

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Cisplatin Induced Hyponatremic Seizures Secondary to SIADH (Syndrome of Inappropriate Antidiuretic Hormone Secretion): A Rare Presentation.

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ABSTRACT

We report a case of a patient aged 65 years' who presented with histopathological proven metastatic squamous cell cancer of the anal canal. After the necessary workup she was planned for Cisplatin and Fluoropyrimidine based palliative chemotherapy. On day 4 following chemotherapy the patient developed an episode of Generalized Tonic Clonic Seizures, which on further evaluation was attributed to hyponatremia as a result of SIADH secondary to Cisplatin. She required ICU care but made a complete recovery. Patient subsequently refused IV chemotherapy, thereafter she was managed on single agent oral capecitabine and is on follow up to date.

Keywords: SIADH (Syndrome of inappropriate Anti-diuretic hormone), Renal salt wasting syndrome (RSWS), Hyponatremia seizures.

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INTRODUCTION

Cisplatin is one of the most commonly used agent for the treatment of solid tumours. So, in view of its widespread usage today, it would be pertinent to keep in mind the rare adverse effects apart from the most common ones. This brings us to two such rare adverse effects into light i.e. Renal salt wasting syndrome (RSWS) and Syndrome of inappropriate Anti-diuretic hormone (SIADH). Apart from being rare, these are also potentially life threatening ones. An accurate diagnosis and proper differentiation between both is necessary as for both the adverse effects the managements are poles apart. In case of RSWS, fluid supplementation is indicated as there is underlying hypovolemia, whereas in case of SIADH, fluid restriction with salt supplementation is the dictum as the patient is euvolemic. This case reinforces the need to for the oncologist to identify this rare complication of Cisplatin chemotherapy correctly and intervene at the earliest possible instance.

Case Presentation

A 65 year old postmenopausal housewife, with no known co-morbidities presented to the surgical outpatient department with the complaints bleeding per rectum of 5 months duration. The clinical examination was remarkable for a 2x3 cms ulcero-proliferative friable growth at the anal verge .She underwent a biopsy and a metastatic workup in view of the clinical suspicion of anal canal malignancy. The biopsy revealed a Moderately Differentiated Squamous Cell Carcinoma of the anal canal.

The metastatic workup was suggestive of multiple metastatic lung nodules along with para-aortic and pelvic lymphadenopathy. As a part of the metastatic workup a MRI scan of the Brain was also done which was reported as normal.

She was subsequently referred to the department Of Radiotherapy and Oncology for further management. In view of the nature of the diagnosis she was planned for palliative chemotherapy based on Cisplatin (100 mg per mt sq.) on Day 1 and Capecitabine (1000mg per mt sq. BD) Day 1 –Day 14. Infusional 5 FU had to be substituted with Capecitabine as the patient was unwilling for a central venous line or a chemoport. Baseline haematological and biochemical parameters were all within normal limits. As per the calculated BSA (Body surface area) of 1.5 mt. sq and the baseline creatinine clearance of ~ 70 ml/min, the patient received full dose of the cytotoxic agents. As per institutional protocol the patient received premedication's and hydration both pre and post cisplatin chemotherapy the with forced mannitol diuresis. The vital parameters and urine output were unremarkable during the entire duration of cisplatin chemotherapy and both the immediate pre and post chemotherapy periods were uneventful.

On day 4 post chemotherapy patient and her bystanders presented to the emergency department with a history of patient having unprovoked generalized tonic clonic seizures. The Clinical examination was significant for a Glasgow Coma Scale score of 8 (eyes 1, verbal 2, motor 5), the neurological examination failed to demonstrate any focal deficits. Her pulse was regular with a rate of around 100 beats per minute. The recorded blood pressure was 110/70 mm of Mercury , the skin turgor was normal and mucous membranes adequately moist thereby clinically ruling out hypovolemia. Patient was afebrile, all her other vital parameters were stable. A blood biochemical and haematological profile was sent.

Investigations

The laboratory studies showed a normal leukocyte count of $7.0 \times 10^9/L$, a haemoglobin level of 11.5 g/dL and a normal platelet count of $2.94 \times 10^9/L$.

The biochemical parameters were suggestive of a low serum sodium level of 98 mmol/L, potassium was 4.0 mmol/L, calcium was 9.6 mg/dL,

A spot glucose test value was 140 mg/dL .

Blood urea nitrogen and serum uric acid were both below normal at 6 mg /dl and 3 .5 mg /dl and serum creatinine was 0.7 mg/dL.

Plasma osmolality was low at 232 mosmol/kg.

The urinary sodium was 104 meq/L, and urinary osmolality was 652 mosmol/kg.

Both the thyroid function test and serum cortisol level were within the normal range there by ruling out adrenal and thyroid pathologies as potential causes for hyponatremia.

Differential Diagnosis and Treatment

SIADH was diagnosed on the basis of hyponatremia with corresponding serum hypo osmolality and an inappropriately high urinary osmolality. RSWS was less likely as no features of hypovolaemia were present. A possible but least probable differential diagnosis was paraneoplastic syndrome secondary to malignancy but was less likely due squamous cell aetiology of the malignancy in our patient.

The patient was started on 3% Sodium Chloride solution intravenously at a rate of 20 ml/hour with 6 th hourly sodium monitoring with fluid restriction. The patient was shifted to intensive care unit , wherein she was also started on anti seizure drugs as per neurology advice. An indwelling Foley's catheter was inserted to monitor the urine output . A CT scan of the Brain was also done which was reported as normal ,ruling out any acute intracranial pathology.

The patient was switched over to 1.6% saline from Day 3 when the Sodium levels had recovered to 112 mmol/ Lt, and her consciousness level was up to GCS 3. On day 4 patient was shifted to the step down ICU and the repeat Sodium levels on that day were 122 mmol/lit. She was then off IV fluids and sodium supplementation was switched to the oral route.

Outcome and Follow-up

A repeat of biochemical parameters on the 6th day showed a normalization of all the biochemical parameters The serum sodium level had recovered to 133 mmol/L. Plasma osmolality had also normalized to 292 mosmol/kg.

The urinary sodium was 42 meq/L, and urinary osmolality was 402 mosmol/kg.

She made an uneventful recovery without any sequel and was discharged on Day 7.

She is on single agent Capecitabine 1000 mg per mt sq. BD and x 14 days Q 3 weekly and has refused any IV chemotherapy. Once Cisplatin was stopped there were no further episodes of hyponatremia.

She completed her 4th cycle of chemotherapy in February 2015 and is on follow up to date.

DISCUSSION

Controversy is part of the nature of art and creativity. Cisplatin has emerged as a very effective drug , especially for solid tumours like testicular , bladder, ovarian and cervical cancers to name a few. However, cisplatin use has also sparked off a few controversies. Cisplatin has been found to be associated with a wide spectrum of adverse effects which include nephrotoxicity, neurotoxicity, hypokalaemia, hypocalcaemia and hypomagnesemia are the most common ones. Hyponatremia , on the other hand , is one of the rare presentations with cisplatin usage[1]. and cases with hyponatremia seizures secondary to renal salt wasting after cisplatin are anecdotal.

Though cases of hyponatremia secondary to SIADH and RSWS after Cisplatin administration have been reported in literature. The review of literature across the Pub med database revealed only two case reports of hyponatremic seizures secondary to Cisplatin, one in a patient of Glioblastoma Multiforme² and another in a patient of Carcinoma of the breast [3].

In our patient once the side effect was notified to the Institutional Adverse Drug Reaction committee, (under Department of Pharmacology) the Naranjo algorithm was used to ascertain the cause of

the adverse drug event , with a score of 7 the probable cause of the adverse event was attributed to cisplatin[4].

Cisplatin is hypothesized to exert its damage on the different segments of the nephron. Impaired sodium and water reabsorption are as a result of cisplatin induced proximal tubular dysfunction . This results in an increased delivery of sodium and chloride ions to the macula densa of the distal tubule, thus the tubule-glomerular feedback mechanism comes into play, causing a decrease in the renal blood flow which results in a decreased glomerular filtration rate [5,6].

Daugaard et al [7,8] have reported that despite the increased delivery of sodium and water to the distal nephron there is no increase in the reabsorption rate at that site, which demonstrates that cisplatin also damages the distal tubule. Cisplatin's nephrotoxic effect also involves the loop of Henle where the loss of the counter current mechanism impairs water reabsorption [9].

Furthermore Kim et al[10] have also reported in their study that cisplatin causes the downregulation of the aquaporin channels in the collecting tubules, leading to further impairment of water reabsorption Some authors suggest ectopic ADH release as a result of tumour lysis while others attribute it to the stimulation of resistant clones of cancer cells in response to cytostatic agents like cisplatin [11].

The distinction between RSWS and SIADH is of paramount importance as the of SIADH warrants fluid restriction and volume repletion is the dictum for RSWS. A wrong diagnosis can potentially have an adverse effect on the outcome. Renal Salt wasting syndrome usually will have clinical findings of hypovolemia[12] as dehydration, polyuria and hypotension .In our patient the absence of these signs and symptoms was essential in coming to a diagnosis of SIADH.

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