Case Report
Hyponatremia in malignant neoplasia: A case report

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Abstract:
Hyponatremia is a frequent electrolyte imbalance with diverse etiology that may occur secondary to chemotherapy or autoimmune pathologies. We report the case of a 76-years-old female who presented for symptoms of severe hyponatremia like digestive intolerance, nausea, vomiting, generalized muscle weakness and vertigo, with a serum sodium level of 110 mEq/L. The patient was known with multiple cardiovascular and malignant comorbidities, being diagnosed with a right breast neoplasm with right radical mastectomy and axillary lymphadenectomy. Subsequently, multiple adenopathies were detected, which is why the patient followed several series of chemotherapy with trastuzumab and capecitabinum. These drugs can cause side effects, such as xerophthalmia, xerostomia, which are also frequently encountered in autoimmune pathologies. Hyponatremia is one of the most frequent side effects of capecitabinum. All these side reactions were investigated later, thus following the immunological tests, the diagnosis of Sjogren's syndrome was established. After ruling out other causes, it was established that hyponatremia appeared secondary to the recent administration of capecitabinum or within a syndrome of inappropriate antidiuretic hormone secretion (SIADH), which can be the result of a Sjogren's syndrome.

Keywords: *hyponatremia, Sjögren syndrome, malignant neoplasia*

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1. Introduction

Hyponatremia, defined as a serum sodium concentration less than 135 mmol/L, is one of the most frequent causes of hospitalization. This can appear as an epiphenomenon secondary to chemotherapy or in very rare cases it can appear within a syndrome of inappropriate antidiuretic hormone secretion (SIADH). SIADH can appear in Sjogren's syndrome, an autoimmune pathology, which can be triggered in a neoplastic context [1,2].

2. Case presentation

A 76-year-old-female presented for digestive intolerance, nausea, vomiting, generalized muscle weakness and vertigo, with onset 4 days before. The patient was known with multiple cardiovascular and neoplastic comorbidities. Ten years

previously (2011), she was diagnosed with right breast neoplasm with radical mastectomy and axillary lymphadenectomy, followed by 6 series of chemoradiotherapy. Three years later, she was diagnosed with thrombosis of the right axillary vein.

In 2016, during the clinical examination, a right laterocervical adenopathy was detected, which was biopsied, and after the histopathological examination, it turned out to be a metastasis of a poorly differentiated breast carcinoma. At that time, chemotherapy with capecitabine and trastuzumab was performed. However, the patient developed side effects, with the appearance of a left bundle branch block, accompanied by cardiac dysfunction, secondary to the administration of trastuzumab. Therefore, trastuzumab was replaced by lepatinib (a dual tyrosine kinase inhibitor that interrupts the HER2/neu and epidermal growth factor receptor pathways). In the same year, the patient underwent surgery for a herniated disc located at the level of the L5-L6 vertebrae.

In the following year, secondary to chemotherapy, the patient was diagnosed with ischemic heart disease, for which angioplasty was performed with an active pharmacological stent on the right coronary artery and circumflex artery. At the same time, the patient was evaluated by computed tomography (CT), where no oncological lesions were detected, so the treatment with capecitabine was continued.

In 2018, the positron emission computed tomography (PET-CT) scan highlighted metabolically active secondary left axillary, latero-cervical and retropectoral lymph node determinations and the treatment with capecitabine was continued.

Nevertheless, in 2019, an important regression of the previously described secondary determinations was observed at CT, but with multiple adenopathies located at the upper jugular level (14/12 mm), submental (9/6 mm), right submandibular (13.5/6 mm) and supraclavicular (9 mm). After cardiological examination, echocardiography revealed a left ventricular ejection fraction of 50%, which is why trastuzumab treatment was restarted plus carboplatin. In 2020, the patient stopped the chemotherapy on her own initiative.

A year later, the oncological evaluation revealed an axillary adenopathy <1 cm and a right laterocervical adenopathy of approximately 3 cm, hard, mobile, but with a tendency to fixate on the deep and superficial planes. CT scan revealed multiple mediastinal adenopathies, with maximum axial diameters of 28/18 mm at the left parathyroid level, increasing in size, several right supraclavicular adenopathies increasing in size 11.5/8 mm, but without images suspicious for secondary pulmonary, hepatic or bone lesions.

To initiate chemotherapy, the patient had again a cardiological examination. Echocardiography revealed a preserved ejection fraction of the left ventricle, so trastuzumab was administered at an interval of 21 days. One month later, in December 2021, the patient presented a rash consisting of violet, non-pruritic papules on the upper and lower limbs, which is why she was examined in the dermatology service, receiving a recommendation for oral and topical corticosteroids, with a slowly favorable evolution.

In December 2022, the patient stopped again any chemotherapy. However, the rash spread to the anterior and posterior chest, as well as the sacrum, with severe skin xerosis, as well as xerophthalmia and xerostomia, symptoms that have worsened recently. Therefore, the patient was admitted in a clinical hospital for infectious and tropical diseases, where a differential diagnosis between a cutaneous vasculitis in a Sjogren's syndrome, systemic lupus erythematosus or an undifferentiated collagenosis was discussed. Later, to confirm the diagnosis, extended Antinuclear Antibody (ANA) profile, total complement, C3 and C4 were recommended. The extended ANA panel revealed intensely positive SS-A, SS-B, Ro-

52 and U1-nRNP antibodies, so the diagnosis of Sjogren's syndrome was established.

Two months later, the patient was hospitalized for algoparesthetic lumbosciatica due to dyscartosis and marked asthenia. At the time, no metastases were visible on the CT scan, but only a few infracentimeter lymph nodes at the right subclavicular, paratracheal, left parotid level, without pleuro-pericardial effusion and the presence of dyscarthrosis at the level of the L2-L3 and L5-S1 vertebrae was detected. A cervical magnetic resonance imaging (MRI) was also performed, which highlighted bilateral parotid adenopathy, more pronounced on the right side, of approximately 14.8 mm. The suspicion of paraneoplastic collagenosis was raised and Medrol 16 mg, 1/4 cp/day and Plaquenil 200 mg, 1 cp/day were recommended, as well as an oncological re-evaluation, considering the patient's history.

One month later, the patient presented at the territorial oncology service, to reevaluate and restart chemotherapy. Thus, an Eastern Cooperative Oncology Group (ECOG) performance status of 1 was identified, with restrictions in performing demanding physical activities. Also, considering the progression of tumor markers (CA-125, CA-15.3 and CA-19.9), it was recommended to perform a PET-CT investigation, which revealed 2 nodular images, with increased metabolic activity, with maximum dimensions of 18/15.5 mm, considered to be either a Whartin tumor or thyroid adenopathies. Also, supradiaphragmatic adenopathies were identified, located at submental level (8.5/8 mm), left middle jugulo-carotid (11.5/8.5 mm), left supraclavicular (12/8 mm) and left paratracheal (maximum 15/13 mm).

At the time of admission in our internal medicine clinic, the patient presented an altered general condition. During the clinical examination, diffuse vasculitis-type skin lesions were observed on the anterior chest, right post-mastectomy scar and lymphedema of the right upper limb. Also, the patient had bilateral eyelid edema and palpation revealed adenopathies at the submandibular and right retrosternocleidomastoid level, apparently adherent to the deep planes. The patient was hemodynamically balanced but had a painful abdomen on palpation in the epigastrium and right hypochondrium.

At admission, the blood tests revealed a moderate normochromic, normocytic anemia (Hb 9.5 g/dL), severe hyponatremia (Na 110 mmol/L), a nitrogen retention syndrome (urea 77 mg/dL, creatinine 1.58 mg/dL), D-dimers with increased values (999 ng/mL), a mild hepatic cytolysis, as well as metabolic acidosis (pH 7.29, HCO3 17.3 mEq/L). The electrocardiogram revealed a known left bundle branch block aspect, secondary to administration of trastuzumab.

The routine chest X-ray showed a moderate pleural effusion on the left basal side and mild interstitial changes on the basal right side, as well as the presence of the chemotherapy chamber with the distal end projected at the level of the superior vena cava (Figure 1).

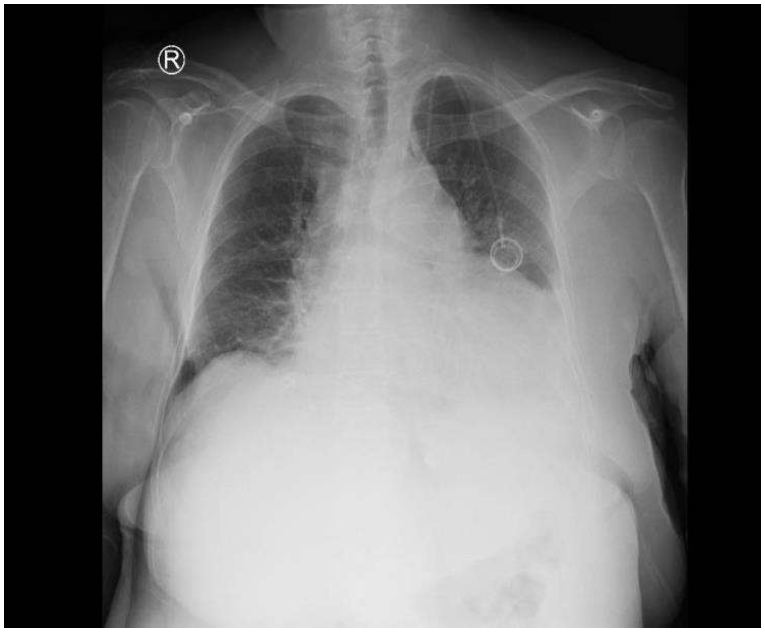

Figure 1. Chest X-ray showed a moderate pleural effusion on the left basal side.

During hospitalization, the patient underwent antihypertensive treatment with beta-blocker and calcium channel blocker, antiplatelet agent, anticoagulant in prophylactic dose, loop diuretic and thiazide, as well as hydro electrolyte rebalancing.

However, shortly after admission, the patient's condition deteriorated, complaining of persistent resting dyspnea, headache, and vertigo, considered to be secondary to severe hyponatremia. Sodium chloride was initiated on continuous infusion, as well as oxygen therapy, with a flow rate of 4 L/min.

An echocardiography was performed, which revealed concentric pericardial fluid of 30 mm and bilateral pleural effusion, 3 cm on the left and 4 cm on the right. Cardiovascular surgery and thoracic surgery consultation was requested. Cervico-thoracic CT scan with contrast substance was performed and reevaluation in view of thoracoscopic puncture and pleurisy.

At the same time, because the bilateral eyelid edema persisted, an ophthalmology consultation was requested, that established the diagnosis of upper eyelid stye in the right eye and nodular blepharoconjunctivitis in both eyes.

During admission, the patient received transfusions with erythrocyte mass, given a hemoglobin value of 7.42 g/dl, in the neoplastic context.

A control chest X-ray was performed, which revealed an important decrease in the size of the pleuro-pericardial fluid (Figure 2).

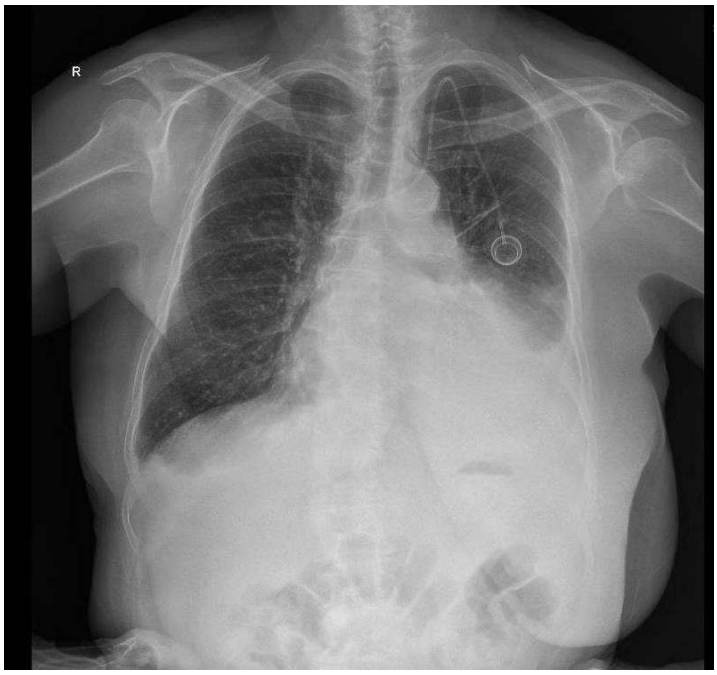

Figure 2. Control chest X-ray

Due to the favorable evolution, with decreasing pericardial and pleural effusion, the patient was treated only with diuretics. Under diuretic treatment, the symptoms ameliorated, with normalization of the serum sodium value. The patient was discharged a few days after, being hemodynamically and respiratory stable, without the need of oxygen therapy.

3. Discussion

We presented the case of a patient with an operated breast cancer, diagnosed with Sjogren's syndrome after chemotherapy, hospitalized with severe hyponatremia, which may be secondary to Sjogren's syndrome or chemotherapy.

Considering that the patient was previously evaluated oncologically with resumption of chemotherapy, her hyponatremia was considered to be due to the administration of capecitabine. Hyponatremia is one of the most frequent side effects of this drug, along with xerophthalmia, xeroderma, erythematous rash and arthralgia[3].

Also, from the patient's history, she was also treated with trastuzumab, a chemotherapeutic drug which, has as very frequent side reactions conjunctivitis, dyspnea, cough, diarrhea, vomiting, nausea, lip edema, abdominal pain, dyspepsia, constipation, erythema, transient rash. As side effects with a lower frequency, we mention xerophthalmia, papillary edema, pericardial exudate, pleural effusion, respiratory failure, xerostomia, xerophthalmia[4].

All these side reactions, which are also found in autoimmune diseases, were investigated later, thus following the performance of the extended ANA panel, the diagnosis of Sjogren's syndrome was established.

Sjogren's syndrome is a systemic autoimmune disease, which causes chronic inflammation of the exocrine glands, frequently affecting the lacrimal and salivary glands, but also the nose, upper respiratory tract, oropharynx and, in the case of women, even the vagina. This pathology has a female predominance, with a 10/1 women/men ratio and is one of the most frequent autoimmune diseases affecting middle-aged individuals[5,6].

Two types of Sjogren's syndrome have been described, primary and secondary. Secondary Sjogren's syndrome is associated with collagen diseases, such as rheumatoid arthritis, systemic lupus erythematosus,

systemic sclerosis, scleroderma and dermatopolymyositis[5,7].

The clinical characteristics of Sjogren's syndrome can be classified into glandular manifestations, which are related to exocrine dysfunction, and extraglandular manifestations, which affect other organs than the exocrine gland. Among the glandular manifestations, Sicca keratoconjunctivitis is described, which manifests with dryness, burning, photophobia, at the level of the salivary glands, symptoms such as xerostomia, dysphagia; loss of the sense of taste due to atrophy of the papillae may appear, but also other glandular effects, such as decreased bronchial secretions, hypochlorhidia, hypopepsinogenemia (atrophic gastritis) and rarely it can also affect the pancreas causing autoimmune pancreatitis[5–7].

The extraglandular manifestations are diverse and involve musculoskeletal system through arthralgias, arthritis, diffuse myalgia, skin damage with xerosis, erythemato-papular eruptions, Raynaud's syndrome, lung damage through interstitial fibrotic lesions and there may even be neurological damage causing sensitive peripheral neuropathy, mixed, mononeuritis multiplex, vegetative neuropathy. This pathology presents a risk of malignant transformation, potentially causing non-Hodgkin's lymphoma[5–7].

One of the easiest methods to quickly establish the diagnosis of Sjogren's syndrome is the complete immunological evaluation of a patient who presents xerophthalmia and xerostomia. The definite establishment of this diagnosis is made according to the American-European Consensus Group (AECG) criteria. These include:

1. Ocular symptoms - dry eyes for more than 3 months;
2. Oral symptoms - feeling of dry mouth for more than 3 months, recurrently swollen salivary glands;
3. Ocular signs - Schirmer test (< 5 mm in 5 min), positive vital dye staining results;
4. Oral signs - abnormal salivary scintigraphy findings, abnormal parotid sialography findings, abnormal sialometry findings (unstimulated salivary flow < 1.5 mL in 15 min);
5. Positive minor salivary gland biopsy findings;
6. Positive anti–SSA or anti–SSB antibody results [6,8].

The diagnosis of primary Sjogren syndrome requires at least four of these criteria. In addition, either criterion number 5 or criterion number 6 must be included[8].

4. Conclusions

There are very rare cases in whom Sjogren's syndrome is diagnosed after chemotherapy because the symptoms can be misleading, being considered in the context of the medication. Also, hyponatremia can appear within a SIADH, which can be secondary to Sjogren's syndrome or chemotherapy.

It has been demonstrated that the administration of capecitabinum causes a decrease in serum sodium levels, so in the case of patients with neoplasms, once chemotherapy with this drug has been initiated, the ionogram must be monitored.

Author Contributions:

D.G, A.D. and C.D. conceived the original draft preparation. D.G, A.D. and C.D. were responsible for conception and design of the review. D.G, A.D. and C.D. were responsible for the data acquisition and for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

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