Letters to the Editor

Unexpected impaired consciousness in RA: A rare complication of SIADH induced by increased IL-6

Sirs,

As infection is the major cause of death in patients with rheumatoid arthritis (RA), it is important to monitor for infectious diseases. Here we report a rare complication of the syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) in an elderly RA patient which was induced by increased IL-6, but not IL-1 nor TNF-α in a chance of infection.

A 78-year-old female with RA consulted our hospital because of fatigue and loss of appetite. She had been treated with prednisolone (2.5 mg/day), bucillamine (100 mg/day), and salazosalfapyridine (1 g/day) for the previous 5 years. On admission, she was afebril and clear in consciousness. However, her symptoms continued, followed by the development of impaired consciousness, apathy and disorientation on the 5th day of hospitalization. Urinalysis revealed marked pyuria. Laboratory studies disclosed the following values: white blood cell count 25,300/μl with 92% neutrophils; CRP 17.9 mg/dl; fasting plasma glucose 5.4 mmol/l; serum sodium 109 mmol/l (normal range 134-144); potassium 4.4 mmol/l (3.3-4.5); chloride 72 mmol/l (98-107); creatinine 0.4 mg/dl (<1.0); ACTH 17 pg/ml (< 60); cortisol 17.9 μg/dl (4.6-24.6); and urinary 17-OHCS 5.3 mg/day (2.2-7.3).

The anti-diuretic hormone (ADH) at 6.7 pg/ml (0.3-3.5) was somewhat increased despite the low plasma and urinary osmotic pressure. Tumor markers of CEA, SCC, CA19-9 and ProGRP were normal. There were no findings in the brain, chest or abdomen by radiographic, ultrasonographic and endoscopic examinations. The patient was treated with antibiotics (2 g/day) and with restriction of fluid intake and sodium supplementation. Soon after starting treatment, the laboratory data recovered, followed by complete disappearance of her symptoms and signs (Fig. 1). Therefore, we diagnosed her illness as SIADH. As malignant neoplasms, endocrine diseases and drug administration that secreted ADH had been excluded, the mechanisms of SIADH were examined in relation to cytokines.

At the nadir of her hyponatremia (Fig. 1), the patient's serum IL-6 level was increased (24.1 pg/ml); however, IL-1β and TNF-α levels were undetectable. Following treatment her symptoms and signs disappeared and serum IL-6 returned to the basal level. Subsequently, the same illness has not recurred. We concluded that SIADH in this case was induced by the increased IL-6.

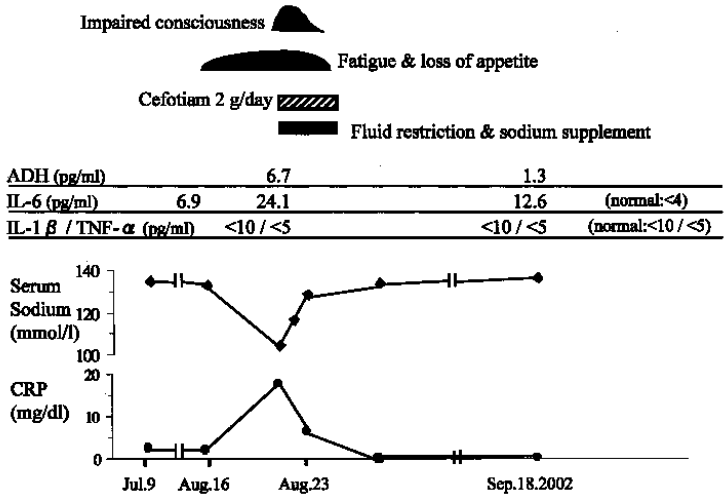

Fig. 1. Clinical course of the symptoms, signs and laboratory data during SIADH.

SIADH is reportedly caused by cytokines including IL-6, IL-1 and TNF-α (1). The role of IL-6 in SIADH has been confirmed in human (2) and in a IL-6 transgenic mice model (3); however, the clinical role of IL-1 and TNF-α in SIADH has not been evaluated. We firstly confirm herein that it is unlikely that either IL-1 or TNF-α induced the SIADH.

To our knowledge, only 3 cases of SIADH associated with chronic arthritis have been reported (4,5). All were elderly Japanese subjects (a 70-year-old female, a 73-year-old female and a 66-year-old male). The first 2 subjects suffered from RA, and the third from pseudogout. In the former 2 subjects, prednisolone (5 and 2.5 mg/day, respectively) was orally administered and infections were present as the trigger. The precise mechanisms of SIADH in our patient and the reported 3 cases remain unclear; however, the similar observations form an entity of clinical features. ADH secretion induced by IL-6 might be enhanced under the suppressed condition of the hypothalamic-pituitary-adrenal (HPA) axis by chronic inflammation and/or immunosuppression. The discrepancy between suppression of the HPA axis and the enhanced ADH secretion is reported in RA (6). Aging also has an effect on inappropriate ADH secretion because elderly subjects show the decreased ability to concentrate urine and increased ADH secretion (7). We could not exclude a possible racial or some background predominance on the present type of SIADH. Therefore, rheumatologists should be on the lookout for hyponatremia followed by the development of SIADH, especially in elderly patients with RAcomplicated by infection.

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