42
Toxoplasmosis After Hematopoietic Stem Cell Transplantation

Rodrigo Martino

Toxoplasma gondii is a protozoan that commonly infects animals and birds. Although *T. gondii* infection in humans is usually asymptomatic, clinical disease occurs in the immune suppressed patient. Infection may be acute (recently acquired) or chronic (latent). *T. gondii* exists in three forms during its life cycle: the tachyzoite, which is the asexual invasive form; the tissue cyst (containing bradyzoites), which persists in the tissues of the infected host during the chronic phase of the infection; and the oocyst (containing sporozoites), which is produced during the sexual cycle in the intestine of the definitive host—the cat. Transmission to humans occurs by ingesting tissue cysts or oocysts, or by blood product transfusion or organ transplantation. Following infection by oral ingestion, tachyzoites disseminate from the gastrointestinal tract and can invade virtually any cell or tissue where they proliferate and produce necrotic foci surrounded by inflammation. In immune suppressed patients, acute infection may result in severe damage to multiple organs. Even in individuals with a normal immune response, tissue cysts form in multiple organs (latent infection), and can subsequently give rise to a severe localized reactivation producing, for example, toxoplasma encephalitis or chorioretinitis.

Toxoplasmosis appears to be a relatively rare opportunistic infection following hematopoietic stem cell transplantation (HSCT). Up to the late 1990s, only 55 cases had been reported after HSCT [1–3], which contrasted with the high frequency of this complication in other patient populations with severe cellular immunodeficiencies, mainly advanced acquired immunodeficiency syndrome (AIDS). Table 42-1 summarizes the case series of toxoplasmosis in HSCT published until mid-2015, and all other cases have been described as case reports. As of mid-2015, around 300 cases of toxoplasmosis have now been reported in HSCT in peer-reviewed manuscripts, a figure that still seems small when compared with other relevant infectious complications in these patients.

The seroprevalence for *T. gondii* varies greatly between and even within countries, ranging from <15% in some North American and Japanese studies [4] and in pediatric wards, to 50–80% of adult HSCT recipients in countries with high endemicity such as France or Turkey [1, 5, 16]. This varying seroprevalence is probably the main reason for the great variability in the frequency of diagnosed cases of toxoplasmosis after HSCT, which has been estimated to average 0.8% [17], with <0.4% in areas of low endemicity to 2–3% in those with high antibody prevalence. The disease, however, is underdiagnosed, since more than half of the cases reported in the literature were diagnosed at autopsy (see Table 42-1).

Toxoplasmosis occurs mainly in allogeneic transplant recipients, although cases after autologous transplants have been published [2, 7, 18], and some are included in Table 42-1. Around 90% of patients are seropositive before HSCT, indicating that reactivation of latent tissue cysts in previously infected individuals is the usual mechanism implicated, as has been demonstrated in AIDS patients. It is, thus, important to determine the patients' serostatus prior to transplant. However, the disease may also develop in seronegative recipients from seronegative donors, suggesting that primary infection after transplant may also occur, and primary infections may be more severe than reactivations [46]. The disease usually begins early after transplant with 95% of the cases occurring within the first 6 months after the procedure, although late cases may occur, usually in patients with chronic graft-versus host disease (GVHD) requiring immunosuppressive treatment [7, 19]. Acute GVHD has been suggested as a possible predisposing factor for Toxoplasma disease, and in a study by the European Group for Blood and Marrow Transplantation (EBMT) [7] 77% of cases occurred in patients with moderate-to-severe acute GVHD or chronic GVHD. The central nervous system (CNS) is the main site of disease, but pneumonitis and myocarditis are also frequent findings, particularly when the diagnosis is made at autopsy. In fact, myocarditis, nephritis, and involvement of other deep organs are rarely made clinically but are frequent findings at autopsy [4, 7, 20].

Several recent patient series have added further insight into the importance of not overlooking this infection in this patient population (Table 42-1). A study from the Memorial Sloan-Kettering Cancer Center in New York described ten cases of disseminated toxoplasmosis among 463 patients

P. Ljungman et al. (eds.), *Transplant Infections*, DOI 10.1007/978-3-319-28797-3_42

TABLE 42-1. Results of published case series of toxoplasmosis after HSCT

Author (references)	No. of cases	Number of transplants (% frequency)	Percentage of seropositivity pretransplant in the entire transplant cohort	No. of patients seropositive pretransplant	Median day onset posttransplant (range)	No. treated for toxoplasmosls	No. survived toxoplasmosls	Comments
Derouin et al. [1]	7	296 AlloBMT (2.4)	NS	7	74 (55–180)	2	2	
Slavin et al. [4]	12	3803 AlloBMT (0.31), 509 autoBMT (0)	15	11/11 tested	59 (35–97)	NS	2	
Bretagne et al. [5]	2	550 AlloBMT (0.3)	70	NS	NS	NS	NS	
Chandrasekar et al. [2]	3	662 (0.5)	NS	NS	46 (1–90)	1	None	
Maschke et al. [6]	20[a]	655 (3.1)	NS	20/20	73 (14–689)	NS	5	
Martino et al. [7]	41	4391 AlloHSCT (0.93), 7097 autoHSCT (0)	Variable	31/33 tested	64 (4–516)	23	14	Late disease (after day +63) and having received therapy were associated with improved survival
Mele et al. [8]	2	631 AlloHSCT	NS	2/2	30, 169	1/2	1/2	
Roemer et al. [9]	8	301 AlloHSCT	NS	8/8	120 (41–280)	4/8	3	CD4+ cell counts <100/μL
Small et al. [10]	10	463 AlloBMT (2.2)	23	7/10	78 (36–155)	5	1	Risk factors for toxoplasmosis were: unrelated donor BMT and recipient seropositivity pretransplant
Matsuo et al. [11]	2	925 AlloHSCT (0.2), 641 autoHSCT (0)	NS	NS	60, 100	2	2	Seroprevalence NS
Janitschke et al. [12]	3	75 AlloBMT (4)	71	3/3	72 (38–135)	3	1	18/22 Seronegative recipients became IgG positive shortly after transplant
Lim et al. [13]	2	220 AlloHSCT (0.9)	30	2/2	45, 95	2	1	All patients received in vivo T-cell depletion with alemtuzumab
Aoun et al. [14]	7	121 AlloHSCT (5), 204 autoHSCT (0.4)	69	4/7	45 (13–140)	7	6	The authors suggest first line therapy with pyrimetha mine clindamycin
de Medeiros et al. [15]	9	789 AlloHSCT (1.14)	NS	9/9	69 (13–265)	1	1	8 cases diagnosed only at autopsy

Rusinakova et al. [35]	4	116 AlloHSCT (2.6%) 395 AutoHSCT (0.3%)	NS	4/4	45 (20–75)	3	3	1 case diagnosed at autopsy only
Mulanovich et al. [36]	9	3626 AlloHSCT (0.25) US pts 0.15 Non-US pts 1.6%	18% US pts >50% Non-US pts	7/7	56 (12–122)	7	1	2 cases diagnosed only at autopsy
Bautista [37]; Martino et al. [38] (cases in adult CBT)	9	148 adult CBT (4%)	45%	6/9	39 (7–98)	7	2	2 cases diagnosed only at autopsy Prophylaxis had been given only to 1/9 cases
Busemann et al. [39]	3	155 AlloHSCT (1.8%)	40%	3/3	75 (32–395)	1	0	2 cases diagnosed only at autopsy None had received prophylaxis
Sumi et al. [40]	6	5/279 AlloHSCT (1.8%) 1/87 AutoHSCT (1.1%)	10%	5/5	NS	2	1	4 cases diagnosed only at autopsy
Hakko et al. [41]	5	170 AlloHSCT (2.9%)	70%	5/5	42 (26–119)	5	2	Study focused only on CNS toxoplasmosis
Nigro et al. [42]	4	12 AlloHSCT (33%)	100%	4/4	25 (18–59)	2	2	2 cases diagnosed only at autopsy, with negative results of the qualitative PCR used for monitoring

Abbreviations: *BMT* bone marrow transplantation, *AlloHSCT* allogeneic hematopoietic stem cell transplantation, *autoHSCT* autologous HSCT, *NS* not specified, *pts* patients, *CBT* cord blood transplantation.
[a]4 definite and 16 possible cases of toxoplasmosis.

who received T-cell-depleted allogeneic bone marrow transplantation (2.2% frequency) [10]. When compared with other studies this frequency appears to be high, especially when considering that the pretransplant seroprevalence was only 23% and that these patients had a very low incidence of moderate-to-severe GVHD. This experience suggests that T-cell depletion may be an independent risk factor for this infection, although a case-control study would be needed to confirm this suspicion. Two other studies have been recently published by the EBMT Infectious Diseases Working Party [7, 21]. The first study summarized the results of a survey among European transplant centers, which showed that this infection occurs almost exclusively after an allogeneic HSCT, with 41 cases diagnosed after 4391 allogeneic HSCT (frequency 0.93%) and none after 7097 autologous HSCT [21]. However, as previously stated, cases have been described after autologous HSCT. Additionally, we have recently seen a case of pulmonary toxoplasmosis 10 months after a CD34+-cell selected autologous HSCT, suggesting that T-cell depletion may also increase the risk after autologous transplants.

Toxoplasma encephalitis typically presents with focal neurologic abnormalities of subacute onset, frequently accompanied by nonfocal signs and symptoms such as headache, altered mental status, and fever. The most common focal neurologic sign is motor weakness, but patients may also present with cranial nerve abnormalities, speech disturbances, visual field defects, sensory disturbances, cerebellar signs, focal seizures, and movement disorders. Meningeal signs are very rare. The cerebral spinal fluid may show slight mononuclear pleocytosis, increased protein, and normal glucose levels. Computed tomography (CT) brain scans often show multiple bilateral cerebral lesions that tend to be located at the corticomedullary junction and the basal ganglia. These lesions are generally hypodense and show ring enhancement after intravenous contrast injection. Magnetic resonance imaging (MRI) scans show lesions as high signal abnormalities on T2-weighted imaging, although other nonspecific space-occupying lesions may be seen [6, 7]. MRI is more sensitive than CT in the early diagnosis of this infection [6].

Toxoplasma pneumonitis may develop in the absence of extrapulmonary disease. Its clinical and radiologic features are nonspecific and may mimic interstitial pneumonitis due to other causes [22–24].

Toxoplasma chorioretinitis appears surprisingly rare compared to the incidence noted in the AIDS population, particularly since many transplant programs utilize eye examination routinely pre- and posttransplant because of the incidence of chronic ocular GVHD posttransplant [25]. Interestingly, two cases of reactivation of toxoplasma chorioretinitis were reported in recipients of autologous transplants [26].

Since toxoplasmosis is so difficult to diagnose histologically in these patients, noninvasive diagnostic tests would be of utmost importance. Isolation of the parasite from blood or body fluids using rodents or cell culture techniques is time-consuming, expensive, and is available only in few routine microbiology laboratories. In the HSCT recipient, the utility of serology is mainly to identify those at risk for developing toxoplasmosis posttransplant, since serologic studies posttransplant are seldom of use. Polymerase chain reaction (PCR) techniques were developed for diagnosis of neonatal infections and for the noninvasive diagnosis of cerebral toxoplasmosis in patients with AIDS [27]. These techniques are applicable in blood, cerebrospinal fluid (CSF), and bronchoalveolar lavage (BAL); the usual samples that are available in HSCT recipients with this infection. However, PCR techniques are not standardized, and thus the results of published studies are difficult to interpret. In AIDS, patients with brain lesions PCR in blood and CSF have a sensitivity of 50–65% and a specificity of 95–100% for toxoplasmosis [28]. Currently, however, the predictive values of any PCR technique for infectious agents in AIDS, HSCT recipients, and other patient populations depend mainly on the type of PCR and laboratory protocols used. However, many centers have developed and use a quantitative PCR with a level of detection as low as 20 parasites/mL, with parasite loads of >600/mL reported in most patients with toxoplasmosis [29]. In the EBMT study 46% of the patients with *Toxoplasma* disease and all six with infection had at least one positive PCR result, thus confirming the widespread use of this diagnostic technology in clinical practice [7]. Particularly interesting are the patients with positive PCR tests from blood samples without evidence of disease [30]. These patients may represent a transitional state between the local reactivation of tissue cysts into tachyzoites and the establishment of localized or disseminated tissue destruction by replicating tachyzoites favored by the intense cellular immunosuppression after transplant or during GVHD. This observation would be somehow similar to the early detection of cytomegalovirus (CMV) infection by PCR or the pp65 antigenemia test. Unlike the latter, however, the clinical significance of detecting *T. gondii* DNAemia is currently unknown. On the other hand, several cases of well-documented disseminated toxoplasmosis with negative serum PCR results have been described [20], and our patient with pulmonary toxoplasmosis described earlier had a negative PCR in blood samples but positive cytology and PCR in BAL samples. The earlier onset of *Toxoplasma* infection (median day 35, range 13–51) than disease (median day 64, range 4–516) in the EBMT study suggests that infection may indeed precede disease in many cases [7]. Thus, research efforts to establish the role of PCR in this setting are clearly warranted. Unfortunately, as with other PCR-based diagnostic tests for infectious diseases, the technique is not standardized, making comparisons between centers difficult unless a quality control is established [29]. Table 42-2 summarizes the published studies that analyze the potential role of screening peripheral blood (PB) samples for the early diagnosis and/or preemptive therapy of toxoplasmosis as of mid-2015. These studies emphasize the

TABLE 42-2. Results of published studies that analyze the role of monitoring PB samples with a PCR for *Toxoplasma gondii* after HSCT

Author (references)	Number of patients	Percentage of seropositivity pretransplant (%)	Number of (percentage) toxoplasma infections in seropositive patients (PCR+)	Number (percentage) toxoplasma disease	Comments
Bretagne et al. [30]	32	75	3 (13)	0	7 samples studied in the first 150 days posttransplant
Janitschke et al. [12]	75	71	7 (13)	3 (5)	Serology was found to be useless in the diagnosis of infection and prediction of disease
Martino et al. [31]	106	100	16 (16)	6 (6)	Cord blood transplantation and noncompliance to cotrimoxazole prophylaxis were risk factors for infection and disease
Edvinsson et al. [32]	12 AlloHSCT/21 AutoHSCT	30	2 (17)	1 (8)	
Fricker-Hidalgo et al. [33]	70 AlloHSCT (none received prophylaxis)	57	9 (13) (PCR+ and IgM−)	4 (5.7)	1 seronegative patient developed disease In the 4 patients with disease, 2 had negative PCR but positive IgM serology, and 1 had positive serology before PCR Confirms that serology can be helpful in the appropriate setting
Daval et al. [43]	40 AlloHSCT	100	1 (4)	0	0/25 in pts on cotrimoxazole vs. 1/15 (7%) in pts not on prophylaxis In this study, french expert parasitologists validated a quantitative PCR with a validated competitive internal control
Meers et al. [44]	208 AlloHSCT (none received prophylaxis)	100	12 (6)	6 (3)	Risk factors for infection were myeloablative conditioning, especially with irradiation, and having a seronegative donor Risk factor for disease was having a high parasitic load in PB
Caner et al. [45]	12 AutoHSCT 18 AlloHSCT	100	3 AutoHSCT (25) 4 AlloHSCT (22)	4 (10)	By two PCR methods, this study analyzed a sample of buffy coat from the infused stem cells, as well as posttransplantation monitoring The 4 patients who developed disease had a positive PCR in the donor "buffy coat" samples analyzed; will require confirmation in further studies

usefulness of this approach, provided a sensitive and specific quantitative PCR technique is readily available.

Since histologically proven toxoplasmosis is a very difficult-to-obtain diagnosis, various levels of diagnostic certainty have been proposed, which will aid in the interpretation of further studies in this area [7]. Histologically defined cases are considered as definite cases of toxoplasma disease, PCR-defined cases as probable, and CNS imaging-defined cases as possible cases. Table 42-3 summarizes the modified proposed EBMT definitions.

In HSCT recipients, initial therapy for toxoplasmosis should be administered for at least 3 weeks and the total

TABLE 42-3. EBMT-IDWP definitions for toxoplasmosis after hematopoietic stem cell transplantation (modified from [7])

Toxoplasmosis disease definite toxoplasmosis	Histologic or cytologic demonstration of tachyzoites in tissue samples obtained either by biopsy, bronchoalveolar lavage (BAL), or at autopsy. Isolation of the parasite by culture in these samples would be evidence of disease
Probable toxoplasmosis (PCR-documented) (rarely, positive IgM serology)	Clinical and radiologic evidence suggestive of organ involvement plus at least one positive PCR test from blood, CSF, and/or BAL, but no histologic confirmation and absence of another pathogen, which may explain the findings In patients capable of mounting a humoral immune response, positivity of *T. gondii* IgM (irrespective of IgG results) with negative PCR in a compatible clinical scenario also represents probable disease [33]
Possible toxoplasmosis (imaging-documented)	CT or MRI highly suggestive of CNS toxoplasmosis (as considered by each hospital's neuroradiologists) and response to antitoxoplasma therapy, but no laboratory evidence of toxoplasmosis and absence of another pathogen which may explain the findings
Toxoplasmosis infection	Positive PCR in blood in a patient without any evidence of organ involvement or seroconversion (positive IgM serology) for *Toxoplasma gondii* after transplant in a previously seronegative patient (with or without fever)

Abbreviations: *CT* computerized tomography scan, *MRI* magnetic resonance imaging, *CNS* central nervous system, *PCR* polymerase chain reaction for *Toxoplasma gondii.*

TABLE 42-4. Suggested treatment and prophylaxis for toxoplasmosis in HSCT recipients

Treatment	Dose
Pyrimethamine (*plus* folinic acid)	Oral, 200 mg loading dose, then 50–75 mg q.d. (folinic acid, oral, or IV 10 to mg q.d.)
	Plus one of the following
Sulfadiazine	Oral, 1–1.5 g q 6-8 h
	Or
Clindamycin	Oral or IV, 600 mg q6h

Prophylaxis	Dose
Trimethoprim *plus* sulfamethoxazole[a]	2 double-strength tablets (160/800 mg) per day, 3 days per week or 1 double-strength tablet (160/800 mg) per day, 4–5 days per week or 1 standard-dose tablet (80/400 mg) daily
	Or
Pyrimethamine and sulfadoxine (Fansidar)[a]	2–3 tables per week
Dapsone[a]	100 mg daily
Atovaquone[a]	1500 mg daily
If the above cannot be given, there is in vitro and anecdotal clinical evidence for the following alternatives [34]	
Spiramycin	Daily 25–50 mg/kg/day, maximum 2–3 g/day
Azithromycin	250–500 mg 3 days per week

[a]Also effective for *Pneumocystis jirovecci* pneumonia prophylaxis, and possibly listeriosis, nocardiosis and, in some geographic areas, partly effective in preventing gram positive cocci and gram negative bacillary (enterobacterial and non-glucose fermenting) infections [47]. The dose can be reduced in patients with mild renal insufficiency.

therapy duration should be continued until 4–6 weeks after all clinical evidences of toxoplasmosis resolves. The dosage of the medications utilized may need to be reduced or the regimen changed if side effects occur (primarily rash, diarrhea, or drug interactions). Extended therapy is with pyrimethamine and sulfadiazine or pyrimethamine and clindamycin (Table 42-4). Most patients respond to one or another of these regimens and neurologic improvement of toxoplasma brain involvement usually occurs within 7 days. Because pyrimethamine is a folic acid antagonist the most common side effect is dose-related bone marrow suppression, and patients receiving pyrimethamine should be placed on daily oral dose of 10–15 mg of folinic acid (not folic acid), and have a complete blood count performed twice weekly. Other side effects of sulfonamides include fever, rash, and hepatitis.

Data from AIDS patients suggest that prophylactic cotrimoxazole is useful in minimizing the risk of reactivation of toxoplasmosis, although there are well-reported cases of toxoplasmosis breaking through cotrimoxazole prophylaxis in marrow transplant recipients [4, 5]. Suboptimal dosing may have contributed to some of these "breakthrough"

infections. In a recent review of 47 patients with breakthrough toxoplasmosis, 37 of whom were on cotrimoxazole prophylaxis, indirect observations suggested a significantly lower efficacy of prophylaxis in regimens that use the drug less than three times a week. Thus, using either 1 standard-dose tablet (80/400 mg) daily or double-strength tablets (160/800 mg) 3 or more days per week is the recommended dosing [47], as shown in Table 42-4.

One study in marrow transplant recipients of pyrimethamine and sulfadoxine (Fansidar) described no proven cases of toxoplasmosis in 69 patients receiving this regimen; additionally, no cases of *Pneumocystis jirovecci* pneumonia were reported [16]. Other less well-studied alternatives include dapsone, atovaquone, and azithromycin. Table 42-4 describes the recommended prophylaxis in seropositive patients.

The prognosis of this infection has been considered to be very poor based on the limited published data, with nearly 90% of patients dying from toxoplasmosis (see Table 42-1). This contrasts with the 70–80% response rates observed in patients with AIDS. However, the results from the New York and the EBMT studies suggest that, if appropriately treated, up to 60% of patients may show clinical–radiologic improvement or even a complete response. This highlights the importance for a high index of suspicion for toxoplasmosis in immunocompromised patients for the appropriate diagnostic tests and for starting therapy as soon as possible. Of utmost importance is knowing the patients' serology pretransplant, since the risk of toxoplasmosis in seronegative recipients appears to be very low. However, seronegative patients may also develop toxoplasmosis, either through infection from the donor or primary infection after transplant [12].

References

1. Derouin F, Devergie A, Auber P, et al. Toxoplasmosis in bone marrow transplant recipients: report of seven cases and review. Clin Infect Dis. 1992;15:267–70.
2. Chandrasekar PH, Momin F, The Bone Marrow Transplant Team. Disseminated toxoplasmosis in marrow transplant recipients: a report of three cases and review of the literature. Bone Marrow Transplant. 1997;19:685–9.
3. Sing A, Leitritz L, Roggenkamp A, et al. Pulmonary toxoplasmosis in bone marrow transplant recipients: report of two cases and review. Clin Infect Dis. 1999;29:429–33.
4. Slavin MA, Meyers JD, Remington JS, et al. *Toxoplasma gondii* infection in marrow transplant recipients: a 20 year experience. Bone Marrow Transplant. 1994;13:549–57.
5. Bretagne S, Costa JM, Kuentz M, et al. Late toxoplasmosis evidenced by PCR in a marrow transplant recipient. Bone Marrow Transplant. 1995;15:809–11.
6. Maschke M, Dietrich U, Prumbaum M, et al. Opportunistic CNS infection after bone marrow transplantation. Bone Marrow Transplant. 1999;23:1167–76.
7. Martino R, Maertens J, Bretagne S, et al. Toxoplasmosis after hematopoietic stem cell transplantation. A study by the European Group for Blood and Marrow Transplantation (EBMT) Infectious Diseases Working Party (IDWP). Clin Infect Dis. 2000;31:1188–94.
8. Mele A, Paterson PJ, Prentice HG, et al. Toxoplasmosis in bone marrow transplantation: a report of two cases and systematic review of the literature. Bone Marrow Transplant. 2002;29: 691–8.
9. Roemer E, Blau IW, Basara N, et al. Toxoplasmosis, a severe complication in allogeneic hematopoietic stem cell transplantation: successful treatment strategies during a 5-year single-center experience. Clin Infect Dis. 2001;32:e1–8.
10. Small TN, Leung L, Stiles J, et al. Disseminated toxoplasmosis following T-cell-depleted related and unrelated bone marrow transplantation. Bone Marrow Transplant. 2000;25:969–73.
11. Matsuo Y, Takeishi S, Miyamoto T, et al. Toxoplasmosis encephalitis following severe graft-vs.-host disease after allogeneic hematopoietic stem cell transplantation: 17 yr experience in Fukuoka BMT group. Eur J Haematol. 2007;79(4): 317–21.
12. Janitschke K, Held T, Kruiger D, et al. Diagnostic value of tests for *Toxoplasma gondii*-specific antibodies in patients undergoing bone marrow transplantation. Clin Lab. 2003;49(5–6): 239–42.
13. Lim Z, Baker B, Zuckerman M, et al. Toxoplasmosis following alemtuzumab based allogeneic haematopoietic stem cell transplantation. J Infect. 2007;54(2):e83–6.
14. Aoun M, Georgala A, Mboumi K, et al. Changing the outcome of toxoplasmosis in bone marrow transplant recipients. Int J Antimicrob Agents. 2006;27(6):570–2.
15. de Medeiros BC, de Medeiros CR, Werner B, et al. Disseminated toxoplasmosis after bone marrow transplantation: report of 9 cases. Transpl Infect Dis. 2001;3(1):24–8.
16. Foot AB, Garin YJ, Ribaud P, et al. Prophylaxis of toxoplasmosis infection with pyrimethamine/sulfadoxine (Fansidar) in bone marrow transplant. Bone Marrow Transplant. 1994;14: 241–5.
17. O'Driscoll JC, Holliman RE. Toxoplasmosis and bone marrow transplantation. Rev Med Microbiol. 1991;2:215–22.
18. Yadlapati S, Dorsky D, Remington JS, et al. Ocular toxoplasmosis after autologous peripheral-blood stem-cell transplantation. Clin Infect Dis. 1997;25:1255–6.
19. Hoyle C, Goldman JM. Life-threatening infections occurring more than 3 months after BMT. 18 UK Bone Marrow Transplant Teams. Bone Marrow Transplant. 1994;14:247–52.
20. Held TK, Krüger D, Switala AR, et al. Diagnosis of toxoplasmosis in bone marrow transplant recipients: comparison of PCR-based results and immunohistochemistry. Bone Marrow Transplant. 2000;25:1257–62.
21. Martino R, Bretagne S, Rovira M, et al. Toxoplasmosis after hematopoietic stem transplantation. Report of a five-year survey from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT-IDWP). Bone Marrow Transplant. 2000;25:1111–3.
22. Saad R, Vincent JF, Cimon B, et al. Pulmonary toxoplasmosis after allogeneic bone marrow transplantation: case report and review. Bone Marrow Transplant. 1996;18:211–2.
23. Pendry K, Tait RC, McLay A, et al. Toxoplasmosis after BMT for CML. Bone Marrow Transplant. 1990;5:65–7.
24. Geissmann F, Derouin F, Marolleau JP, et al. Disseminated toxoplasmosis following autologous bone marrow transplantation [letter]. Clin Infect Dis. 1994;19:800–1.
25. Pauleikhoff D, Messmer E, Beelen DW, et al. Bone marrow transplantation and toxoplasmic retinochoroiditis. Graefes Arch Clin Exp Ophthalmol. 1987;225:239–43.

26. Peacock JF, Greven CM, Couz JM, et al. Reactivation toxoplasmic retinochoroiditis in patients undergoing bone marrow transplantation: is there a role for chemoprophylaxis? Bone Marrow Transplant. 1995;15:983–7.
27. Hohlfeld P, Daffos F, Costa JM, et al. Prenatal diagnosis of congenital toxoplasmosis with a polymerase chain-reaction test on amniotic fluid. N Engl J Med. 1994;331:695–9.
28. Ellis JT. Polymerase chain reaction approaches for the detection of *Neospora caninum* and *Toxoplasma gondii*. Int J Parasitol. 1998;28:1053–60.
29. Costa JM, Munoz C, Kruger D, et al. Quality control for the diagnosis of *Toxoplasma gondii* reactivation in SCT patients using PCR assays. Bone Marrow Transplant. 2001;28:527–8.
30. Bretagne S, Costa JM, Foulet F, et al. Prospective study of toxoplasma reactivation by PCR in allogeneic stem cell transplant recipients. Transplant Infect Dis. 2000;2:127–32.
31. Martino R, Bretagne S, Einsele H, et al. Early detection of Toxoplasma infection by molecular monitoring of *Toxoplasma gondii* in peripheral blood samples after allogeneic stem cell transplantation. Clin Infect Dis. 2005;40(1):67–78.
32. Edvinsson B, Lundquist J, Ljungman P, et al. A prospective study of diagnosis of *Toxoplasma gondii* infection after bone marrow transplantation. Acta Pathol Microbiol Immunol Scand. 2008;116(5):345–51.
33. Fricker-Hidalgo H, Bulabois CE, Brenier-Pinchart MP, et al. Diagnosis of toxoplasmosis after allogeneic stem cell transplantation: results of DNA detection and serological techniques. Clin Infect Dis. 2009;48:e9–15.
34. Paya E, Noemi I, Tassara R, Catalan P, Aviles CL. [Prophylaxis against *Toxoplasma gondii* disease in pediatric and adult patients undergoing solid organ and hematopoietic stem cells transplantation]. Rev Chilena Infectol. 2012;29(Suppl 1): S37–9.
35. Rusinakova Z, Raida L, Faber E, et al. [Toxoplasmosis after immunosuppressive therapy--our experience]. Klin Mikrobiol Infekc Lek. 2009;15:95–8.
36. Mulanovich VE, Ahmed SI, Ozturk T, et al. Toxoplasmosis in allo-SCT patients: risk factors and outcomes at a transplantation center with a low incidence. Bone Marrow Transplant. 2011; 46:273–7.
37. Bautista G, Ramos A, Fores R, et al. Toxoplasmosis in cord blood transplantation recipients. Transpl Infect Dis. 2012;14:496–501.
38. Martino R, Bautista G, Parody R, et al. Severe infections after single umbilical cord blood transplantation in adults with or without the co-infusion of CD34+ cells from a third-party donor: results of a multicenter study from the Grupo Espanol de Trasplante Hematopoyetico (GETH). Transpl Infect Dis. 2015;17:221–33.
39. Busemann C, Ribback S, Zimmermann K, et al. Toxoplasmosis after allogeneic stem cell transplantation—a single centre experience. Ann Hematol. 2012;91:1081–9.
40. Sumi M, Aosai F, Norose K, et al. Acute exacerbation of *Toxoplasma gondii* infection after hematopoietic stem cell transplantation: five case reports among 279 recipients. Int J Hematol. 2013;98:214–22.
41. Hakko E, Ozkan HA, Karaman K, Gulbas Z. Analysis of cerebral toxoplasmosis in a series of 170 allogeneic hematopoietic stem cell transplant patients. Transpl Infect Dis. 2013;15: 575–80.
42. Nigro MG, Figueroa C, Ledesma BA. [Retrospective study of the implementation of the qualitative PCR technique in biological samples for monitoring toxoplasmosis in pediatric patients receiving hematopoietic stem cell transplantation]. Rev Argent Microbiol. 2014;46:24–9.
43. Daval S, Poirier P, Armenaud J, Cambon M, Livrelli V. [Development of a real-time PCR assay for quantitative diagnosis of *Toxoplasma gondii* after allogeneic bone marrow transplantation]. Pathol Biol (Paris). 2010;58:104–9.
44. Meers S, Lagrou K, Theunissen K, et al. Myeloablative conditioning predisposes patients for *Toxoplasma gondii* reactivation after allogeneic stem cell transplantation. Clin Infect Dis. 2010; 50:1127–34.
45. Caner A, Donmez A, Doskaya M, et al. Determining Toxoplasma high-risk autologous and allogeneic hematopoietic stem cell transplantation patients by systematic pre-transplant PCR screening of stem cell originated buffy coat. Parasitol Int. 2012;61:565–71.
46. Osthoff M, Chew E, Bajel A, et al. Disseminated toxoplasmosis after allogeneic stem cell transplantation in a seronegative recipient. Transpl Infect Dis. 2013;15:E14–9.
47. Gajurel K, Dhakal R, Montoya JG. Toxoplasma prophylaxis in haematopoietic cell transplant recipients: a review of the literature and recommendations. Curr Opin Infect Dis. 2015;28: 283–92.