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Cotrimoxazole-induced SIADH — a unique challenge during treatment of pulmonary nocardiosis

Abstract

A 62 year old male non-smoker diagnosed with pulmonary nocardiosis was initiated on Cotrimoxazole therapy at a dose of 20 mg/kg per day in three divided doses. He developed hyponatremia (serum sodium 105 mEq/L) on day 3 of therapy. The potential causes of hyponatremia were evaluated. After ruling out other causes, the cause was suspected to be Cotrimoxazole-induced syndrome of inappropriate anti-diuretic hormone secretion (SIADH). We subsequently re-initiated therapy with Cotrimoxazole and the hyponatremia (serum sodium 110 mEq/L) recurred. Upon discontinuation of therapy, serum sodium levels returned to normal. The patient was started on Amoxicillin-Clavulanic Acid as an alternative therapy for pulmonary nocardiosis which resulted in resolution of the hyponatremia. Cotrimoxazole-induced SIADH is a rare occurrence. This case is representative of a patient with Cotrimoxazole-induced SIADH and the causal relationship was confirmed once resumption of therapy with the offending medication resulted in hyponatremia.

Clinicians should be aware of this rare adverse effect of Cotrimoxazole and should monitor serum electrolytes during therapy, especially in the elderly and in those receiving high doses.

Key words: cotrimoxazole, SIADH, nocardiosis

Adv Respir Med. 2020; 88: 352–355

Introduction

Pulmonary nocardiosis, previously thought of as a disease that occurs mainly in the immunocompromised population, has become increasingly reported in individuals with structural lung diseases [1, 2]. Cotrimoxazole is the drug of choice for the treatment of nocardiosis. Although widely considered to be a drug with a decent safety profile, it has its own major and minor adverse effects [3, 4]. SIADH is a rare but serious complication associated with Cotrimoxazole therapy. Its occurrence is more frequently observed than previously recorded. SIADH is a disorder caused by the inability to suppress secretion of anti-diuretic hormone. There is impairment of water excretion and if water intake is in excess of urine output, water retention occurs leading to hyponatremia [5, 6]. The risk appears to be highest in the elderly population and is essentially dose-dependent [5, 7].

Case history

A 62-year-old male non-smoker was admitted due to complaints of acute worsening of breathlessness, fever, and cough with expectoration that had been present for 5 days. The fever was intermittent and high grade, and was associated with chills and rigor. Cough was productive with copious yellowish non-foul-smelling sputum. He had a history of sputum smear-positive pulmonary tuberculosis six years ago for which he received antitubercular therapy. He had developed obstructive airway disease as a sequela of pulmonary tuberculosis which was confirmed by spirometry. He was treated with inhaled bronchodilators for five years.

On admission he was severely ill, febrile (oral temperature 38.9°C), tachypneic, tachycardic, and normotensive with an oxygen saturation of 82% on room air.

Respiratory system examination revealed bilateral diffuse coarse crackles and rhonchi.

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DOI: 10.5603/ARM.2020.0113

Received: 19.02.2020

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ISSN 2451–4934

Other systemic examinations were unremarkable.

On evaluation, he had neutrophilic leukocytosis. The total count was 21,010 (89% neutrophils). Liver and renal function parameters were normal. Other unordinary lab results were documented as follows: serum sodium on admission was 134 mg/dL, the C-reactive protein level was 190 mg/L, and serum procalcitonin was 2.86 ng/mL. Chest X-ray showed bilateral non-homogenous opacities with haziness over the right upper zone (Figure 1).

He was started on empirical antibiotic therapy with IV Piperacillin-Tazobactam (4.5 g 4 ×/diem) and oral Azithromycin (500mg 1 ×/diem). Oxygen supplementation, nebulized bronchodilators, and other supportive therapy was provided. On day four, in view of inadequate clinical improvement, a contrast-enhanced computed tomogram of the thorax was completed which showed ground-glass opacities over the right upper lobe with multiple bilateral patchy areas of consolidation and centrilobular nodules (Figure 2).

Flexible fiberoptic bronchoscopy was planned and completed under continuous oxygen supplementation by nasal cannula with a target oxygen saturation of 90%. It showed purulent secretions from the right lobar and segmental bronchi. Bronchial anatomy was normal and aerobic cultures of bronchial secretions, Ziehl Nielsen staining, Gram-staining, Mycobacterium culture were sent. There was no bronchoscopy-related complication. An aerobic culture of bronchial fluids showed growth of *Nocardia* (the specific species were not identified). Modified acid-fast bacilli (AFB) stain after bronchial lavage showed filamentous branched acid-fast positive bacilli. Fungal stain and culture were negative. Mycobacterium culture was negative at the end of the required 42-day culture period.

As part of the *Nocardia* pneumonia treatment regimen, the patient was started on oral Cotrimoxazole at a dose of 20 mg/kg body weight. After 3 days of treatment, the patient developed asymptomatic hyponatremia. Sodium levels had fallen from 134 mEq/L to 129 mEq/L, and then subsequently to 105mEq/L. Even at this point, he did not have any symptoms. Causes of this electrolyte imbalance were investigated. Thyroid function tests were done and serum cortisol was measured and both results were found to be normal. A CT scan of the brain was normal. After ruling out other causes, the cause of the hyponatremia was suspected to be Cotrimoxazole-induced SIADH (serum sodium 105 mEq/L,



Figure 1. Chest radiograph PA view showing multiple bilateral air space opacities and bilateral flattened diaphragms

urine osmolality 468 mOsm/kg, serum osmolality 250 mOsm/kg, and urine sodium 82 mmol/L). Fluid restriction was initiated, and hypertonic saline was administered. Cotrimoxazole was stopped and serum sodium levels returned to normal after continuing the above measures.

Since the treatment of *Nocardia* involves the use of long-term antibiotics, we decided to re-introduce Cotrimoxazole to see if it was the cause of the hyponatremia. On reintroduction of Cotrimoxazole, a fall in serum sodium levels was observed by day 3 (a level of 110 mEq/L). As a result, Cotrimoxazole was stopped and the patient was started on IV Amoxicillin-clavulanate (1.2 g, 3 ×/diem) as an alternative regimen. He received parenteral antibiotics for 10 days. There was a serial fall in total WBC count to 14,320, and serum procalcitonin had fallen from an initial 2.86 ng/mL to 0.11 ng/mL. The patient's clinical condition improved gradually and he was weaned off oxygen therapy while continuing therapy with Amoxicillin-clavulanate (625 mg 3 ×/diem) which was now administered orally. He was discharged in a stable condition and advised to continue oral Amoxicillin-clavulanate therapy at a dose 625 mg thrice daily for a duration of three months. Subsequent chest radiographs taken on follow up after 40 days of therapy showed significant clearance of radiological opacities (Figure 3).



Figure 2. Contrast-enhanced tomogram of the thorax showing bilateral upper lobe ground-glass opacities and right upper lobe consolidation



Figure 3. Chest radiograph showing clearance of previously noted opacities during follow-up

Discussion

Nocardiosis is classically known to be an opportunistic infection associated with impaired immunity, particularly cell-mediated immunity. However, up to one-third of patients have been found to be immunocompetent [2, 8].

Risk factors for Nocardiosis include infection with the Human Immunodeficiency Virus, transplants, cancers, rheumatic diseases, diabetes mellitus, steroid abuse, chronic obstructive pulmonary disease, and poor socio-economic conditions [8, 9].

Pulmonary involvement is the most common presentation of nocardiosis. Symptom onset may be acute, sub-acute or chronic and includes cough, dyspnea, chest pain, hemoptysis, fever, weight loss, and fatigue [2, 10]. Lobar consolidation is the most common radiographic presentation, followed by nodules/reticulations [10].

Although Trimethoprim-Sulfamethoxazole is the mainstay of treatment, the final drug regimen is decided on the basis of antimicrobial sensitivity, the severity of the disease process, and the organ of involvement [2, 10].

Cotrimoxazole is a sulfonamide antibiotic which contains Trimethoprim and Sulfamethoxazole. Trimethoprim is a heterocyclic weak base and is related in structure to the potassium-sparing diuretics amiloride and triamterene which act by blocking sodium reabsorption at the eNaC (epithelial sodium channel) in the distal nephron [10]. High doses of TMP has been shown to act as epithelial sodium channel inhibitors in the distal tubule.

SIADH can be caused by a variety of pulmonary and extra-pulmonary infections/malignancies, as well as by a range of medications [7]. SIADH is a common cause of hyponatremia. In a retrospective cohort study by Tsapepas et al, the incidence of hyponatremia was found to be 72.3% among those on high dose therapy with Cotrimoxazole [4]. Severe hyponatremia and SIADH is rare and described in only a few case-reports [11, 12].

In describing hyponatremia and its treatment, the cerebral effects are worth mentioning. The rate of sodium correction in hyponatremia of acute onset should be $\leq 10\text{mEq/L}$ in the first 24 hours and $\leq 8\text{mEq/L}$ for any 24-hour period thereafter. Effective serum osmolality is determined by serum sodium concentration. Hypotonic hyponatremia, if acute and severe, can lead to the entry of water into brain cells and ultimately, to cerebral edema [13, 14]. The brain adapts to such a level of hypotonicity by losing intracellular solutes, principally potassium and organic solutes called osmolytes. Hyponatremia, which develops within two or three days, is less likely to be complicated by cerebral edema because of this brain adaptation. Once the adaptation is complete, the rate of correction of hyponatremia is important. Overt rapid correction of hyponatremia can induce Osmotic Demyelination Syndrome (ODS) [13]. However, rapid correction in acute and severe hyponatremia does not induce ODS because the cerebral adaptation is still in its early stage [14].

In our case, the patient's thyroid and adrenal function, as well as brain imaging, were normal.

In view of no other plausible explanation for the hyponatremia, we considered Cotrimoxazole as the likely causative agent. The presence of low serum osmolality, high urine osmolality, and high urinary sodium in the absence of hypothyroidism and peripheral signs of hypovolemia pointed towards a potential iatrogenic cause. Once the hyponatremia was resolved with the cessation of Cotrimoxazole, and subsequently reappeared when therapy was re-started, the diagnosis of Cotrimoxazole induced-SIADH was evident.

Conclusion

This case report presents a rare but potentially fatal complication associated with Cotrimoxazole therapy: SIADH. Probable risk factors for this in our case are advanced age and a high dose of Cotrimoxazole. A high index of suspicion and close monitoring of serum electrolytes is necessary, especially in older patients.

Conflict of interest

None declared.

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