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Case Report

A Hidden Carcinoma with Mixed Squamous and Neuroendocrine Differentiation Revealed Through Paraneoplastic Hypercalcemia: A Case Report

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ABSTRACT

Hypercalcemia of malignancy is most associated with squamous cell carcinomas, but can also be observed in many advanced cancers. It is usually mediated through parathyroid hormone-related protein and is known as humoral hypercalcemia of malignancy. We present a rare case of humoral hypercalcemia of malignancy associated with a poorly differentiated carcinoma exhibiting both neuroendocrine and epithelial differentiation.

A 67-year-old man was found to have elevated serum calcium on presentation to the emergency department for shortness of breath and abdominal pain. Further investigation revealed low serum parathyroid hormone (indicating a non-parathyroid etiology of hypercalcemia) and elevated serum parathyroid hormone-related protein (supporting a diagnosis of humoral hypercalcemia of malignancy). Imaging revealed numerous disseminated subcutaneous nodules, peritoneal carcinomatosis with liver, cecal, lymph nodes, and bone metastases. Histopathology and immunohistochemistry revealed a poorly differentiated carcinoma exhibiting features of both squamous and neuroendocrine differentiation, along with a high level of cell proliferation. The patient was treated with intravenous fluids and intravenous bisphosphonates as per hypercalcemia management guidelines, with only minimal improvement in his serum calcium level. Our patient succumbed to the metabolic complications within a few days of presentation before the primary site could be identified or definitive treatment could be initiated.

Hypercalcemia of malignancy is a common presentation of advanced cancer and is associated with poor prognosis. We describe a case of hypercalcemia of malignancy in a patient with a poorly differentiated carcinoma of unknown primary origin with neuroendocrine and squamous differentiation, which is a rare phenomenon.

1. Introduction

Hypercalcemia is a common electrolyte abnormality encountered in clinical practice, typically associated with hyperparathyroidism or malignancy. Among malignancy-related hypercalcemia cases, humoral hypercalcemia of malignancy (HHM) mediated by parathyroid hormone-related protein (PTHrP) is the most prevalent mechanism [1]. While HHM frequently accompanies squamous cell carcinomas, its occurrence in tumors with neuroendocrine and epithelial differentiation is rare. Here, we describe an unusual case of severe hypercalcemia as the initial presentation of a poorly differentiated carcinoma of unknown primary origin with neuroendocrine and squamous differentiation. This case highlights the challenges of recognizing diagnostic and therapeutic limitations in a poorly differentiated cancer of unknown primary with neuroendocrine and epithelial differentiation presenting as humoral hypercalcemia of malignancy.

2. Case Presentation

A 67-year-old man presented to the emergency department with an acute onset of shortness of breath and abdominal pain. His past medical history included hypertension, hyperlipidemia, heart failure with reduced ejection fraction, and chronic obstructive pulmonary disease on home oxygen therapy following bilateral lung volume reduction. His current medications include metoprolol, sacubitril/valsartan, spironolactone, empagliflozin, rosuvastatin, and long-acting and short-acting inhalers. On presentation, the patient had a temperature of 38.2°C, a heart rate of 112 beats per minute, a blood pressure of 92/60 mmHg, a respiratory rate of 24 breaths/min, an oxygen saturation of 80% on room air and 86% on home oxygen at 2 L.

2.1. Laboratory Data

The initial laboratory investigations revealed hypercalcemia with a total serum calcium level of 13.9 mg/dL (normal reference range: 8.5 – 10.5 mg/dL). Blood albumin was 3.4 g/dL (normal reference range: 3.4 – 5.4 g/dL) and corrected calcium was 14.4 mg/dL (normal reference range: 8.5 – 10.5 mg/dL). His renal function was normal, with a creatinine level of 1.1 mg/dL (within the normal reference range of <1.28 mg/dL) and an estimated glomerular

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Table 1: Timeline and Trends in Biochemical Profile

Parameter	Reference Range & Units	Day 1	Day 2	Day 3	Day 4	Day 5
Creatinine	<1.28 mg/dL	1.1	1.13 (H)	1.60 (H)	3.03 (H)	3.90 (H)
Calcium	8.5 - 10.5 mg/dL	13.9 (H)	12.7 (H)	12.4 (H)	12.9 (H)	12.8 (H)
Albumin	3.4-5.4 g/dL	3.4				
Calcium, Ionized	1.00 - 1.35 mmol/L	1.64 (H)	1.75 (H)	1.78 (H)	1.63 (H)	1.66 (H)
Corrected Calcium	8.5 - 10.5 mg/dL	14.4 (H)	13.2 (H)	12.9 (H)	13.4 (H)	13.3 (H)
Alkaline Phosphatase	40 - 140 IU/L	166 (H)				
Estimated Glomerular Filtration Rate (eGFR)	>60 mL/min/1.73m^2	97	74	58 (L)	48 (L)	40 (L)
Magnesium	1.8 - 2.3 mg/dL	1.7 (L)	2.1		1.7 (L)	2.2
Phosphorus	2.5 - 4.5 mg/dL	2.5	1.9 (L)	4.1	4	3.7
PTH Related Protein	11 - 20 pg/mL	119 (H)				
PTH, Intact	15 - 65 pg/mL	6 (L)				
25-Hydroxy vitamin D	>20 ng/mL	12 (L)				
1,25-Dihydroxy vitamin D	20 - 79 pg/mL	14 (L)				

H, High; L, Low.

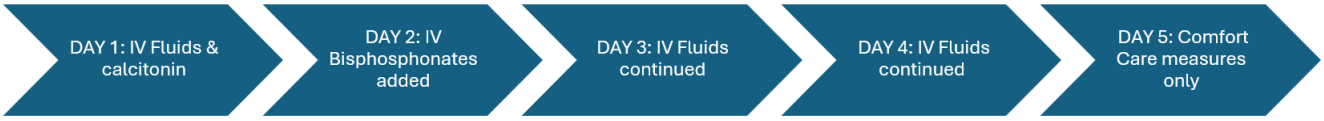

Figure 1: Serial Biochemical Trends During Hospitalization in a Patient with Paraneoplastic PTHrP-Mediated Hypercalcemia.

filtration rate in the 90s (within the normal reference range of >60 mL/min/1.73 m²). His ECG showed normal findings.

Hypercalcemia was further confirmed with an ionized calcium of 1.64 mmol/L (normal reference range: 1.1 – 1.35 mmol/L). Parathyroid hormone (PTH) levels were suppressed at 6 pg/mL (normal reference range: 10–65 pg/mL), suggesting a non-parathyroid etiology for the hypercalcemia. Further workup for hypercalcemia revealed a low 25- OH vitamin D level of 12 ng/mL (reference range >20 ng/mL), a low 1,25- vitamin D level of 14 pg/mL (normal reference range: 20 – 79 pg/mL) and an elevated PTH-related peptide (PTHrP) at 119 pg/mL (normal reference range: < 27 pg/mL). This confirmed humoral hypercalcemia of malignancy **(Figure 1)**.

2.2. Imaging

A contrast-enhanced CT scan of the chest, abdomen, and pelvis revealed numerous disseminated subcutaneous nodules, peritoneal carcinomatosis, and liver metastases. Multiple metastatic lymph nodes were present in the chest and abdomen, along with lucent lesions in the lower lumbar spine. A 5.2 cm mass-like thickening was noted at the cecal base, which was suspected to be either a primary malignancy or an infiltrative metastatic deposit **(Figure 2)**.

A biopsy of a right chest wall lesion was performed. Histopathology showed a poorly differentiated carcinoma with features of both squamous and neuroendocrine differentiation. Immunohistochemical staining was positive for cytokeratin (CK AE1/3, an epithelial marker), synaptophysin (a neuroendocrine marker), and markers for squamous cell carcinoma, including CK 5/6 and p40 (patchy), with a high MIB-1 (Ki-67) index of 90%, indicating a high level of cell proliferation. It was negative for markers of lung cancer (TTF-1), colorectal cancer (CK20), and lymphomas (LCA). The presence of both squamous and neuroendocrine markers was interpreted as an aberrant expression due to high-grade, poorly differentiated carcinoma.

2.3. Management

Management Treatment of severe hypercalcemia was initiated with intravenous hydration using normal saline at 200 mL/hour and calcitonin 4 units/kg subcutaneously every 6 hours (for a total of 48 hours). Due to inadequate response with minimal to no improvement in hypercalcemia, Zoledronic acid 4 mg IV was given on day 2 of hospitalization. Despite prompt initial treatment with intravenous hydration, calcitonin, and zoledronic acid, our patient's calcium level did not improve, reflecting the aggressive tumor biology and limited efficacy of conventional measures in advanced malignancy-associated hypercalcemia **(Table 1)**. Ultimately, the patient wished for comfort care measures only, and he passed away within a week of his presentation. The primary site of the tumor remained unidentified.

3. Discussion

Hypercalcemia of malignancy (HCM) is a common presentation of a paraneoplastic syndrome associated with poor prognosis in cancer patients [2]. It is seen in almost 10% of patients with advanced cancer, and most patients fail to receive definitive treatment for cancer before succumbing to the complications [3, 4]. Common signs and symptoms of HCM are non-specific and include gastrointestinal disturbances, fatigue, polyuria, neurological changes, or even cardiac arrest.

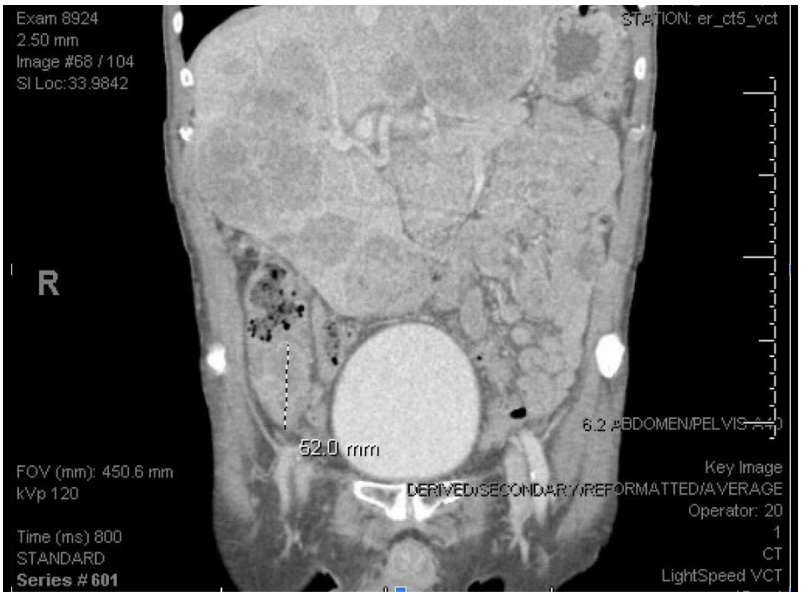

Figure 2: CT scan of the abdomen and pelvis showing multiple metastatic lymph nodes, peritoneal carcinomatosis, and liver metastases.

Hypercalcemia of malignancy primarily occurs through four mechanisms, with the most common being humoral hypercalcemia of malignancy, mediated by parathyroid hormone-related protein (PTHrP), which accounts for approximately 80% of cases [1]. Other mechanisms include local osteoclast stimulation by tumor cells (20%), resulting in bone destruction and calcium release. Rare causes include the production of active Vitamin D (1,25-dihydroxyvitamin D) by some lymphomas, and very rarely, tumors secreting authentic parathyroid hormone [1].

PTHrP-mediated hypercalcemia is classically associated with squamous epithelial malignancies (e.g., head and neck, lung) but can occur in other advanced malignancies as well [5]. The expression of both epithelial (cytokeratin) and neuroendocrine (synaptophysin) markers on immunohistochemistry, with a high Ki-67 index (90%), complicated the classification in our case, a phenomenon rarely described in the literature. Immunohistochemistry did not suggest lung, colorectal, or lymphoma as the primary site but was consistent with poorly differentiated tumors, showing positivity for both squamous and neuroendocrine markers. Establishing the primary site of cancer was thus challenging in our case due to widespread metastasis and complex immunohistochemistry with mixed epithelial and neuroendocrine differentiation. Such expression may represent an advanced stage of an undifferentiated tumor and portends a poor prognosis. PET-CT and further testing with tumor markers were considered to help identify the primary site or additional metastasis, but this could not be due to a change in the patient's goals of care. Our patient's presentation with severe hypercalcemia and elevated PTHrP raised suspicion for an underlying malignancy; however, the failure to identify the primary tumor highlights the diagnostic and therapeutic dilemma.

4. Conclusions

Hypercalcemia of malignancy, most commonly mediated by parathyroid hormone-related protein (PTHrP), is typically seen in squamous epithelial malignancies. Our case describes an uncommon phenomenon of a tumor with neuroendocrine features coexisting with squamous differentiation, presenting as paraneoplastic PTHrP secretion and severe hypercalcemia with severe metabolic complications.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research

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None

Informed consent

Verbal consent was obtained from the patient for the case report.

Large Language Model

We have employed an advanced Large Language Model (LLM) to enhance and refine the English-language writing. This process focused solely on improving the text's clarity and style, without generating or adding any new information to the content.

Authors Contribution

FM and AS contributed to conceptualization, AS wrote the original draft, and AIPS and FM were responsible for review and editing.

Data Availability

None

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