Key words

Plasma exchange, cryosupernatant plasma, thrombotic thrombocytopenic purpura

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Post-transplant cerebral toxoplasmosis diagnosed by magnetic resonance imaging

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Cerebral toxoplasmosis is a rare late complication in allogeneic bone marrow transplanted patients. Neuroradiological findings may suggest the correct diagnosis. We report a patient in whom cerebral magnetic resonance imaging (MRI) showed a lesion characteristic of toxoplasmosis. Anti-toxoplasma treatment led to clinical and radiological improvement. MRI seems to be a valid tool for detection and follow-up of cerebral toxoplasmosis.

Toxoplasmosis is the most common opportunistic infection affecting the central nervous system in patients with AIDS. Cerebral toxoplasmosis occurs in about 30% of toxoplasma-seropositive patients when $CD4^+$ cells fall below 100/mL.[1] It has also been reported in bone marrow transplanted (BMT) patients.[2,3] In principle, a definitive diagnosis of toxoplasmosis must be supported by positive serology and proven by histological evidence of tachyzoites in a brain lesion. However, in BMT recipients brain biopsy may not be performable because of thrombocytopenia, and serology may be uninformative because of concurrent immunosuppression. We report a case of cerebral toxoplasmosis in a patient with Hodgkin's disease (HD) who underwent allogeneic BMT followed by donor lymphocyte infusions (DLI) for a post-transplant relapse.

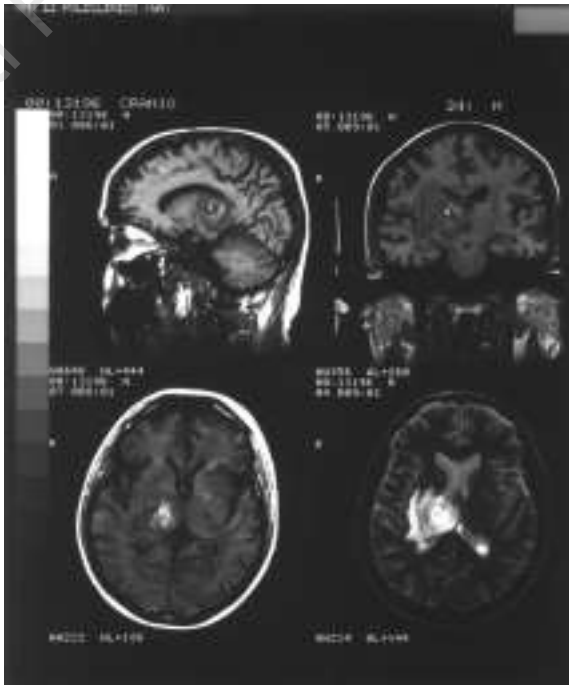

Figure 1. Cerebral MRI. Gradient recalled echo (GRE) sagittal and coronal T1-dependent pre-contrast images (top) demonstrate a round lesion in the right thalamus, with several concentric components (central: high intensity; intermediate: low intensity; peripheral: high intensity) surrounded by a low intensity edema. In the edematous region a post-contrast (Gadolinium-DTPA) GRE image (bottom, left) shows the presence of a thin ring-shaped enhancement. In the spin-echo (SE) T2-dependent image (bottom, right) the center of the lesion appears hypointense.

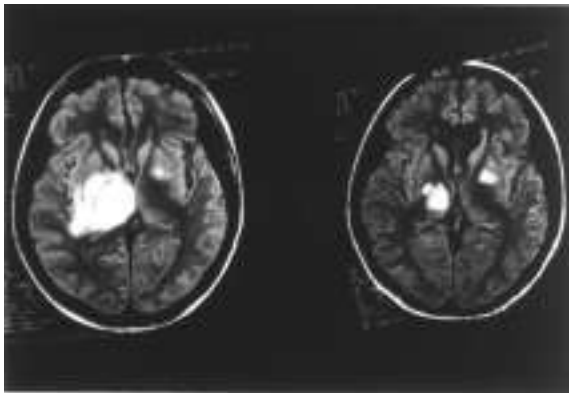

Figure 2. Pre-and post-therapy SE proton density-dependent images showing the presence of a second lesion in the left pallidus. In the post-therapy image (right) the dimension of the main lesion is markedly reduced, with disappearance of the edematous component. No change is observed in the smaller lesion.

HD, nodular sclerosis, stage IV B was diagnosed in a 22 year-old man in October 1995. After 16 doses of VEBED (vinblastine, epirubicin, bleomycin, etoposide, deflazacort), he achieved partial response. In June 1996 the patient underwent allogeneic BMT from his HLA-identical sister. Conditioning was busulfan-cyclophosphamide; graft versus host disease (GVHD) prophylaxis was carried out with cyclosporine; *Pneumocystis carinii* prophylaxis was performed by aerosolized pentamidine. Engraftment was documented on day +25. Six months later, with a bone marrow karyotype XX, mediastinal and liver HD relapse occurred; the patient was treated by a single C-MOPP course and two DLI (infused lymphocytes: 0.25 and 0.9×10^8/kg, respectively). Complete remission (CR) was achieved, but severe cutaneous and hepatic GVHD occurred, requiring intense immunosuppression by cyclosporine and methylprednisolone. A month later fever and neurological symptoms appeared. ESR and serum LDH were elevated. Brain CAT scan showed a hypodense right thalamic lesion of undefined nature; magnetic resonance imaging (MRI) showed a target-shaped lesion in the right thalamic area with a spontaneous hyperintense centre on T1-weighted images (Figure 1), likely due to hemorrhage, and a hypointense centre on T2-weighted images. A smaller hyperintense lesion was present in the left lenticula. Brain biopsy could not be performed because of thrombocytopenia. A low titer of serum anti-toxoplasma IgG was detected. Pyrimethamine-sulfadiazine treatment was started, leading to marked clinical and neuroradiological improvement within two months (Figure 2). At present, pyrimethamine-sulfadiazine treatment is continued at lower doses. HD is still in CR; the patient presents mild cutaneous and hepatic GVHD, and some neurological disturbances persist.

Toxoplasmosis has to be considered a possible cause of focal cerebral disease in allogeneic BMT patients.[4] Main risk factors are delayed immunological reconstitution and prolonged immunosuppression needed to control severe forms of GVHD. In absence of definite histological evidence, a presumptive diagnosis of toxoplasmosis can be based on MRI findings and is confirmed by response to specific anti-toxoplasma treatment. Peculiar findings at MRI are multiple round shaped lesions, with ringed or nodular gadolinium enhancement and mass effect.[5] The lesions are most often localized at the cerebral cortical or corticomedullary junction. A target-shaped lesion with hypointense centre on T2-weighted images is considered typical,[5] while other findings, such as the ringed gadolinium enhancement, may also be found in other diseases.[6] In our case, as in others,[7] aerosolized pentamidine was an insufficient prophylaxis against toxoplasmosis. The intense immunosuppression used to control the DLI-induced GVHD has certainly favored the infectious complication; on the other hand, DLI treatment may have contributed to achieve HD remission. To the best of our knowledge, no other case of relapsed HD has been treated by DLI.[8]

Key words

Cerebral toxoplasmosis, bone marrow transplantation, magnetic resonance imaging, donor lymphocyte infusion

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Thrombopoietin: a potential T-helper lymphocyte stimulator. Change in T-lymphocyte composition and blood cytokine levels in thrombopoietin cDNA transferred mice

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The aim of this study was to evaluate the effect of thrombopoietin (TPO) on T lymphocyte in Balb/c mice delivered hTPO cDNA with plasmid vector. Both mature and immature T lymphocytes in central organs increased, but only the CD4⁺ subset was preferably proliferated in circulation. High serum IFN-γ was coinciding with the declination of platelet counts, but TNF-α was positively associated with the platelet count, while high IL-2 level was similar to the course of TPO expression. Our data suggested that TPO is a stimulator for T lymphocytes, especially the CD4⁺ subset.

Accumulating materials have enlightened the participation of thrombopoietin (TPO) in immunological processes. TPO stimulates the proliferation of endothelial cells and enhanced their expression of cell adhesion molecules.[1] It also indirectly induces the production of interferon-α *in vitro*.[2] We previously observed macrophage proliferation and endothelial cell activation in the spleens of TPO gene therapy mice. Here we have investigated the T lymphocyte composition and cytokine production of mice with TPO cDNA delivery.

Female Balb/c mice were delivered with the pcDNA3/hTPO plasmid as previously described.[4] The dose was 60 μg plasmid DNA for each mouse. Null-treated mice as control. Mononuclear cells isolated from thymocytes, plenocytes, fumer marrow cells and blood cells were directly stained with FITC conjugated-anti-mouse CD4 (L3T4) and PE conjugated-anti-mouse CD8a (Ly-2)(Pharmingen). Samples were analyzed using a FacStar flow cytometer (Becton Dickinson). For each sample, 5,000 events were acquired. Sera collected from 5 mice at set times were analyzed in duplicate with IFN-γ, IL-2 ELISA kits (Genzyme) and TNF-α kits (Biotinge, China).

Both mature T lymphocytes ($CD4^+$ or $CD8^+$) and immature ones ($CD4^+CD8^+$) in central and peripheral immune tissues were affected. They assumed different characters in the 2nd week. As Figure 1 shows, in marrow and spleen, all the three T lymphocyte subsets increased, while only the immature cells increased in the thymus. However, $CD4^+$ subset predominantly and selectively increased in blood.

Serum IFN-γ, TNF-α and IL-2 concentrations began to change early within 24 hr. of gene delivery (Figure 2). IFN-γ peak was 9-12 folds that of the controls and maintained from the 2nd week. Striking peak TNF-α level was about 120 folds of the controls but only occurred in the first week. Meanwhile, IL-2 was high at the most times.

Our data indicated the stimulatory effect of TPO on T cell production. In this process, T helper subset was subject to be selectively enhanced, as implied by the increase in blood $CD4^+$ cells. Elevated immature but low mature T ratio in the thymus might suggest a speed-up development. Furthermore, high IFN-γ and IL-2 production implied activation of Th1 and possibly NK cells in the time.

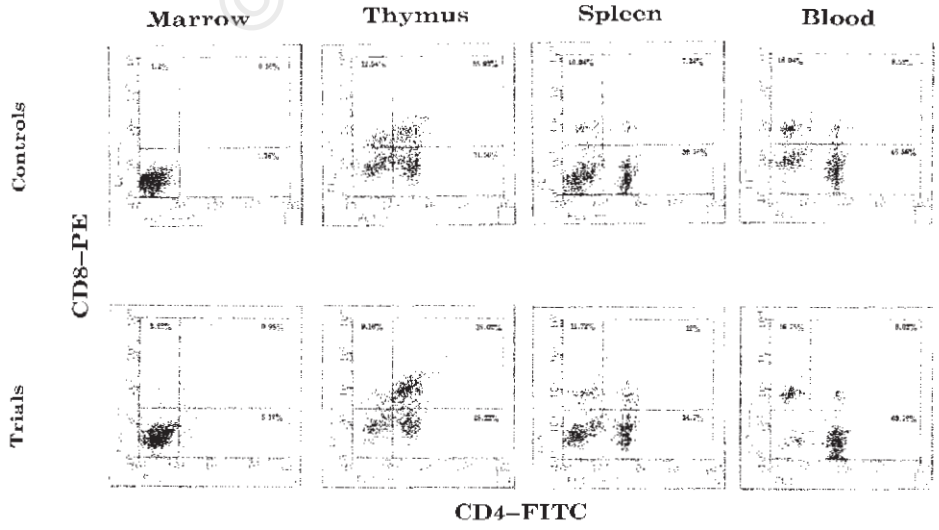

Figure 1. T-lymphocyte frequency alterations.