Case Report

Calcitriol-mediated Reversible Hypercalcemia in a Patient with Primary Adrenal Lymphoma

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Abstract

Primary adrenal lymphomas (PAL) are rare occurrences with only less than 150 cases reported in the literature. Two-thirds of these cases were reported in the last decade due to the advancements in imaging techniques and immunohistochemistry. The non-specific signs and symptoms have resulted in a delayed onset of symptoms and diagnosis of these tumors. Reports of the results of chemotherapy are not gratifying, and most patients die within one year of the diagnosis. We report a 65-year-old male with adrenal non-Hodgkin's lymphoma (NHL), who presented with hypercalcemia and renal failure. We reviewed all adrenal NHL cases presented with hypercalcemia and attempted to comprehend its etiology and overall survival effect.

Keywords: *hypercalcemia, adrenal insufficiency, lymphoma, calcitriol*

Introduction

The adrenal gland is a frequent site of neoplastic diseases, including both primary as well as metastatic diseases. Primary adrenal lymphoma (PAL) is a rare condition with only less than 150 such cases reported worldwide (1). Adrenal masses are found in the functional and non-functional adrenal adenomas, pheochromocytomas, infection sites, traumatic hemorrhage, adrenocortical carcinomas, and metastatic organs (2). Here, we report a case of bilateral adrenal diffuse large B-cell lymphomas in association with hypercalcemia.

Case Report

In June 2012, a 65-year-old male presented with pain in the left hip, anorexia, weight loss, and night sweats for six months. The history of the patient was insignificant. General physical examination revealed 106/80 mm Hg blood pressure without any postural drop. No lymphadenopathy was observed, and abdominal examination revealed mild splenomegaly.

Initial investigations revealed hemoglobin of 11.2 g/dl, mean corpuscular volume of 73.2 fL, mean corpuscular hemoglobin of 29 pg, total leukocyte count of 10.4, and platelet count of 2.13×106. The patient showed normal liver function test. The kidney function tests revealed

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urea -49.98 mmol/l, creatinine -1.71 mg/dl, serum calcium -3.55 nmol/l, and phosphorus -1.84 mmol/l. Serum electrolytes test revealed conditions of mild hypokalemia. Serum parathyroid hormone (PTH) was 0.528 pmol/l (1.1–7.15 pmol/l), vitamin D3 level was 99.1 nmol/l (50–250 nmol/l), vitamin 1, 25-D was 512.2 pmol/l (47–188 pmol/l), and parathyroid hormone-related protein (PTHrP) was within the normal range. Lactate dehydrogenase (LDH) was found to be 699 U/L (normal range, 320–460 U/L).

The patient underwent normal overnight dexamethasone suppression test (ONDST) and 24 hour vanillyl mandelic acid (VMA). The chest X-ray was normal. Ultrasonographic study of the abdomen demonstrated a bilateral adrenal mass. Computed tomography (CT) scan of the abdomen showed a large, heterogeneously bilateral mass with calcification. Magnetic resonance imaging (MRI) of the patient's hip revealed features of osteoarthritis. CT-guided biopsy showed a lesion suggestive of non-Hodgkin's lymphoma (NHL) large B-cell type. Immunohistochemistry analysis of the lesion demonstrated that the cells were positive for CD 20 and negative for CD3. Examination of the bone marrow and CT imaging of chest was normal.

The patient was subjected to adrenocorticotrophic hormone (ACTH) test, which revealed peak cortisol at one hour 695.2 nmol/l (normal value of > 500 nmol/l). Meanwhile, the patient was subjected to combination chemotherapy drugs such as Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP). After the completion of four cycles of chemotherapy, the patient developed hypotension and recurrent vomiting. Random cortisol level was observed to be 113.9 nmol/l, and the patient was put on replacement of glucocorticoid and mineralocorticoid.

The patient showed marked symptomatic improvement after the completion of six cycles of chemotherapy. A follow-up was done by contrast-enhanced computed tomography (CECT) of the patient's abdomen that showed a marked regression in the adrenal size (Figure 1). Serum creatinine level dropped to 1.39 mg/dl, and LDH dropped to 349 IU. Serum calcium and phosphorus levels of the patient were normalised to 2.22 nmol/l and 1.43 mmol/l, respectively. The patient did well and walked without any support. However, during the follow-up after nine months of chemotherapy, the patient developed irrelevant talking and respiratory tract symptoms with deteriorating conscious level. CT scan of the brain revealed a large hypodense area in the front temporal region and another area in the occipital frontal region. The present biochemical profile of the patient that included calcium, kidney function tests, and LDH was in the normal range. The CT scan of the abdomen did not reveal any lesion in the adrenal area, except few old calcifications that were also present preciously at the time of complication of the sixth cycle of R-CHOP. The patient was given dexamethasone and antibiotics but had seizures and died on the fourth day of hospitalisation, probably due to pneumonia and central nervous system (CNS) relapse.

Discussion

Hypercalcemia is common in malignancy and is one of the predictors of the poor prognosis of PAL. The presence of hypercalcemia and its etiology is not well documented in PAL. The review of literature in PubMed (http://www.ncbi.nlm.nih.gov) and other data base revealed that out of 126 patients with PAL, only six had hypercalcemia (Table 1). Out of these patients, PTHrP was raised in three patients; in two patients, no workup was done to assess the cause of hypercalcemia, and in one case, the complete data of patient could not be retrieved. Among the PAL patients with hypercalcemia, four were females and three males. The majority of patients, except those reported by Feldberg et al. (3), were above 60 years. Major cell type was large B-cell (four patients) although one patient had diffuse histolytic and T-cell type (4, 5). The majority of patients died within two months. Hypercalcemia in lymphomas has a bad prognosis. Eighty percent of cancer patients expire within a year with a median survival of five months. Our patient and one reported by Al-Fiar et al. survived for more than ten months (2).

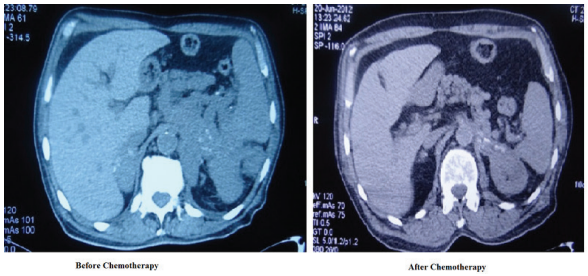


Figure 1. CT abdomen showing bilateral adrenal masses before chemotherapy.

Table 1. List of studies showing presence of hypercalcemia in PAL

Author (Reference)	Year	Sex	Age	Cell type	Cause of hypercalcemia	Adrenal insufficiency	Death after diagnosis
Feldberg et al. (3)	1986	M	43	Diffuse histocytic	NA	No	2 months
Oppong et al. (4)	1991	M	63	T cell type	NA	Yes	2 months
Al-Fiar et al. (2)	1997	F	61	Diffuse large cell type	NA	No	11 months
Iwamizu-Watanabe et al. (10)	2003	F	73	Diffuse large cell type	PThrP	No	9 days
Otta et al. (8)	2003	F	95	Diffuse lage B cell	PThrP	Yes	NA
Alama-Zaragoza et al. (9)*	2002	NA	NA	NA	NA	Yes	NA
Present case	2015	M	65	Diffuse large cell type	Calcitriol	Yes	12 months

NA: Not available * complete data of patient could not be retrieved.

In the case of our patient, hypercalcemia was caused by increased calcitriol, which was demonstrated by a significant decrease in calcium and normalisation of calcitriol and kidney functions after four cycles of chemotherapy. Hypercalcemia in PAL is caused either by humoral factors secreted by tumor cells or by local osteolysis due to bone marrow infiltration by the tumor cells. Some lymphomas or tumor-associated macrophages express 25-hydroyvitamin D 1 hydroxylase that converts inactive vitamin to calcitriol, which causes increased calcium reabsorption. Our patient did not show adrenal insufficiency initially but later developed the insufficiency after the completion of four chemotherapy cycles. Studies show that adrenal insufficiency is present in around 70% of PAL as compared to 3% of secondary adrenal metastasis (5). Some authors have suggested underlying autoimmune adrenalitis in patients with PAL, which may predispose them to adrenal insufficiency even if the adrenal are smaller in size (5). The present case revealed that adrenal insufficiency may not appear initially and may manifest during chemotherapy. Thus, careful and frequent follow-up should be maintained for testing adrenal reserve. Four patients of PAL with hypercalcemia reported adrenal insufficiency whereas three cases did not show adrenal insufficiency. Hence, patients presented with hypercalcemia may not act as a predictor of adrenal insufficiency. However, owing to the small number of reported cases, no appropriate conclusion can be drawn. Interestingly, our patient's calcium and LDH was normalized after four cycles of chemotherapy, and calcium and LDH did not rise when the patient developed CNS relapse. Patients with adrenal lymphomas with CNS replace are even rare with less than 10 documented in literature, and majority of them were older than 50 years (median age was 65 years) and were mostly males with bilateral involvement and raised LDH at the time of relapse. Histologically, all patients except one (High-grade Burkitt lymphoma) had diffuse large-B-cell lymphoma (DLBCL) (12). All of them had raised LDH during relapse and were presented with mental confusion, mental deterioration or cranial nerve palsies; a majority had relapse between four to five months of the primary disease (6, 7). Our patient was presented with mental confusion and showed remarkably normal levels of LDH and calcium during CNS relapse.

It is a well-known fact that the addition of Rituximab to the CHOP regimen increases the complete response rate, event-free and overall survival rate of patients with DLBCL; however, the optimal management of primary adrenal DLBCL is presently open to arguments because of the few cases documented in literature. Before the introduction of Rituximab in the CHOP therapy, 20–50% of overall survival rate was reported in lymphomas patients. Data by Kim et al. (11) revealed a complete response rate of 54.8% and partial response rate of 32.3% after the R-CHOP therapy (11). There is a high risk of CNS relapse in primary adrenal NHL, and the risk remains almost same even after the addition of R-CHOP therapy. Thus, CNS prophylaxis should be considered in primary adrenal DLBCL like any other extra-nodal NHL.

Although adrenal lymphoma is a rare cause of bilateral adrenal enlargement, differential diagnosis is an apt requisite. Sometimes, cases present with hypercalcemia may reverse after the treatment of the primary lesion. Hypercalcemia and raised LDH may not manifest at what time the patient will have CNS relapse. Due to the rarity of this disorder, the cause of hypercalcemia and its prognostic significance needs subsequent assessment in these patients.

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Conflict of Interest

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Conception and design: SAM
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Drafting of the article: IH

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