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Prikaz slučaja
Case report

SECONDARY ADRENAL INSUFFICIENCY IN PATIENT WITH COVID-19 AND HEAD AND NECK CANCER: PITFALLS IN DIAGNOSIS AND TREATMENT

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Syndrome of inappropriate antidiuretic hormone (SIADH) secretion is an endocrinological disorder which occurs when there is an evidence of continued antidiuretic hormone (ADH) secretion in the absence of an appropriate osmotic volume stimulus. Most commonly it is caused by different types of cancer or medications (eg. diuretics, antidepressants, antipsychotics…). Secondary adrenal insufficiency is caused by the insufficient adrenocorticotropic hormone (ACTH) secretion and cortisol production. In the hypocortisolism, the inhibitory mechanism on ADH secretion vanishes causing increased ADH secretion and leading to SIADH-like state. Both conditions, SIADH and hypocortisolism, manifest in euvolemic hyponatremia, however, its cause can be misdiagnosed and result in an inadequate treatment and potentially fatal outcome. Our case is about fifty-seven-year-old male patient who was treated with chemoradiotherapy for hematological malignancy of the oropharynx and who presented with severe hyponatremia several times that almost ended fatally. Considering his malignant disease, patient was diagnosed with SIADH as a cause of hyponatremia and was treated with hypertonic saline fluids and fluid intake restriction. However, after having suffered Covid-19 infection the patient was given glucocorticoids according to the protocol at the time. The sodium levels finally corrected, and the secondary adrenal insufficiency has been declared as the real cause of hyponatremia. SIADH is often thought to be the cause of hyponatremia in patients with malignant disease. However, SIADH represents a diagnosis of exclusion. Before making a final diagnosis, thyroid and secondary adrenal insufficiency must be ruled out. Moreover, secondary adrenal insufficiency imitates SIADH and results in euvolemic hyponatremia but the management and potential outcomes of these two conditions differ significantly. In patients who have been previously treated for malignancies with the treatment options that increase the risk of adrenal insufficiency (chemotherapy, neck or skull base radiotherapy, immunotherapy), adrenal reserve must be evaluated. If introduced, the glucocorticoid therapy should be carefully deescalated in these patients because of the risk of previously unrecognized adrenal insufficiency. This especially applies to conditions that include glucocorticoid therapy in the treatment protocol, such as Covid-19 infection.

Keywords: SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION, ANTIDIURETIC HORMONE, HYPONATREMIA, SECONDARY ADRENAL INSUFFICIENCY, HYPOCORTISOLISM, PLASMACYTOMA, RADIOTHERAPY, SARS COV2 INFECTION, GLUCOCORTICOIDS

Background

Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion is an endocrinological disorder which occurs when there is evidence of continued secretion of antidiuretic hormone (ADH) in the absence of an appropriate osmotic volume stimulus (1). This condition is the most common cause of euvolemic hyponatremia. Diagnosis of SIADH is established if a patient is clinically euvolemic with reduced plasma sodium and osmolality levels, as well as an increased urine osmolality level (greater than 100 mOsm/kg) (1-3). Before establishing the diagnosis of SIADH, it is crucial to exclude renal, adrenal, thyroid or pituitary dysfunction. The most common conditions in which body produces too much ADH are malignant diseases (such as small-cell lung cancer (SCLS), prostate, breast, neuroendocrine tumours), central nervous system diseases (infection, psychosis, mental illness, haemorrhage, trauma, stroke), and respiratory disorders (mechanical ventilation, chest trauma, infection) (3). Numerous drugs are also associated with SIADH, like various antipsychotics, antidepressants, or chemotherapeutic drugs (1, 3, 4). Severity of hyponatremia symptoms depend on the degree and velocity of changes in plasma sodium levels and osmolality and may include weakness, lethargy, confusion, seizures, or even respiratory depression, paralysis, and death (1, 5). Secondary adrenal insufficiency is caused by the insufficient adrenocorticotropic hormone (ACTH) production and cortisol secretion. One of the risk factors for its development is head or neck radiotherapy due to the radiation exposure of surrounding healthy tissues and consequent pituitary insufficiency (5). Normally, corticotropin releasing hormone (CRH) and ADH are both secreted from the same neurons in hypothalamus, and both hormones work synergistically to release ACTH from the adenohypophysis and ADH from the neurohypophysis (6). On the other hand, lack of cortisol increases ADH release to enhance water reabsorption and leads to hyponatremia (1). In this brief case report, we present case of 57-year-old man with severe hyponatremia caused potentially by both conditions.

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Case presentation

A 57-year-old patient presented with symptoms of nasal congestion. He was examined by an otorhinolaryngologist who noticed a polypoid lesion in the left nasal cavity. Shortly after, the multislice computed tomography (MSCT) of oropharynx and paranasal cavities was performed and revealed an obliteration of the nasopharynx with a solid lesion measuring 2.9 x 2.0 x 2.5 cm that was characterized as a possible adenoid vegetation (Figure 1). To obtain a tissue sample, a biopsy was performed, and the tissue was characterized as the extramedullary plasmacytoma. Hematologic evaluation excluded bone marrow infiltration with clonal plasma cells and end organ damage that could be attributed to symptomatic multiple myeloma.

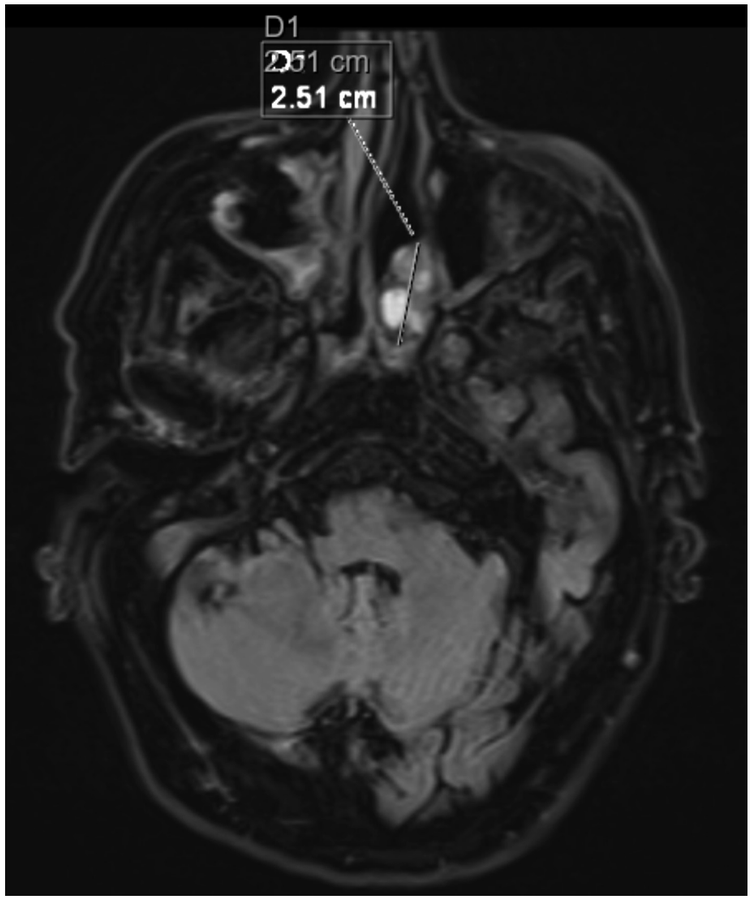

Figure 1.
The nasopharynx obliterated by contrast-enhanced soft tissue formation caudally extends to the initial part of the oropharynx, i.e. in contact with the uvula, and through the left hoana protrudes into the left lower nasal passage and measures approximately 2.9 x 2 x 2.5 cm. The formation obliterates both lateral pharyngeal recesses.

The patient was diagnosed with solitary plasmacytoma according to IMWG (International Myeloma Working Group) criteria (7). The patient was treated with local radiotherapy (nasopharynx and skull base) and received 46 Gy in 23 fractions over a period of two months. Retrograde insight into the medical records revealed that after radiotherapy, mild hyponatremia (Na=130 mmol/l) accompanied with lower blood pressure was noticed probably due to the unrecognized, secondary (post-radiation) adrenal insufficiency. Two months after radiotherapy a positron emission tomography-computed tomography (PET CT) was performed and revealed a highly fluorodeoxyglucose (FDG) avid (SUVmax=24.9) residual tumour tissue in epipharynx. Due to residual disease a chemotherapy treatment according to VCD (bortezomib, cyclophosphamide and dexamethasone) protocol was started. Unfortunately, on the day of the second application of chemotherapy symptomatic, severe hyponatremia occurred (Na=109 mmol/L) and the patient was admitted to the Department of Haematology during the weekend, where he was shortly treated with hypertonic saline infusion. Two days later, the patient insisted on leaving the hospital at his own request. After missing third cycle of chemotherapy, the hospital staff called the patient multiple times (without answering) and then decided to call the firemen to check his home. After broking into his house, the firemen found the patient unconscious. He was brought to the hospital and admitted to the Intensive Care Unit because of the central respiratory insufficiency and coma caused by severe hyponatremia (Na=103 mmol/L). Severe and symptomatic hyponatremia was corrected gradually with 3% sodium chloride (NaCl) infusion by the protocol. An emergency CT scan of the brain was done and excluded brain pathology. Shortly after hospitalization, the patient acquired SARS CoV-2 pneumonia and was transferred to COVID department

for 8 days. After manifestation of severe hyponatremia, haematologists decided to postpone chemotherapy treatment due to the complications he developed and severe hyponatremia considered to be a consequence of active malignancy and/or use of chemotherapy. In COVID Department, the pneumonia was treated with high daily doses of methylprednisolone (125 mg) among other drugs. After improvement of the general condition, the patient was discharged with high doses of glucocorticoids and advised on gradual weekly dose deescalation (starting from 25 mg of dexamethasone orally). One month after being discharged from the hospital, the patient was found unconscious at home again. He was hospitalized for severe hyponatremia (Na=111 mmol/L). The patient stopped taking glucocorticoid therapy 10 days before the hospitalization, and during the period he had been taking dexamethasone regularly, he was feeling well. At the Department of Haematology PET-CT scan was repeated and showed total regression of the plasmacytoma but showed enhanced 18F-FDG accumulation in the rectosigmoid colon. Colonoscopy was performed and rectal exulcerated polypoid lesion was found that was later confirmed as adenocarcinoma. He was then transferred from the Department of Haematology and admitted to the Department of Endocrinology, Diabetology, and Metabolic disease for hyponatremia correction. Substitutional therapy with hydrocortisone was initiated and a couple of days later normonatremia was achieved. A brain MRI was also done which excluded brain pathology. Function of other pituitary cells was not impaired. Six months after discharge from the hospital, Synacthen test was performed and confirmed persistent adrenal insufficiency (basal cortisol level was 179.4 nmol/L and after 60 minutes 393.2 nmol/L).

Conclusion

Our patient developed mild and unrecognized secondary adrenal insufficiency caused by radiation of the skull base field and potentially chemotherapy, but because of his malignant disease SIADH was suspected as a cause. After suffering COVID-19 pneumonia patient received high doses of glucocorticoids that corrected sodium levels but were discontinued abruptly later which damaged already impaired adrenal reserve. This led to severe, symptomatic hyponatremia which was again inappropriately diagnosed as SIADH. However, hyponatremia in this case was due to unrecognized secondary adrenal insufficiency. Both times patient presented with severe symptoms, was hospitalized, and treated with 3% NaCl infusions. Hyponatremia completely resolved only after glucocorticoid therapy was initiated. Cancer patients with hyponatremia are often diagnosed with SIADH (because of chemotherapy, radiation, or malignant disease itself). However, it must be taken into consideration that SIADH is a diagnosis of exclusion. Before making a final diagnosis, thyroid and adrenal insufficiency must be ruled out. Moreover, adrenal insufficiency itself results in the state of "inappropriate ADH secretion" causing water retention and dilutional hyponatremia. The easiest way to distinguish these two conditions is to evaluate adrenal reserve. Secondary adrenal insufficiency is a diagnosis that is often unrecognized and untreated can lead to death. This is the reason why glucocorticoid therapy shouldn't be discontinued abruptly in patients diagnosed with Covid-19 pneumonia and at risk of developing adrenal insufficiency.

Abbreviations:

SIADH - syndrome of inappropriate antidiuretic hormone
ADH - antidiuretic hormone
ACTH - adrenocorticotropic hormone
CRH - corticotropin releasing hormone
MSCT - multislice computed tomography
PET CT - positron emission tomography-computed tomography
MRI - magnetic resonance imaging
VCD - protocol (bortezomib, cyclophosphamide and dexamethasone protocol)
NaCl - sodium chloride
IMWG - International Myeloma Working Group

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Sažetak

SEKUNDARNA ADRENALNA INSUFICIJENCIJA KOD PACIJENTA S COVID-19 INFEKCIJOM TE TUMORSKOM TVORBOM GLAVE I VRATA: ZAMKE U DIJAGNOSTICI I LIJEČENJU

Višnja Kokić Maleš, Paula Radić, Tanja Miličević Milardović, Viktor Blaslov

Sindrom neodgovarajućeg izlučivanja antidiuretskog hormona (SIADH) je endokrinološki poremećaj koji nastaje kada postoji kontinuirano lučenje antidiuretskog hormona (ADH) u odsutnosti odgovarajuće osmotske stimulacije. Najčešći uzrok SIADH u kliničkoj praksi su tumori ili primjena lijekova (diuretici, antidepresivi, antipsihotici…). Sekundarna adrenalna insuficijencija je uzrokovana nedovoljnom produkcijom adrenokortikotropnog hormona i posljedično kortizola. U stanju hipokortizolizma gubi se inhibitorni utjecaj kortizola na lučenje ADH te posljedično dolazi do pojačanog lučenja ADH što u svojoj osnovi imitira SIADH. Oba entiteta se prezentiraju euvolumnom hiponatremijom, ali njezin pravi uzrok može biti pogrešno dijagnosticiran što u konačnici može rezultirati neadekvatnim liječenjem i lošim ishodom. Naš prikaz slučaja je o pedesetsedmogodišnjem muškarcu koji je liječen kemoradioterapijom zbog hematološkog maligniteta u području orofarinksa. a koji se u više navrata prezentirao teškom hiponatremijom s prijetećim smrtnim ishodom. Uzimajući u obzir onkološku bolest, pacijentu je kao uzrok hiponatremije postavljena dijagnoza SIADH te je liječen hipertoničnim otopinama NaCl i restrikcijom unosa tekućine. Bolesniku je nedugo zatim dijagnosticirana COVID-19 infekcija te je po tadašnjem protokolu, među ostalim, započeto liječenje glukokortikoidima. Uz ovu terapiju došlo je do korekcije vrijednosti serumskog natrija pa je kao uzrok hiponatremije potvrđena, do tada neprepoznata, sekundarna adrenalna insuficijencija. Iako je SIADH najčešći uzrok euvolumne hiponatremije u bolesnika s malignom bolešću, treba imati na umu da je SIADH ipak dijagnoza isključivanja. Svakako je potrebno prethodno isključiti hipotireozu i sekundarnu adrenalnu insuficijenciju kao moguće uzroke. Sekundarna adrenalna insuficijencija nalikuje SIADH po kliničkoj prezentaciji, ali liječenje i ishodi ova dva stanja su različiti. Adrenalnu rezervu potrebno je evaluirati kod bolesnika s malignom bolešću, naročito ukoliko su liječeni nekom od terapijskih opcija koja povećava rizik nastanka adrenalne isuficijencije (kemoterapija, zračenje vrata ili baze lubanje, imunoterapija). Ako su ovim bolesnicima iz nekog razloga u terapiju uvedeni kortikosteroidi, ukoliko se javi potreba za prekidom terapije, dozu kortikosteroida je potrebno postepeno i oprezno reducirati te procijeniti adrenalnu rezervu, naročito ukoliko postoji rizik podležeće, neprepoznate adrenalne insuficijencije. Ovo naročito treba imati na umu ukoliko se radi o bolestima/stanjima koje u svom protokolu liječenja uključuju primjenu kortikosteroida, kao što je Covid-19 infekcija.

Ključne riječi: SINDROM NEPRIMJERENOG LUČENJA ANTIDIURETSKOG HORMONA, ANTIDIURETSKI HORMON, HIPONATREMIJA, SEKUNDARNA ADRENALNA INSUFICIJENCIJA, HIPOKORTIZOLIZAM, PLAZMOCITOM, RADIOTERAPIJA, SARS COV2 INFEKCIJA, GLUKOKORTIKOIDI

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