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CASE REPORT

Hypercalcemia: Uncovering a Rare Case of Skeletal Muscle Non-Hodgkin's Lymphoma

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Abstract
We report a case of an 80-year man who presented with a two-week history of confusion and poor oral intake. He was found to be dehydrated with acute kidney injury, hypercalcemia, and pancytopenia. A previously undetected right leg mass was discovered. Radiologic studies of the right knee found a fibula shaft fracture. MRI confirmed this finding and showed the presence of a heterogeneous mass involving most of the calf muscles. Biopsy confirmed the diagnosis of a rare musculoskeletal non-Hodgkin's lymphoma of the right leg. A brief discussion to this type of pathology follows this rare presentation.

Key words: musculoskeletal lymphoma, bone fracture, hypercalcemia, bisphosphonates.

Case Presentation
An 80 year-old man, known to have hypertension and vitiligo, presented to the Emergency Room with a two-week history of confusion and poor oral intake. He was on no medications. Physical examination revealed: temperature 37ºC, pulse 76 bpm, respiratory rate 23 per minute, BP 175 / 51 mm Hg, and SPO2 92 % on room air. The patient was disoriented to time and place. Upon skin inspection, multiple vitiligo patches were noted. The right leg was larger than the left. Midcalf circumferences were 43 cm on the right and 30 cm on the left (Figure 1). A firm irregular mass was palpable at the postero-lateral aspect of the right leg involving the calf and extending upward above the knee; dorsiflexion of the right foot produced severe leg pain. There was no organomegaly, palpable lymph nodes or neurologic deficits. The remainder of his examination was negative.

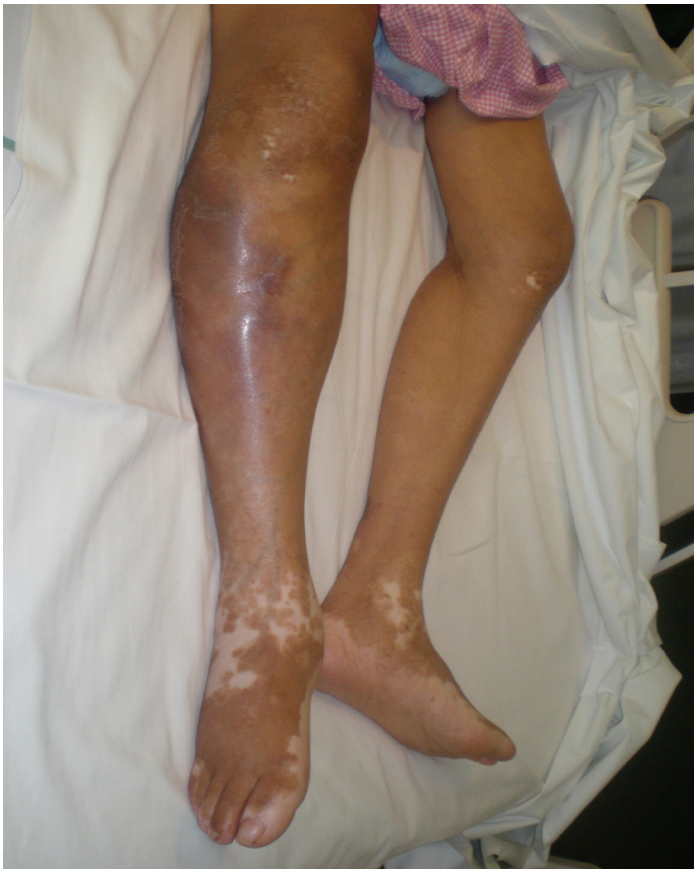

Figure 1. Right leg swelling

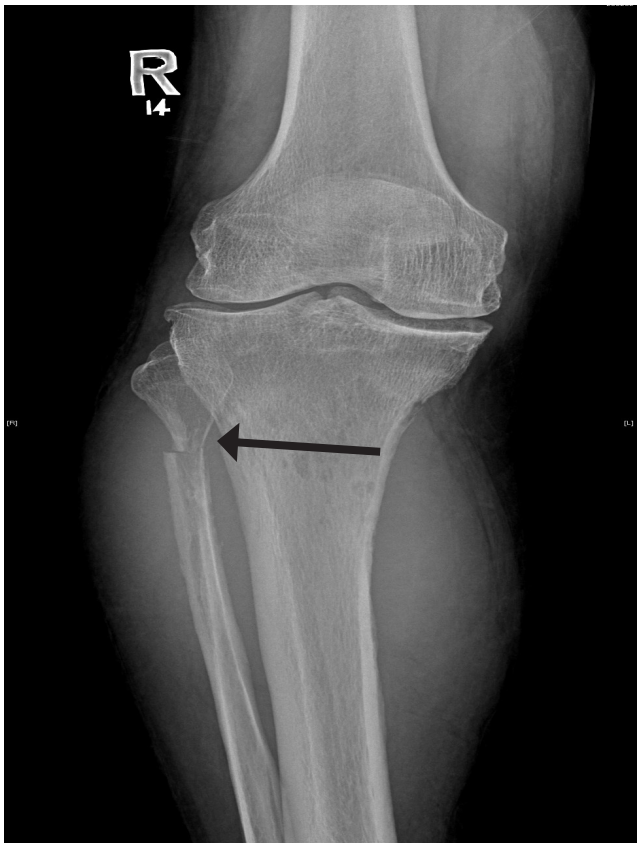

Figure 2. right knee X-ray showing fracture of the right fibular shaft (arrowhead)

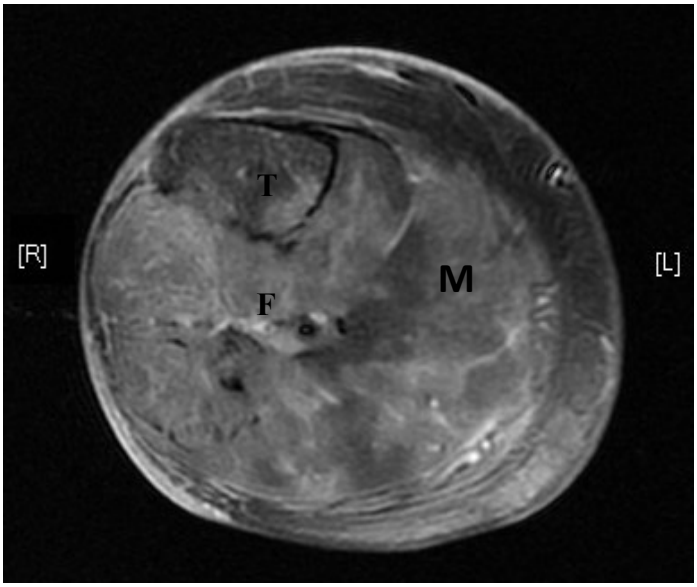

Figure 3. MRI of the right leg showing infiltration of the muscles by a heterogeneous mass (M); Tibia (T); Fibula (F).

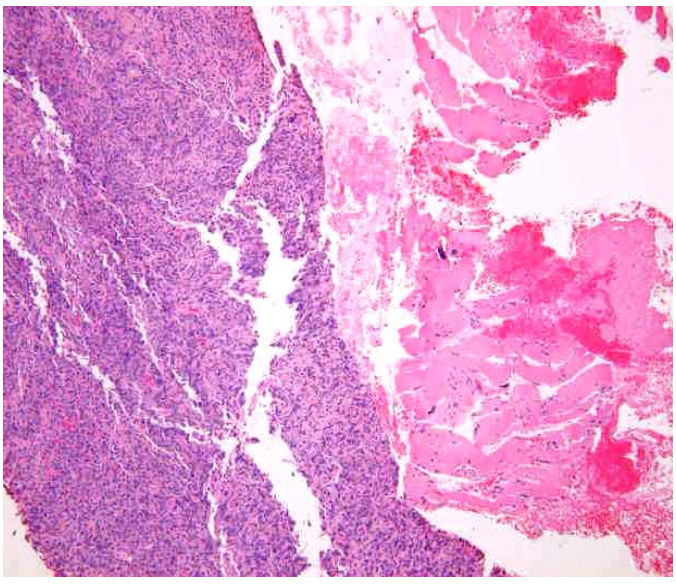

Figure 4. Skeletal muscle fibers (right side) showing infiltration by lymphoma cells. (Hematoxilin & Eosin stain; 10X)

T

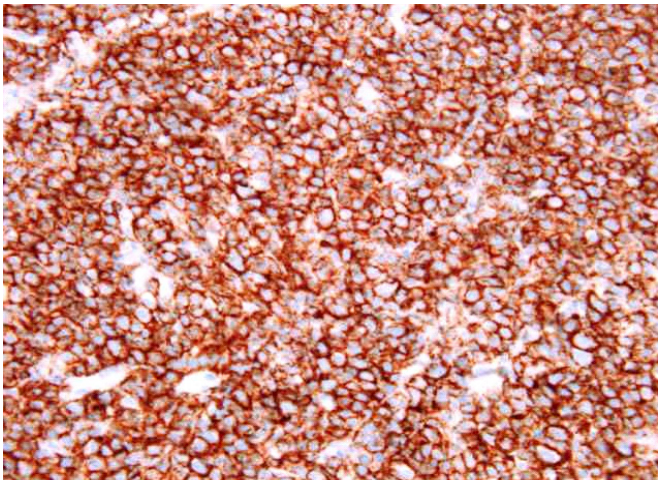

Figure 5. Lymphoma cells showing strong, diffuse & membranous positive immunohistochemical stain for CD20 (B lymphocyte marker).

Pertinent laboratory findings included: BUN 18 mmol/L, serum creatinine 263 μmol/L, LDH 487 U/L, total serum calcium: 327 mmol/L, ionized serum calcium 1.93 mmol/L, serum intact parathyroid hormone (i-PTH) level 0.3 pmol/L [1.6-7.2 pmol/L], 25-Hydroxyvitamin D: 24 nmol/L [75-200 nmol/L], WBC 2.8x10^6/L (differential: 49% neutrophils, 50%lymphocytes, 1% monocytes), hemoglobin 84 gm/L, platelets 71x10^6/L, and normal serum protein electrophoresis. Duplex studies of bilateral lower extremities ruled out deep venous thrombosis.

Right knee X-ray (Figure 2) showed fracture of the proximal right fibula shaft associated with periosteal reaction. There were multiple lytic bony lesions (moth-eaten appearance) of the proximal tibia and right femoral metaphysis; also noted was soft tissue swelling surrounding this area. A magnetic resonance imaging (MRI) of the right knee and leg (Figure 3) shows heterogeneous signal intensity involving most of the calf muscles, including gastrocnemius lateral head, and the anterior muscle groups with pathological fracture of the proximal fibula and erosion of the medial aspect of the proximal tibia. A biopsy of the right leg mass demonstrated a diffuse proliferation of cells, with large vesicular hyperchromic nuclei, macronucleoli, and frequent mitoses. These cells were infiltrating adjacent skeletal muscle fibers without significant bone pathology (Figure 4). Immunohistochemistry was consistent with large B-cell Lymphoma (Figure 5). A computed tomography scan (CT scan) of the chest, abdomen and pelvis showed one lytic defect in the right ileum. The final diagnosis was Large B-cell Lymphoma of the anterior group muscles of the right leg. The patient's hypercalcemia was corrected with intravenous saline infusion, furosemide, and zoledronic acid. His renal function improved. Following the patient's wishes, he was transferred to palliative care.

Discussion

Malignancy-associated hypercalcemia occurs in 5-10% of patients with advanced cancer (1). Like many malignant solid tumors, non-Hodgkin's lymphoma (NHL) can cause hypercalcemia. Its incidence was estimated to be 9% in one retrospective study of 156 patients. However this percentage rises to 23% in high grade NHL (2). The serum elevation of calcium can be caused by two main mechanisms: humoral hypercalcemia of malignancy (HHM) and local osteolytic hypercalcemia (3). HHM is a complex phenomenon; its enigma is still not clearly understood. Tumoral cells have the potential to secrete parathyroid hormone-related peptide (PTHrp) (4, 5), 1-25-Dihydroxyvitamin D (6), TNF-alpha and Interleukin 6 (7) leading to hypercalcemia. Authors have described increased expression of osteoclast-activating factors (MIP-1alpha, MIP-1beta and RANKL) by lymphoma cells, thus causing osteolysis and hypercalcemia (8). Local osteolytic hypercalcemia is still not fully understood, with many factors playing a role in its pathogenesis. It is observed when there is direct tumoral adherence or metastatic deposition to the bone (9-10).

The patient described in this report had a unique presentation of severe hypercalcemia caused by the rare form of musculoskeletal NHL. Less than 100 cases of musculoskeletal lymphoma have been published in the literature (11). We believe the mechanism of his calcium disturbance was both humoral and local bony destruction. Indeed both his 25-Hydroxyvitamin D and i-PTH levels were suppressed. We suspect he had elevated PTHrp, but it was not measured due to test unavailability. We also think the location of his tumor played a direct local role in the fracture and osteolysis observed, in all likelihood, in his right fibula, tibia and femur. The diagnosis of multiple myeloma was ruled out by a normal serum protein electrophoresis while the possibility of plasmacytoma was not entertained by the histopathological examination.

Intravenous saline infusion and furosemide are classical treatments of hypercalcemia; more recently bisphosphonates have been gaining a central therapeutic role. Their mechanism of action reduces bone resorption, osteolytic lesions, and even fractures (12). Other forms

of therapy for lymphoma-induced hypercalcemia include calcitonin, glucocorticoids, and calcium-free hemodialysis (13). Despite all modern interventions and biologic advances, hypercalcemia in high grade lymphoma still carries a poor prognosis (5,7).

In conclusion, this case report contributes to an extended body of literature related to lymphoma-associated hypercalcemia. Its pathophysiology is complex and is only partially understood. It can occur with the rare form of primary extra-nodal musculoskeletal NHL. The prognosis of this disturbing calcium imbalance remains poor despite many interventions including parenteral bisphosphonates.

Conflict of Interest: none reported.

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