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Case Report

Oncology Section

Cisplatin Induced SIADH in Patients Receiving Concurrent Chemoradiation Therapy: A Rare Clinical Observation

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ABSTRACT

The Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) can be attributed to various causes such as CNS disorders like head trauma, stroke, pulmonary lesions like TB, bacterial pneumonia, as paraneoplastic syndromes in malignancies, drugs like antidepressants, antineoplastics like cyclophosphamide, vincristine, vinblastine, bortezomib, carboplatin and others. Cisplatin induced SIADH is very uncommon and hence, scarcely reported in literature. Here, we report two cases of dilutional hyponatremia secondary to SIADH that developed in two patients receiving radiotherapy with concomitant cisplatin.

Keywords: Chemotherapy, Concomitant, Dilutional hyponatremia

CASE REPORT

Case-1

A 45-year-old male patient diagnosed as carcinoma of distal oesophagus and GE junction (cT3N1M0, Stage III) was admitted for neoadjuvant chemoradiotherapy and planned with a total dose of 50 Gy in 25 fractions along with three weekly regimen of cisplatin-5 FU chemotherapy. His routine haemogram, liver function test, renal function test, serum electrolytes, 2D-echocardiography were within normal limits. Cisplatin 60 mg was given on day 1 and 60 mg on day 2 and 5 FU 1000 mg was given on day 1 to day 4. On day 5, patient complaint of severe chest discomfort, confusion, dizziness and developed seizures of Generalized Tonic Clonic Type (GTCS) for nearly five minutes with uprolling of eyeballs & frothy discharge with post ictal confusion. He was managed symptomatically with intravenous phenytoin infusion. Serum electrolytes samples were sent and sodium was reported as 120 meq/L. Repeat sample after three hours was sent and sodium was 113 meq/L, suspected of chemotherapy induced SIADH and endocrinology consultation was sought. Other laboratory investigations were sent that showed serum osmolality 289 mOsm/kg, urine osmolality was 140 mOsm/kg, urine sodium was 32 mmol/L as shown in [Table/Fig-1] and diagnosed to be chemotherapy induced SIADH and corrected with 3% NaCl and fluid restriction to 750 mL per day. Serum TSH, cortisol advised after one week were within normal range as shown in [Table/Fig-1] which ruled out possibility of associated conditions such as thyroid and adrenal insufficiency. Values got normalised after 7days and the planned second, three weekly cisplatin chemotherapy was deferred in view of anticipated comorbidity and poor patient compliance. The patient was discharged after completion of radiotherapy.

Parameter	Values
S.Osmolality	289 mOsm/Kg
U.Osmolality	140 mOsm/Kg
U.Sodium	32 mmol/L
RFT (creatinine)	0.62 mg/dL
TSH	1.2 mIU/L
Cortisol	10 micrograms/dL

[Table/Fig-1]: List of laboratory investigations. (Case 1)

Case-2

A 46-year-old female diagnosed case of carcinoma of left buccal mucosa cT4aN3M0 having no co morbidities was admitted for concomitant chemoradiation and planned with a dose 66 Gy in 33 fractions along with concurrent cisplatin chemotherapy. His routine laboratory parameters such as haemogram, LFT, RFT, viral markers and electrolytes were within normal range. Cisplatin 40 mg was administered in view of acceptably low GFR and routine investigations were sent on fouth day of post chemotherapy. Serum Na+ was 130 mmol/L i.e., hyponatremia with normal K+, Ca++, Mg++ but the patient was asymptomatic. We tried to manage it conservatively by giving extra salt in routine diet but values were persistently low even after eight days and the lowest value being recorded after day12 post chemo-radiotherapy as 127 mmol/L. Patient was suspected to have chemotherapy induced SIADH and therefore endocrinology opinion was sought. The following investigations were sent and reported serum osmolality was 283mOsm/kg, urine osmolality 698 mOsm/kg, urine Na+ 130mmol/l, serum creatinine, cortisol and TSH were normal as shown in [Table/Fig-2]. Final diagnosis of cisplatin induced SIADH was thus made and patient was advised fluid restriction to one litre per day. Sodium values came to normal within 2 days and further chemotherapy was deferred. Patient completed radiotherapy and got discharged and is on regular follow up.

Parameter	Values
S.Osmolality	283 mOsm/Kg
U.Osmolality	698 mOsm/Kg
U.Sodium	130 mmol/L
RFT (creatinine)	0.55 mg/dL
TSH	0.7 mIU/L
Cortisol	20 micrograms/dL

[Table/Fig-2]: List of laboratory investigations. (Case 2)

DISCUSSION

The concomitant administration of chemotherapeutic drugs with radiation was found to be superior to radiation therapy alone in locoregional disease control and in improving patient survival [1]. Chemotherapy acts as a radiosensitizer in the management of malignant solid tumour treatment. The goals of combining chemotherapeutic drugs with radiation therapy are to improve survival by increasing locoregional tumour control and decreasing or eliminating distant metastases. They make tumour cells more susceptible to killing by radiation and increase therapeutic effectiveness of radiation therapy [1].

Various chemotherapy drugs such as cisplatin, 5-fluorouracil, taxanes, temozolamide, vincristine etc., act as radiosensitisers. Cisplatin is likely to be the most commonly used chemotherapeutic agent in combination with radiation. Most common side effects of cisplatin include nausea, vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy [2]. Cisplatin induced SIADH has been scarcely reported in the literature and is therefore considered as a rare clincal observation in regular practice of clincal oncology.

SIADH is a disorder of impaired water excretion caused by the abnormal secretion of ADH and results in hyponatremia and hypo-osmolality [3]. Causes of SIADH include CNS disorders like head trauma, stroke, subarachnoid haemorrhage; pulmonary lesions like TB, bacterial pneumonia. As paraneoplastic syndromes in malignancies like small cell carcinoma of lung, bronchogenic carcinoma, pancreatic carcinoma, prostate cancer, lymphoma, leukaemias, RCC; Drugs like antidepressants, antineoplastics like cyclophosphamide, vincristine, vinblastine, bortezomib, carboplatin and other causes include postoperative pain, stress etc., [4,5].

In SIADH, the release of ADH is not inhibited by a reduction in plasma osmolality. The increased secretion of ADH results in enhanced water reabsorption, leading to dilutional hyponatremia. Then volume receptors are activated and natriuretic peptides are secreted which causes loss of sodium in urine. Hyponatremia and hypo-osmolality cause acute cerebral oedema that causes the symptoms and signs of SIADH.

Signs and symptoms depend on the degree of hyponatremia and rate at which hyponatremia develops [3]. When sodium concentration decreased slowly, patient will be asymptomatic or non specific symptoms like anorexia, nausea, vomiting, irritability, headache and abdominal cramps develop. Rapid decline results in more severe symptoms like seizures, stupor, coma and respiratory arrest. Serum sodium concentration <120 mEq/L or serum osmolality <240 mOsm/kg are having serious clinical implications irrespective of rate of decline.

Laboratory tests [6] for diagnosis of SIADH include serum sodium <135 mEq/L; serum potassium remains unchanged; Urinary Na+ excretion >20 mEq/L; urinary osmolality >100 mOsm/kg, BUN<10 mg/dL, serum uric acid <4 mg/dL. Other tests include serum cortisol, TSH to rule out hypothyroidism and adrenal insufficiency. Hyponatremia that occur in SIADH can be because of other causes like abnormalities of kidney, thyroid, cardiac and adrenal gland. So before diagnosing SIADH, these causes should be ruled out. Hyponatremia, urine hyperosmolality (>100 mOsm/kg), serum hypo-osmolality (<275 mOsm/kg) in a euvolemic patient with normal cardiac, renal, adrenal, hepatic and thyroid function in the absence of any diuretic therapy, in the absence of other factors that stimulate ADH secretion makes the diagnosis of SIADH.

Firstly, the cause of SIADH is to be identified. If the hyponatremia is thought to be drug-induced, the offending drug should be discontinued. The rapidity of correction is guided by the severity of the clinical presentation and the rate at which the hyponatremia developed. In most of the cases, SIADH resolves within 1-4 weeks of initiating chemotherapy. Serum sodium can be managed with fluid restriction and maintained above 128 mEq/L. Fluid restriction is the mainstay of therapy in most of the patients with SIADH. The intake should be less than 800 mL/day.

The choice of therapy in hyponatremia due to SIADH varies with the severity of hyponatremia and the presence or absence of symptoms [3]. Severe symptomatic hyponatremia who present with seizures or other severe neurologic abnormalities, urgent intervention with hypertonic saline is preferred along with antiepileptics. Demeclocycline can also be used along with fluid restriction when fluid restriction alone is insufficient. Vasopressin receptor antagonists like tolvaptan [7,8] can also be used in the management of SIADH. On the otherhand, the rapid correction of hyponatremia with hypertonic saline may lead to irreversible neurologic injury.

In the first case reported, the patient was symptomatic and managed successfully with prompt medical intervention as described above. In view of unanticipated and unusual symptomatic presentation and of meagre prior clinical experience, thyroid and adrenal insufficiency could not be ruled out by regular laboratory parameters such as serum cortisol and TSH but by indirectly by noticing signs and symptoms such as absence of cold senstivity, constipation, no skin changes, no history of dizziness on standing. Serum TSH, cortisol advised after one week was within normal range as shown in [Table/Fig-1]. The second case of SIADH has been diagnosed taking into account the principles of exclusion that ensures freedom from other clinically related disorders as shown in [Table/Fig-2].

CONCLUSION

Although SIADH has been described as a possible and potential life threatening complication of various chemotherapeutic agents, data on cisplatin induced SIADH are largely anecdotal reports and few series as institutional experiences. It can therefore be advocated that the patients who are either on cisplatin chemotherapy or cisplatin based chemoradiotherapy, prompt attention has to be made to diagnose dilutional hyponatremia due to SIADH and hence, on time medical management to be ensured in order to overcome any adverse clinical outcome.

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