CASE REPORT

ANCA-associated Vasculitis with Central Retinal Artery Occlusion Developing during Treatment with Methimazole

Takuji Yasude, Dai Kishida, Ko-ichi Tazawa, Masayuki Matsuda, Wataru Ishii, Masahide Yazaki and Shu-ichi Ikeda

Abstract

A 63-year-old woman suddenly developed central retinal artery occlusion following a slight fever while being treated with methimazole (MMI) for hyperthyroidism. She was diagnosed to have anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) based on increased inflammatory reactions with positive myeloperoxidase-ANCA in the serum. Her visual acuity remained low despite immediate treatment with corticosteroids and cyclophosphamide after cessation of MMI, which may have played a role in the pathogenesis of AAV. Central retinal artery occlusion is a rare manifestation of AAV; however, it is important with regard to the possibility of serious sequelae.

Key words: ANCA-associated vasculitis, central retinal artery occlusion, methimazole, MPO-ANCA


Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is an inflammatory systemic disorder characterized clinically by the involvement of multiple visceral organs, particularly the lungs and kidneys, and histologically by infiltrations of inflammatory cells, including neutrophil leukocytes, in small arteries and arterioles with fibrinoid necrosis or granuloma formation (1). Myeloperoxidase-ANCA (MPO-ANCA) frequently appears in the sera of patients with microscopic polyangiitis (MPA) or Churg-Strauss syndrome (CSS), and is widely recognized as a laboratory hallmark of these diseases. We herein report the case of a patient with hyperthyroidism who developed central retinal artery occlusion (CRAO) along with MPO-ANCA in the serum following a slight fever while being treated with methimazole (MMI). The patient did not meet the clinical criteria of either MPA or CSS; however, AAV most likely underlay her clinical symptoms and strong inflammatory reactions. We focused on the pathogenesis of AAV in the present patient, particularly from the view of the relationship between this disease and MMI and the clinical importance of CRAO.

Case Report

A 61-year-old woman who was a nonsmoker and had no past history of hypertension developed body weight loss and palpitations. She was treated with MMI at a dose of 30 mg daily on a diagnosis of hyperthyroidism at a neighboring hospital. Her symptoms quickly improved, and she continued to take MMI with no complaints of decreased vision. At age 63 she suddenly became aware of decreased visual acuity in the left eye following a slight fever of approximately 37°C without any precipitating causes. This ocular symptom quickly worsened over one day. When she visited the emergency outpatient clinic of the neighboring hospital, laboratory data demonstrated a marked increase in inflammatory reactions. She was referred to our hospital, and admitted for treatment.

On admission, her body temperature, radial pulse and blood pressure were 38°C, 93/min and 142/72 mmHg, respectively. A physical examination showed slight exophthalmos in the eyes bilaterally; however, no abnormal findings were detectable in the chest, abdomen or extremities. The thyroid was not palpable. The patient’s visual acuity in the right and left eyes was 1.0 and 0.15, respectively. The labo-
Figure 1. Ophthalmofunduscopy on admission revealed paramacular whitening with papilledema in the left eye, suggesting occlusion of a branch of the central retinal artery (A). These findings were almost absent six weeks after admission (B).

Figure 2. The clinical course of the patient. As the CRP level (closed circles) fluctuated even after starting treatment, we administered additional mPSL pulse therapy. The level of MPO-ANCA (closed rhombi) quickly decreased after starting treatment, and no further increases were seen while tapering the dose of oral PSL. CPA: cyclophosphamide, CRP: C-reactive protein, HBO: hyperbaric oxygen therapy, mPSL: methylprednisolone, PSL: prednisolone

Laboratory data demonstrated increases in WBCs (11,860/μL, normal 3,040-8,720/μL), C-reactive protein (CRP, 10.61 mg/dL, normal <0.1 mg/dL) and the erythrocyte sedimentation rate (ESR, 31 mm/hr, normal 2-10 mm/hr) suggestive of positive inflammatory reactions. Significant eosinophilia was not present. There were no abnormal findings in either renal indices, including a urinalysis, or endocrine function except for thyroid stimulating hormone (0.066 μIU/mL, normal 0.2-4.0 μIU/mL). Rheumatoid factor, anti-nuclear antibodies, anti-phospholipid antibodies and proteinase-3-ANCA were all undetectable, while MPO-ANCA was positive (75.8 U/mL, normal <9.0 U/mL). No abnormal findings were seen on either the chest X-ray examination or electrocardiogram. Ophthalmofunduscopy revealed paramacular whitening with papilledema in the left eye, thus suggesting occlusion of a branch of the central retinal artery (Fig. 1A).

Immediately after admission we started treatment with methylprednisolone pulse at a dose of 1,000 mg daily for three days and continuous intravenous infusion of dalteparin at 5,000 U/day along with hyperbaric oxygen therapy after cessation of MMI (Fig. 2). The CRP level decreased quickly; however, a fever higher than 38°C frequently reappeared with no improvement in left visual acuity despite the administration of oral PSL and cyclophosphamide at 40 mg/day and 50 mg/day, respectively. An additional three cycles of methylprednisolone pulse therapy were administered and, thereafter, the doses of oral prednisolone and cyclophosphamide were increased to 60 mg/day and 100 mg/day, respectively. The patient’s fever disappeared in conjunction with normalization of the CRP level; however, visual acuity in the left eye remained at 0.1, although hemoperfusion of the retina apparently improved on ophthalmofunduscopy six weeks after onset of CRAO (Fig. 1B). The level of MPO-ANCA decreased quickly after starting treatment. Cy-
Table. Central Retinal Artery Occlusion in MPO-ANCA-positive Patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Onset age/ gender</th>
<th>Underlying disorder</th>
<th>CRP at onset of CRAO (mg/dL)</th>
<th>CRAO Laterality</th>
<th>Interval between onset and treatment</th>
<th>Funduscopic findings</th>
<th>Treatment</th>
<th>Immuno-suppressant</th>
<th>Anti-coagulant and/or anti-platelet drugs</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bastiansen et al (1993)</td>
<td>65/M</td>
<td>CSS</td>
<td>ND</td>
<td>Right</td>
<td>Immediately</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>CR</td>
</tr>
<tr>
<td>Sutcliffe et al (1997)</td>
<td>58/M</td>
<td>CSS</td>
<td>WNL</td>
<td>Left</td>
<td>More than 1 day</td>
<td>Paramacular</td>
<td>-</td>
<td>+</td>
<td>AZT</td>
<td>NR</td>
</tr>
<tr>
<td>Udono et al (2003)</td>
<td>68/M</td>
<td>CSS</td>
<td>ND</td>
<td>Bilateral</td>
<td>7 days</td>
<td>R: Diffuse</td>
<td>+</td>
<td>CP</td>
<td>+</td>
<td>NR</td>
</tr>
<tr>
<td>Chan et al (2004)</td>
<td>55/F</td>
<td>GCA</td>
<td>20.2</td>
<td>Left</td>
<td>Immediately</td>
<td>Diffuse</td>
<td>+</td>
<td>+</td>
<td>CP</td>
<td>PR</td>
</tr>
<tr>
<td>Asako et al (2011)</td>
<td>68/M</td>
<td>CSS</td>
<td>7.27</td>
<td>Bilateral</td>
<td>3 days</td>
<td>Diffuse</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Present patient</td>
<td>63/F</td>
<td>ANCA-related angiitis</td>
<td>10.61</td>
<td>Left</td>
<td>Immediately</td>
<td>Paramacular</td>
<td>-</td>
<td>+</td>
<td>CP</td>
<td>NR</td>
</tr>
</tbody>
</table>


clophosphamide was discontinued two months after admission due to repeated infections, including cytomegalovirus viremia; however, no increases in the levels of either CRP or MPO-ANCA were seen while tapering the dose of oral prednisolone. The patient was discharged from our hospital approximately three months after admission. The patient’s hyperthyroidism did not worsen throughout her clinical course. She has since remained in good general health for nine months under treatment with oral prednisolone at 5 to 10 mg daily.

Discussion

The present patient developed a sudden decrease in visual acuity of the left eye and was diagnosed as having occlusion of a branch of the central retinal artery based on ophthalmomadundoscopic findings. She simultaneously showed high inflammatory reactions, particularly a marked increase in serum CRP, with positive MPO-ANCA on admission to our hospital. This antibody is considered to play a central role in the pathogenesis of disorders of systemic vasculitis such as MPA and CSS. The former primarily involves the lungs and/or kidneys, while the latter is clinically characterized by multiple mononeuritis and bronchial asthma with eosinophilia (1). The present patient did not fulfill the classification criteria of either MPA or CSS (2, 3); however, the development of CRAO following the fever suggests that AAV may have underlain her clinical symptoms. The short interval between the onset of vasculitis and admission probably prevented visceral organ involvement of the lungs and kidneys. Performing histopathology is necessary to confirm the diagnosis of AAV; however, the present patient showed no clinical signs or symptoms indicating sites suitable for biopsy.

The precise cause of AAV in the present patient is of course unclear; however, its development during treatment with MMI is notable. Certain drugs are known to frequently cause AAV, including propilthiouracil (PTU), which is used in the treatment of hyperthyroidism (4, 5). This drug accumulates in neutrophils, and is oxidized by MPO and hydrogen peroxide to the reactive intermediate, which can activate immunocompetent cells, such as lymphocytes, via covalently binding to self-proteins, leading to the production of MPO-ANCA (6). MMI can also cause AAV, although the frequency of this is lower than that observed with PTU (4, 5). According to a recent report from Japan, MMI is a causative agent in 25% of patients with AAV induced by anti-thyroid drugs (5). MMI produces various adverse events such as pancytopenia and hepatic dysfunction in the first few months of treatment, while AAV induced by this drug can occur even after several years, as seen in the present patient (4, 5). MPO-ANCA in anti-thyroid drug-induced AAV sometimes remains at high titers even after clinical remission (5); however, in the present patient, this antibody quickly decreased in parallel with the disease activity, and no further increases were seen while tapering the dose of corticosteroids. To confirm the pathogenic role of MMI in AAV, cessation of this drug is necessary. Some patients with anti-thyroid drug-induced AAV have been reported to show spontaneous remission of clinical symptoms, including fever and eruptions, only with cessation of the causative agent (5). In the present patient, however, methylprednisolone was used for treatment soon after cessation of MMI in order to avoid serious visual sequelae due to worsening of CRAO, and we could not clarify the cause-effect relationship between MMI and AAV. Hyperthyroidism in the present pa-
tient did not worsen throughout the clinical course even after cessation of MMI; however, we plan to select surgical treatment such as thyroidectomy if further worsening of thyroid function occurs in the future.

CRAO is a relatively rare symptom of MPO-ANCA-associated vasculitis. The clinical profiles of six reported patients with this disease with CRAO are summarized in Table (7-12). The diagnoses include CSS in five patients and giant cell arteritis in one patient. The preferential association of CRAO in CSS has been hypothesized to attribute to eosinophilia-related hypercoagulation (13). Considering that all of the reported patients showed an advanced onset age of over 50 as seen in the present case, aging and atherosclerosis may also play a role in the development of CRAO. High-dose corticosteroids such as methylprednisolone pulse therapy were administered in all of the reported cases irrespective of the use of anti-coagulant and/or anti-platelet drugs, which are usually employed in the treatment of CRAO. However, four of the six patients showed loss of visual acuity or some sequelae in the affected eyes. In the present case, visual acuity of the left eye fell to 0.15 soon after the development of CRAO and remained at approximately the same level despite the administration of intensive treatment, including hyperbaric oxygen therapy. Irreversible ischemic damage to the maculopapillary bundle, which is important for visual function, was probably relevant to the persistence of lowered vision in the present case, although the affected areas were apparently small and localized on ophthalmofunduscopy. These clinical findings suggest that immediate treatment using high-dose corticosteroids with or without immunosuppressive agents should actively be considered as soon as possible after the onset of CRAO ascribable to AAV in order to suppress central retinal artery vasculitis and avoid persistent visual disturbance.

In conclusion, MMI is widely used as a first-line treatment for hyperthyroidism; however, it occasionally induces AAV, as seen in the present patient. In such cases immediate administration of corticosteroids may be necessary in addition to cessation of MMI, particularly when serious complications such as CRAO are present.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement
This work was supported in part by a Health and Labour Sciences Research Grant on Intractable Diseases (Neuroimmunological Diseases) from the Ministry of Health, Labour and Welfare of Japan.

References

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