A case of hypercalcemia with double pathology
Ahmed Abdalla, Ghassan Bachuwa and Samer Al Hadidi

Hurley Medical Center, Michigan State University, Flint, MI, USA

ABSTRACT
Hypercalcemia has many causes including primary hyperparathyroidism, malignancy, and other rare etiologies. In most of the cases, hypercalcemia is secondary to one etiology. In this case, we are reporting hypercalcemia with two causes. The initial workup showed primary hyperparathyroidism due to parathyroid adenoma. But because all features were not fully explained by primary hyperparathyroidism, further work-up revealed multiple myeloma. This case represents coexistence of two different diseases, which was rarely reported in the literature previously. Usually, the co-diagnosis was made subsequently after failure to correct hypercalcemia. In our case, both diagnoses were established at the same time of the patient’s presentation as of high suspicion. Establishing the diagnosis early will aid in the initiation of treatment in a timely fashion.

1. Introduction
Hypercalcemia is a common problem in medical practice. Several causes of hypercalcemia have been described. Primary hyperparathyroidism and malignancy have been responsible for more than 80% percent of cases [1].

Coexistence of multiple myeloma and primary hyperparathyroidism as a cause of hypercalcemia is extremely rare with fewer than 30 cases reported in the literature [1]. Most of the cases were diagnosed after failure to correct calcium level targeting the initial diagnosis. A high index of suspicion can help uncover serious causes early in the management, which will help in initiating treatment.

In this case, we are reporting a female patient who presented to our hospital with hypercalcemia, her initial workup showed primary hyperparathyroidism due to parathyroid adenoma. Her clinical presentation could not be explained by her parathyroid disease alone. Subsequently, further work-up showed multiple myeloma.

2. Case presentation
A 59-year-old African American female presented to our hospital because of nausea and vomiting of one week prior to presentation. She did not have abdominal pain, diarrhea, fever or chills. She reported unintentional weight loss of 50 pounds in the last seven months.

The patient denied constipation, polyuria, polydipsia, bone pain, or change in mental status. No significant previous medical history was reported. She did not take any medication at home.

The patient was not a smoker, denied the use of alcohol or illicit drugs. Her family history was significant for prostate cancer in her father but was otherwise negative for endocrine pathologies and hematological malignancies.

On physical examination, her vitals were within normal limits, she looked pale and dehydrated. No skin abnormality or lymphadenopathy noted. Lung and heart exam were unremarkable. Abdomen was soft with no palpable masses or organomegaly. No bone tenderness.

3. Investigations
Her initial laboratory workup showed elevated calcium level at 17.7 mg/dl (Reference range: 8.7–10.4 mg/dl), low phosphorus of 1.7 mg/dl (Reference range: 2.7–4.5 mg/dl) and parathyroid hormone level of 558 pg/ml (Reference range: 14–72 pg/ml). Other abnormalities showed anemia and thrombocytopenia. The rest of the results are summarized in Table 1.

Ultrasonography of the neck showed a complex cystic mass measuring 2.5 by 1.7 cm near the upper pole of the left lobe of the thyroid gland (Figure 1). The parathyroid scan showed hyperactive left upper parathyroid area (Figure 2).

Despite the rarity of coexistence of primary hyperparathyroidism and multiple myeloma, bone marrow biopsy was obtained from our patient due to high suspicious features, i.e. weight loss, anemia, and thrombocytopenia even after confirming primary hyperparathyroidism. It revealed hypercellular marrow with decreased trilineage hematopoiesis and extensive...
involvement by plasma cells. Approximately there were 50% plasma cells in the aspirate smears and 80% in the core biopsy. (Figures 3–4)

Computed tomography of the abdomen showed mild splenomegaly and no lymphadenopathy. The bone survey didn’t show evidence of focal lytic lesions.

4. Treatment

She was treated with intravenous fluids, calcitonin and zoledronic acid. Her calcium level decreased to 9.8 mg/dl after three days of treatment. Surgical Parathyroidectomy was delayed as of concern of surgical risk per patient’s family request. She was started on bortezomib and high-dose dexamethasone for her multiple myeloma.

5. Outcome and follow up

The patient followed up as an outpatient. She was receiving chemotherapy with bortezomib and high dose dexamethasone. After two months, she was admitted again to the hospital due to hypercalcemia with calcium of 13.6 mg/dl and parathyroid hormone level 471 pg/ml.

She had marked progression of her multiple myeloma with the appearance of plasmacytoma in the anterior chest and in the right mandible. She also had malignant pleural effusion, which was positive for neoplastic plasma cells. Supportive management initiated. Patient was provided with hospice care, she died after two days secondary to her multiple myeloma.

Table 1. Laboratory result at initial presentation investigation.

|                     | Result          | Reference range |
|---------------------|-----------------|-----------------|
| Sodium              | 146 MEQ/L       | 136–145         |
| Potassium           | 3.4 MEQ/L       | 3.4–5.4         |
| Chloride            | 104 MEQ/L       | 98–107          |
| Bicarbonate         | 28 MEQ/L        | 23–29           |
| Blood urea nitrogen | 30 mg/dl        | 6–20            |
| Creatinine          | 1.1 mg/dl       | 0.5–1.1         |
| Calcium             | 17.7 mg/dl      | 8.7–10.4        |
| Ionized calcium     | 2.35 mmole/l    | 1.1–1.3         |
| Phosphorous         | 1.7 mg/dl       | 2.7–4.5         |
| Magnesium           | 1.7 mg/dl       | 1.5–2.6         |
| Hemoglobin          | 7.9 g/dl        | 12–16           |
| Mean corpuscular volume | 80.2 FL | 80–100          |
| Red cell distribution width | 25.3% | 0–15%          |
| Platelets           | 63 K/UL         | 130–430         |
| White blood cells   | 8.3 K/UL        | 4.0–10.8        |
| Neutrophils         | 50%             | 36–75%          |
| Lymphocyte          | 39%             | 20–50%          |
| Reticulocyte        | 2.41%           | 0.5–2.0%        |
| Lactate dehydrogenase | 375 mg/dl     | 1–14            |
| Peripheral smear    |                 |                 |
| PTH                 | 558 pg/ml       | 14–72           |
|PTH-related peptide | 8 pg/ml         | 14–27           |
|Vitamin D 1,25       | 10 pg/ml        | 20–79           |
| 24-hour urine collection |             |                 |
| Bence Jones protein |                 |                 |
| Flow cytometry (bone marrow) |         |                 |
| Hemoglobin electrophoresis |   |                 |
| Immunoglobulin A    | 9 mg/dl         | 60–400          |
| Immunoglobulin G    | 441 mg/dl       | 700–1500        |
| Immunoglobulin M    | <4 mg/dl        | 60–300          |

Figure 1. Ultrasonography of the neck showed a mass near the upper pole of left lobe of the thyroid.
6. Discussion

Primary hyperparathyroidism can cause hypercalcemia through increasing calcium reabsorption by distal tubules in the kidneys, increasing bone resorption and increasing activation of vitamin D, which will increase gastrointestinal absorption of calcium [1].

On the other hand, hypercalcemia is the most common metabolic complication in multiple myeloma and occurs in 20–30% of patients [2,3]. The mechanism of hypercalcemia in multiple myeloma is secondary to cytokines secreted by myeloma cells that induce osteoclastic bone resorption. Tumor necrosis factor-B and Interlukin-6 are the main cytokines involved. Another possible theory is that multiple myeloma can cause hypercalcemia through parathyroid hormone-related peptide [3].

Hypercalcemia presents with similar symptoms and signs, but a careful history, physical examination, and interpretation of investigations can give a clue to the underlying cause [4]. The diagnostic approach of hypercalcemia usually starts with checking parathyroid hormone (PTH). Elevation of PTH in the absence of lithium use with low urinary calcium excretion supports the diagnosis of primary hyperparathyroidism and no further workup for other causes is indicated. [5] Identifying the cause will help in selection of appropriate treatment plan.

Unfortunately, the family decided not to do a definitive diagnosis of the parathyroid gland pathology because of perceived surgical risk. The differential diagnosis includes parathyroid adenoma, functional parathyroid cyst as it appeared in the ultrasound and parathyroid carcinoma as suggested by the very high parathyroid hormone blood level [6].

A 2013 review of the literature summarized 28 published cases with co-diagnosis of primary hyperparathyroidism and multiple myeloma. The co-diagnosis occurred more in females in 22 out of 28 patients. All patients had calcium above 11 mg/dl [2]. Parathyroidectomy, a combination of radiotherapy and chemotherapy had been used with variable success. Eight of the 28 patients died within one year of the co-diagnosis and an additional two died within five years [2].

Furthermore, some studies have shown increase parathyroid hormone blood levels with malignancies [7]. On the other hand, a prospective study done in 2002 showed the prevalence of monoclonal gammapathies is higher in patients with primary hyperparathyroidism when compared to the general population. That finding supports the hypothesis of an association between monoclonal gammapathy of undetermined significance or multiple myeloma with primary hyperparathyroidism [1,8].

Medical management has been successful in previous cases with hypercalcemia due to primary hyperparathyroidism accompanying multiple myeloma [9].

In conclusion, we are reporting a case of hypercalcemia with possible double pathology. Work-up diagnosed both primary hyperparathyroidism and multiple myeloma as a cause of her hypercalcemia. This case highlights the fact that hyperparathyroidism and multiple myeloma can co-occur and are not mutually exclusive. To solve problems and avoid errors, attempts should be made to
determine the medical reasoning for all the data obtained from the history, exam, and laboratory investigations. Ignoring small details or missing small points can lead to missing serious conditions [10].

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Conflict of interest statement

The authors declare that there is no conflict of interest regarding the publication of this paper.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Samer Al Hadidi http://orcid.org/0000-0003-4297-8042

References

[1] Hussain N, Khan M, Natarajan A, et al. A case of multiple myeloma coexisting with primary hyperparathyroidism and review of the literature. Case Rep Oncol Med. 2013;2013:420565.
[2] Hoorn EJ, Zietse R. Disorders of calcium and magnesium balance: a physiology-based approach. Pediatr Nephrol. 2013;28(8):1195–1206.
[3] Oyajobi BO. Multiple myeloma/hypercalcemia. Arthritis Res Ther. 2007;9(Suppl 1):S4.
[4] Bazari H, Palmer WE, Baron JM, et al. Case 24-2016: A 66-year-old man with Malaise, weakness, and hypercalcemia. New England J Med. 2016;375(6):567–574.
[5] Khan AA, Hanley DA, Rizzoli R, et al. Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. Osteoporos Int. 2016;28(1):1–19.
[6] Al-Kurd A, Mekel M, Mazeh H. Parathyroid carcinoma. Surg Oncol. 2014;23(2):107–114.
[7] Patel N, Talwar A, Donahue L, et al. Hyperparathyroidism accompanying multiple myeloma. Clin Nucl Med. 2005;30(8):540–542.
[8] Arnulf B, Bengoufa D, Sarfati E, et al. Prevalence of monoclonal gammopathy in patients with primary hyperparathyroidism: a prospective study. Arch Intern Med. 2002;162(4):464–467.
[9] Fanari Z, Kadikoy H, Haque W, et al. Medical management of primary hyperparathyroidism with concomitant multiple myeloma. Intern Med. 2010;49(6):581–584.
[10] Sopeña B, Rodríguez GJ, De La Fuente J, et al. Two causes of hypercalcemia: learning by the holmesian method. Mayo Clinic Proc. 2004;79(5):article 708.