Syndrome of Inappropriate Antidiuretic Hormone Associated with Eosinophilic Granulomatosis with Polyangiitis

Shin-ichi Tokushige, Kako Kodama, Takuto Hideyama, Hanae Kumekawa, Jun Shimizu, Risa Maekawa and Yasushi Shiio

Abstract

A 78-year-old woman with a history of bronchial asthma presented with distal dominant sensory disturbance and weakness in the upper and lower extremities. A biopsy of the left peroneus brevis muscle showed active vasculitis with inflammation extending into muscle fascicles and fibrinoid necrosis of the vessel wall, consistent with eosinophilic granulomatosis with polyangiitis (EGPA). Despite her decreased serum osmolality, her serum antidiuretic hormone level was not reduced, consistent with the syndrome of inappropriate antidiuretic hormone (SIADH). Intravenous and oral steroid therapy improved her neurological symptoms. Clinicians should consider EGPA as a concurrent, and potentially causative, disorder in cases of SIADH.

Key words: syndrome of inappropriate antidiuretic hormone (SIADH), eosinophilic granulomatosis with polyangiitis (EGPA), hyponatremia, vasculitis

(Intern Med 55: 1199-1202, 2016)
(DOI: 10.2169/internalmedicine.55.5122)

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss syndrome, is a systemic necrotizing vasculitis that involves the small and medium-sized blood vessels in a variety of organs (1). Despite the various clinical manifestations of EGPA, it is not recognized as a condition that could be associated with the syndrome of inappropriate antidiuretic hormone (SIADH), as only two previous case reports have documented the two conditions occurring simultaneously (2, 3). We herein describe a rare case of EGPA associated with SIADH.

Case Report

A 78-year-old woman with a two-year history of bronchial asthma presented with a disturbance of consciousness due to hyponatremia (111 mEq/L). During treatment with sodium infusion, she developed subacute distal dominant sensory disturbance, weakness and hyporeflexia in the upper and lower extremities, and was admitted to our department. Her distal muscle weakness was severe. The manual muscle testing (MMT) grade of her bilateral wrist extensor muscles was 3, while that of the bilateral tibialis anterior muscles was 0. She had no fever during the clinical course. She presented no apparent autonomic symptoms such as orthostatic hypotension, diarrhea, constipation, urinary disturbance or sweating disorder.

The patient’s white blood cell count was 13,700/μL (eosinophils, 12.0%), serum C-reactive protein was elevated to 5.56 mg/dL, and serum IgE was elevated to 365 IU/mL (normal range <300 IU/mL). She tested positive for serum myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA). Brain magnetic resonance imaging (MRI) showed a small acute cerebral infarction in the left centrum semiovale (Fig. 1). Magnetic resonance angiography showed no stenosis or occlusion of the intracranial arteries including the internal carotid arteries. Nerve conduction studies (Table 1) revealed decreased amplitudes in the multifocal sen-

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Received for publication February 9, 2015; Accepted for publication August 3, 2015
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sorimotor nerves with almost normal conduction velocities, suggesting an axonal, rather than demyelinating, mononeuropathy multiplex. A biopsy of the left sural nerve and peroneus brevis muscle showed nerve swelling (Fig. 2A) and many vacuolar degenerations due to acute axonal damage with Wallerian degeneration of the nerve fibers (Fig. 2B), and active vasculitis with inflammation extending into the muscle fascicles (Fig. 2C). Given the clinical course and pathological findings, the patient was diagnosed with EGPA.

The patient also presented with hyponatremia (134 mEq/L) and hypoosmolality (271 mOsm/kg water), but her serum antidiuretic hormone level did not decrease (1.3 pg/mL; normal range 0.3-4.2 pg/mL). Additionally, her urine osmolality was as high as 456 mOsm/kg water while her urine sodium was as high as 91.2 mEq/L, a pattern consistent with SIADH. Renal dysfunction was ruled out because her serum creatinine level was not elevated (0.44 mg/dL). Although her serum adrenocorticotropic hormone (ACTH) was undetectably low (<1.0 pg/dL), her cortisol was normal (6.2 μg/dL; normal range 4.0-19.3), which ruled out the possibility of adrenal dysfunction.

Intravenous methylprednisolone (1,000 mg/day, three days) and subsequent oral steroids (prednisolone 60 mg/day) were administered. Her neurological symptoms and hyponatremia began to improve after the treatment was initiated. However, because certain laboratory test results such as those for the eosinophil count, serum IgE and MPO-ANCA were not sufficiently improved one month after admission and treatment with steroids, cyclophosphamide (25 mg/day) was added to her treatment for the next three months. The dose of prednisolone had been gradually reduced to 10 mg/

## Table 1. Nerve Conduction Studies.

<table>
<thead>
<tr>
<th>Nerve</th>
<th>CMAP (mV)</th>
<th>MCV (m/s)</th>
<th>SNAP (μV)</th>
<th>SCV (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>R 0.98</td>
<td>58.8</td>
<td>0.9</td>
<td>42.8</td>
</tr>
<tr>
<td></td>
<td>L 8.54</td>
<td>55.9</td>
<td>6.5</td>
<td>46.5</td>
</tr>
<tr>
<td></td>
<td>(&gt;5.4)</td>
<td>(&gt;50)</td>
<td>(&gt;7.5)</td>
<td>(&gt;40)</td>
</tr>
<tr>
<td>Ulnar</td>
<td>R 1.0</td>
<td>50.0</td>
<td>4.0</td>
<td>51.7</td>
</tr>
<tr>
<td></td>
<td>L 9.51</td>
<td>61.0</td>
<td>4.1</td>
<td>42.1</td>
</tr>
<tr>
<td></td>
<td>(&gt;7.5)</td>
<td>(&gt;51)</td>
<td>(&gt;7.5)</td>
<td>(&gt;40)</td>
</tr>
<tr>
<td>Tibial</td>
<td>R 0.36</td>
<td>N.D.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>L 1.8</td>
<td>40.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(&gt;5.8)</td>
<td>(&gt;40)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sural</td>
<td>R -</td>
<td>-</td>
<td>3.3</td>
<td>46.0</td>
</tr>
<tr>
<td></td>
<td>L -</td>
<td>-</td>
<td>1.4</td>
<td>41.3</td>
</tr>
<tr>
<td></td>
<td>(&gt;1.9)</td>
<td>(&gt;36)</td>
<td>(&gt;1.9)</td>
<td>(&gt;36)</td>
</tr>
</tbody>
</table>

R: Right, L: Left, CMAP: compound muscle action potential, MCV: motor conduction velocity, SNAP: sensory nerve action potential, SCV: sensory conduction velocity, ND: not detected. Abnormal values are indicated by bold and italic font.
Table 2. Previous Cases of EGPA with SIADH.

<table>
<thead>
<tr>
<th>Age/ Sex</th>
<th>Neurological findings</th>
<th>Serum Na (mEq/L)</th>
<th>Serum ADH (pg/mL)</th>
<th>MPO-ANCA</th>
<th>Brain MRI</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>64/M</td>
<td>Muscle weakness in four limbs, sensory disturbance, hyporeflexia</td>
<td>125</td>
<td>13.0</td>
<td>+</td>
<td>No lesion</td>
<td>PSL, CPM</td>
<td>Improved (2)</td>
<td></td>
</tr>
<tr>
<td>56/M</td>
<td>Muscle weakness in the lower limbs, sensory disturbance, hyporeflexia</td>
<td>123</td>
<td>1.4</td>
<td>+</td>
<td>Acute infarction in the hypothalamus</td>
<td>PSL</td>
<td>Improved (3)</td>
<td></td>
</tr>
<tr>
<td>78/F</td>
<td>Disturbance of consciousness, muscle weakness in four limbs, sensory disturbance, hyporeflexia</td>
<td>111</td>
<td>1.3</td>
<td>+</td>
<td>Acute infarction in the left centrum semiovale</td>
<td>PSL, CPM</td>
<td>Improved Our patient</td>
<td></td>
</tr>
</tbody>
</table>

PSL: prednisolone, CPM: cyclophosphamide

day by the time she was discharged, four months after admission. At discharge, her serum IgE level finally normalized (9 IU/mL; normal range <300 IU/mL), the eosinophil fraction of the white blood cells was also normalized (2.8%), and MPO-ANCA was negative. The MMT grade of her wrist extensor muscles had improved from 3 to 5, and that of her tibialis anterior muscles had improved from 0 to 1. She has experienced no relapse with a maintenance dose of prednisolone (10 mg/day).

Discussion

We herein describe a rare case of EGPA with hyponatremia as a result of SIADH. To the best of our knowledge, there have been only two other reported cases of EGPA with SIADH (2, 3; Table 2). In both of these previous cases as well as in our case, serum MPO-ANCA was positive, and immunosuppressive therapy, including prednisolone, was effective. In one previous case, brain MRI showed an acute infarction in the hypothalamus (3); in the other, there was no intracranial lesion (2).

One plausible explanation for the coexistence of SIADH and EGPA is that EGPA could cause some damage to the hypothalamus or the posterior pituitary gland. The syndrome of inappropriate antidiuretic hormone is recognized as a complication of several intracranial diseases that involve the hypothalamus, including encephalitis (4), meningitis (5), neuromyelitis optica (6) and pituitary adenoma apoplexy (7). Saito et al. described a 56-year-old male EGPA patient with SIADH whose brain MRI showed a small cerebral infarction in the right paraventricular nucleus of the hypothalamus (3), which may have been caused by cerebral vasculitis related to EGPA. Similarly, our patient had a small cerebral infarction in the left centrum semiovale, also possibly due to cerebral vasculitis related to EGPA. Although MRI detected no lesion in the hypothalamus or pituitary gland, compromised blood flow to these regions may have contributed to the hypothalamic dysfunction.

Another possible explanation for the coexistence of EGPA and SIADH is that an autonomic neuropathy resulted in afferent baroregulatory pathway dysfunction. The syndrome of inappropriate antidiuretic hormone may result from a variety of peripheral neuropathies, such as Guillain-Barré Syndrome (8-10), chronic inflammatory demyelinating polyneuropathy (11, 12) and paraneoplastic neuropathy (13). The mechanism underlying SIADH in these neuropathies is discussed in various ways. For example, it has been argued that the binding of anti-GD2 antibody to the pituicytes in the posterior pituitary causes SIADH (14). Another author suggested that SIADH accompanying infectious polyneuropathy is caused by neuropathy involving peripheral afferent fibers from the vascular stretch receptors (15).

The relationship between peripheral autonomic neuropathy and SIADH has been examined in detail in one case report, describing a patient with paraneoplastic neuropathy with SIADH and orthostatic hypotension (13). Involvement of the afferent fibers from baroreceptors was the suspected cause of SIADH and orthostatic hypotension because an orthostatic hypertension-induced reactive increase in vasopressin was blunted and reflex hypertension in the cold pressor test was preserved, while there was no reaction to Valsalva’s maneuver (13). Although no apparent autonomic dysfunction such as orthostatic hypotension was observed in our patient, some neuropathy involving the afferent fibers from baroreceptors may be the cause of SIADH, because the extent of neuronal damage may vary greatly depending on the nerve fibers in the mononeuritis multiplex.

Our findings suggest that SIADH can be caused by EGPA. When a patient with EGPA presents with hyponatremia, SIADH should therefore be considered in the differential diagnosis.

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

References