Case Report

Chronic Lymphocytic Leukemia-Induced Paraneoplastic Hypercalcemia

Kronik Lenfositik Lösemiye Bağlı Paraneoplastik Hiperkalsemi

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ABSTRACT

Paraneoplastic hypercalcemia is common, especially in advanced stage solid organ malignancies (breast cancer, renal cancer, lung cancer) and multiple myeloma, and is associated with poor prognosis. Paraneoplastic hypercalcemia is rarely observed in chronic lymphocytic leukemia. Due to its low incidence, there is not enough data in the literature about the effect of hypercalcemia on prognosis and its treatment. We reported this rare condition that a 68-year-old male who was followed up with a diagnosis of chronic lymphocytic leukemia and developed symptomatic malignant hypercalcemia. We concluded that ibrutinib was effective in the control of hypercalcemia due to chronic lymphocytic leukemia.

Keywords: leukemia, lymphocytic, chronic, B-cell, hypercalcemia, ibrutinib

ÖZET

Paraneoplastik hiperkalsemi, özellikle ileri evre solid organ malignitelerinde (meme kanseri, böbrek kanseri, akciğer kanseri) ve multipl miyelomda yaygındır ve kötü prognoz ile ilişkilidir. Kronik lenfositik lösemide paraneoplastik hiperkalsemi nadiren görülür. Düşük insidansı nedeniyle literatürde hiperkalseminin prognoza ve tedavisine etkisi hakkında yeterli veri bulunmamaktadır. Kronik lenfositik lösemi tanısı ile takip edilen ve semptomatik malign hiperkalsemi gelişen 68 yaşındaki erkek hastada nadir görülen bu durumu bildirdik. İbrutinibin kronik lenfositik lösemiye bağlı hiperkalsemi kontrolünde etkili olduğu sonucuna vardık.

Anahtar kelimeler: kronik lenfositik lösemi, hiperkalsemi, ibrutinib

Introduction

Malignant hypercalcemia is a common paraneoplastic syndrome that occurs especially due to malignancies. Malignant hypercalcemia is usually symptomatic and indicates a poor prognosis [1]. It is seen less frequently in hematological malignancies compared to solid tumors. Paraneoplastic hypercalcemia is an extremely rare condition in chronic lymphocytic leukemia (CLL) and there is no data in the literature that clearly explains the mechanism of malignant hypercalcemia development in chronic lymphocytic leukemia. In this case report, a patient who was followed up with a diagnosis of chronic lymphocytic leukemia and developed symptomatic malignant hyper-calcemia was discussed.

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Case Report

A 68-year-old male with no concomitant disease and no history of drug use and diagnosed with CLL in May 2016 was treated one year after diagnosis due to disease progression with 6 cycles of fludarabine + cyclophosphamide + rituximab (FCR) chemotherapy. The patient's Rai stage was stage 1, and FISH analysis was normal at the diagnosis. While being followed without treatment for three years in remission, in June 2020, the patient applied with complaints of weakness, fatigue, frequent urination and constipation. Anemia, thrombocytopenia, hypercalcemia, and acute renal failure were detected in the patient. It was found that cervical, axillary and inguinal lymphadenopathies (LAP) reappeared. No other mass was detected in the tomographic evaluation. At admission, the leukocyte count was $10{,}1x10^3/\mu L$, hemoglobin was 10,9 g/dL, platelet count was $61x10^3/\mu L$, creatinine was 2,57 mg/dL, calcium was 17,29 mg/dL, albumin was 42 g/L. Peripheral smear showed 32% neutrophils, 64% lymphocytes, 4% monocytes, smudge cells and thrombocytopenia. The rapidly growing lymph node in the submandibular region was excised. The biopsy result was reported as CLL infiltration, thus Richter transformation and metastasis were excluded. In examinations for hypercalcemia, parathormone (PTH) was 1,8 pg/mL (14-72 pg/mL), 1,25-dihydroxy vitamin D (calcitriol) was 41,7 ng/dL (30-100 ng/dL). Paraneoplastic hypercalcemia due to CLL was considered. After the patient's hydration and diuretic treatment, calcium decreased to 14.03 mg/dL and creatinine to 1.61 mg/dL, and zoledronic acid was administered to the patient on day 4. Flow cytometry was found to be compatible with B-cell CLL. There was 80% mature lymphocyte infiltration in bone marrow aspiration. FISH analysis was normal. On day 6, the patient was re-treated as Rai stage 4 CLL and due to Cumulative Illness Rating Scale (CIRS) >6

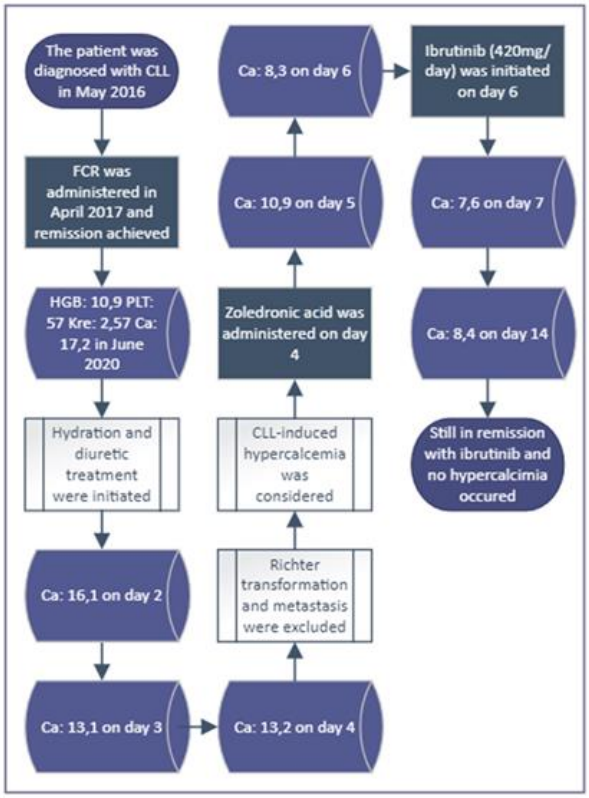

Figure 1 - Flow chart of the patient's clinical course

and recurrence after chemotherapy. During the follow-up, calcium returned to normal limits, anemia and thrombocytopenia improved (Figure 1). He is currently being followed in remission with ibrutinib treatment.

Discussion

Malignant hypercalcemia is a paraneoplastic condition seen in 20-30% of patients followed up with solid or hematological malignancies and is the most common cause of hypercalcemia in hospitalized patients. The malignancies most associated with malignant hypercalcemia are breast cancer, renal cancer, lung cancer and multiple myeloma [2]. Although malignant hypercalcemia is seen in hematological malignancies, especially in multiple myeloma and T-cell lymphomas, this frequency is quite low compared to malignant hypercalcemia due to solid tumors. It is rare in B-cell lymphomas and the majority of these cases are aggressive lymphomas [3]. There

are very rare data in the literature in malignant hypercalcemia due to CLL. In a retrospective study, it was shown that only 7 of 1200 patients with CLL developed malignant hypercalcemia [4].

Major mechanisms in the development of malignant hypercalcemia are parathyroid hormone-associated peptide secretion (PTHrP) from the tumor, osteolytic lesions causing local cytokine secretion, 1,25-dihydroxy vitamin D synthesis from the tumor and ectopic secretion of PTH from tumor cells. Hypercalcemia mediated by PTHrP secretion occurs due to an increase in both bone resorption and renal distal tubular calcium reabsorption [5]. Hypercalcemia via osteolytic metastases occurs due to increased bone reabsorption and increased calcium release from bones [6]. Hypercalcemia mediated 1,25-dihydroxy vitamin D occurs due to an increase in both intestinal calcium absorption and bone resorption [7]. Malignant hypercalcemia can be seen in CLL with one of these mechanisms. Salahudeen et al. treated a case of PTHrP-induced resistant hypercalcemia in a patient with CLL with denosumab [8]. Kampfenkel et al. reported cases with CLL who developed hypercalcemia associated with PTHrP [9]. Fain et al. reported a case of malignant hypercalcemia in a patient with CLL who developed with an increased 1,25-dihydroxy vitamin D level [4]. Malignant hypercalcemia has been reported in the literature in a few cases with prolymphocytic leukemia or immunoblastic lymphoma transformation (Richter Syndrome) while being followed up with a diagnosis of CLL [10].

In our case, low PTH, normal 1,25-dihydroxy vitamin D, absence of Richter transformation findings suggested hypercalcemia associated with PTHrP release in the foreground; however, this diagnosis could not be confirmed because PTHrP levels could not be studied in our center. CLL-induced hypercalcemia in our patient was successfully controlled with ibrutinib. Hypercalcemia did not recur during the period of ibrutinib use, In our case, it was observed that ibrutinib was effective in the control of hypercalcemia due to CLL.

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