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RENAL SALT WASTING SYNDROME ET CAUSA CISPLATIN INDUCED

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Abstract

This study examines the nephrotoxic effects of cisplatin, a platinum antineoplastic agent widely used in cancer treatment. Despite its efficacy against malignancies, cisplatin can induce apoptosis in the proximal tubule of the nephron, leading to a reduction in the glomerular filtration rate. The primary focus of this research is on hyponatremia as a potential side effect, with inappropriate antidiuretic hormone secretion syndrome (SIADH) and Renal Salt Wasting Syndrome (RSWS) being the main mechanisms. A case of RSWS is reported in a 34-year-old adult male following cisplatin chemotherapy for osteosarcoma *cruris sinistra*. Understanding the pathophysiological distinctions between SIADH and RSWS is crucial for proper management, as errors in diagnosis and therapy can exacerbate the patient's condition. RSWS therapy involves restoring intravascular volume through oral and intravenous fluids, along with correcting hyponatremia with saline. The patient demonstrated improvement after 12 days of treatment, offering valuable insights for similar conditions in patients undergoing cisplatin chemotherapy.

Keywords: Renal Salt Wasting Syndrome, Cisplatin-Induced Nephrotoxicity, Hyponatremia in Cisplatin Therapy.

INTRODUCTION

Cisplatin, a potent antineoplastic agent derived from platinum, is commonly utilized in treating head and neck malignancies and bladder, ovarian, testicular, and other solid tumours. Approximately 20% of all cancer patients receive platinum-based chemotherapy. Despite its high effectiveness, cisplatin is nephrotoxic, causing apoptosis in the proximal tubule of the nephron and decreasing the glomerular filtration rate. Nephron injury results in inflammation, reducing medullary blood flow and causing additional ischemic damage to tubular cells. Since the proximal tubule reabsorbs 67% of sodium, cisplatin-induced nephron injury can lead to hyponatremia (Russo et al., 2021).

The primary mechanism of cisplatin chemotherapy-induced hyponatremia involves the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and renal salt wasting syndrome (RSWS). Despite their similar presentations, these diagnoses require distinct therapeutic management due to pathophysiological differences. Misdiagnosis and inappropriate therapy can exacerbate the patient's condition (Russo et al., 2021).

Renal salt wasting is defined as decreased extracellular volume (ECV) due to abnormalities in renal sodium transport, presenting with hyponatremia, increased sodium concentration (UNa), and, in some cases, brain abnormalities while maintaining normal adrenal and thyroid function (Maesaka et al., 2009). The following section presents a case of RSWS induced by cisplatin chemotherapy in a 34-year-old adult male.

CASE

The patient, named IWEPP, a 34-year-old male, presented to the hospital with the primary complaint of a lump on the left leg that had been increasing in size since December. The lump initially appeared in August without pain but became painful in early December. The patient had previously been diagnosed with osteosarcoma *cruris sinistra* and experienced weakness and decreased consciousness after undergoing chemotherapy. Additionally, the patient reported symptoms of delirium, nausea, and frequent urination (BAK) following chemotherapy, accompanied by excessive thirst. The past medical history includes diabetes since 2020 with Metformin therapy. The patient has a social history as an entrepreneur and no history of alcohol consumption. Upon physical examination, the patient exhibited somnolence, with blood pressure measured at 100/60 mmHg, a pulse rate of 90 beats per minute, respiratory rate of 18 breaths per minute, a temperature of 36 ºC, and oxygen saturation at 98%. Local examination of the left *cruris sinistra* revealed swelling, *venectasis*, and limited range of motion (ROM).

RESULTS AND DISCUSSION

1. Hematology Laboratory Examination

The initial complete blood examination showed the results as shown in table 1.

Table 1: Complete Blood Examination Results

Parameter	01/12/2022	06/12/2022	Reference Value
WBC (10^3/µL)	11.23	8.52	4.1- 11.0 x 10^3/µL
% Neu	76.30	86.80	47 – 80%
% Lym	13.90	9.40	13 - 40 %
% Mono	6.50	3.30	2.0 – 11.0 %
% Eos	2.90	0.40	0.0 - 5.0 %
% Baso	0.40	0.10	0.0 – 2.0 %
RBC (10^6/µL)	4.64	4.08	4.50 – 5.9 x 10^6/µL
HGB (g/dL)	12.80	11.40	13.5 – 17.5 g/dL
HCT (%)	39.10	32.50	41.0- 53.0%
MCV (fL)	84.30	79.70	80.0 – 100.0 fl
MCH (pg)	27.60	27.90	26.0 - 34.0 pg
MCHC (g/dL)	32.70	35.10	31 - 36 g/dL
RDW (%)	12.70	11.90	11.6 – 14.8 %
PLT (10µ/µL)	398.0	332.0	150 - 440 10^3/µL
MPV (fL)	9.10	9.30	6.80-10.0 fl

2. Clinical Chemistry and Immunology Laboratory Examination

Table 2: Clinical Chemistry Examination Results

Parameter	01/12/22	06/12/22	07/12/22	08/12/22	09/12/22	Reference Value
Sodium (mmol/L)	134	114	112	115	114	136 – 145
Potassium (mmol/L)	3.73	3.51	-	3.04	2.75	3.50 - 5.10
BUN (mg/dL)	5.60	5.40	-	-	-	8 – 23
Serum Creatinine (mg/dL)	0.49	0.64	-	-	-	0.72 – 1.25
eGFR	142.57	127.75	-	-	-	>= 90
Momentary glucose (mg/dL)	179	130	135	-	-	70 – 140
SGOT (U/L)	24.8	-	-	-	-	5 – 34
SGPT (U/L)	62.3	-	-	-	-	11–50
Plasma osmolality	-	230.18	-	-	-	280-295

Table 3: Clinical Chemistry Examination Results (Continued)

Parameter	10/12/22	11/12/22	12/12/22	Reference Value
Sodium (mmol/L)	122	128	127	136 – 145
Potassium (mmol/L)	3.19	-	-	3.50 - 5.10
BUN (mg/dL)	17	-	10.7	8 – 23
Serum Creatinine (mg/dL)	0.78	-	0.68	0.72 – 1.25
eGFR	117.77	-	124.60	>= 90
Momentary glucose (mg/dL)	204	-	154	70 – 140
Uric acid (mg/dL)	5.15	-	3.60	3.5-7.2
Plasma osmolality	253.32	-	257.59	280-295

Table 4: Hba1c examination results

Parameter	3/11/2022	Reference Value
HbA1c	8.3	< 6.5%

Table 5: Results of Thyroid Function Examination

Parameter	11/12/2022	Reference Value
FT4	1.59	0.7 – 1.58 ng/dL
TSHs	0.62	0.27 – 4.20 uIU/mL

3. Urinalysis and Urine Osmolality Laboratory Examination

Table 6: Urinalysis Examination Results

Parameter	11/12/2022	Unit	Reference Value
Specific gravity	1.014		1.003-1.035
Turbidity	Clear		
pH	6.50		4.5-8
Leukocytes	Negative	Leuko/uL	Negative
Nitrite	Negative	mg/dL	Negative
Proteins	Negative	mg/dL	Negative
Glucose	Negative	mg/dL	Negative
Ketones	Negative	mg/dL	Negative
Blood	Negative	ery/uL	Negative
Urobolinogen	Normal	mg/dL	Normal
Bilirubin	Negative	mg/dL	Negative
Color	Yellow		Yellow
Urine sediment	:		
Bacteria	58.30	u/L	≤ 26.4
Sedimentary Leukocytes	0	/LPB	≤ 2
Sediment Erythrocytes	1	/LPB	≤ 2
Sedimentary Epithelial Cells	2	/LPB	≤ 1

Table 7: Results of Urine Osmolality Examination

Parameter	08/12/22	10/12/22	12/12/22	Reference Value
Body fluid glucose (mg/dL)	-	1	9	1 – 15
Urine urea nitrogen (UUN) (mg/dL)	-	257.4	352.8	
24 hour urine sodium (mmol/24 hours)	487.85	166.84	94.60	40– 220
24-hour urine potassium (mmol/24 hours)	-	53.45	27.54	25 – 100
24 hour urine volume (ml/24 hours)	5500	4300	2200	
24 hour uric acid (g/24 hours)	-	0.90	0.71	0.25-0.75
24 hour urine creatinine (mg/24 hours)	-	736.59	824.34	980-2200
Urine osmolality	-	194.99	250.66	500-800
Feurat (%)	-	18.5	16.2	< 10

4. Radiological Examination

a. Photo Left legAP/Lat (25/10/2022)

Impression: Osteolytic lesion permeative expansion on left metaphysis bone clasp impressive primary malignant bone tumor, susp. Osteosarcoma

b. Photo Femur Sinitra AP/Lat (25/10/2022)

Effect:

- Currently there are no visible bone fractures or joint dislocations in the region left femur
- Osteolytic lesions in trochanter mayor you left femur, susp. MBD

c. Photo Genu Sinistra AP/Lat (25/10/2022)

Impression: Osteolytic lesion permeative expansion at the Meta diaphysis you left fibula impressive primary malignant bone tumor, susp. osteosarcoma

d. MRI Leg S (09/11/2022)

Support image primary malignant bone tumor dd/ osteosarcoma on intramedullary epi-meta-diaphyseal 1/3 proximal os fibula sinistra accompanied soft tissue mass surrounding large ones, with osteoid calcified matrix, which extends to the popliteal region, anterior compartment, lateral,superficial and deep posterior as well as encase the medial 1/3 of the left tibia, infiltrate lateral and medial head

m. gastrocnemius, m. plantaris, m. popliteus, m. soleus, m. tibialis anterior dan posterior, m. extensor digiti longus, m. fibularis longus, m. extensor hallucis longus, m. flexor digitorum longus, m. flexor hallucis longus, dan m. short collar, encase the neurovascular bundle.. -Skip lesion from bone marrow replacement on aspects medial metaphysis 1/3 proximal of tibia sinistra.

5. PA check

Conclusion: Left proximal fibula, core biopsy:

Histomorphology is suitable for Conventional Osteosarcoma (Osteoblastic type)

Table 8: Observation of Fluid Balance

	9/12/2022	10/12/2022	11/12/2022
Inlet fluid (ml)	4750	4300	3100
Urine production (ml)	4800	4300	2200
IWL (ml)	630	630	630
Fluid balance (ml)	-680	-630	+270

B. Working Diagnosis

1. Renal salt wasting syndrome et causa Cisplatin induced
2. Primary bone tumor at left proximal tibia ec Osteosarcoma stadium advance stage
    - Cancer pain
    - Post Chemotherapy Cisplatin-Doxorubicin
3. DM type 2

C. Therapeutic Management

1. IVFD NaCl 0.9% adjusts fluid balance
2. Cisplatin 120/mg/m2 give intravenously in 250 cc NaCl 0.9% for 4 hours (204 mg)
3. Doxorubicin 25 mg/m2 give intravenously in 250 cc cc 0.9% NS for 24 hours for 3 days
4. Drip KCl 25 meq
5. Metformin 1 x 500 mg per oral
6. MST 10 mg every 8 hours orally

DISCUSSION

Renal salt wasting (RSW) is defined as a decrease in extracellular volume due to abnormalities in renal sodium transport. It is characterized by hyponatremia with increased urinary sodium concentration (UNa), with or without brain abnormalities, along with normal adrenal and thyroid function (Maesaka et al., 2009).

In this case, the patient underwent cisplatin chemotherapy on 3/12/2022 and received doxorubicin for three consecutive days from 3-5 December 2022. Three days after the first chemotherapy session (6/12/2022), the patient experienced weakness and decreased consciousness and reported an increase in urination frequency to 10 times per day, along with a urine volume increase of 4 litres per day.

The initial laboratory examination on admission showed sodium levels of 134 mmol/L and potassium levels of 3.73 mmol/L. Post-chemotherapy revealed a decrease in sodium to 114 mmol/L (hyponatremia) and potassium to 3.51 mmol/L.

Electrolyte imbalance, notably hyponatremia, is a common condition observed in patients undergoing chemotherapy, particularly with cisplatin. Rhoney et al. (2006) reported hyponatremia as the most prevalent electrolyte disturbance. Abnormal electrolyte levels, particularly sudden changes, are often associated with symptoms, such as seizures, especially in patients with hyponatremia, hypocalcemia, and hypomagnesemia (Castilla-Guerra et al., 2006).

Hyponatremia, defined as a plasma sodium level <135 mmol/L, can be categorized as mild, moderate, or severe based on sodium levels. Depending on the onset time, it can also be classified as acute or chronic. Acute hyponatremia occurs rapidly (within 48 hours), while chronic hyponatremia develops slowly (more than 48 hours). In cases where the timing cannot be determined, hyponatremia is considered chronic unless clinical evidence indicates otherwise (ERBP, 2015).

Clinical manifestations of hyponatremia vary widely, ranging from asymptomatic to severe or life-threatening conditions. Acute hyponatremia is associated with more severe symptoms like nausea, vomiting, headache, confusion, somnolence, seizures, and coma. In this case, the patient exhibited a decrease in consciousness and delirium, possibly attributed to brain cell oedema resulting from the movement of water into cells with higher osmolarity. Cerebral edema and herniation are the main dangers of acute hyponatremia, typically occurring when sodium values fall to approximately 115 mmol/L or lower. In contrast, chronic hyponatremia tends to present with milder

symptoms, such as being asymptomatic, weak, or drowsy (Castilla-Guerra et al., 2006; ERBP, 2015).

Three basic mechanisms contribute to hyponatremia: inability to excrete excess water, loss of large amounts of sodium, or inadequate sodium intake. Early cause identification involves checking plasma osmolality and determining the patient's volemic status (ERBP, 2015; Vale et al., 2015).

Plasma osmolality examination aims to establish whether the patient is hypotonic, isotonic, or hypertonic. Osmolality is calculated using the formula (Scott et al., 2012; Martin-Calderon et al., 2015):

$$Osmolalitas\ plasma = 1{,}86\ (Na\ \frac{mmol}{L}) + \frac{glukosa\ (\frac{mg}{dL})}{18} + \frac{Urea\ (\frac{mg}{dL})}{2{,}8} + 9$$

Hypotonic hyponatremia is called if plasma osmolality is <280 mOsm/kg. Isotonic hyponatremia occurs when plasma osmolality is 280 – 295 mOsm/kg. Hypertonic hyponatremia occurs when plasma osmolality is > 295 mOsm/kg (Desai, 2004).

If hypotonic hyponatremia is found, the examination also needs to be continued by measuring urine osmolality. Urine osmolality is used to evaluate the kidney's ability to concentrate and discuss urine. Urine osmolality was calculated using the formula (Millionis et al., 2002; Paganand Pagana, 2018).):

Apart from its tonicity, hyponatremia must also be differentiated based on the patient's *volemic* status, namely hypovolemic, *euvolemic* or *hypervolemic*. Each *volemic* status has different possible causes. Table 9 explains the signs found during the physical examination to help determine the patient's *volemic* status (Desai, 2004).

Table 9: Physical Examination Findings for Determining Patient *Volemic* Status (Desai, 2004)

Mark found	*Volemic* status of the patient
1. Changes in blood pressure and heart rate due to orthostatic influences 2. Dry mucous membranes 3. Decreased skin turgor 4. Flat jugular vein 5. Reduced sweating	Hypovolemic

In this case, from the anamnesis and physical examination it was discovered that the patient experienced decreased consciousness, polyuria, slightly decreased blood pressure and negative fluid balance observations. These symptoms and signs indicate a hypovolemic condition in the patient. Apart from that, the results of the plasma osmolality examination when the patient experienced hyponatremia for the first time (6/12/2022) was 230.18 mOsm/kg, which indicated that the patient was in a hypotonic condition. So, the patient has a condition of hypotonic hypovolemic hyponatremia.

In hypovolemic conditions, the causes of hyponatremia are divided into renal and extrarenal causes. Renal causes include diuretic therapy, osmotic diuresis (glucose, mannitol), mineralocorticoid deficiency, ketonuria, and cerebral/renal salt wasting syndrome. Extrarenal causes are loss of fluid from the gastrointestinal tract, skin, and third-space loss (intestinal obstruction, peritonitis, burns) (Desai, 2004).

The mechanism of cisplatin-induced RSW is that cisplatin damages the proximal tubule, the main site of sodium and water reabsorption, causing natriuresis, with increased urine output and urinary sodium. RSWS is relatively rare, it is not known whether it is associated with a low incidence or underdiagnoses of this syndrome. Vassal et al reported an incidence of 1%, while Hutchison et al reported 10%. RSWS can be detected 12 hours to 1 month after administration of cisplatin. The dose of cisplatin used ranges from less than 200 mg/m2 to 600 mg/m2 (Russo et al, 2021).

RSWS and SIADH need to be differentiated carefully because there are several similar symptoms and signs, but have different management. Diagnosis can be made based on evaluation and monitoring of sodium levels, water loss (water loss), and extracellular fluid volume. The main difference between RSWS and SIADH is the sum of plasma volume and urine volume. RSWS is characterized by low plasma volume (hypovolemic), with symptoms of dehydration, hyponatremia with low serum osmolality, and increased urine volume. In contrast, in SIADH, sufficient or high plasma volume (euvolemic or hypervolemic) is found with low plasma osmolality and normal urine volume. Table 1 shows the differences in characteristics between RSWS and SIADH (Zieg, 2014).

Table 10: Differences between RSWS and SIADH (Zieg, 2014; Kulkarni, 2016)

	RSWS	SIADH
State volume	Hypovolemia	Euvolemia, or hypervolemia
Water balance	Negative	Increased or normal
Signs of dehydration	There is	There isn't any
Urine volume	Increase	Decreased or normal
Urine sodium	Increase	Increase
Initial FEUA	Increase	Increase
FEUA after sodium correction	Increase	Normal
Therapy	Giving fluids	Fluid restrictions

In RSWS and SIADH patients, a decrease in uric acid levels (hyperuricemia) will be found. In RSWS, hyperuricemia occurs due to disturbances in the proximal tubule of the kidney, while in SIADH it is caused by expansion of fluid volume. However, these two conditions can be distinguished by FEUA calculations after sodium correction. FEUA is the uric acid excretion fraction, which can be calculated using the formula below. FEUA is said to have increased if the value is more than 10%. In RSWS, FEUA will remain elevated after sodium correction is carried out, whereas in SIADH, FEUA will become normal (Maesaka et al., 2009; A million et al., 2002; Russo et al., 2021).

$$FEUA\ (\%) = \frac{Urat\ urine\ x\ kreatinin\ plasma}{Urat\ plasma\ x\ kreatinin\ urin}\ x\ 100$$

The flow of examinations to help determine the cause of hyponatremia in this patient is shown in Figure 1.

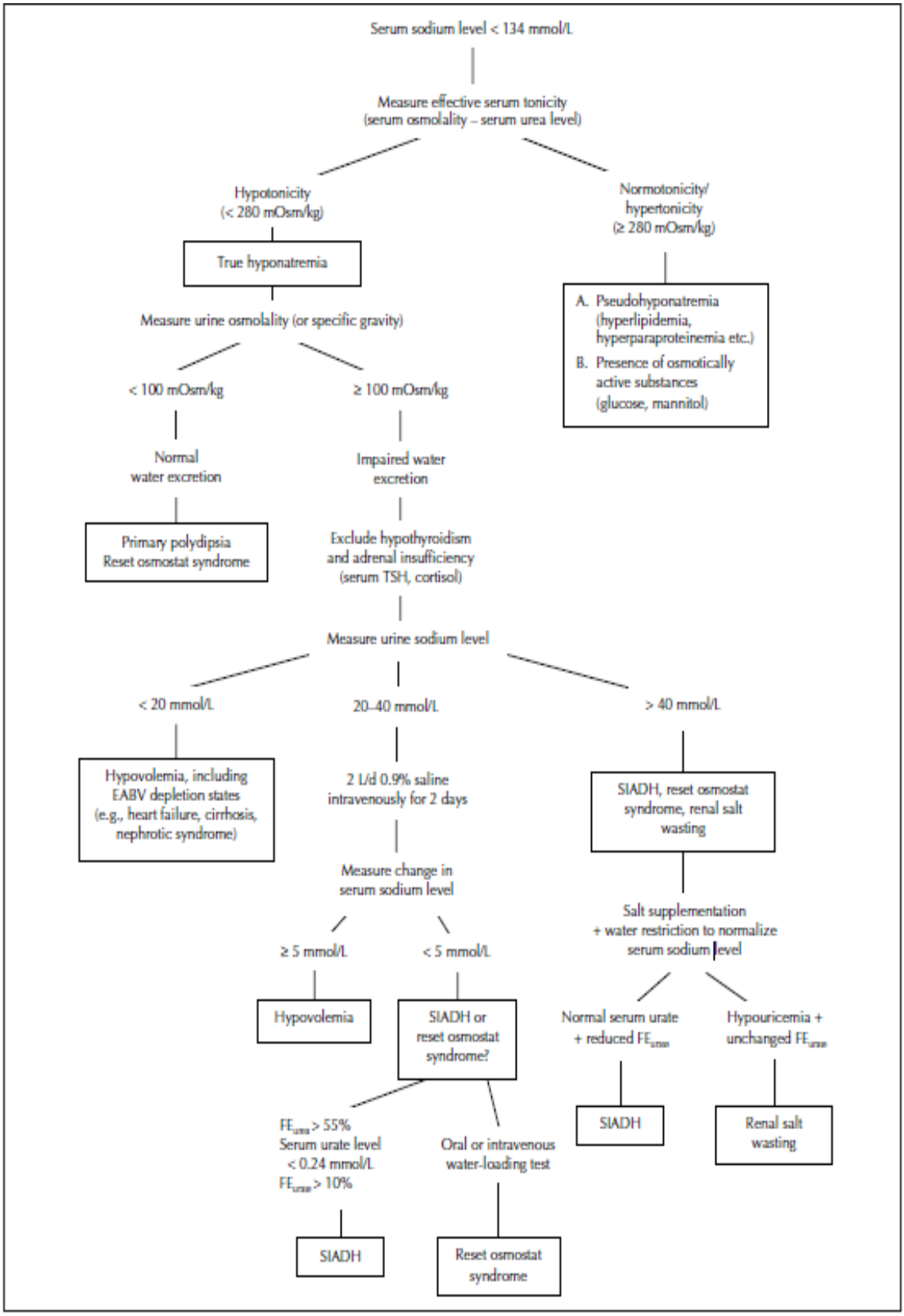

Fig. 1: Clinical diagnostic algorithm for hyponatremia. TSH = thyroid-stimulating hormone, EABV = effective arterial blood volume, SIADH = syndrome of inappropriate secretion of antidiuretic hormone, FE = fractional excretion.

Figure 1: Hyponatremia examination flow (Milionis et al., 2002)

Based on the flow in Figure 1, this patient's condition is more in line with the diagnosis of RSWS than SIADH. The patient's physical examination showed signs of intravascular fluid depletion, such as slightly decreased blood pressure and balanced negative fluid. The initial hematology laboratory examination showed results within normal limits. The results of the clinical chemistry laboratory examination after receiving chemotherapy results showed electrolyte imbalance in the form of hyponatremia (Na 114 mmol/L).

Plasma osmolality in this patient decreased (230.18 mOsm/kg). This condition shows the condition of true hyponatremia. Furthermore, the patient also had urine osmolality checked, with a result of 194.99mOsm/kg (>100 mOsm/kg). After chemotherapy, the patient experienced hypokalemia. The cause of hypokalemia could be due to low intake, or it could be because of renal loss. In this patient, the results of the urine potassium examination were still within normal limits. However, the urine potassium examination was carried out when the plasma potassium level had gradually improved (3.19 mmol/L), so the suspected cause of hypokalemia in this patient could be renal loss or low intake. The patient's uric acid, BUN and creatinine examination results were within normal limits. BUN and creatinine results within normal limits rule out kidney disease in the patient. Patients with a history of type 2 DM. The average blood glucose test results were within normal limits, but the patient's Hba1c test results increased (8.3%).

The patient's urinalysis results were still within normal limits. Then, the patient was also checked for thyroid function, with the results of the patient's TSH and FT4 examinations still within normal limits so that the possibility of hyponatremia due to hypothyroidism could be ruled out. Cortisol testing was not performed, which aims to exclude the possibility of adrenal insufficiency. From the 24-hour urine sodium examination, it was found to be 487.85 mmol/24 hours, and the urine volume was 5.5 L, so the urine Na was found to be 88.7 mmol/L (> 40 mmol/L). The FEUA examination was carried out twice; it was found that the FEUA increased by 18.5% and 16.2% when the sodium levels improved. Based on this flow, the condition experienced by the patient indicates renal salt wasting syndrome (RSWS).

Therapy in RSWS aims to restore intravascular volume with oral and intravenous fluids. Salt tablets may help maintain sodium sources in patients with suboptimal oral intake. In patients with hypovolemia, the first management is the administration of intravenous fluids with normal saline to achieve adequate intravascular volume. Then, correction of hyponatremia is carried out using saline solution, especially if serum sodium reaches a value <125 mEq/L.

Replacement therapy should be carried out slowly to avoid further complications, such as pontine myelinolysis. The increase in serum sodium should not be more than 0.7 mEq per litre per hour, and the maximum daily change should be no more than 20 mEq per litre. Another therapy that can increase serum sodium and intravascular volume is mineralocorticoids, such as fludrocortisone. The appropriate time for administering fludrocortisone is still tricky in clinical application. The recommended dose is 0.1 to 1 mg/day. This drug will stimulate sodium and water reabsorption in the distal tubule, thereby helping to increase extracellular fluid volume. This drug is recommended several days after the diagnosis, and fluid and sodium replacement therapy has been carried out well. However, it still does not provide satisfactory

results. RSWS usually improves after 3 days to 3 weeks (Hamdi et al., 2010; Pearl et al., 2010).

In accordance with this theory, during treatment, this patient received 0.9% NaCl infusion fluid therapy (isotonic fluid), with the amount adjusted to the daily fluid balance to achieve a state of euvolemia. The patient was not given mineralocorticoids because sodium levels had been improved by administering 0.9% Nacl fluid. The patient was given a KCl drip to correct hypokalemia. For DM therapy, this patient was given metformin 1 x 500 mg according to the patient's usual therapy. To reduce pain complaints, patients are given MST orally. Clinicians also perform serial monitoring of electrolytes throughout treatment. After 12 days of treatment, the patient's condition gradually improved and stabilized; the sodium level approached normal. Finally, the patient was sent home and advised for control at the internal medicine and orthopedics clinic.

CONCLUSION

One case of an adult male with the diagnosis has been reported renal salt wasting syndrome (RSWS) after administration of chemotherapy (cisplatin).Renal salt wasting syndrome is a condition of hypovolemic hypotonic hyponatremia and needs to be differentiated from SIADH for appropriate management. After 12 days of treatment, the patient's condition gradually improved and stabilized, the sodium level approached normal, and finally the patient was sent home and advised for control at the internal medicine and orthopedics clinic.

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