ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 12, Issue, 03, pp. 54318-54321, March, 2022
https://doi.org/10.37118/ijdr.23963.03.2022

RESEARCH ARTICLE OPEN ACCESS

METASTATIC CARCINOID TUMOR OF LIVER AND BREAST DUCTAL CARCINOMA IN A 26-YEAR-OLD WOMAN: DIAGNOSIS AFTER DETECTION OF HYPERCALCEMIA

Gabriela Maria C. Ferreira*[1], Débora Akemi L. Katori[1], Sarah Adelaide M. Campos[1], Elisa B. B. Nico[2], Jessica S. Morlin[3], Ana Martha F. Lacerda[4], Luís Ronan M. F. Souza[5], Adilha R. Micheletti[6], Sílvia Maria P. Camilo[7] and Geisa P. M. Gomide[7]

[1]Medical Residency Program in Medical Clinic, Federal University of Triângulo Mineiro, Avenida Getúlio Guaritá, 130 CEP 38025-440 Uberaba, Minas Gerais, Brazil (UFTM); [2]Medical Residency Program in Endocrinology, UFTM; [3]Medical Residency Program in Obstetrics and Gynecology, UFTM; [4]Imaging Diagnostic Unit, Clinical Hospital of UFTM; [5]Imaging Discipline, UFTM; [6]Special Pathology Discipline, UFTM; [7]Discipline of Internal Medicine I (Gastroenterology), UFTM

ARTICLE INFO

Article History:
Received 19th January, 2022
Received in revised form
30th January, 2022
Accepted 06th February, 2022
Published online 19th March, 2022

Key Words:
Hypercalcemia; Carcinoid Tumor;
Liver Neoplasms; Carcinoma, Ductal, Breast.

Corresponding author:
Gabriela Maria C. Ferreira

ABSTRACT

The authors describe the case of a 26-year-old woman who started with dyspeptic symptoms and fever. She was referred to the hospital with a suspected diagnosis of liver abscess. Laboratory tests showed severe hypercalcemia. Hypercalcemia associated with malignancy is described in 20 to 30% of cancer patients at some stage of the disease, and means a poor prognosis. Two primary tumors were diagnosed: luminal invasive ductal carcinoma of the breast and metastatic hepatic neuroendocrine disease of undetermined site. This report demonstrates an atypical case of different primary neoplasms in two different locations in a young woman with no previous risk factors.

Citation: ***Gabriela Maria C. Ferreira, Débora Akemi L. Katori, Sarah Adelaide M. Campos, Elisa B. B. Nico, Jessica S. Morlin, Ana Martha F. Lacerda, Luís Ronan M. F. Souza, Adilha R. Micheletti, Sílvia Maria P. Camilo and Geisa P. M. Gomide.*** "Metastatic carcinoid tumor of liver and breast ductal carcinoma in a 26-year-old woman: diagnosis after detection of hypercalcemia*", International Journal of Development Research*, 12, (02), 54318-54321.

INTRODUCTION

Breast cancer is the second most common type of cancer in the world and the most common malignancy in women. Its incidence rates vary worldwide and increase with age[1]. Female breast cancer is most often diagnosed among women aged 65 to 74, with a percentage of new cases of 26%. Among them, there is a special and rare group of patients that includes very young women (≤35 years) with breast cancer. In this age group, the percentage of new cases is 1.9%, based on data from 2014–2018[2]. Recent studies indicate that the most aggressive and invasive breast cancer subtypes are more frequent in young women[3].The main causes of "aggressive" breast cancer in young women appear to be related to advanced stage presentation, more aggressive pathological features, higher rate of triple-negative tumors, and human epidermal growth factor receptor 2 (HER2) overexpression[4]. Carcinoid tumors are rare neoplasms with an estimated incidence of 1 to 2 cases per 100,000 inhabitants. They are derived from enterochromaffin cells capable of producing a wide variety of neuroendocrine mediators including serotonin. Carcinoid syndrome occurs when these mediators, which are normally metabolized by the liver, are present in the systemic circulation. This is due to the occurrence of liver metastases or extra-abdominal tumors, or when they are large and / or multiple tumors that produce a level of mediators that exceeds the capacity of hepatic metabolism. Carcinoid tumors are more prevalent in the fifth or sixth decades of life, affecting women (55%) more than men[5,6]. Hypercalcemia is a common electrolyte disorder in cancer practice, which can be triggered by different etiologies, the most common causes being primary hyperparathyroidism and malignancy[7,12]. Generally, in cases of cancer, patients have high concentrations of serum calcium and are more symptomatic than patients with primary hyperparathyroidism. After observing the manifestations that are useful to assist in the investigation, it is important to have a serum measurement of parathyroid hormone (PTH) and a subsequent distinction between calcium elevations mediated and not mediated by this hormone. Elevations in calcium and PTH correspond to hyperparathyroidism, while elevations in calcium and normal PTH values correspond to malignancy[8,12]. The increase in serum calcium levels is relatively

common in cancer patients, occurring in approximately 20-30% of cases and predominating in solid tumors, such as breast, lung and kidney, and hematologic tumors, such as multiple myeloma[8,13]. In view of the importance of hypercalcemia in the approach and diagnostic definition of neoplasms, it is extremely necessary to confirm the elevation of calcium in the blood and further investigate its etiology. In addition, the presence of this electrolyte disturbance is associated with worse prognosis and advanced cases of cancer. It is essential to mention that the control of symptoms triggered by hypercalcemia are useful for improving the quality of life of these patients, despite not interfering with long-term survival[7-9,12-13]. The present report aims to disclose the importance of hypercalcemia for the suspicion of malignant tumors in a young woman and the severity of the late diagnosis of such neoplasms.

CASE REPORT

Female patient, 26 years old, previously healthy, mother of a healthy 10-year-old child, complained of epigastric pain for six days, in addition to nausea, vomiting and fever of 38ºC. On physical examination, she was in regular general condition, normocolored, dehydrated, acyanotic, eupneic in room air. Flat abdomen, hydro-air noises present, flaccid, presence of pain on deep palpation in the epigastrium and right hypochondrium region, palpable liver 5 cm from the right costal margin. Presence of diffuse erythematous micropellules with raised edges in the abdominal region, denied pruritus. Laboratory tests showed an increase in aspartate aminotransferase (AST 64), alanine aminotransferase (ALT 59), gamma glutamyltransferase (GGT 851) and hypercalcemia (Ca 16.74). Abdominal tomography showed hepatomegaly associated with multiple confluent hypodense lesions attributed to abscesses. Due to hypercalcemia, dosed PTH and 25-hydroxyvitamin D for better investigation. As the service does not have parathyroid hormone-related peptide (PTHrP) dosage and the levels of PTH and 25-hydroxyvitamin D were low, the case was classified as hypercalcemia not mediated by PTH and thus the investigation of malignancy began. Computed tomography of the upper abdomen showed: Liver of enlarged dimensions and heterogeneous sign with multiple focal lesions (Figure 1). A liver biopsy was performed that demonstrated proliferation of small, round cells with hyperchromatic nuclei, delicate chromatin and slightly eosinophilic cytoplasms, growing in an organoid or nodular pattern and infiltrating the liver parenchyma (Figure 1).

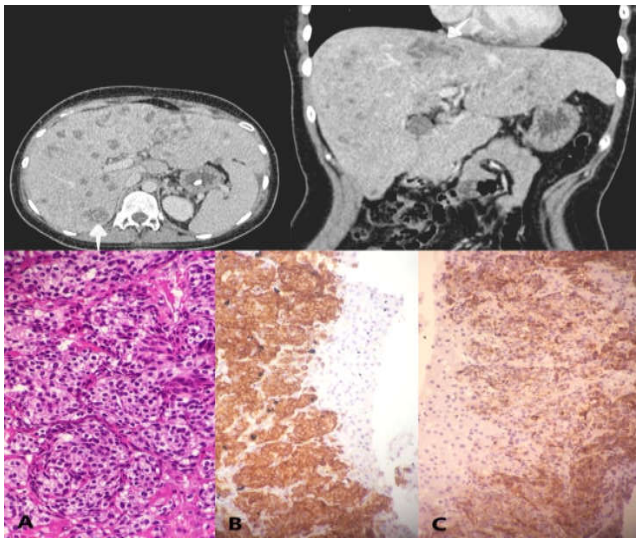

Figure 1. On top: Computed tomography of the abdomen with contrast in the portal phase. Numerous hypodense focal lesions are observed, randomly distributed across the liver parenchyma, with slight contrast enhancement, the largest of which are indicated by arrows. At the bottom: Liver biopsy. A - Photomicrography showing neoplasm of small and round cells, with hyperchromatic nuclei, arranged in an organoid pattern (HE, 40x). B - Immunohistochemical reaction for Synaptophysin positive in neoplasm (Synaptophysin, 20x). C - Immunohistochemical reaction for Chromogranin A positive in neoplasm (Chromogranin A, 20x)

Investigation of the primary site of the carcinoid tumor was started with upper digestive endoscopy, which was normal. Cholangioresonance that did not show changes in the pancreas or bile ducts. Enterotomography that did not identify lesions suggestive of a primary site. Chest tomography with a solid mammary nodule on the right, hypervascularized, with contoured lobes and spicules in the medial quadrant, measuring approximately 4.4x2.7 cm, suspicious for neoplasm, with a focus of calcification inside, without invasion of the chest wall. Mammography and ultrasound of the breasts were performed, which showed an oval nodule in the retroareolar region of the right breast, measuring 3.6 x 1.4 x 2.9 cm (Figure 2). In addition, a smaller, periareolar nodule was found in the upper medial quadrant (UMQ), measuring 1.1 x 0.6 x 1.1 cm. Intramammary lymph node in UMQ of the left breast of 0.3 cm. Lymph node in the right axillary region, measuring 1.1 x 0.6 x 1.0 cm, globular in appearance, with loss of adipose hilum. Categorized as Breast Imaging Reporting and Data System (BI-RADS) 5.

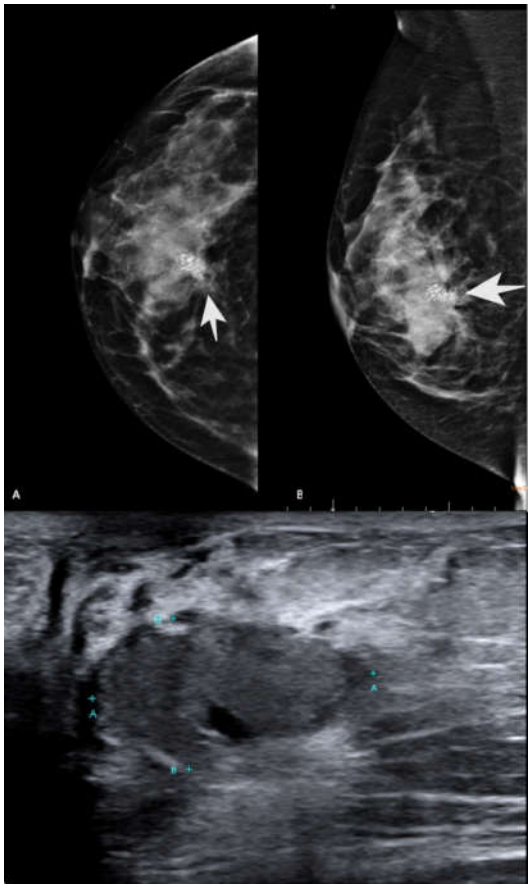

Figure 2. On top: Mammography in the Craniocaudal (A) and Mediolateral Oblique (B) views of the right breast showing coarse, heterogeneous and thin pleomorphic calcifications grouped in the central region (arrows), associated with architectural distortion. At the bottom: Ultrasonography of the right breast shows an oval, hypoechoic nodule, with non-circumscribed margins, parallel to the skin, associated with a certain architectural distortion later, in correspondence to mammography

A breast nodule biopsy was performed, and an intermediate grade breast invasive ductal carcinoma was diagnosed (Figure 3).

Thus, the hypothesis of primary neuroendocrine carcinoma of the breast with metastasis in the liver was ruled out. Then, chemotherapy treatment began, and the patient remains in outpatient follow-up. The patient used cyclophosphamide and epirubicin at the time of diagnosis. She was recently submitted to right adenomastectomy with axillary emptying + breast prosthesis insertion. She is currently well, using octreotide, paclitaxel and radiotherapy, fourteen months after the diagnosis of the two malignant neoplasms. In compliance with the Declaration of Helsinki and the Brazilian ethical standards, the reported case was approved by the Research Ethics Committee of the

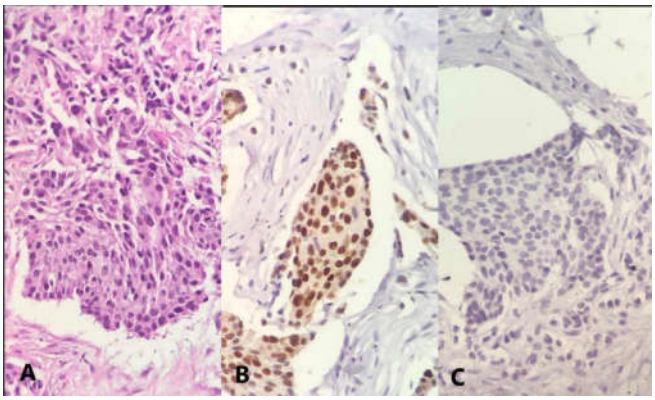

Figure 3. Breast biopsy. A - Photomicrography showing infiltrative neoplasia of atypical cells with mild karyomegaly, growing in cohesive groups (Hematoxylin-eosin, 10x). B - Immunohistochemical reaction for positive estrogen receptor in neoplasia (estrogen receptor, 20x). C - Immunohistochemical reaction for Chromogranin A negative in neoplasia (Chromogranin A, 20x

Clinical Hospital of the Federal University of Triângulo Mineiro, according to Resolution no. 466/2012, which deals with research in humans (approval no. 4.599.875). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

DISCUSSION

The present case includes a very young woman who presented an initial clinical case of nausea, vomiting and who, after an initial laboratory investigation, presented severe hypercalcemia. This disorder is a relatively common clinical problem, with primary hyperparathyroidism and malignancy as the main causes, representing more than 90% of cases[10,11, 17]. Thus, the diagnostic approach generally involves distinguishing between the two. After the laboratory alteration was evidenced and confirmed, the patient's clinical history was reviewed for family history, diet and medications that could lead to hypercalcemia. During the evaluation of a patient with hypercalcemia, confirmation of the change is necessary, correcting for albumin and, in addition, assessing the personal history of the case. Reviewing the diet and medications is necessary to rule out milk-alkali syndrome and drug-induced hypercalcemia, which, when present, should have their usage discontinued[12-15]. In the case presented, such hypotheses were discarded. The signs and symptoms of hypercalcemia, regardless of etiology, are similar, with some characteristics that can help in differentiation. Patients with malignant hypercalcemia usually have higher concentrations and faster increases in serum calcium and are therefore symptomatic. As for primary hyperparathyroidism, the patient may be asymptomatic with chronic hypercalcemia or be a postmenopausal woman with normal physical examination and no other evident cause of hypercalcemia[12-15]. The 26-year-old patient presented with acute clinical manifestations, tending to the diagnosis of hypercalcemia of the malignancy.

After reviewing the clinical history, a laboratory investigation was started, with an initial dosage of PTH and 25-hydroxyvitamin D. Laboratory evaluation is necessary to differentiate hypercalcemia mediated by parathyroid hormone (PTH) from hypercalcemia not mediated by PTH. The first includes primary and tertiary hyperparathyroidism and familial hyperparathyroidism syndromes as causes. The second mainly includes malignancy, vitamin D intoxication, and granulomatous disease. Thus, after confirmation of hypercalcemia, it is necessary to measure PTH[12,13]. In the case in question, low PTH was evidenced, classifying the patient in the group of hypercalcemia not mediated to PTH. In these cases, the literature recommends the measurement of PTH-related proteins (PTHrP) for investigating diseases that secrete the similar PTH peptide as neoplasms[12-15]. However, such an exam is not available in our service.

In addition, a patient presented, on imaging exams, numerous focal lesions with thick walls and varying sizes, affecting all the hepatic segments and the mammary nodule on the right with spiculated contours, suggestive of neoplasms. Thus, biopsies of the lesions of both organs were performed, with metastatic grade 1 neuroendocrine tumor being evidenced in liver biopsy and intermediate grade invasive ductal carcinoma in breast biopsy. The patient was then classified in the hypercalcemia group of the malignancy. It is known that the main cause of hypercalcemia in hospitalized patients is cancer, being a late manifestation and occurring in about 20-30% of patients with malignant neoplasms[12-16]. This disorder can be observed, both in solid tumors and in hematological malignancies, especially in lung, breast and multiple myeloma cancers[15]. The malignancy becomes clinically evident, usually when it causes hypercalcemia, and when present, it presents a worse prognosis. As for its pathogenesis, there are three main mechanisms as previously mentioned, namely tumor secretion of protein related to parathyroid hormone (PTHrP), bone involvement with activation of osteoclasts and osteolysis and secretion of 1,25-dihydroxyvitamin D (calcitriol). The first is present in most cases, mainly squamous cell carcinomas, breast cancer and renal cell carcinoma. The second, related to bone metastases and the third and rarest, occurring in some lymphomas[12-15].This report demonstrates an atypical case of different primary neoplasms in two different sites in a previously healthy young woman without risk factors. We must be aware of clinical signs associated with hypercalcemia, requiring further investigation and exclusion of a possible malignant cause.

Funding: This study was not funded.

Competing and conflicting Interests: No competing financial interests exist.

Abreviations

ALT - Alanine Aminotransferase
AST - Aspartate Aminotransferase
BI-RADS – Breast Imaging Reporting and Data System
Ca - Calcium
GGT - Gamma Glutamyl Transferase
HER2 – Human Epidermal Growth Factor Receptor 2
PTH - Parathyroid Hormone
PTHrP – Parathyroid Hormone-related Peptide
UMQ - Upper Medial Quadrant

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