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ORIGINAL ARTICLE

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Toxoplasma gondii infection in patients with hematological malignancies

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Abstract Toxoplasmosis is one of the most common parasitic infections in humans, but in most cases it does not cause serious illness; this protozoan can nevertheless cause devastating disease in immunocompromised hosts such as HIV-positive individuals. Only rarely is toxoplasmosis documented in hematological patients, and among them, those who undergo a transplant procedure are more frequently affected. In a retrospective multicenter survey, we collected data on six cases of toxoplasmosis in hematological patients. In the majority of cases, patients had undergone transplant procedures (five had undergone autologous or allogeneic transplantation). This complication needed special care in diagnosis, usually based on serology, neuroradiology, and PCR examination. However, in our experience the appropriate therapeutic approach was successful in the majority of cases.

Keywords Bone marrow transplantation · Leukemia · *Toxoplasma gondii*

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Introduction

Toxoplasmosis is a rare but often lethal complication in the immunocompromised host such as AIDS patients or bone marrow transplant (BMT) recipients, so that most of the published reports about this topic refer to these two categories of patients; its rates have risen since the outbreak of HIV and the more widespread use of BMT procedures in the management of hematological malignancies [1–4].

In immunocompetent individuals, acute toxoplasmosis most often results in asymptomatic infection [5]. In the immunocompromised patient, conversely, toxoplasmosis may cause fulminant disseminated disease, localized in most cases in the central nervous system (CNS).

In a review of current literature, approximately 112 cases of disseminated toxoplasmosis following BMT were reported [3]. In most of the cases, the diagnosis was made only at autopsy; brain, lungs, and heart were the most frequently involved organs.

In the present study we want to analyze the clinical characteristics of *Toxoplasma gondii* infection and the procedures that favored diagnosis of, and a better outcome for, patients affected by hematological malignancies admitted during a 10-year period in GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) centers.

Materials and methods

All cases of toxoplasmosis in adult patients (>12 years of age) with hematological malignancies, observed between January 1993 and December 2002 in 21 GIMEMA centers, were retrospectively collected. Hospital records of patients with toxoplasmosis were reviewed to gather information regarding demographic data (age, sex), and type and stage of underlying hematological disease; patients with a hematological malignancy related to HIV infection were excluded from the study, because of the high incidence of toxoplasmosis in AIDS patients.

Further, the date of diagnosis of each new case, clinical manifestations at presentation, radiological imaging, and antigen detection in serum were reviewed. Data on type of drugs employed and total doses and duration of treatment for toxoplasmosis were

also noted. Patients had a follow-up of 100 days after the diagnosis of toxoplasmosis. Mortality was judged to be due to toxoplasmosis when death occurred within 30 days of the diagnosis. An autopsy was carried out on all patients who died.

In clinical practice, diagnosis of toxoplasmosis, particularly of CNS localization, is based on noninvasive methods:

(a) Serology and polymerase chain reaction (PCR)
(b) Response to antitoxoplasmosis therapy: clinical improvements are generally observed after 2 or 3 weeks of treatment
(c) Radiological pattern, in particular nuclear magnetic resonance (NMR), with characteristic features, such as multiple ring-enhancing lesions, with edematous reaction and mass effect

When the clinical or radiological evidence is not conclusive, a brain biopsy should be considered as soon as possible [6].

Results

During the study period, a total of six toxoplasmosis cases were observed in five hematological centers. In the remaining 16 centers, no toxoplasmosis cases occurred. The hematological diagnosis was Hodgkin's disease (HD) and acute lymphoblastic leukemia (ALL) in two cases each, and non-Hodgkin's lymphoma (NHL) and acute myeloid leukemia (AML) in one case each. Apart from the case with AML, all patients had undergone a transplant procedure before developing toxoplasmosis.

Except for one patient who presented toxoplasmosis at diagnosis of AML, four patients were in remission of the malignancy, after autologous transplantation (autoBMT) or allogeneic transplantation (alloBMT), at the time of diagnosis of the complication, while the other one presented a relapse after alloBMT. The allogeneic transplant recipients presented graft-versus-host disease (GVHD) when toxoplasmosis occurred (Table 1).

In the absence of documented cases of toxoplasmosis from 16 centers participating to the survey, the incidence of toxoplasmosis was evaluated only in the centers that reported a proven or suspected case; furthermore, this evaluation was conducted only on transplant patients, who represented the majority of cases. During the study period, in the five centers that observed cases of toxoplasmosis, 2,574 transplant procedures were performed: 2,193 patients underwent an autologous transplantation, the remaining 381 patients were treated with an allogeneic transplantation. Thus, the global incidence of toxoplasmosis was 1.9/1,000 patients, while the incidence relative to autologous or allogeneic transplantation was 0.9/1,000 patients and 8/1,000 patients, respectively. General features of patients are shown in Table 1; the proportion of males to females was 4:2; ages ranged between 18 years and 66 years.

Table 1 General features of patients with toxoplasmosis. *HD* Hodgkin's disease, *N-S* nodular sclerosis, *ALL* acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *NHL* non-Hodgkin's lymphoma, *autoPBSCT* autologous peripheral blood stem cell transplantation, *alloBMT* allogeneic bone marrow transplantation, *PR* partial remission, *CR* complete remission, *Na* not applicable.

Patient	Sex	Age	Pathology	BMT	GVHD	Status
1	M	46	HD N-S IIIB	autoPBSCT	Na	PR
2	M	18	ALL	MUD	Yes	CR
3	M	22	HD	AlloBMT	Yes	CR
4	M	54	AML	No	Na	Onset
5	F	29	ALL	AlloBMT	Yes	Relapse
6	F	66	NHL	autoPBSCT	Na	CR

Four patients received steroid treatment: in three cases, steroids were still administered at the time of diagnosis of infection; these patients received steroid therapy for a median period of 35 days (30–150), with a median daily dosage of 37.5 mg of methyl-prednisolone (range 15–60) and a median total dose of 1,800 mg (range 900–2,100).

Five patients presented a low absolute neutrophil count at the time of diagnosis of toxoplasmosis, with a median level of 0.9×10^9 l^{-1} (range $0.45–1.2\times10^9$ l^{-1}); in four of these cases, lymphocyte count also was lower than normal, with a median level of 0.45×10^9 l^{-1}, ranging between 0.2 and 0.6.

Prophylactic approaches differ according to each participating center and according to the personal clinical experience. Only one patient had received a prophylactic treatment with pentamidine, while in the other five cases, no prophylaxis was administered.

Table 2 shows the clinical presentation of toxoplasmosis in these patients. In five cases, CNS was involved, as the only localization or as one of the sites of infection. The most frequent signs in these patients were neurological disorders, such as seizure, cephalalgia, and projectile vomiting: the only case who did not show such a symptomatology presented a blood-limited infection. Fever was present in four patients: in three patients with CNS involvement, and in the patient with blood-limited infection; two patients with CNS involvement did not show fever. None of these patients suffered for pneumonia.

In four cases, a brain magnetic nuclear resonance (MNR) was performed, revealing multiple bilateral hypodense or hyperdense subcortical areas; in another patient a brain computed tomography (CT) scan was positive for "multiple hypodense lesions" with a moderate contrast enhancement.

In all cases, the test for serological positivity for anti–*T. gondii* IgM/IgG was performed; in two of these patients serological examinations performed before the transplant procedure had shown an IgG positivity.

During infection, IgM positivity was found in only two cases. In one of these patients, *T. gondii* was also detected in the spinal fluid by microbiological examination. The other patient presented a concomitant *Cryptococcus neoformans* infection. As a rule, all hematological patients are screened for *Toxoplasma* infection, and the rate of IgG positivity is about 50%, as in the general population.

In the only patient who underwent a CNS biopsy, a PCR analysis was conducted on cerebral tissue, showing the presence of the parasite's DNA. The immunohistochemical assay conducted at the same time gave a negative result. Only in one case did the infection remain undiagnosed until death; in this case, time of onset of the complication remained unknown; in one case, toxo-

Table 2 Clinical presentation of *Toxoplasma* infection. *C* communitarian, *N* nosocomial, *CNS* central nervous system, *MNR* magnetic nuclear resonance, *PCR* polymerase chain reaction

Patient	Source	Symptoms	Site of infection	Absolute neutrophil count (per mm^3)	Empirical treatment	Radiological findings	Diagnosis
1	C	Fever, fatigue, cephalalgia	CNS	600	Yes	Brain MNR: multiple lesions	PCR on CNS biopsy
2	C	Fever, projectile vomiting	CNS	1,100	Yes	Brain CT: multiple lesions	Presumptive
3	C	Fever, left side paresis	CNS	1,200	Yes	Brain MNR: two lesions	Presumptive
4	C	Fever	Blood	450	No	None	Presumptive
5	N	Fever, cephalalgia projectile vomiting	Disseminated	900	No	Brain MNR: multiple lesions	Autopsy
6	C	Fatigue	CNS	3,000	No	Brain MNR: multiple lesions	Serology, lumbar puncture

plasmosis was diagnosed at the onset of the hematological malignancy, while in the other cases the detection of *T. gondii* occurred between 40 and 120 days after the last chemotherapy. Three patients were empirically treated with high dose broad-spectrum antibiotics at the onset of fever; the other patients did not receive any empirical treatment.

Once the diagnosis was at least presumptively achieved in five patients, they were specifically treated with pyrimethamine and sulfadiazine, or spiramycin. The patient who remained undiagnosed and presented a disseminated infection did not receive any antimicrobial treatment and died. All the remaining five patients showed good improvement in their CNS lesions.

All patients were alive at day 30 from the diagnosis of infection, or from the probable onset of infection in the undiagnosed case. After 6 months from diagnosis, two of them were still alive, three had died because of the basic pathology; only in one case did toxoplasmosis account for death; an autopsy was carried out only in one case.

Discussion

This study, conducted on the basis of a retrospective multicenter survey, clarifies the relevance of toxoplasmosis in the managing of oncohematological malignancy patients. Our data demonstrate that toxoplasmosis is quite negligible in those patients with hematological malignancies who do not undergo transplant procedures, in fact we observed only one case of toxoplasmosis in this kind of patient. Furthermore, while toxoplasmosis is very rare during autologous procedures (less than 1/1,000), its incidence seems to be appreciable in allogeneic transplantation (8/1,000): these findings confirm previously reported data [7]. In consideration of the fact that in the majority of centers no cases were registered we must consider that the incidence there is lower than that in centers that reported cases.

This series allows us to confirm the importance of heavy immunosuppression in the development of this complication. In fact all alloBMT recipients suffered from a GVHD at the time of infection, and three patients presented a low lymphocyte count, as happens in AIDS patients: these data are consistent with the widespread occurrence of toxoplasmosis among HIV patients [8].

Toxoplasma gondii encephalitis is the main clinical presentation and can be difficult to confirm by serological test; usually the clinical diagnosis is supported by demonstration of brain lesions on CT scan or, better, NMR [9]. The radiological findings often show typical multiple lesions in the basal ganglia and in the corticomedullary junction of the cerebral and cerebellar hemispheres.

In our series, diagnosis remained presumptive in three out of six patients until the response to antimicrobial therapy [10]; in the other cases, diagnosis was achieved by cultural examination of liquor [11], by PCR testing of a cerebral lesion [12], and by autopsy.

Only in one case could the infection be reasonably associated with death, based on its resistance to antimicrobial therapy, but even this patient was still alive at day 30 from diagnosis. In contrast to the 66% mortality rate in bone marrow recipients that has been reported in the literature, we observed a mortality rate of 20% among our BMT recipients with toxoplasmosis [3, 8].

In conclusion, it is possible that diagnostic problems lead to an underestimation of the real incidence of this infectious complication [13]: a diagnostic approach is still not standardized in GIMEMA centers; usually it should consist of serological, radiological, histopathological (when possible), and PCR-based techniques [14]. On the other hand, the rarity of toxoplasmosis in this setting could be associated with the widespread use of trimethoprim/

sulfametoxazole (or pentamidine)–based prophylaxis [7]: in our series, five out of six patients who developed toxoplasmosis had not received any prophylactic treatment.

The absence of observations of toxoplasmosis at autopsy in the patients who died in the participating centers in this study, induces us to retain our view that toxoplasmosis represents an infectious complication that is rarely of concern in hematological malignancies.

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