

# Three Separate Instances of Cytarabine-induced SIADH

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## Abstract

We present a case of cytarabine-induced syndrome of inappropriate secretion of antidiuretic hormone (SIADH), a rare manifestation and complication, which based on review of the medical literature was reported only in one prior case report. It involves a 74-year-old male with acute myeloid leukemia who developed asymptomatic hyponatremia during three cycles of consolidation chemotherapy with high-dose cytarabine (HiDAC). Urine studies were consistent with SIADH. Due to the rapid onset and timing throughout all three cycles, the SIADH was suspected to be secondary to cytarabine. Serum sodium quickly corrected after the final administered dose of cytarabine in all cycles, and fluid restriction was only instituted during the third cycle.

## Résumé

Nous présentons un cas de syndrome de sécrétion inappropriée d'hormone antidiurétique (SIADH) induit par la cytarabine, une manifestation et une complication rares que l'on ne rapporte que dans une seule étude de cas antérieure reposant sur une revue de la documentation médicale<sup>1</sup>. Il s'agit d'un homme de 74 ans atteint d'une leucémie myéloïde aiguë (LMA) chez qui est apparue une hyponatrémie asymptomatique pendant trois cycles de chimiothérapie de consolidation à des doses élevées de cytarabine. Les analyses d'urine sont compatibles avec le SIADH. En raison de la rapidité d'apparition et de la périodicité tout au long des trois cycles, on soupçonne que ce syndrome est attribuable à la cytarabine. La concentration sérique du sodium s'est corrigée rapidement après l'administration de la dernière dose de cytarabine à chaque cycle, et une restriction liquidienne n'a été instaurée qu'au cours du troisième cycle.

**Keywords:** Cytarabine-induced SIADH; asymptomatic hyponatremia

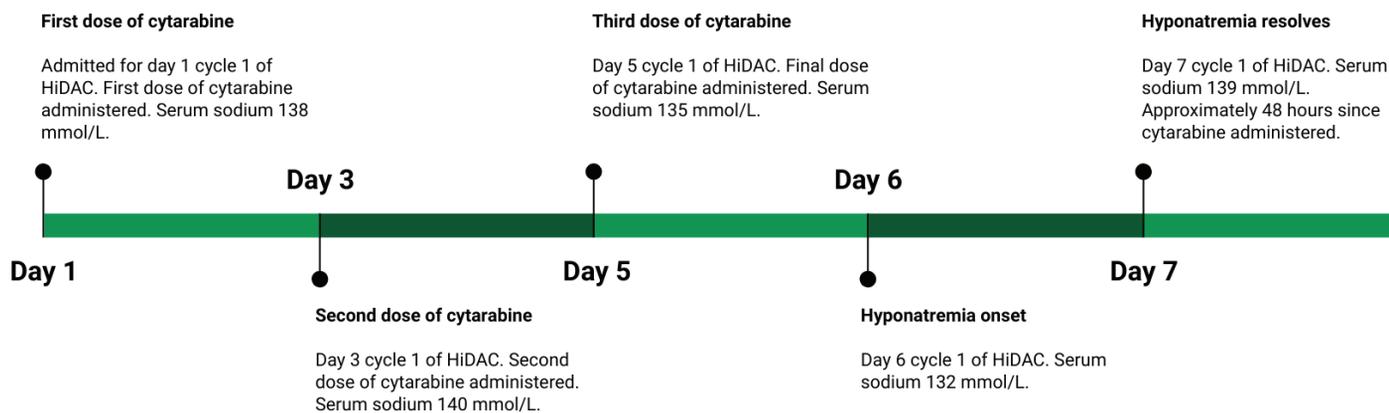
## Introduction

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) describes all syndromes in which the vasopressin level or the kidney's responsiveness to vasopressin is inappropriately high and not attributable to osmolar or volume stimuli.<sup>1,2</sup> SIADH is caused by euvolemic hyponatremia. In euvolemic hyponatremia, there is neither an osmolar nor a volume stimulus to the release of vasopressin, as mentioned previously. High levels of vasopressin or augmented renal response to it causes an increased reabsorption of free water relative to sodium.<sup>2</sup> This results in concentrated urine (urine sodium usually greater than 40 mmol/L) and relative serum hyponatremia. SIADH is diagnosed first by confirming that there is true hyponatremia, followed by volume status assessment of the patient. If the patient is found to be euvolemic, SIADH is confirmed with a low serum osmolality, high urine osmolality, and high urine sodium.<sup>3</sup> The list of conditions that can cause SIADH is extensive and includes drugs and medications, malignancy, tumors, intrathoracic disease, and central nervous system lesions or disease.<sup>2</sup> Treatment includes addressing the underlying cause if identified, as well as free water restriction +/- salt tablets. In rare and difficult to manage cases, vasopressin receptor antagonists are also available. It is also important to note that hypothyroidism and adrenal insufficiency can clinically and biochemically mimic SIADH. Cytarabine is not a known cause of SIADH. It is an antineoplastic agent used to treat leukemia and lymphoma. Its active compound, aracytidine triphosphate, is a pyrimidine analog which incorporates into DNA. It acts by inhibiting DNA polymerase, resulting in decreased DNA synthesis and repair.<sup>3</sup> With this case,

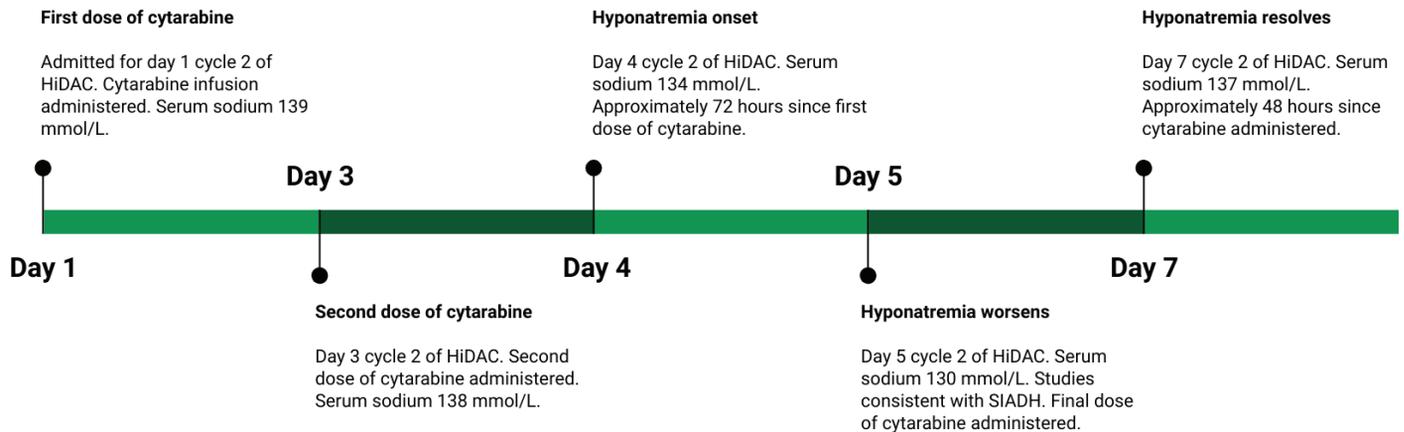
we propose a causal relationship between cytarabine and SIADH.

## Case

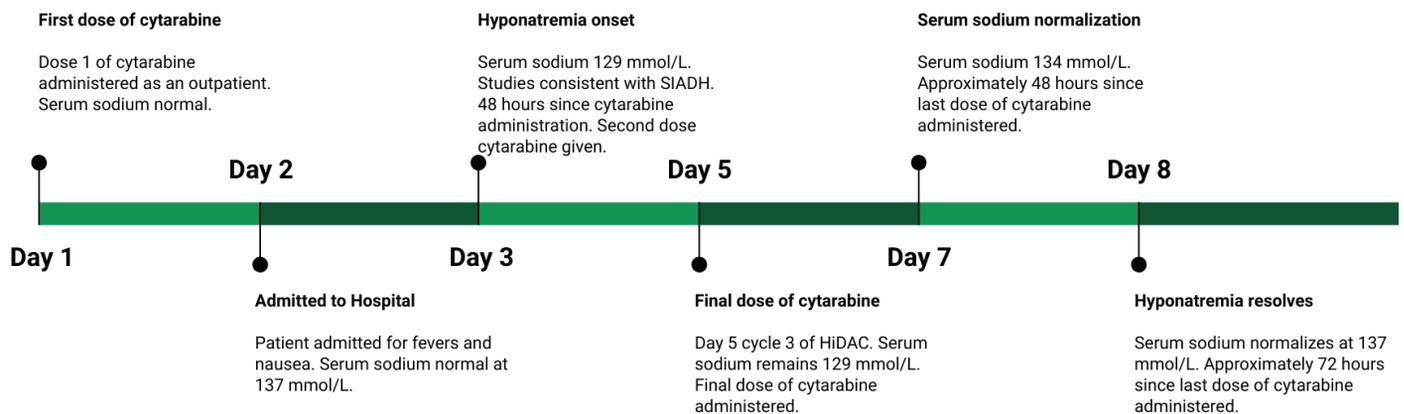
Although similar patterns of hyponatremia occurred during Cycle 1 (Figure 1) and Cycle 2 (Figure 2) of consolidation chemotherapy, we will focus on Cycle 3 (Figure 3) during the case description. A 74-year-old male with acute myeloid leukemia (NPM1+/IDH1+/FLT3-) presented to the hospital with nausea and fever on Day 2 of Cycle 3 of consolidation chemotherapy with high-dose cytarabine (HiDAC). He had previously undergone 7+3 gemtuzumab induction therapy with achieved remission and two cycles of HiDAC. Upon arrival, he reported a temperature of 38.3°C, chills, and nausea. Physical exam was unremarkable. Initial investigations revealed a serum sodium of 137 mmol/L, creatinine 61 µmol/L, WBC  $4.0 \times 10^9/L$ , and glucose 7.8 mmol/L. Remaining blood work was unremarkable. Antibiotics were not initiated, given a normal physical exam and no clear signs of infection. Ringer's lactate was initiated at 125 ml/h, and blood cultures were obtained. The following day, the patient was found to have a serum sodium level of 129 mmol/L and was euvolemic. Further workup revealed a urine osmolality of 700 mOsm/kg, a random urine sodium of 72 mmol/L, and a blood osmolality of 274 mOsm/kg. TSH and morning serum cortisol levels were normal. The laboratory values were consistent with SIADH. Intravenous fluids were discontinued, and a fluid restriction of less than 800 mL/day was initiated. Approximately 48 h after the final administered dose of cytarabine, serum sodium had risen to 134 mmol/L. After 72 h, serum sodium was 138 mmol/L.



**Figure 1.** Cycle 1 of HiDAC consolidation chemotherapy timeline.



**Figure 2.** Cycle 2 of HiDAC consolidation chemotherapy timeline.



**Figure 3.** Cycle 3 of HiDAC consolidation chemotherapy timeline.

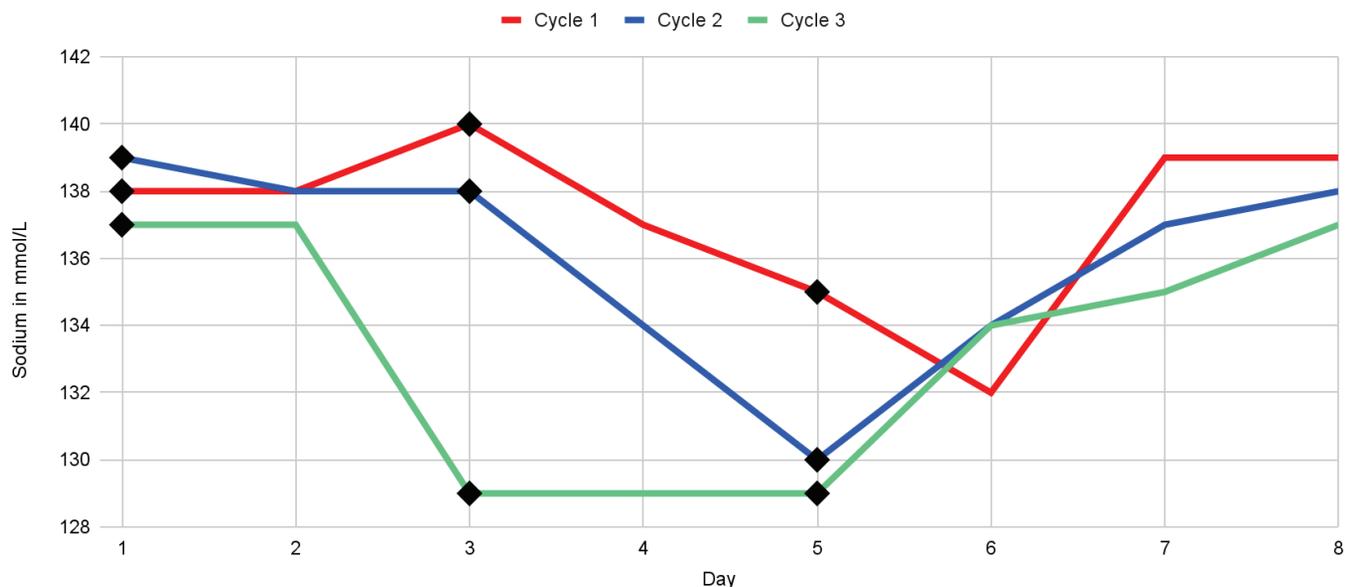
Fevers and nausea had also resolved by this time. A timeline of this hospitalization is shown in Figure 3, and sodium levels in relation to the timing of cytarabine administration in each cycle can be seen and compared in Figure 4. Cytarabine was administered on Days 1, 3, and 5 of the cycle as planned. The patient was discharged home 4 days after the final dose of cytarabine was given with a plan for outpatient follow-up.

## Discussion

As mentioned previously, SIADH can be secondary to a wide variety of conditions. It is a common paraneoplastic phenomenon that occurs in the setting of malignancy. We propose, however, that in this case, SIADH was due to cytarabine, supported by the absence of detectable malignancy and the biochemical evidence of SIADH in three

successive cycles. To our knowledge only one instance of the association of SIADH with cytarabine therapy has previously been reported. In our case, hyponatremia occurred 2 days after the first administered dose of cytarabine. Cytarabine has a terminal half-life of 1–3 h with a peak concentration time of 20–60 min.<sup>3</sup> Serum sodium began to normalize 2 days after the last administered dose of cytarabine, along with fluid restriction measures (Figure 3). The patient developed SIADH during Cycles 1 and 2 at nearly the same point in time when compared to Cycle 3 (Figure 4). The consistent pattern of onset of hyponatremia over the three cycles reinforces the causal relationship between cytarabine and SIADH. Serum and urine studies were consistent with SIADH, and no alternative cause was identified, including review of medications the patient was taking concurrently. This was true for all three cycles. However, it is important to note that Ringer's lactate was administered during the first 6–12 h of admission which could cause

## Serum Sodium Level During Cycles 1, 2 &amp; 3 of HiDAC



**Figure 4.** Serum sodium levels throughout each course of HiDAC consolidation chemotherapy. The symbol  $\blacklozenge$  represents the day on which cytarabine was administered.

or worsen hyponatremia. This is particularly true during Cycle 3. Inappropriate ADH secretion is often the result of increased hypothalamic production, ectopic secretion, or exogenous administration.<sup>2</sup> There is also a fourth category, drug-induced, which is consistent with our case.<sup>4</sup> Although cytarabine is presumably a rare cause of SIADH, it has a well-documented association with other chemotherapeutic agents. A proposed mechanism is the sudden release of ADH from destroyed malignant cells upon the initiation of chemotherapy. This tumor lysis results in release of intracellular ADH, and in turn hyponatremia post chemotherapy could signify adequate treatment response.<sup>5</sup> This mechanism is plausible; however, there were no classical biochemical markers of tumor lysis syndrome in our patient, such as hyperkalemia, hyperphosphatemia, hyperuricemia, or acute kidney injury or renal failure, to support this. It is also possible that the cause of SIADH in this patient was secondary to paraneoplastic ADH secretion. However, given that the patient was in remission and the serum sodium rapidly corrected contextual to discontinuation of cytarabine therapy in all three instances, this is felt to be less likely. While the mechanism may remain unknown, cytarabine should be recognized as a cause of drug-induced SIADH in the correct clinical context.

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