Case Report :

Methotrexate-induced Hyponatremia in Rheumatoid Arthritis:A Case Report

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Abstract

Methotrexate is a widely used medication with immunosuppressive and immunomodulatory effects on cancers and autoimmune diseases, it is known that hyponatremia may be a side effect of its use in high doses when treating cancers, but it is unknown in low doses when used as an immunomodulator. Hyponatremia may be asymptomatic initially but can progress to fatal consequences if left untreated. Here we present a case of hyponatremia secondary to a low dose of methotrexate in an elderly patient with rheumatoid arthritis.

Keywords:

methotrexate, hyponatremia, rheumatoid arthritis, SIADH, adverse event.

Introduction

Methotrexate (MTX) is a dihydrofolate reductase (DHFR) inhibitor; it is a potent immunosuppressant used in different types of cancers and a disease-modifying anti-rheumatic drug when used in smaller doses. It has been effectively used to treat patients with arthritis of autoimmune diseases like rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, and others. Many side effects have been documented when methotrexate is used at different doses and routes. One that is considered a rare side effect of high doses of intrathecal methotrexate in treating different types of cancer[1-3] is hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone (SIADH) and other etiologies[4-6]. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a disorder of impaired water excretion resulting from an inability to suppress antidiuretic hormone secretion (ADH). If water intake exceeds the decreased urine output, the resultant water retention causes hyponatremia. Any patient with hypona-

tremia, hypo-osmolality, and urine osmolality greater than 100 mOsmol/Kg should be evaluated for SIADH. The causes of SIADH fall into four broad categories: disorders of the nervous system, neoplasia, pulmonary diseases, and drug-induced, which include antidepressants, anticonvulsants, antipsychotic agents, cytotoxic agents, and medications used to treat pain like duloxetine, pregabalin, and tramadol[7]. In SIADH, the urine sodium concentration is typically greater than 40 mEq/L, the serum potassium concentration is normal, there is no acid-base disturbance, and the serum uric acid concentration is often low. We present a case of hyponatremia secondary to SIADH after using a lower dose of MTX to treat a patient with rheumatoid arthritis.

Case presentation

A 68-year-old man with no history of chronic medical conditions presented to the rheumatology clinic with a two-month history of joint pain affecting his metacarpophalangeal joints (MCPJ) and proximal interphalangeal joints (PIPJ) bilaterally, along with at least 30 minutes of morning stiffness. There was no history of skin rash, nail changes, Raynaud's phenomenon, sicca symptoms, recent infections, or constitutional symptoms. The exam revealed a temperature of 36.9 degrees Celsius, blood pressure of 100/66 mm of Hg, a heart rate of 72 beats per minute, a respiratory rate of 18 breaths per minute, and a body mass index of 22.9 kg/m^2. His right 4th and 5th MCPs, 2nd and 3rd PIPs, as well as his left 3rd and 5th MCPs, 3rd and 4th PIPs, were affected by active synovitis. Erythrocyte sedimentation rate (ESR) was 41 mm/1st hour; C-reactive protein (CRP) value was 16 mg/L; while rheumatoid factor (RF), anti-nuclear antibodies (ANA), and anti-cyclic citrullinated peptide (anti-CCP) were negative. Ultrasound of his hands and wrists revealed grade 1 synovitis of the following joints: right 1st carpometacarpal joint (CMCJ), 2nd and 3rd PIPJ, 4th and 5th MCPJ, 4th and 5th PIPJ. 1st CMCJ and MCPJ to the left, 2nd MCPJ and PIPJ, 3rd CPJ, 5th CPJ and PIPJ. Synovitis, grade 2, of the left 3rd and 4th PIPJ. Mild tenosynovitis of the bilateral 4th and 6th extensor compartments. With the diagnosis of seronegative rheumatoid arthritis, he was started on a short course of oral corticosteroid (20mg/day) on September 21, 2022, along with methotrexate 15mg weekly orally and folic acid 10mg weekly. His baseline screening for hepatitis B and C was negative, and his CBC, renal, liver functions, and electrolytes were normal. After weeks of discontinuing the oral corticosteroid and maintaining the same dosage of methotrexate and folic acid, he returned on December 5, 2022, with a sig-

nificant improvement in his symptoms. On examination, there was no evidence of active synovitis, and a blood test was ordered to monitor any potential adverse effects of methotrexate. The level of inflammatory markers normalized, and the patient's liver and renal functions and complete blood count (CBC) remained within normal limits. However, the patient's electrolytes analysis revealed a recent decline in the serum sodium level to 119 mmol/L. Upon further inquiry, he denied a history of nausea, dizziness, abnormal movements, confusion, or altered level of consciousness. There were no signs of fluid overload in his extremities, abdomen, or chest. In addition, there were no signs of hypovolemia, and his vital signs at the time were as follows: temperature of 36.6 degrees Celsius, blood pressure of 105/66 mm of Hg, heart rate of 82/min, oxygen saturation of 97% at room air, respiratory rate of 17/min, and body mass index of 23 kg/m^2. The urine sodium was 12.58 mmol/L (normal range is 20-110 mmol/L), the urine osmolality was 252 mOsm/Kg (50-1200 mOsm/Kg), random urine protein was 15.51 mg/dL (0-11.9 mg/dL), serum albumin was 36.74 g/L (35-50 g/L), and his serum osmolality was 236 mOsm/Kg (261-260 mOsm/Kg), urine protein electrophoresis and ultrasound of his kidneys were unremarkable. The patient was instructed to limit his daily water intake to 1L, and methotrexate was replaced with sulfasalazine. After one week, his serum sodium improved to 131 mmol/L, and his arthritis symptoms remained well-controlled.

Discussion

The majority of side effects of MTX in low doses when treating RA are non-life-threatening and include gastrointestinal problems like nausea, stomach upset, stomatitis, hepatic toxicity, hematologic toxicity, as well as neurological symptoms such as fatigue, poor concentration, and headache. While nephrotoxicity and disturbances in the electrolytes are almost always associated with high doses of MTX in the treatment of cancers. A number of case reports have documented hyponatremia as a side effect with the use of high doses of MTX ($\geq$500mg/m^2) treating different types of cancers like leukemia[1], lymphoma[2], and leptomeningeal carcinomatosis[3]. However, it has not been documented in the use of lower doses of methotrexate in the treatment of inflammatory arthritis (7.5-25mg). The exact cause of methotrexate-induced hyponatremia is not known[2,4,5]. Several theories have been proposed, including increased secretion of ADH4, activation of central nervous system-derived natriuretic peptide[2], its toxic effects on the neurosecretory areas of the cerebrum, changes in

the distribution of body fluid volumes[4,5], and by the increased renal expression of NKCC2 as found in rats[6], while it is known in humans that NKCC2 dysfunction causes Bartter syndrome type 1, characterized by severe natriuresis, hypercalciuria, magnesuria, inability to concentrate urine, leading to hyponatremia, hypochloremia, metabolic alkalosis, and low blood pressure.[8-10]. In order to reduce the risk of developing serious adverse events associated with hyponatremia, patients using MTX should undergo additional monitoring for hyponatremia as part of their routine lab tests, particularly in elderly patients. It is not currently included in the list of recommended laboratory tests for monitoring patients receiving low doses of MTX[11,12], as it only emphasizes the significance of monitoring the patient's complete blood count, liver transaminase levels, and serum creatinine levels.[13-15]

Conclusion

The diagnosis of SIADH is not always straightforward, as it can present with a variety of vague symptoms or, in many cases, be asymptomatic. A failure to detect hyponatremia during routine follow-ups could result in the progression of this electrolyte imbalance, which could be fatal without immediate intervention. In order to reduce the risk of developing serious adverse events associated with hyponatremia, patients using MTX should undergo additional monitoring for hyponatremia as part of their routine lab tests, particularly in elderly patients.

Conflict of interest

None.

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