Cyclophosphamide-induced Acute Hyponatremic Encephalopathy in Patient with Breast Cancer

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INTRODUCTION

Cyclophosphamide is an alkylating agent used in immunosuppressive and antineoplastic therapies.[1-4] NCCN Category 1 recommended treatment for hormone positive, node positive, Her2/neu- invasive ductal carcinoma (IDC) is dose-dense AC (doxorubicin/cyclophosphamide) therapy followed by paclitaxel every two weeks.[9] Cyclophosphamide has many potential side effects ranging in severity from diarrhea and emesis to hemorrhagic cystitis and ototoxicity.[1-3,6] Previously known side effects with cyclophosphamide at high (>30 to 50 mg/kg) and moderate (20 to 30 mg/kg) IV doses includes the appearance of the syndrome of inappropriate antidiuretic hormone (SIADH).[2,3,10,11] SIADH can occur with low-dose (<15 mg/kg) cyclophosphamide treatment for breast cancer- however less than ten cases have been reported.[1,3,4-6,8]

CASE DESCRIPTION

A 53-year-old female with past medical history of ductal carcinoma in situ of the left breast status post lumpectomy and radiation therapy presented with newly diagnosed Stage IIIA pT1c pN2a IDC of the right breast.

- She underwent bilateral mastectomies and presented for adjuvant chemotherapy.
- Her baseline weight 69 kg, BSA 1.76 m^2.
- Pretreatment assessment:
  - normal physical exam
  - laboratory results

Sodium	Potassium	Creatinine
140 mmol/L	3.9 mmol/L	0.68 mg/dl

  - medications:
    hydration with 500 ml of 0.9% normal saline, dexamethasone 12 mg IV push, and anti-nausea therapy including palonosetron 0.25 mg IV and fosaprepitant dimeglumine 150 mg IV

CASE DESCRIPTION CONT.

- She was started on dose-dense AC therapy:
  1. Doxorubicin at 60 mg/m^2- total dose 106 mg.
  2. Cyclophosphamide at 600 mg/m^2- total dose 1000 mg IV (rounded down from 1056 mg), equivalent to 14.4 mg/kg.
- No side effects were noted during the treatment.
- One day later, she was found on the floor of her house, unarousable.
- On presentation to the emergency department, she was unresponsive, in status epilepticus and acute hypoxic respiratory failure.

HOSPITAL COURSE

- She was admitted to the intensive care unit (ICU) for endotracheal intubation and mechanical ventilation.
- Evaluation for another etiology for her altered level of consciousness was negative.
- Emergent laboratory results

Sodium	113 mmol/L	Glucose	129 mg/dl
Potassium	3.7 mmol/L	CPK	1044 IU/L
BUN	9 mg/dl	Sensitive TSH	854 IU/L
Creatinine	0.49 mg/dl	Urine Osmolality	213 mOsm/kg
Calcium	8.4 mg/dl	Urine Sodium	24 mmol/L

- Electrolytes were quickly corrected within twenty-four hours with 3% saline and 0.9% normal saline treatment to

Sodium	Potassium	Creatinine
140 mmol/L	3.9 mmol/L	0.68 mg/dl

- She was extubated and transferred to the floor for further monitoring within two days.
- On discharge from the hospital, her physical exam was normal with neurological status intact.
- Discharge laboratory results

Sodium	Potassium	Creatinine
137 mmol/L	3.3 mmol/L	0.45 mg/dl

FOLLOW UP

- She presented for continued chemotherapy.
- She had no recollection of events from her arrival for cycle 1 chemotherapy to release from the ICU.
- Physical examination at one week revealed memory loss but no other neurological deficits.
- She was very hesitant to continue therapy given her recent complication.
- She has since completed chemotherapy and is undergoing radiation therapy. No further electrolyte disturbances were noted for the duration of treatment.

DISCUSSION

Mild hyponatremia is a known side effect of chemotherapeutic agents.[1,10,11]

Cyclophosphamide in high (>30 to 50 mg/kg) and moderate (20 to 30 mg/kg) IV doses has been shown to induce severe hyponatremia.[2,3,8,11]

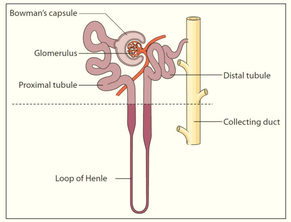
This case represents an extremely rare event of severe symptomatic hyponatremia associated with low-dose cyclophosphamide therapy (<15 mg/kg), in the treatment of malignancy.

In our patient:
- no structural brain lesions to explain altered mental status
- no other definitive etiology to explain sudden hyponatremia
- no risk factors such as concurrent recreational drug use[3]
- while patients are recommended to increase fluid intake post treatment to prevent hemorrhagic cystitis,[2,3] she appeared euvolemic on physical exam
- no other medications expected to have contributed

We conclude the patient developed cyclophosphamide-induced acute hyponatremic encephalopathy.

DISCUSSION CONT.

Hypotheses for mechanism of cyclophosphamide-induced acute hyponatremia[3,4,11]:
1. Direct toxic effect of cyclophosphamide or its metabolites on renal collecting tubule epithelium and release of vasopressin.
2. Antidiuretic hormone-like activity of cyclophosphamide or its metabolites and resulting inability to excrete dilute urine.



Severe hyponatremia can lead to psychosis, seizure, permanent brain damage, coma, and death.[6-8]

Low-dose cyclophosphamide is a commonly used therapy in treatment of many cancers.[3]

If a patient presents following treatment with fatigue, lethargy, or altered level of consciousness, clinicians must include hyponatremia in the differential diagnosis.[3,6]

Clinicians should be aware of this potentially serious adverse effect regardless of treatment dosage and duration.[1-7]

Only prompt diagnosis and immediate management can help prevent significant and permanent neurological deficits.[6-8,10]

There is one documented case of successful continued treatment with cyclophosphamide and concurrent 0.9% saline hydration.[8] We did not reintroduce cyclophosphamide therapy.

CONCLUSION

Patients should be monitored before and after receiving low-dose cyclophosphamide therapy for breast cancer with early follow-up.

The emotional trauma patients may endure from this complication including ICU admission, memory loss, fear or refusal of further therapy, and residual neurological deficits should not be overlooked.

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