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Case Report

Hypercalcemia of Malignancy: Simultaneous Elevation in Parathyroid Hormone-Related Peptide and 1,25 Dihydroxyvitamin D in Sarcoma

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ABSTRACT

Objective: Hypercalcemia is a common finding in patients who have an underlying malignancy. Only a few cases of hypercalcemia of malignancy have been linked to more than one mechanism of hypercalcemia. Here, we present a patient with liposarcoma and hypercalcemia of malignancy in the setting of simultaneous elevations in parathyroid hormone-related peptide (PTHrP) and 1,25 dihydroxyvitamin D [1,25(OH)₂D] levels. Sarcoma-associated hypercalcemia is a rare disorder.

Methods: The patient was an 89-year-old woman with sarcoma-associated hypercalcemia. Multiple mechanisms were uncovered, and treatments were adjusted for them. Literature search for hypercalcemia of malignancy with multiple mechanisms was conducted.

Results: This is the first report describing dual mechanisms of sarcoma-associated hypercalcemia and only the fifth report on PTHrP and 1,25(OH)₂D simultaneously causing hypercalcemia of malignancy.

Conclusion: Based on this finding, we recommend measuring the 1,25(OH)₂D levels in conjunction with the PTHrP level in patients with malignancy as this would allow for a more proactive approach to the diagnosis and treatment of hypercalcemia of malignancy.

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Introduction

Hypercalcemia is a common finding in patients who have cancer. Up to 20% to 30% of patients with cancer experience hypercalcemia at some point in the course of their disease.¹ Multiple mechanisms can lead to hypercalcemia of malignancy, but the most common mechanism is humoral hypercalcemia of malignancy resulting from overproduction of parathyroid hormone-related peptide (PTHrP).¹ Other mechanisms of hypercalcemia associated with malignancy include local osteolytic hypercalcemia, overproduction of 1,25 dihydroxyvitamin D [1,25(OH)₂D] by the enzyme

1- α hydroxylase, and, rarely, ectopic hyperparathyroidism. Different malignancies are often associated with a specific mechanism of hypercalcemia. For example, prostate cancer is associated with humoral hypercalcemia of malignancy due to PTHrP production, whereas non-Hodgkin lymphoma is associated with elevated levels of 1,25(OH)₂D.² Only a few cases of hypercalcemia of malignancy have been linked with more than one mechanism of hypercalcemia.³ Here, we present a patient with liposarcoma and hypercalcemia of malignancy in the setting of simultaneous elevations in PTHrP and 1,25(OH)₂D levels.

Case Report

An 89-year-old woman with a past medical history of atrial flutter, sick sinus syndrome status post pacemaker placement, hypothyroidism on levothyroxine therapy, and suspected liposarcoma was admitted to the hospital after a fall that resulted in multiple rib fractures and subsequent right hemopneumothorax requiring chest tube placement. The patient's suspected liposarcoma was

Abbreviations: PTHrP, parathyroid hormone-related peptide; 1,25(OH)₂D, 1,25 Dihydroxyvitamin D.

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Table 1
Select Laboratory Studies

Test	Hospital admission 1	Hospital admission 2	Reference range
Calcium (mg/dL)	12.1	12.2	8.6–10.2
Albumin (g/dL)	3.1	3.0	3.2–4.6
Corrected calcium (mg/dL)	12.8	13.0	8.6–10.2
Phosphorus (mg/dL)	3.9	2.9	2.5–4.5
eGFR (mL/min/1.73 m ²)	42	16	>60
PTH (pg/mL)	12	9	8–54
25 OH vitamin D (ng/mL)	71	100	20–80
25 OH vitamin D2 (ng/mL)	<4	<4	20–80
25 OH vitamin D3 (ng/mL)	71	100	20–80
1,25(OH) ₂ D (pg/mL)	103.0	570.0	19.9–79.3
PTHrP (pmol/L)	5.6	8.0	0.0–3.4

Abbreviations: eGFR = estimated glomerular filtration rate; PTH = parathyroid hormone; PTHrP = parathyroid hormone-related peptide.

diagnosed based on an abdominal computed tomography performed earlier in the year for the evaluation of increased abdominal pressure and pain. Imaging characteristics were documented as suspicious for liposarcoma; however, at the time of the current hospitalization, she did not undergo a biopsy of the mass. Her hospital course was complicated by an acute kidney injury, hypercalcemia (maximum corrected calcium level, 14.5 mg/dL), and hyponatremia. The endocrinology team was consulted to evaluate the etiology of the hypercalcemia and assist with its management.

On initial interview with the endocrinology team, the patient reported that she had mental fogging and fatigue. She denied having constipation, mood changes, nausea, palpitations, myalgia, history of immobility, or kidney stones. Medications prior to the admission included cholecalciferol, which was discontinued on admission, as well as guaifenesin, metoprolol, nystatin, levothyroxine, amlodipine, fluticasone, and vitamin B12. Vital signs included a blood pressure of 131/63 mm Hg, pulse of 77 beats per minute, temperature of 36.7°C, and respiratory rate of 18 breaths per minute. Physical examination was notable for a dry oropharynx and lower extremity edema. Abdominal and neurologic examination were benign. Initial laboratory testing revealed hypercalcemia with a corrected calcium level of 14.5 mg/dL (8.6–10.2 mg/dL) and an ionized calcium level of 2.00 mmol/L (1.15–1.29 mmol/L). Prior calcium values from an outside institution showed a normal corrected calcium level of 9.6 mg/dL 8 months prior to this admission. Table 1 includes the full set of admission laboratory values from the patient's initial hospitalization (hospital admission 1). She was initially treated by the primary team with intravenous normal saline at 125 mL/hour for a total of 3 L; however, after 48 hours, her corrected calcium level remained elevated at 14.6 mg/dL. At this time, she developed acute kidney injury, with creatinine level 1.46 mg/dL (0.52–1.04 mg/dL) higher than the baseline value of 0.9 mg/dL. Initial work up of her hypercalcemia showed a parathyroid hormone level of 12 pg/mL (8–54 pg/mL), 25 hydroxyvitamin D level of 71 ng/mL (20–80 ng/mL), bone-specific alkaline phosphatase level of 13.6 µg/L (7–22.4 µg/L), N-telopeptide level of 638 pg/mL (104–1008 pg/mL), and thyroid stimulating hormone level of 3.87 mIU/L (0.47–4.68 mIU/L). Serum and urine protein electrophoresis results were negative for monoclonal predominance. The PTHrP and 1,25(OH)₂D samples were collected, but the results were not available until after discharge.

Based on the available test results, hypercalcemia of malignancy was the leading diagnosis for the etiology of hypercalcemia. Due to the acute kidney injury, the patient was treated with one dose of 60 mg of pamidronate intravenously instead of zoledronic acid. Within 6 days of receiving pamidronate, her corrected calcium level improved but was still elevated at 10.8 mg/dL, and the ionized calcium level improved to 1.36 mmol/L. At time of the first

discharge, she was taking guaifenesin, metoprolol, nystatin, levothyroxine, amlodipine, fluticasone, and vitamin B12.

After the hospital discharge, the patient was scheduled for close follow-up, including weekly laboratory calcium studies and appointments with the primary care and endocrinology teams to monitor for the recurrence of hypercalcemia. She missed these appointments and was readmitted to the hospital 4 weeks later due to confusion and worsening hypercalcemia. Laboratory evaluation on arrival to the hospital showed a corrected calcium level of 14.3 mg/dL and creatinine level of 3.33 mg/dL. The full set of admission laboratory values is presented in Table 1 (hospital admission 2). The previously sampled levels of PTHrP and 1,25(OH)₂D were both elevated (PTHrP 5.6 pmol/L [0.0–3.4 pmol/L], 1,25(OH)₂D 103 pg/mL [19.9–79.3 pg/mL]). PTHrP and 1,25(OH)₂D levels were repeated during the patient's second hospital admission and were even higher (PTHrP 8.0 pmol/L [0.0–3.4 pmol/L], 1,25(OH)₂D 570 pg/mL [19.9–79.3 pg/mL]). In addition, the 25 hydroxyvitamin D level also increased from 71 to 100 ng/mL in the setting of continued vitamin-D supplementation.

During this admission, the calcium levels were initially controlled with 200 units of calcitonin subcutaneously every 12 hours for a total of 4 doses and intravenous plasmalyte administered at 100 mL/hour. These interventions improved the corrected calcium level from 14.3 to 12.76 mg/dL, but did not normalize the calcium levels. Therefore, the patient was given 1 dose of 30 mg of pamidronate intravenously. Three days after receiving the dose of pamidronate, the calcium levels failed to significantly improve, with the corrected calcium level at 12.16 mg/dL. While bisphosphonate treatment targeted the PTHrP component of her hypercalcemia, the continued persistent elevation in the calcium level was thought to be also due to the elevated 1,25(OH)₂D level. Prednisone at 40 mg daily was started to inhibit 1-α hydroxylase and the conversion of 25 hydroxyvitamin D to 1,25 dihydroxyvitamin D. With the addition of prednisone, the corrected calcium levels declined to a nadir of 8.4 mg/dL 11 days after the initiation of prednisone and 14 days after the dose of pamidronate (Fig. 1).

During the second hospitalization, the presumed liposarcoma was biopsied. Immunohistochemistry of the tissue was positive for desmin and vimentin as well as focally positive for CD34. These results were consistent with those of dedifferentiated liposarcoma, with a follow-up MDM2 fluorescence in situ hybridization analysis showing positive result (Fig. 2).

Due to its large size, the sarcoma was deemed to be unresectable. Chemotherapy was offered; however, the patient and her family declined because of her overall clinical status. She was eventually discharged to home hospice.

Discussion

While malignancy-associated hypercalcemia is not rare and affects up to 20% to 30% of patients with cancer,¹ the identification of 2 different mechanisms simultaneously playing a role in hypercalcemia of malignancy is uncommon. To date, only 4 patients with hypercalcemia of malignancy resulting from simultaneous elevations in PTHrP and 1,25(OH)₂D levels have been described (Table 2).^{3–6} Similarly rare, only 6 cases of sarcoma-associated hypercalcemia of malignancy have been previously reported (Table 3).^{7–12}

Other nonparathyroid hormone mechanisms of hypercalcemia, including vitamin-D intoxication, were considered in the differential diagnosis of the patient's hypercalcemia. The suspicion for vitamin D intoxication typically occurs with intakes >10,000 IU daily; however, our patient was taking only 1000 IU of cholecalciferol daily.¹³ The mechanism of hypercalcemia in vitamin-D intoxication involves supraphysiological levels of 25

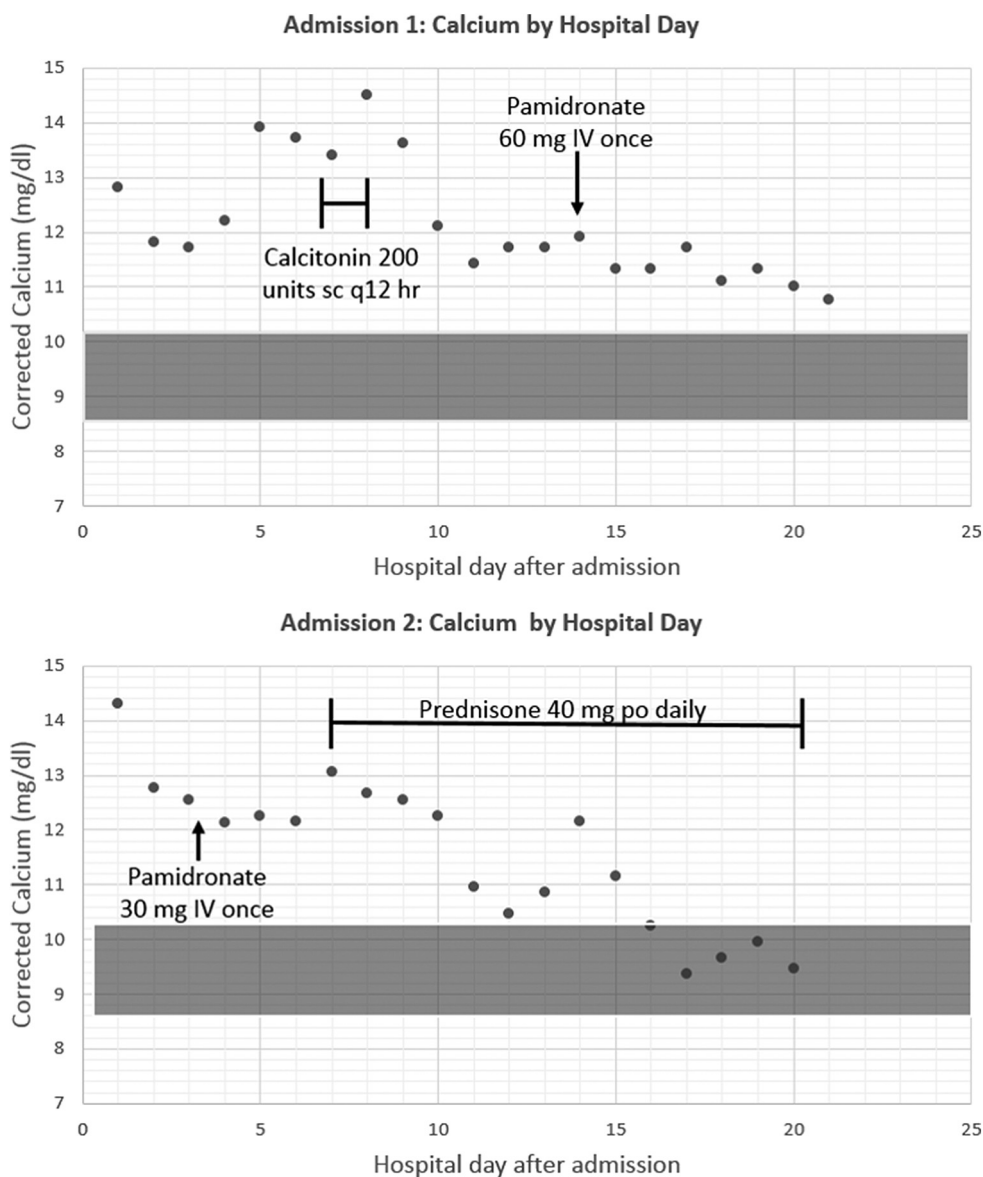


Fig. 1. Graph of hypercalcemia trend and interventions. IV = intravenous; po = orally; sc = subcutaneously.

hydroxyvitamin D binding to the vitamin D receptor, similar to 1,25 dihydroxyvitamin D but with low affinity. Classically, the 25(OH)D levels with vitamin-D intoxication are ≥ 150 ng/mL,¹⁴ which was not the case for our patient. The patient’s normal phosphorus levels (2.9 mg/dL in November 2018) were also against hypervitaminosis D. Finally, in most reports on vitamin-D intoxication, the serum 1,25(OH)₂D levels were normal.¹³ In this case, the rise in 1,25 dihydroxyvitamin D level from 103 pg/mL upon the initial admission to 570 pg/mL upon the second admission indicates that other mechanisms, such as tumor-related production of 1- α hydroxylase, were a major factor affecting the persistent hypercalcemia.

The goals of the treatment of hypercalcemia of malignancy are to lower calcium levels and treat the underlying malignancy. Fluids are the first-line therapy for hypercalcemia, ameliorating the dehydration typically seen in hypercalcemic patients and reversing the decrease in glomerular filtrate rate that reduces the kidney’s

ability to excrete calcium.¹ Bisphosphonates are the best studied for use in this setting and work by blocking osteoclastic bone resorption.¹ Another agent to treat hypercalcemia includes calcitonin, which works by inhibiting osteoclast activity and increasing renal calcium excretion.² Our patient’s lack of response to pamidronate prompted the switch to glucocorticoids, which is the standard treatment for 1,25(OH)₂D-related hypercalcemia. The mechanism of 1,25(OH)₂D-mediated hypercalcemia likely involves malignant cells recruiting adjacent macrophages to express 1- α hydroxylase, leading to an increased conversion of 25 hydroxyvitamin D to 1,25(OH)₂D.² An increased 1,25(OH)₂D level leads to heightened enteric calcium reabsorption and lower urinary calcium excretion.¹⁵ Immunohistochemistry of tumors from patients with 1,25(OH)₂D-mediated hypercalcemia has demonstrated the expression of 1- α hydroxylase.¹⁵ Glucocorticoids inhibit 1- α hydroxylase-mediated conversion of 25 hydroxyvitamin D to

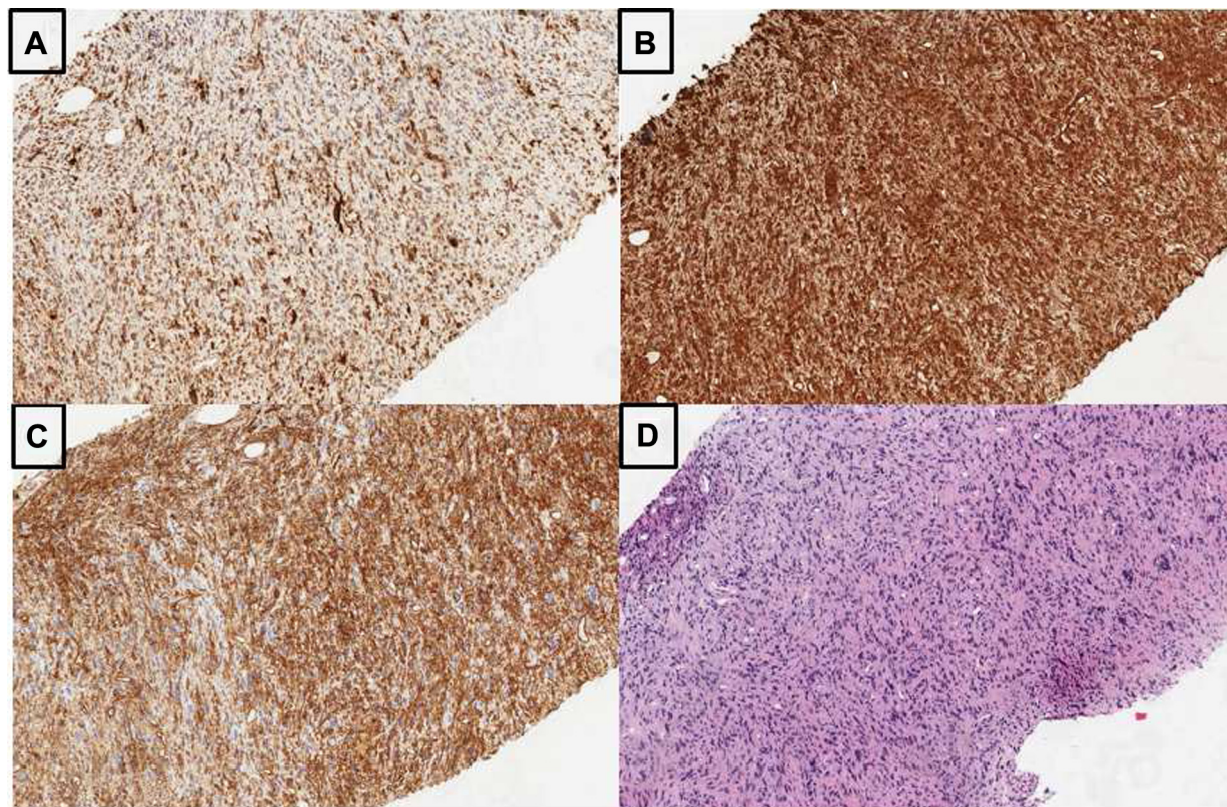


Fig. 2. Pathology of liposarcoma. Biopsy of the patient’s abdominal mass showed staining and morphology consistent with that of dedifferentiated liposarcoma. A, IHC desmin staining. B, IHC vimentin staining. C, CD34 staining. D, Hematoxylin-eosin staining. Follow-up *MDM2* fluorescence in situ hybridization analysis result was positive. IHC = immunohistochemical.

Table 2
Case Reports of Hypercalcemia of Malignancy Caused by Simultaneous Elevations in PTHrP and 1,25(OH)₂D Levels

Case report	Malignancy	PTH (pg/mL)	PTHrP (pmol/L)	25(OH)D (ng/mL)	1,25(OH) ₂ D (pg/mL)	CCa (mg/dL)	Phos (mg/dL)	Treatment of hypercalcemia
Hoekman et al ⁴	Clear cell ovarian carcinoma	<1	170	20	222	13.31	2	Tumor resection led to normalization of calcium levels
Nemr et al ⁶	Squamous cell lung cancer	7	30	<4	76	13.6	1.8	Refractory to zoledronic acid. Patient opted for comfort care
Shivnani et al ³	Renal cell carcinoma	<2.5	3.4	38	79	12.9	2.3	Refractory to bisphosphonates (90 mg IV pamidronate) then responded to prednisone 40 mg orally daily
Van Den Eynden et al ⁵	Pancreatic neuroendocrine tumor	<5	7.3	4.5	71.5	18.9	3.57	Refractory to 90 mg IV pamidronate and 8 mg zoledronic acid. Calcium normalized after chemotherapy and surgical resection.

Abbreviations: 25(OH)D = 25 hydroxy vitamin D; 1,25(OH)₂D = 1,25 dihydroxy vitamin D; CCa = corrected calcium; IV = intravenous; phos = phosphorus; PTH = parathyroid hormone; PTHrP = parathyroid hormone-related peptide.

Table 3
Case Reports of Sarcoma and Hypercalcemia of Malignancy

Case report	Malignancy	PTH (pg/mL)	PTHrP (pmol/L)	25(OH)D (ng/mL)	1,25(OH) ₂ D (pg/mL)	CCa (mg/dL)	Phos (mg/dL)	Mechanism
Arakawa et al ⁷	Clear cell sarcoma	NA	NA	NA	NA	NA	NA	Osteolytic
Brooks et al ⁸	Alveolar rhabdomyosarcoma	95.88	NA	NA	NA	15.91	1.28	Ectopic PTH
Cross et al ⁹	Retroperitoneal myxoid liposarcoma	300	NA	NA	NA	14.07	3.22	Likely PTHrP
Jensen et al ¹⁰	Angiosarcoma	147	6.8	15.6	129.4	14.7	2	1° HPTH and PTHrP
Oleffe et al ¹¹	Synoviosarcoma	10	22.5	2.5	<6	18.3	2.8	PTHrP
Takamatsu et al ¹²	Uterine carcinosarcoma	<5	4	NA	13	14.2	NA	PTHrP

Abbreviations: 25(OH)D = 25 hydroxy vitamin D; 1,25(OH)₂D = 1,25 dihydroxy vitamin D; CCa = corrected calcium; phos = phosphorus; 1° HPTH = primary hyperparathyroidism; NA = not available; PTH = parathyroid hormone; PTHrP = parathyroid hormone-related peptide.

1,25(OH)₂D. Lowering the 1,25(OH)₂D levels reduces calcium absorption in the gut and increases urinary excretion of calcium.¹⁵ Our patient's lack of response to bisphosphonates is analogous to a case described by Van Den Eynden et al,⁵ in which a 59-year-old man with a neuroendocrine tumor developed hypercalcemia with elevations in both PTHrP and 1,25(OH)₂D levels. The patient did not respond to bisphosphonate therapy (pamidronate 90 mg and zoledronic acid 8 mg). As primary treatment with interferon alfa and surgical resection led to regression of the tumor and normalization of calcium level, glucocorticoids were not required.⁵

In another case of hypercalcemia of malignancy with dual mechanisms [simultaneously elevated PTHrP and 1,25(OH)₂D levels] published by Shivnani et al,³ a 57-year-old man with renal cell carcinoma failed to respond to 2 doses of 90-mg intravenous pamidronate administered 4 weeks apart. The serum 1,25(OH)₂D level was measured and found to be elevated. A trial of prednisone at 40 mg orally per day was initiated, leading to a prompt decrease in calcium level. The normalization of the calcium level with glucocorticoids provides additional evidence that 1,25(OH)₂D was the driver of hypercalcemia in this patient.

Conclusion

Sarcoma-associated hypercalcemia is a rare disorder, with only 6 previously reported cases. This is the first case describing the dual mechanisms of sarcoma-associated hypercalcemia and only the fifth case of PTHrP and 1,25(OH)₂D simultaneously causing hypercalcemia of malignancy. Recent reviews of the evaluation and management of hypercalcemia of malignancy have described a sequential evaluation, including testing for PTHrP and, if negative, testing for 1,25(OH)₂D levels. However, a rising number of reports have illustrated that multiple mechanisms of hypercalcemia may simultaneously be in play in patients with malignancy. Based on this finding, we recommend measuring the 1,25(OH)₂D levels in conjunction with the PTHrP level in patients with malignancy as this would allow for a more proactive approach to the diagnosis and treatment of hypercalcemia of malignancy.

Author Contributions

A.M. contributed to this journal while employed at the University of Maryland. This manuscript reflects the views of the author and should not be construed to represent the Food and Drug Administration's views or policies.

Disclosure

The authors have no multiplicity of interest to disclose.

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