

CASE REPORT

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Tocilizumab-associated posterior reversible encephalopathy syndrome in giant-cell arteritis – case report

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Abstract

Background: We describe one of the first cases of a Posterior reversible encephalopathy syndrome (PRES) under tocilizumab as treatment of Giant cell arteritis (GCA).

Case presentation: A 65-year-old female with known GCA and treatment with Tocilizumab (TCZ) developed a convulsive epileptic seizure for the first time. MRI was suggestive of PRES and an associated left sided occipital hemorrhage. Extensive high blood pressure values were not detected. The patient recovered within a week and no further seizures occurred under anticonvulsive medication.

Conclusion: PRES during the treatment with Tocilizumab hasn't been described in GCA so far. There are single reports of an association between TCZ and PRES in other entities. Thus, a link between interleukin-6 and the integrity of the vasculature could be considered. The clinical consequence should be a stringent blood pressure monitoring in the ambulant setting of patients receiving TCZ.

Keywords: Tocilizumab, Posterior reversible encephalopathy syndrome, Giant cell arteritis

Background

Giant cell arteritis (GCA) is the most common vasculitis in adult Caucasians affecting large and medium sized vessels leading to critical ischemia. In approximately 50% of the patients polymyalgia rheumatica is coexistent. Headache including claudicatio masticatoria are the most frequent symptoms. Vessels of all body regions can be affected in principle, however, ophthalmic manifestations are most feared and frequent, while involvement of extra- and intracranial arteries with subsequent strokes are rare complications [1].

Tocilizumab (TCZ) is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R), which was first approved for the treatment of rheumatoid arthritis (RA) [2]. The approval for GCA followed in 2017, further

indications are systemic-onset juvenile idiopathic arthritis, cytokine release syndrome and others [3]. The most relevant adverse drug reactions are infections, hepatotoxicity, neutropenia and gastrointestinal perforations [4].

Posterior reversible encephalopathy syndrome (PRES) is a rare, mainly hypertension-associated condition with symptoms comprising headache, seizures, confusion, disturbed vision and consciousness as correlate of oedema, in particular affecting the occipital lobes. An association of PRES with some autoimmune disorders and especially with immunosuppressive treatments (mostly cyclosporine and tacrolimus) is known [5].

Here we present one of the first cases of PRES under tocilizumab *for the treatment of a GCA*.

Case presentation

We describe a 65-year-old Caucasian female with known GCA since 2018 with (ultrasound detected) affection of the left axillary artery, left temporal artery and right

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sided carotid artery. Under ongoing therapy with low-dose prednisolone (4 mg per day) and tocilizumab (162 mg per week subcutaneously since the initial diagnosis), she was admitted to our department of neurology after occurrence of a convulsive epileptic seizure in October 2019. The patient showed only mild symptoms with a left sided latent sensorimotor hemiparesis and slight cognitive impairment. A mild hypertension was known in the patient's history without any specific medication. During the transport and the admission to our hospital the patient developed moderate hypertensive values up to a maximum of 170/90 mmHg.

Computer tomography (CT) of the brain revealed bilateral distinct occipital hypodense lesions with left sided hemorrhagic features. Brain magnetic resonance imaging (MRI) showed bilateral extent T2 hyperintense lesions occipital, parietal, frontal and cerebellar without diffusion restriction with the known hemorrhagic changes on the left side (Fig. 1). We performed CT-angiography which was inconspicuous. At that date there was no evidence of active inflammation (halo sign) in the vertebral and temporal arteries using ultra sound. The electroencephalogram (EEG) showed bilateral occipital slowing without epileptic activity. The analysis of the cerebrospinal fluid (CSF) was unremarkable, especially without any evidence of JC-virus.

After immediate initiation of antihypertensive and anticonvulsive (Levetiracetam 2 × 750 mg) medication the patient recovered from neurological symptoms within a week and no further seizures appeared since then.

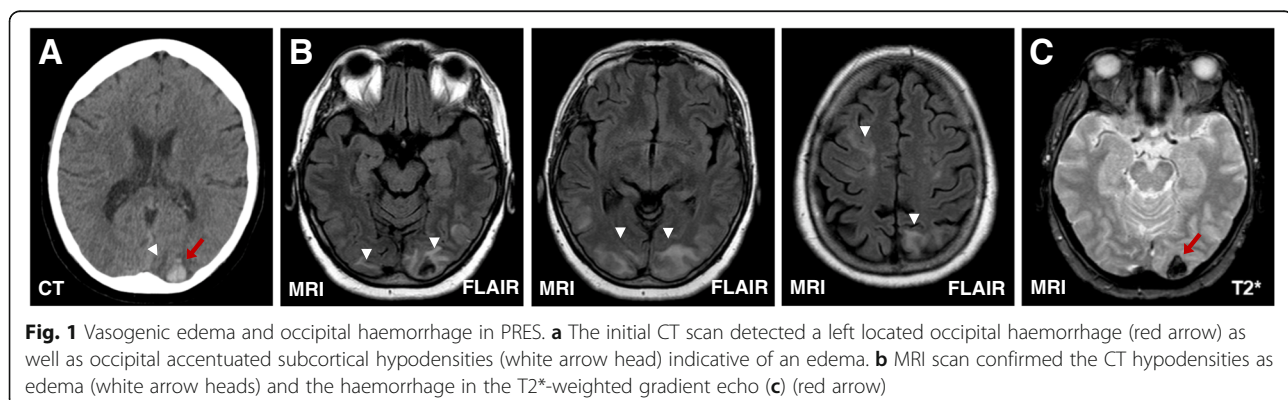
Diagnosis of PRES was established by typical clinical findings and the specific changes in the brain MRI. Several cases of PRES have been reported under other immunosuppressive regimens. So we consider that TCZ - as part of a multi-hit hypothesis in combination with slightly increased blood pressure values against the backdrop of the autoimmune disease itself - caused PRES [6]. Thus, we discontinued TCZ application and continued oral glucocorticosteroids with remaining remission of GCA.

Discussion and conclusion

Tocilizumab-associated neurological complications have been reported previously. In 2009 a patient with RA developed a leukoencephalopathy and more recently a patient with juvenile idiopathic arthritis exhibited PRES in 2018 [7, 8]. Another case described the occurrence of PRES after infusion of anti-BCMA directed CAR T cells and application of tocilizumab but also of high dose methylprednisolone and hydrocortisone to limit the cytokine release syndrome. The authors discussed the cytokine release storm itself as responsible for PRES but did not consider the immunosuppressive therapies as possible reason [9]. Especially hemorrhage in PRES, like in our case seems to be associated to immunosuppression [10]. A presentation of PRES in GCA-patients treated with TCZ has not been reported to date.

The association between TCZ and PRES has not been investigated yet, neither in humans nor in an appropriate animal model, speculating a link between cerebral vasculature and the influence of cytokines, e.g. IL-6. It is suggested that elevated IL-6 levels in brain microvascular endothelial cells lead to a loss of integrity, which was inhibited by IL-6 receptor blockade [11, 12]. But that is counterintuitive referring to the presented case.

A link between IL-6 and the activation of endothelial cells is more conceivable. IL-6 can induce endothelin-1 (ET-1), which serves as the most potent mediator for vasoconstriction. IL-6 binds soluble sIL-6R and builds a complex with gp130 which in turn could elevate endothelin-1 expression in endothelial cells [13]. TCZ binds IL-6R and inhibits IL-6 mediated actions and thus could lead to decreased endothelin-1 concentrations. Impaired (exhausted) autoregulation of cerebral arteries is thought to be a part of the pathophysiology behind PRES, thus it is tempting to speculate that lower ET-1 concentration impairs the function of endothelial smooth muscle cells. Brain vessels of the posterior circulation are more susceptible to develop edema under high blood pressure, due to less adrenergic innervation [14]. They might be even more sensitive to a lower ET-1



concentration, potentially leading to compromised regulation of higher blood pressure values. In order to get beyond speculation and due to rare cases in humans, a suitable animal model to investigate the association between blocking IL-6 receptors and PRES should be considered. In order to get beyond speculation and due to rare cases in humans, a suitable animal model to investigate the association between blocking IL-6 receptors and PRES should be considered.

Abbreviations

BCMA: B-cell maturation antigen; CAR: Chimeric antigen receptor; CSF: Cerebrospinal fluid; CT: Computer tomography; EEG: Electroencephalogram; ET-1: Endothelin-1; GCA: Giant cell arteritis; gp130: Glycoprotein 130; IL-6: Interleukin-6; IL-6R: Interleukin-6 receptor; JC-virus: John Cunningham-virus; mg: Milligram; MRI: Magnetic resonance imaging; PRES: Posterior reversible encephalopathy syndrome; RA: Rheumatoid arthritis; TCZ: Tocilizumab

Acknowledgements

Not applicable.

Authors' contributions

MB and JN have access to all the data and take responsibility for the data, accuracy of the data analysis and interpretation of the data and drafting the manuscript for intellectual content. SM, OB, CM: Design and conceptualization of the case; revising the manuscript for intellectual content. EF: Study supervision. All authors read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Competing interests

MB received meeting/accommodation expenses from Shire and Zambon. EF received honoraria, grant support and meeting/accommodation expenses from Roche/Chugai. SW, OB, CM and JN: The authors declare that they have no competing interests.

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Received: 20 October 2020 Accepted: 11 May 2021

Published online: 22 June 2021

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