Minireview Article

CAUSES OF DYSNATREMIA IN CANCER PATIENTS – A BRIEF REVIEW

ABSTRACT

Dysnatremias occur with high incidence in cancer patients and have negative impact on quality of life, survival, hospitalization length. Both cancer and its therapy are responsible; coexisting comorbidities may also be involved. Hyponatremia is the most common electrolyte disorder and is usually multifactorial. Hypernatremia, although more rare, is associated with poorer outcome. Diagnosis of true dysnatremias may be a challenge in patients with active cancer, as they must be often differentiated from spurious dysnatremias. Assessing the extracellular volume is the first step for establishing the cause of a dysnatremia; as such hypovolemic, euvolemic and hypervolemic dysnatremias have distinct etiology. The present article briefly reviews cancer-specific and treatment-specific causes of dysnatremias.

Key words: cancer, cancer therapies, hyponatremia, hypernatremia, pseudodysnatremias, extracellular volume status, kidney dysfunction

1. INTRODUCTION

Nephrologists are frequently confronted with dyselectrolytemia in cancer patients, both in acute settings or in ambulatory consultations. Cancer itself, side effects of conventional chemotherapy and of newer anticancer therapies, acute kidney injury or chronic kidney disease, malnutrition and comorbid conditions and their treatment are all potential drivers of electrolyte disorders. Quite often more than one electrolyte disorder is noted in cancer patients. Dyselectrolytemia has negative impact on quality of life, survival, and length of hospitalization. It also negatively influences the timing of anticancer treatment initiation.

In a recent study on 1,088 patients with various neoplasms enrolled in phase 1 trials, most of them (1,044) without renal dysfunction, an electrolyte panel performed before beginning therapy revealed an increased incidence of dyselectrolyemia: 62% had hyponatremia, 40% hypokalemia, 32% hypophosphataemia, 17% hypomagnesaemia and 12% hypocalcemia [1]. The same study also showed that patients with high-grade dyselectrolytemia had a survival 1.61 times lower compared to other patients (without electrolyte disorders or low-grade) [1].

Acute kidney injury is the source of most life-threatening acute and complex electrolyte disorders in the neoplastic patients [2]. In a study of 25,881 patients with various neoplasms, 79% of whom had acute kidney injury, 58% had at least one electrolyte or acid-base disorder; 27.8% of patients had hypocalcemia, 26.7% hypophosphataemia, 22.5% hyponatremia [3]. The same study showed that the mortality of patients with electrolyte disturbances was 7 times higher than those without electrolyte disturbances, and the duration of hospitalization was 3 times longer [3].

2. DYSNATREMIAS

Dysnatremias are the most common electrolyte disturbances in cancer patients and represent major cause for nephrology consultations. Normal serum sodium has a range between 135 to 145 mEq/L,

hyponatremia being defined as serum sodium less than 135 mEq/L and hypernatremia as serum sodium higher than 145 mEq/L. Both hyponatremia and hypernatremia are noted with increased incidence in cancer and the clinicians must differentiate pseudodysnatremias from real sodium disturbances before exploring the cause and recommend a treatment.

Pseudohyponatremia (a serum sodium concentration of less than 135 mEq/L in the setting of a normal serum osmolality) may be present due to increased serum lipid concentrations (hypertriglyceridemia, hypercholesterolemia) or in case of abnormal high serum levels of proteins (malignant monoclonal gammopathies, such as multiple myeloma; hypergammaglobulinemia; malignant lymphoproliferative disorders; immunoglobulin deposition diseases, such as amyloidosis; intravenous immunoglobulin therapy, etc) [4,5].

Pseudohypernatremia (false increase of serum sodium above 145 mEq/L) is noted in case of decreased serum levels of proteins [6,7]. As patients with cancer are prone to protein malnutrition, pseudohypernatremia may be more frequent than pseudohyponatremia, especially in advanced stages of cancer and in critically ill patients admitted to intensive care units.

Pseudonormonatremia is defined as a falsely normal sodium levels in the presence of predisposing factors for dysnatremia [6,7]. As such, a normal value of serum sodium must draw attention to a real hyponatremia in the case of a patient with increased serum lipids or proteins. Alternatively, if serum sodium is normal in a patient with hypoalbuminemia, there is a high probability that real value of sodium is higher than normal.

For differentiation of spurious dysnatremia from a real sodium disturbance, clinicians must be aware of both method of dosing serum sodium and also presence of serum abnormalities in a patient (serum levels of albumin, presence of abnormal proteins, serum levels of cholesterol and triglycerides). Regarding the method of measuring serum sodium, it is important to know if a direct ion-selective electrodes method is used – in this case the results from the laboratory are true, or an indirect method is used – in this case corrections of the results are necessary [8].

3. CAUSES OF HYPONATREMIA IN CANCER

Hyponatremia is the most common electrolyte disturbance in patients with neoplasms [9]. The most frequent neoplasia associated with hyponatremia is small cell lung cancer in which it is secondary to syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH) [10].

The etiology of hyponatremia in cancer is very heterogeneous (Table 1); from the management point of view, it is important to classify hyponatremia as hypovolemic, normovolemic and hypervolemic.

TABLE 1. ***Etiology of hyponatremia in cancer patients***

Type of hyponatremia	**Etiology**
Hypovolemic	Vomiting, diarrhea Cancer extension Kidney salt loss Cerebral metastases
Euvolemic	SIADH
Hypervolemic	Coexisting cardiac failure or secondary to cardiotoxic chemotherapy Nephrotic syndrome

	Acute kidney injury Advanced chronic kidney disease

Hypovolemic hyponatremia occurs in more than 1/3 of cancer patients [8] and is often secondary to increased water and salt loss from vomiting and/or diarrhea following cytostatic regimens. However, increased gastrointestinal losses can also occur secondary to the extension of digestive neoplasms (bowel obstructions, peritonitis, gastrointestinal bleeding, etc.), in acute or chronic uremia, etc. Increased renal losses of salt and water may cause hypovolemic hyponatremia; they may occur after some chemotherapeutics such as cisplatinium which has a direct toxic tubular effect [11], after increased doses of diuretic or in the context of brain metastases in which the kidney-hypothalamus axis is interrupted [12]. Rare causes like paraneoplastic atrial natriuretic peptide or brain natriuretic peptide secretion may also be accompanied by renal salt wasting.

Euvolemic hypovolemia is caused in most cases by SIADH; more rarely it can occur in the context of hypothyroidism, adrenal insufficiency, other coexisting or neoplastic endocrine disorders. SIADH may arise by several mechanisms:

- ectopic secretion of ADH from tumor cells is most often noted in bronchogenic small cell carcinoma (up to more than 40% of the patients), but it has been also reported in head and neck neoplasms and in some hematologic cancers [13-15].
- enhancing the effect of ADH may be noted after cyclophosphamide, non-steroidal anti-inflammatory drugs or anticonvulsants [16].
- increased hypothalamic secretion of ADH may be induced by numerous chemotherapeutics (vincristine, vinblastine, platinum derivatives, cyclophosphamide, ifosfamide, melphalan, interferon, methotrexate, etc.), by most opiates or anticonvulsants [17]; SIADH can also occur in brain metastases by the same mechanism.

Hypervolemic hyponatremia is characterized by an excess of free water in the body. It may occur after increased water intake especially when associated with low-sodium diet and other predisposing condition like treatment with cyclophosphamide. More often in clinical practice hypervolemic hyponatremia is a consequence of congestive heart failure (coexisting or caused by cardiotoxic chemotherapeutics), nephrotic syndrome, decompensated cirrhosis or oliguric stage of acute kidney injury or advanced stages of chronic kidney disease [16,18].

4. CAUSES OF HYPERNATREMIA IN CANCER

In contrast with hyponatremia, true hypernatremia, defined by an increase in serum sodium above 145 mEq/L, is rare in cancer patients, reported in less than 3% of patients [19], but, also compared with hyponatremia, it is associated with higher mortality and hospitalization length [19]. More often cancer patients present with factitious hypernatremia secondary to hypoalbuminemia especially in advanced stages [6].

Presence of hypernatremia denotes reduced water intake, free water loss, or increased sodium intake. Assessing extracellular volume status is important for classification of hypernatremia: hypovolemic, euvolemic or hypervolemic (Table 2).

TABLE 2. ***Etiology of hypernatremia in cancer patients***

Type of hypernatremia	**Etiology**
Hypovolemic	Renal water losses

	Gastrointestinal water losses
Euvolemic	Low fluid intake Central or nephrogenic diabetes insipidus
Hypervolemic	Diet rich in salt Sodium-containing parenteral solutions

Legend: AKI= acute kidney injury

Hypovolemic hypernatremia can occur secondary to predominant water losses or to reduced water intake, especially when associated with a normal or high sodium diet. The general causes of hypovolemic hypernatremia which are frequently reported in neoplasms are gastrointestinal water losses (vomiting / diarrhea after cytostatics, abdominal neoplasms complicated by enteric-cutaneous fistulas, prolonged nasogastric aspiration without parenteral replacement of losses, etc.). Renal water losses may be responsible of hypovolemic hypernatremia during recovery stage of AKI, after increased parenteral doses of mannitol or during severe hyperglycemia (osmotic diuresis) [20]. Enteral nutrition with hyperproteic solutions may also induce hypovolemic hypernatremia if is not associated with enteral or parenteral fluid supplementation [21].

Euvolemic hypernatremia occurs frequently after reduced oral water intake especially in patients with brain tumors, brain metastases or in the context of advanced age. Decreased fluid intake may also occur secondary to reduced appetite or due to esophagitis, mucositis, or nausea after some chemotherapeutics. Euvolemic hypernatremia is a feature of central diabetes insipidus (low ADH secretion) occurring in primary or metastatic tumors of the pituitary gland or hypothalamus, after ablative surgery of these tumors or secondary to whole brain radiation in patients with central nervous system lymphomas or brain tumors [22,23]. In some of these patients, lesions involving hypothalamic osmoreceptors may lead to reduced thirst and decreased water intake with severe dehydration, a dangerous and rare syndrome called adipsic diabetes insipidus [24,25]. Some chemotherapeutics may interfere with the renal action of ADH by inducing nephrogenic diabetes insipidus; the most commonly involved are amphotericin B, ifosfamide, platinum derivatives [26].

Hypervolemic hypernatremia is most often an iatrogenic disorder: excessive parenteral administration of hypertonic sodium chloride or sodium bicarbonate solutions; it rarely occurs due to increased oral salt intake [20].

5. CANCER THERAPY-RELATED DYSNATREMIA

Anticancer therapy is recognizing a major diversification in the last decades and, in parallel with higher remission rates of neoplasms and improved survival rate of the patients, several side-effects are increasingly noted. Dysnatremias are associated with both conventional and novel cancer therapies and the same drug may act by different mechanisms in producing a sodium disturbance (Table 3) [2,27]. In order to search the mechanism for drug-related dysnatremia, the first step is, as stipulated above, to establish the extracellular volume status in each patient. Moreover, as a lot of cancer therapies may induce acute kidney injury through direct tubular toxicity, by acute allergic tubulointerstitial nephropathies or by thrombotic microangiopathy, assessment of kidney function is mandatory for establishing the etiology of dysnatremias [2].

TABLE 3. Main anticancer therapies associated with dysnatremias

Medication class	Type of dysnatremia	Mechanism
Almost all conventional chemotherapeutics	Hypovolemic hyponatremia	Vomiting, diarrhea, esophagitis, decreased appetite and reduced oral fluids
Platinium derivates	Hypovolemic hyponatremia	Tubular toxicity, renal salt wasting
	Euvolemic hyponatremia - SIADH	Unknown mechanism
	Euvolemic/hypovolemic hypernatremia	Tubular toxicity – nephrogenic diabetes insipidus
Vinca alcaloids	Euvolemic hyponatremia - SIADH	Direct toxicity to hypophysis or hypothalamus
Alkylating agents	Euvolemic hyponatremia - SIADH	Stimulate central release of ADH or potentiate the renal effects of ADH
Immune check point inhibitors	Hypovolemic/euvolemic/ hypervolemic hyponatremia	Thyroiditis, adrenalitis, hypophysitis
Tyrosine-kinase inhibitors	Euvolemic hyponatremia - SIADH	Increased release of ADH
Proteasome inhibitors	Euvolemic hyponatremia - SIADH	Unknown mechanism

6. RENAL-DYSFUNCTION ASSOCIATED DYSNATREMIAS

Dysnatremias are specific features of kidney dysfunction, either acute or chronic where they are usually accompanied by other electrolyte disturbances [2,3].

Cancer patients are at increased risk for acute kidney injury secondary to cancer extension, medication or coexisting diseases [2]. Hypovolemic hyponatremia of various etiologies may itself complicate with acute tubular necrosis if left untreated. Hypervolemic hyponatremia (dilutional hyponatremia) is a common feature of oliguric stage of acute kidney injury, being often indication for emergency dialysis. In patients recovering from acute kidney injury and evolving with marked polyuria, hypovolemic hyponatremia or

hypovolemic hypernatremia may develop, depending the oral fluid intake or type of parenteral solutions used for replacement.
Chronic kidney disease is also noted with increased prevalence in cancer patients [28]. Besides dysnatremias secondary to impaired of both urine concentration and dilution abilities, overdosing of kidney-excreted chemotherapeutics may be noted and therefore augmented dysnatremic side-effects.

7. CONCLUSIONS

Dysnatremias are noted with high incidence in cancer patients, have heterogeneous etiology and are often multifactorial. Detailed history and laboratory assessment are necessary to establish the cause of sodium disturbances. Assessing the kidney function and extracellular volume status is mandatory for a precise diagnosis and management. Differentiating true from factitious dysnatremias is often required in clinical practice in cancer patients.

COMPETING INTERESTS DISCLAIMER:

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REFERENCES

1. Ingles Garces AH, Ang JE, Ameratunga M, Chénard-Poirier M, Dolling D, Diamantis N, et al. A study of 1088 consecutive cases of electrolyte abnormalities in oncology phase I trials. Eur J Cancer. 2018; 104: 32-38. doi: 10.1016/j.ejca.2018.08.019. Epub 2018 Oct 10. PMID: 30316017; PMCID: PMC6259582
2. Lameire N, Van Biesen W, Vanholder R. Electrolyte disturbances and acute kidney injury in patients with cancer. Semin Nephrol. 2010; 30(6): 534-547
3. Li Y, Chen X, Shen Z, Wang Y, Hu J, Xu J, et al. Electrolyte and acid-base disorders in cancer patients and its impact on clinical outcomes: evidence from a real-world study in China. Ren Fail. 2020; 42(1): 234-243
4. Adashek ML, Clark BW, Sperati CJ, Massey CJ. The Hyperlipidemia Effect: Pseudohyponatremia in Pancreatic Cancer. Am J Med. 2017; 130(12): 1372-1375. doi: 10.1016/j.amjmed.2017.08.018. Epub 2017 Sep 4. PMID: 28882662
5. Theis SR, Khandhar PB. Pseudohyponatremia. 2022 May 1. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 31985988
6. Liamis G, Liberopoulos E, Barkas F, Elisaf M. Spurious electrolyte disorders: a diagnostic challenge for clinicians. Am J Nephrol. 2013; 38(1):50-57. doi: 10.1159/000351804. Epub 2013 Jun 26. PMID: 23817179
7. Lang T, Prinsloo P, Broughton AF, Lawson N, Marenah CB. Effect of low protein concentration on serum sodium measurement: pseudohypernatraemia and pseudonormonatraemia! Ann Clin Biochem. 2002; 39(Pt 1): 66-7. doi: 10.1258/0004563021901586. PMID: 11853193

8. Dimeski G, Barnett RJ. Effects of total plasma protein concentration on plasma sodium, potassium and chloride measurements by an indirect ion selective electrode measuring system. Crit Care Resusc. 2005 Mar;7(1):12-5. PMID: 16548813
9. Castillo JJ, Glezerman IG, Boklage SH, Chiodo J 3rd, Tidwell BA, Lamerato LE, et al. The occurrence of hyponatremia and its importance as a prognostic factor in a cross-section of cancer patients. BMC Cancer. 2016; 16: 564. doi: 10.1186/s12885-016-2610-9. PMID: 27473121; PMCID: PMC4966824
10. Hansen O, Sørensen P, Hansen KH. The occurrence of hyponatremia in SCLC and the influence on prognosis: a retrospective study of 453 patients treated in a single institution in a 10-year period. Lung Cancer. 2010; 68(1): 111-114
11. Hamdi T, Latta S, Jallad B, Kheir F, Alhosaini MN, Patel A. Cisplatin-induced renal salt wasting syndrome. South Med J. 2010; 103(8): 793-799
12. Momi J, Tang CM, Abcar AC, Kujubu DA, Sim JJ. Hyponatremia-what is cerebral salt wasting? Perm J. 2010; 14(2): 62-65
13. Yoo M, Bediako EO, Akca O. Syndrome of inappropriate antidiuretic hormone (SIADH) secretion caused by squamous cell carcinoma of the nasopharynx: case report. Clin Exp Otorhinolaryngol. 2008; 1(2): 110-112. doi: 10.3342/ceo.2008.1.2.110. Epub 2008 Jun 20. PMID: 19434282; PMCID: PMC2671796
14. Zohar Y, Talmi YP, Finkelstein Y, Nobel M, Gafter U. Syndrome of inappropriate antidiuretic hormone secretion in cancer of the head and neck. Ann Otol Rhinol Laryngol. 1991; 100 (4 Pt 1): 341–344
15. Goldvaser H, Rozen-Zvi B, Yerushalmi R, Gafter-Gvili A, Lahav M, Shepshelovich D. Malignancy associated SIADH: Characterization and clinical implications. Acta Oncol. 2016; 55(9-10): 1190-1195. doi: 10.3109/0284186X.2016.1170198. Epub 2016 May 4. PMID: 27142293
16. Castillo JJ, Vincent M, Justice E. Diagnosis and management of hyponatremia in cancer patients. Oncologist. 2012; 17(6):756-765
17. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. Am J Kidney Dis. 2008; 52(1): 144-153
18. Berardi R, Rinaldi S, Caramanti M, Grohè C, Santoni M, Morgese F, et al. Hyponatremia in cancer patients: Time for a new approach. Crit Rev Oncol Hematol. 2016; 102: 15-25
19. Salahudeen AK, Doshi SM, Shah P. The frequency, cost, and clinical outcomes of hypernatremia in patients hospitalized to a comprehensive cancer center. Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer. 2013; 21(7): 1871-1878
20. Lindner G, Kneidinger N, Holzinger U, Druml W, Schwarz C. Tonicity balance in patients with hypernatremia acquired in the intensive care unit. Am J Kidney Dis. 2009; 54(4): 674-679
21. Gault MH, Dixon ME, Doyle M, Cohen WM. Hypernatremia, azotemia, and dehydration due to high-protein tube feeding. Ann Intern Med. 1968; 68(4): 778-791
22. Arima H, Azuma Y, Morishita Y, Hagiwara D. Central diabetes insipidus. Nagoya J Med Sci. 2016; 78(4): 349-358
23. Yılmaz H, Kaya M, Can M, Özbek M, Keyik B. Metastatic Prostate Adenocarcinoma Presenting Central Diabetes Insipidus. Case Reports in Medicine. 2012; 2012: 452149
24. Dalan R, Chin H, Hoe J, Chen A, Tan H, Boehm BO, et al. Adipsic Diabetes Insipidus-The Challenging Combination of Polyuria and Adipsia: A Case Report and Review of Literature. Front Endocrinol (Lausanne). 2019; 10: 630. doi: 10.3389/fendo.2019.00630. PMID: 31620086; PMCID: PMC6759785
25. Pereira MC, Vieira MM, Pereira JS, Salgado D. Adipsia in a Diabetes Insipidus Patient. Case Rep Oncol. 2015; 8: 385-388
26. Berardi R, Torniai M, Lenci E, Pecci F, Morgese F, Rinaldi S. Electrolyte disorders in cancer patients: a systematic review. J Cancer Metastasis Treat. 2019; 5:79
27. Verzicco I, Regolisti G, Quaini F, Bocchi P, Brusasco I, Ferrari M, et al. Electrolyte Disorders Induced by Antineoplastic Drugs. Front. Oncol. 2020; 10:779.doi: 10.3389/fonc.2020.0077
28. Cosmai L, Porta C, Gallieni M. Chapter 13: CKD as a complication of cancer. Onco-Nephrology Curriculum. American Society of Nephrology. Available at: https://www.asn-online.org/education/distancelearning/curricula/onco/Chapter13.pdf. Accessed May 23, 2022