Open Access Case Report

Hypercalcemia Induced Respiratory Failure as the Primary Presentation in Chronic Myelomonocytic Leukemia

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Abstract

Chronic Myelomonocytic Leukemia (CMML) is a rare hematopoietic stem cell disorder characterized by persistent monocytosis and bone marrow dysplasia. Although hypercalcemia is prevalent in various malignancies, its role in CMML-associated respiratory failure remains poorly understood. This report presents a case involving a 69 years old woman with no prior health issues, who presented with symptoms of intermittent fever, dry cough, and generalized weakness. Investigations revealed leukocytosis and an elevated monocyte count. Despite initial treatment with intravenous fluids and antibiotics, her condition deteriorated, manifesting as increased drowsiness and respiratory difficulties. Blood gas analysis revealed elevated pCO2 levels, and an MRI of the brain demonstrated focal temporal lobe enhancement. Neurological assessments were inconclusive; however, due to elevated calcium levels, zoledronic acid was administered alongside intravenous fluids. Following the correction of metabolic abnormalities, her condition improved. Bone marrow aspirate and trephine biopsy findings were consistent with Chronic Myelomonocytic Leukemia I (CMML). This case underscores the importance of considering hematological malignancies in elderly patients presenting with unexplained hypercalcemia and respiratory failure.

Keywords: Respiratory Failure, Hypercalcemia, Chronic Myelomonocytic Leukemia, Malignancy

Introduction

Chronic Myelomonocytic Leukemia (CMML) is a rare disorder affecting hematopoietic stem cells, characterized by monocytosis in the blood and dysplastic changes in the bone marrow.[1] This disease shares features with both Myelodysplastic Syndromes (MDS) and Myeloproliferative Neoplasms (MPN). Some of its common symptoms include fatigue, weight loss, bleeding, fevers, and night sweats.[2]

Hypercalcemia of malignancy is most common metabolic complication in patients with advanced cancer. It frequently occurs in those with hematologic cancers such as multiple myeloma, non-Hodgkin lymphoma, and leukemia, as well as in individuals with solid tumors like renal and breast cancers, and squamous cell carcinomas in various organs.[3] Early recognition of elevated serum calcium levels and prompt therapeutic intervention can help to improve symptom burden.[3]

In older adults without other health conditions, identifying hypercalcemia as the cause of respiratory failure can be challenging. This case report highlights the unusual and clinically important presentation of Chronic Myelomonocytic Leukemia. It aims to assist clinicians in considering hypercalcemia caused by hematologic malignancies in patients with respiratory failure and altered mental status, thereby enhancing diagnostic precision and treatment.

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Case Report

A 69 years old lady with no past significant medical history presented to the outpatient department with complaints of intermittent fever for the past 12 days, accompanied by a dry cough and progressively worsening generalized weakness over the last 6 days. She took Levofloxacin prescribed by a General Physician for 4 days, but her symptoms did not resolve. On initial presentation, she was febrile with fever of 38°C. Baseline investigations including fever work-up were done. CBC done showed leukocytosis and monocytosis (table I).

Neutrophilic and lymphocytic count were in normal range. Dengue IgM antibody and Malarial Antigen tests all came out be negative. General physical examination was unremarkable. She was then electively admitted for further management and monitoring. Pan-cultures were sent. Nasal biofire was done to rule out viral infection which also came out be negative. She was then managed initially with empiric antibiotics and IV fluids. Ongoing cultures were negative for any infection. Transthoracic Echocardiography was also normal with

no evidence of vegetation or valvular pathology. On initial work-up her electrolytes including Calcium levels were all in normal range. Her Calcium on arrival was 9 mg/dl.

The patient eventually became afebrile, but her drowsiness worsened, and her Glasgow Coma Scale (GCS) dropped from 15/15 to 10/15. Her arterial blood gas revealed normal pH but elevated pCO2 and bicarbonate levels (Table I). To support her breathing, non-invasive positive pressure ventilation (NIPPV) was applied. An extensive neurological work-up was conducted to identify the cause of her muscular weakness and altered level of consciousness. This included cerebrospinal fluid analysis, nerve conduction studies, and an MRI of the brain. All of the test results were unremarkable and within normal limits. Her repeat calcium levels were found to be significantly elevated (Table I). Thus, IV fluids were started and one dose of Zoledronic acid was also administered. Parathormone levels were found to be in normal range. As her underlying metabolic issues got resolved, her consciousness improved, and the need for NIV support decreased, with noticeable improvements in her ABG results.

Table I: Laboratory Investigations and Results Highlighting Deviations from Normal Values in the Patient's Presentation.

Investigations	Results	Normal Range
Hemoglobin	10.8 g/dl	11.0-14.5 g/dl
White Blood Cell Count	12.8 x 10^9/L	4.6-10.8 x 10^9/L
Neutrophils	40.9 %	34.9-74.2%
Lymphocyte	25.4%	17.5-45.0%
Monocyte	31.6%	3.9-10 %
Platelets	341 x 10^9/L	154-433 x 10^9/L
Serum BUN	56 mg/dl	6-20 mg/dl
Serum Creatinine	1.4 mg/dl	0.6-1.2 mg/dl
Calcium level (initial)	9.0 mg/dl	8.5-10.5 mg/dl
Calcium level (repeated)	15.2 mg/dl	8.5-10.5 mg/dl
pH (ABG)	7.44	7.35-7.45
pCO2 (ABG)	50.3 mmHg	35-45 mmHg
Bicarbonate (ABG)	33.6 mmol/L	22-28 mmol/L
Albumin (SPEP)	3.15 g/dl	3.2-5.5 g/dl
Total Protein (SPEP)	5.75 g/dl	6.4-8.3 g/dl
Free Kappa Chains	21.10 mg/L	3.3-194 mg/dl
Free Lambda Chains	31.7 mg/L	5.71-26.3 mg/dl
Beta-2-microglobulin	7954 ng/ml	<3000 ng/ml

The persistently elevated monocyte count, along with hypercalcemia, raised concerns about the possibility of underlying hematological malignancy. Peripheral blood film showed occasional myelocytes, 2% blast cells along with dysplastic monocytes. Bone marrow aspirate showed aspicular and moderately cellular specimen exhibiting erythroid and myeloid precursors, normoblastic erythropoiesis, intact myelopoiesis with all stages of maturation and differentiation, dysplastic monocytes and blast cells of less than 5%. Bone marrow trephine revealed hypercellularity for age with overall cellularity of around 55-60%. Cellular areas showed granulocytic hyperplasia on a background of patchy fibrosis (figure 1). Erythroid precursors were also seen along with adequate megakaryocytes (figure 1). The overall results of the bone marrow aspirate and trephine biopsy were consistent with Chronic Myelomonocytic Leukemia I (CMML). She was subsequently discharged on request, with recommendations for further evaluation and management of CMML on an outpatient basis.

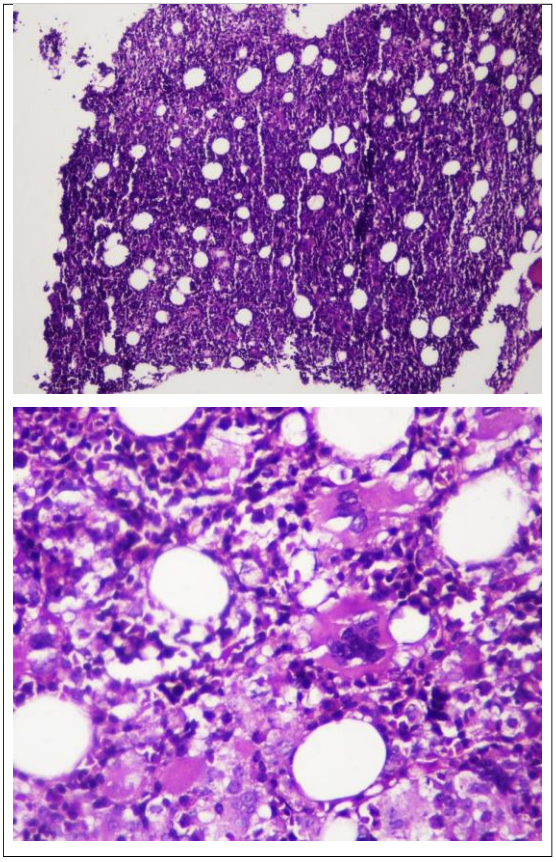

Figure 1. Histological section of bone marrow trephine showing hypercellularity (55-60%) for age, with granulocytic hyperplasia in cellular areas. The background reveals patchy fibrosis, while erythroid precursors and adequate megakaryocytes are also present.

She was again admitted after 4 weeks under Hematology services with complains of fever and drowsiness. Her Calcium levels were again found to be raised again. Serum protein electrophoresis (SPEP) revealed slightly low total protein and albumin with normal alpha, beta and gamma chains. Further investigations, including immunofixation studies, revealed mildly elevated free kappa and lambda chains (table I). The serum FLC kappa to lambda ratio was within the normal range. Beta-2 microglobulin levels were found to be raised. (table I)

This time again she was managed conservatively with IV fluids, antibiotics and BiPAP support. Another dose of Zoledronic acid was administered again during this admission for hypercalcemia.

Patient's condition transiently improved but fever persisted with increment in oxygen demand for which BiPAP was applied. Given her clinical condition, she was considered unfit for the administration of any type of chemotherapy or immunotherapy. Conservative management was continued. Family was counselled regarding poor prognosis of patient's condition and the code was changed to comfort care. Her condition worsened and she eventually passed away.

Discussion

Around 90% of individuals experiencing hypercalcemia have either primary hyperparathyroidism or malignancy. Those with hypercalcemia of malignancy are generally more symptomatic and have higher calcium levels than those with primary hyperparathyroidism.[4] Acute hypercalcemia can present with neuropsychiatric symptoms such as altered mental status, hyporeflexia, fatiguability, along with musculoskeletal manifestations like muscle weakness. In extreme cases, it may lead to confusion, stupor, or coma.[4] In our case, the patient experienced a gradual onset of confusion, drowsiness, and widespread muscle weakness, which ultimately progressed to respiratory failure.

In a study conducted by Sulaiman S et al, malignancy was found to be most common cause of hypercalcemia in hospitalized patients.[5] Serum calcium is an independent predictor of overall mortality, indicating a higher mortality rate among individuals with moderate to severe hypercalcemia compared to those with mild hypercalcemia.[5]

Diallo AO et al reported a case of malignant hypercalcemia in a patient who was previously diagnosed with chronic myelomonocytic leukemia. That patient also had sudden onset of drowsiness and psychomotor retardation during a hospital admission with broncho pneumopathy and work-up revealed hypercalcemia. However, upon further investigations diffuse large B-cell lymphoma was diagnosed co-existing with CMML. Despite aggressive measures, patient's condition did not improve and he expired.[6] Likewise in our case also, patient experienced hypercalcemia as a result of an underlying chronic myelomonocytic leukemia and was not being able to revive back despite aggressive management and eventually palliative intent was opted by family.

In a case reported by Siddiqui WT et al, a patient presented with shortness of breath. Upon baseline work-up he was found to have anemia, leukocytosis along with peripheral monocytosis. Further investigations revealed, chronic myelomonocytic leukemia which was co-existing with multiple myeloma. He was managed conservatively due to multiple co-morbities and advanced age.[7] This resembles our case, as our patient also had shortness of breath and was eventually diagnosed with CMML which was treated conservatively.

Furthermore, sustained monocytosis should never be ignored. In majority of cases, it is because of reactive or secondary reasons. An underlying malignant process should be suspected if the monocyte count is consistently raised, after ruling out other secondary causes.[8] In order to rule out underlying hematological malignancy other investigations like bone marrow examination and cytogenetic work-up may be required. [8]

Conclusion

In conclusion, it is extremely important to take into account haematological malignancies and illnesses like Chronic Myelomonocytic Leukaemia while dealing with an older patient who exhibits unexplained hypercalcemia, increased somnolence, and respiratory failure. Early diagnosis can improve overall patient's quality of life and facilitate timely management of the underlying malignancy. Moreover, hypercalcemia can serve as a predictive indicator for mortality in future studies as well.

Disclosure: This study was reviewed and approved for exemption from ethical approval by the Ethics Review Committee of Aga Khan University, Pakistan.

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