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Hypercalcemia Unmasks Peripheral T-Cell Lymphoma, NOS: A Case Report

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ABSTRACT

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), is an uncommon and aggressive subtype of mature T-cell lymphomas, representing a heterogeneous group of malignancies without specific defining immunophenotypic or genetic features. It often presents with systemic “B” symptoms, generalized lymphadenopathy, and extranodal involvement. Diagnosis requires the exclusion of other well-defined T-cell lymphoma subtypes through detailed histopathological and immunohistochemical evaluation. Hypercalcemia is a recognized paraneoplastic manifestation in various cancers, particularly in solid tumors and some hematological malignancies; however, it is rarely the initial presentation of PTCL-NOS. We report the case of a 53-year-old female who presented with persistent fatigue, and vague abdominal discomfort. Laboratory investigations revealed severe hypercalcemia with normal renal function and intact parathyroid hormone levels. Imaging demonstrated diffuse bone marrow infiltration without radiological evidence of lytic bone lesions. Bone marrow biopsy showed diffuse infiltration by atypical lymphoid cells, and immunohistochemistry confirmed the diagnosis of PTCL-NOS. Hypercalcemia was attributed to a paraneoplastic mechanism mediated by parathyroid hormone related protein by the lymphoma cells. Following initiation of combination chemotherapy all systemic symptoms improved.

This case highlights an unusual presentation of PTCL-NOS, where severe hypercalcemia preceded other overt clinical signs. The absence of lytic lesions and the rapid correction of calcium levels with lymphoma-directed therapy further support a humoral paraneoplastic process rather than direct bone destruction. It also underscores the need for a thorough and systematic diagnostic workup in patients presenting with unexplained hypercalcemia, particularly when conventional etiologies have been excluded. It also highlights the importance of considering PTCL-NOS as part of the differential diagnosis in such atypical clinical scenarios, enabling timely diagnosis and appropriate management.

Keywords: *Hypercalcemia, Immunohistochemistry, Paraneoplasm, PET-CT, PTCL-NOS, T-cell lymphoma.*

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1. INTRODUCTION

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), represents a heterogeneous and distinctive diagnostic category within the spectrum of mature T-cell neoplasms. The diagnosis is typically established only after excluding all other well-defined subtypes of peripheral T-cell lymphomas, as no unique morphological, immunophenotypic, or genetic hallmark consistently defines this entity.[1] The worldwide prevalance of PTCL-NOS comprises about 25–30% of all the documented peripheral T-cell lymphoma cases, making it one of the more common subtypes within this rare group of hematologic malignancies.[2] Pathophysiologically, PTCL-NOS arises from mature, post-thymic T lymphocytes and shows marked heterogeneity. Key features include aberrant T-cell receptor signaling, dysregulated cytokine production, and immune evasion. Common molecular changes involve transcription factor overexpression, mutations in epigenetic regulators (TET2, DNMT3A, IDH2), and tumor suppressor loss (TP53). Immunophenotypically, tumors usually express pan–T-cell markers (CD2, CD3, CD5) with frequent antigen loss (e.g., CD7) and variable CD4/CD8 expression.[3] Compared to B-cell lymphomas, T-cell lymphomas tend to present more frequently with extranodal disease involvement, including the skin, gastrointestinal tract, and bone marrow, and are generally associated with a poorer prognosis. Clinical presentation is often variable and non-specific, ranging from constitutional "B" symptoms to organ-specific manifestations, which can delay diagnosis.[3]

Hypercalcemia, although recognized as a paraneoplastic feature in several malignancies, is an uncommon but clinically significant manifestation in PTCL-NOS. Its pathophysiology is thought to involve tumor-induced osteoclastic activation through cytokine release or, in rare cases, ectopic production of parathyroid hormone-related peptide (PTHrP).[4] The presence of hypercalcemia can contribute to a spectrum of symptoms such as fatigue, neurocognitive changes, gastrointestinal disturbances, and renal impairment, further complicating the clinical picture.[5]

Early recognition of atypical presentations such as paraneoplastic hypercalcemia is essential, as it may prompt more urgent diagnostic work-up, enabling timely initiation of therapy and potentially improving patient outcomes. In this report, we describe a rare case of PTCL-NOS presenting with hypercalcemia, diagnosed through integrated imaging with positron emission tomography–computed tomography (PET-CT) and confirmatory bone marrow biopsy. This case highlights the importance of considering PTCL-NOS in the differential diagnosis of unexplained hypercalcemia, particularly in the context of generalized lymphadenopathy and systemic symptoms.

2. THE CASE

A woman in her early 50s, with a known history of systemic hypertension and type 2 diabetes mellitus presented to our tertiary care center in 2025. She reported experiencing generalized fatigue and frequent episodes of lightheadedness for the past month, along with vague abdominal discomfort over the preceding four days. Additional symptoms included constipation, significant unintentional weight loss, and a noticeable loss of appetite. She denied fever, night sweats, rash, pruritus, or bone pain. There was no notable family history of malignancy.

On physical examination, her vital signs were stable. She appeared pale, and palpable lymph nodes were noted in the suboccipital region. Cardiovascular, respiratory, abdominal, and neurological examinations were otherwise unremarkable. Initial laboratory investigations are summarized in Table 1.

An FDG PET-CT scan revealed (Figure 1A, B, C):

- Metabolically active lymphadenopathy involving the right occipital, right supraclavicular, level V cervical, right axillary, bilateral internal mammary, right epiphrenic, anterior cardiophrenic, gastrohepatic, periportal, portocaval, and retroperitoneal nodes.
- Metabolically active ill-defined hypodense lesions in the spleen.
- Low-grade metabolically active nodular thickening in the left adrenal gland.
- Patchy, heterogeneously increased metabolic activity along the dura of the bilateral frontal and parietal convexities.
- Diffuse, intensely increased metabolic activity in the axial and appendicular bone marrow, with metabolically active mild soft tissue thickening in the pre- and paravertebral regions of the lower dorsal and upper lumbar vertebrae.
- Focal increased metabolic activity in the occipital bone on both sides adjoining the mastoid process and in the left lateral aspect of the clivus.

Bone marrow biopsy demonstrated infiltration by atypical lymphoid cells. Immunohistochemistry (Figure 1D) showed diffuse positivity for CD3, CD5, CD45, CD15, and BCL-2 in atypical lymphoid cells, with scattered positivity for CD20 (Figure 1E). Staining for CD10, PD-1, ICOS, and CXCL13 was negative.

Based on the combination of radiologic characteristics and histopathological findings, a diagnosis of Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) was established. The patient was started on CHOP chemotherapy,

following which both her hypercalcemia and overall clinical condition showed significant improvement.

3. DISCUSSION

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), is a heterogeneous and often aggressive subtype of mature T-cell neoplasms. PTCL encompasses multiple subtypes, including PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL), and several rarer variants. Collectively, PTCLs account for approximately 10–15% of all non-Hodgkin lymphomas.[1] Pathogenesis involves complex molecular alterations, including recurrent chromosomal translocations, mutations in epigenetic regulators and , and dysregulated signaling pathways. PTCLs are characterized by aggressive clinical behavior, frequent extranodal involvement, and poor response to conventional chemotherapy, with 5-year overall survival rates often below 30%.[3] Diagnosis requires an integrated approach combining histopathology, immunophenotyping, and clinical assessment, as no single pathognomonic marker exists, making the process challenging in atypical presentations.

Hypercalcemia is an uncommon but recognized paraneoplastic manifestation of T-cell lymphomas and, in rare circumstances, may present as the earliest clinical sign of disease.[4] When it occurs, it often signifies an advanced tumor burden and may contribute substantially to patient morbidity through symptoms such as fatigue, anorexia, constipation, neurocognitive impairment, and renal dysfunction. The underlying mechanism is believed to involve tumor-mediated stimulation of osteoclastic bone resorption, primarily through the release of pro-inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α). In certain cases, ectopic secretion of parathyroid hormone-related peptide (PTHrP) by malignant T-cells has been implicated, mimicking the action of parathyroid hormone and promoting calcium mobilization from bone and increased renal tubular calcium reabsorption.[5] In our patient, hypercalcemia was both pronounced and persistent, occurring in the absence of primary hyperparathyroidism, or evident osteolytic lesions, thereby supporting a paraneoplastic etiology.

Several case reports have described hypercalcemia as an initial manifestation of PTCL-NOS. Luyin Ding reported a 61-year-old male presenting with a hypercalcemic crisis (serum calcium 3.87 mmol/L) as the first sign of PTCL-NOS, with PET-CT showing widespread lymphadenopathy and splenic lesions; the hypercalcemia resolved after chemotherapy initiation.[6] Similarly, Michael Munoz described a 54-year-old woman with PTCL-NOS and severe hypercalcemia, in whom PTHrP-mediated humoral hypercalcemia was confirmed.[7] These cases, along with our findings, underscore the importance of considering lymphoma in patients with unexplained hypercalcemia, particularly in the absence of primary hyperparathyroidism or overt bone destruction.

In this case, PET-CT proved invaluable for both diagnosis and staging, revealing diffuse marrow uptake and splenic involvement without osteolytic lesions—findings that prompted further biopsy. Histopathology confirmed diffuse infiltration by atypical lymphoid cells. Immunohistochemistry demonstrated positivity for CD3, CD5, and CD45, along with aberrant CD15 expression, a feature previously reported in T-cell lymphomas that may mimic classical Hodgkin lymphoma.[8] Scattered CD20 positivity likely represented reactive B-cell populations. The absence of TFH markers (PD-1, ICOS, CXCL13) helped exclude angioimmunoblastic T-cell lymphoma and other TFH-derived neoplasms.[9]

18F-FDG uptake on PET-CT correlates closely with tumor metabolic activity, disease burden, and prognosis in PTCL, making it a valuable tool not only for initial staging but also for assessing treatment response and detecting early relapse. High baseline standardized uptake values (SUVs) often reflect aggressive disease biology and have been associated with poorer outcomes, whereas a marked reduction in FDG avidity following therapy is suggestive of favorable response.[10] Following initiation of CHOP chemotherapy, repeat imaging demonstrated a significant reduction in metabolic activity, which paralleled the patient's clinical improvement and normalization of serum calcium levels.

In summary, this case illustrates the diagnostic complexity of PTCL-NOS and the value of a multidisciplinary approach. It highlights the need for clinicians to maintain a high index of suspicion for lymphoma in patients with otherwise unexplained hypercalcemia, as early recognition and treatment may improve outcomes.

4. CONCLUSION

This case demonstrates the rare presentation of paraneoplastic hypercalcemia in PTCL-NOS and underscores the pivotal role of immunohistochemistry and PET-CT imaging in establishing the diagnosis while accurately excluding other T-cell lymphoma subtypes. Given the generally aggressive clinical course and poor prognosis associated with PTCL-NOS, especially when presenting with paraneoplastic features, timely recognition and initiation of appropriate therapy are crucial for optimizing patient outcomes. Clinicians should maintain a high index of suspicion in cases of unexplained hypercalcemia, particularly in the absence of other common causes. Further research is warranted to better understand the pathophysiological mechanisms linking hypercalcemia to PTCL-NOS, to identify prognostic biomarkers, and to develop

more effective therapeutic strategies aimed at improving survival and quality of life in affected patients..

CONFLICT OF INTEREST: None

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TABLES AND FIGURES

TABLE 1: Laboratory investigations at presentation

Test	Results	Normal Reference range
Hemoglobin	7.6 g/dL	*12-15.5 g/dL*
Total WBC Count	7110 /µL	*4000-11000 /µL*
Platelet count	113,000 /µL	*150,000 - 450,000 /µL*
Urea	113 mg/dL	*10-50 mg/dL*
Creatinine	0.9mg/dL	*0.6-1.3 mg/dL*
Sodium	129 mmol/L	*135-145 mmol/L*
Potassium	2.9 mmol/L	*3.5-5.0 mmol/L*
Calcium	>13.0 mg/dL	*8.5-10.5 mg/dL*
Phosphorus	5.0 mg/dL	*2.5-4.5 mg/dL*
Albumin	3.9 g/dL	*3.4-5.4 g/dL*
LDH	692 U/L	*140-280 U/L*
Uric acid	9.1	*1.5-6 mg/dl*
Vitamin D3	48.7 ng/mL	*20-50 ng/mL*
Peripheral smear	Severe normocytic normochromic anaemia	

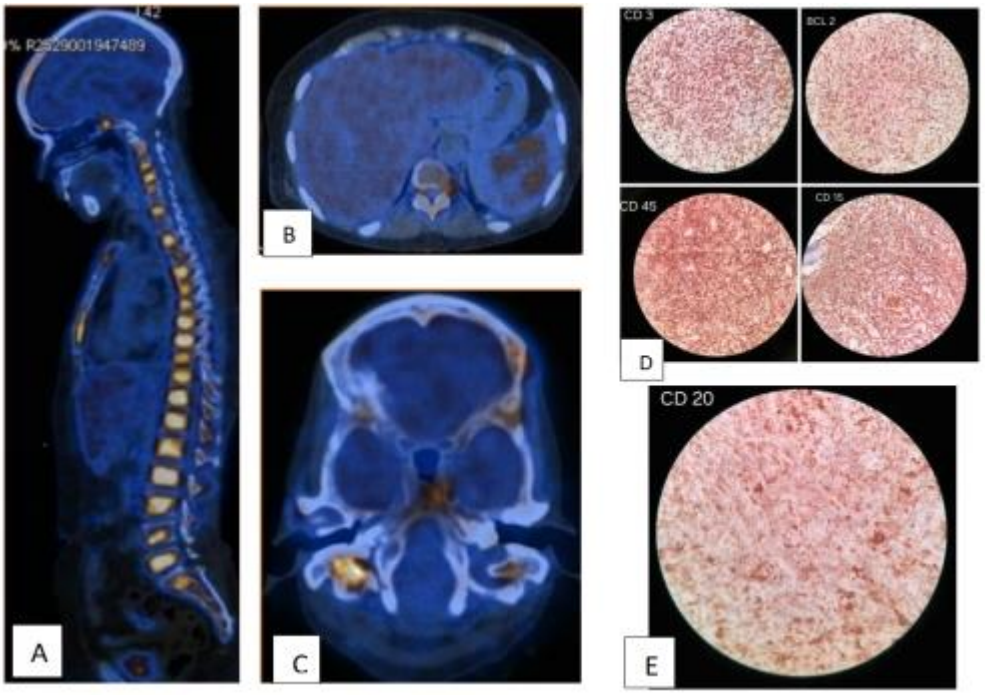

Figure 1: (A) Increased FDG uptake in pre and paravertebral regions of lower dorsal and upper lumbar vertebrae.

(B) Ill-defined hypodense lesions in spleen
(C) Increased FDG uptake along dura in frontal and parietal regions
(D) CD3, CD45, CD15 and BCL2 -diffuse positivity in atypical lymphoid cells
(E) Scattered CD20 positivity