INTRODUCTION

Toxoplasma, a protozoan parasite, an opportunist in immunodeficient individuals, exhibits a worldwide prevalence having infected 10–80% of the general population. The prevalence of toxoplasma infection in India is reported to vary from 4.7–22% in North India to 37.3% in South India. The course of infection is generally benign and most infected individuals remain asymptomatic or mildly symptomatic. However, the infection can cause significant morbidity and mortality in developing fetus if the infection is acquired during pregnancy. Furthermore, a well-established relationship exists between the severity of toxoplasmosis and level of immunosuppression. Immunosuppressed individuals include patients with hematologic malignancies, especially Hodgkin’s disease and other lymphomas, AIDS patients, and patients receiving immunosuppressive therapy with cytotoxic drugs or corticosteroids or patients with organ transplants. Reactivation of latent disease due to a mismatch between the seropositive organ donor and seronegative recipient (D+/R−) or de novo infection is responsible for the transmission of disease. Solid organ transplants (SOTs) including heart, liver, kidney, pancreas and small bowel, and bone marrow transplants have been implicated in the risk of acquiring infection. Varied presentations

KEY WORDS
Parasite, solid organ transplant, stem cell transplant, toxoplasmosis, transplant

ABSTRACT

Toxoplasmosis in organ transplant patients can be a result of donor-transmitted infection, or reactivation of latent infection, or de novo infection. Solid organ transplants including heart, liver, kidney, pancreas and small bowel, and hematogenous stem cell transplants have been implicated in the risk of acquiring infection. In contrast to a benign course in immunocompetent individuals, the spectrum of illness is severe in transplant recipients. Clinical manifestations usually occur within the first 3 months of transplant and may present as encephalitis, pneumonitis, chorioretinitis, meningitis, and disseminated toxoplasmosis with multi-organ involvement. The diagnosis of toxoplasmosis in organ transplant patients is often difficult and is an integration of clinical, radiological, and microbiological workup. Preventive measures include pretransplant evaluation and chemoprophylaxis in view of rapidly progressing and fatal outcome of toxoplasmosis in immunocompromised individuals.
include encephalitis, pneumonitis, chorioretinitis, meningitis, and disseminated toxoplasmosis with multi-organ involvement as opposed to the self-limiting spectrum in immunocompetent individuals. In today’s scenario, with the increase in number of organ transplant surgeries, this review provides an insight into the evaluation, implication, and prevention of toxoplasmosis.

SOLID ORGAN TRANSPLANTS

Presenting within the first 3 months posttransplant, toxoplasmosis as an infectious complication in SOT is a well-recognized entity. In contrast to hematopoietic stem cell transplant (HSCT), graft transmission is a more common mechanism than reactivation in SOT. However, when disease occurs >3–6 months after SOT, it is more likely due to reactivation, or de novo disease following immunosuppressive therapy given when rejection is anticipated or suspected. The transmission of infection from a seropositive donor having acquired infection in the past to a seronegative recipient (D’/R+) is maximum after heart transplant (50–75%), followed by liver (20%) and renal (<1%) transplants, in the absence of prophylaxis. During posttransplant-induced immunosuppression, the encysted bradyzoites from donor or recipient transform into proliferating tachyzoites that destroy the infected cells. In the case of seronegative recipients, the infection becomes disseminated in the absence of preexisting antitoxoplasma immunity. For pretransplant seropositive recipients, reactivation of latent infection is rare and less severe than donor-transmitted infection. Data from retrospective studies show the incidence to vary between 9% and 56%, being governed by factors such as the prevalence of infection in the region, and the use and response to chemoprophylaxis. Studies from various countries have reported the varying prevalence of organ-transmitted and reactivated toxoplasmosis in heart and heart-lung recipients. Montoya et al. 2001 reported the prevalence of clinical toxoplasmosis in the United States via organ transmission to be 12.5% in seronegative recipients and 25% in patients without prophylaxis. Toxoplasmic disease and disseminated aspergillosis were associated with highest mortality rates attributable to an infectious complication in heart transplant recipients. From another heart transplant center, Luft et al. observed the prevalence to be 75%. In Switzerland, Gallino et al. reported a prevalence of 16.7% while Wreghitt et al. in the United Kingdom found it to be 28.5% in patients on chemoprophylaxis and 57% in patients without prophylaxis. A few studies on reactivation in seropositive recipients report the serological prevalence to vary between 4% and 53% but with very few cases presenting clinically. After noncardiac SOT, nonimmunized recipients have the propensity to acquire infection after transplants of kidney, liver, pancreas, and small bowel. Campbell et al. 2006 reviewed 52 toxoplasma cases after noncardiac SOT reported in literature over a period of 40 years. The cases were maximum after the transplantation of kidney (34), liver (12), multi-organ (4) pancreas, and small bowel (1 each). Most cases were donor-transmitted (42%) which also had a higher rate of dissemination and fatality. Hence, the inference that can be drawn from the above data is that the number of cases after noncardiac SOT is much less as compared to cardiac SOT.

The type of immunotherapy used after transplant also affects the risk predisposition and progression of the disease. The main treatment modalities for acute T cell-mediated rejection that includes antithymocyte globulin, OKT3, and corticosteroids increase the risk of opportunistic parasitic infections including toxoplasmosis. Furthermore, many drugs used during induction such as alemtuzumab also increase the same risk.

HEMATOGENOUS STEM CELL TRANSPLANTS

The risk predisposition for toxoplasmosis is more in HSCT because of the greater duration of immunosuppression as compared to SOT. The risk is particularly high, 2–4 months posttransplant. Only <10% cases occur before 1 month and 15–20% cases occur after 100 days. Reactivation of latent infection is a more common mechanism than donor-transmitted infection, with allogeneic stem cell transplants more predisposed as compared to autologous stem cell transplant. Cord blood transplantation, associated with a higher degree of immunosuppression, has been shown to be at the highest risk. The prevalence of toxoplasmosis is reported to be 0.2–5.7% in toxoplasma seropositive transplant recipients from various parts of the world. Thus, the toxoplasma seropositive status of the recipient is the main risk factor though it has been reported that the risk increases further if the donor is seronegative while the recipient is seropositive (D’/R+).

Table 1 summarizes the risk factors for acquiring infection in transplant recipients.

CLINICAL PRESENTATION

In immunocompetent individuals, in more than 80% of cases, there is an asymptomatic infection. In the remaining cases, fever, cervical lymphadenopathy, myalgia, and other nonspecific clinical symptoms are present. This is in stark contrast to the presentation in immunosuppressed individuals. The time of presentation in SOT recipients can be as early as 2 weeks posttransplant but with a usual presentation in the first 3 months. The severity of clinical features
depends on the degree of immunosuppression induced and timing of appropriate antitoxoplasma therapy. Initially, symptoms can be nonspecific with fever, respiratory or neurological features. Central nervous system manifestation occurs in 10–25% of transplant recipients with toxoplasmosis and encephalitis is the usual presentation. Severe manifestations include myocarditis, encephalitis, pneumonitis, or multi-organ involvement. Pulmonary involvement is usually bilateral and presents as interstitial pneumonitis.\[23,24\] Toxoplasmosis in heart transplant recipients may simulate organ rejection in which disseminated disease may occur if immunosuppression is intensified.\[25\] The fatality rate in disseminated disease is >80%. In HSCTs, the most common presentation is brain abscess presenting within first 2 months of transplant. In <10% cases, the patients present within <30 days and 15–20%, later than 100 days.\[15\]

**EVALUATION**

The diagnosis of toxoplasmosis in organ transplant patients is often difficult and is an integration of clinical, radiological, and microbiological workup. Clinically, the patient presents with nonspecific signs and symptoms, with various differentials which need to be ruled out. Computerized tomography scan and magnetic resonance imaging can provide suggestive pointers to diagnosis. Radiological imaging of the brain showing focal single or multiple contrast-enhancing lesions with surrounding edema or sometimes diffuse lesions points toward encephalitis. Alveolar consolidation with interstitial pneumonitis can be well appreciated in pulmonary toxoplasmosis. However, a definitive diagnosis of infection necessitates the identification of parasites. When myocarditis presents in cardiac transplant recipients, endomyocardial biopsy is crucial in differentiating infection from rejection. As the presentation of toxoplasmosis in organ recipients is usually in the form of a multi-organ involvement, microscopy of a Giemsa-stained smear of blood, body fluids such as cerebrospinal fluid, bronchoalveolar lavage, bone marrow, and other tissue samples would help in identification of tachyzoites.\[7,15,17\] However, the low sensitivity of microscopy makes use of polymerase chain reaction (PCR) targeting repeated B1 and AF146527 genes a more favorable option.\[24\] A positive PCR in whole blood with a clinical evidence of multi-organ involvement means the presence of active disease. Real-time PCR helps in measuring the parasite load which helps in the monitoring and progression of the disease and a negative PCR can help rule out the disease.\[15\] It has been reported that real-time PCR can detect the disease before the onset of clinical manifestations.\[15\] The other techniques for demonstration of parasite include mouse inoculation and cell culture technique; however, the disadvantage is the longer time to diagnosis, at least 4 weeks for mouse inoculation and 1–2 weeks for cell culture. Serology can be helpful in differentiation of graft-transmitted and reactivation toxoplasmosis. Seroconversion with presence of IgM and IgG antibody titers is an indication toward an acquired infection whereas the presence of IgG antibody titers with a high avidity index alone in the absence of IgM titers suggests reactivation. The disadvantage of serological diagnostic techniques is the absence of seroconversion in some cases because of profound immunosuppression. In HSCT recipients, a transient rise in IgG antibodies may occur due to passive antibody transmission via graft or blood transfusions. Table 2 categorizes the patients after HSCT into definite, probable, and possible toxoplasmosis as defined by the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation in the year 2000.\[15\]

**PREVENTION**

Preventive measures include pretransplant evaluation which involves screening of both organ donor and recipient for various tropical infections, so that appropriate measures to eradicate the infection can be taken if possible, or else to start suitable chemoprophylaxis to patients at higher risk of reactivation disease. Serological tests performed for the toxoplasma antibody status of both donor and recipient can help prevent infection by taking appropriate measures in the form of primary prevention, i.e., hygienic precautions, or secondary prevention in the form of chemoprophylaxis.

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**Table 1: Toxoplasma serostatus and risk of toxoplasmosis in transplant recipients**

| Type of transplant | Type of risk | Donor-transmitted disease | Reactivation |
|--------------------|--------------|---------------------------|-------------|
| Heart/heart-lung transplant | High in D+/R− | Low even in R’ | None in R’ |
| Liver | Low in D+/R− | Low in R’ | None in R’ |
| Kidney | Low in D+/R− | Low in R’ | None in R’ |
| Intestine | Low in D+/R− | None in R’ | None in D’ |
| Autologous | No risk | Nil in R’ | Very low in R’ |
| Allogeneic | No risk | High in R’ | Risk more if donor seronegative |

D+: Pretransplant donor antitoxoplasma serology positive, R−: Pretransplant recipient antitoxoplasma serology positive, R+: Pretransplant recipient antitoxoplasma serology negative, SOT: Solid organ transplant, HSCT: Hematopoietic stem cell transplant.
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Table 2: The Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation definitions for toxoplasmosis after hematopoietic stem cell transplant (adapted from Martino et al., 2000)

| Category           | Criteria                                                                 |
|--------------------|--------------------------------------------------------------------------|
| Definite toxoplasmosis | Demonstration of parasite in tissue obtained by biopsy or BAL or autopsy or isolation of parasite by culture or animal inoculation |
| Probable toxoplasmosis | Clinical and radiologic pointers plus at least one positive PCR test from blood, CSF, and/or BAL in the absence of direct demonstration or isolation of parasite |
| Possible toxoplasmosis | CT or MRI suggestive of toxoplasma encephalitis and therapeutic response to antitoxoplasma therapy, absence of no demonstration of parasite on laboratory investigation, and absence of any other etiology |
| Toxoplasma infection | Positive PCR in a patient in the absence of evidence of organ involvement or presence of seroconversion for Toxoplasma gondii in a recipient seronegative before transplant, (with or without fever) |

CT: Computerized tomography scan, MRI: Magnetic resonance imaging, PCR: Polymerase chain reaction for Toxoplasma gondii, CSF: Cerebrospinal fluid, BAL: Bronchoalveolar lavage

Varying incidence rates of toxoplasmosis among various countries govern the decision of screening. In Europe, of 29 countries included in the Eurotransplant network, toxoplasma serology is mandatory as a pretransplant evaluation modality in 11 countries.[25] In France, all patients are screened before transplantation, in contrast to the United States where it largely depends on the transplant center.[26] Posttransplant, serological follow-up is specifically useful in case of mismatched SOT recipients (D+/R−) since seroconversion indicates the transmission of Toxoplasma gondii. However, a rise in antibody titer in other SOT recipients as well as in HSCT is not of much significance. A more beneficial test would be a molecular test such as PCR which would be a confirmation of the presence of active disease. This would be helpful in patients not receiving prophylaxis.

CHEMOPROPHYLAXIS

Chemoprophylaxis is important in view of the rapidly progressing and fatal outcome of toxoplasmosis in immunocompromised individuals. An ideal drug should be useful for eradication of cysts. Atovaquone has been tried in mice models, but its efficacy in humans still needs to be validated. Dihydrofolate reductase inhibitors, sulfonamides, are drugs active against the replicative stages (tachyzoites) proven both in vitro and in vivo. At present, trimethoprim-sulfamethoxazole (160–800 mg) daily or thrice weekly has proven to be effective in SOT in mismatched patients.[27] Pyrimethamine (25 mg/day) alone can be given as an alternative in case of intolerance to sulfa drugs.[27] Furthermore, in cardiac transplants, pyrimethamine alone has been proposed for prophylaxis.

For bone marrow transplants, all seropositive recipients should be given prophylaxis. As for SOT, co-trimoxazole daily or thrice weekly is the preferred drug; however, in some European HSCT centers, pyrimethamine-sulfadoxine is preferred as it can be administered weekly.[25–29] The usage of a combination of clindamycin, pyrimethamine, and leucovorin has been proposed in co-trimoxazole intolerant patients. There is no clear-cut guideline for initiation or duration of prophylaxis. While an early prophylaxis decreases the risk of toxoplasmosis, on the other hand, there is more chance of delayed engraftment due to the toxicity of drugs. Many centers administer prophylaxis from day −7 to −2 and restart on day +30 post-HSCT.[28] In case of delayed initiation of prophylaxis, PCR needs to be done weekly on blood samples in high-risk categories. A 6-month prophylactic treatment is recommended post-HSCT.[27] In seronegative recipients, hygienic measures should be taken so as to prevent attainment of infection by ingestion of undercooked meat or raw vegetables infected with oocysts. In case of a donor with recent acquisition of infection, pyrimethamine along with sulfadiazine should be given to the donor for treatment. Furthermore, at-risk recipient should be given prophylactic treatment following transplant. Some problems with prophylaxis are the few side effects with these drugs which include skin rashes, nephrotoxicity, and myelotoxicity, and the possibility of the emergence of drug-resistant parasites.

TREATMENT

The first choice of treatment comprises pyrimethamine 200 mg PO once, followed by 50–75 mg POQD depending on the body weight plus sulfadiazine 4–6 g/day in four divided doses plus folic acid 10 mg PO QD.[30] The duration of treatment is up to 6 weeks till the time of resolution of symptoms. In case of ocular involvement, adjunctive therapy with prednisone 80–120 mg PO QD can be given. In case of patients allergic to sulfa drugs, the regimen chosen is pyrimethamine 200 mg PO once, then 50–75 mg PO QD plus folic acid 10 mg PO QD plus either clindamycin 1.2–4.8 g/day intravenous or atovaquone 750 mg PO QD for 6 weeks.[30] The other alternative drugs include pyrimethamine and folic acid as in the standard regimen plus one of the following: atovaquone (1500 mg q12h PO) or clarithromycin (500 mg q12h PO) or azithromycin (900–1200 mg QD PO) or dapsone (100 mg PO QD).[30]
CONCLUSION

Toxoplasmosis in immunosuppression is a serious entity with a fatal outcome. With advancing technology, the organ transplant number is on the rise. Like in other infections such as HIV, cytomegalovirus, hepatitis B virus, and hepatitis C virus, it is of utmost importance to evaluate the status of both the donor and recipient. More than 50–75% infections in transplant recipients are the result of lack of prophylaxis. Thus, it becomes essential to implement preventive measures and keep a high index of clinical suspicion. A combination of serological screening and chemoprophylaxis can help combat the disease. A serological and PCR follow-up of high-risk patients will help in timely detection of the disease and ultimately better outcome.

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Conflicts of interest
There are no conflicts of interest.

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