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# Hypercalcaemia: An Extremely Rare Presentation of Hepatosplenic T-Cell Lymphoma

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## ABSTRACT

Hypercalcaemia is a frequent finding in malignancies including lymphomas. However, there are no reports of hypercalcaemia in hepatosplenic T-cell lymphoma (HSTCL). HSTCL is a rare and aggressive neoplasm which is usually difficult to diagnose. We present a case of HSTCL in which hypercalcaemia was the initial presentation.

## LEARNING POINTS

- Hepatosplenic T-cell lymphoma (HSTCL) is difficult to diagnose, has a poor prognosis and usually presents with hepatosplenomegaly, B symptoms and cytopenias.
- Hypercalcaemia is an extremely rare clinical presentation of HSTCL.
- Severe hypercalcaemia is a life-threatening condition and should always be corrected and investigated.

## KEYWORDS

Hypercalcaemia, hepatosplenic lymphoma, hepatosplenomegaly, B symptoms, bone marrow

## INTRODUCTION

Hypercalcaemia is a frequent alteration in some malignancies and usually is explained by mechanisms such as the secretion of parathyroid hormone-related peptide, the production of extra-renal 1,25-dihydroxyvitamin D, osteolytic activity or the production of ectopic parathyroid hormone (PTH).

Hepatosplenic T-cell lymphoma (HSTCL) is a rare and aggressive neoplasm, most frequently presenting with hepatosplenomegaly, B symptoms and cytopenias. It is often a challenging diagnosis and carries a poor prognosis.

We present a case of HSTCL whose initial manifestations were hypercalcaemia and hepatosplenomegaly, which is an extremely uncommon presentation of this disease.

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## CASE DESCRIPTION

A 39-year-old man presented to the emergency room with a 5-week history of asthenia, anorexia, 4–5 kg weight loss and bilateral lower limb pain and paraesthesia. His previous medical history included renal lithiasis and a left-sided pneumectomy due to pulmonary tuberculosis. He denied other personal or familial history as well as alcohol or drug consumption. On physical examination, he was drowsy, slightly polypnoeic and had a mildly tender abdomen without palpable organomegaly or clinically detectable ascites. There was no palpable lymphadenopathy and neurological examination was unremarkable. His vital signs were stable.

Initial blood tests revealed severe hypercalcaemia (15.88 mg/dl; reference range 8.1–10.2 mg/dl) corrected for albumin, phosphate 2.4 mg/dl (2.5–4.5 mg/dl), aspartate aminotransferase 155 IU/l (normal <40 IU/l), gamma-glutamyltransferase 511 IU/l (normal <60 IU/l), alkaline phosphatase 436 IU/l (normal 40–129 IU/l), lactate dehydrogenase (LDH) 6146 IU/l (100–250 IU/l) and lactate 13.7 mmol/l (1.0–1.8 mmol/l). He presented with high anion gap metabolic acidosis and normal creatinine. Haemoglobin was 12.9 g/dl (11.5–18.0 g/dl), platelet count was 130×109/l (130–400×$10^9$/l) and white blood cell count was 6.2×109/l (4.0–11.0×$10^9$/l). He was admitted to our intermediate care unit and started calcium correction with isotonic saline, zoledronic acid and denosumab, which resulted in a small decrease in calcium and lactate levels. However, he later developed confusion while maintaining severe hypercalcaemia and hyperlacticaemia, which prompted initiation of haemodialysis with subsequent improvement of calcium and lactate levels.

Subsequent investigation revealed: intact parathyroid hormone <1.2 pg/ml (15–65 pg/ml), parathyroid hormone-related protein (PTH-rp) 0.9 pmol/l (<1.3 pmol/l), 1,25-dihydroxyvitamin D 73 pmol/l (39–193 pmol/l), 25-hydroxyvitamin D 9.8 ng/ml (≥30 ng/ml), urinary calcium 24.10 mg/dl (6.60–21.30 mg/dl), beta-2 microglobulin 13.64 mg/l (0.8–2.4 mg/l) and normal serum protein electrophoresis.

A thoracic-abdominal-pelvic computed tomography scan revealed homogenous hepatosplenomegaly without pathologically enlarged lymph nodes (*Fig. 1*). Positron emission tomography was performed, which revealed pathological infiltration of the spleen and liver with possible lymph node involvement, in addition to medullary expansion. These findings, as well as the development of anaemia and thrombocytopenia, prompted a liver biopsy and a bone marrow study.

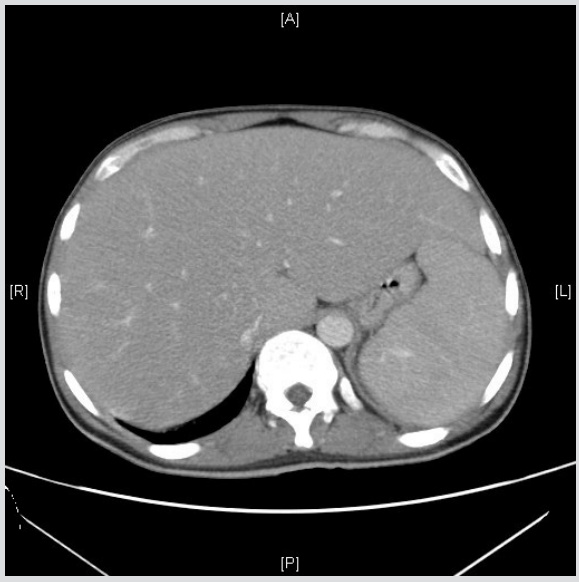


*Figure 1. Abdominal computed tomography showing homogeneous hepatosplenomegaly (liver right lobe longitudinal diameter 20 cm; spleen cranial-caudal, antero-posterior and transverse diameters 17.6, 14 and 5 cm, respectively)*

On the 9th day of admission, the patient developed methicillin-susceptible *Staphylococcus aureus* haemodialysis catheter-related bloodstream infection and was treated with flucloxacillin. On the 15th day of admission, the patient's condition deteriorated due to nosocomial pneumonia with septic shock and acute respiratory distress syndrome. He was submitted to endotracheal intubation, initiated fluids and vasopressors, blood cultures were repeated and broad-spectrum antibiotics were initiated. The patient was transferred to the intensive care unit but died due to multiple organ failure. Liver biopsy results revealed HSTCL (CD3+, CD4–, CD5+, CD8+; CD20–, CD30–; Epstein Barr Virus (EBV) negative) (*Figs. 2 and 3*) and bone marrow biopsy also showed infiltration by T-cell lymphoma.

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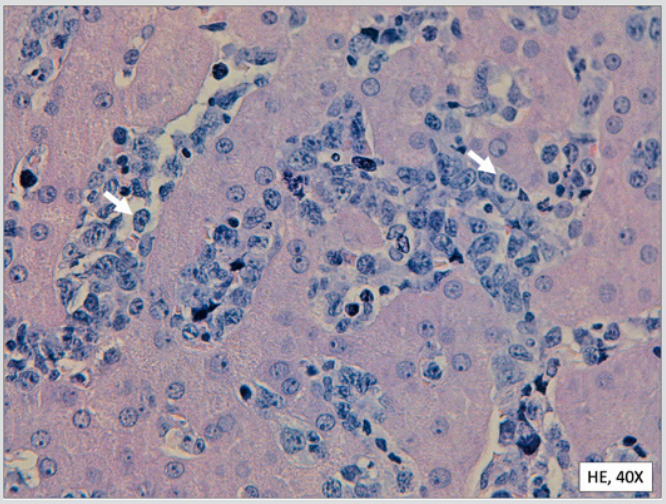


*Figure 2. Liver biopsy: medium-sized lymphoid cells, with scant cytoplasm and prominent nucleoli (white arrows) infiltrating the sinusoidal spaces of the liver are seen*

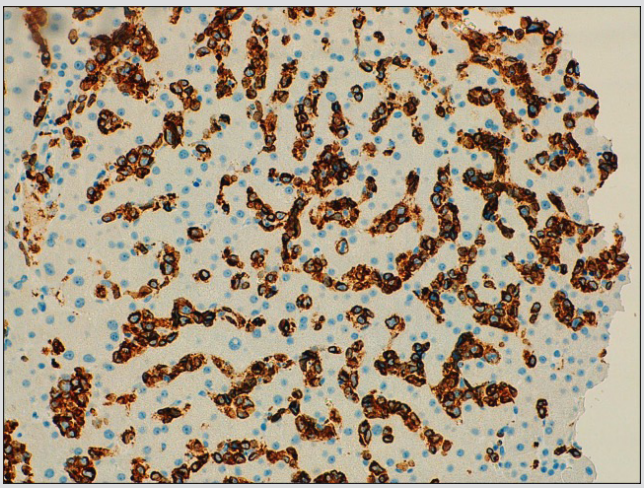

*Figure 3. Liver biopsy: the neoplastic lymphoid cells were positive for CD3, CD5, CD8 and negative for CD4, CD20, CD30 and cytokeratin AE1/AE3, by immunohistochemistry, favouring the diagnosis of a hepatosplenic T-cell lymphoma*

## DISCUSSION

HSTCL is a rare and aggressive type of peripheral T-cell lymphoma, representing less than 1% of non-Hodgkin lymphomas [1]. HSTCL is more frequent in young males, with a median age at diagnosis of 35 years, varying according to studies [1, 2]. There is a described association with chronic immunosuppression in approximately 20% of cases [1], some related to post-organ transplantation and most with chronic immunosuppressive therapy, especially in Crohn's disease.

HSTCL clinical presentation is characterized by hepatosplenomegaly (with almost all patients presenting with splenomegaly) and B symptoms, with lymphadenopathy reported in only a few cases [3]. Some patients may manifest jaundice and the majority also have bone marrow involvement. The most common laboratory abnormalities are cytopenias, followed by abnormal liver biochemistry and elevated LDH and beta-2 microglobulin levels. We did not find any reports of hypercalcaemia in the literature.

Hypercalcaemia of malignancy occurs mainly due to the following mechanisms: secretion of PTH-rp by the tumour, osteoclast activation related to osteolytic metastases, and secretion of 1,25-dihydroxyvitamin D by the tumour. The first is the most common mechanism in solid tumours and has also been reported in lymphomas [4]. Osteoclast activation related to osteolytic metastasis is present in multiple myeloma and is less frequent in leukaemias and lymphomas, being in some cases the result of bone marrow infiltration. Elevated levels of 1,25-dihydroxyvitamin D are the cause of hypercalcaemia in the majority of lymphomas [4].

HSTCL histological features include infiltration of the cords and sinuses of the splenic red pulp by atypical lymphocytes as well as involvement of the sinusoidal spaces of the liver and bone marrow [2]. The immunophenotype is variable, but the most frequent profile is CD3+, CD4–, CD5–, CD8–, CD20–, CD30–. CD5 and CD8 positivity has been rarely reported [1, 2]. Usually HTSCL cells are negative for EBV [2, 5].

The rarity of the disease and the lack of specificity of the initial clinical presentation make the diagnosis challenging and a splenectomy or liver biopsy are usually required to establish it [5].

The prognosis is poor and the median length of survival is 0–72 months [3]. There are no standardized treatments targeting HSTCL and studies are limited [1]. Some patients achieve complete remission with chemotherapy with or without a stem cell transplant [3].

Our patient presented with B symptoms, hypercalcaemia and hepatosplenomegaly. Hypercalcaemia was not suggestive of a PTH-rp or 1,25-dihydroxyvitamin D-mediated mechanism and other hypercalcaemia aetiologies were excluded. Because no other cases of HSTCL-related hypercalcaemia are described in the literature, it was very difficult to establish a diagnosis before the biopsy results were received. After the histological diagnosis, we postulated that the hypercalcaemia was due to osteoclastic activity secondary to bone marrow involvement; further case reports are needed to confirm this hypothesis.

This case represents an extremely atypical presentation of a rare disease and it indicates that hypercalcaemia, especially in the setting of hepatosplenomegaly and B symptoms, must be considered as a possible manifestation of HSTCL.

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