Fungal encephalitis following bone marrow transplantation: Clinical findings and prognosis

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ABSTRACT

Background: Central nervous system fungal infections (FI) are important complications and a cause of mortality in patients who receive hematopoietic stem cell transplantation (HSCT). Aims: To study the clinical aspects of fungal encephalitis (FE). Settings and Design: The study was carried out at the HSCT Center of the Hospital de Clínicas, Federal University of Paraná, Curitiba, Brazil. Materials and Methods: Clinical records and autopsy reports from patients submitted to HSCT with a diagnosis of FE. Results: Twelve patients were diagnosed with FE presenting with lowered level of consciousness, hemiparesis and seizures. We were able to identify two subgroups regarding susceptibility to FE: (1) patients with early onset FI and severe leucopoenia, and (2) patients with later onset FI with graft-versus-host disease using immunosuppressive drugs. Eleven of the patients died directly due to the neurological complication, all had post-mortem confirmation of the diagnosis of FI. Conclusions: These clinical, paraclinical and temporal patterns may provide the opportunity for earlier diagnosis and interventions.

KEY WORDS: Allogeneic hematopoietic stem cell transplantation, A*spergillus* sp, central nervous system infection, fungal encephalitis, mucormycosis

Several factors are responsible for the severe suppression of cell-mediated immunity in subjects receiving hematopoietic stem cell transplantation (HSCT). These include: the underlying disease, receipt of pre-transplant chemotherapy and radiotherapy, graft-versus-host disease (GVHD) and its treatment. Infections of various etiologies involving the central nervous system (CNS) may be an important source of morbidity and mortality in these patients.[1,2] Acute encephalitis is characterized by headache, fever, focal neurological signs, seizures, CSF pleiocytosis, focal EEG changes and imaging abnormalities.[3] The intervals from the HSCT procedure to onset, frequency and prognosis of fungal encephalitis (FE) have not been systematically reported. Through this publication, we intend to determine and describe clinical features and prognosis of patients who developed FE after having undergone HSCT.

Materials and Methods

This was a retrospective study that included the database of the HSCT Center of the Hospital de Clínicas, Federal University of Paraná, Curitiba, Brazil. This tertiary healthcare center has been active for the last 25 years and is the most important in Brazil. The center's most recent updated database includes information of 1616 recipients of HSCT (1493 allogenic and 123 autologous). This study was approved by the Hospital de Clínicas of the Federal University of Paraná Ethics Committee.

Post-bone marrow transplantation (BMT) clinical data and complications for 1000 patients were routinely recorded in a database and these subjects constituted the study population. Additional information was obtained from chart records and autopsy reports. We reviewed the records of all patients diagnosed with FE after BMT. Diagnosis of FE was made based on the presence of neurological signs, associated with evidence of fungal infection (FI) of the lung or para-nasal sinuses or presence of disseminated FIs. Graft-versus-host disease was diagnosed and graded from II to IV according to the Seattle criteria.[4]

Results

Infections of the CNS were found in 90 (9%) patients. All of them were recipients of allogenic BMT. Amongst them, 12 patients (1.2%, 10 males) had FE. The fungi were isolated from the sputum (six cases) and paranasal aspiration biopsy (five cases). In the remaining patient the diagnosis of FI could be ascertained only on the basis of post-mortem examination. Incidentally, all patients had post-mortem neuropathological confirmation of FE. The mean age of patients with FE was 24 ± 17.6 years (range: 3-61 years). The underlying diseases for which the patients had undergone BMT included: aplastic anemia (n = 5), chronic myeloid leukemia (n = 3), Fanconi anemia (n = 1), acute myeloid leukemia (n = 1), Hurler disease (n = 1), and idiopathic myelofibrosis (n = 1).

The most frequent clinical presentations were altered level of consciousness in seven (58%) patients, focal and generalized seizures in six (50%) and hemiparesis in five (42%) [Table 1].

Table 1: Fungal encephalitis following bone marrow transplantation - demographics and clinical findings

Patient	Age*	Gender	Primary diagnosis	Symptoms onset†	Clinical presentation	Successful engraftment	GVHD	Leukocyte count (cells/mm³)	Isolated fungus	Death due to fungal infection
1	12	M	SAA	13	Seizures, Coma	No	No	8	*A*spergillus sp	Yes
2	6	F	SAA	12	Coma	No	No	0	*Fusarium* sp	Yes
3	33	M	SAA	0	Hemiparesis, Coma	No	No	10	*Aspergillus* sp	Yes
4	14	M	SAA	10	Hemiparesis, Headache	No	No	5	*Aspergillus* sp	Yes
5	11	M	SAA	30	Seizures, Headache	No	No	35	*Aspergillus* sp	No (RSV pneumonia)
6	61	M	AML	12	Status Epilepticus, Hemiparesis	No	No	15	*Aspergillus* sp	Yes
7	9	F	FA	77	Seizures, Coma	Yes	Yes	2500	*Aspergillus* sp	Yes
8	39	M	CML	50	Seizures, Hemiparesis	Yes	Yes	7300	*Aspergillus* sp	Yes
9	36	M	CML	227	Sinusitis, Proptosis, Ophtalmoplegia	Yes	Yes	1430	*Mucor* sp	Yes
10	38	M	CML	144	Seizures, Hemiparesis	Yes	Yes	2300	*Aspergillus* sp	Yes
11	3	M	HD	160	Coma	Yes	Yes	3000	*Aspergillus* sp	Yes
12	26	M	IM	107	Coma	Yes	Yes	5	*Aspergillus* sp	Yes
Mean	24			9.7	-	-	-	1384	-	-
(SD)	(17.6)			(63.5)	-	-	-	(2192.8)	-	-

*Age at BMT (in years); Gender (M = Male, F = Female); Disease (SAA - Severe aplastic anemia; AML - Acute myeloid leukemia; FA - Fanconi anemia; CML - Chronic myeloid leukemia; HD - Hurler disease; IM - Idiopathic myelofibrosis); †Onset of symptoms after BMT (days); GVHD = Graft-versus-host-disease; RSV = Respiratory syncytial virus

Table 2: Fungal encephalitis after BMT - Subgroups

Subgroup	1	2
Number of cases	6	6
Time of onset (days)	12.8 ± 9.7 (0-30)	129.1 ± 63.5 (50-227)
White-cell count (per mm³)	12.1 ± 12.2 (0-35)	2755.1 ± 2462 (5-7300)
Graft-versus-host disease	No	Yes
Use of steroids/immunosupressive drugs	No	Yes

Aspergillus sp was isolated from the brain tissue in 10 patients, *Mucor* sp and *Fusarium* sp accounted for the remaining two subjects. All of these patients also had other foci of FI, including pulmonary infection (50%) and paranasal sinus infection (41,6%).

Two subgroups of patients could be identified with regards to timing of FI, blood leukocyte count (BLC) and association with GVHD. In six patients the mean time to onset of FE was 12.8 ± 9.7 (range: 0-30) days after the BMT. In these subjects, none developed GVHD, the mean BLC was 12.1 ± 12.2/mm³, neutrophil cell count (NCC) 5.9 ± 12/mm³. The remaining six patients had a longer mean time to onset of FE of 129.1 ± 63.5 (range: 50-227) days, higher mean BLC (2755.1 ± 2462/mm³) with mean NCC of 1505.3 ± 716/mm³. All the subjects in this subgroup developed GVHD (Grade II, III and IV) and were taking corticosteroids and/or immunosuppressive drugs [Table 2]. Eleven of the 12 patients died directly due to FE. One subject succumbed to respiratory syncytial virus (RSV) pneumonia [Table 1]. Cerebrospinal fluid analyses (performed in four cases) showed cell count, protein and glucose levels within normal range. Computerized tomography (CT) was performed in all cases, six also underwent magnetic resonance imaging (MRI). The CT scans were normal in three cases and showed hypodense lesions without contrast enhancement in the remaining. The MRI scans of all patients showed hyperintense signals in basal ganglia on T1-weighted sequences, compatible with the diagnosis of encephalitis. None of the findings from brain imaging were particular to any of the two subgroups described above.

Discussion

In our series, the vast majority of the cases of FE was caused by *Aspergillus* sp (83.34%) but also included one case of FE by *Fusarium* sp (8,33%) and one case by *Mucor* sp (8,33%). One of our main findings was the identification of two subgroups with susceptibility to develop FI: 1) patients who developed FI soon after BMT and had severe leukopenia due to unsuccessful engraftment, and 2) patients with later onset of FI who had GVHD and were taking corticosteroids or immunosuppressive agents. In both groups the most frequent clinical presentation included impairment of consciousness, focal seizures (both in 50% of cases) and hemiparesis (41.6%). Headache and ophthalmoplegia with proptosis were found in one case each. In our series, the mortality rate was 100%, and out of 12 patients, 11 died directly due to FE. The reasons for the occurrence of these two distinct patterns in patients with FE remain unknown as we cannot identify any specific factor that could have significantly contributed for the different presentations. On the other hand, we believe that this observation may have future implications in regard to prevention, earlier identification and interventions.

Previous studies have shown that CNS aspergillosis has a poor prognosis and a high mortality rate (more than 90%), which is compatible with our findings.[5] Occurrence of invasive FIs in HSCT recipients remains a significant cause of morbidity and mortality, especially when the CNS is affected.[4,6,7] *Aspergillus* sp is the fungus most frequently isolated in cases of FE, followed by *Candida* sp. Central nervous system involvement occurs in 40-50% of patients with invasive aspergillosis, and a 1.2-5% incidence of aspergillosis of the CNS in allogeneic HSCT recipients has been reported.[4-10]

In humans, aspergillosis occurs mainly in immunocompromised patients after inhalation of the spores of the microorganism causing primarily lung infections. This fungus is angioinvasive and causes CNS infarcts (usually hemorrhagic) by occlusion of intracerebral blood vessels. Abscesses may be formed later, by invasion of the brain parenchyma. Clinical presentation includes focal signs and is associated with headache, impairment of consciousness, hemiparesis and seizures. Almost all patients typically have CNS involvement associated with invasive pulmonary aspergillosis.[7,8,10,11]

Routine and microscopic examination of the CSF does not usually provide definitive evidence of aspergillosis of the CNS. The CSF examination may be totally normal or may show only a moderate increase in the protein concentration and/or mild pleocytosis.[11] Definitive diagnosis requires histological documentation of the infection on CNS samples, positive culture for *Aspergillus* sp from the CNS lesions, a positive PCR on CSF examination or positive enzyme-linked immunosorbent assay (ELISA) and latex agglutination test (galactomannan antigen of *Aspergillus* sp). Awaiting results of these specialized investigations could delay initiation of therapy.[10,11] Although aspergillus galactomannan antigen detection is commonly used in the diagnosis of invasive apergillosis, this test was not available at our center. Brain imaging studies show acute infarcts, most commonly in the basal ganglia with no parenchymal enhancement. Magnetic resonance imaging is considered to be more accurate and sensitive for the diagnosis of these multiple lesions as compared to CT. Abscesses or granulomas may appear as ring or nodular enhancing lesions, and these normally occur when the host immunological system is capable of responding to the infection.[9] There is only one previous report of encephalitis caused by mucormycosis, a rare opportunistic infection caused by inhalation of fungi of the family *Mucoraceae* (*Absidia, Apophysomyces, Mucor, Rhizomucor and Rhizopus*). Risk factors for developing this infection in HSCT recipients include neutropenia, impaired humoral immunity and prolonged use of corticosteroids. A case of *Fusarium* sp. encephalitis in a six-year-old child with severe aplastic anemia (SAA) who underwent allogeneic BMT has been described. This case was reported by Bleggi-Torres *et al.*,[12] in 1996 and represents the first description of *Fusarium* sp encephalitis in a BMT patient with SAA.

In conclusion, our series of patients showed two subgroups regarding susceptibility to FE. The findings of these two distinct patterns of clinical, paraclinical and temporal presentations may provide opportunities for earlier diagnosis and interventions.

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