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Imaging characteristics of toxoplasmosis encephalitis after bone marrow transplantation: report of two cases and review of the literature

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Abstract Toxoplasmosis encephalitis is a severe, but often misdiagnosed complication in patients after bone marrow transplantation (BMT). We describe the unique computed tomography (CT) and magnetic resonance (MR) imaging features of cerebral toxoplasmosis in two bone marrow recipients and compare them to the cases in the literature. To our knowledge, this is the first report analyzing the appearance of cerebral toxoplasmosis on diffusion-weighted MR imaging (DWI).

Keywords Bone marrow transplantation · Toxoplasmosis · Brain · Magnetic resonance imaging

Introduction

Toxoplasmosis is an opportunistic protozoal infection primarily affecting patients with immune deficiencies. The incidence varies geographically, with a higher frequency of seropositivity in the general population in Central Europe than in North America [1, 2]. Toxoplasmosis is most commonly seen in human immunodeficiency virus (HIV) -positive patients and is a rare but almost always fatal complication in patients following allogeneic bone marrow transplantation.

Disseminated toxoplasmosis after bone marrow transplantation (BMT) has been reported in 1% to 7.6% of allogeneic transplant recipients [3–5]. Due to the deranged cellular and humoral immune response during the first year after BMT, patients usually do not show typical clinical or imaging signs of cerebral infection [4, 6]. The final diagnosis of intracranial toxoplasmosis is usually made at autopsy.

Since 1992, approximately 100 cases of toxoplasmosis encephalitis in patients after BMT have been reported in the literature [6–15]. The diagnosis was based on imaging findings, polymerase chain reaction (PCR) and/or brain biopsy, and standardized treatment with pyrimethamine and sulfodiazine was given in some of the cases. In the majority of the published cases, the diagnosis was established at autopsy without specific anti-microbial therapy being given prior death.

We describe two proven cases with isolated cerebral toxoplasmosis in patients following BMT with a fatal outcome despite antitoxoplasmosis therapy.

Case reports

Case 1

A 41-year-old woman had allogeneic BMT for treatment of acute myelocytic leukemia (AML). Immediately after BMT, she received intravenous steroids to prevent graft-versus-host disease (GVHD). Two months later, based on increasing CMV-copies in the blood, cytomegaly virus (CMV) infection was diagnosed and successfully treated with gancyclovir. At day +119 after BMT, the patient was hospitalized because of apathy, abnormal fatigue and reduced general condition. Her leukocyte count was 6,400/μl and the thrombocyte count was 26,000/μl. Computed tomography (CT) scan showed three hyperdense lesions with mild perifocal edema located

in the grey-white matter junction and in the deep central nuclei. The initial magnetic resonance (MR) examination two days later revealed 34 lesions in both hemispheres and in the cerebellum, with a maximum size of 2 cm. On fluid-attenuated inversion recovery (FLAIR)-weighted MR images most lesions were hyperintense, and some lesions were slightly hypointense centrally (Fig. 1a). On unenhanced T1-weighted images two lesions were hyperintense, two lesions were hypointense and all other lesions were isointense (Fig. 1b). The lesions showed no contrast enhancement on post-contrast images and no mass effect. On diffusion-weighted imaging (DWI), the lesions with hyperintensity on T1-weighted images showed low signal with a hyperintense rim consistent with subacute hemorrhage. The other lesions were isointense on DWI. The findings were suggestive of toxoplasmosis encephalitis and treatment with pyrimethamine and sulfodiazine was initiated. Despite therapy, the patient showed neurologic deterioration and was somnolent 5 days after the onset of symptoms. Follow-up CT and MR scans 8 days and 10 days after the initial CT scan revealed significant progression with more than 40 lesions supra- and infratentorially. All lesions were hyperintense on unenhanced T1-weighted MR images on follow-up scan. On gradient-echo MR images, the lesions were of mixed signal-intensity centrally and surrounded by a hypointense rim (Fig. 1c). On DWI, all lesions showed a low signal with a hyperintense rim (Fig. 1d). To rule out other infectious agents, stereotactic biopsy of a subcortical lesion was performed. Histology showed necrotizing encephalitis compatible with toxoplasmosis and the antitoxoplasmic therapy was continued. Nevertheless, the patient died 18 days after hospitalization. Brain autopsy revealed widespread hemorrhagic-necrotizing toxoplasmosis encephalitis of the cerebral hemispheres, cerebellum, basal ganglia and pons (Fig. 1e).

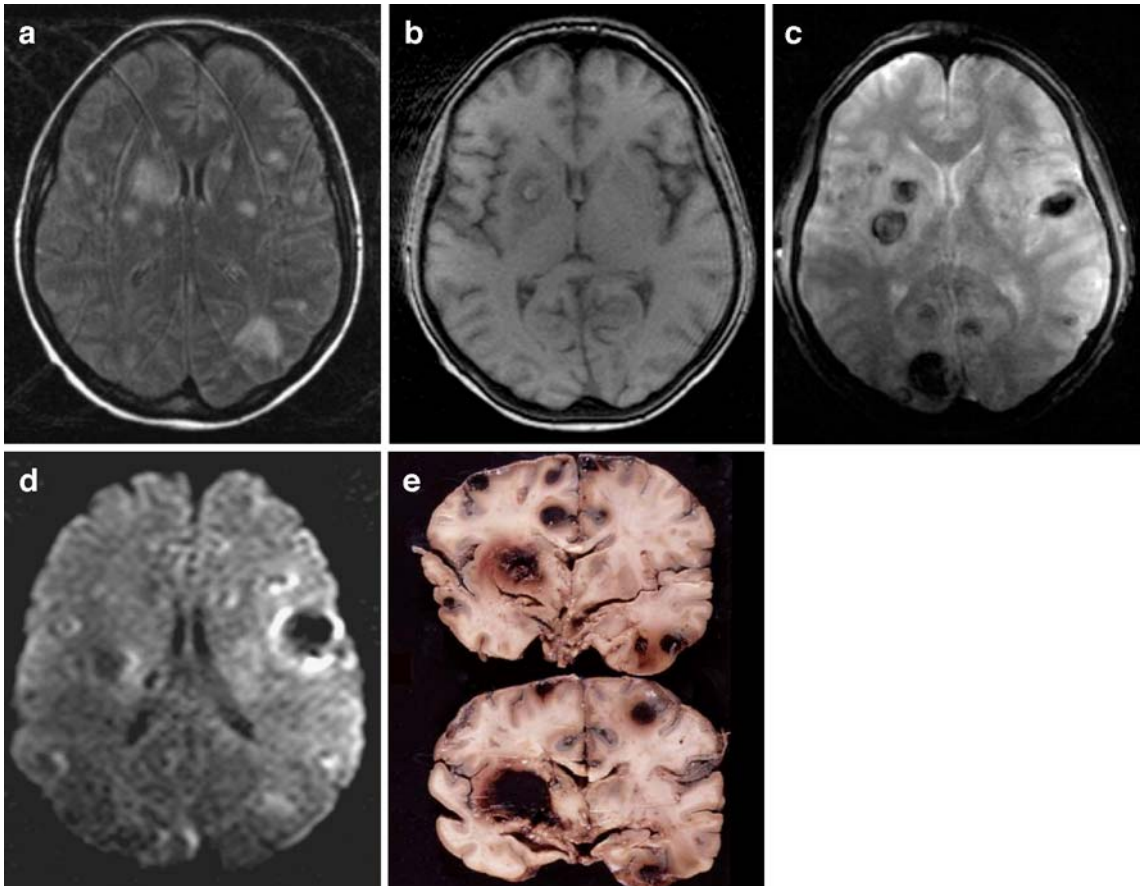

Fig. 1 **a** Axial fluid-attenuated inversion recovery (FLAIR) MR image (TR/TE/TI=11,000/120/2,800) shows multiple hyperintense lesions located in subcortical regions bilateral and in the basal ganglia. **b** On unenhanced axial T1-weighted MR image (TR/TE/Flip°=239/2/90°) the lesion in the right basal ganglia is slightly hyperintense and surrounded by a hypointense rim, suggesting subacute hemorrhage. Most of the lesions seen on the FLAIR-weighted MR image are isointense on T1-weighted MR image. **c** On gradient-echo MR image (TR/TE=1,027/23) the lesions are iso/hyperintense with a hypointense rim or heterogenous representing hemorrhagic transformation. **d** On DWI (TR/TE=3,987/145; b=1,000 s/mm^2) the lesions show low signal with a hyperintense rim consistent with early subacute hemorrhage. **e** Brain autopsy (coronal section) reveals a large collection of blood in the right basal ganglia and multiple hemorrhagic-necrotizing lesions in the subcortical white matter in both hemispheres, representing multifocal toxoplasmosis encephalitis

There was no sign of toxoplasmosis in liver, spleen or lung immunohistochemically.

Case 2

A 63-year-old man underwent two autologic BMTs two and three years prior to presentation, and finally received an allogeneic BMT for treatment of multiple myeloma. Nine months after the last BMT, he was admitted to the hospital because of thrombotic-thrombocytopenic purpura and activation of a known chronic hepatitis B. In addition, he had a chronic extensive GVHD of skin, oral mucosa, eyes and liver which was treated with aprednisolon (1 mg/kg/day). His leukocyte count was 6,000/μl. Six weeks after hospitalization (day +280 after BMT) he showed increasing fatigue and listlessness. One week later, he developed a palsy of the VII cranial nerve and a left-sided spasticity. Initial CT scan showed multiple hypodense lesions in both cerebral hemispheres and in the cerebellum, with a maximum size of 2 cm (Fig. 2a). MR examination revealed more than 20 lesions that showed hyperintensity on T2-weighted images (Fig. 2b,c). None of the lesions showed contrast enhancement and only some of the lesions were surrounded by mild edema (Fig. 2d). On DWI, two types of lesions were seen. Two lesions showed a low signal with a hyperintense rim and were hyperintense on T1-weighted images. These imaging findings were consistent with hemorrhagic lesions. All other lesions showed high signal on DWI and low signal on the ADC map, and were iso- or slightly hypointense on T1-weighted images consistent with restricted diffusion (Fig. 2e,f). The MRI findings were suspicious for toxoplasmosis encephalitis and antimicrobial therapy with pyrimethamine, sulfodiazine and dalacin was started immediately. After a short-term clinical improvement, the patient showed rapid deterioration and died 14 days after the onset of neurologic symptoms. Brain autopsy revealed multifocal hemorrhagic-necrotizing toxoplasmosis encephalitis. There was no evidence of toxoplasmosis in other organs.

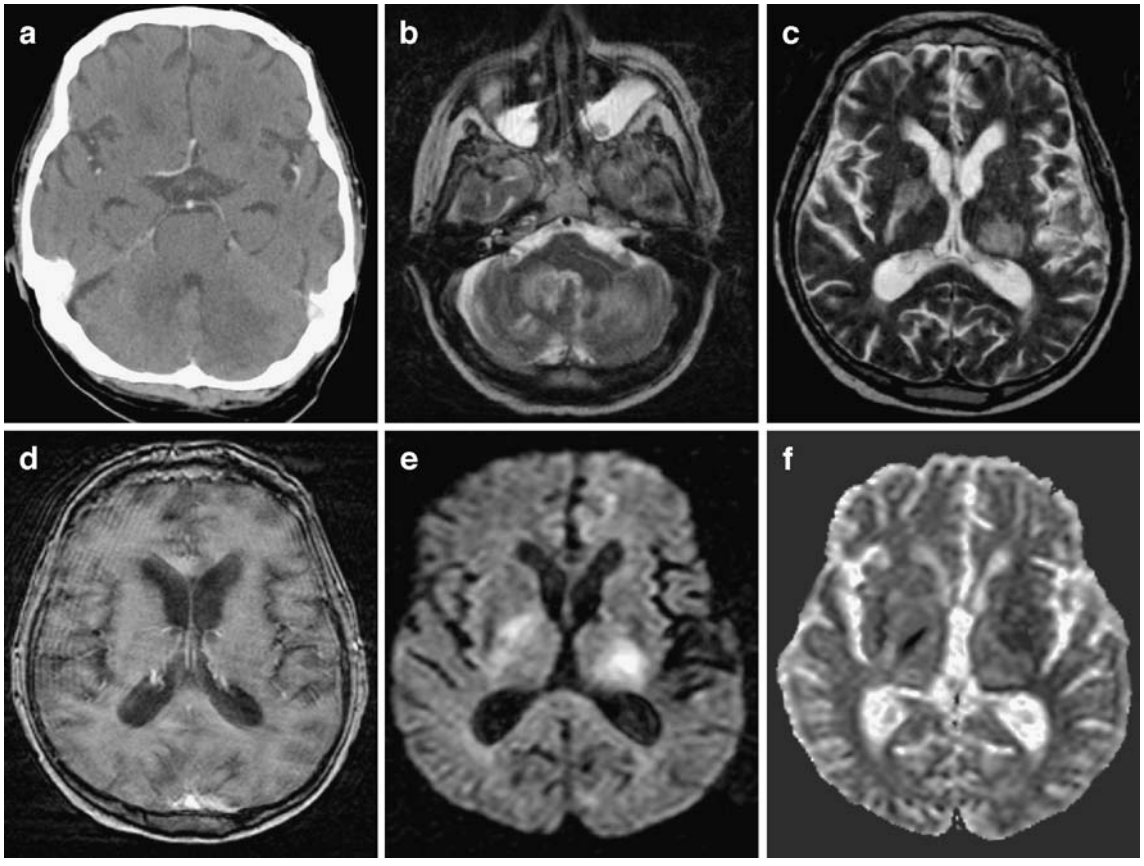

Fig. 2 **a** Post-contrast CT scan shows non-enhancing lesions with irregular margins bilateral in the cerebellum. **b** On the corresponding T2-weighted MR image (TR/TE=4,774/110) the lesions are hyperintense and show mild perifocal edema. **c** Axial T2-weighted MR image (TR/TE=4,774/110) at the higher level reveals two other hyperintense lesions in the left thalamus and in the right basal ganglia. **d** The bithalamic lesions did not enhance on post-contrast T1-weighted MR image (TR/TE/Flip°=259/2/90°). **e** On DWI (TR/TE=3,596/125; b=1,000 s/mm^2) the bithalamic lesions show high signal, which is consistent with restricted water diffusion. **f** At the same level as the image in **e**, this ADC map shows hypointensity, consistent with restricted water diffusion, within the toxoplasmic lesions

Discussion

Toxoplasmosis encephalitis is a rare, but severe complication in bone marrow recipients usually appearing between the 2nd and 6th month after BMT [4, 16]. The clinical symptoms are non-specific, with fever, seizures, headaches or altered mental status the most common manifestations [5, 8]. Cerebrospinal fluid (CSF) analysis is often inconclusive and PCR for toxoplasmosis DNA in different organs, including the brain in BMT patients, is reported to be positive only in 75% of infected organs [11, 17]. These facts emphasize the importance of recognizing the patterns of toxoplasmosis encephalitis on initial imaging examinations. In HIV-positive patients, the imaging findings in toxoplasmosis are well known. MRI usually shows multifocal lesions with hypo-, iso- or hyperintensity on T2 and iso- or hypointensity on T1-weighted images [18]. After application of gadolinium, the lesions typically show ring or nodular enhancement and, commonly, edema and hemorrhage are present.

One of the main differences between patients with HIV and patients after BMT is the fact that toxoplasmic lesions are often initially hemorrhagic in BMT population, whereas hemorrhagic transformation will be only seen in HIV population after initiation of the antitoxoplasmic therapy. Enhancement of the lesions will be present in all patients with HIV and improves characterization of a lesion seen on the unenhanced images, but may be absent in BMT group [19].

To the best of our knowledge, we have found seven reports describing the CT and MRI features of toxoplasmosis encephalitis after BMT in the English literature to date, for a total of 26 patients [5, 6, 10–14]. The time interval between BMT and onset of cerebral toxoplasmosis for these patients was between 14 and 689 days (mean, 154.3±178.5 days). Twelve patients survived without relapse, and the survival time of the 13 patients who died due to toxoplasmosis ranged from 10 days to 456 days (mean: 219.5±224.2 days). The death of one patient was not due to cerebral toxoplasmosis. In two cases, diagnosis was made postmortem by brain autopsy; in all other cases diagnosis was based on neuroradiological and clinical criteria (19 cases) or brain biopsy (5 cases). All patients with suspected or confirmed toxoplasmosis encephalitis received a therapy regimen with pyrimethamine and sulfadiazine (22 cases) or pyrimethamine and clindamycin (4 cases). In our two cases, the onset of cerebral symptoms due to toxoplasmosis was on day 119 (Case 1) and on day 280 after BMT (Case 2), and the diagnosis was based on CT and MR imaging findings; in one patient, a brain biopsy was performed. Both patients died 18 and 14 days, respectively, after symptom onset despite immediate antitoxoplasmic therapy with pyrimethamine and sulfodiazine.

In 24 of the 26 patients described in the literature, MR examination showed multiple lesions in the basal ganglia and, subcortically in supra- and infratentorial location. In two patients, MRI showed only one and two lesions in the cerebral hemispheres, respectively. Depending on the enhancement characteristics of the lesions and the presence of edema, MRI revealed two different features. In 16 patients, the lesions showed the typical MR appearance of cerebral toxoplasmosis with nodular or ring-enhancement surrounded by moderate to extensive edema. In contrast, the lesions in 10 patients showed no enhancement and there was no edema. In seven cases, some lesions were hyperintense on non-enhanced T1-weighted images, suggesting hemorrhage. In our two cases, MRI revealed multiple lesions in a supra- and infratentorial location that were also non-enhancing and showed no or mild edema. In our first patient, all lesions were hemorrhagic, whereas in the second patient, only two out of more than 20 lesions were hemorrhagic.

In a previous study involving seven patients with cerebral fungal or viral infection after BMT, Yuh et al. also reported a lack of contrast enhancement and edema in patients with low total white blood cell count (WBC), whereas in one patient with a normal total WBC, all lesions showed marked contrast enhancement and edema [20]. Therefore, they explained the lack of contrast enhancement as a result of reduced inflammatory response due to the impaired humoral and cellular immunity, preventing the passage of gadolinium through the blood-brain barrier. This hypothesis is supported by two other studies dealing with the MRI features of toxoplasmosis encephalitis. In a study by Maschke et al., patients with non-enhancing lesions also had low leukocyte counts compared to patients with a typical appearance of cerebral toxoplasmosis and normal leukocyte counts [12]. In addition, a recent study of cerebral toxoplasmosis in immunocompetent patients showed marked linear or ring enhancement of all brain lesions [21].

Because of the limited data, a correlation between contrast enhancement and leukocyte count in the 26 cases from the literature was not possible. However, it is remarkable that in the two patients from our institute, leukocyte counts were within normal limits and the lesions showed no contrast enhancement and only discrete or no edema. These findings suggest that the WBC is not the only predictor for the inflammatory response against cerebral toxoplasmosis. In general, patient 2 was at higher risk of developing a toxoplasmosis infection because he received immunosuppressive therapy with high-dose corticosteroids for treatment of a chronic GVHD. The literature reveals that prior GVHD is a risk factor for toxoplasmosis after BMT [15, 22]. The corticosteroid therapy in our patient may also be responsible for the lack of enhancement and edema of the toxoplasmic lesions. Only a few studies have commented upon the influence of corticosteroids on the enhancement of brain lesions. They reported a reduced enhancement after application of corticosteroids, but the effect on the blood-brain barrier is still unclear [23–25]. Patient 1 did not receive any immunosuppressive medication and we have no explanation for the lack of enhancement and edema of the brain lesions on her initial CT and MR scan. On follow-up CT and MR scan all lesions were hemorrhagic; therefore, we cannot comment on enhancement. The extensive hemorrhagic transformation

of the lesions in this patient was probably due to the distinct depression of thrombocytes.

With regard to the outcome of the 10 patients with atypical appearance of cerebral toxoplasmosis and our two cases, the overall mortality was 76% (9/12 patients). In the 16 patients with typical ring-enhancing lesions, the overall mortality rate was 38% (6/16 patients). These findings suggest that typical MRI features of toxoplasmosis encephalitis (i.e., contrast enhancement of the lesions) indicate an inflammatory response due to a more intact immune system and, therefore, a higher probability of survival.

Another fact influencing the outcome of the patients with toxoplasmosis encephalitis is the time of onset of disease. According to a retrospective study of 110 cases of toxoplasmosis after BMT, the outcome was better in the subjects with a late onset of disease (>100 days) which is obviously due to recovery of the immune system in this period of time. The outcome was worst in disseminated infection (64% of fatal cases had disseminated toxoplasmosis) [8]. In contrast to these findings, both of our patients showed a fulminant and fatal course of disease despite late onset (day 119 and 180 after BMT) and isolated cerebral manifestation of toxoplasmosis.

The literature regarding DWI of cerebral toxoplasmic lesions in BMT patients is sparse. We only found a single case report by Ionita et al. describing few hyperintense lesions on DWI in a patient; however, the apparent diffusion coefficient (ADC) was not measured [6]. On DWI of our patients, two types of lesions were seen: lesions with low signal on DWI and a hyperintense rim consistent with hemorrhage, and lesions hyperintense on DWI with reduced ADC consistent with restricted diffusion. Restricted diffusion was found in brain abscesses [17]. The same imaging features have been described in AIDS patients with toxoplasmosis encephalitis [26].

In conclusion, cerebral toxoplasmosis should be considered in the differential diagnosis of bone marrow recipients presenting with multiple lesions in CT and MRI even if there is an absence of contrast enhancement and edema. Normal white blood cell count and the late onset of disease do not exclude toxoplasmosis. DWI showed two different patterns depending on whether hemorrhagic transformation occurred. The role of DWI in the differentiation of toxoplasmosis from other infections/neoplastic lesions should be more extensively investigated.

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