Case Report with Review of Literature

Hypercalcemia in Chronic Myeloid Leukemia: An Unusual Presentation

Khushboo Agarwal[1] Naveen Gupta[1] Hemant Malhotra[1]

[1] Department of Oncolgy, Mahatma Gandhi Medical College, Jaipur, Rajasthan, India

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Address for correspondence Khushboo Agarwal, MD, Flat No 203, Real Orchid Apt, B141 Vijaypath, Tilak Nagar, Jaipur 302004, Rajasthan, India (e-mail: Khushboo.agrwl@gmail.com).

Abstract

Hypercalcemia in CML is an unusual paraneoplastic syndrome and is associated with worse prognosis and reduced survival. It usually seen in blast crisis or accelerated phase but can also indicate bony infiltration by cancer cells. Multiple mechanisms can be involved in a patient. We present a case of hypercalcemia in CML in chronic phase without bony infiltration or increased parathormone levels. Increased calcium levels may also be first indication of tyrosine kinase inhibitor resistance. Patient was managed symptomatically with subsequent change of the drug for managing CML. He is currently stable at six months follow-up. Therefore, careful evaluation of the cause of hypercalcemia is necessary for appropriate management.

Keywords

- hypercalcemia
- CML
- tyrosine kinase resistance

Background

Hypercalcemia occurring in Chronic Myeloid Leukemia (CML) is uncommon and usually associated with advanced disease and poor prognosis.[1] We present an unusual case of CML-chronic phase (CP) with no bone involvement associated hypercalcemia developing during treatment.

Case Report

A 35-year-old male came to our hospital with a history of confusion and inability to walk since last two days. He was diagnosed with CML-CP six years ago. He was treated with imatinib 400mg once daily for a year and when in complete hematological remission, he was lost to follow up. He had been on irregular treatment since then with multiple treatment interruptions. On admission, he had stable vitals with heart rate 98 bpm and blood pressure 130/80 mm Hg. Physical examination revealed altered mental status and splenomegaly. There was no neck rigidity or neurological deficit present. Initial blood investigations are presented in ►**Table 1**. He did not have history of any medication intake that could cause increased calcium. HE did not take any native medications, thiazides or vitamin D supplements. PTHrp (parathyroid hormone related protein) and active Vitamin D levels were not measured. Bone marrow biopsy showed fibrosis and supressed erythroid series with increased myeloid cells and a shift to left with 5% blasts. Skeletal X-rays did not reveal any lytic lesion.

The patient was managed for hypercalcemia with aggressive hydration, glucocorticoids and calcitonin. The patient became conscious and alert after normalization of calcium and renal function. He was started on nilotinib 400 mg twice daily.

Discussion

There have been ~30 cases of hypercalcemia associated with CML reported with or without destructive bone lesions.[2] Development of hypercalcemia is usually associated with median survival time of two months.[3] Most of the cases in the literature have been reported in the blast phase of CML.[1,4] Osteolytic lesions in the bone develop either due to destruction by tumor cells or humoral medicated via hormones.[1]

PTHrP-related hypercalcemia due to bone resorption is most effectively treated by tyrosine kinase inhibitors.[5] PTH can be increased due to concomitant primary

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Table 1 Blood investigations

Investigation	Serum Level
Haemoglobin	11.1 g/dl
WBC	58.62 $\times 10^9$/l (blasts 5%, myelocytes 12%, basophils 7%, neutrophils 69%)
Platelet count	469 $\times 10^9$/l
Calcium	19.7 mg/dl
Sodium	127.5 meq/l
Potassium	2.7 meq/l
Uric acid	15.6mg/dl
LDH	1063u/ml
Blood urea	177.5mg/dl
Serum creatinine	2.5mg/dl
ALP	176 IU/ml
PTH	7.4 pg/ml (7.5–53.5 pg/ml)
Vitamin D	34.4 ng/ml (20–50 ng/ml)

hyperparathyroidism or production by malignant cells.[3] Various other humoral factors have been shown to have osteolytic effects such as interleukins, tumor necrosis factor and prostaglandins.[3] Hypercalcemia can also be due to Vitamin D toxicity causing leukemic arthrtitis.[4]

There is evidence that disruption of calcium homeostasis is an unintended side effect of imatinib and other tyrosine kinase inhibitors. They inhibit osteoclasts, and activate osteoblast activity by inhibiting PDGFR (platelet derived growth factor receptor), causing sequestration of calcium and phosphorous to bone. Calcium levels are then normalized by increasing PTH and decreasing phosphate levels further. Alternatively, increased calcium levels may be first signal of resistance to tyrosine kinase inhibitors. Disruption of calcium homeostasis by calcium channel blockers is toxic to TKI-resistant CML cells.[6]

In our case, there were no osteolytic lesions, serum PTH and Vitamin D were normal and the disease was in chronic phase. Treatment is symptomatic consisting of mainly hydration with or without forced diuresis and calcitonin. Steroids have been used in blast phase or with lytic lesions[4] Bisphosphonates have been used sparingly with one case which responded to zolendronic acid.[1] Our patient was not restarted on imatinib given the long history of treatment spaced with interruptions. He remains stable 6 months post presentation managed on nilotinib alone with no further episodes of hypercalcemia.

Conclusion

The most common mechanisms of hypercalcemia in CML are due to lytic lesions in bones and PTHrP or vitamin D toxicity related which are most commonly seen in blast crisis. There is no known relation between the severity of hypercalcemia and osteolytic lesions. In the cases where above mentioned mechanisms are ruled out, it is imperative to rule out drug resistance or bone injury by leukemic cells. Better understanding of the mechanisms involved can lead to targeted therapy in the future for better outcome for these patients.

Note

Informed consent was taken from the patient.

Conflict of Interest

None declared.

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None.

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