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Case Report

Hypercalcemia and Acute Kidney Injury in a Case of Angiosarcoma

Marco Tondo[1*], Francesca Romana Della Rovere[1], Francesca Moccia[1], Teresa Valentina Ranalli[2] and Sandro Feriozzi[1]

[1]Nephrology and Dialysis Unit, Belcolle Hospital, Viterbo, Italy

[2]Pathology Unit, Belcolle Hospital, Viterbo, Italy

*Address for Correspondence: Marco Tondo, Nephrology and Dialysis Unit, Belcolle Hospital, Strada Sammartinese snc, 01100 Viterbo Italy, Tel: +39 07613338602; Fax: + 39 0761338600; E-mail: marco.tondo@asl.vt.it

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Abstract

Hypercalcemia can be due to various disorders and may be associated with a spectrum of clinical manifestations, ranging from few (if any) symptoms in patients with mild and chronic hypercalcemia to obtundation and coma with severe hypercalcemia.

We report a case of a 64-year-old male admitted to our emergency room for an altered mental state, severe hypercalcemia (serum calcium 17,5 mg/dl) and Acute Kidney Injury (AKI) treated with loop diuretics, fluid infusion and bisphosphonates with normalization of calcium, improvement of renal function and subsequent discovery of a bleeding lesion in the right inguinal region diagnosed as epithelioid angiosarcoma with osteolytic metastases.

Angiosarcoma is a rare and highly aggressive malignant tumour originating from lymphatic or vascular endothelial cells. It makes up less than 2% of all soft tissue sarcomas and can occur in any organ with a high rate of local recurrence and metastasis [1].

Tumour-induced hypercalcemia is a frequent complication of advanced cancers, but it has been rarely reported in patients with angiosarcoma.

Although this type of neoplasm diagnosis is often late and carried out in the most advanced states, we report a particular mode of presentation of angiosarcoma in this clinical case.

We emphasize the necessity of screening for the potential existence of neoplasms for patients with hypercalcemia and AKI. We also point out the importance of accurate and appropriate management of hypercalcemia.

Keywords: Acute kidney injury; Hypercalcemia; Angiosarcoma

Introduction

Hypercalcemia can be due to various disorders, but primary hyperparathyroidism and malignancy account for most cases. Hypercalcemia may be associated with a spectrum of clinical manifestations, ranging from few (if any) symptoms in patients with mild and chronic hypercalcemia to obtundation and coma in severe hypercalcemia patients. The symptoms and signs associated with hypercalcemia are typically independent of the aetiology and usually correlate with serum values. Clinical renal features of hypercalcemia are polyuria, nephrolithiasis, and acute or chronic renal failure. Severe hypercalcemia (>12 mg/dL or 3 mmol/L) can lead to a reversible fall in glomerular filtration rate. The impairment of renal function is mediated by direct renal vasoconstriction natriuresis-induced volume contraction [2,3].

We report the case of a middle-aged male presenting with severe obtundation and acute kidney injury associated with severe hypercalcemia. The diagnostic procedures were unsuccessfully carried out. A casual event (bleeding from an overlooked skin lesion) led to the diagnosis of angiosarcoma with osteolytic metastases.

Case Presentation

A 64-year-old Caucasian male was admitted to our emergency room, presenting with an altered mental state and respiratory failure. The patient had a past medical history of hypertension, dyslipidemia and was a chronic smoker. Moreover, he had undergone a surgical intervention of aortoiliac endoprosthesis for an aneurysm of the abdominal aorta. The patient was lethargic, disoriented in time and space, and non-cooperative during the examination. A physical exam revealed regular heart activity, signs of mucus-skin dehydration and absence of oedema. Arterial blood pressure was 115/70 mmHg, body temperature 36°C, SpO2 96% in oxygen therapy at 3 l/min. Diuresis was in the normal range, and there were no significant ECG alterations. Brain CT was negative. Chest radiography showed no ongoing parenchymal alterations. An abdomen CT showed normal morphology and size of the kidneys, absence of obstructions to the urinary tract, increased prostate volume, and lymphadenopathies.

Laboratory Investigations carried out on admission showed that serum calcium was 17,5 mg/dl, serum creatinine 3,74 mg/dl, while the other parameters are listed in Table 1. The serum electrophoresis did not show monoclonal components; free light chains in the blood and urine were in the normal range (75,7 k mg/l and 60,7 λ mg/l, ratio 1,25). PTH 8 pg/ml, 25OH-Vitamin D 22 ng/ml. PTHrp not dosed. The prostatic specific antigen was in the normal range.

Further diagnostic investigations led to finding a 10 mm hypoechoic thyroid nodule with vascularization in the left para-isthmic site and sub-centimetric nodular formations at the posterior segment of the posterior lobe and the middle lobe of the right lung. Skeletal radiography was negative.

We treated the patient with furosemide 20 mg/day and fluid infusion with NaCl 0.9% at a rate of 150 ml/h during the emergency. Afterwards, we added zoledronic acid at an appropriate dose to the degree of renal failure (3 mg/day) for three days. Treatment with methylprednisolone 20 mg/day was started and continued for ten days.

While we were assisting in the evolution of the clinical course and looking for a diagnosis, sudden and unexpected bleeding from the right inguinal region revealed the presence of an overlooked brownish, bruise-like bulging lesion which was surgically removed. The histological examination showed an ulcerated and partially thrombosed epithelioid angiosarcoma (Figure 1).

Technetium-99m-pertechnetate whole-body SPET/CT scan showed a pathological increase in the radiopharmaceutical concentration in the right sacroiliac region and ipsilateral femur in the pertrochanteric area.

During the subsequent clinical course, there was a progressive reduction of the serum calcium returning to average serum values of 9 mg/dl. A simultaneous improvement of the renal function occurred with a gradual decrease of the serum creatinine to 1.26 mg/dl eGFR 63 ml/min/1.73 m^2 at the time of discharge.

Simultaneously, there was an improvement in general clinical conditions with an increase and normalization of attention and of awareness. Because of these events, the patient was moved to the oncology department to treat angiosarcoma with chemotherapy.

Table 1: The table summarizes essential laboratory tests at the Nephrology unit admission.

Variable	Reference range	Detected parameter
Azotemia (mg/dl)	17 - 45	201
Creatinine (mg/dl)	0,7 – 1,5	3,74
Glycemia (mg/dl)	60 - 110	97
Kalium (mmol/L)	3,5 – 5,3	4,1
Natrium (mmol/L)	134 - 147	142
WBC (x 1000/mmc)	4,1 – 10,2	13
Hb (g/dl)	13,5 – 17,5	13,2
PLT (x 1000/mmc)	150 - 400	145
pH	7,35 – 7,45	7,5
pCO2 (mmHg)		44,5
pO2 (mmHg)		53,9
Serum free calcium (mmol/L)	1,15 – 1,29	2,13
Chlorine (mmol/L)	98 - 106	95
HCO3- (mmol/L)		35,3
Anion Gap (mmol/L)	8 - 16	10
Uric acid (mg/dl)	3,5 – 8,5	10,2
Phosphorus (mg/dl)	2,5 – 4,5	3,5
Magnesium (mg/dl)	1,6 – 2,6	1,96
PCR (mg/l)	0 - 5	97,5
VES (mm/h)	1 - 20	41
Proteinaemia (g/dl)	6,1 – 8,2	4,6

Discussion

This case is challenging because of the peculiar symptomatology, including alterations of the state of consciousness. An extensive investigation was required to find the cause of hypercalcemia and acute renal failure.

Changes of mental state represent a frequent cause of admission to the emergency room and are a complex challenge for the clinical doctor because of the multiple possible etiologies [4,5].

Hypercalcemia can determine various clinical manifestations ranging from few or no symptoms to severe obtundation and coma. Patients with serum calcium below 11.5 mg / dL are usually asymptomatic and, therefore, may not require any immediate treatment. When calcium levels exceed 12.5 mg / dL, patients are instead more likely to be symptomatic. Regardless of whether they are or not, there is a high risk of developing complications such as tissue calcifications. Further increases in values, particularly over 14 mg / dL, can lead to severe volume depletion, acute kidney injury, arterial hypotension, drowsiness, and altered mental state as occurred in our patient [6-8].

Primary hyperparathyroidism and cancer-associated hypercalcemia are the most frequent causes of hypercalcemia. Tumour-induced hypercalcemia has been reported to occur in 10-15% of patients with advanced cancer [8, 9]. It can be observed in any type of tumour with the following mechanisms: mediated by parathyroid hormone-related peptide (PTHrP), ectopic secretion of PTH, or osteolysis secondary to bone metastases. In our case, the PTH and VitD values were in the normal range, and the diagnosis of primary hyperparathyroidism was excluded.

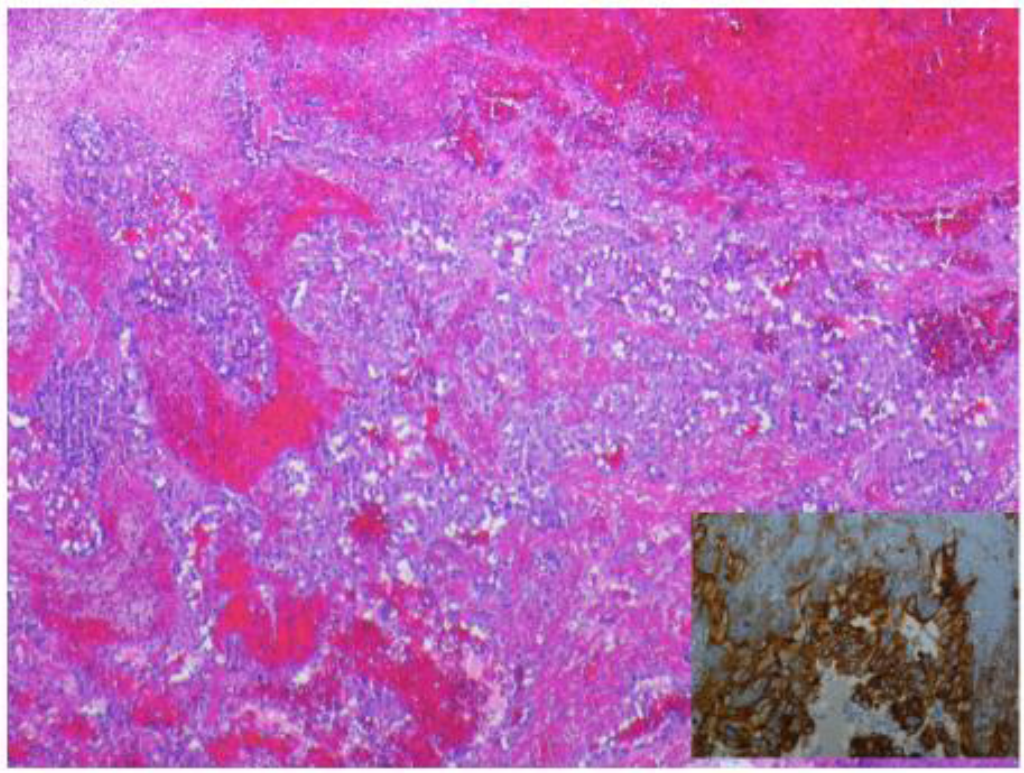
The most frequent pathologies associated with hypercalcemia are malignant tumours with osteolytic lesions (such as breast cancer and renal cell carcinomas), multiple myeloma and other hematologic malignancies which affect the bone marrow. Some malignant tumours (lung, kidney, urogenital system) and granulomatous tumours (sarcoidosis, tuberculosis, leprosy and histoplasmosis) release PTH or vitamin D-like molecules or other hypercalcemia-inducing substances [9-13]. The lytic lesions can also be due to the release of cytokines (TNF, IL-1) by neoplastic cells, which stimulate the differentiation of precursor cells to active osteoclasts [13]. Other causes of hypercalcemia are endocrine diseases and drug intake [14].

In this case, anamnestic and laboratory data (hypercalcemia, anaemia, renal failure) were highly indicative for diagnosing multiple myeloma. However, the relevant investigations' negative results (serum immune-electrophoresis, serum and urinary free light chains and Rx skeleton) ruled out this diagnostic hypothesis.

The correct diagnosis was made by chance after unexpected bleeding from a skin lesion in the right inguinal region turned out to be an angiosarcoma.

Angiosarcoma is a subtype of sarcoma consisting of a malignant tumour of the endothelium. It is a relatively rare disease representing about 1-2% of all soft tissue sarcomas, with an average of

Figure 1: A medium-power magnification of the image of neoplastic vessels dissecting dermal collagen. Neoplastic vascular channels lined by epithelioid endothelial cells with abundant eosinophilic cytoplasm. (H&E 40x) In the insert, immune-histochemistry staining shows neoplastic cells CD31 positive (endothelial cells).



approximately 2-3 cases per million inhabitants. Angiosarcoma is typically formed in soft tissues and skin, but there are development cases in the bones, liver, spleen, or heart. It is an aggressive tumour regardless of its grade with high reoccurrence rates, and the mortality rate is exceptionally high. Early diagnosis in deep soft tissue sarcomas is usually not easy to make because angiosarcoma can be asymptomatic until an advanced stage [1].

Patients typically present with a blue or purple lesion that has been present for several months [1]. These lesions may appear macular, nodular, or plaque-like. Diffuse, clinically undetectable intradermal spread leads to indistinct borders and a high incidence of multicentricity [1]. Advanced lesions can show bleeding or ulceration.

The factors associated with an adverse prognosis were patient age >70 years, necrosis, large tumour size, greater tumour depth and epithelial morphology [16]. However, prompt recognition can allow the complete surgical removal of the tumour, significantly improving the outcome [17].

After surgery, chemotherapy is widely used for metastatic cutaneous angiosarcoma. The therapeutical regimens with doxorubicin-based and taxanes are considered the gold standard for treating soft tissue sarcomas [15].

Tumour-induced hypercalcemia is a frequent complication of advanced cancers, but it has been rarely reported in patients with angiosarcoma [18,19]. In our case, the low value of PTH and the bone lesions in the per-trochanteric sacroiliac region suggest a pathogenetic mechanism due to bone lytic metastasis.

Therefore, in our patient, the hypercalcemia was sustained by lytic bone lesions due to osteosarcoma metastasis demonstrated by CT at the sacroiliac region, the right femur and the proximal portion of the tibia. The hypercalcemia in this patient caused mental alteration and acute renal failure.

Conclusions

Among all the causes of hypercalcemia, diagnostic investigations

relating to identifying possible neoplastic causes besides the multiple myeloma are sometimes neglected. Here, we presented a case of acute kidney injury, altered mental state and severe hypercalcemia due to osteolytic lesions, in turn, due to angiosarcoma metastasis.

We emphasize the necessity of screening for the potential existence of neoplasms for patients with hypercalcemia and associated acute kidney injury, as well as multiple myeloma.

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Conflict of Interest

The authors have declared that no conflict of interest exists.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Human and Animal Rights

This article does not contain any studies with human participants or animals performed by any of the authors.

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