

Cerebral toxoplasmosis after allogeneic hematopoietic stem cell transplantation diagnosed by megagenomic analysis

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To the Editor: A 19-year-old Chinese man, who received haploidentical allogeneic hematopoietic stem cell transplantation (allo-HSCT) for acute T-lymphoblastic leukemia 6 months ago, was evaluated for dysarthria, vomiting, high fever, and headache. Efforts to identify infectious pathogens all yielded negative results like cerebrospinal fluid (CSF) culture, serum toxoplasma antibody, serum galactomannan antigen assay, (1,3)- β -D-glucan antigen assay and tuberculosis (TB) interferon gamma release assay. His cerebral magnetic resonance imaging (MRI) showed multifocal mass and nodular mixed-density lesions with obvious peripheral edema in T2 sequence. An obvious eccentric target sign was observed in enhanced T1 sequence [Figure 1]. Flow cytometry of his CSF revealed increased monocytes but no evidence of leukemic blasts. Although empirical antibiotics including imipenem and antifungal agents like caspofungin had been administered, he developed generalized epilepsy and coma in 2 weeks after admission. Thereafter emergent decompressive craniectomy and cerebral biopsy were conducted. Post-surgery pathology study found no signs of tumor but only a marked number of foamy macrophages in brain tissue. Hexamine silver staining and anti-fast staining failed to spot any germs. Finally, high-throughput pathogenic megagenomic sequencing of the biopsied tissue revealed abundance of *Toxoplasma gondii* (*T. gondii*) genomes (7046 reads), which specifically led to the diagnosis of cerebral toxoplasmosis. Unfortunately, he failed pyrimethamine plus sulfadiazine therapy and died of uncontrolled disease.

Toxoplasmosis is an uncommon but potentially fatal opportunistic parasitic infection following allo-HSCT. Post-transplant toxoplasmosis is often a reactivation of prior latent infection and 90% of toxoplasmosis occur within the first 6 months after transplant.^[1] Serological testing of donor and recipient of allo-HSCT for *T. gondii* IgG is recommended and it is of critical importance for patients from endemic areas.^[2] Delayed immune reconsti-

tution like haploidentical allo-HSCT and continued immunosuppression for graft-versus-host disease are risk factors for *T. gondii* reactivation.^[3]

Typically, cerebral toxoplasmosis appears in MRI images as multiple lesions that are hypointense on T1-weighted pre-contrast MRI. On T2-weighted and fluid attenuated inversion recovery (FLAIR) MRI, the lesions are usually hyperintense with focal nodular or ring enhancement after administration of gadolinium contrast.^[1] However, besides parasite, targeted signs on MRI image often suggest tumor growth, invasive fungal infection, and also TB. It is noteworthy that *T. gondii* antibodies may not be detected by ordinary serological assay in immunocompromised patients. Thus, the negative *T. gondii* IgG antibody test result in our patient was misleading. Brain tissue biopsy may be helpful in certain settings but sampling bias may also lead to false negativity.

Diagnostic metagenomics once working in research now has a role to play in identifying the pathogenic causes in clinical setting.^[4] As in this case, the multiple intracranial lesions with a typical target sign on MRI was finally proven to be toxoplasmosis by megagenomic analysis after conventional methods failed to identify the responsible pathogen. This case has highlighted the potential of using high-throughput metagenomic analysis to identify unknown pathogens in difficult clinical settings.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initial will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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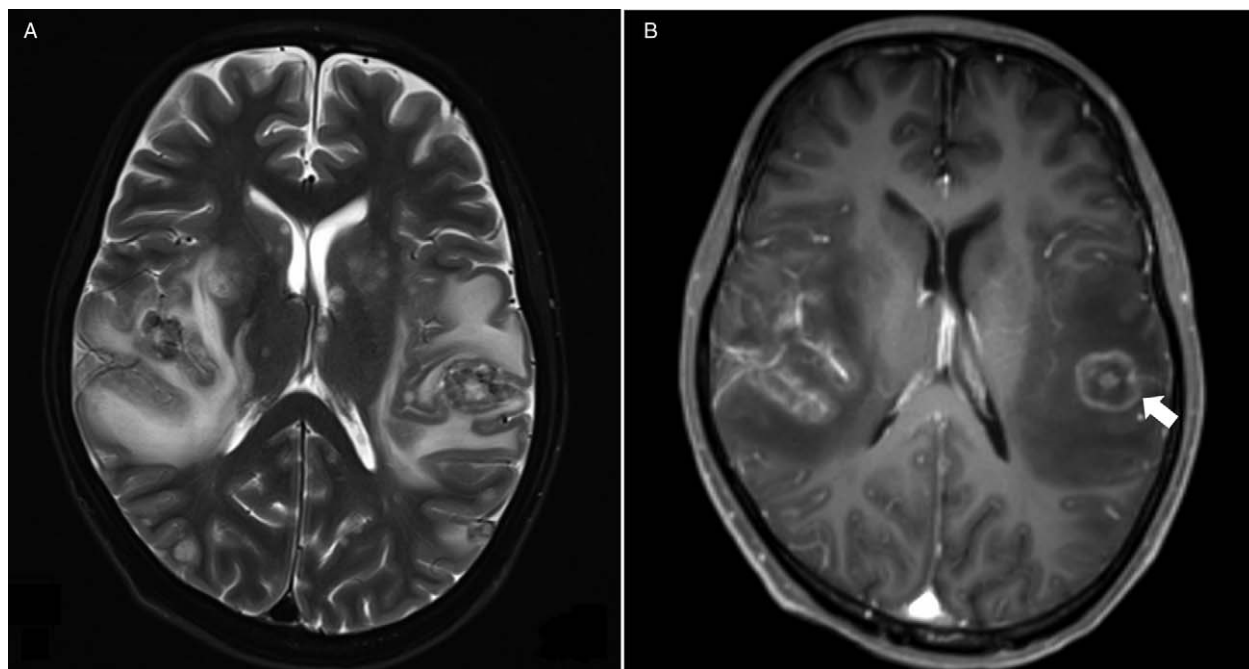


Figure 1: Cerebral magnetic resonance imaging of the patient. (A) T2-weighted sequence shows multifocal masses and nodular mixed-density lesions with obvious peripheral edema. (B) T1-weighted sequence with gadolinium contrast revealed an obvious eccentric target sign (arrow) in the left temporal lobe.

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Conflicts of interest

None.

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