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MRI of intracranial toxoplasmosis after bone marrow transplantation

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Abstract Toxoplasma encephalitis was confirmed by biopsy in three patients with bone marrow (BMT) or peripheral blood stem-cell transplantation (PBSCT). All had MRI before antimicrobial therapy. The intensity of contrast enhancement was very variable. One patient had one large, moderately enhancing cerebral lesion and several smaller almost nonenhancing lesions. The second had small nodular and haemorrhagic lesions without any enhancement. The third had late cerebral toxoplasmosis and showed multiple lesions with marked contrast enhancement. The moderate or absent contrast enhancement in the two patients in the early phase of cerebral toxoplasmosis may be related to a poor immunological response, with a low white blood cell count in at least one patient. Both received higher doses of prednisone than the patient with late infection, leading to a reduced inflammatory response. In patients with a low leukocyte count and/or high doses of immunosuppressive therapy, typical contrast enhancement may be absent.

Key words Bone marrow, transplantation · Toxoplasmosis, cerebral · Magnetic resonance imaging

Introduction

With an increasing number of patients suffering from immune deficiencies the varying radiological appearances of infectious brain lesions is becoming more important. Beside patients with chronic disease and AIDS, organ-transplant recipients are of major interest. Patients with allogeneic bone-marrow (BMT) or peripheral blood stem-cell (PBSCT) transplants have the most severe immune deficiencies. There were reports of 55 cases of toxoplasmosis in BMT recipients up to 1997, and the diagnosis was usually made at autopsy [1]. The true prevalence of cerebral toxoplasmosis seems to be higher, because confirming the diagnosis without tissue analysis is difficult [2]. Diagnosis in vivo is possible by direct detection of toxoplasma cysts or tachyzoites, histological demonstration of necrotising encephalitis, positive or increasing IgG or IgM antibodies in serum or cerebrospinal fluid (CSF), or by the response to anti-toxoplasmosis therapy [3, 4]. It is important for radiologists to know that these inflammatory lesions do not have any typical contrast enhancement pattern on CT or MRI [5, 6].

Case reports

Case 1

A 31-year-old man had allogeneic BMT for treatment of chronic myeloid leukaemia. On day 65 after BMT he had focal seizures with secondary generalisation, dysarthria and mild cerebellar ataxia. MRI revealed multiple brain lesions: small ones in the cerebellum and basal ganglia, and a larger right temporal lobe lesion seen as a high-signal ring on T1-weighted images. There was moderate ring enhancement of the temporal lesion and little or no contrast enhancement of the smaller ones (Fig. 1). The patient had a leukocyte count of 3100/μl and received 80 mg prednisone for treatment of graft-versus-host disease (GVHD) grade III. Lumbar

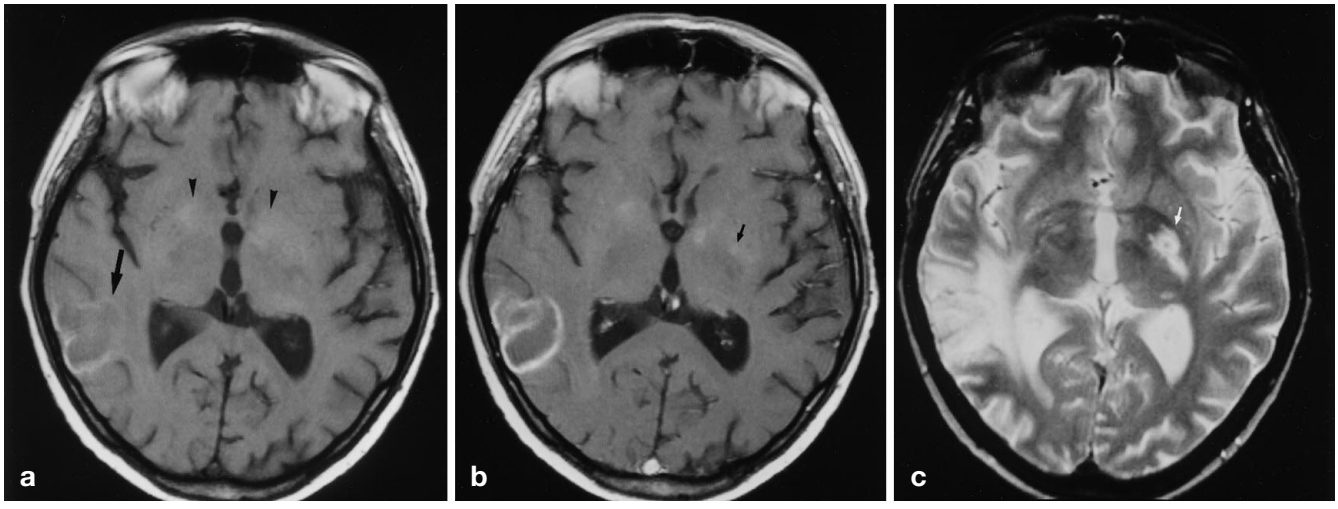

Fig. 1 **a** Axial T1-weighted image reveals a low-signal temporal lesion with an incomplete high-signal ring suggesting a necrotic infectious lesion *(large arrow)*. Bilateral foci of high signal in the basal ganglia *(arrowheads)* were thought to be due to calcium or manganese. **b** There is moderate ring enhancement of the right temporal lesion and only faint enhancement of a left basal ganglion lesion *(small arrow)*. **c** Perifocal oedema is better seen on T2 weighting *(white arrow)*. This helped to distinguish between metabolic and infectious basal ganglion changes

puncture revealed 115 cells/µl, predominantly lymphocytes. Serological tests were positive for IgG antibodies against *Toxoplasma gondii* but negative for IgM antibodies. Moreover, *Aspergillus, Candida,* and CMV pp65 antigens were negative. Antitoxoplasmosis treatment was started with pyrimethamine and sulfadiazine. MRI 10 days later revealed only partial regression of the right temporal lesion, and stereotactic biopsy was performed to rule out other infectious agents. Histology confirmed necrotising encephalitis, suggestive of toxoplasmosis. Therapy was continued, with gradual resolution of symptoms and small residual lesions on MRI. A year later the patient died from a relapse of cerebral toxoplasmosis, confirmed by autopsy.

Case 2

A 38-year-old woman received allogenic PBSCT for treatment of relapsing acute lymphatic leukaemia after allogeneic BMT 8 months previously. She was admitted 118 days after BMT with focal seizures, with secondary generalisation. Examination revealed a spastic left hemiparesis, from a previous intracerebral haemorrhage. MRI revealed focal atrophy of the right frontal lobe caused by the old haematoma. Adjacent to the lesion and the basal ganglia bilaterally were multiple small nodules with high signal intensity on T1 weighting, suggesting haemorrhage. No pathological contrast enhancement could be identified (Fig. 2). The leukocyte count was 9500/µl. The patient received 50 mg prednisone for treatment of grade II GVHD. Serological tests were positive for IgG and IgM antibodies against *Toxoplasma gondii,* while *Aspergillus, Candida* and CMV pp65 antigens were negative. Moreover, *Toxoplasma gondii* was detected by histological examination of bone marrow smears. Treatment with pyrimethamine and sulfadiazine was started, with complete recovery of neurological, radiological and laboratory findings; the patient survived.

Case 3

A 37-year-old man had PBSCT for treatment of chronic myeloid leukaemia, and 689 days later developed a left hemiparesis, with a Babinski sign and a right homonymous hemianopia. MRI showed multiple space-occupying lesions with marked contrast enhancement in both cerebral hemispheres and the cerebellum (Fig. 3). The patient had a leukocyte count of 7500/µl and received 5 mg prednisone and 50 mg cyclosporine for treatment of grade II GVHD. Serological tests were positive for IgG antibodies against toxoplasma. *Aspergillus, Candida,* and CMV pp65 antigens were negative. Despite treatment with pyrimethamine and sulfadiazine the patient showed progressive deterioration. Stereotactic biopsy revealed necrotising encephalitis, suggesting toxoplasmosis. Antimicrobial therapy was changed to clindamycin and sulfadiazine, but only slow, incomplete remission of symptoms was achieved. MRI, however, revealed a marked decrease in the lesions and of contrast enhancement. The patient was sent to a rehabilitation unit and survived without relapse.

Discussion

Infection with *Toxoplasma gondii* leads to progressive encephalitis in immuncompromised patients. Patients with successful BMT initially have a severe decrease in blood cells followed by an increase in cell counts after 4 months [7]. Deranged cell-mediated and humoral immunity may persist up to a year. During the period of profound leukopenia the patients are at high risk of opportunistic infection and do not show typical signs of cerebral infection clinically or radiologically [8].

Toxoplasmosis in BMT recipients usually occurs within 6 months of BMT, with a peak at 2–3 months. Clinical manifestations are seizures, lethargy, altered mental status, hemiparesis, dysarthria, urinary incontinence and fever [9–12]. Toxoplasma encephalitis is

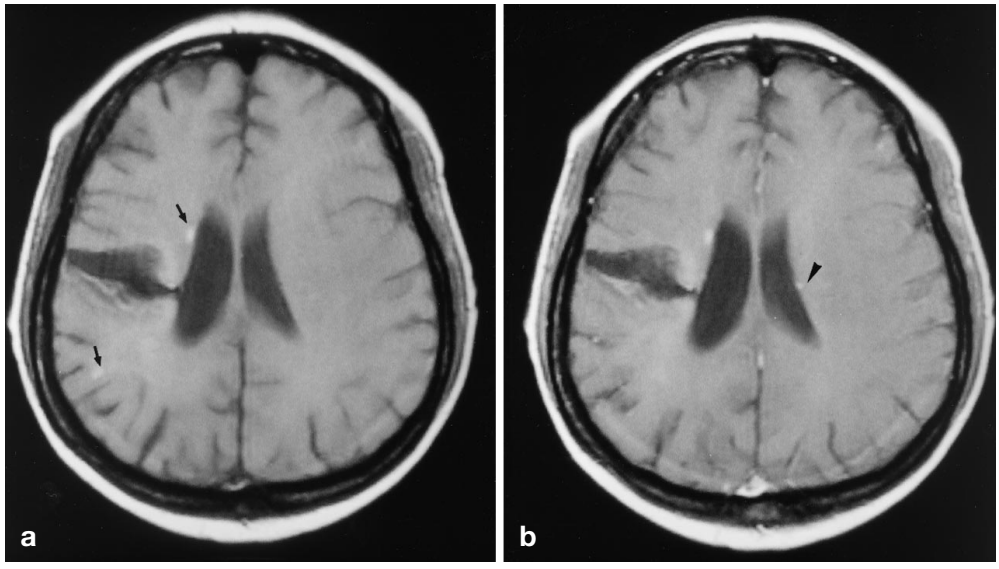

Fig. 2 **a** Axial T1-weighted image reveals a right frontal lobe defect due to old haemorrhage and small high-signal subcortical and periventricular nodules *(arrows)* suggesting small haemorrhagic infectious lesions. **b** No pathological contrast enhancement is visible. A high-signal focus near the left lateral ventricle *(arrowhead)* is a subependymal vein

difficult to confirm by serological tests. An increasing antibody titre after BMT is of limited value in diagnosis of an active infection [13]. A clinical diagnosis is supported by demonstration of brain lesions on MRI and improvement of clinical and radiological findings after therapy.

Definite evidence of toxoplasma infection can be obtained by identification of toxoplasma cysts or tachyzoites in body fluids or biopsies [14, 15]. In other patients histological examination is necessary to confirm toxoplasma encephalitis. The findings, however, are very variable, depending on the stage of infection and on treatment [16]. In two of our patients stereotactic biopsy confirmed a necrotising encephalitis suggestive of toxoplasmosis, and in one, toxoplasma organisms were detected in a bone marrow biopsy before the start of treatment.

MRI usually reveals multiple lesions in the basal ganglia and at the corticomedullary junction of the cerebral and cerebellar hemispheres. The centre of the lesions is coagulation necrosis and gives low or isointense signal on T1- and isointense or high signal on T2-weighted images. The periphery of the lesions is an accumulation of encysted organisms. Inflammatory and vascular changes lead to the formation of isointense or

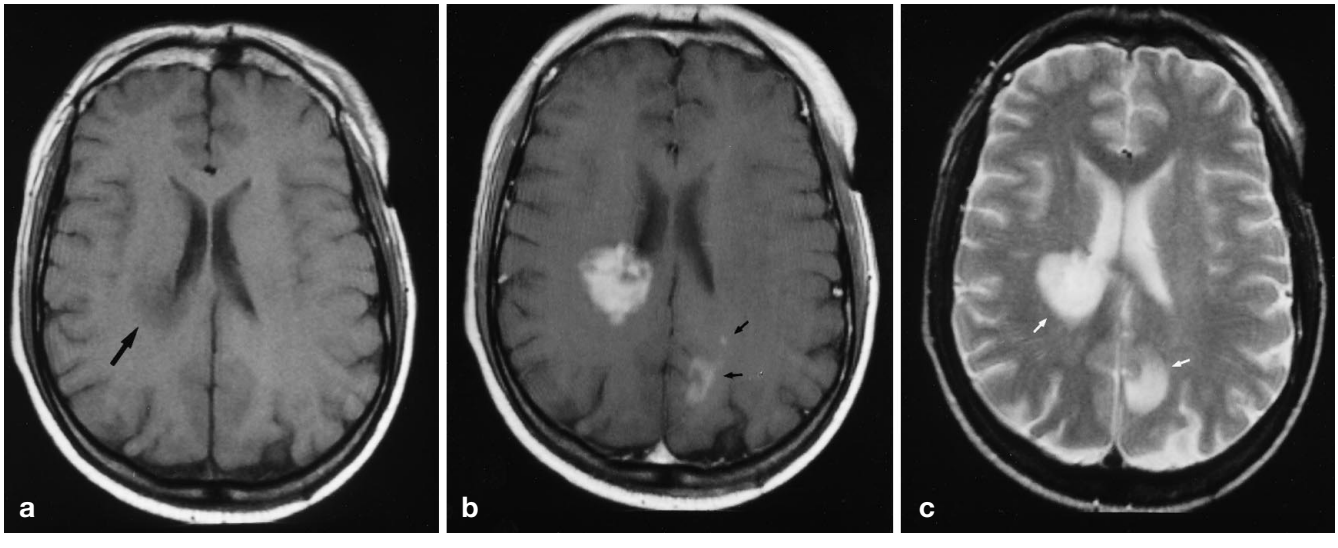

Fig. 3 **a** A T1-weighted image reveals a low-signal lesion in the right parietal white matter *(arrow)* with minimal mass effect. **b** There is marked contrast enhancement of this lesion and of smaller lesions in the left parietal white matter *(small arrows)*. **c** The large lesions are visible *(white arrows)* on T2 weighting

high-signal rings which may show contrast enhancement [17]. Nodular enhancement is seen in smaller lesions and in lesions without necrosis. In patients with AIDS cerebral toxoplasmosis is usually seen as enhancing lesions, but nonenhancing or haemorrhagic foci may be present [18, 19].

In BMT recipients toxoplasma encephalitis often remains undiagnosed due to the lack of specificity of the clinical features and negative or nonspecific CT or MRI. In immuncompromised patients the inflammatory response is poor, so that contrast enhancement can be minimal, absent, or delayed [20]. Yuh et al. [21] found a correlation between contrast enhancement and leukocyte counts in seven patients with cerebral fungal or viral infection after BMT. Patients with low counts, particularly low lymphocyte counts, showed no contrast enhancement and no significant oedema. Detection and follow-up of areas of high signal on T2-weighted images may be of value in determining the presence and activity of brain lesions [22].

Leukocyte counts were low in our first patient, who showed only a single necrotic lesion representing active infection. There were several smaller, nonenhancing lesions, better seen on T2-weighted images indicating an inadequate immune response. MRI of the second patient showed haemorrhagic lesions without contrast enhancement, probably explained by depression of all blood elements, including thrombocytes. Patients 1 and 2 were treated with high doses of prednisone. Patient 3 showed dense contrast enhancement almost 2 years after BMT. Solid enhancement of chronic infectious lesions indicates a granulomatous inflammation and suggests a better immune response. Late toxoplasmosis after BMT was recently reported. One patient had nonenhancing lesions on CT [23], the second haemorrhagic, enhancing and nonenhancing lesions [24], and the third bilateral intensely enhancing masses on MRI [25].

A definite diagnosis of cerebral toxoplasmosis cannot be made from MRI, alone because fungal infections may also cause multiple lesions. Contrast enhancement of brain lesions does not help in characterising the lesions or predicting their activity. Biopsy therefore was considered necessary.

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