectious mononucleosis, to a severe neoplastic disease, the post-transplant lymphoproliferative disorder (PTLD) [26]. In PTLD, infection of a clone of B-cells by EBV combined with reduced T-cell surveillance, due to immunosuppressive therapy, results in unrestrained proliferation of the B-cell clone. This lymphoma may spread to extra-nodal sites, including the CNS, either in the form of focal brain lesions or as diffuse lymphomatous meningitis. PTLD has also been associated with para-

neoplastic neurological syndromes: 2 patients with paraneoplastic neuropathy and anti-Tr antibodies have been reported [15]. PTLN is associated with a very poor prognosis. JC virus infection of the CNS causes progressive multifocal leukoencephalopathy (PML), a distinct syndrome which presents with visual, cognitive, and motor symptoms [27]. Brain MRI typically shows multifocal non-enhancing asymmetric white matter hyperintense lesions in T2 and FLAIR sequences. DNA of the JC virus can be detected in CSF by PCR. Prognosis is also sombre. Bacterial infections are rare, unless there is coexistent GVHD. The most common causative agents are encapsulated bacteria (*Pneumococcus*, *Meningococcus*, *Haemophilus influenzae*), especially in patients who have not been properly vaccinated. They all may cause meningitis. Fungal infections include cerebral toxoplasmosis and meningitis due to *Cryptococcus neoformans*. *Toxoplasma gondii* is an obligate intracellular parasite. It causes opportunistic infections of the CNS in the form of discrete mass lesions (abscesses) or diffuse meningoencephalitis. Lesions of necrotizing encephalitis may also be associated with secondary vascular changes, including vasculitis, oedema, and haemorrhage.

GVHD developing or persisting beyond the 100th day post-transplant is defined as chronic. This condition emulates autoimmune diseases. Clinical manifestations will thus resemble those of primary dysimmune disorders, such as progressive sclerosis, Sjögren's syndrome, systemic lupus, or primary biliary cirrhosis. The skin and mucosae are often involved. Patients may develop lichenoid lesions, sicca syndrome, and malar rash. Other systemic manifestations include arthritis, obliterative bronchiolitis, and cholestasis. Neurologic complications are common and involve most frequently the peripheral nervous system: polymyositis, myasthenia gravis, neuromyotonia, and acute or chronic demyelinating neuropathies. Treatment follows the same guidelines used for their primary autoimmune counterparts, combined with basal treatment for chronic GVHD. Rarely, chronic GVHD may affect the central nervous system in the form of cerebral angiitis [28].

Conclusions

Neurologic complications of HSCT are frequent. As the use of these procedures expands and their indications widen, the prevalence of these complications is expected to increase. Diagnosis of the neurological problems in this setting is difficult and requires for the physician to be familiar with the steps of the procedure, the most common medical complications, the treatments employed, and their possible adverse reactions. Research is important, not only to optimize prevention and treatment of these often devastating complications but also to help understanding the mechanisms underlying dysimmune disorders and the biological interactions between stem cells and the nervous system, which might eventually allow for the development of regenerative therapies for neurological disorders.

Conflict of Interest

None.

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