Life-threatening hypercalcemia and primary plasma cell leukemia: a case report of a rare presentation

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ABSTRACT

Background: Hypercalcemia can cause a multitude of non-specific symptoms, although it can manifest as a life-threatening metabolic emergency. Several underlying causes should be considered in the emergency department (ED). Life-threatening hypercalcemia as the initial manifestation of primary plasma cell leukemia (pPCL) is quite unusual.

Case Presentation: We present a case of a 63-year-old man who presented to the ED with symptomatic hypercalcemia and acute renal failure that was linked to a diagnosis of pPCL. Despite adequate treatment, his course was associated with significant morbidity and was severe enough to threaten his life.

Conclusion: Severe hypercalcemia with particular attention to the peripheral blood smear should alert physicians to this highly deadly entity.

Keywords: pPCL, hypercalcemia, peripheral blood smear, poor prognosis, emergency, case report.

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Background

Primary plasma cell leukemia (pPCL) is a rare and aggressive form of plasma cell malignancies. It occurs *de novo* in the absence of a prior history of multiple myeloma (MM). Clinically, patients with pPCL have a higher incidence of hepatosplenomegaly and lymphadenopathy, and less lytic bone lesions [1]. Hypercalcemia caused by pPCL in its initial stage is quite rare. Herein, we describe the case of a 63-year-old man who presented with life-threatening hypercalcemia revealing a diagnosis of pPCL.

Case Presentation

A 63-year-old man, without previous disease, presented to emergency department (ED) with 3 days complaints of marked weakness, vomiting, and abdominal pain associated with constipation that had evolved over the previous 3 weeks. His initial vital signs revealed a blood pressure of 120/59 mm Hg, a heart rate of 110 beats/minute, a respiratory rate of 18, a temperature of 37.2°C, and oxygen saturation of 99% on room air. His bedside blood glucose measurement was 90 mg/dl. electrocardiogram (ECG) showed sinus tachycardia and non-specific ST-T wave changes with short QT interval.

The examination was significant for the confusion regarding time and place, pallor, and dehydration. His abdomen was soft with no peritoneal signs or organomegaly. The other physical examination features were normal. Blood analysis revealed hyperleucocytosis (white blood cell count, 35×10^9/l); anemia (hemoglobin, 65 g/l); thrombopenia (platelets, 69×10^9/l); profound hypercalcemia (serum total calcium 4.5 mmol/l); evidence of acute renal failure (creatinine 627 µmol/l); and hyperuricemia (uric acid 13.4 mg/dl). His intact parathyroid hormone (PTH) level was decreased at 5 pg/ml and 1,25-$(OH)_2$ vitamin D_3 level was below the normal range. PTH-related peptide (PTH-rP) measurement was not done. He had normal kalemia, pancreatic and liver function tests, coagulation profile, and thyroid function tests.

A review of his peripheral blood smear showed 47% circulating plasma cells with marked rouleaux formation (Figure 1). Bone marrow aspiration showed a 79% infiltration of plasma cells (Figure 2). Serum protein electrophoresis showed a strong monoclonal spike at gamma globulin region, identified as IgA kappa chain on immunofixation.

Ultrasound showed that both kidneys were in normal size. X-rays of skull and chest were unremarkable with no evidence of lytic lesions. Based on all these findings, the final diagnosis of pPCL was made. Treatment with aggressive hydration with 0.9% saline and calcitonin 400 units subcutaneous was administered. In addition, a single session of emergent hemodialysis with low calcium bath was initiated to treat the patient's severe hypercalcemia with associated acute renal injury. Unfortunately, his course was rapidly complicated by a worsening

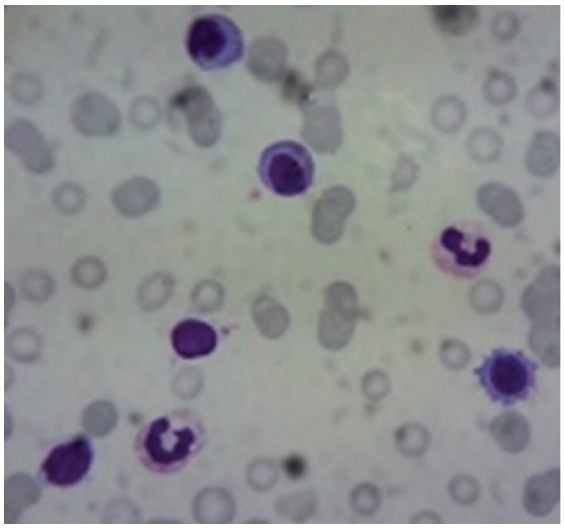

Figure 1. *May–Grünwald Giemsa-stained blood smear (1,000× magnification) showing red blood cells in rolls, and polymorphic plasma cells.*

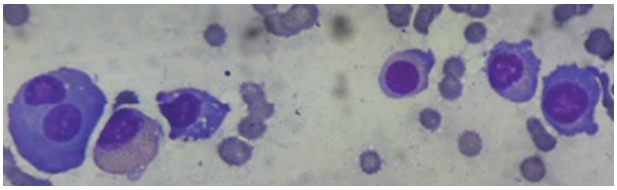

Figure 2. *May–Grünwald Giemsa-stained bone marrow smear (1,000× magnification) showing medullary invasion by dysmorphic plasma cells.*

cardiac dysrhythmia, and he passed away after 1 week of hospitalization.

Discussion

Plasma cell leukemia (PCL) is an uncommon disorder with an incidence less than one case per million population [2]. It is characterized by plasma cells >2 × 10^9/l and/or >20% of the peripheral blood white cells. It can occur either *de novo* (pPCL) or as a leukemic transformation of underlying MM. The disease has acute onset, rapid progression, and poor prognosis and response to therapy.

Patients of PCL may present with symptoms due to end organ damage (anemia, renal failure, hypercalcemia, and lytic bone lesions) or to leukemia (leukocytosis, thrombocytopenia, and organomegaly).

There are several causes of hypercalcemia that should be considered in a patient who is presented to the ED. Hypercalcemia caused by pPCL in its initial stage is quite rare. To the authors' knowledge, this is the first reported case in the English literature of pPCL presenting with severe refractory hypercalcemia.

Trying to extrapolate information from other malignancies, several etiologic factors could be involved in its development. Hypercalcemia develops as a result of paraneoplastic production of humoral factors, mainly interleukin (IL)-1, IL-2, IL-6, tumor necrosis factor alpha (TNF-α), TNF-β, tumor growth factor beta (TGF-β), macrophage inflammatory protein (MIP 1-α), $1,25(OH)_2$ vitamin D, parathormone-associated proteins (PTH-rP), prostaglandin E2, and rarely excessive secretion of parathormone. Another mechanism is local osteolytic hypercalcemia secondary to direct bone invasion.

PTH-rp is a protein that exerts certain PTH like effects [3] and acts to stimulate bone mineral dissolution, increase renal calcium reabsorption, and release calcium into serum [4]. Unfortunately, PTH-rp was not measured, so its role could not be assessed.

Elevation in the level of PTH is rare but reported in up to 18% of patients with calcium disturbances associated with hematological malignancies [5]. Furthermore, prostaglandins E are powerful stimulators of bone resorption [6], although their precise role in bone destruction associated with malignancy remains to be determined. IL-1, IL-6, TNF-α, TNF-β, TGF-β, and MIP 1-α may also be produced in malignant hematological cells [4–5] and have been identified to promote bone resorption *in vitro* by stimulating osteoclast formation and activity. However, it has not been possible to establish convincingly so far that any of these cytokines are playing a predominant role as solitary triggers in the pathogenesis of hypercalcemia *in vivo* [7–8].

Hypercalcemia may result from localized bone destruction due to a direct effect of tumor cells. However, the absence of radiographic abnormalities does not exclude their action. Renal failure could be a cause and consequence of hypercalcemia. A possible mechanism of induced renal failure could be partly the deposition of calcium in the kidney and the direct effects of hypercalcemia on renal function.

It is important to consider that these above-mentioned mechanisms are not exclusive of each other; in fact, these events might act concomitantly in PCL patients presenting with hypercalcemia.

Hypercalcemia is rare but has severe complications that should be treated immediately. The treatment options include IV hydration, calcitonin, bisphosphonates, denosumab, and corticosteroids. Loop diuretics are sometimes used to promote calciuresis, though evidence to support this is lacking, and it may worsen renal failure. Patients with severe refractory hypercalcemia or that cannot be safely hydrated because of underlying cardiorenal diseases that should be urgently considered for hemodialysis. The prognosis for pPCL is dismal with a median survival of about 2–8 months even with aggressive treatment.

Conclusion

Incidence of life-threatening hypercalcemia in pPCL is very unusual, especially as the initial manifestation of the disease. Earlier identification of the etiology is unlikely to have changed the outcome in this case, but the presence

of severe hypercalcemia with particular attention to the peripheral smear should alert physicians to this highly deadly entity.

Acknowledgement
None.

List of abbreviations
ED	Emergency department
MIP	Macrophage inflammatory protein
PCL	Plasma cell leukemia
pPCL	Primary plasma cell leukemia
PTH	Parathyroid hormone
PTH-rP	PTH-related peptide
TGF	Transforming growth factor
TNF	Tumor necrosis factor

Consent for publication
Written informed consent was obtained from the patient's next of kin for publication of this case report and any accompanying images.

Ethical approval
Not applicable.

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Summary of the case
Patient (gender, age)	1	Male, 63 years old
Final diagnosis	2	pPCL
Symptoms	3	Weakness, vomiting, and abdominal pain
Medications	4	Hemodialysis with low calcium bath
Clinical procedure	5	Peripheral blood smear and bone marrow aspiration
Specialty	6	Hematology