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CASE REPORT

UNVEILING THE HIDDEN CAUSES OF HYPERCALCEMIA: A JOURNEY THROUGH COMPLEX DIAGNOSIS

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Rezumat:
Introducere: *Hipercalcemia, definită ca un nivel al calciului seric >10,7 mg/dL, este relativ frecventă, afectând 1-2% din populația globală. Principalele cauze includ hiperparatiroidismul primar și malignitățile. Hipercalcemia poate avea o varietate de manifestări clinice, de la forme asimptomatice până la cazuri severe, care pot pune viața în pericol. Hipercalcemia pe termen lung poate duce la afectarea mai multor organe, în special a oaselor, rinichilor și sistemului cardiovascular.*
Prezentarea cazurilor*: Prezentăm trei cazuri de hipercalcemie cu etiologii diferite. Primul caz este al unui bărbat de 60 de ani cu o tumoră paratiroidiană, evidențiată prin ecografie și scintigrafie, iar excizia chirurgicală și examinarea histopatologică ulterioară au confirmat un adenom paratiroidian. Al doilea caz este al unui bărbat de 69 de ani, cunoscut cu hiperparatiroidism primar și diabet zaharat de tip II, care s-a prezentat cu oboseală și edeme periferice. Al treilea caz este al unei femei de 58 de ani cu hipercalcemie secundară unui sindrom paraneoplazic asociat cu un carcinom mamar, confirmat histopatologic.*
Discuție*: Primul caz a evidențiat rolul PTH în apariția hipercalcemiei, cu imagistica sugerând o tumoră paratiroidiană drept posibilă etiologie. Al doilea caz a subliniat asocierea dintre patologiile endocrine, în special hipertiroidismul și hiperparatiroidismul, cu diabetul zaharat de tip II și bolile cardiovasculare. Al treilea caz a prezentat o hipercalcemie secundară sindromului*

paraneoplazic, cu malignitate determinând producția ectopică de proteină asociată hormonului paratiroidian (PTHrP).

Concluzie: *Tehnicile imagistice precum ecografia și scintigrafia sunt necesare pentru presupunerea diagnosticului de hiperparatiroidism primar, în corelație cu testele sanguine specifice, în timp ce hipercalcemia asociată cu malignitate necesită o abordare interdisciplinară. Identificarea precoce și managementul combinat sunt esențiale pentru prevenirea complicațiilor pe termen lung, hidratarea și bifosfonații fiind pilonii principali ai terapiei. Intervenția chirurgicală pentru adenoamele paratiroidiene rămâne curativă, așa cum s-a demonstrat în două dintre cazurile noastre.*

Cuvinte cheie: *hipercalcemie, adenom paratiroidian, PTH, sindrom paraneoplazic, malignitate*

Abstract: *Introduction: Hypercalcemia, defined as an elevated serum calcium above >10.7 mg/dL, is relatively common, affecting 1-2% of the global population. The main causes include primary hyperparathyroidism and malignancies. Hypercalcemia has a wide range of clinical symptoms, from asymptomatic cases to severe cases and life-threatening conditions. Long-term hypercalcemia can lead to multiple organ damage, particularly affecting bones, kidneys and the cardiovascular system.*

Case Presentation: *We hereby present three cases of hypercalcemia with different etiologies. The first case involves a 60-year-old male with parathyroid tumor diagnosed by both ultrasound and scintigraphy findings, subsequent surgical removal of the primary tumor and further histopathological examination confirmed the clinical suspicion of parathyroid adenoma. The second case, a 69-year-old male with known primary hyperparathyroidism and type II diabetes who presented with fatigue and peripheral edema. The third case, features a 58-year-old female with secondary hypercalcemia to a paraneoplastic syndrome associated with breast carcinoma, confirmed through histopathology.*

Discussion: *The first case highlighted the role of PTH in causing hypercalcemia, with imaging suggesting parathyroid tumor as the potential etiology. The second case emphasized the association between endocrine pathologies, specifically hyperthyroidism and hyperparathyroidism, with type II diabetes and cardiovascular disease. The third case presented hypercalcemia secondary to paraneoplastic syndrome, with malignancy leading to ectopic Parathyroid hormone-related protein (PTHrP) production.*

Conclusion: *Imaging techniques such as ultrasound and scintigraphy are required while*

presuming the diagnosis of primary hyperparathyroidism, correlated with specific blood tests, while malignancy-related hypercalcemia requires an interdisciplinary approach. Timely diagnosis and interclinical management are essential to prevent long-term complications, while hydration and bisphosphonates remain the mainstays of therapy. Surgical intervention for parathyroid adenomas remains curative, as presented in two of our cases.
Keywords: *hypercalcemia, parathyroid adenoma, PTH, paraneoplastic syndrome, malignancy*

Introduction

Calcium is a cation of vital importance in the human body, being involved in both functional and structural enzymatic processes [1]. Hypercalcemia is a condition that affects about 1-2% of the global population [2]. The diagnosis of hypercalcemia is based on a concentration of serum calcium over 10.7 mg/dL or ionized calcium over 5.2 mg/dL; a significant increase over a short period of time raises the suspicion of malignancy. The main causes representing 90% of all reported cases are primary hyperparathyroidism (parathyroid adenoma) and cancer, these being the first to address in the clinical diagnosis [1,3]. In neoplasic disease, hypercalcemia is caused by local osteolysis, ectopic production of parathyroid hormone or the correlation with calcitriol increase[4,5].

The parathyroid hormone (PTH) variations are mainly caused by parathyroid gland disorders, an important pathology being represented by the parathyroid adenoma, accompanied by a hormonal increase (primary hyperparathyroidism) [5]. The other 10% of hypercalcemia may occur after vitamin D intoxication, familal genetic disorders, multiple endocrine neoplasia, medication (e.g., thiazide diuretics, lithium), sarcoidosis, and other granulomatous diseases (tuberculosis, berylliosis0 or inflammatory bowel disease [1, 3-7]. Certain endocrine diseases such as thyrotoxicosis, adrenal insufficiency or pheochromocytoma can also be incriminated as secondary causes in hypercalcemia[5].

Depending on the serum calcium level and the period of time in which this phenomenon occurred, upon clinical examination patients can be asymptomatic or with symptoms of varying intensity [1]. The mild-moderate forms of hypercalcemia are associated with concentration problems, depression, and increased risk of bone fractures, while the serious ones (serum calcium values higher than 12–13 mg/dL) are characterized by important gastrointestinal disorders and altered general conditions that can lead to coma[1,5,8-10].

Long-term complications of hypercalcemia cause multiple organ damage. Due to the increased release of calcium from the bones into the blood (secondary to the effect of PTH), bone demineralization occurs along with osteoporosis and reorientation of calcium to other predisposed organs [1, 10-12]. Another targeted organ is the kidney, forming calcium crystals through the accumulation of the ion at the urinary level; over time, they converge, generating kidney stones. Damage at this level can lead to kidney failure. Other targeted tissues are represented by the nervous tissue and the digestive system. Due to the positive inotropic effect of calcium, it

exerts a parasympathetic-like effect on the heart that could indicate patients' admission in the intensive care department [1,5,8-10].

The purpose of the study is to emphasize the various clinical presentations of hypercalcemia, considering its common causes: parathyroid adenomas and paraneoplastic hypercalcemia. The study aims to follow the sequence of diagnostic and treatment methods, taking into consideration the patients medical history and correlating hypercalcemia with the associated comorbidities . This article presents the cases of three patients aged between 58 and 69 years with moderate-severe levels of increased calcium, along with other significant serological changes. Two patients were diagnosed with parathyroid gland adenoma, both having elevated levels of PTH. The second patient had been diagnosed with type II diabetes.

The third patient was diagnosed with hepatic hemangioma, osteoporosis, and a benign nodule in the right breast; in its analyses, multiple tumor markers were also found outside the parameters.

Case presentations

- *Unveiling the Hidden Causes of Hypercalcemia: Parathyroid Adenoma in a 60-year-old Patient with Fatigue and Altered General Status*

  This case report is organized according to CARE guidelines. We present the case of a 60-year-old male who presented to the emergency room with fatigability and altered general status. The patient was known with unobstructed hypertrophic cardiomyopathy, atypical angina class II CCS, and chronic kidney disease stage G3bA2 without a previous diagnosis of primary or secondary hyperparahtyroidism. The patients medication previous to admission included: Acetylsalicylic Acid 75 mg 1 tablet (tb) daily, Metoprolol 50 mg 1 tablet x 2 daily, and Atorvastatin 20 mg 1 tablet daily.

On clinical examination, there were no abnormal findings. The biochemistry panel revealed moderate-severe hypercalcemia of 16.81 mg/dL (reference range: 8.2-10.7 mg/dL) and ionized calcium of 7.8 (reference range: 4.2-5.2 mg/dL), PTH 142 pg/mL (reference range 15-65 pg/mL), Vitamin D 13 ng/mL (reference range 20-40 ng/mL), hyperuricemia of 145 mg/dL (reference range: 12-45 mg/dL), sodium of 124 mmol/dL (reference range: 135-150 mmol/dL), potassium of 88 mmol/dL (reference range: 98-108 mmol/dL), whereas phosphoric levels were greater than normal (5.6 mg/dL, reference range: 2.4-5.1 mg/dL). Serum ferritin was elevated (572.6 ng/mL, reference range: 30–400 ng/mL), raised amylase (412 U/L, reference range: 30–118 U/L), and

ANALYSIS	PACIENTS' VALUE	NORMAL VALUE
Seric calcium	16.81 mg/dL	8.2-10.7 mg/dL
Ionied calcium	7.8 mg/dL	4.2-5.2 mg/dL
PTH	142 pg/mL	15-65 pg/mL
Vitamin D	13 ng/mL	20-40 ng/mL
Urea	145 mg/dL	12-45 mg/dL
Sodium	124 mmol/dL	135-150 mmol/dL
Potassium	88 mmol/dL	98-108 mmol/dL
Phosphoric acid	5.6 mg/dL	2.4-5.1 mg/dL
Ferritin	572.6 ng/mL	30-400 ng/mL
Amylase	412 U/L	30-118 U/L
Alkaline phosphatase	150 U/L	46-116 U/L
WBC	14.8 × 10^3/µL	3.6-10.3 × 10^3/µL
MCHC	36.8 g/dL	32.5-36.3 g/dL
PLT	354 × 103/µL	152-348 × 103/µL
Free T4	1.66 ng/dL	0.61-1.12 ng/dL
TSH	0.158 µIU/mL	0.34–5.6 µIU/mL

Table 1. *The main patients biochemical findings.*

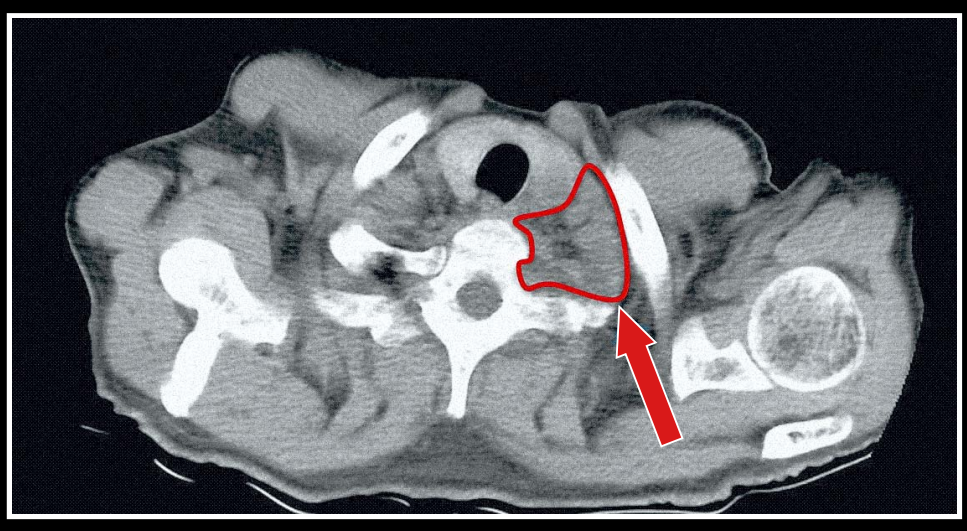

Figure 1. *Native CT scan that shows a macronodule with non-homogeneous structure due to round hypodensities (arrow), with axial dimensions of 32/30 mm and a cranio-caudal dimension of 33 mm, projected posteriorly and inferiorly to the left thyroid lobe.*

increased alkaline phosphatase (150 U/L, reference range: 46–116 U/L). Other parameters from the biochemistry panel were in the normal range. The blood analysis revealed elevated white blood count (WBC) of 14.8 × 10^3/µL (reference range: 3.6-10.3 × 10^3/µL), slightly elevated mean corpuscular hemoglobin concentration (MCHC) at 36.8 g/dL (reference range: 32.5-36.3 g/dL), and platelets' count (PLT), respectively 354 × 103/µL (reference range: 152-348 × 103/µL). Free Thyroxine (Free T4) was raised to 1.66 ng/dL (reference range: 0.61–1.12 ng/dL), and thyroid stimulating hormone (TSH) was lowered to 0.158 µIU/mL (reference range: 0.34–5.6 µIU/mL). No abnormal levels in urine were discovered. Table 1 reveals the main biochemical findings of the 1st patient.

Given the elevated thyroid hormone levels, hyperthyroidism was suspected. As parathyroid adenomas stand as cause for hypercalcemia following an increased PTH production, a neck ultrasound was performed.

The right lobe was measured at 15.8/24/47 mm and described as heterogenous, hypoechoic with 4-5 cystic nodules with regular margins, the largest being sized at 5.2/3.9 mm, possibly of colloid nature. The left lobe measured 21/23/42 mm and was described as heterogenous, hypoechoic with 4 cystic nodules with regular margins, the largest being sized at 6/4 mm, possibly of colloid nature. On the inferior parathyroid was described a cystic nodule with relatively regular margins, a diameter of 32/20 mm, possibly of colloid nature, with a Doppler signal. The isthmus was measured at 38 mm and described as homogenous, with normal margins and an intact capsule. No cervical adenopathies were found.

The bone scintigraphy was performed with a Technetium-99m hydroxy diphosphonate [99mTc-HDP] with an activity of 666 MBq/5.328 mSv administered intravenously. The two captured incidences were whole-body anterior and posterior. The parathyroid scintigraphy was performed with [99 mTc-SESTAMIBI], with an activity of 740 MBq/2.04 mSv, following a wash-out protocol: early scan, 30 minutes after administration, both static and SPECT/CT, and tardive scan, 90 minutes after administration. The latter revealed a hypercaptating nodule, sized at 32/30/30 mm, localized posteriorly and inferiorly of the left thyroid lobe, left to the trachea. The nodule was visible on both early and late scans and suggests a left inferior parathyroid adenoma.

The patient was discharged upon stabilization and referred to the thoracic surgery department for excision of the suspected parathyroid adenoma. Thiamazole 20 mg 1 tb x 2 daily, Furosemide 40 mg 1 tb daily in the morning, and oral hydration 3000 mL daily were added to the patient's chronic

ANALYSIS	PACIENTS' VALUE	NORMAL VALUE
Seric calcium	15.15 mg/dL	8.2-10.7 mg/dL
Ionized calcium	6.27 mg/dL	4.2-5.2 mg/dL
Urea	68 mg/dL	12-45 mg/dL
PTH	126 pg/mL	15-65 pg/mL
Vitamin D	19 ng/mL	20-40 ng/mL
Uric acid	11.5 mg/dL	2.4-7.2 mg/dL
Ferritin	348.3 ng/mL	15-300 ng/mL
Lipase	100 U/L	8-78 U/L

Table 2. *The main biochemical abnormalities of the 2nd patient*

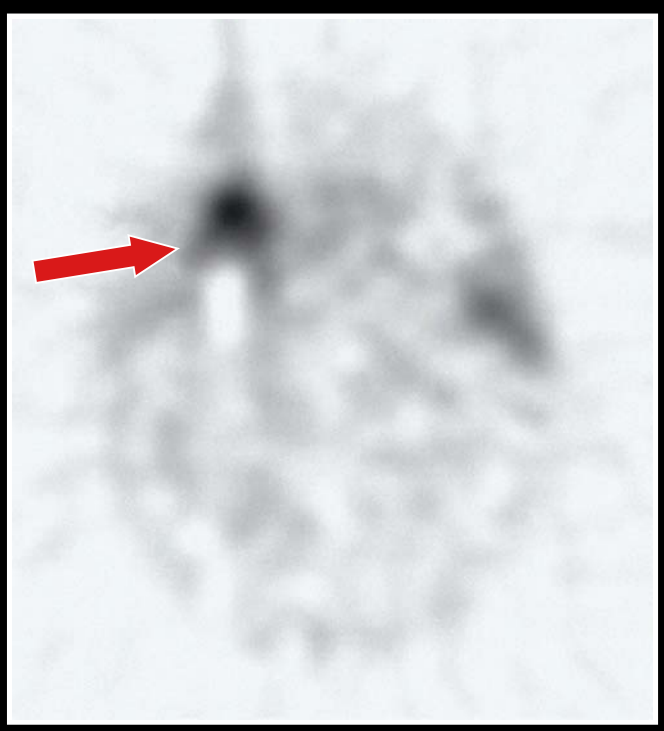

Figure 2. *Parathyroid scintigraphy with [99 mTc-MIBI] showing hypercaptating latero-cervical mas on the right (arrow), suggestive of a parathyroid adenoma measured at approximately 2.6 cm.*

medication. Histopathological examination confirmed the clinical suspicion of left inferior parathyroid adenoma.

- *Unveiling the Hidden Causes of Hypercalcemia: Primary Hyperparathyroidism in a 69-year-old Patient with Confusion and Peripheral Edema*

  This case report is organized according to CARE guidelines. We present the case of a 69-year-old male who presented to the emergency room with fatigue, confusion, and peripheral edema. The patient was previously diagnosed with primary hyperparathyroidism due to a right parathyroid adenoma confirmed with biopsy and histopathological exam, along with hypertension stage II ESC/ESH with high additional risk group, type 2 diabetes, CHD class III NYHA, and left ventricular failure. The patient was on chronic medication with Sacubitril/ Valsartan 49/51 mg 1 tb daily, Spironolactone 25 mg 1 tb daily, Dapaglifozin 10 mg 1 tb daily, Metoprolol 50 mg 1 tb x 2 daily, Metformin 500 mg 1 tb x 2 daily, and Atorvastatin 20 mg 1 tb daily.

On clinical examination, there were no abnormal findings other than peripheral edema. The biochemistry panel revealed moderate-severe hypercalcemia of 15.15 mg/dL (reference range: 8.2 – 10.7 mg/dL) and ionized calcium of 6.27 (reference range: 4.2 – 5.2 mg/dL), hyperuricemia of 68 mg/dL (reference range: 12 - 45 mg/dL), PTH 126 pg/mL (reference range 15-65 pg/mL), Vitamin D 19 ng/mL (reference range 20-40 ng/mL), and uric acid levels were greater than normal 11.5 mg/dL (reference range: 2.4 – 7.2 mg/dL). Ferritin 348.3 ng/mL (reference range: 15–300 ng/mL), increased lipase 100 U/L (reference range: 8–78 U/L). No other parameters were outside limits. The main biochemical changes in the 2nd patient are presented in Table 2:

A thyroid ultrasound was performed preoperatively. The right lobe was measured at 14.3/17.3/38 mm and described as heterogenous, hypoechoic with 5 cystic nodules with regular margins, the largest being sized at 5.6/4 mm, possibly of colloid nature, but with Doppler signal. The left lobe measured 12.4/17/37 mm and was described as heterogenous diffusely, hypoechoic with 3-4 cystic nodules with regular margins, the largest being sized at 3/2 mm, possibly of colloid nature, avascular. Left to the thyroid, an isoechoic mass with regular margins, measured at 13/9 mm and with Doppler signal, was described. The isthmus was measured at 3 mm and described as homogenous, with normal margins and an intact capsule. No cervical adenopathies were found. A parathyroid scintigraphy was performed with $^{[99m}$Tc-MIBI$]$, with an activity of 555

ANALYSIS	PACIENTS' VALUE	NORMAL VALUE
Seric calcium	15.15 mg/dL	8.2-10.7 mg/dL
Ionized calcium	6.22 mg/dL	4.2-5.2 mg/dL
Urea	86 mg/dL	12-45 mg/dL
Sodium	134 mmol/dL	135-150 mmol/dL
Creatinine	2.3 mg/dL	0.5-1.5 mg/dL
Uric acid	15.7 mg/dL	2.4-7.2 mg/dL
Ferritin	>500 ng/mL	15-300 ng/mL
Alkaline phosphatase	245 U/L	46-136 U/L
Cholesterol	251 mg/dL	50-220 mg/dL
LDH	340 U/L	125-220 U/L
Triglycerides	128 mg/dL	30-115 mg/dL
LDL-C	161.6 mg/dL	0-110 mg/dL
PLT	150 × 103/µL	179 – 408 × 103/µL
Fibrinogen	672 mg/dL	238-498 mg/dL
CRP	62.6 mg/L	0-5 mg/L
AST	74 U/L	0-34 U/L
ESR	56 mm/h	5-10 mm/h
Beta-HCG	8.15 mLU/mL	0-2.9 mLU/mL
CA-153	70.5 U/mL	0-31.3 U/mL
CEA	12.04 ng/mL	0-3 ng/mL
CA-125	485.8 U/mL	0-35 U/mL
PTH	20 pg/mL	15-65 pg/mL
PTHrP	9 pmol/L	<2.5 pmol/L
Vitamin D	23 ng/mL	20-40 ng/mL

Table 3. *The main biochemical findings of the 3rd patient*

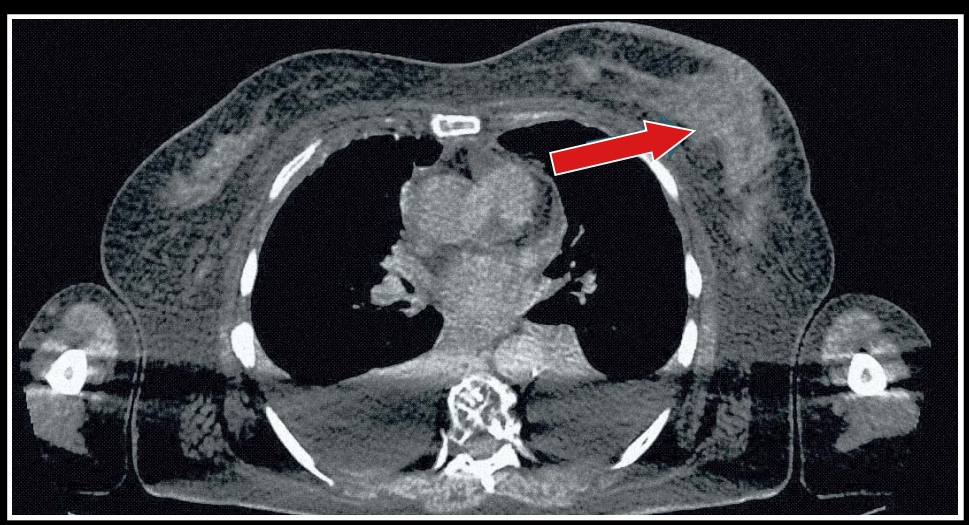

Figure 3. *Low dose CT Scan that shows multiple osteolysis processes due to osteoporosis, multiple pre- and infra-carinal adenopathies and a suspicious aspect of the left breast (arrow), skin thickening and possible nodules. Results were confirmed by mammogram*

Internal Medicine

Clinical Cases

MBq/2.040 mSv administered intravenously, SPECT, and static acquisitions 10 and 90 minutes after administration, in addition to the CT scan performed 90 minutes after (Fig.2).

It showed a latero-cervical mass on the right, suggesting a parathyroid adenoma. The CT scan shows an inframandibulary mass, measured at approximately 2.6 cm. The imagistic findings were highly representative for a parathyroid adenoma.

The patient underwent surgical excision of the mass. A 1.5/1/0.5 cm, yellow mass, with a 70% cystic area was resected and sent to pathology. A microscopic diagnosis confirmed confirmed the diagnosis of parathyroid adenoma.

- *Unveiling the Hidden Causes of Hypercalcemia: Breast Cancer and Bone Metastases in a 58-year-old Patient with Headaches, Nausea, and Dyspnea*

  This case report is organized according to CARE guidelines. We present the case of a 58-year-old female who presented to the emergency room with headache, nausea, dyspnea, and fatigue. The patient was known with stage II hypertension (ESC/ESH) with a high additional risk group. The patient received chronic medication: Candesartan 8 mg 1 tb x2 daily and Furosemide 40 mg 1 tb daily in the morning.

On clinical examination, there were no abnormal findings. The blood panel revealed moderate-severe hypercalcemia 15.15 mg/dL (reference range: 8.2 – 10.7 mg/dL) and ionized calcium of 6.22 (reference range: 4.2 – 5.2 mg/dL), hyperuricemia 86 mg/dL (reference range: 12 - 45 mg/dL), sodium 134 mmol/dL (reference range: 135 - 150 mmol/dL), creatinine 2.3 (reference range 0.5 – 1.5 mg/dL), uric acid levels were greater than normal (15.7 mg/dL, reference range: 2.4 – 7.2 mg/dL). Ferritin >500 ng/mL (reference range: 15–300 ng/mL), increased alkaline phosphatase (245 U/L, reference range: 46–136 U/L). The patient had dyslipidemia: cholesterol 251 mg/dL (reference range: 50-220 mg/dL), LDH 340 U/L (reference range: 125-220 U/L), triglycerides 182 mg/dL (reference range: 30-115 mg/dL), and LDL-C 161.60 mg/dL (reference range: 0-110 mg/dL). The patient had thrombocytopenia 150 × 103/µL (reference range: 179 - 408 × 103/µL). Fibrinogen 672 mg/dL (reference range: 238 - 498 mg/dL), C-reactive protein (CRP) 62.6 mg/L (reference range: 0 - 5 mg/L), AST 74 U/L (reference range: 0 - 34 U/L), ESR 56 mm/h (reference range: 5 - 10 mm/h) along with beta-HCG 8.15 mLU/mL (reference range 0 – 2.90 mLU/mL), CA-153 70.5 U/mL (reference range: 0 – 31.3 U/mL), CEA 12.04 ng/mL (reference range: 0 - 3 ng/mL), CA-125 485.8 U/mL (reference range: 0 - 35 U/mL) were elevated, PTH 20 pg/mL (reference

range 15-65 pg/mL), PTHrP 9 pmol/L (reference range <2.5 pmol/L), Vitamin D 23 ng/mL (reference range 20-40 ng/mL),. No other parameters were outside the normal range. The main biochemical findings are summarized in Table 3.

Abdominal ultrasound revealed a 40 mm hepatic hemangioma lovated in the VI segment and free fluid in costo-diaphragmatic recesses bilateral. Cardiopulmonary x-rays showed peribronchovascular, hilum, and basal interstitial thickening along with bilateral pleural effusion, more severe on the right side. A CT scan showed multiple osteolysis processes due to osteoporosis. Multiple pre- and infra-carinal adenopathies were present. Suspicious aspect of the left breast, skin thickening, and possible nodules were also noted.

A mammogram was performed for proper diagnosys of the breast tumor mass. The right breast was of heterogenous consistency, with nodular opacities >1 cm in the exterior quadrants, central-inferior, and in depth, and isolated calcifications deemed to be benign. The left breast was of heterogenous consistency with raised focal density of the exterior quadrants, especially at the border between them, associated with architectural disorganization. No foci of suspicious microcalcifications or spiculated opacities were found. A few infra and juxtacentrimetric nodular opacities partially masked by adjacent tissues, projected in the outer and lower central, deep inferior, and central quadrants. Isolated calcifications with benign appearances were present.

Numerous diffusely scattered nodular opacities (including in the axillary extension and in the axilla, some of which were most likely adenopathies), the largest one 23/20 mm projecting deep inferior centrally on oblique incidence, with no foci of suspicious microcalcifications were described. Mammographically, there were suspicious abnormalities in the left breast and left axilla (BIRADS 5) and probably benign abnormalities in the right breast.

A general surgery consultation was requested for a biopsy of the left breast tumor mass. Macroscopically, the biopsy material consisted of multiple whitish tissue fragments, ranging in size from 1.5 to 0.5 cm.

Microscopically, epithelial malignant tumor proliferation was identified with a predominantly solid plaque growth pattern, cell cirdoids, and small clustered cells, as well as irregularly appearing glandular structures. The tumor proliferation was composed of relatively cohesive, large cells with marked cyto-nuclear pleomorphism with infiltrative and destructive character on adjacent histological structures. The tumor proliferation showed desmoplastic stroma (more than 30% of the analyzed tumor mass). Tumor proliferation was invasive and insinuated among the connective-adipose structures. Normal terminal duct-lobular structures (TDLU), sequestered in the tumor mass, were occasionally observed. Tumor cells showed severe dyskaryosis and are mitotically active. Some tumor cell cords were arranged around small vascular structures.

Histopathologic features were suggestive for NST (no special type/ductal invasive) breast carcinoma with G2 (moderately differentiated) differentiation grade: Elston-Ellis' Score = 7 (Nothingam modification of Scarff-Bloom Richardson Score) calculated as follows: 2 points for nuclear pleomorphism + 3 points for tubular structures' formation occupying less than 10% of the tumor mass + 2 points for the number of mitotic cells/10 HPF (high-power field). An endocrinologic consult was requested for evaluation of hypercalcemia, who recommends Denosumab 60 mg

subcutaneously administered, saline 0.9% 3000 mL daily, and Furosemide 20 mg/2 mL, 1 ampoule every 6 hours.

Discussion

Calcium homeostasis is maintained through feedback mechanisms regulated by 3 essential factors: PTH, calcitonin and vitamin D [1]. PTH is one of the hormones secreted by the parathyroid glands, and it is the most important element in the occurrence of hypercalcemia. One of the mechanisms by which it acts in this sense consists of the release of calcium from bones, while the other targets kidneys, where it increases the reabsorption in the distal tubules and the synthesis of 1,25-dihydroxyvitamin D in the proximal tubules, increasing the absorption of calcium in the gastrointestinal tract [1,11]. It involves the occurrence of hypercalcemia and hyperphosphatemia; in about 90% of cases, a single benign nodule appears[1-4,9].

The first patient is a middle-aged female patient with a known medical history of chronic heart and kidney diseases. The diagnosis of hypercalcemia secondary to parathyroid adenoma was established due to modified laboratory analyses: high levels of uric acid, phosphoric acid, ferritin, amylase, and alkaline phosphatase and low concentrations of sodium and potassium. Paradoxically, this patient presents high levels of phosphoric acid, which could be explained by the persistence of chronic kidney disease [13]. In the context of chronic kidney disease, the effective excretion of phosphates can no longer be achieved, causing an increase in its serum level instead of urinary increased, as would happen under normal conditions[13].

In this case, diagnostic imaging helped to establish the diagnosis by identifying a tumor mass by both ultrasound and scintigraphy for the visualization of the thyroid and parathyroids. The presence of a visible mass suggestive for lower left parathyroid adenoma and histopathological findings were conclusive for parathyroid adenoma, while the normal scintigraphic aspect of the other three parathyroid glands excludes tertiary hyperparathyroidism. According to the study conducted by Xi Mei in the article entitled "Prevalence of hyperthyroidism with hypercalcemia in Xindu district and the efficacy of vitamin D3 treatment in these patients: a randomized trial", out of a total of 184 patients diagnosed with hypertyroidism, 19.57% of them associated hypercalcemia [14]. The laboratory analyses show an elevated thyroxine level, which supports the diagnosis of thyroid toxicosis. Thyroid hormones influence the metabolism of calcium, leading to its serum increase, with the basic mechanism being bone reabsorption through the activation of osteoclasts[14].

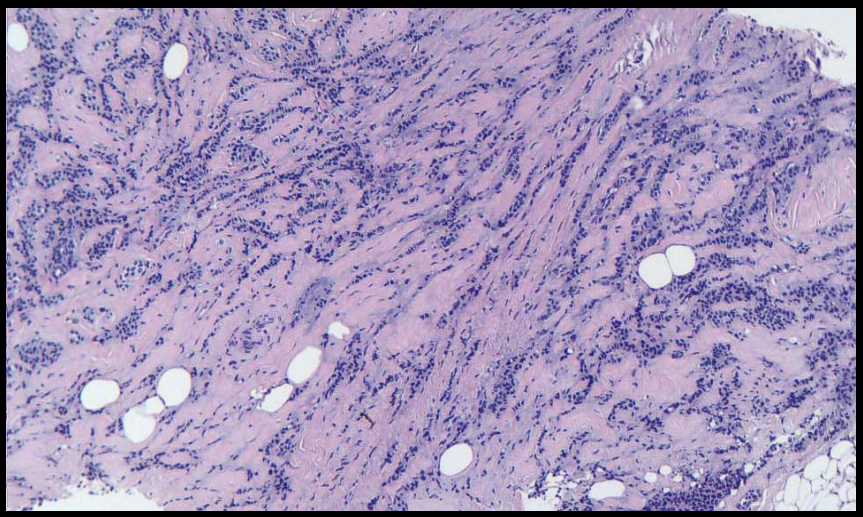

Figure 4:
Hematoxyline Eosin stain, 100x: Cords with infiltrative characteristics of epithelial cells with hyperchromatic nuclei; collagen bands; rare adipocyte cells.

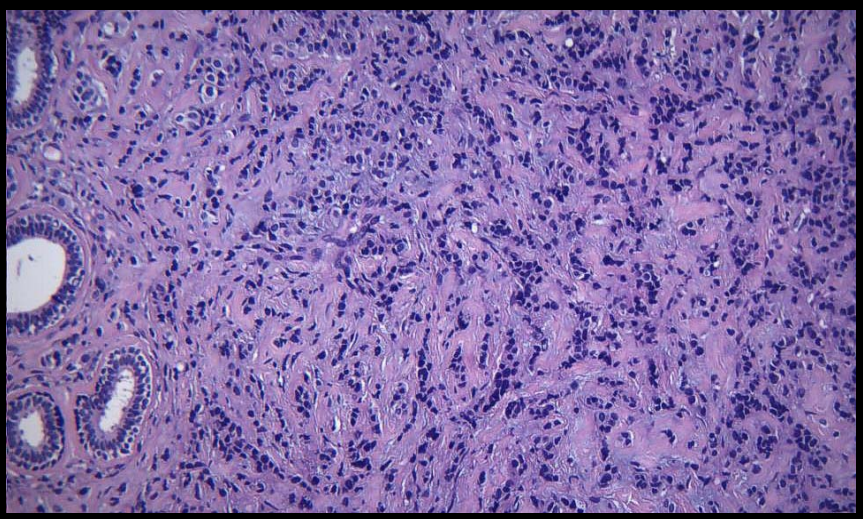

Figure 5:
Hematoxyline Eosin stain, 200x: Cords and groups of atypical epithelial cells with pleomorphic nuclei, with infiltrative characteristics; rare ductal structures.

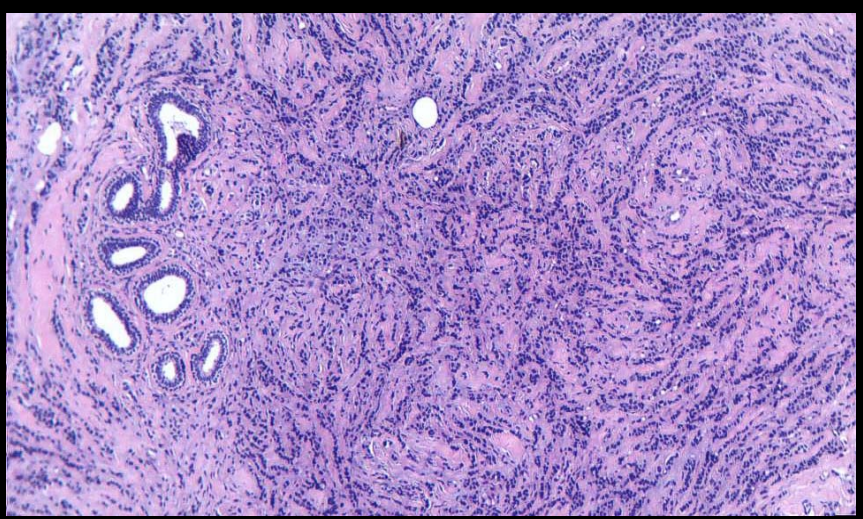

Figure 6:
Hematoxylin eosin, 100x: Cords and groups of atypical epithelial cells with hyperchromatic nuclei and reduced cytoplasm; infiltrative characteristics; rare ductal structures.

The second case emphasized the association of structural changes of both thyroid and parathyroid glands in a patient with a medical history of chronic heart disease and complex endocrinological pathology: type II diabetes mellitus (DM) and parathyroid adenoma. Specifically, based on this hospital admission, thyroid pathology was also highlighted. The association of primary hyperthyroidism with other chronic conditions is well established in the literature: kidney, bone, increased incidence of cardiovascular diseases[13,15].

Thus, a particularity of the case consists in the association of multiple endocrine pathologies like parathyroid adenoma and type 2 diabetes mellitus, respectively, as in our case [16]. We can consider a possible association with multiple endocrine neoplasia type 1 (MEN 1), with autosomal dominant transmission detected as having the maximum incidence in patients over 40 years old.

Primary hyperparathyroidism occurs in over 95% of all investigated cases and can be associated with glucose intolerance and type 2 diabetes [16]. At the same time, the thyroid pathology could have been associated with MEN type 2, a situation however disproved by the establishment of the diagnosis of hyperthyroidism, based on blood and imaging investigations, and the absence of pheochromocytoma [1]. The concurrent treatment of thyroid pathology was, in this case, prioritized among surgical removal of the parathyroid adenoma. Our data are in accordance with W. H. Taylor et al. that highlighted the coincident diabetes mellitus and primary hyperparathyroidism, out of a sample of 205 patients known with primary hyperthyroidism, 7.8% also found the presence of diabetes, predominantly type 2 (78%) [17]. Moreover, the study showed that there are higher chances of developing diabetes over a pre-existing hyperthyroidism, to the detriment of the reverse situation [16,17].

One mechanism involved in this association is based on the increased amount of intracellular calcium that interferes with glucose carriers, thereby generating insulin resistance[17].

The third patient highlights hypercalcemia secondary to paraneoplastic syndrome. According to literature, about 30% of patients with malignancies have been found to develop hypercalcemia over time [18]. The two main mechanisms are PTHrP-related hypercalcemia and hypercalcemia secondary to osteolysis. The PTHrP is a protein produced by tumor cells that mimics the action of PTH; hypercalcemia induced by osteolysis caused by metastases[19].

Our case suggests an elevated calcium level as a cause of paraneoplastic syndrome, with ectopic production of PTHrP, without evidence of possible bone metastases. The

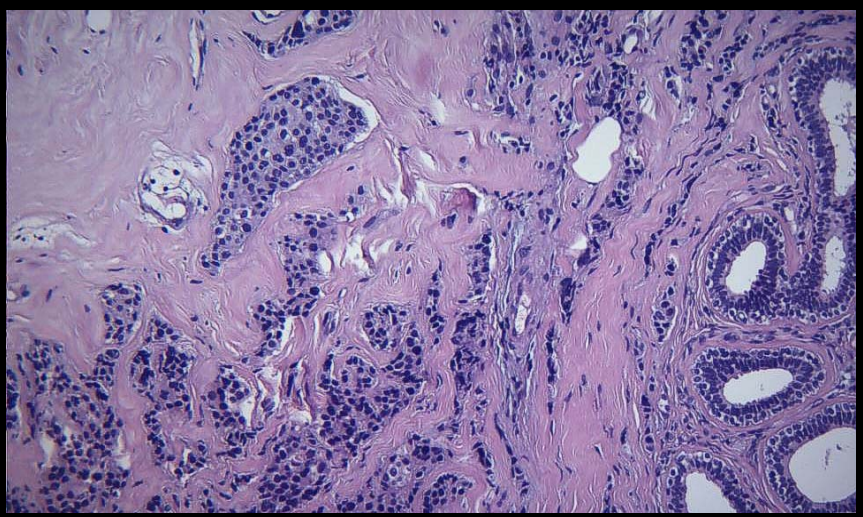

Figure 7:
Hematoxylin eosin stain , 100x: Nests and trabeculae of cells with carcinomatous infiltrative appearance, areas of sclerosis, and adipocyte cells.

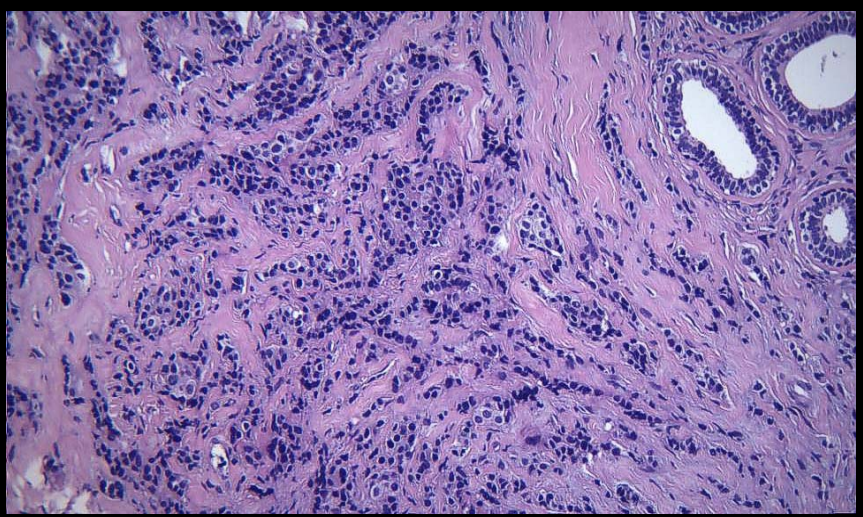

Figure 8:
Hematoxyline eosin stain, 200x: Nests and cords of epithelial cells with carcinomatous infiltrative appearance; rare typical ductal structures.

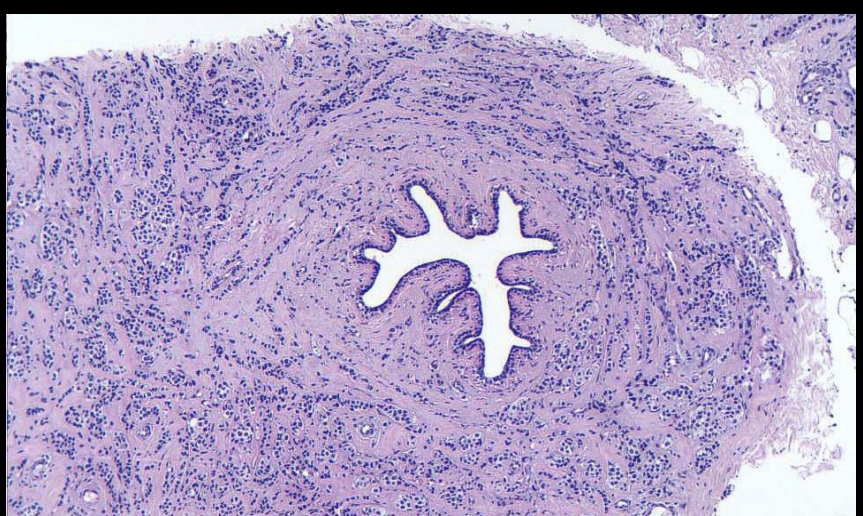

Figure 9:
Hematoxyline Eosin stain, 100x: Trabeculae of epithelial cells with carcinomatous appearance surrounding a dilated and deformed mammary duct.

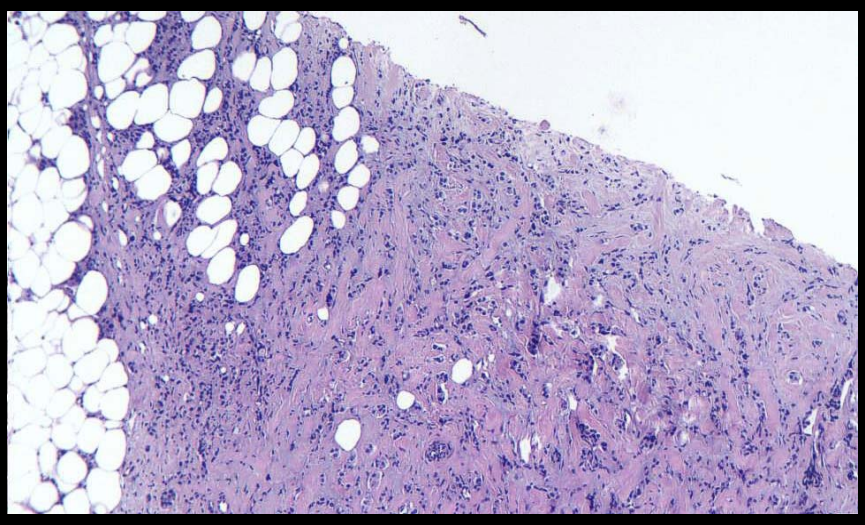

Figure 10: *Hematoxyline Eosin stain, 100x: Trabeculae of epithelial cells with infiltrative carcinomatous appearance in adipose tissue.*

difference between malignant hypercalcemia and the one caused by other factors that lead to increased serum calcium levels is the clinical manifestation; the malignant type involves rapid and progressive growth, not allowing the body to adapt [4].

Regarding the treatment of hypercalcemia, the goal is to increase elimination of extracellular calcium and to reduce absorption from the gastrointestinal tract. Bone resorption should also be reduced [20]. We adopted this therapy in the third case by using Denosumab.

The first line of treatment is intravenous hydration with 0.9% saline to stimulate sodium-linked calciuresis. Saline solution was shown to reduce calcium by 2.4 mg/dL. This measure is effective in mild cases of hypercalcemia, starting with 1-2 L, followed by 200-300 mL/hour. The goal is to normalize diuresis (100-150 mL/h) [10]. Hydration should be followed by electrolyte replacement, such as potassium and magnesium[10].

The second pillar for treating hypercalcemia is represented by bisphosphonates. In cases of severe hypercalcemia (over 12 mg/dL), saline with bisphosphonate infusion is the first line of treatment, with level one evidence [2,10]. Calcitonin is another effective treatment, usually used alongside hydration and bisphosphonates. Its effect takes place in around two hours after intramuscular or

subcutaneous injection, quicker than bisphosphonates. Calcitonin is not useful in chronic therapy, and the effect only lasts around 4 to 7 days[21].

The biggest concern in severe hypercalcemia and some of the main reasons for ICU admission is the risk for cardiac rhythm disorders and acute kidney injury [22, 23]. In an ICU setting, the first line of treatment remains aggressive hydration with saline and bisphosphonates. Other measures for severe, non-responsive hypercalcemia, renal dialysis, or replacement therapy might be an option if renal failure occurs [24]. None of our patients needed ICU admission. The first and second cases were deferred to surgery.

Study limitations

The most important study limitation is the lack of some laboratory analyzes that could have improved the diagnostic approach and their correlation with the common pathology of the three patients, hypercalcemia.

To begin with, in approaching the second case, we suggest the dosage of thyroid hormones earlier, which could have guided the differential diagnosis between thyroid and parathyroid pathology, before imaging. Continuing with the third patient, we complete the list of tumor markers for an easy direction towards the breast neoplasm, considering as etiology genetic causes or possible associated risk factors and the correlation of cancer with hypercalcemia. According to literature, dosing BRCA 1 and 2 genes could have confirmed or excluded hereditary transmission, respectively CA 27.29 which would help to establish the diagnosis correlated with CA 153.

However, the diagnosis of certainty can only be made after the histopathological examination.

Conclusions

Hypercalcemia presents in multiple clinical ways, as depicted above, depending on the underlying cause and severity. Imaging techniques such as ultrasound and scintigraphy are required while presuming the diagnosis of primary hyperparathyroidism, correlated with specific blood tests, while malignancy-related hypercalcemia requires an interdisciplinary approach in order to be confirmed. Early identification and appropriate management are critical in order to prevent long-term complications. Management of these cases is mainly comprised of proper hydration and bisphosphonate treatment; these represent the key elements of therapy in these cases. Surgical intervention for parathyroid adenomas remains curative, as seen in two of our cases. This article paves the way for future studies and case presentations that will exemplify the various manifestations of hypercalcemia.

Conflicts of Interest: The authors declare no conflicts of interest.

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