

Tocilizumab-associated multifocal cerebral thrombotic microangiopathy

Paul Jewell, BA (Hons); Olaf Ansorge, MD, FRCP; Wilhelm Kuker, MD, PhD; Sarosh R. Irani, DPhil, MRCP (Neurol); Giovanna Zamboni, MD, DPhil

Practical Implications

Consider cerebral multifocal microangiopathy as possible side effect of tocilizumab in patients taking the drug who develop acute neurologic symptoms.

Tocilizumab is a humanized monoclonal antibody that targets the interleukin-6 receptor (IL-6-R). It is approved for use in moderate to severe refractory rheumatoid arthritis and more recently has been found to be effective in treating neuromyelitis optica.¹ Common side effects include raised hepatic transaminases, gastroenteritis, infections, and hypertension. Neurologic side effects have been described in 2 single case reports, which were confounded by the concomitant use of other antirheumatic therapies and lengthy durations between tocilizumab administration and onset of neurologic symptoms.^{2,3} We describe the clinico-histologic analysis of an acute neurologic deterioration 2 weeks after the first infusion of tocilizumab.

Case report

A 61-year-old man with a long history of severe seronegative rheumatoid arthritis (RA) was admitted with sudden onset of rapidly progressive speech disturbances and limb weakness over 24 hours. Neurologic examination showed global dysphasia, nystagmus, right facial droop, and severe right arm and left leg weakness with a left Babinski sign. He developed respiratory failure secondary to aspiration pneumonia, which required intubation and ventilation, and continued to rapidly deteriorate neurologically with a quadriparesis and right homonymous hemianopia. CT brain showed multifocal cortical and subcortical hypointensities with normal venography. Blood tests including platelet count and renal function were normal (except for raised C-reactive protein at 14 mg/L). CSF analysis showed raised protein (742 mg/L), no white cells, and normal CSF/serum glucose ratio.

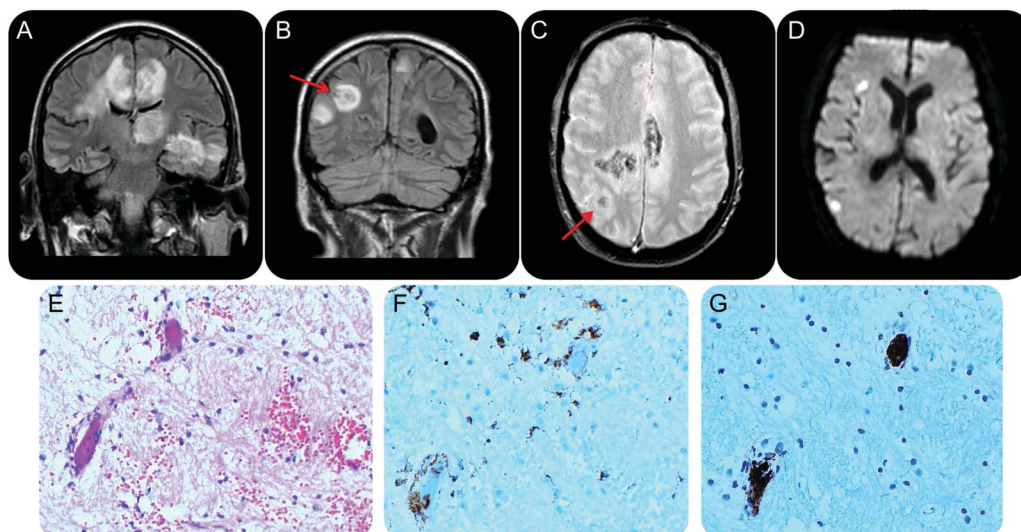
Fifteen days prior to admission, the patient had received his first infusion of 560 mg tocilizumab. He had not been treated with any antirheumatic medications for the previous 6 months. He had no major history of cardiovascular disease but had had a deep vein thrombosis and was found to be a heterozygote for Factor V Leiden 10 years earlier.

MRI brain performed 4 days after admission revealed multiple lesions predominantly affecting gray matter structures, surrounded by edema, with evidence of hemosiderin deposition and some subtle contrast enhancement (figure, A–D). An accessible large parietal lesion was biopsied. Histopathology examination revealed microangiopathy with microthrombus and petechial hemorrhages surrounded by edematous white matter. There was no histopathologic evidence of vasculitis, neoplasm, infective organisms, or necrosis (figure, E–G). Extensive tests were normal and included antibodies for HIV, toxoplasma, and cryptococcus, fungal and viral PCRs on CSF and blood, cultures on CSF, blood, nose swab, and bronchoalveolar lavage, antiphospholipid antibodies, transesophageal echocardiogram, and CT body.

Nuffield Department of Clinical Neuroscience, University of Oxford, UK.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

Correspondence to: giovanna.zamboni@ndcn.ox.ac.uk

Figure Radiologic and histopathologic features

(A-D) Cerebral MRI performed 4 days after presentation. (A, B) Coronal views from the T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI show lesions in the left thalamus, cingulate gyri, left medial temporal lobe, brainstem, and right parietal lobe. (C) Axial view from the gradient echo sequence shows hemorrhagic transformation with hemosiderin deposition in the lesions. (D) Axial view from diffusion-weighted imaging shows restricted diffusion in some of the lesions. Red arrows point to the biopsied right parietal lesion. (E-G) Cerebral biopsy, serial sections ($\times 400$ magnification), demonstrate thrombotic microangiopathy with petechial hemorrhages and edematous white matter. (E) Hematoxylin & eosin stain. Note microhemorrhage on right, edema, and a small-caliber cerebral vessel with a fibrinoid bright eosinophilic thrombus (left), which is highlighted in (F) with immunohistochemistry against CD31, expressed on thrombocytes (brown intravascular reaction product). (G) CD68 immunohistochemistry highlights scattered perivascular and parenchymal activated microglia and macrophages (brown reaction product).

After the biopsy, the patient was commenced on IV steroids for 3 days, followed by oral tapering. Subsequently, he showed a gradual and progressive improvement of weakness and dysphasia. On cognitive assessment, he showed disinhibition and executive dysfunction, which also subsequently progressively improved. MRI brain scans performed at 7 and 15 weeks from admission showed marked improvement and reduction in size of the multifocal lesions and associated edema. Nine months after presentation, the patient has residual mild proximal weakness with hyperreflexia in the left leg and a residual right superior quadrantanopia. MRI shows residual small subcortical matured lesions with hemosiderin staining, with no contrast enhancement or surrounding edema.

DISCUSSION

We report a case of acute-onset multifocal microvascular thrombotic, noninflammatory pathology affecting the CNS, which began shortly after a single tocilizumab infusion in a patient with severe RA on no other medications. We speculate that the single administration of the IL-6-R blocker tocilizumab, in combination with the patient's underlying autoimmune disease (RA) and Factor V Leiden heterozygosity, triggered an immune-mediated vasculopathic reaction, possibly by blocking an autoregulatory and inhibitory pathway and leading to a disinhibited provasculopathic autoimmune state. This is consistent with the antithrombotic/fibrinolytic effects of tocilizumab through its action on Factor XIII, chemerin, and plasminogen activator inhibitor 1.^{4,5} Furthermore, the membrane-bound IL-6-R is expressed in the brain microvasculature.⁶

This case differs from 2 previously described cases of encephalopathy following tocilizumab therapy. In these cases, the onset of neurologic symptoms was gradual, occurring after 3 and 40 months, respectively, from the initiation of tocilizumab, the presentation was predominantly

cognitive, brain imaging showed nonfocal widespread lesions restricted to the white matter,^{2,3} and histopathology revealed diffuse perivascular lymphocytic infiltration.² It also differs from previous cases presenting neurologic side effects following tumor necrosis factor- α antagonists.⁷

The potential side effect of cerebral multifocal microangiopathy secondary to tocilizumab may be effectively treated with discontinuation of the drug.

REFERENCES

1. Irani SR, Vincent A. Targeting interleukin 6 receptor to treat neuromyelitis optica. *JAMA Neurol* 2015;72:747–748.
2. Yamaguchi Y, Furukawa K, Yamamoto T, Takahashi Y, Tanaka K, Takahashi M. Multifocal encephalopathy and autoimmune-mediated limbic encephalitis following tocilizumab therapy. *Intern Med* 2014;5:879–882.
3. Kobayashi K, Okamoto Y, Inoue H, et al. Leukoencephalopathy with cognitive impairment following tocilizumab for the treatment of rheumatoid arthritis. *Intern Med* 2009;48:1307–1309.
4. Makrilakis K, Fragiadakis K, Smith J, Sfikakis PP, Kitas GD. Interrelated reduction of chemerin and plasminogen activator inhibitor-1 serum levels in rheumatoid arthritis after interleukin-6 receptor blockade. *Clin Rheumatol* 2015;34:419–427.
5. Mokuda S, Murata Y, Sawada N, et al. Tocilizumab induced acquired factor XIII deficiency in patients with rheumatoid arthritis. *PLoS One* 2013;8:e69944.
6. Eskilsson A, Mirrasekhian E, Dufour S, Schwaninger M, Engblom D, Blomqvist A. Immune-induced fever is mediated by IL-6 receptors on brain endothelial cells coupled to STAT3-dependent induction of brain endothelial prostaglandin synthesis. *J Neurosci* 2014;34:15957–15961.
7. Yamamoto M, Takahashi H, Wakasugi H, et al. Leukoencephalopathy during administration of etanercept for refractory rheumatoid arthritis. *Mod Rheumatol* 2007;17:72–74.

Received September 14, 2015. Accepted in final form November 6, 2015.

AUTHOR CONTRIBUTIONS

P. Jewell: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, acquisition of data. O. Ansorge: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, acquisition of data. W. Kuker: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, acquisition of data. S.R. Irani: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision. G. Zamboni: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision.

ACKNOWLEDGMENT

The authors thank the patient and his family.

STUDY FUNDING

No targeted funding reported.

DISCLOSURES

P. Jewell reports no disclosures. O. Ansorge has received funding for travel from Simons Foundation, New York, and receives research support from NIHR Biomedical Research Centre, Medical Research Council, and the Motor Neurone Disease Association. W. Kuker serves on the editorial board of *Neuroradiology*. S.R. Irani serves on scientific advisory boards for the Encephalitis Society and MedImmune Ltd.; has received honoraria for speaking at scientific conferences; is a co-applicant and receives royalties on a patent application licensed to Euroimmun AG for the development of assays for LGI1 and other VGKC-complex antibodies; receives associated royalties from ISIS Ltd for the VGKC-complex antibody patent; serves as a consultant for MedImmune Ltd.; receives/has received research support from the Wellcome Trust, the Fulbright UK-US commission, and the MS Society; and has received a NIHR fellowship, Department of Health, UK, to fund his DPhil/PhD. G. Zamboni reports no disclosures. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

Neurology® Clinical Practice

Tocilizumab-associated multifocal cerebral thrombotic microangiopathy

Paul Jewell, Olaf Ansorge, Wilhelm Kuker, et al.

Neurol Clin Pract 2016;6:e24-e26 Published Online before print January 29, 2016

DOI 10.1212/CPJ.0000000000000220

This information is current as of January 29, 2016

Updated Information & Services	including high resolution figures, can be found at: http://cp.neurology.org/content/6/3/e24.full.html
References	This article cites 7 articles, 1 of which you can access for free at: http://cp.neurology.org/content/6/3/e24.full.html##ref-list-1
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://cp.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://cp.neurology.org/misc/addir.xhtml#reprintsus

Neurol Clin Pract is an official journal of the American Academy of Neurology. Published continuously since 2011, it is now a bimonthly with 6 issues per year. Copyright © 2016 American Academy of Neurology. All rights reserved. Print ISSN: 2163-0402. Online ISSN: 2163-0933.

