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A CASE OF INTRAVASCULAR LARGE B-CELL LYMPHOMA COMPLICATED BY HYPERCALCAEMIA

Masahiro Yabe[1], Takashi Abe[2], Saori Yamaga[1], Seiga Ozaki[1], Katsuhiro Tomiyama[3], Hideki Hashidate[4]

[1] Department of General Internal Medicine, Niigata City General Hospital, Niigata, Japan
[2] Department of Hematology, Niigata City General Hospital, Niigata, Japan
[3] Department of Dermatology, Niigata City General Hospital, Niigata, Japan
[4] Department of Pathology, Niigata City General Hospital, Niigata, Japan

Corresponding author's e-mail: yabe0724@jeans.ocn.ne.jp

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ABSTRACT

Introduction: Hypercalcaemia in intravascular large B-cell lymphoma (IVLBCL) is extremely rare, occurring more often in other non-Hodgkin's lymphomas (NHL).

Case description: A 68-year-old man was admitted with a fever of unknown origin, mild disturbance of consciousness and respiratory failure. Laboratory findings showed hypercalcaemia with elevated parathyroid hormone-related protein (PTHrP) and decreased intact parathyroid hormone and 1,25-dihydroxyvitamin D. The patient was diagnosed with IVLBCL via random skin biopsy. Chemotherapy resulted in complete remission and normalised PTHrP levels.

Conclusion: More than half of all cases of hypercalcaemia in NHL are not associated with PTHrP or 1,25-dihydroxyvitamin D, and the cause of the hypercalcaemia is unknown. However, PTHrP levels are elevated in most cases of IVLBCL with hypercalcaemia, which may present as humoral hypercalcaemia of malignancy.

KEYWORDS

Intravascular large B-cell lymphoma, hypercalcaemia, parathyroid hormone-related protein, humoral hypercalcaemia of malignancy

LEARNING POINTS

- Intravascular large B-cell lymphoma, a rare, clinically aggressive type of B-cell non-Hodgkin's lymphoma, is prone to central nervous system disturbances, including altered consciousness.
- Hypercalcaemia, which causes impaired consciousness, is extremely rare in intravascular large B-cell lymphoma, occurring more often in other non-Hodgkin's lymphomas.
- Parathyroid hormone-related protein is elevated in most cases of intravascular large B-cell lymphoma with hypercalcaemia, which may present as humoral hypercalcaemia of malignancy.

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INTRODUCTION

Patients with hypercalcaemia due to malignant tumours exhibit a poor prognosis[1]. Cancer-associated hypercalcaemia is classified into four categories: humoral hypercalcaemia of malignancy (HHM), due to the production of parathyroid hormone-related protein (PTHrP) by tumours; local osteolytic hypercalcaemia, due to bone invasion; 1,25-dihydroxyvitamin D-mediated hypercalcaemia; and ectopic hyperparathyroidism[1].

Hypercalcaemia, which occurs in 1.4% of malignant lymphoma cases[2], 7–34% of non-Hodgkin's lymphoma (NHL) cases[3] and 18.4–23% of diffuse large B-cell lymphoma cases[4,5], is associated with poor prognosis in lymphoma[2,4,5]. In 61.1% of NHL cases with hypercalcaemia, it is not caused by PTHrP or 1,25-dihydroxyvitamin D, and the cause is unknown[3]. In contrast, 9–40% of B-cell NHL patients with HHM exhibit elevated PTHrP levels[3]. Intravascular large B-cell lymphoma (IVLBCL), a rare, clinically aggressive type of

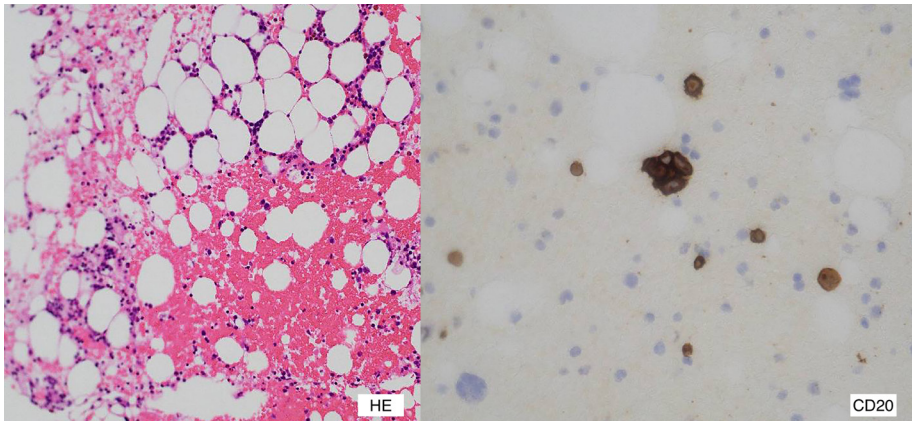


Figure 1. Histopathological examination of the bone marrow biopsy. Small clusters of somewhat large lymphocyte-like cells, but no haemophagocytosis, were observed. Left panel, haematoxylin & eosin (HE) staining, ×100. Right panel, immunohistochemical staining, revealing that the cells were CD20⁺.

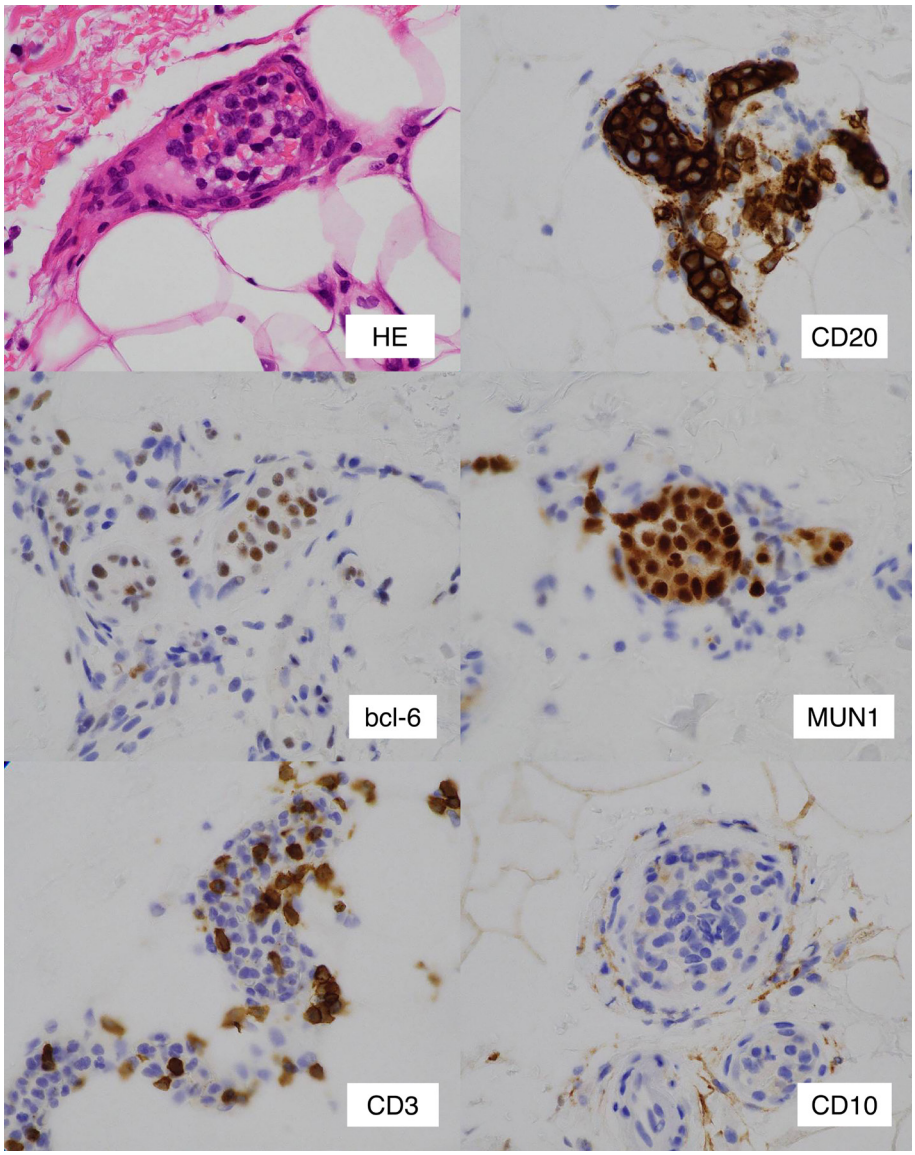


Figure 2. Histopathological examination of random skin biopsy. Medium-to-large, atypical lymphocytes infiltrated the blood vessels of the specimens. Top left, haematoxylin & eosin (HE) staining, ×100. The cells were CD20⁺, BCL-6⁺, MUN1⁺, CD3⁻, and CD10⁻, based on immunohistochemical staining.

Table 1. Details from reported cases of patients with intravascular large B-cell lymphoma (IVLBCL) and hypercalcaemia.

Reference	Age/gender	Ethnicity	Serum calcium (mg/dl)	PTHrP	Histopathological evidence of PTHrP secretion from lymphoma cells	LDH (IU/l)	Pathologically involved sites	Symptoms	Treatment	Prognosis
Yousem et al.[9]	40/F	N/A	N/A	N/A	N/A	N/A	Bone marrow, lung	Fever, obtundation, progressive dyspnoea	Chemotherapy	Death
Curtis et al.[10]	76/M	Guatemalan	15.3	N/A	N/A	N/A	Bone marrow (lung, spleen, brain, liver, spinal cord, adrenal gland, kidney at autopsy)	Dyspnoea, confusion	Steroid	Death
Hanihara et al.[11]	64/F	Asian	13.1	151 pg/ml	N/A	1750	Bone marrow (brain at autopsy)	Recurrent seizures, progressive mental deterioration	CHOP	Death
Knobel et al.[12]	52/M	Caucasian	18.6	8 pmol/l	N/A	N/A	Bone marrow, liver	N/A	MACOP-B	NA
Chinen et al.[8]	71/M	Asian	14.9	113 pmol/l	positive	2140	Bone marrow, kidney	Lethargy, apathy, drowsy, hypoxemia	R-CHOP+MTX	Relapse
Ha et al.[7]	68/M	Asian	20.6	2.7 pmol/l	N/A	2668	Bone marrow	Stuporous mentality, fever, lethargy	R-CHOP	Alive
This case	68/M	Asian	14.0	7.9 pmol/l	N/A	742	Bone marrow, skin	Fever, dyspnoea, impaired consciousness	pola-R-CHP	Alive

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; LDH, lactate dehydrogenase; MACOP-B, methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; MTX, methotrexate; N/A, not applicable; pola-R-CHP, polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisone; PTHrP, parathyroid hormone-related protein.

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B-cell NHL, can involve central nervous system disturbances, including altered consciousness[6]. Hypercalcaemia, which causes impaired consciousness, is extremely rare in intravascular large B-cell lymphoma (IVLBCL), occurring more often in other types of NHL. Here, we report a case of hypercalcaemia in IVLBCL.

CASE DESCRIPTION

A 68-year-old man with a history of colorectal polyps was referred to our hospital with fever of unknown origin and dyspnoea and was admitted. On physical examination, he had a Glasgow Coma Scale score of 13 (E3V4M6), impaired consciousness, respiratory failure (87% SpO_2 in room air) and an Eastern Cooperative Oncology Group performance status of 4. No lymphadenopathy, hepatosplenomegaly or skin rashes were observed. A complete blood count was performed (leukocytes, 2,990 cells/μl; erythrocytes, 3,880,000 cells/μl; haemoglobin, 12.6 g/dL; platelets, 38,000 cells/μl). A peripheral blood smear revealed no atypical lymphocytes. Serum chemistry indicated mild renal dysfunction and hypercalcaemia (lactate dehydrogenase, 742 IU/l; soluble interleukin-2 receptor, 8,854 U/ml; ferritin, 548.7 ng/ml; C-reactive protein, 5.6 mg/dl; creatinine, 1.23 mg/dl; albumin, 2.5 g/dl; serum calcium, 12.8 mg/dl; corrected calcium, 14.0 mg/dl). Serum PTHrP was elevated (7.9 pmol/l; normal, <1.0 pmol/l). Intact parathyroid hormone (iPTH) was below normal (6 pg/ml; normal, 10–65 pg/ml), as was 1,25-dihydroxyvitamin D (11.1 pg/ml; normal, 20.0–60.0 pg/ml). Computed tomography revealed no lymphadenopathy, hepatosplenomegaly, adrenal tumours or bone lesions. Bone marrow biopsy revealed small clusters of relatively large $CD20^+$ cells, but no haemophagocytosis *(Fig. 1)*. Random skin biopsies of the chest, abdomen and thigh revealed medium-to-large round atypical lymphocytes in the vessels. Immunohistology revealed that the atypical lymphocytes were positive for CD20, BCL-6 and MUM1 and negative for CD3 and CD10 *(Fig. 2)*. Based on these findings, the patient was diagnosed with IVLBCL and HHM due to PTHrP production. The patient received a pola-R-CHP regimen (polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisone). This resulted in rapid improvement of hypercalcaemia and normalisation of PTHrP to <1.0 pmol/l after two courses of pola-R-CHP therapy. IVLBCL remained in complete remission after six courses of the pola-R-CHP regimen.

DISCUSSION

Reports of hypercalcaemia in IVLBCL are rare, with only six cases reported *(Table 1)*. Of the three reports from Asia, two are from Japan. In these six reports, mean serum calcium was 14.0 mg/dl. Clinical symptoms included impaired consciousness in five of the patients (83%) and fever, dyspnoea or hypoxaemia in two (33%). The impaired consciousness was judged to be due to hypercalcaemia, with only one case showing brain involvement of IVLBCL at autopsy. Lymphoma cells were histopathologically confirmed in all six patients in the bone marrow and in one patient (17%) in the lungs, liver and kidneys. Ha et al.[7] have speculated that bone marrow involvement of the Asian IVLBCL variant and haemophagocytosis may be associated with hypercalcaemia. Here, our patient showed bone marrow infiltration but no haemophagocytosis.

Regarding the cause of hypercalcaemia in IVLBCL, PTHrP was elevated in four of the six cases reported *(Table 1)*. Only one study has shown histopathological evidence of PTHrP secretion from lymphoma cells[8]. In our case, the pola-R-CHP regimen rapidly normalised calcium levels and caused PTHrP to decline from 7.9 pmol/l to <1.0 pmol/l; iPTH did not increase, and 1,25-dihydroxyvitamin D remained within the normal range. We attributed the hypercalcaemia in our case to PTHrP production from lymphoma cells, as in the other cases. Hypercalcaemia in IVLBCL is thought to be mainly due to PTHrP-induced HHM. Considering that hypercalcaemia in IVLBCL is extremely rare, more cases should be reported.

CONCLUSION

Hypercalcaemia is rare in IVLBCL. PTHrP is elevated in most cases of IVLBCL with hypercalcaemia, which may present as HHM.

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