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Severe disseminated toxoplasmosis after unrelated bone marrow transplantation: a case report

We report on a case of disseminated toxoplasmosis that occurred 39 days after unrelated bone marrow transplantation in a patient in good clinical and hematologic condition. The clinical course was characterized by presentation of septic shock and the evolution of sudden and rapidly overwhelming respiratory failure which was unresponsive to emergency and anti-shock therapy. Disseminated toxoplasmosis was diagnosed at autopsy.

Sir,

A 16-year old boy with myelodysplastic syndrome which developed into refractory anemia with excess blasts in transformation (RAEB-t), underwent HLA identical bone marrow transplantation from an unrelated donor. Pre-transplant recipient anti-toxoplasma IgG was 240 IU/mL and anti-toxoplasma IgM was negative. No information on toxoplasma donor serology was available. The conditioning regimen included busulfan, cyclophosphamide and melphalan. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporin A, antilymphocyte globulin and a short course of methotrexate. Polymorphonuclear cell engraftment occurred on day +13, whereas the patient never became platelet transfusion independent. The boy developed acute GVHD grade I-II which was treated with methylprednisolone up to a dose of 10 mg/kg/die i.v.

Figure 1. Myocardial tissue: evidence of tachyzoites and bradyzoites.

On day +39 the patient developed fever and a blood culture showed *Pseudomonas aeruginosa* which was treated with cephtazidime i.v. On day +44, signs of septic shock syndrome abruptly appeared, with high grade fever (>39.5°C), sudden dyspnea, severe hypoxemia and renal dysfunction. Seizures and a dramatic worsening of the boy's general condition led to severe lethargy. As a result of progressive hypoxemia, the patient was put on life-support where breathing was mechanically assisted. Despite an initial improvement, nitric oxide had to be administered, 3 hours later. Notwithstanding the administration of norepinephrine 2 µg/kg/min, 4L of crystalloids and 1L of plasma expander, the boy's blood pressure was 80/30 and heart rate 156 bpm. An echocardiogram showed reduced myocardial function with an ejection fraction of 40%. His blood pressure fell to 60/20 and methylene-blue was infused, with no improvement. Further increments in vasoactive drugs failed to provide hemodynamic improvement and the patient died 8 hours later.

Post-mortem histologic examination was carried out with the parents' consent. Liver, lung, heart and brain specimens revealed multiple *Toxoplasma gondii* cysts. Bacterial, fungal and viral cultures were negative. There were no signs of GVHD.

This report outlines an interesting case of a severe systemic infection due to *Toxoplasma gondii* which presented with septic shock features in a BMT recipient and was diagnosed at autopsy. Toxoplasmosis is an unusual opportunistic infection which can be life-threatening in immunocompromised patients such as BMT recipients.[1-3] The etiologic diagnosis is usually made *post-mortem*.[3,4] In all such cases, profound immunosuppression results in reactivation of latent *Toxoplasma gondii*[5] and the most frequently presenting features are: isolated pneumonitis,[4,6] isolated ocular disease[5,7] and disseminated encephalitis.[2,5,8,9] Since any one of these complications[4,6] can be life-threatening in spite of prophylaxis[3,5,7] and standard treatment, Foot has suggested including pyrimethamine-sulfadoxine in the BMT setting.[10]

Several cases of disseminated toxoplasmosis have been reported after BMT[1,3,10] but none showed such a dramatic clinical course as that observed in our patient. We ascribed the acute deterioration of pulmonary function and hemodynamics to septic shock but neither vasoactive drugs, fluid load, mechanical ventilation or nitric oxide were able to restore adequate levels of oxygenation. Arterial hypotension was unresponsive to treatment because myocardial dysfunction was caused by the massive infiltration of toxoplasma in the myocardium (Figure 1).

In conclusion, toxoplasma serology should be tested in both recipients and donors before transplant to identify patients at risk of reactivation and physicians should be more aware of this possible evolution of toxoplasmosis. Finally, post-mortem histologic examination should be more widely performed to provide useful information regarding the prevalence of this disease.

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Immunological short term reconstitution after tandem unselected peripheral blood progenitor cell transplantation (uPBPCT) for multiple myeloma

Since no data are available on lymphocytes recovery after double transplant for multiple myeloma (MM), four consecutive MM patients submitted to double PBPCT were studied. Lymphocytes subpopulation were studied before and at days +15, +30, +60, +90, +120 after first and second transplantation. No statistical differences were observed on immunological recovery after first and second transplant, hematological recovery, rate of sepsis, supportive care, days of fever and hospitalization.

Sir,

High dose chemotherapy followed by autologous PBPCT has been shown to improve response rates, disease-free and overall survival in a randomized study compared with standard chemotherapy in MM.[1,2] Immunological recovery after chemotherapy vs unselected PBPCT,[3] $CD34^+$ selected vs unselected PBPCT,[4-6] in lymphoproliferative disorders has been extensively reported. Four MM patients (M/F: 1/3; median age 55, range 50-58) at diagnosis were submitted to VAD (vincristine 0.5 mg, adriamycin 10 mg/m^2, dexamethasone 40 mg; daily for 4 days by continuous infusion), followed by high-dose cyclophosphamide (7 g/sm) and G-CSF for leukapheretic collection of PBPC. BuMel (busulfan 16 mg/kg of body weight on days -6 though -3 and melphalan 90 mg/sm/day on day -2) was followed by uPBPCT and in case of partial (PR) or complete remission (CR) a second uPBPCT was performed within six months using melphalan (100 mg/sm/days -3 through -2). A median of 6.95×10^6 (range 1.37-27.3) CD34+ cells/kg was reinfused. α-IFN maintenance, 3MU, subcutaneously three times a week was started four months after second PBSCT when granulocytes exceeded 1,500/µL and platelets 150,000/µL and continued until disease relapse.

A median of 17.2×10^6/kg of total lymphocytes (range 2.68-308), 15.8×10^6/kg $CD3^+$ T-cells (range 0.21-148), 4.15×10^6/kg $CD4^+$ T-cells (range 0.32-46.6), 11.5×10^6/kg (range 0.13-170), 0.7×10^6/kg B-