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Primary Hepatic Lymphoma with Hypercalcemia-A Case Report and Literature Review

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Abstract

This is the case of a 59-year-old female treated for osteoporosis and arthritis. On routine examinations since 6 months the patient has persistent hypercalcemia. Further evaluation revealed primary hepatic lymphoma as the source of her hypercalcemia.

It is already known that hypercalcemia is a common complication of malignancy as described by Rodríguez-Gutiérrez et al. [1]. Hypercalcemia happens due to osteolytic metastases or secretion of parathyroid hormone related peptide (PTHrP). In both situations, calcitriol is suppressed so that the intestinal absorption, renal reabsorption, and bone resorption of calcium can be decreased. In some instances, hypercalcemia can be mediated by calcitriol. This is more common in sarcoidosis; however, have been such reports even in mycobacterium infections and hematologic malignancies [2]. Calcitriol-mediated hypercalcemia accounts for less than 1% of all malignancy-related hypercalcemia cases and it is usually found in non-Hodgkin's lymphoma (NHL), specifically diffuse large B-cell lymphoma (DLBCL).

Case Presentation

A 59-year-old female with a history of osteoporosis and arthritis presented with a 6-month history of hypercalcemia. The patient initially presented to her rheumatologist with complaints of weakness, dizziness, confusion, and difficulty with ambulation. One deeper anamnesis, the patient reports an 8.36 kg weight loss during the preceding three-month but denied any other symptoms.

Laboratory Revealed

- hypercalcemia at 12.0 mg/dL (normal: 8.7–10.7 mg/dL) and albumin of 3.2 g/dL (normal: 3.5–4.8 g/dL).
- radiological examination was negative for lytic lesions, computed tomography (CT) of the chest did not reveal any lymphadenopathy or findings suggestive of granulomatous disease, CT of the abdomen and pelvis revealed a 13.6 × 8.7 × 6.1 cm mass in the right lobe of the liver
- Further testing determined that she had PTH-independent hypercalcemia; parathyroid hormone (PTH) was decreased at 6 pg/mL (normal: 3–65 pg/mL), PTHrP was normal at 13 pg/mL (normal: 14–27 pg/mL), calcifediol (25-hydroxyvitamin D) was decreased at 12 ng/mL (deficiency < 20 ng/dL; insufficiency: 20–29 ng/mL; optimal ≥ 30 ng/dL), and calcitriol (1,25-dihydroxyvitamin D) was elevated at 183 pg/mL (normal: 18–72 pg/mL).
- CBC- hemoglobin of 7.1 g/dL (normal: 12–16 g/dL), hematocrit of 21.4% (normal: 37–47%), and mean corpuscular volume of 108.9 fL (83–101 fL)
- A peripheral blood smear were no important changes
- Blood urea nitrogen was 19 mg/dL (normal: 7-23 mg/dL) and creatinine was 0.63 mg/dL (normal: 0.5–1.2 mg/dL).
- Serum iron, ferritin, transferrin, total iron binding capacity, transferrin saturation, folate, and vitamin B12 levels were all within normal limits
- AST 36UI/L, ALT 29U/L, Bilirubine 1.13 mg/dL, AFP 1.4ng/mL, CEA1.1 ng/mL, ALP134IU/L, LDH 867 IU/L
- Biopsy of the lesion revealed malignant cells while cytology revealed CD45+, CD20+, CD10−, CD30−, BCL2−, BCL6+. These findings were most consistent with DLBCL.

Differential Diagnosis

- The differential diagnosis of her PTH-independent hypercalcemia, included:
- milk-alkali syndrome
- paraneoplastic syndrome, CT imaging were negative for any lytic bone lesions which made metastatic disease as the cause of her hypercalcemia less likely.
- granulomatous disease, CT imaging was negative for any signs of granulomatous disease
- metastatic disease
- hematological malignancy, particularly lymphoma. Among lymphomas, those with non-Hodgkin's lymphoma, chron-

ic myeloid leukemia (blast phase), and adult T-cell leukemia-lymphoma may have PTHrP-induced hypercalcemia [3-8].

- On the hepatic differential diagnoses for a solitary hepatic lesion we take in consideration:
- included hepatic cyst,
- hemangioma,
- hepatic adenoma,
- hepatocellular carcinoma,
- cholangiocarcinoma, or metastatic disease.

Treatment

First, we took care of the patient hypercalcemia and then the patient underwent on R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). At time of discharge, the patient's calcium level was 9.2 mg/dL and remained normalized at 8.8 mg/dL in her follow-ups.

Taking in consideration the age, elevated LDH, Eastern Cooperative Oncology Group (ECOG) performance status of two, and Ann Arbor stage IV-B disease, the patient's International Prognostic Index (IPI) was four, corresponding to 26% five-year survival [10].

Ann Arbor staging

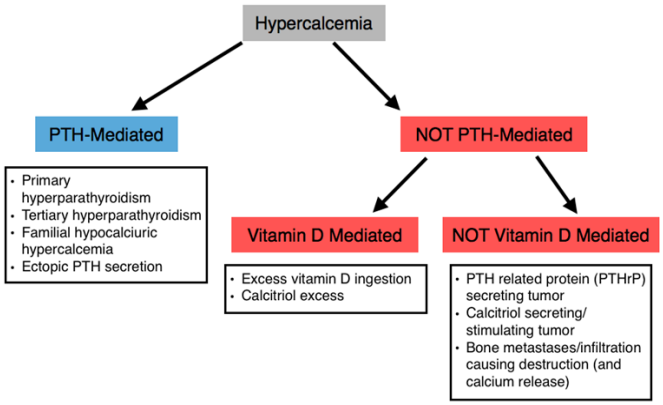
- **stage I:** involvement of a single lymph node region or of a single extra lymphatic organ or site
- **stage II:** involvement of two or more lymph node regions on the same side of the diaphragm or localized involvement of an extra lymphatic organ or site
- **stage III:** involvement of lymph node regions or structures on both sides of the diaphragm
- **stage IV:** diffuse or disseminated involvement of one or more extra lymphatic organs, or either:
- isolated extra lymphatic organ involvement without adjacent regional lymph node involvement, but with disease in distant sites
- involvement of the liver, bone marrow, pleura or cerebrospinal fluid
- Additional sub staging variables include:
- A: asymptomatic
- B: presence of B symptoms (including fever, night sweats and weight loss of ≥10% of body weight over 6 months)
- E: involvement of a single, extra nodal site, contiguous or proximal to a known nodal site (stages I to III only; additional extra nodal involvement is stage IV)
- S: splenic involvement
- X: bulky nodal disease: nodal mass >1/3 of intra thoracic diameter or 10 cm in dimension

Grade Ecog Performance Status

0. Fully active, able to carry on all pre-disease performance without restriction
1. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2. Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3. Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4. Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5. Dead

Discussion

There are two main entethies that can be associated with hypercalcemia, the PTH-dependent (PTHD) and PTH-independent (PTHI). PTHD hypercalcemia is suspected when hypercalcemia is associated with high levels (or normal) of PTH levels, suggesting inadequate suppression of PTH. The most common cause of this, is primary hyperparathyroidism (PHPT). Such a situation can be seen as in adenomas, hyperplasia's and parathyroid malignancy.



There are many potential causes that may lead to hypercalcemia but above all there have been underlined hyperparathyroidism and malignancies [11]. Among the most discussed mechanisms there are mentioned:

- the production of PTHrP [12]. PTHrP acts on osteoblasts, leading to enhanced synthesis of RANKL, with subsequent activation of osteoclasts and bone resorption with calcium release into the bloodstream. Increased renal calcium reabsorption is another mechanism through which PTHrP leads to hypercalcemia Squamous cell cancers, urinary tract cancers (renal cancer and bladder cancer), breast cancer, no Hodgkin's lymphoma, and ovarian cancer account for the majority of malignancies leading to hypercalcemia via PTHrP [12].
- osteolytic metastases and excessive calcium release from bone, accounting for approximately 20% of malignancy-related hypercalcemia [12].
- ectopic activity of 1-alpha-hydroxylase and the formation of 1,25-dihydroxycholecalciferol, which seem more frequent in lymphomas and ovarian germ cell tumors [12]. It has been theorized that, in lymphomas, surrounding macrophages may have 1-alpha hydroxylase activity which contributes to the elevation of calcitriol levels. Hewison et al. demonstrated this phenomenon using immunolocalization [11].
- The fourth mechanism by which cancer can lead to hypercalcemia includes ectopic production of PTH, or in rare cases PTH can be secreted by parathyroid carcinoma [13, 14].
- PHL is rare and comprises 0.4% of all cases of extra nodal

NHL and 0.016% of all cases of NHL [15]. The diagnostic criteria for PHL were proposed by Lei et al in 1998, these include:

- -at presentation, the patient's symptoms are caused mainly by liver involvement
- -absence of palpable lymphadenopathy and no radiologic evidence of distant lymphadenopathy - absence of leukemic blood involvement in the peripheral blood smear [16].
- The majority of primary hepatic lymphomas are found to be DLBCL [12].
- PHL is a rare disease with non-specific clinical presentation, varying laboratory and radiologic features. Primary hepatic tumors, liver metastases, and systemic lymphoma with secondary hepatic involvement can all present in a fashion similar to PHL. In addition, there are case reports of PHL presenting as acute liver failure [17].
- The possible mechanisms proposed for the development of lymphoma in these patients include:
- B-cell stimulation leading to polyclonal and then monoclonal B-cell expansion,
- HCV induced (14; 18) translocation leading to over expression of the anti-apoptotic factor, bcl-2, and monoclonal IgH rearrangement [18].
- alteration in the transcriptional regulation of genes like p21, p53, and H-ras by the viral core and/ or NS35 proteins [19-20].

PHL has been well described in patients prescribed methotrexate for rheumatoid arthritis [13].

PHL more commonly occurs in the fifth decade of life and is three times more common in males [13]. Laboratory tests can help differentiate between hepatocellular carcinoma and PHL; ALP and LDH are typically elevated while AFP and CEA are within normal ranges as was the case in our patient [3-6]. Overall, there is no pathognomonic radiographic finding in PHL and therefore biopsy is considered the gold standard for the diagnosis of PHL. FNA should not be performed as the tissue may be necrotic and result in a false-negative result [6-15].

Treatment options include: i) Surgery ii) Chemotherapy iii) Radiation iv) Combinations of the above modalities. Standard therapy for DLBCL is chemotherapy, particularly with the regimen of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) [6]. Other treatment regimens with and without radiotherapy and surgery have also been described in the literature. For small localizing lesions, surgical resection may be sufficient as a stand-alone therapy, but this is not routinely practiced as relapse after surgery is common [5].

Conclusion

Calcitriol-mediated hypercalcemia in malignancy is rare and accounts for less than 1% of all malignancy-related hypercalcemia cases. When present, it most commonly occurs in NHL, specifically DLBCL. PHL has known association with immunosuppressive therapy and autoimmune diseases and is well described in patients with rheumatoid arthritis treated with methotrexate [15-20].

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