



# Syndrome of inappropriate secretion of antidiuretic hormone after infusional vincristine

RUBEN S. ESCURO, MD; DAVID J. ADELSTEIN, MD; SUSAN G. CARTER, MD

■ A 77-year-old woman with refractory multiple myeloma was treated with a 4-day continuous intravenous infusion of vincristine and doxorubicin and 4 days of oral dexamethasone. Nine days after her second cycle she presented with lethargy and weakness associated with hyponatremia. Evaluation revealed the syndrome of inappropriate secretion of antidiuretic hormone, which was attributed to the vincristine infusion. After normal serum sodium levels returned, further doxorubicin and dexamethasone chemotherapy without vincristine did not produce this complication.

□ INDEX TERMS: INAPPROPRIATE ADH SYNDROME; VINCRISTINE; DOXORUBICIN; DEXAMETHASONE; MULTIPLE MYELOMA

□ CLEVE CLIN J MED 1992; 59:643-644

**T**HE SYNDROME OF INAPPROPRIATE secretion of antidiuretic hormone (SIADH) is a side effect of bolus intravenous vincristine.<sup>1,2</sup> Its mechanism is postulated to be a direct neurotoxic effect of vincristine on sites in the hypothalamus, the neurohypophyseal tract, or the posterior pituitary gland that affect ADH formation and storage.<sup>2</sup> The use of vincristine given as a continuous infusion has recently increased, particularly as a component of the VAD (vincristine, doxorubicin [Adriamycin], and dexamethasone) regimen for refractory multiple myeloma, as described by Barlogie and associates.<sup>3</sup> Infusions of vincristine have also induced hyponatremia<sup>4</sup>; however, the mechanism of this hyponatremia has not been clarified. We describe a

patient who developed SIADH while receiving a continuous infusion of vincristine as part of the VAD regimen for multiple myeloma.

## CASE REPORT

A 77-year-old white female with a history of remote pulmonary tuberculosis presented in October 1986 with back pain. She was found to have a compression fracture of the twelfth thoracic vertebra. Further evaluation revealed IgA-lambda multiple myeloma. She received radiation therapy to the spine, and chemotherapy with melphalan and prednisone was started. This regimen controlled her disease for 18 months, but subsequently her disease progressed, with an increase in painful bone lesions, anemia, and thrombocytopenia. She was enrolled in an Eastern Cooperative Oncology Group phase-II study for relapsed myeloma and received three monthly courses of carboplatin, but without response.

Chemotherapy was then changed to the VAD regimen of vincristine (0.4 mg/day) and doxorubicin (9 mg/m<sup>2</sup>/day), both administered as a 4-day continuous intravenous infusion, and oral dexamethasone (40 mg/day) for 4 consecutive days. At the start of the

From the Division of Hematology/Oncology, Department of Medicine, Cleveland Metropolitan General Hospital (R.S.E., S.G.C.), and the Department of Hematology and Medical Oncology, The Cleveland Clinic Foundation (D.J.A.).

Address reprint requests to R.S.E., 5360 Oberlin Avenue, Lorain, OH 44053.

Supported in part by a clinical fellowship award from the American Cancer Society.

first cycle (January 10, 1989) her serum sodium level was 136 mEq/L. Fourteen days later, her serum sodium level transiently dropped to 124 mEq/L at a time when she developed significant constipation. The patient began a second cycle of the same chemotherapy regimen on February 14, 1989, with a serum sodium level of 134 mEq/L. No antiemetics, analgesics, or other medications were required. On February 23 she was hospitalized with generalized weakness.

Laboratory data on admission revealed serum sodium 118 mEq/L, potassium 4.7 mEq/L, chloride 91 mEq/L, bicarbonate 24 mEq/L, blood urea nitrogen 21 mg/dL, and creatinine 0.6 mg/dL. The white blood cell count was 3100/mm<sup>3</sup>, hematocrit 27.6%, and platelet count 59,000/mm<sup>3</sup>. Spot urinary sodium excretion was 78 mEq/L; serum osmolality was 246 mOsm/L; and simultaneous urine osmolality was 634 mOsm/L. ACTH stimulation test and thyroid function tests were normal. Chest roentgenography showed old pulmonary tuberculosis, but was otherwise unremarkable. The patient was afebrile. Serum total protein was 9.0 g/dL, with an albumin of 3.5 g/dL. Other tests for liver function were within normal limits.

A diagnosis of SIADH was made, and the patient was managed with fluid restriction (average of 870 cc/day) and oral demeclocycline (150 mg qid). Her serum sodium level then improved marginally to 123 mEq/L. She was discharged home, but at home she arbitrarily did not take the demeclocycline. On March 9, 23 days after the start of the second cycle of VAD, her serum sodium level was 132 mEq/L, and it rose to 134 mEq/L after another week. A third cycle of chemotherapy, this time without vincristine, was begun on March 29, 1989, at which time her serum sodium was normal. This cycle was tolerated well, and all subsequent serum sodium determinations were normal. Multiple additional courses of doxorubicin and dexamethasone were given, as were several other chemotherapy regimens not containing vincristine. No further hyponatremia was encountered. She eventually became refractory to further therapy and died in March 1991.

#### DISCUSSION

Hyponatremia associated with intravenous bolus doses of vincristine therapy has been reported several times.<sup>1,2</sup> In these reports, the diagnosis of SIADH was established by the presence of a urine osmolality greater than the serum osmolality in a hyponatremic patient with normal renal and adrenal function and no clinical

evidence of volume depletion. The hyponatremia was often accompanied by other manifestations of vincristine toxicity, such as ileus or hyporeflexia, and it usually resolved with fluid restriction. Demeclocycline, an antibiotic that inhibits antidiuretic hormone, may also be of value in resolving hyponatremia.

Jackson et al<sup>4</sup> reported the development of hyponatremia in a phase I trial of vincristine given via continuous intravenous infusion. In their study, 30 patients with refractory malignancies received vincristine infusions in doses of either 0.5 mg/m<sup>2</sup>, 0.75 mg/m<sup>2</sup>, or 1.0 mg/m<sup>2</sup> daily for 5 days. Among those who received the lowest dose, hyponatremia occurred in only one patient (5%), but the incidence was 58% in the patients who received the highest dose. The mechanism for the hyponatremia was not discussed.

Our patient was treated with VAD combination chemotherapy, a regimen reported to be effective in patients with refractory multiple myeloma.<sup>3</sup> The vincristine dose of 0.4 mg/day for 4 days was significantly less than the lowest dose of vincristine studied by Jackson<sup>4</sup> and has not been previously reported to cause SIADH or hyponatremia. The diagnosis of SIADH was confirmed in this patient by appropriate measurements of urine and serum osmolality in the setting of normal renal, hepatic, adrenal, and thyroid function.

Our patient's serum sodium level responded slowly to initial fluid restriction and treatment with demeclocycline. Normalization of her serum sodium level only occurred after discharge home, where she stopped taking the demeclocycline and did not adhere to fluid restriction. Subsequent courses of chemotherapy without vincristine did not produce hyponatremia, confirming that the vincristine infusion was responsible for the hyponatremia. SIADH should be recognized as a possible complication of vincristine given by continuous intravenous infusion, as well as by bolus administration.

#### REFERENCES

1. Nicholson RG, Feldman W. Hyponatremia in association with vincristine therapy. *Can Med Assoc J*. 1972; **106**:356-357.
2. Stuart MJ, Cuaso C, Miller M, Oski FA. Syndrome of recurrent increased secretion of antidiuretic hormone following multiple doses of vincristine. *Blood* 1975; **45**:315-320.
3. Barlogie B, Smith L, Alexanian R. Effective treatment of advanced multiple myeloma refractory to alkylating agents. *N Engl J Med*. 1984; **310**:1353-6.
4. Jackson DV, Sethi VS, Spurr CL et al. Intravenous vincristine: phase I trial. *Cancer* 1981; **48**:2559-2564.