Cisplatin-induced Acute Hyponatremia Leading to A Seizure and Coma: A Case Report

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We report a rare case of cisplatin-induced acute hyponatremia leading to a seizure and coma. A 66-year-old woman with breast cancer received adjuvant chemotherapy with docetaxel and cisplatin. She had no nausea, vomiting, or diarrhea during or after chemotherapy administration. She had an acute onset of a generalized seizure and coma on the fourth day after chemotherapy. On arrival in the emergency department, she was unconscious with a Glasgow Coma Score of 6 (eyes 1, verbal 1, motor 4). Computed tomography of the brain did not show any lesions. She had no underlying diseases except breast cancer. The laboratory studies showed severe hyponatremia (Na 113 mmol/L) with low plasma osmolality, and elevation of both urinary sodium and urinary osmolality. In addition, polyuria (about 4 L/day) was also noted. Her consciousness level gradually improved the next day with a rise in serum sodium after 3% NaCl infusion. She recovered fully with no sequelae. Assessment using the Naranjo probability scale suggested that cisplatin was the probable cause for the adverse event. The mechanism of hyponatremia induced by cisplatin in our case was thought to be renal salt wasting syndrome (RSWS). In conclusion, cisplatin-induced acute hyponatremia leading to seizures and coma is seen rarely. When RSWS is suspected, hypertonic saline should be administered. *(Chang Gung Med J 2011;34(6 Suppl):48-51)*

Key words: cisplatin, hyponatremia, seizure, coma, renal salt wasting syndrome

Cisplatin is one of the most widely used agents in cancer treatment. Cisplatin regimens can lead a more or less pronounced hyponatremia in 4 to 10% of cases.[1] Severe hyponatremia is usually grave if a correct diagnosis is not made and proper treatment is not given in time. We report a patient with acute hyponatremia leading to a seizure and coma the fourth day after cisplatin-based chemotherapy. The patient was treated with a sodium supplement and recovered fully without sequelae.

CASE REPORT

A 66-year-old postmenopausal woman was diagnosed with estrogen- and progesterone-receptor positive, human epidermal growth factor receptor 2-negative breast cancer (invasive ductal carcinoma, T2N2M0, stage IIIA). She was treated with a modified radical mastectomy and received 6 cycles of adjuvant chemotherapy with cyclophosphamide/epirubicin/5-fluorouracil. Afterwards she was admitted to our hospital for her first cycle of another regimen of adjuvant chemotherapy (docetaxel 70 mg/m^2 on day 1 and cisplatin 50 mg/m^2 on day 2). She denied nausea, vomiting, abdominal pain, and diarrhea during hospitalization. She was discharged on schedule in stable condition.

However, the patient complained of intermittent

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dizziness and malaise at home. She still had a normal appetite and fair food intake, and neither vomiting nor diarrhea occurred. She had acute onset of a generalized seizure for about 2 minutes and could not be awakened the evening of the fourth day after cisplatin administration. She was sent to our emergency department.

The patient was afebrile, her vital signs were stable, and she had a Glasgow Coma Score of 6 (eyes 1, verbal 1, motor 4). Neurological examination revealed a severely confused woman without any focal defects. Computed tomography of the brain did not show any lesions. She had no underlying diseases except breast cancer. The laboratory studies showed a normal leukocyte count of 5.0 x 10^9/L, hemoglobin level of 12.8 g/dL, hematocrit of 34.5%, and platelet count of 194 x 10^9/L. The serum sodium level was 113 mmol/L, potassium was 4.0 mmol/L, calcium was 8.6 mg/dL, and creatinine was 0.72 mg/dL. A spot finger glucose was 245 mg/dL. Plasma osmolality was 238 mosmol/kg. The urinary sodium was 104 mmol/L, and urinary osmolality was 623 mosmol/kg. A thyroid function test and serum cortisol level were within the normal range. In addition, polyuria (about 4 L/day) was also noted.

An indwelling Foley catheter was inserted and the patient was given 0.9% NaCl solution intravenoulsy at a rate of 100 ml/hour. After 6 hours, her serum sodium level had increased slightly to 115 mmol/L and her mental status was still altered but improved (eyes 2, verbal 1, motor 5). Her serum sodium level began to rise on the next day after the infusion was changed to 3% NaCl at 20 ml/hour and continued to rise until reaching the normal level on the fifth day in our oncology ward. Her consciousness gradually improved with the increase in her serum sodium. Her urinary output decreased to 1.7 L/day and 1.8 L/day, the last 2 days she rerceived hypertonic saline.

DISCUSSION

An objective causality assessment of our case with the Naranjo Score suggested that cisplatin was the probable cause for the adverse event described.[2] Cisplatin is a well-known chemotherapeutic agent that is associated with hyponatremia. However, cisplatin-induced clinically apparent hyponatremia is rare. A search of the Pubmed database using the following keywords: ("Cisplatin" [Mesh]) AND ("Hyponatremia" [Mesh] OR "Sodium" [Mesh]) AND ("Coma" [Mesh]) AND ("Seizures" [Mesh] OR "Epilepsy, Tonic-Clonic" [Mesh]) as well as the first three items, yielded no results. Only one case report was identified when "Coma" [Mesh] was subtracted from the above four items.[3] That case involved a patient with progressive glioblastoma multiforme who developed hyponatremia accompanied by decreased mental awareness and seizures following cisplatin chemotherapy.[3] Both central nervous system tumors and progressive malignancy may be contributing factors in seizures and altered mental status. However, our patient had no intracranial tumor. She had early breast cancer and underwent adjuvant chemotherapy. In addition, she was in a coma.

After cisplatin is administered, 10% of it is freely filterable through the renal glomeruli,[4] and then taken up into the proximal and distal tubular epithelial cells mainly through an active transporter-dependent mechanism.[5] In addition, cisplatin is known to modulate sodium-coupled uptake and membrane fluidity in renal proximal tubular cells.[6] The mechanism of cisplatin-induced hyponatremia is thought to be mainly renal salt wasting syndrome (RSWS),[7-13] and sometimes the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[3,14] RSWS develops when cisplatin damages the renal proximal tubules, the major site of sodium and water reabsorption, leading to an obligatory natriuresis, with increases in urine output and urine sodium. Because of the resulting volume depletion due to a renal sodium transport abnormality, antidiuretic hormone (ADH) is secreted as an appropriate response.[9] It's difficult to make a diagnosis of RSWS and it is commonly misdiagnosed as SIADH, because the conditions share similar laboratory values, such as hypotonic hyponatremia and increased urine sodium. SIADH also occurs in many malignancies. Volume assessment is the most critical step in differentiating the conditions because patients with SIADH are euvolemic, but those with RSWS are hypovolemic.[13] However, the clinical signs of volume depletion are not always apparent, and it is difficult to assess volume status accurately. Moreover, excessive urinary excretion of sodium (urinary sodium output exceeds sodium intake), a high percentage of fractional excretion of sodium, and persistence of

both hypouricemia and increased fractional excretion of urate are all indicators of RSWS instead of SIADH.[12,13,15,16] Serum renin and aldosterone levels have diagnostic value as well.[15,16] Management of RSWS and SIADH is quite different. The treatment for RSWS is supplementation with saline fluids, but SIADH is treated with water restriction.[12,13] Our patient developed hypotonic hyponatremia and polyuria at the onset. Although she did not have any of the laboratory data cited above, we assumed the mechanism of hyponatremia was RSWS according to the following criteria. (1) The sodium balance calculated on the day of hyponatremia showed the sodium output was 24 g versus a sodium intake of 14 g. (2) Although she had no signs of hypovolemia, we did not know her actual volume status. (3) Polyuria is one of the clinical manifestations of RSWS, but not of SIADH. (4) After receiving 0.9% saline solution followed by 3% saline, her consciousness became clear with the rise of serum sodium. That meets the treatment goals of RSWS.

In conclusion, hyponatremia should be considered when seizures or mental changes occur in patients treated with cisplatin. The mechanism of hyponatremia induced by cisplatin is thought to be mainly RSWS, and sometimes SIADH. Differentiating RSWS and SIADH remains a diagnostic challenge. A key to the diagnosis of RSWS is a sodium output that exceeds the sodium input in the face of increased urinary output, hypovolemia, and appropriate ADH secretion. When RSWS is suspected, hypertonic saline should be administered. Patients usually respond well to the treatment, and their renal tubules will recover from the chemotherapeutic agent-induced insult in a few days.

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Cisplatin 引起急性低血鈉導致全身抽搐和昏迷之案例報告

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本文我們報導一個極罕見的案例：一乳癌患者因使用 cisplatin 引起急性低血鈉導致全身抽搐和昏迷。這位個案爲 66 歲女性乳癌病患，手術切除乳房後接受輔助性化學治療— docetaxel 和 cisplatin。在化療過程中和結束化療後，她沒有出現噁心、嘔吐和腹瀉現象。然而，四天後，她因全身抽搐和昏迷來到本院急診。當時，她的昏迷指數爲 6 分 (E1V1M4)。其大腦電腦斷層掃瞄顯示腦部沒有任何病變。個案除了罹患乳癌外，沒有其他潛在疾病。抽血生化檢驗值發現她有嚴重低血鈉 (113 mmol/L) 和低血漿滲透壓，又其尿鈉值和尿液滲透壓皆偏高。此外，她也有出現多尿 (約 4 升／天) 情形。隔天，當我們給予她 3% 食鹽水靜脈輸注後，其血鈉值開始回升，同時她的意識也逐漸改善，最後意識完全恢復，無任何後遺症。本案例經 Naranjo score 評分後顯示 cisplatin 可能是造成此次事件的元兇，其引起低血鈉的機轉被認爲是腎性耗鹽症候群 (renal salt wasting syndrome, RSWS)。結論是 cisplatin 引起急性低血鈉導致全身抽搐和昏迷之案例十分罕見，一旦懷疑是 RSWS 時就應給予高張食鹽水。(長庚醫誌 2011;34(6 Suppl):48-51)

關鍵詞：cisplatin，低血鈉，抽搐，昏迷，腎性耗鹽症候群

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