Case Report

The co-occurrence of Guillain-Barré syndrome and inappropriate ADH syndrome in a Rheumatoid arthritis patient

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Abstract. Rheumatoid Arthritis (RA) is the most frequently seen connective tissue disorder. In RA, the peripheral nervous system involvements including distal sensory or sensorimotor polyneuropathy and entrapment neuropathies are more common than the central nervous system involvements. Guillain-Barré syndrome (GBS), an autoimmune disorder, can be encountered in any age groups. The syndrome of inappropriate secretion of ADH (SIADH) is characterized by the non-physiologic release of ADH, resulting in impaired water excretion with normal sodium excretion that causes hyponatremia. Herein, we present the co-occurrence GBS and SIADH in a RA patient treated with Methotrexate (Mtx). A 57 year-old female developed ascending weakness, starting from the legs and spreading to the arms while having pneumonia. Electromyography findings were consistent with sensorimotor demyelinating polyneuropathy. The laboratory investigations were compatible with SIADH. In conclusion, the SIADH in GBS should be taken into account for RA patients on Mtx.

Key words: Methotrexate, Guillain-Barré syndrome, syndrome of inappropriate ADH, Rheumatoid arthritis

1. Introduction

Rheumatoid Arthritis (RA) is two times more common in females than males. RA can occur at any age, but the peak of onset is the fourth and fifth decades of life. The onset of RA is more common in summer time than winter (1). In RA treatment, the administration of high-dose steroid may be required to control inflammation at the onset. In addition, anti-cytokine drugs can be used in the treatment (2).

Guillain-Barré syndrome (GBS) can occur as a result of different immunologic, toxic, infectious, or metabolic etiological causes. Seventy-five percent of GBS patients have a history of recent gastrointestinal or respiratory infections before the onset of the symptoms (3). GBS is classified into several subgroups based on clinical and electrophysiological findings such as acute inflammatory demyelinating polyneuropathy, acute sensorimotor axonal neuropathy, acute motor axonal neuropathy, Miller-Fischer syndrome, and acute pandysautonomia. The electrophysiological tests are beneficial for the confirmation of the diagnosis of GBS. Intravenous immunoglobulin (IVIG) and plasmapheresis are the main treatment options for GBS (4).

The syndrome of inappropriate secretion of ADH (SIADH) is caused by insufficient suppression of ADH secretion, resulting in impaired water excretion. SIADH should be suspected in a patient with euvolemic hyponatremia. Even only isotonic fluid replacement can cause hyponatremia in SIADH (5). Several medications, such as vincristine, vinblastin, methotrexate (Mtx), vasopressin, oxytocin, thiazides, and non-steroid anti-inflammatory drugs can cause SIADH (6). Other common causes of SIADH are neoplasms including: pancreas cancer, thymoma, small cell lung cancer, and lymphoma; lung diseases such

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as tuberculosis, pulmonary abscess, empyema; and central nervous system disorders such as infections, trauma, subarachnoid hemorrhage, GBS, and porphyria (7).

Herein, we present the co-occurrence GBS and SIADH in a RA patient treated with Mtx.

2. Case report

A 57 year-old female with 25-year history of RA initially was admitted to the hospital for pneumonia. She was consulted to our department for five-day history of lower extremity weakness and one-day history of upper extremity weakness. She had difficulties in swallowing as well. Family history revealed that the presence of diabetes in her sister and brother. For RA treatment, she had been on Mtx for 3 years and steroid treatment for a while. In physical examination blood pressure: 130/80 mmHg; pulse: 80 minute; bilateral secretary rhonchus and rales in the both lungs; and 2/6 systolic murmurs from the apical part of the heart were detected. No organomegaly or edema was detected. In a neurological examination; she was alert, cooperated, and oriented to time, place and person. No neck stiffness or meningeal irritation signs were detected. Cranial nerves were normal. The muscle strength (based on Medical Research Council scale) was 2/5 in bilateral proximal and 3/5 in bilateral distal lower extremity muscles, 4/5 in bilateral proximal and distal upper extremity muscles. Deep tendon reflexes (DTRs) were absent in upper and lower extremities. Pathological reflexes (including babinski, hoffman and palmomental) were absent as well. Sensory exam was normal to all modalities. No urinary incontinence or retention was detected.

The laboratory investigations showed mild anemia (hemoglobin: 9.2 gr/dL, hematocrit: 29.3%, MCV: 74.6 fL), mildly elevated sedimentation rate and c-reactive protein (c-reactive protein: 73.8 mg/l, sedimentation rate: 50 mm/h), sodium: 106 mEq/L, potassium: 4.5 mmol/L, glucose: 95 mg/dL, BUN: 30 mg/dL, plasma osmolality 237 mOsm/kg (270-295), and urine osmolality was 500 mOsm/kg (50-1400). The rest of the tests including comprehensive metabolic panel, thyroid function test, hepatitis panel, cortisone level, ACTH level were normal. The chest computed tomography revealed bilateral mild infiltration of the lower part of lungs. Lumbar puncture was suggested, but the patient did not accept the procedure. The nerve conduction study showed non-obtainable bilateral sural sensory nerve action potentials (SNAP), bilateral superficial peroneal SNAP, bilateral median SNAP and bilateral ulnar SNAP responses, marked slowing of nerve conduction velocity (NCV) and decreased amplitude of ulnar motor nerve, non-obtainable proximal median compound muscle action potential (CMAP), marked slowing of NCVs and decreased amplitudes of peroneal motor and tibial motor nerve, temporal dispersion and conduction blocks were detected. F response was absent and A wave was present. These findings were consistent with acute inflammatory demyelinating polyneuropathy.

When the patient was transferred to our clinic, she still had pneumonia-related complaints. Thus, she was consulted with a pulmonologist, and then sefazolin sodium 2 gr/day and levofloksasin 1 gr/day was initiated. A five-day IVIG treatment course was performed for GBS. After IVIG treatment, her weaknesses of the lower limbs (4/5 in both distal and proximal muscles) and upper limbs (4+/5) were improved. She consulted with a rheumatologist that recommended to continue Mtx and steroid, and to add chloroquine to the current RA regimen. She also consulted with an internist for hyponatremia. Because of normal adrenal, thyroid, pituitary, and kidney functions, no history of diuretic use, and higher plasma osmolality than urine, she was diagnosed with SIADH. Sodium replacement with fluid restriction was administered. She was discharged after correction of sodium and completing IVIG treatment with weakness improvement.

3. Discussion

GBS is the most common acute peripheral polyneuropathy. GBS is caused by immunological factors and may cause fatal consequences (3). Terui et al. reported a patient with lymphoblastic lymphoma and Mtx treatment presenting with GBS and encephalopathy. Although, their case was presented with irritability and hemiparesis that were related with central nervous system involvement, decreased DTR and progressive bulbar paralysis were consistent with GBS. GBS was confirmed by the nerve conduction study and the lumbar puncture. The patient was improved with IVIG therapy. Even GBS is a rare neurological complication, but should be considered in a patient with Mtx treatment**.** Because GBS is able to mimic a acute methotrexate-associated encephalopathy (8). In our case, the patient was on Mtx for 3 years and initially had lower limb weakness and bulbar symptoms that were improved with IVIG therapy.

Hyponatremia, an absence of edema, a presence of normal thyroid and adrenal gland function,

high urine sodium, and a higher plasma osmolality than urine are diagnostic criteria of SIADH (6). Our patient qualified all these criteria. In literature, the co-occurrence of GBS and SIADH was also reported. The GBS and SIADH were diagnosed based on clinical, laboratory, and electrodiagnostic findings. The SIADH pathogenesis was postulated autoimmune-related mechanism similar to GBS (9). In our case, we believe that SIADH may be associated with GBS and/or pneumonia rather than Mtx side effect SIADH. The SIADH in GBS is a very often overlooked entity even though it is well-described. However, most of the previous observations are case reports. There are no systematic studies of SIADH in GBS. Saifudheen and et al. detected SIADH in 24 of the 50 patients at some stage of the disease. This article emphasized that SIADH is a common and important electrolyte disorder encountered in GBS. It has significant association with severity of GBS and is an indicator of poor prognosis. It can be symptomatic even though the majority of patients are asymptomatic (10). Inoue and et al. described a 73-year-old Japanese male was admitted because of difficulty in standing up after acute upper respiratory inflammation with mild fever followed by watery diarrhea. Neurological examination revealed moderate proximal muscle weakness and loss of tendon reflexes in all extremities. The blood sodium level was 106 mEq/L on admission. The plasma osmolality was 221 mOsm/kg (270-295), and the urine osmolality was 416 mOsm/kg (50-1400). EMG and nerve conduction studies suggested acute demyelination in the motor and sensory nerves. It is postulated that SIADH, like GBS, might be caused by an autoimmune mechanism (11). During high-dose methotrexate therapy we recognized a significant increase in vasopressin secretion as it has previously been reported for other cytostatics. Frahm and et al. reported an excessive augmentation of vasopressin excretion in 24 h urine in 9 patients receiving high-dose methotrexate combined with considerable water retention. The pathomechanism is so far unknown. From experimental data it may be assumed that methotrexate alters directly the neurosecretory areas of the cerebrum as well as effects the distribution of body fluid volumes. The considerable risk of water intoxication seems to be of highly clinical importance (12). But, in our case, Mtx dosage is also not high dose.

In conclusion, a patient with RA and Mtx may rarely develop GBS. The SIADH in GBS is a very overlooked entity even if it is well-described. However, most of the previous observations are case reports. We emphasized that the SIADH in GBS should be taken into account for RA patients on Mtx.

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