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Reversible cerebral vasoconstriction syndrome in idiopathic multicentric Castleman disease under treatment with tocilizumab

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ABSTRACT

Background Idiopathic multicentric Castleman disease (iMCD) is a rare polyclonal lymphoproliferative disorder characterised by systemic inflammation resulting from overproduction of interleukin 6 (IL-6). While iMCD primarily affects the lymph nodes and related tissues, it can also rarely involve the central nervous system.

Case presentation We report the case of a 58-year-old female patient with at least a 3-year history of iMCD, who experienced acute thunderclap headaches due to reversible cerebral vasoconstriction syndrome (RCVS). RCVS occurred 3 months after initiating treatment with tocilizumab, a humanised anti-IL-6 receptor monoclonal antibody, and was accompanied by focal cortical subarachnoid haemorrhage (SAH). Elevated IL-6 levels were found in both serum and cerebrospinal fluid. MR angiography revealed multiple diffuse stenotic lesions in the bilateral middle and posterior cerebral arteries, which, along with bilateral cerebral oedema, resolved within 3 months. The diffuse nature of the cerebral vasospasm and the presence of bilateral brain oedema suggested that cerebral vasospasm was due to RCVS rather than SAH.

Conclusions In patients with Castleman disease, RCVS may occur due to IL-6-dependent chronic cerebral vascular inflammation, either as a primary condition or as a complication of tocilizumab treatment.

INTRODUCTION

Castleman disease (CD) is a rare polyclonal lymphoproliferative disorder that affects lymph nodes and related tissues. CD is histologically classified into three types: hyaline-vascular, plasma cell (PC) and mixed. Multicentric CD (MCD) is characterised by generalised lymph node enlargement and systemic inflammatory manifestations such as hyperthermia, splenomegaly, hepatomegaly, pulmonary disorders, oedema and ascites. MCD is further subclassified as follows: human herpesvirus 8-associated MCD; polyneuropathy, organomegaly, endocrinopathy, monoclonal PC disorder and skin changes (POEMS)-associated MCD (POEMS-MCD) and idiopathic MCD (iMCD).[1] Recent clinicopathological studies have identified iMCD-idiopathic plasmacytic lymphadenopathy (iMCD-IPL) as a subtype of iMCD.[2] iMCD-IPL is characterised by an indolent clinical course, prominent polyclonal hypergammaglobulinaemia, thrombocytosis, fewer pleural effusions and ascites compared with other subtypes, multicentric lymphadenopathy, PC-type histology demonstrating normal to hyperplastic germinal centres and sheet-like proliferation of polyclonal PCs in the lymph nodes.[2]

In MCD, a complex cytokine network comprising interleukin (IL)-6, IL-1β, and vascular endothelial growth factor (VEGF) is thought to contribute to systemic inflammation.[1] Given that IL-6 is a major factor in the development of MCD, treatment often involves the use of tocilizumab, a humanised anti-IL-6 receptor (IL-6R) monoclonal antibody.

In CD, systemic inflammation rarely causes neurological symptoms secondary to central nervous system (CNS) involvement; however, among the subtypes of MCD, CNS involvement is most commonly observed in POEMS-MCD. Here, we present the rare case of a 58-year-old female patient with iMCD-IPL who developed reversible cerebral vasoconstriction syndrome (RCVS) that may have been triggered by treatment with tocilizumab.

CASE REPORT

During a health screening at age 48, a female patient was found to have elevated serum levels of C reactive protein (CRP) and hypergammaglobulinaemia. At age 55, she presented with lymph node swelling at multiple sites. Laboratory tests revealed hyperproteinaemia (11.0 g/dL), hypoalbuminaemia (2.7 g/dL), elevated serum inflammatory markers (white

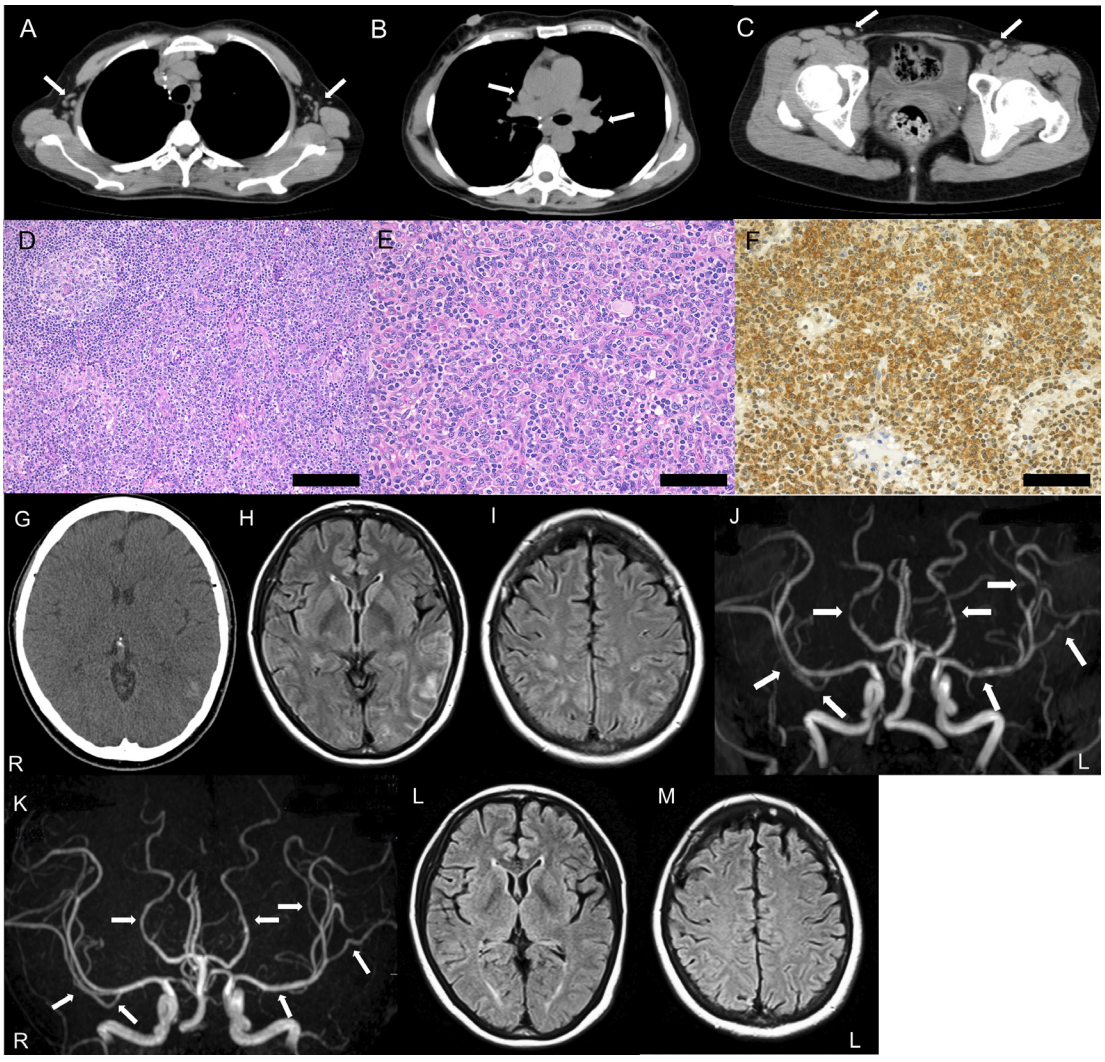

Figure 1 Images from a CT scan conducted at the time of Castleman disease diagnosis (A–C), histopathological findings of the resected inguinal lymph node (D–F) and neuroimaging findings at admission (G–J) and 3 months after the initiation of verapamil hydrochloride therapy (K–M). Enlarged lymph nodes (arrows) are present in the axilla (A), mediastinum (B) and inguinal regions (C). (D) The resected lymph node exhibits interfollicular expansion with a normal germinal centre (H&E). Scale bar=200 µm. (E) Sheet-like proliferation of mature plasma cells (PCs) is present in the expanded interfollicular area H&E). Scale bar=100 µm. (F) The cytoplasm of proliferating PCs showed granular positivity for IL-6 (IL-6 immunostaining). Scale bar=100 µm. (G) A CT scan image shows SAH in the left temporal and occipital lobes. (H, I) FLAIR sequence MRI shows high-intensity signals both in the left cortical regions, corresponding to SAH and in the bilateral parieto-occipital subcortical regions. (J) MRA shows multiple stenotic lesions in the bilateral middle and posterior cerebral arteries (arrows). (K) MRA shows resolution of stenosis in the bilateral middle and posterior cerebral arteries (arrows). (L, M) FLAIR sequence MRI shows resolution of the abnormally high-intensity signals in the left cortical regions and bilateral subcortical regions. FLAIR, fluid-attenuated inversion-recovery; IL-6, interleukin 6; MRA, MR angiography; SAH, subarachnoid haemorrhage.

cell count, 11.4x10^9/L; CRP, 5.9 mg/L; IL-6, 17.3 pg/mL (normal range, 0–4 pg/mL)) and an increase in polyclonal serum immunoglobulins (IgG, 6134 mg/dL (normal range, 870–1700 mg/dL); IgA, 537 mg/dL (normal range, 110–410 mg/dL)). A CT scan revealed lymph node enlargement in the axillary, mediastinal and inguinal regions (figure 1A–C). An inguinal lymph node biopsy showed enlarged interfollicular areas with normal germinal centres (figure 1D) and interfollicular PC infiltration (figure 1E). Immunohistochemical staining demonstrated a normal distribution of T and B cells in the mantle and interfollicular zones. Ki-67, a marker for proliferative cells, was highly expressed in the germinal centres. PCs were positive for CD79a and IL-6 (figure 1F). These clinical and histological findings were consistent with the diagnostic criteria for iMCD-IPL.[2] At age 58, the patient developed renal dysfunction, prompting the initiation of monthly intravenous treatment with tocilizumab. 3 months after starting tocilizumab therapy, she experienced a thunderclap headache and visited our hospital 5 days later. On admission, the neurological examination results were unremarkable. Laboratory tests showed highly elevated IL-6 levels in both the serum and cerebrospinal fluid (CSF) (614 pg/mL and 119 pg/mL, respectively). A

CT scan of the head revealed subarachnoid haemorrhage (SAH) in the left temporo-occipital region (figure 1G). Further investigations using fluid-attenuated inversion recovery (FLAIR) sequences in brain MRI showed high-intensity signals in the left cortical regions (figure 1H), corresponding to cortical SAH, as well as in the bilateral parietooccipital subcortical regions (figure 1I). MR angiography (MRA) identified multiple segmental vasoconstrictions in the bilateral middle and posterior cerebral arteries (figure 1J). Treatment with oral verapamil hydrochloride was initiated while tocilizumab was continued for CD treatment, and the patient's headache gradually subsided, disappearing completely after 1 month. At that time, serum CRP and CSF IL-6 levels had markedly decreased to 0.07 mg/L and 10.4 pg/mL, respectively, although serum IL-6 levels remained elevated at 559 pg/mL. Follow-up MRI and MRA scans performed 3 months later showed resolution of cerebral vasoconstrictions (figure 1K) and high-intensity FLAIR lesions (figure 1L,M), suggesting that the FLAIR abnormalities in the bilateral parietooccipital subcortical regions were due to brain oedema.

DISCUSSION

In the present case, imaging studies performed 5 days after the onset of a severe thunderclap headache confirmed both cortical SAH and segmental narrowing of the bilateral middle and posterior cerebral arteries (figure 1G,J). This presents a diagnostic dilemma regarding which condition occurred first. RCVS is characterised by reversible narrowing of the cerebral arteries and is typically associated with thunderclap headaches. It may occasionally be followed within a few days by cortical SAH, intracerebral haemorrhage, cerebral infarction and reversible vasogenic brain oedema.[3] Our patient met the criteria for RCVS, as evidenced by the thunderclap headache and the reversibility of cerebral vasospasm and oedema within 3 months (figure 1K–M).[3] While SAH-related cerebral vasospasm usually occurs near the bleeding site, RCVS-related SAH is characterised by diffuse segmental vasoconstriction in distant arteries.[3] Therefore, the current imaging findings are more consistent with RCVS-related SAH than with vasoconstriction secondary to SAH.

In MCD, damage to cerebral blood vessels arises from chronic inflammation of vascular endothelial cells (cerebral angiitis) due to excessive production of cytokines such as IL-6 and VEGF. Although vascular endothelial cells do not express membrane-bound IL-6R (mIL-6R), IL-6 binds to soluble IL-6R, forming a complex with a homodimer of gp130 expressed on these cells, thereby transmitting IL-6R signals via trans-signalling.[4] In hepatocytes, IL-6 binds to mIL-6R and induces CRP expression through a classic signalling pathway.[4] In the present case, elevated levels of IL-6 (17.3 pg/mL) and CRP (5.9 mg/dL) were observed at the time of diagnosis, suggesting that chronic inflammation, including endothelial cell involvement, had been present for at least 3 years and possibly up to 10 years before the onset of neurological symptoms. IL-6R signalling regulates vascular smooth muscle tone by inducing the expression of vascular endothelial cell-derived endothelin-1 (ET-1), the most potent mediator of vasoconstriction.[5] Thus, a background of enhanced IL-6R signalling may have contributed to the development of RCVS in this case. Indeed, a previous report described two cases of MCD in which IL-6-induced cerebral angiitis led to RCVS.[6]

Interestingly, our patient paradoxically developed RCVS and subsequent cortical SAH just 3 months after initiating tocilizumab treatment. Tocilizumab suppresses all modes of IL-6R signalling, including classical and trans-signalling,[4 7] which theoretically should reduce vasoconstriction. Indeed, in a rabbit model of SAH, tocilizumab was shown to suppress SAH-associated vasoconstriction.[8] One possible explanation for this paradox is that tocilizumab's suppression of IL-6R signalling may not have been sufficient to overcome the long-standing vascular endothelial damage associated with elevated IL-6 levels, leading to the development of RCVS. Another explanation is that while tocilizumab reduces ET-1 levels by inhibiting IL-6R signalling, if its effect is stronger on ETB receptors (which induce vasodilation) than on ETA receptors (which mediate vasoconstriction), it could promote vasoconstriction.[5] Therefore, the reduction of ET-1 due to tocilizumab might occasionally result in an imbalance that leads to vasoconstriction.

Similar to our case, a previous report described a patient with mixed connective disease who developed RCVS 3 months after tocilizumab initiation.[9] In this case, tocilizumab was discontinued after the onset of RCVS and cerebellar infarction. Although sequelae from the infarction remained, cerebral vessel narrowing improved after 1 month. In our case, treatment with a calcium channel blocker, which is commonly used for RCVS, and continuation of tocilizumab treatment led to complete resolution of both the symptoms and cerebral vasospasm. As RCVS generally follows a self-limited course, it remains unclear to what extent discontinuing tocilizumab after the onset of RCVS affects the clinical course and prognosis. However, discontinuing tocilizumab—unless essential for treating the underlying disease—may be a safer option because it can induce persistent cerebral vasoconstriction and may contribute to stroke after RCVS. In addition, several patients have presented with tocilizumab-induced posterior reversible encephalopathy syndrome (PRES), which may be part of the RCVS disease spectrum.[10–12] PRES occurred 2 days after tocilizumab administration in a patient with juvenile idiopathic arthritis[10] and after approximately 1 year in a patient with giant cell arteritis.[11] In four patients who received tocilizumab as treatment for severe COVID-19, PRES developed as late as 48 days after administration.[12] In all of these cases, tocilizumab was discontinued, and no further deterioration of the PRES condition was observed, although sequelae from PRES remained in some cases. Notably, tocilizumab-induced

RCVS or PRES can occur at various times, from a few days to a year after administration.

In our case, the onset of RCVS 3 months after the initiation of tocilizumab suggests the potential influence of medication-related adverse effects. However, it is important to note that patients with CD may have underlying primary endothelial dysfunction due to elevated IL-6 levels. As a result, these individuals are at increased risk of cerebrovascular disorders due to both primary vascular endothelial cell dysfunction and the potential adverse effects of tocilizumab. Clinicians should remain vigilant for the possibility of RCVS in patients with CD who present with severe headaches, regardless of whether or not they are receiving tocilizumab.

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