Cyclophosphamide-induced syndrome of inappropriate antidiuretic hormone secretion

Sir,

Pulse therapy with dexamethasone and cyclophosphamide (DCP) is effective in the treatment of pemphigus. The adverse effects of cyclophosphamide include hemorrhagic cystitis, bone marrow suppression, gastrointestinal symptoms and gonadal suppression. We report a 26-year-old female who developed the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion following DCP and subsequently also developed features of disseminated intravascular coagulation (DIC) and secondary septicemia.

A 26-year-old unmarried female with uncontrolled pemphigus vulgaris was administered dexamethasone pulse for three days. Oral steroids were continued since we wanted to avoid antimetabolites, but she continued to develop new vesicles. Eighteen days following admission we administered DCP pulse. One day following DCP she developed malaise, headache, nausea, anorexia and excessive thirst. On evaluation, the patient had severe hyponatremia (117 mEq) with elevated urinary spot sodium and urine osmolality (280 mmol/kg) suggestive of SIADH. She was treated with 3% sodium chloride; however, circulatory volume was not compromised. Simultaneously, the patient developed features of DIC, such as thrombocytopenia, d-Dimer positive and low-normal serum fibrinogen levels that gradually progressed to septicemia and Type I respiratory failure. She required critical care management and was supported with noninvasive ventilator and administered four units of platelets, four units of fresh frozen plasma along with 3% NaC1 for hyponatremia. Five days later, serum sodium reverted to normal, platelets gradually improved and vital parameters settled. She was maintained on prednisolone 1 mg/kg/day after which she stopped developing new vesicles. On review after one month, prednisolone was tapered to 30 mg and the patient is doing well.

Syndrome of inappropriate antidiuretic hormone (SIADH) is characterized by hyponatremia because of dilution of body fluids by an excess of water relative to total solute.[1] If SIADH develops rapidly, it is accompanied by symptoms of water intoxication which include nausea, vomiting, headache, confusion and coma.[1] These occur as osmotic fluid shifts result in cerebral edema and increased intracranial pressure. Inappropriate secretion of the antidiuretic hormone (ADH), also known as vasopressin, due to any cause interferes with renal excretion of water and results in production of concentrated urine and hyponatremia.

Antidiuretic hormone (ADH) is secreted by the posterior pituitary gland. The key action of ADH in the kidney is the insertion of water channels like aquaporin-2 and -3 into the principal cells of the collecting duct, thus increasing the permeability of water. These channels allow free water to be reabsorbed from the collecting duct within the hypertonic renal medulla. In SIADH, the inappropriately elevated level of vasopressin enhances the reabsorption of water, thereby leading to production of concentrated urine, inability to excrete water and consequently hyponatremia.[2] The proposed mechanism by which a drug interferes with the normal secretion and action of ADH depends on the drug.[3] Drugs that stimulate the release of ADH from the posterior pituitary gland include nicotine, phenothiazines and tricyclics. Some drugs increase or potentiate the renal action of ADH. They include desmopressin, oxytocin and prostaglandin synthesis inhibitors. Drugs that cause SIADH by means of mixed or uncertain mechanism of action include chlorpropamide, carbamazepine, cyclophosphamide and vincristine.[3]

Prior to establishing a diagnosis of SIADH, a detailed history should be obtained in order to exclude the numerous disorders capable of causing hyponatremia. These include congestive heart failure, hepatic dysfunction, adrenal insufficiency, renal failure and thyroid diseases.[2]

On physical examination, evaluation of the volume status is important as SIADH is characterized by euvolemic hyponatremia. Edema in a hyponatremic patient should lead to the consideration of conditions

other than SIADH, such as congestive cardiac failure, cirrhosis and nephrotic syndrome, which present with hypervolemic hyponatremia. Other findings consistent with euvolemia include normal blood pressure, absence of orthostatic instability, moist mucus membranes and normal skin turgor.

We conclude that although DCP is effective, unusual and life-threatening side-effects such as SIADH might occur following DCP.

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