Introduction

Tuberculosis remains a worldwide infectious problem [1]. Treatment should follow recently published recommendations [2]. SIADH is a possible cause of hyponatremia in patients with pulmonary diseases – especially in granulomatous diseases. However, the number of case reports on patients with a SIADH exclusively related to pulmonary TB is low and the mechanism poorly understood. Hypoxia, decreased vascular volume [3] and ectopic ADH production have been discussed as possible causes [4].

The case

A forty-nine-year-old cachectic woman (height 1.60 m, weight 30.4 kg, BMI 11.9 kg/m²) was admitted to our hospital due to strong suspicion of pulmonary tuberculosis (TB) (Fig. 1a, b). The patient was an active smoker (17 pack-years) until the day of admission to our hospital. For a couple of years, she had been abstinent from alcohol abuse. Initial microbiological examination revealed acid-fast bacilli in auramine staining, confirmed by Ziehl-Neelsen stain. Antituberculous treatment with isoniazide (H), rifampicine (R), ethambutol (E) and pyrazinamide (Z) was initiated following approved protocols [2, 5]. Later on, cultural results showed mycobacterium tuberculosis (MTB) sensitive to H and R. From the day of her admission, we observed hyponatremia. Later on, the patient developed severe hypokalemia (Table 1). Clinically, these electrolyte imbalances caused no specific symptoms. For treatment of hyponatremia, fluid intake was consequently restricted to a total of 1000 ml per day. Oral potassium substitution was started but did not result in normalization of hypokalemia. Therefore, continuous parenteral potassium administration via a central line was initiated, again without sustained success.

Abstract

A forty-nine-year-old female patient with pulmonary tuberculosis developed syndrome of inadequate antidiuretic hormone secretion. Consequently restriction of fluid intake as a therapeutic measure was just as ineffective as a medication with tolvaptan which was performed later on. A probable explanation for the inefficacy of the aquaretic drug is an interaction of rifampicine and tolvaptan. This case report gives a short summary of SIADH in pulmonary TB and discusses possible reasons for the difficult antituberculous treatment in this patient.

Zusammenfassung


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Evolution of laboratory parameters

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<th>20</th>
<th>35</th>
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Laboratory reference range:
Serum Na⁺: 135 – 145 mmol/L
Serum K⁺: 3.5 – 5 mmol/L
Serum Osmolality: 280 – 295 mos/kg
Urine Osmolality: 50 – 1200 mos/kg
CRP: 0 – 95 nmol/L
ADH: <0.5 – 4.2 pmol/L
SUSPUP: 0.6 – 5.3
SUSPPUP: 0 – 0.42 pmol/L
ACTH: 2 – 11.4 µmol/L
Cortisol: 193 – 689.8 nmol/L
Renin: 0.1 – 0.36 pmol/L
H through level: 1.5 – 7.3 µmol/L
R through level: 0.1 – 12.2 µmol/L


1 H peak level (laboratory reference range 10.9 – 72.9 µmol/l); H through level controlled on day 135 after admission: 4.4 µmol/l.

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Biochemical analysis revealed serum osmolality being reduced, urine osmolality normal and sodium urine concentration reduced, fulfilling formal criteria for syndrome of inadequate antidiuretic hormone secretion (SIADH) with hypoosmolar hyponatremia. Reduced sodium urine concentrations with consecutively elevated SUSPUP (serum sodium to urinary sodium to serum potassium to urinary potassium ratio) and SUSPPUP (serum sodium to urinary sodium to serum potassium to urinary potassium ratio) [6] suggested reactive hyperaldosteronism as a compensatory mechanism. There were no clinical hints for an extrarenal sodium loss. Renal function was slightly reduced during the whole in-hospital stay, thyroid gland function normal. In the absence of edema, there were no signs of heart failure. Hemodynamically, the patient was stable at all times.

Further laboratory evaluations revealed antidiuretic hormone (ADH) being markedly increased as well as serum renin and aldosterone levels, while aldosterone-renin ratio was normal. These findings confirmed our diagnosis of SIADH with secondary hyperaldosteronism as a compensatory mechanism for hyponatremia. With regard to etiology of the SIADH, there were no hints for medication-related effects or a possible malignant disease. Also, no central nervous affections were found, so we had reason to assume the SIADH to be due to the pulmonary TB. At no point of hospitalization, we had clues for extrapulmonary tuberculosis. Despite antituberculous treatment using directly observed therapy (DOT) from the very beginning, sputum analyses revealed still significant smear-positive TB and cultural results MTB being furthermore multi-sensitive to first-line antituberculotic medication. We excluded interaction with co-medication and confirmed alcohol and tobacco-smoke abstinence. Additionally and pragmatically, we switched antituberculotic treatment from oral to intravenous administration at this point of the hospitalization to exclude malabsorption as a reason for treatment failure.

Due to persisting hyponatremia we started treatment with tolvaptan. Consequently, hydration restriction was stopped. Surprisingly, tolvaptan remained ineffective and was stopped after eight days of unsuccessful treatment.

After five weeks of intravenous antituberculotic therapy, sodium and potassium levels increased and normalized finally in parallel with clinical and radiologic response to the antituberculotic treatment (Fig. 1c, d). Moreover, several consecutive sputum samples were negative for MTB. As a further effect of successful treatment, the patient gained weight (39.4 kg at the end of hospitalization).

The reason for the difficult antituberculotic treatment despite proven multi-sensitivity of MTB may be seen in sub-therapeutic H-levels measured repeatedly during treatment and necessitating dose adjustments. Probably, the patient belongs to a group of fast-acylators (polymorphism of the NAT2-gene). Written consent for further genetic testing was denied. In view of the clinical course, we are convinced that the SIADH was directly attributable to pulmonary TB. As part of follow-up, the patient presented at our hospital three months after discharge, i.e. 7.5 months after first admission. Under continued antituberculotic treatment, there were no signs of infectious pulmonary TB. Sodium and potassium levels were normal without substitution or further specific therapy.

Discussion

Tolvaptan is a nonpeptide, vasopressin V2 receptor antagonist, a new class of pharmaceuticals for treatment of hyponatremia, especially when SIADH-induced [7]. These aquaretics selectively antagonize the antidiuretic effect of vasopressin by competitively binding to renal V2 receptors.

The mechanism of TB-related SIADH is poorly understood. Notably, a correlation between floridity of TB and severity of SIADH has not been examined so far. Thus, it is difficult to conclude unambiguously, why tolvaptan remained ineffective in this case. A probable explanation is drug-interaction of R and tolvaptan. R is a strong inductor of cytochrome P450-dependent monoxygenases (CYP), notably CYP3A4, 1A2, 2C9, 2C8 and 2C18/19 in intestinal epithelium and liver [8]. Tolvaptan is a sensitive CYP3A4 substrate with no inhibitory activity. In healthy subjects, mean maximum concentration Cmax and AUC of tolvaptan were reduced when co-administered with R [9]. Gene polymorphisms of N-acetyltransferase2 (NAT2) are known to cause individual variation in N-acetylation capacity of H. In a study of H pharmacokinetics and pharmacodynamics most homozygous fast acetylators needed a dose twice as high as homozygous slow acetylators to achieve equivalent AUC and 2-hours H serum concentration [10]. Acetylation status has not been described to influence the metabolism of tolvaptan, and CYP3A4 has previously been identified as the only enzyme to be involved in the metabolism of this aquaretic drug [9]. Therefore, it seems unlikely that the reduced effectiveness of tolvaptan is caused by a polymorphism of NAT2.

Conclusion

In this case of TB-related SIADH, tolvaptan remained ineffective. A probable reason is seen in a clinically relevant drug-interaction of rifampicine and tolvaptan. Consequently, dose adjustments of tolvaptan may be necessary when co-administered with R. This would be in agreement with results of a previous trial in healthy volunteers [9]. Further studies on the mechanisms of TB-related SIADH and interactions of antituberculotic and aquaretic drugs in this population are necessary.

Author contributions

All authors planned the work and interpreted the results. H. Knoop, U. Knoop, J.W. Dietrich and J. Behr wrote the article. C.M. Heyer, S.Kuert, D. Roggenland and M. Suermann made substantive suggestions for revision. All authors approved the final version.

Conflict of interest

The authors have no conflict of interest.
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