SELF-LIMITED *TOXOPLASMA* PARASITEMIA AFTER LIVER TRANSPLANTATION[1]

Although toxoplasmosis is often a mild or asymptomatic infection in normal subjects, it may cause lethal disease in immunocompromised patients (*1–3*). Detection of the disease is difficult and often requires histological evidence. Many cases are diagnosed at autopsy. We recently isolated *Toxoplasma gondii* in tissue culture from the blood of a febrile liver transplant patient who later developed lymphocytic meningitis. The patient recovered completely, despite receiving only short courses of antimicrobials active against *Toxoplasma*. Our experience illustrates that isolation of *Toxoplasma* from the blood of a solid organ transplant patient may occur with limited disease.

A 57-year-old woman with a two-year history of chronic active hepatitis underwent orthotopic liver transplantation and received cyclosporine (CsA) and prednisone immunosuppression. Ampicillin and cefotaxime (4 g each) were given daily for five days as antibiotic prophylaxis. At 18 days after the operation, a liver biopsy showed acute rejection and a 10-day intravenous course of mouse OKT3 antibody was administered. At 24 days after the operation, the patient had a temperature elevation to 39.5°C. A computerized tomographic scan of the abdomen showed a hypodense 3.5×4.5-cm area in the liver. Percutaneous aspiration of this yielded heavy *Streptococcus fecalis* on culture. Pipercillin, gentamicin, and cefoxitin were administered, but then switched to ampicillin, gentamicin, and clindamycin. A drain was left in the liver abscess cavity. Clindamycin was discontinued after three days, but ampicillin was continued 8 days and gentamicin was continued for 10 days. The patient continued to have significant fever while receiving these antibiotics. By 39 days after the operation the patient was afebrile, but she then developed confusion. A computerized tomographic scan of the head was normal, but examination of the cerebrospinal fluid showed 360 red blood cells and 50 white blood cells (1 neutrophil, 1 mononuclear, and 48 lymphs); the glucose was 46 mg% and the protein 48 mg%. Cultures of the spinal fluid were sterile. Her peripheral blood smear showed a white count of 12,700 with 8% atypical lymphocytes, 22% lymphocytes, 63% polymorphonuclear cells, 5% monocytes and 2% eosinophils. At this time a single dose of i.v. sulfamethoxazole/trimethoprim (1 g/200 mg) was administered when a weakly positive *Pneumocystis carinii* serum antigen (1:2) was reported (Linda L. Pifer, Memphis, TN, personal communication). This was discontinued because the patient's illness was not compatible with *Pneumocystis* infection. Thereafter, the patient improved clinically and was discharged from the hospital 48 days after the operation with no fever or neurological problems. Before discharge a buffy coat culture of the blood taken 26 days after the operation and inoculated in tubes of human foreskin fibroblasts showed cytopathic effect, with swollen cells containing multiple inclusions. A wet preparation of the culture supernatant showed 2×6-μ oval bodies that were motile. These were later identified by electron microscopy as *T gondii* (Fig. 1).

The same buffy coat was positive for cytomegalovirus, which was also isolated from buffy coats obtained on days 34 and 39 after transplantation. Pretransplant serum showed a titer of Epstein-Barr viral capsid antigen of 1:80, and Epstein-Barr early antigen of <1:5. Serum from day 39 after transplantation showed a 16-fold titer rise of IgG antibody to viral capsid antigen, and an 8-fold titer rise of IgG antibody to early antigen. Thus the patient showed a significant rise in titer of Epstein-Barr virus antibodies suggesting reactivation infection.

Stored donor and pre- and posttransplant recipient sera were tested for anti-*Toxoplasma* IgG antibody by Fiax (M.A. Bioproducts, Walkersville, MD). This is a semiautomated solid-phase fluorescent antibody test wherein the toxoplasma antigen

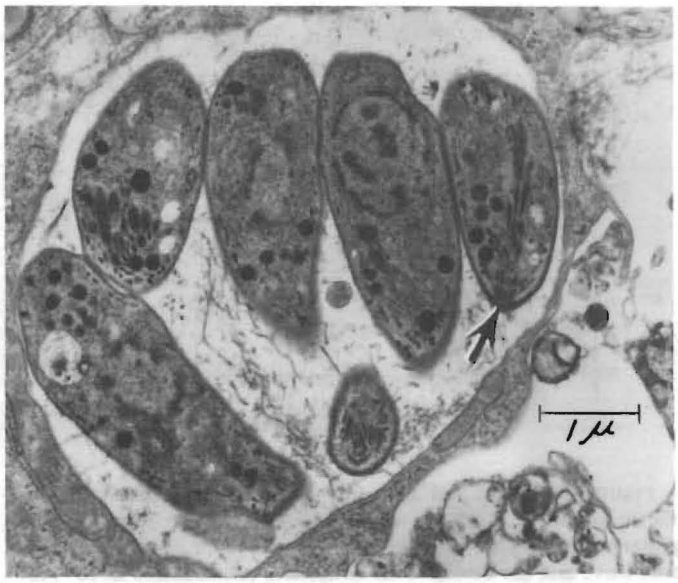

FIGURE 1. Electron microscopy of *Toxoplasma gondii* organisms isolated in tissue culture and seen within an intracellular vacuole. The arrow points to the characteristic conoid at the anterior end of the organisms, from which densely staining rophtries arise.

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is impregnated onto paper strips that are reacted with the patient's serum and then with a fluorescein-labeled antihuman IgG. The results of these tests and the serial clinical events are shown in Figure 2. The recipient showed a seven-fold rise in titer by 47 days after transplant. The two seven-day courses of low-dose (500 mg/day) oral sulfisoxazole were administered as infection prophylaxis but discontinued once a defined infection (the liver abscess) was discovered.

Shepp recently described the isolation in tissue culture of *Toxoplasma* from the blood of three bone marrow transplant recipients, all of whom died. Invasive disease was shown in the two patients who had a full autopsy (*4*). This is the first report of isolation of *Toxoplasma* in tissue culture from a solid organ transplant recipient and is remarkable for the relatively benign course of the infection. Although the patient received antimicrobials that may have been active against *Toxoplasma*, these were given in very low doses (sulfisoxazole) or for very short courses (clindamycin and sulfamethoxazole/trimethoprim). It is possible, of course, that the low doses of sulfisoxazole modified the illness without actually preventing it. In addition to *Toxoplasma* infection the patient also had cultural evidence of cytomegalovirus infection, serological evidence of Epstein-Barr virus infection, and a bacterial liver abscess. However, her fever persisted for 10 days after drainage of the liver abscess and during administration of antibiotics active against the bacterial isolates from the abscess, and only disappeared after the antibiotics were stopped.

The lymphocytic meningitis could be explained by *Toxoplasma* infection, but also by cytomegalovirus and Epstein-Barr virus infections. Both viruses can rarely cause meningoencephalitis with lymphocytic pleocytosis in the cerebral spinal fluid (*5*, *6*).

The source of the *Toxoplasma* infection was unknown, and it might have arisen by reactivation of latent infection or been transmitted by blood products (*7*, *8*). Transmission by the donor organ is also a possibility, but this has not been demonstrated in a liver transplant recipient.

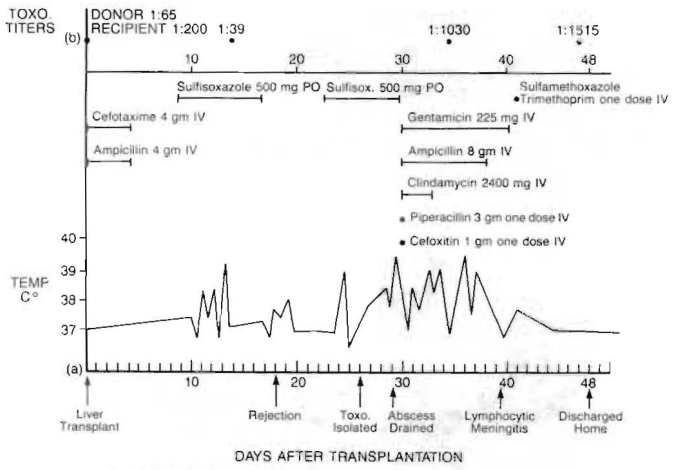

FIGURE 2. Clinical and laboratory events after transplantation. On the horizontal axis (a) are shown the key clinical events in days posttransplantation. Above the horizontal are a longitudinal temperature curve and the timing of all antibiotics administered in the postoperative period. The horizontal (b) shows *Toxoplasma* IgG antibody titers (FIAX) of donor and recipient sera collected before and after transplantation. A positive titer is greater than 24. The *Toxoplasma* organisms were isolated from a buffy coat culture taken on day 26 but were not actually detected until 46 days after transplantation, when the patient was well.

The significant *Toxoplasma* antibody rise suggests that the isolate represented more than transient toxoplasmemia. Remington has stressed that toxoplasma infection is more likely to be severe when a seronegative patient undergoes primary infection after transplantation, and some centers recommend antimicrobial prophylaxis in such patients (*9*, *10*). This patient's established immunity before transplantation may have been an important factor in her rapid and complete recovery.

Although tissue culture of blood is probably not a sensitive technique for diagnosing toxoplasmosis, its sensitivity might be improved by culturing larger quantities of blood. Awareness that *Toxoplasma* may be isolated in routine viral cultures may occasionally aid in the detection of the disease.

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REFERENCES

1. Ruskin J, Remington JS. Toxoplasmosis in the compromised host. Ann Intern Med 1976; 84: 193.
2. Anthony CW. Disseminated toxoplasmosis in a liver transplant patient. J Am Med Wom Assoc 1972; 27: 601.
3. Carey RM, Kimball AC, Armstrong D, Lieberman PH. Toxoplasmosis: clinical experiences in a cancer hospital. Am J Med 1973; 54: 30.
4. Shepp DH, Hackman RC, Conley FK, Anderson JB, Meyers J. *Toxoplasma gondii* reactivation identified by detection of parasitemia in tissue culture. Ann Intern Med 1985; 103: 218.
5. Klemola E, Kaariainen L, Von Essen R, Hatia K, Koivuniemi A, von Bonsdorff CH. Further studies on cytomegalovirus mononucleosis in previously healthy individuals. Acta Med Scand 1967; 182: 311.
6. Grose C, Henle W, Henle G, Feorino PM. Primary Epstein-Barr virus infections in acute neurologic diseases. N Engl J Med 1975; 292: 392.
7. Anderson SE Jr, Remington JS. The diagnosis of toxoplasmosis. South Med J 1975; 68: 1433.
8. Siegel SE, Lunde MN, Gelderman AH, et al. Transmission of toxoplasmosis by leukocyte transfusion. Blood 1971; 37: 388.
9. Luft BJ, Naot Y, Araujo FG, Stinson EB, Remington JS. Primary and reactivated toxoplasma infection in patients with cardiac transplants. Ann Intern Med 1983; 99: 27.
10. Hakim M, Esmore D, Wallwork J, English TAH. Toxoplasmosis in cardiac transplantation. Br Med J 1986; 292: 1108.

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