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RESEARCH ARTICLE

HYPERCALCEMIA AND LYMPHOMA: A RARE BUT CHALLENGING ASSOCIATION

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ABSTRACT

Background: Major hypercalcemia is a rare therapeutic emergency in lymphoma, its two most common causes are hyperparathyroidism and bone metastases, its clinical signs are not specific, which stresses the difficulty to formally establish a diagnostic etiology. **Case presentation:** we report a case of a 46-year-old man who presented with tumefaction of the left leg with inguinal lymphadenopathy of the same member, concluding to the diagnosis of diffuse large B cell lymphoma (DLBCL) associated with major hypercalcémia (3,9mmol/l), the patient was hospitalized in intensive care, the serum calcium level was normalized only after the administration of two doses of bisphosphonates and a significant rehydration at the rate of 3l/ m^2/24h. **Conclusion:** This case report shows, that hypercalcemia can revealed malignant hemopathy, and its draw attention to the difficulties of initial therapeutic management, which constitutes a real challenge between the establishment of rapid symptomatic and etiological treatment because any delay can put the patient's vital prognosis at risk.

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INTRODUCTION

Hypercalcemia is commonly associated with solid tumor malignancies, but less often with hematologic malignancies, it is considered to be rare in B-cell non-Hodgkin's lymphoma (B-NHL) (Shad, 1997 and Majumdar, 2002) but is associated with a poor prognosis. The etiology of hypercalcemia in non-Hodgkin lymphoma (NHL) has been most often attributed to either elevated serum levels of 1, 25-dihydroxycholecalciferol (calcitriol) or parathyroid-related protein (PTHrP). We report the case of a 46-year-old who presented with a major hypercalcemia at 160mg / l before any signs of malignancy became evident. First the patient was admitted to the intensive care unit, the etiological diagnosis of lymphomatous origin was made after the histological and immunohistochemical study of the biopsy of inguinal left lymphadenopathy.

Observation

A 46-year-old man having as antecedent non-insulin dependent diabetes for 3 years and hypertension under treatment for 5 years, was admitted to intensive care with a 5-day history of lethargy, confusion, nausea, abdominal pain and tumefaction of the lower left limb. On the physical examination the patent was dehydrated and confused, he was in a bad general condition, ECOG was at 4, afebrile, Glasgow score at 13 / 15th. The exam found painful hot and red inguinal swelling with inflammatory signs suggesting venous thrombosis and homolateral inguinal lymphadenopathy (2/2 cm) of the same limb. Initial investigation revealed on adjusted calcium of at 3.9mmol / l (N = 2.20-2.55), it was accompanied by an LDH level of 965 IU / l (N = 210-390), haemostasis, ionogram, liver biology and renal function were normal. The CBC revealed: Hb: 9,9g/dl, MCV: 88%, WBC: 3740 el/mm^3, PNN: 1050 el/mm^3, Platelets: 438.000 el/mm^3. The venous Doppler ultrasound showed deep thrombophlebitis of the left lower limb, associated with many inguinal and iliac nodes. The patient was treated with 0.9% saline intravenously with injection of zoledronate at 4mg intravenously, as well as anticoagulant treatment based on low molecular weight heparin with a curative dose although his condition improved (calcium concentration returned to within reference range after 1 week). The evolution was favorable by the improvement of the clinical state of the patient, after the stabilization of the patient, a biopsy of the inguinal adenopathy was carried out: objectifying a diffuse large b cell lymphoma, an extension assessment was performed, showing the presence of bilateral axillary lymph-nodes, the largest of which measures 24mm, left retroperitoneal mass including the aortic bifurcation and the iliac arteries, measuring 67x234 mm and a left inguinal mass of 90x80mm. The bone marrow biopsy was infiltrated by malignant cells, this is how the patient was classified as stage IV by the marrow according to the ANN ARBOR

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classification with an International Prognostic Index at 4, the patient was classified as high risk group. Chemotherapy was started according to RCHOP protocol (Rituximab, Cyclophosphamid, Vincristine, Doxorubin and steroid), the patient received eight cures with complete remission midway through the treatment. Three months after the end of the chemotherapy, the patient presented a tumoral recovery with deterioration of the general state and reappearance of adenopathies. The positron emission tomography imaging revealed ever-evolving disease with hypermetabolic lymphnodes on both sides of diaphragm, hypermetabolic bilateral pulmonary lesions, muscular, subcutaneous, and bony secondary localizations (Fig1).

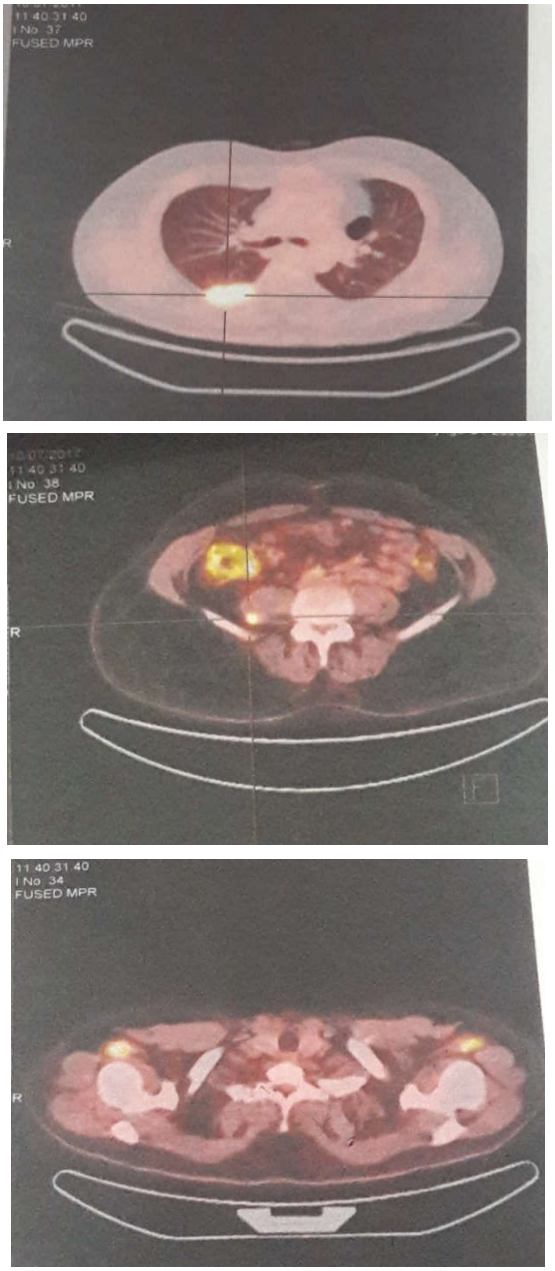

Fig. 1. Hypermetabolic adenopathies above and below diaphragmatic and pulmonary lesions

After a multidisciplinary meeting proposed second line therapeutic according to the R-DHAP protocol (Rituximab, Cisplatin, Aracytine, Dexamethasone) with intensification by autograft. The patient received 2 coures of RDHAP but the disease remained ever evolutive and the patient showed up 2 necrotic and purulent masses on the left thigh (20 cm for the first and 12 cm for the second) (Fig. 2).

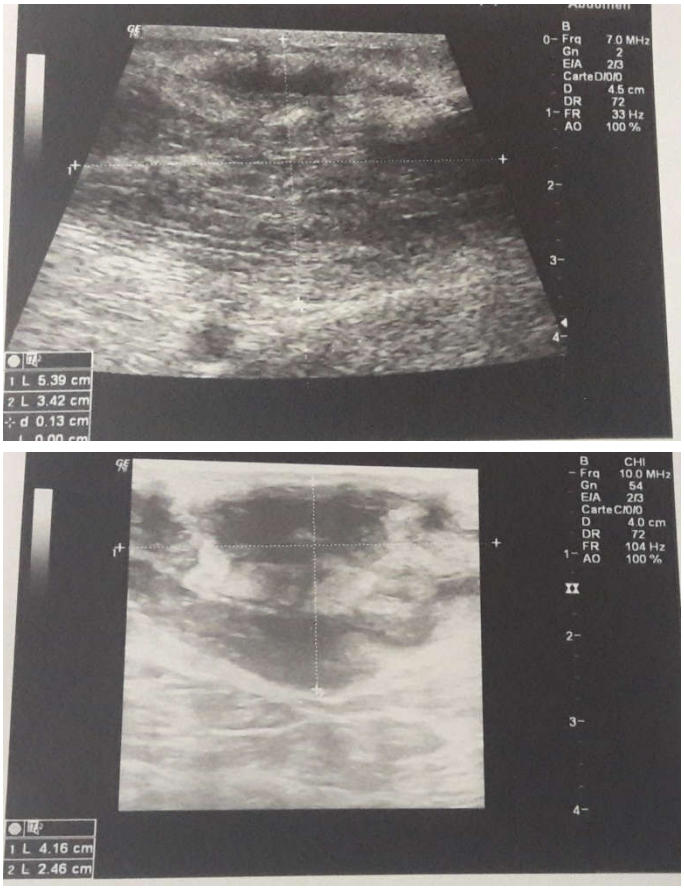

Fig.2. Two contiguous formations non-vascular at doppler heterogeneous and hypochecogene measuring 41.6x 25.5 mm and 53x 34mm associated with a large infiltration of the soft parts

A third line treatment was proposed according to the R-ICE protocol (Rituximab, Ifosfamide, Carboplatine, Etoposide), the patient received a single course of treatment, the condition got worse by the appearance of multi-organ dysfunction and the patient died by the evolution of his illness.

DISCUSSION

hypercalcemia is a therapeutic emergency, its prevalence varies between series 1.1 and 3.9% in the ambulatory population and between 0.2 and 2.9% in the hospital (Shallis et al., 2018 and Christensson, 1976). The most common etiologies of hypercalcemia are malignant hypercalcemia (MH) and primary hyperparathyroidism (PPH) with approximately 45% and 50% of cases respectively (Dent et al., 1987; Fisken, 1981 and Burckhardt et al., 1981). MH remains the leading cause of hypercalcemia in the hospital endangering the life of the patients; its incidence varies between 0.5 and 10.9% (Lamy, 2002). In haematological neoplasms it often occurs in the course of multiple myeloma (about 33% of cases) and is nearly always associated with extensive osteolytic skeletal involvement (Mundy, 1982 and Mundy, 1986). Only 1–2% of patients with lymphoma and leukaemia (Freina, 2007), develop this complication (except with adult T-cell leukaemia in which it is common). However, MH remains rare in B-cell non-Hodgkin's lymphoma (B-NHL) (Shad et al., 1997 and Majumdar, 2002), is observed in less than 15% of lymphomas (Mundy, 1982), but several individual case reports have appeared over the years (Firkin, 1996 and Lobato-Mendizabal, 1990) and is usually the translation of aggressive lymphoma and appears at an advanced stage of the oncological disease, it is recognized as an independent marker of increased mortality

risk (Lam, 2003). The median survival of patients with Major hypercalcemia is 1 to 3 months, and would be even shorter when the serum calcium level is higher (Lamy, 2002), most often depends on the histological type of cancer. In Majumdar's article (Majumdar, 2002), eight cases with hypercalcemia among 112 patients (7.1%) diagnosed with B-NHL over a period of five years. Five patients with high grade B-NHL presented with hypercalcaemia and another patient developed hypercalcaemia at the time of relapse. One patient with low grade B-NHL developed hypercalcaemia at the time of transformation to Richter's syndrome. One other patient with low grade B-NHL developed hypercalcaemia at the time of relapse. All patients had advanced disease; the median survival time from developing hypercalcemia was nine months. In general, hypercalcemia remains a real therapeutic emergency, it darkens the prognosis of the hematological malignancy with which it is associated, its initial and rapid management is essential because any delay can put the patient's vital prognosis at risk. The case that we report had an unusual revealing circumstance of his lymphoma. Emergency management of this major hypercalcemia allowed patient stabilization and permet the diagnosis of the lymphoma. Hypercalcemia in the setting of malignancy is associated with poor prognosis; B-NHL appears to be no exception. Particularly in the high grade type, and carries a poor prognosis. Treatment of hypercalcemia does not improve survival. As reported in the literature, the lymphoma of our patient revealed by hypercalcemia was marked by it's aggressively. Despite the initial response to treatment, the relapse was too fast resulting in the death of the patient.

Conclusion

Hypercalcemia in non-Hodgkin's lymphoma is rare but exists, it is an indicator of poor prognosis, it reflects the worsening of the disease and most often a resistance of lymphoma to different chemotherapies even if there is a good initial response to bisphosphonates.

Declarations

Ethics approval and consent to participate : All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication : I give my full permission for the publication

Availability of data and material : Not applicable

Competing interests : No conflict of interest

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Authors' contributions : M.Bendari : conceived of the presented idea. encouraged and supervised the findings of this work. All authors discussed the case and contributed to the final manuscript.

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