Case report

Development of intracranial vasculitis in giant cell arteritis during tocilizumab treatment

N. Naderi

Department of Rheumatology, Danderyd Hospital, Stockholm, Sweden.

Nazanin Naderi, MD

Please address correspondence to: Nazanin Naderi, Department of Rheumatology, Danderyd Hospital, Armbågsvägen 3, Målpunkt P, 8th floor, 182 88 Stockholm, Sweden.
E-mail: nazanin.naderi.f@gmail.com

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ORCID-ID: 0000-0001-8232-9923

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ABSTRACT

Giant cell arteritis (GCA), a systemic large-vessel vasculitis, is a disease that has been treated with glucocorticoids since 1950. Over the years, several disease-modifying anti-rheumatic drugs have been evaluated as steroid-sparing agents with disappointing results.

Tocilizumab, an interleukin-6 inhibitor, has in recent years been approved for the treatment of GCA. It remains uncertain whether the drug suppresses disease activity and maintains remission or just alleviates the symptoms and masks the signs of smoldering disease.

This case describes the clinical findings at diagnosis and the course of the disease with the subsequent development of intracranial vasculitis in a 70-year-old male treated with tocilizumab.

The present case illustrates the need for further studies regarding tocilizumab in the treatment of GCA patients and the need for meticulous evaluation at follow-ups.

Introduction

Giant cell arteritis (GCA), a vasculitis of the medium- and large-sized arteries, was first described 130 years ago (1). It has been treated with glucocorticosteroids (GC) since 1950 (2). GC remain the mainstay of treatment but carry significant long-term side effects (3).

Tocilizumab (TCZ), an interleukin-6 receptor inhibitor (IL-6-I), was approved for GCA treatment in late 2017 when the Giant Cell Arteritis Actemra (GiACTA) study showed superior efficacy compared to standard treatment with GC (4). The trial did not assess the presence or absence of physical findings, *i.e.* heart murmur, vessel bruit or unequal blood pressures of the four extremities at diagnosis or follow-ups, the development of which may be an indicator of active disease. This limitation leads to some uncertainty about IL-6-I. Does TCZ effectively suppress disease activity and maintain remission or just alleviate and mask the symptoms of active disease through its mode of action? The following case illustrates this question and the need for better assessment protocols.

Clinical presentation

A 70-year-old male was referred to the rheumatology clinic from the diagnostic centre (DC) because of vasculitis of the large arteries. He had been referred to the DC due to fatigue, morning nausea, weight loss, anaemia and increased erythrocyte sedimentation rate (ESR). At the DC a positron emission tomography-computed tomography (PET-CT) scan had been ordered which revealed increased uptake throughout the aorta, bilaterally in carotid, vertebral, superficial temporal, subclavian, iliac, femoral, popliteal and proximal tibial arteries, an ectatic intrathoracic aorta and a slightly aneurysmal abdominal aorta above the bifurcation.

The patient complained of fatigue, weight loss of 5 kg in the previous 6 months and increasing pain in the feet and lower legs. He had good appetite, did not experience any fever, night sweats, respiratory or abdominal symptoms. He had had no visual symptoms, headaches, temporal or scalp tenderness, polymyalgia rheumatica (PMR) symptoms, jaw claudication, joint pain, morning stiffness or back pain.

His medical background was of active smoking, previous hypertension, tinnitus, polyneuropathy, atrial flutter on anticoagulant treatment, multiple severe depressions, an episode of anaemia in 2013 with normal endoscopic assessment and a rectal polyp extirpation showing low grade dysplastic tubular adenoma in September 2018.

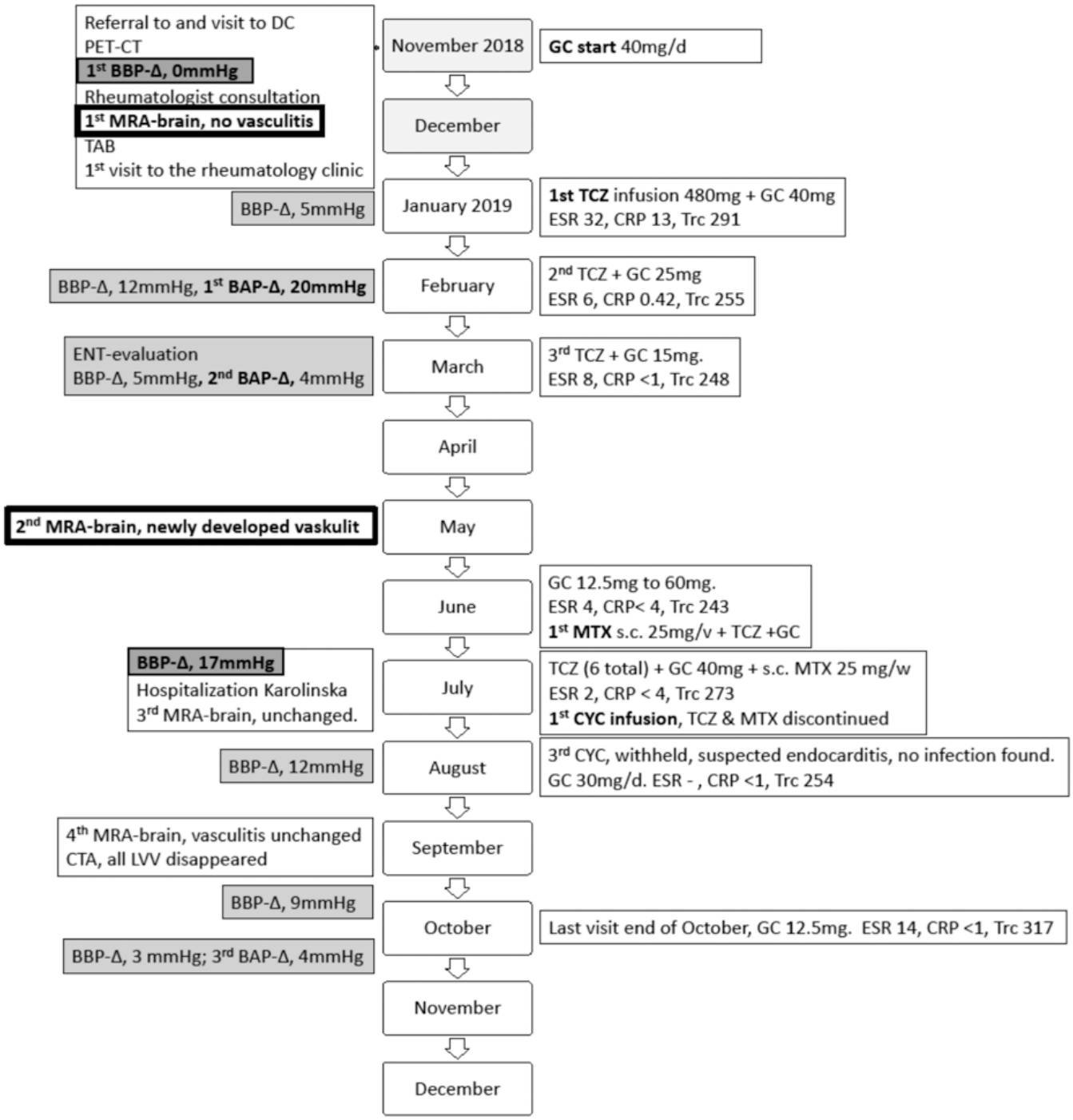

Fig. 1. Investigations, treatments, imaging, pressure measurements and blood work.
DC: diagnostic centre; PET-CT: positron emission tomography-computed tomography; GC: glucocorticoid, here prednisolone; TAB: temporal artery biopsy; BBP-Δ: bilateral brachial pressure difference; MRA-brain: magnetic resonance angiography of the brain; BAP-Δ: bilateral ankle pressure difference; TCZ: tocilizumab; ENT: ear-nose-throat; MTX; methotrexate; CYC: cyclophosphamide; CTA: computed tomography angiography; LVV: large-vessel vasculitis.

Physical assessment with uneven heart rhythm, no heart murmur, normal temporal arteries and equal blood pressures between the arms. There was no vessel bruit over the carotid, subclavian, axillary, renal or common femoral arteries. The radial and femoral pulses were unremarkable.

Laboratory analysis showed ESR 129 mm/h, C-reactive protein (CRP) 144 mg/L, thrombocytes (Trc) 489 x 10^9/L and haemoglobin 83 g/L.

A diagnosis of GCA with extracranial vasculitis was made and GC (prednisolone) 40 mg/d was initiated. A temporal artery biopsy (TAB) and a magnetic resonance angiography of the brain (MRA-brain) for possible intracranial vasculitis was planned.

Investigations, treatments and disease course

The TAB was positive and the MRA-brain found no vasculitis. At the first

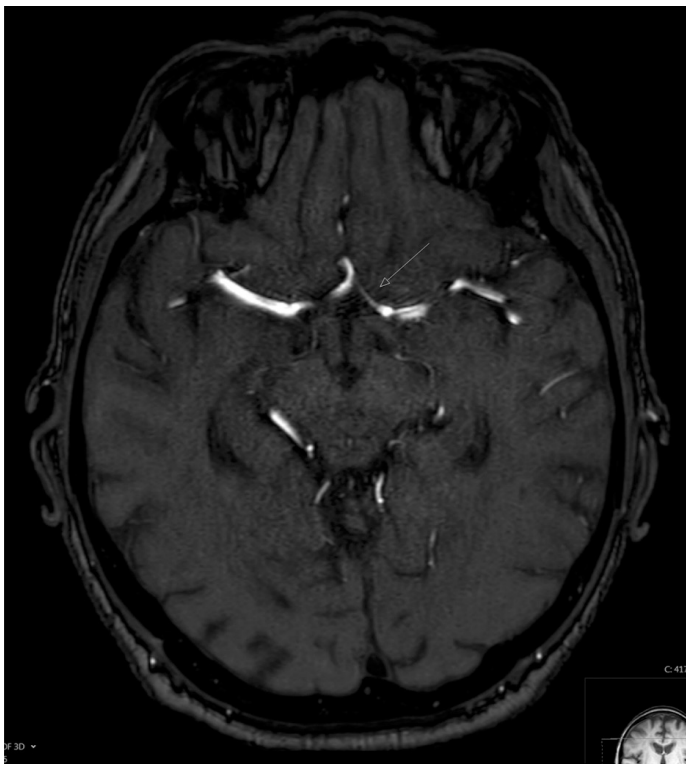

Fig. 2. Magnetic resonance angiography of the brain, showing vasculitis of the left anterior cerebral artery.

follow-up two weeks later, no improvement in fatigue was reported, GC 40mg/d; ESR 127, CRP 27, Trc 636. GC was increased to 60 mg/d and TCZ was considered. Periodic blood tests and pressure measurements were planned at each TCZ infusion (Fig. 1).

At the third TCZ infusion, there were no symptoms of GCA/PMR but complaints of thickness in the head, continued severe tiredness in the whole body and the feeling of getting worse instead of better. A new MRA-brain showed a thin anterior cerebral artery (ACA), contrast enhancement along the left A1 with stenosis and newly developed non-recent infarctions in the white matter in two places within the left ACA supply area (Fig. 2). Due to newly developed intracranial vasculitis, complaints of progressing imbalance, severe fatigue and again a swelling sensation of the right side of the head and neck, the GC dose was escalated from 12.5 mg to 60 mg/d and subcutaneous methotrexate (MTX) was added.

At follow-up a bilateral brachial pressure difference (BBP-Δ) of 17mmHg was measured. The treatment was considered a failure due to development of BBP-Δ and intracranial vasculitis and no amelioration of the fatigue or headache. The patient was admitted to the rheumatology clinic at Karolinska Hospital for in-depth evaluation and consideration of cyclophosphamide (CYC) as rescue therapy. A new MRA-brain showed patchy contrast enhancement in the vessel walls of both vertebral and the right common carotid arteries and unchanged intracranial vasculitis. TCZ and MTX were discontinued and CYC treatment was started.

Computed tomography angiography of the aorta and MRA-brain after five completed CYC pulses showed complete regression of wall thickening from all previously described sites and unchanged intracranial vasculitis. Abatacept was initiated as the next treatment.

Discussion

The present case demonstrates persisting disease activity during TCZ treatment, in line with a previous case report. Unizony *et al*. described a patient treated with TCZ who died of myocardial infarction, and active disease was detected at autopsy (5).

In GCA patients, follow-up with inquiries about general health, relapse of previous symptoms or appearance of new ones, appears inadequate. Monitoring ESR/CRP is also insufficient, since none can be relied on, neither at the time of diagnosis (6) nor during flares (6, 7) although they are helpful in most cases. In the case of TCZ-treated patients they become virtually useless (7). Studies have been made in search of new biomarkers to evaluate disease activity in GCA (8).

Although the observations discussed here are limited to two cases, a more rigorous assessment seems justified. Evaluation protocols including periodic peripheral artery assessments are simple and have been shown to be reliable (9).

In conclusion, more research is needed to determine the true frequency of persisting inflammation in TCZ-treated GCA patients. Studies are also needed to identify the best way to follow up on these patients.

The patient's written informed consent was obtained for publication.

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