



Toxoplasmosis initially presenting as neurological sequelae of chimeric antigen receptor T-cell therapy

Maria A V Marzolini, Zane Jaunmuktane, Claire Roddie, Maeve O'Reilly, Peter Chiodini, Karl S Peggs

Lancet Infect Dis 2019; 19: 788

Department of Haematology, University College London Cancer Institute and University College London Hospitals NHS Foundation Trust, London, UK (M A V Marzolini MBBS, C Roddie MBChB, M O'Reilly MBChB, K S Peggs MBBCh); Division of Neuropathology, Institute of Neurology, The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

(Z Jaunmuktane MD); Department of Clinical Parasitology, Hospital for Tropical Diseases, University College London Hospitals NHS Foundation Trust, London, UK (P Chiodini MBBS)

Correspondence to: Dr Maria A V Marzolini, Department of Haematology, University College London Cancer Institute and UCLH NHS Foundation Trust, London WC1E 6DD, UK
m.marzolini@ucl.ac.uk

A 46-year-old man with relapsed B-cell acute lymphoblastic leukaemia following allogeneic sibling haematopoietic stem cell transplantation presented with neurological signs including limb weakness, imbalance, cognitive impairment, and seizures. His most recent treatment had been CD19 chimeric antigen receptor (CAR) T-cell therapy (3×10^6 cells per kg) 4 months previously. His underlying leukaemia remained at a level of low minimal residual disease according to molecular monitoring. The differential diagnoses included CNS relapse of B-cell acute lymphoblastic leukaemia, neurotoxicity secondary to CAR T-cell therapy, and atypical infections.

A CT scan of the head showed an extensive white matter abnormality involving both frontal lobes and the corpus callosum. An MRI of the brain showed a large, peripherally enhancing lesion within the right frontal lobe that extended across the anterior corpus callosum and into the left frontal lobe (figure).

The most likely cause was thought to be a malignant process, but, considering the patient's complex history, a brain biopsy was done. Haematoxylin and eosin staining showed a dense infiltrate of lymphocytes (mostly CD3

positive and CD20 negative), and CD68 staining confirmed macrophage infiltration. Immunostaining showed scattered *Toxoplasma gondii* tachyzoites. PCR showed that the cerebrospinal fluid was positive for toxoplasma. The patient commenced treatment with pyrimethamine (75 mg once daily for 6 weeks, followed by 25 mg once daily for maintenance), sulfadiazine (1.5 g four times daily for 6 weeks, followed by 500 mg four times daily for maintenance), and folinic acid (10 mg once daily), all delivered orally. 1 year later, he has made an almost complete neurological recovery, with residual proximal muscle weakness in the right arm. On repeat imaging, the right frontal lesion has improved, whereas the corpus callosum lesion remains stable compared with the original MRI. Repeat biopsy revealed no evidence of active infection or other pathology.

Neurotoxicity following CD19 CAR-T cell therapy has been well described and usually presents with an encephalopathy syndrome, occasionally complicated by seizures. In this case, however, the cause of the neurological dysfunction was underlying cerebral toxoplasmosis. At the time of the transplant, the patient was toxoplasma (IgG) seropositive, whereas his donor was seronegative, and so he had been receiving azithromycin as prophylaxis.

This case emphasises the importance of doing a biopsy to obtain a histological diagnosis, particularly in patients with profound immunosuppression who are receiving novel immunotherapies.

Contributors

MAVM and KSP wrote the report. All authors treated the patient and revised the report.

Declaration of interests

CR has received speakers' fees from Gilead and Novartis, and has served on the advisory board of Celgene outside of the submitted work. KSP has received personal fees from Autolus, Kite (Gilead), and Juno (Celgene) outside of the submitted work. All other authors declare no competing interests.

Acknowledgments

KP receives funding from the National Institute for Health Research (NIHR) Blood and Transplant Research Unit in Stem Cells and Immunotherapy at University College London (UCL), in partnership with NHS Blood and Transplant, and in collaboration with UCL Hospitals and Imperial College Healthcare NHS Trust (which received support from the UK Department of Health and Cancer Research UK funding schemes for NIHR Biomedical Research Centres and Experimental Cancer Medicine Centres).

© 2019 Elsevier Ltd. All rights reserved.

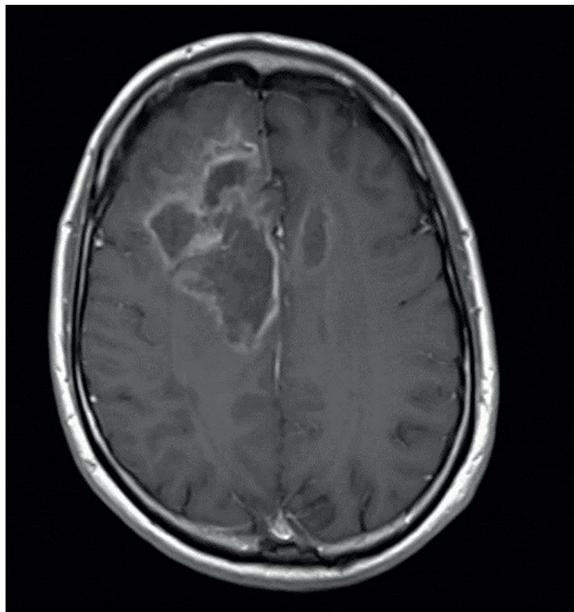


Figure: Brain lesion on MRI (transverse view)