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The coexistence of renal cell carcinoma and diffuse large B-cell lymphoma with hypercalcemic crisis as the initial presentation

[1]Yilmaz H, [2]Namuslu M, [1]Bilgic MA, [1]Bavbek N, [1]Akcay A

[1]Turgut Ozal University, Department of Internal Medicine, Section of Nephrology, Ankara, Turkey; [2]Turgut Ozal University, Department of Clinical Biochemistry, Ankara, Turkey
E-mail: drhakkiyilmaz@yahoo.com

Introduction. Severe hypercalcemia can be life threatening. The causes of hypercalcemia can be divided into seven categories: hyperparathyroidism, vitamin D-related causes, malignancy, medications, other endocrine disorders, genetic disorders, and miscellaneous causes. Evaluation of a patient with hypercalcemia should include a careful history and physical examination focusing on clinical manifestations of hypercalcemia, risk factors for malignancy, causative medications, and a family history of hypercalcemia-associated conditions (e.g. kidney stones). Hypercalcemia was clasified as serum levels of calcium: 1) mild hypercalcemia (calcium < 12 mg/dl), 2) moderate hypercalcemia (calcium between 12 and 14 mg/dl), and 3) severe hypercalcemia (calcium > 14 mg/dl). We should keep in mind that severe hypercalcemia was originated from two or more causes. This is the first report in the literature; renal cell carcinoma (RCC) and diffuse large B-cell lymphoma (DLBCL) presented severe paraneoplastic hypercalcemia.

Case presentation. We report a case of a 63-year-old Turkish man with RCC and DLBCL who showed severe hypercalcemia (calcium=15.01 mg/dl) accompanied by elevation of serum parathyroid hormone-related protein (PTH-rP) as the initial presentation. While hypercalcemia is one of the complications of various types of cancerous diseases, it has not been reported still as the first presentation of the coexistence of RCC and DLBCL. After radical nephrectomy, the patient underwent six courses of chemotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone and achieved a complete remission that lasts 2 years.

Conlusion. This case report describes a patient with two different malignancies (RCC and DLBCL) with the unusual presentation of hypercalcemia. We review the differential diagnosis and treatment of malignant hypercalcemia. We suggest that coexistence of DLBCL with RCC, although rare, should be considered as a possible causative in hypercalcemia of unknown underlying disease.

Key words: severe hypercalcemia, paraneoplastic syndrome, renal cell carcinoma, diffuse large B-cell lymphoma

Hypercalcemia is a relatively common clinical problem. Among all causes of hypercalcemia, primary hyperparathyroidism and malignancy are the most common, accounting for more than 90% of cases. Therefore, the diagnostic approach to hypercalcemia typically involves distinguishing between the two.

Usually, it is not difficult to differentiate between them. Malignancy is often evident clinically by the time it causes hypercalcemia, and patients with hypercalcemia malignancy have usually higher calcium concentrations and are more symptomatic from hypercalcemia than individuals with primary hyperparathyroidism.

Corresponding author: Dr. Hakki Yilmaz, M.D., Turgut Ozal University, Department of Internal Medicine, Section of Nephrology, Alparslan Turkes Cad. No: 57 06510 Emek/Ankara, Turkey; phone: + 90-0312-2035555; fax: + 90-0312-2035029; e-mail: drhakkiyilmaz@yahoo.com.

Although hypercalcemia in otherwise healthy outpatients is usually due to primary hyperparathyroidism and malignancy is more often responsible for hypercalcemia in hospitalized patients, other potential causes of hypercalcemia must be considered.

The initial goal of the laboratory evaluation is to differentiate parathyroid hormone (PTH)-mediated hypercalcemia (primary hyperparathyroidism and familial hyperparathyroid syndromes) from non-PTH mediated hypercalcemia (primarily malignancy, vitamin D intoxication, granulomatous disease). Thus, once hypercalcemia is confirmed, the next step is measurement of serum PTH. An elevated or high-normal value indicates primary hyperparathyroidism.

It appears to be a higher incidence of primary hyperparathyroidism in patients with malignancy (nearly 10%) than in the general population. Thus, despite the increased cost, it is reasonable to order an intact PTH assay, as a part of the routine evaluation of hypercalcemia, even in a patient with known malignant disease.

In the presence of low serum PTH concentrations (< 20 pg/ml), PTH-rP and vitamin D metabolites should be measured to assess for hypercalcemia of malignancy and vitamin D intoxication. If PTH-rP and vitamin D metabolites are also low, another source for the hypercalcemia must be considered. Additional laboratory data (including serum protein electrophoresis for possible multiple myeloma, thyroid-stimulating hormone (TSH), vitamin A) will often lead to the correct diagnosis.

Cancer-induced hypercalcemia (CIH) occurs in 5% to 30% of patients with cancer during the course of their disease, depending on the type of tumor (Grill and Martin 2000). CIH represents the most common paraneoplastic syndrome, with an incidence of 15 cases per 100 000 people per year (Strewler 1997; Shoback and Funk 2001). Lung cancer, breast cancer and myeloma have the highest incidence of CIH, accounting for more than 50%, while this paraneoplastic syndrome occurs rarely in patients with colorectal and prostate cancer (Strewler 1997). Except in patients with multiple myeloma and breast cancer, the prognosis of the cancer patients with CIH is usually poor, with a mean survival rate of 2-3 months (Strewler 2005).

In retrospective studies, to determine the etiology of hypercalcemia in all patients, 28-36% of cases are attributed to malignancy (Lee et al. 2006). The most common malignancies in patients with developed hypercalcemia are lung and kidney malignancies (Lee et al. 2006). Among patients with RCC, it is the most common paraneoplastic syndrome affecting between 13-20% of patients (Cohen and McGovern 2005; McLaughlin et al. 2006). Aprroximately 75% of patients with hypercalcemia and RCC have high-stage lesions (Zagoria et al. 1990). However, neither the presence nor degree of hypercalcemia has been shown to have a significant correlation with tumor grade or survival (Gutzeit et al. 2005). Albright (1941) was first who described that hypercalcemia in RCC can be divided into two categories: metastatic and nonmetastatic.

The coexistence of RCC and non-Hodgkin's lymphoma (NHL) is more common than expected in the general population. One hospital-based study reported a standardized incidence ratio (SIR) [SIR was calculated as observed/expected number of second cancers] of 1.67 for the coexistence of the two malignancies (Tihan and Filippa 1996). However, the exact reason for this coexistence has not been clearly delineated; genetic mutations, environmental factors, and side effects of chemotherapy and radiotherapy have been proposed as possible causes. We present the first case report with severe hypercalcemia induced by the coexistence of RCC and NHL. There were no metastatic and lytic bone lesions. So hypercalcemia was paraneoplastic. RCC and NHL therapy improved hypercalcemia.

Case Report

A 63-year-old Turkish man who had previously been in a good health, except for a history of treated hypertension and osteoarthritis, presented to our hospital in May 2012 with polyuria, polydipsia, anorexia, vomiting, constipation, confusion, and left-sided abdominal pain that radiated around the left flank. A written informed consent was obtained from the patient for publication of this manuscript and accompanying images.

His physical examination did not reveal a palpable abdominal mass; blood pressure was 152/94 mmHg. ECG showed that bradycardia (heart rate=56 beats per min), corrected QT interval was 310 ms (normal range: 370-440 ms) and PR interval was 210 ms (normal range: 120-200 ms) with no extrasystoles.

Laboratory investigations revealed hypercalcemia with serum calcium level of 15.01 mg/dl (normal range: 8.6-10.2 mg/dl), elevated lactate dehydrogenase (LDH) level of 520 IU/l (normal range: 135-225 IU/l) and a mild anemia with microscopic hematuria. In addition, serum intact PTH level was decreased to 3.3 pg/ml (normal range: 11-79 pg/ml), but serum levels of 25-hydroxycholecalciferol [25(OH)D] (28 ng/ml,

normal range: 10-40 ng/ml), alkaline phosphatase (68 IU/l, normal renge: 33-107 IU/l for male), 1,25-dihydroxycholecalciferol [1,25(OH)2D] (78 pg/ml, normal range: 16.4-81 pg/ml), albumin (4 g/dl, normal range: 3.9-5.1 g/dl) were normal.

An abdominal ultrasound examination was performed. This revealed a large left-sided renal mass. A subsequent computed tomographic (CT) scan confirmed a 9 cm x 7 cm x 7 cm left upper pole renal mass. Before surgery, PTH-rP (9.5 pmol/l) was determinated by immunochemilluminometric assay (ICMA) (normal range: <2.0 pmol/l). The patient was operated and radical nephrectomy with extended lymphadenectomy was performed. On histopathological examination, the mass was diagnosed as a grade II clear RCC (Fig. 1 and Fig. 3).

However, the pathology of lymph node revealed DLBCL (Fig. 2). The lymphadenopathy was only a result of DLBCL. Whole body-bone scintigraphy was normal, and no distant metastasis was observed. DLBCL was stage IIIAS based on Ann Arbor staging system [stage IIIAS refers to two or more involved lymph node regions on the same side of the diaphragm with localized involvement of a spleen (stage IIIS)]. Administration of hydration, loop diuretics and zoledronic acid produced only transient resolution of hypercalcemia until the final diagnosis of DLBCL and RCC. Cyclophosphamide, doxorubicin, vincristine, prednisone plus rituxumab (R-CHOP) treatment currently represents the most effective chemotherapy regimen for DLBCL in patients over 60 years of age. The patient underwent six courses of chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine, prednisolone and rituxumab and achieved a complete remission that lasts 2 years. The patient's general condition and serum levels of calcium (Table 1) and LDH improved soon after six courses of R-CHOP therapy.

Discussion

Hypercalcemia is relatively common in patients with cancer, occurring in approximately 20 to 30% of cases (Steward 2005). It occurs in patients with both solid tumors and hematologic malignancies. The most common cancers associated with hypercalcemia are breast

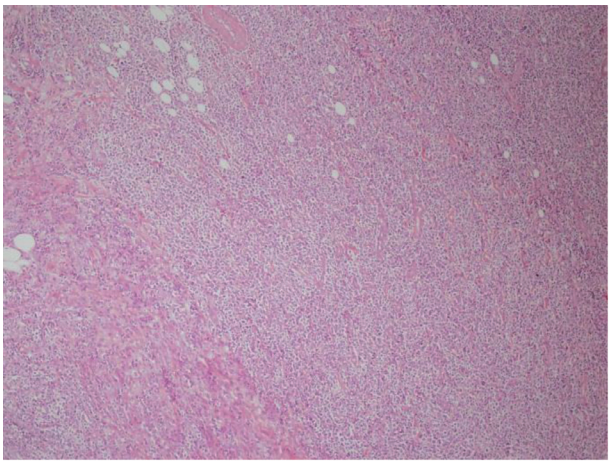

Fig. 2. Exicison of lymph node showing infiltration with a population of large cells (B cells) consistent with diffuse large cell lymphoma. The architecture of the node is lost, with a diffuse pattern of involvement. Hematoxylin and eosin stain x 100.

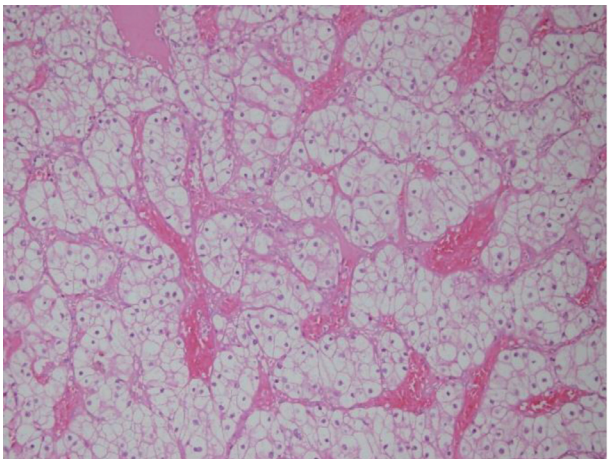

Fig. 1. Micrograph of clear cell renal cell carcinoma. Nephrectomy specimen. Hematoxylin and eosin stain x 200.

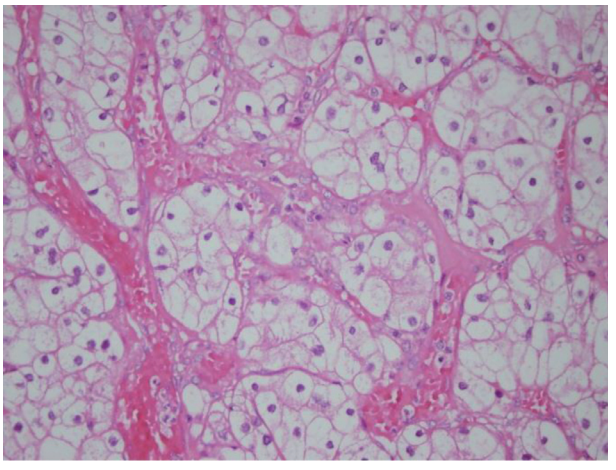

Fig. 3. Nephrectomy specimen showed clear cell carcinoma. Hematoxylin and eosin stain x 400.

and lung cancers, and multiple myeloma (Steward 2005; Horwitz and Stewart 2006). Malignancy is often evident clinically by the time it causes hypercalcemia, and patients with hypercalcemia of malignancy often have a poor prognosis.

Hypercalcemia in patients with cancer is primarily due to increased bone resorption and release of calcium from bone. It can be classified into four categories (Steward 2005; Clines and Guise 2005; Horwitz and Stewart 2006): humoral hypercalcemia of malignancy (HHM); local osteolytic hypercalcemia (LOH); 1,25-dihydroxyvitamin D (calcitriol)-induced hypercalcemia; and ectopic secretion of authentic PTH.

LOH accounts for 20% of cases malignancy-associated hypercalcemia (Steward 2005; Clines and Guise 2005; Horwitz and Stewart 2006). LOH-producing tumors include breast and prostate cancers, and hematologic neoplasms (multiple myeloma, lymphoma/leukemia). LOH is caused by locally produced osteoclast-activating cytokines, including PTH-rP and interleukin (IL)-1, IL-6, IL-8, hepatocyte growth factor (HGF), macrophage inflammatory protein alfa (MIP-1α) and receptor activator of nuclear factor kappa B ligand (RANKL) (Steward 2005; Clines and Guise 2005; Horwitz and Stewart 2006). Our case showed that there is no metastasis and osteolytic lesion.

HHM from increased secretion of PTH-rP by a malignant tumor accounts for approximately 80% of cases (Ratcliffe et al. 1992). Numerous types of malignancies are associated with HHM and secretion of PTH-rP, including squamous cell cancer (e.g. of the head and neck, esophagus, cervix, or lung) and renal cell, breast, and ovarian carcinomas. Lymphomas may be associated with PTH-rP-mediated hypercalcemia as well.

It has been reported that PTH-rP levels are elevated in up to 47% of patients with malignancy and hypercalcemia (Kao et al. 1990). PTH-rP is elevated in up to 15% of all patients with RCC, but it is also expressed in normal tissue (Papworth et al. 2005). This peptide binds to the common PTH/PTH-rP receptor to cause increased resorption of bone and increased renal calcium absorption. In patients with NHL, the reported incidence of HHM is only 1% to 4% (Muggia 1990; Seymour and Gagel 1993). It was, however, noted that the incidence of hypercalcemia in high-grade NHL such as DLBCL can be as great as 30% (Burt and Brennam 1980; Seymour and Gagel 1993). In contrast to HHM in RCC, HHM in lymphoma is mediated by secretion of calcitriol leading to normal or suppressed PTH and PTH-rP levels (Seymour and Gagel 1993). However, HHM in lymphoma associated with elevated PTH-rP levels has also been occasionally reported (Firkin et al. 1996). In our case, the PTH-rP level was increased, the calcitriol levels were in the normal range and PTH levels were suppressed without bone metastases. We report on a patient who presented with hypercalcemia and a concomitant renal mass. The clinical staging examination showed lymphadenopathy, but no distant metastases. It was suspected that the patient had HHM due to RCC. Thus, the patient underwent radical nephrectomy. There was surprising pathologic result of histopathological examination that revealed the coexistence of DLBCL and RCC.

Other humoral factors that have been associated with hypercalcemia in RCC include IL-6, IL-1, tumor necrosis factor alpha (TNFα), and transforming growth factor alpha and beta (TGFα, β) (Clines and Guise 2005). Many studies have attempted to determine the exact role of IL-6 in hypercalcemia of RCC. IL-6 has been shown to activate osteoclastic bone resorption, and it acts synergistically when coexpressed with PTH-rP. Some studies suggest that IL-6 stimulates tumor growth (Weissglas et al. 1997). It is not clear whether this cytokine causes hypercalcemia either directly or indirectly by increasing the effect of PTH-rP on bone resorption (Ueno et al. 2000). The pathogenesis of IL-6-mediated hypercalcemia appears to be multifactorial at this time.

Table 1

Monitoring of laboratory values in our case

	Normal values	On admission	After nephrectomy	After six courses of chemotherapy (R-CHOP)
Corrected calcium* (mg/dl)	8.6-10.2	15.01	13.3	9.5
PTH (pg/ml)	11-79	3.3	9.5	41.6
PTH-rP (pmol/l)	< 2	9.5	5.8	0.8
25(OH)D (ng/ml)	10-40	28	----	----
1, 25(OH)2D (pg/ml)	16.4-81	78	----	----

*Corrected calcium (mg/dl) = measured total calcium (mg/dl) + 0.8 (serum albumin 4.0 g/dl)

Table 2

Treatment of hypercalcemia of malignancy

General Measures	Remove calcium in diet. Stop hypercalcemic medications. Reduce sedatives. Stimulate deambulation
Hydration	Normal saline 200-500 ml/h
Glucocorticoids	Prednisone 40 to 100 mg daily for up to one week. Hydrocortisone 100 mg I.V. q6h. Dexamethasone 4 mg S.C. q6hr for 3 to 5 days.
Bisphosphonates	Pamidronate 60 to 90 mg intravenously over 2 to 24 h. Zoledronate 4 mg intravenously over at least 15 min.
Calcitonin	Calcitonin 4 to 8 international units per kg given S.C. or I.M. q12h (can titrate up to q6h)
New therapeutics	The anti-RANKL monoclonal antibody denosumab
Dialysis	Hemodialysis with little or no calcium in the dialysis fluid and peritoneal dialysis (though it is slower) are both effective therapies for hypercalcemia, and are considered treatments of last resort. Dialysis may be indicated in patients with severe malignancy-associated hypercalcemia and renal insufficiency or heart failure, in whom hydration cannot be safely administered

Adapted from Robertson et al. 1975; Basso et al. 2011; Clines 2011

Prostaglandins of E series (PGE1 and PGE2) can be secreted in large amounts by especially renal tumors and also stimulate osteoclastic resorption. In these cases, nonsteroidal anti-inflammatory drugs may be effective in reducing calcium by inhibiting prostaglandin production by the tumor (Robertson et al. 1975; Basso et al. 2011; Clines 2011). Our patient was on chronic aspirin treatment of osteoarthritis; therefore prostaglandin-mediated hypercalcemia is unlikely in this case.

Surgery is curative in the majority of patients without metastatic RCC and is therefore the preferred treatment for patients with stages I, II, and III disease. Nephrectomy will improve hypercalcemia in many patients with RCC. But calcium levels decreased just to 13.4 mg/dl after nephrectomy in our case. After six courses of chemotherapy with R-CHOP, hypercalcemia has improved (Table 1). To our best knowledge, this is first case report; RCC and NHL induced HHM as initial presentation.

We summarized the treatment options for hypercalcemia (Robertson et al. 1975; Basso et al. 2011; Clines 2011) in Table 2.

Conclusion

In the literature, there is no reported case of paraneoplastic severe hypercalcemia associated with RCC and NHL at the same time. The initial evaluation should focus on whether the hypercalcemia is parathyroid-dependent or medication-related. Basic laboratory investigations for hypercalcemia include PTH, PTH-rP, and 25(OH)D. Bone-resorbing cytokines may be present in those patients in which the cause of the hypercalcemia is unclear. In our case, we could not determine the specific cytokine that caused the hypercalcemia, as IL-1, IL-6, PGE1, PGE2 and TNF were below the limit of detection by commercially available ELISA kits. If laboratory tests are unrevealing, bone scan, MRI, CT scan, or PET-CT should be considered to evaluate of lytic bone lesions or underlying malignancy. Evaluation for carcinoma should be persistently pursued in a patient who has symptoms suggestive of paraneoplastic hypercalcemia. We suggested only RCC before the nephrectomy. But after the surgery patient showed two different kinds of malignancy (RCC and DLBCL). Finally, IV fluids and bisphosphonates are often helpful to control the hypercalcemia. Nephrectomy followed by six courses of R-CHOP can improve and even normalize hypercalcemia in patients with RCC and NHL. Before treating patients with hypercalcemia it is necessary to consider many causes of the elevated serum calcium level carefully.

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