Reversible Cerebral Vasoconstriction Syndrome due to Atovaquone

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Abstract
A 72-year-old Japanese woman with rheumatoid arthritis whose activity decreased with previous treatments had recurrent thunderclap headaches during an atovaquone regimen for the treatment of pneumocystis pneumonia. The recurrent headaches disappeared after discontinuation of the drug. Brain magnetic resonance images showed multiple cerebral vasoconstrictions of cerebral arteries with vasogenic cerebral white matter edema, which diminished several weeks later. We diagnosed the patient’s headaches as reversible cerebral vasoconstriction syndrome due to atovaquone.

Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by severe headaches with diffuse segmental constrictions of cerebral arteries, and the nature of the headaches is usually recurrent thunderclap headaches. There are various precipitants of RCVS including catecholamine-secreting tumors, eclampsia, and the use of illicit drugs, antidepressants, triptans, intravenous immunoglobulin, or red-blood-cell transfusion [1]. RCVS is often accompanied by vasogenic edema in cerebral white matter, which can be considered poste-
rior reversible encephalopathy syndrome (PRES), and the coexistence of RCVS and PRES suggests that there is a dysfunction of vascular endothelium in the development of those conditions [1].

Pneumocystis infection can occur in association with immunosuppressants including prednisolone and methotrexate in rheumatoid arthritis (RA) patients. Atovaquone is one member of the class of hydroxynaphtoquinones that has potent activity against *Pneumocystis carinii* [2]. Although headaches can be observed as an adverse effect of atovaquone use [2], to our knowledge, RCVS associated with atovaquone has not been reported previously. Here, we report the case of a woman who had recurrent thunderclap headaches while taking atovaquone, with cerebral vasoconstrictions that diminished over 8 weeks following the discontinuation of atovaquone.

**Case Presentation**

A 72-year-old Japanese woman with hypertension and diabetes mellitus had been suffering from RA for 20 years when she was admitted to our hospital for the treatment of pneumocystis pneumonia. Her immune condition was probably suppressed due to 20 mg prednisolone and 8 mg methotrexate (MTX) which she had been taking for her RA. We discontinued MTX, but 20 mg prednisolone was continued. For the treatment of the patient’s pneumonia, 2 g sulfamethoxazole trimethoprim was started, but it was switched to 1,500 mg atovaquone because severe diarrhea was observed.

The patient’s blood pressure was normal (130/80 mm Hg) on admission. However, excessive hypotension was observed after admission, and antihypertensive drugs including 10 mg amlodipine, 100 mg irbesartan, and 50 mg eplerenone were discontinued. Her diabetes mellitus was continuously treated with 50 mg sitagliptin and 0.5 mg glimepiride.

Sixteen days after the patient had started taking atovaquone, thunderclap headaches lasting several hours repeatedly occurred twice a day. She had no medical history of recurrent headaches. No remarkable elevation of blood pressure was observed during the headache attacks. The recurrent headache could not be relieved by nonsteroidal anti-inflammatory drugs. No abnormal neurological signs or arthralgia were observed.

The duration and the intensity of the recurrent headache increased for 3 days after the onset of the headache. Blood tests, CT, and MRI of the brain were examined. The blood tests showed an elevated white blood cell count and erythrocyte sedimentation rate (11,000/μL and 90 mm/h, respectively). The brain CT showed no abnormal findings including subarachnoid hemorrhage, cerebral hemorrhage, and infarction, but the brain MRI showed multiple vasoconstrictions with vasogenic white matter edema (Fig. 1). As the headache of the patient was considered to occur and increase in relation with taking atovaquone, we stopped administrating it. Three days after discontinuing this drug, the patient’s headache disappeared. Lumbar puncture was not performed because the headache did not recur after the discontinuation of atovaquone. Eight weeks after the initial MR images, the white matter abnormalities and the vasoconstrictions of the cerebral arteries disappeared except for slight necrotic white matter lesions on follow-up brain MRI (Fig. 2). She was diagnosed with RCVS with PRES due to atovaquone.
Discussion

The recurring thunderclap headaches of our patient occurred during the atovaquone regimen, we continued her other medications except for MTX, which was discontinued 3 weeks before the onset of the headaches. There was no obvious elevation of blood pressure when the headaches occurred despite the discontinuation of antihypertensive drugs for the patient’s excessive low blood pressure. The headaches disappeared within 3 days after discontinuing atovaquone. A brain MR angiography showed reversible cerebral vasoconstrictions that had improved on follow-up MRI scans. Our patient’s recurrent thunderclap headaches could thus be diagnosed as RCVS in association with the atovaquone regimen.

It is important to identify causes of RCVS based on the medication history and the time course of the clinical symptoms such as headache. In the presented case, the headache successfully improved several days after the discontinuation of atovaquone along with the disappearance of RCVS on MRI, so it is speculated that the headache was caused by RCVS due to atovaquone. Regarding the clinical outcome of RCVS in general, women are at a high risk of RCVS with intracranial hemorrhage which determines long-term prognosis of RCVS [3]; though most patients with RCVS have a good clinical outcome [1, 3]. Although the recurrence of thunderclap headache is not significantly related to RCVS with intracranial hemorrhage [3], early diagnosis of RCVS as a cause of headache and appropriate treatment result in good clinical outcome. The primary treatment of patients with RCVS should be the identification and elimination of aggravating factors including drugs, the recommendation of rest, and the administration of drugs targeting vasospasms, such as nimodipine and verapamil, in addition to symptomatic management including analgesics, antiepileptic drugs for seizures, and antihypertensive agents with monitoring of the patient’s blood pressure [1].

The mechanism by which the use of atovaquone induces RCVS is not clear. Though the exact mechanisms of RCVS are unknown, it is possible that endothelial dysfunction [1] or alterations in vascular tone [4] may have a role in the occurrence of RCVS. In addition, PRES has been speculated to have underlying mechanisms similar to those of RCVS, e.g., specific alterations of vascular endothelial function. It has been reported that nearly half of the patients with PRES have autoimmune disorders [5]. In the presented case, it is possible that any alterations of endothelial functions, associated with some pharmacological effects of atovaquone, or comorbid autoimmune disorders, such as RA, may induce an abnormality of vascular tone, and subsequently cause RCVS with PRES.

The probability of the association between headaches and the administration of atovaquone is scaled as “likely” by the Naranjo Adverse Drug Reactions Probability Scale, which is used to objectively evaluate adverse drug effects [6]. In a review, adverse effects of atovaquone on the central nervous system, such as headaches, dizziness, and insomnia, have been observed in 14% [2]. RCVS may account for some of the headaches associated with the administration of atovaquone.

We have presented the case of a patient with recurrent thunderclap headaches due to RCVS associated with the administration of atovaquone. When recurrent headaches are experienced by an individual who is taking atovaquone, RCVS should be considered.

Statement of Ethics

The patient provided informed consent to participate in this study and for publication of this paper with figures. This case report was approved by the institutional review board.
Disclosure Statement

The authors declare no conflicts of interest.

References

1. Ducros A: Reversible cerebral vasoconstriction syndrome. Lancet Neurol 2012;11:906-917.
2. Haile LG, Flaherty JF: Atovaquone: a review. Ann Pharmacother 1993;27:1488-1494.
3. Ducros A, Fiedler U, Porcher R, et al: Hemorrhagic manifestations of reversible cerebral vasoconstriction syndrome: frequency, features, and risk factors. Stroke 2010;41:2505–2511.
4. Calabrese LH, Dodick DW, Schwedt TJ, et al: Narrative review: reversible cerebral vasoconstriction syndromes. Ann Intern Med 2007;146:34–44.
5. Fugate JE, Rabinstein AA: Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. Lancet Neurol 2015;14:914–925.
6. Naranjo CA, Busto U, Sellers EM, et al: A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–245.

Fig. 1. The initial fluid-attenuated inversion recovery image (A) and the apparent diffusion coefficient map (B) show vasogenic white matter edema in the parietal lobe. Time of flight MR angiography (C–E) shows multiple vasoconstrictions in bilateral anterior communicating, middle, and posterior cerebral arteries. Enlarged images of the posterior cerebral artery (D) and the anterior communicating artery (E) show multiple vasoconstrictions (arrows).
Fig. 2. On follow-up images obtained 8 weeks after the initial images, parietal white matter lesions (A, B) and vasoconstrictions of the cerebral arteries (C–E) are not found except for slight necrotic white matter lesions.