Inappropriate Antidiuretic Hormone Following Adenine Arabinoside Administration

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A patient with disseminated herpes zoster developed a syndrome of inappropriate antidiuretic hormone and profound hyponatremia secondary to the administration of adenine arabinoside.

Adenine arabinoside (Ara-A) is an investigational antiviral (2, 8) agent. It inhibits synthesis of nuclear DNA and is under evaluation for the treatment of DNA viral infections. We recently had the opportunity to observe a patient with disseminated herpes zoster who developed a syndrome of inappropriate antidiuretic hormone (SIADH) with profound hyponatremia while receiving Ara-A.

Case report. A 44-year-old man who had stage IIIIB histocytic lymphoma diagnosed in April, 1977, was admitted to the University of Maryland Hospital on 3 April, 1978, complaining of fever in addition to rash and pain over the right gluteal area. He had received multiple courses of chemotherapy, including a combination of cyclophosphamide (Cytoxan), vincristine (Oncovin), prednisone, and procarbazine (Matulane) followed by bleomycin (Blenoxane) and then doxorubicin (Adriamycin). In addition, between October, 1977, and December, 1977, he received 3,000 rads of irradiation to all pelvic lymph node-bearing areas. Since that time the patient has been in clinical remission for his lymphoma and has received no further chemotherapy. Eight days before the present hospitalization, he noted a macular rash over the left gluteal area followed in 3 days by severe pain. Over the next 5 days, the patient noted dissemination of the rash over the entire body. On the day before admission, he developed fever and chills. On admission, the physical examination showed a well-developed male in no acute distress. The weight was 73.2 kg, his temperature was 38°C, his pulse was 76 and regular, and his blood pressure was 130/80. There was a patch (5 by 15 cm) of discrete and confluent vesicles and pustules over an erythematous base on the right buttck. In addition, there were generalized and extensive eruptions with discrete, dense to umbilicated vesicles and vesicopustules over his entire body, including face, genitalia, and the palms of his hands and feet. The chest, heart, and abdominal examinations were unremarkable. The genitalia revealed 2+ edema of the scrotum. The lower extremities revealed no peripheral edema. The neurological examination was normal. The leukocyte count was 7,300 with 84% segmented neutrophils, 3% bands forms, 6% lymphocytes, and 6% monocytes; the hematocrit was 32%. The urea nitrogen was 12 mg; glucose was 103 mg; calcium was 8.6 mg; uric acid was 5.4 mg, creatinine was 1.0 mg, and total protein was 6.5 g (albumin, 3.0 g and globulin, 3.5 g) per 100 ml. The serum sodium was 134 milliequivalents (mEq), chloride was 96 mEq, potassium was 4.1 mEq, and carbon dioxide was 23 mEq per liter. The urine had a specific gravity of 1.014 and gave a 2+ test for protein. The sediment contained 4 to 5 leukocytes per high-power field. Chest X ray and electrocardiogram were normal. A Tzanck preparation of vesicular scrapings was positive, showing multinucleated giant cells and intranuclear inclusions. A diagnosis of disseminated herpes zoster was made, and on 4 April, 1978, he was started on Ara-A (Vidarabine) at 10 mg/kg per day in 2 liters of 5% dextrose in normal saline by continuous infusion. Over the next 2 days, he had continued fever, and, although no evidence of infection other than zoster was apparent, he was begun empirically on cephalothin and gentamicin. In addition he received propoxyphene (Darvon) for pain. Chest X ray and neurological examinations were normal.

On the morning of 7 April, 1978, he was found to be somewhat confused and disoriented. With the exception of generalized weakness, the neurological examination was otherwise normal. No nuchal rigidity was noted. His weight had risen to 75.1 kg. Laboratory data at the time revealed a serum sodium of 106 mEq; chloride, 85 mEq; and potassium, 4.3 mEq and an osmolality of 225 mosmol per liter. The blood urea nitrogen was 8 mg/100 ml. The urine sodium was 22 mEq.
chloride was 21 mEq, and the osmolality was 690 mosmol per liter. The patient was treated with fluid restriction to 600 ml per day and 1 liter of 3% saline infusion over a period of 12 hours followed by intermittent administration of furosemide to ensure a greater urine output than the total intake. His mental status improved within 24 h, and the serum sodium gradually returned to normal with a decrease in his urine osmolality. Additional laboratory data included a creatinine clearance of 150 ml/min, and 24-h urine collection contained 800 mg of protein. The total T3 and T4 were normal, as was an 8 a.m. serum cortisol. On 11 April, 1978, the Ara-A and the furosemide were discontinued. A standard water-loading test was done 7 days after discontinuation of the Ara-A and was found to be normal. A repeat 24-h collection revealed a creatinine clearance of 135 ml/min and 700 mg of protein. The varicella-zoster complement fixation titer rose from 1 to 8 on 6 April, 1978, to 1 to 64 on 24 April, 1978.

This patient developed severe hyponatremia caused by an impairment of water excretion during the period of Ara-A administration. The presence of plasma hypotonicity and urinary hypertonicity and the absence of hypotension, hypovolemia, congestive heart failure, and adrenal insufficiency confirmed the diagnosis of SIADH (1). In addition, at the time of the occurrence of the hyponatremia, his creatinine clearance was within normal limits, and, although he had 800 mg of protein in the urine on a 24-h collection, his serum albumin was 3 g/100 ml.

Disseminated herpes zoster often affects only skin but may progress to involve lungs (9), mucosal membranes, glomeruli (5), and the central nervous system (6). Central nervous system involvement by herpes zoster occurs to some degree in most patients because a cerebrospinal fluid evaluation will often reveal leukocytes and increased protein even with localized zoster (3). This patient had widely disseminated cutaneous zoster but no evidence of mucosal or pulmonary involvement. At the time of the hospital admission, he had no clinical evidence of either renal or central nervous system involvement; no further dissemination occurred.

Disorientation and other symptoms of hyponatremia were first noted 3 days after starting the Ara-A, at which time an SIADH was documented. He continued to have no evidence of further dissemination; indeed, the cutaneous lesions were beginning to heal. A lumbar puncture was not performed because of the frequency of abnormal findings with zoster in the absence of clinical signs of encephalopathy, and at no time did he exhibit evidence of pneumonitis. The central nervous system clinical picture was more consistent with hyponatremia than encephalitis.

Other possible causes of SIADH were considered but felt to be unlikely in this case. Although vincristine and cyclophosphamide are known to induce SIADH, the patient was in clinical remission and had received neither drug during the 3 months before this admission. He was receiving propoxyphene for pain, but this continued long after the SIADH resolved. Transient fever also occurred, but did not relate chronologically to the SIADH. We therefore concluded, given this clinical setting and temporal association, that the SIADH was related to the Ara-A.

Ara-A is a purine derivative, is a new antiviral agent effective in vitro against DNA viruses. Animal as well as human studies so far have shown the drug to be free of serious toxicity (10). Side effects reported to date include nausea, vomiting, erythroid megaloblastosis, thrombophlebitis at the site of infusion, and tremors (7). The generalized tremors reported have been accompanied by weakness, occasionally confusion, and abnormal slowing in the electroencephalogram. These clinical and electroencephalographic changes are consistent with an acute encephalopathy. In four cases, described by Ross et al. (7), the clinical and electroencephalographic abnormalities improved after discontinuation of Ara-A. Ara-A has been shown to cross the blood brain barrier, with concentration in the spinal fluid being lower than the plasma (4). The timing in the development of hyponatremia in this patient, 3 days after the institution of a 7-day course of Ara-A, at a time when the zoster was beginning to resolve, suggests that the SIADH was drug induced. The water-loading test done after the discontinuation of the Ara-A clearly showed that the patient could tolerate a water load and dilute his urine appropriately.

Although the investigational nature of this drug precluded our challenging the patient at a later date with Ara-A, we believe that the course of events in this patient is consistent with the development of SIADH secondary to administration of Ara-A.

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LITERATURE CITED


