1,25 OH Vitamin D Mediated Hypercalcemia in a Patient With Malignancy Without Lymphoma (Poster)

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1,25 OH Vitamin D Mediated Hypercalcemia in a Patient With Malignancy Without Lymphoma

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ABSTRACT:

Objective: Describe an unusual case of 1,25 OH vitamin D mediated hypercalcemia in a patient with colonic adenocarcinoma and mesothelioma.

Methods: Case Report.

Case: A 62-year-old male presented with constipation and left abdominal pain of 1-month duration. Abdominal CT revealed rectal thickening concerning for cancer with metastatic lymphadenopathy, metastatic peritoneal lesion and a 20cm liver mass. Biopsy of sigmoid colon showed invasive moderately differentiated adenocarcinoma. Four months prior, his labs were calcium 9.8mg/dL (8.2-10.4 mg/dL), albumin 4.6gm/dL (3.5-5.0g/dL), eGFR 96mL/min/1.73m2 with normal BUN and creatinine. At presentation his labs were calcium 10.5mg/dL, albumin 4.2gm/dL, BUN 29mg/dL (10-26mg/dl), creatinine 1.59mg/dL (0.7-1.50 mg/dL) and eGFR 46. During subsequent hospitalization for right leg cellulitis, he had calcium 11.9mg/dL and ionized calcium 6.45mg/dL with low albumin 3.4gm/dL. He developed sepsis and due to concern for liver abscess the liver mass was biopsied. Pathology showed high grade malignant neoplasm consistent with epithelioid mesothelioma. Septicemia and renal failure requiring dialysis complicated his course.

Hypercalcemia workup showed no evidence of osteolytic lesions on imaging, normal 25 OH vitamin D 46ng/mL (30-100ng/mL), low intact parathyroid hormone (PTH) 12pg/mL (14-72 pg/mL), normal parathyroid hormone related protein (PTHrP) at 1.1pmol/L (<2.0 pmol/L) and absent monoclonal proteins on serum and urine protein electrophoresis. 1,25 OH vitamin D was high on two samples at 95 and 77pg/mL (18-64pg/mL).

The patient's calcium gradually improved with administration of pamidronate to 7.0mg/dL with an albumin of 1.9gm/dL and a corrected calcium 8.7mg/dL. Despite being on 3 vasopressors, antibiotics and continuous renal replacement therapy, his condition deteriorated and patient died on comfort measures.

Discussion: Hypercalcemia resulting from calcium homeostasis imbalance is seen in one third of malignancies and is a poor prognostic factor. Solid malignancies cause hypercalcemia from high PTHrP and less commonly from osteolytic cytokines. Excessive 1,25 OH vitamin D seen mostly in lymphoma causes hypercalcemia by 1-hydroxylation of 25 OH vitamin D. This mechanism has also been reported in dysgerminoma, myofibroblastic tumour and gastrointestinal stromal tumours. This patient had hypercalcemia from high 1,25 OH vitamin D with mesothelioma and colon cancer. Ex vivo upregulation of 1-hydroxylase in colon cancer has been described but there are no colon cancer case reports of 1,25 OH vitamin D mediated hypercalcemia. Hypercalcemia in mesothelemia from high 1,25 OH vitamin D with calcium normalization following resection has been reported. We could not establish which malignancy caused elevation of 1,25 OH vitamin D in this patient.

Conclusion: Elevated 1,25 OH vitamin D could be a hypercalcemia etiology in non lymphoma malignancies and needs to be considered when work up for elevated PTHrP and osteolytic hypercalcemia is negative.

INTRODUCTION:

Hypercalemia is one of the most common endocrine and electrolyte derangements seen in malignancies. Paraneoplastic mechanisms leading to hypercalcemia include tumor production of parathyroid hormone related protein (PTHrP), osteolytic bone lesions, ectopic parathyroid hormone (PTH) production or elevated 1,25 OH vitamin D levels through activation of an extrarenal 1-alpha-hydroxylase. Hypercalcemia from elevated 1,25 OH vitamin D is commonly seen in patients with lymphoma.[1] We report a case of 1,25 OH vitamin D mediated hypercalcemia in a patient with two primary malignancies: adenocarcinoma of the rectum and epitheloid mesothelioma.

CASE PRESENTATION:

- A 62-year-old male presented to his primary care physician's office with 1 month duration of difficulty moving bowels, bloating, gas, and abdominal pain.
- Abdominal CT revealed rectal thickening concerning for cancer with metastatic lymphadenopathy, metastatic peritoneal lesion and a 20cm liver mass (Figure 1) (Figure 2).
- Biopsy of sigmoid colon showed invasive moderately differentiated adenocarcinoma (Figure 3).
- Routine laboratory evaluation at this visit reported elevated calcium level (Table 1).
- Five days following colonoscopy and biopsy, the patient presented to the emergency department with a right lower extremity cellulitis leading to hospitalization for IV antibiotics.
- Sepsis developed, the patient deteriorated, and due to concern for liver abscess the liver mass was biopsied. Pathology showed high grade malignant neoplasm consistent with epithelioid mesothelioma (Figure 4).
- During his hospitalization, calcium levels rose (Table 1) and work up for the etiology of hypercalcemia began (Table 2). There was no evidence of osteolytics lesions on imaging, serum and urine electrophoresis were negative, thyroid stimulating hormone was within normal limits, no evidence of granulomatous disease, no evidence of granulomatous infection.
- Administration pamidronate brought calcium level down within normal range.
- Despite being on three vasopressors, antibiotics and continuous renal replacement therapy, his condition deteriorated and patient died on comfort measures.

TABLE 1.

	July 10	At Presentation October 22	Hospitalization October 31	Administration of Pamidronate
Calcium (8.2-10.4 mg/dL)	9.8	10.5	11.9 (corrected - 12.4)	7.0 (corrected 8.7)
Albumin (3.5-5.0g/dL)	4.6	4.2	3.4	1.9
Ionized Calcium (4.6-5.4 mg/dL)	-	-	6.45	-
eGFR (>60mL/min/1.73m^2)	96	46	36	14
BUN (10-26mg/dl)	19	29	79	89
Creatinine (0.7-1.50 mg/dL)	0.79	1.59	1.95	4.31

TABLE 2.

Vitamin D, 25 OH total (30-100ng/mL)	46
Vitamin D, 1,25-Dihydroxy (18-64pg/mL)	95 and 77
Intact PTH (14-72 pg/mL)	12
PTHrP (<2.0 pmol/L)	1.1

Table 1: Routine laboratory evaluation reported elevated calcium level with diagnosis of moderately differentiated adenocarcinoma of the sigmoid colon and epitheloid mesothelioma.

Table 2: Hypercalcemia workup showed no evidence of osteolytic lesions on imaging, normal 25 OH vitamin D, low intact PTH, normal PTHrP and absent monoclonal proteins on serum and urine protein electrophoresis. 1,25 OH vitamin D was high on two samples.

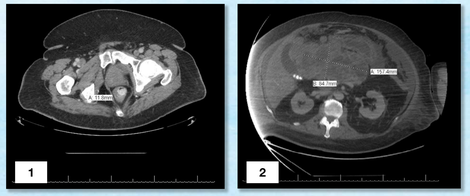
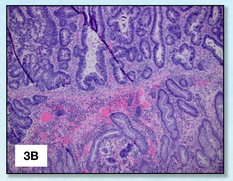


Figure 1: Sagittal view of CT scan abdomen and pelvis with contrast demonstrating circumferential rectal wall thickening suggesting a mass measuring up to 11.8mm in thickness.

Figure 2: CT scan abdomen and pelvis with IV contrast demonstrating a large 15.7cm by 8.4cm mass which appears to be centered within the left lobe of the liver but is exophytic, abutting the pancreas and stomach but not appearing to originate in either of these organs.



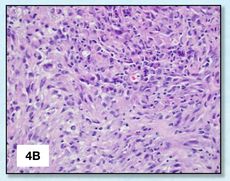


Figure 3: Sigmoid biopsy in formalin showing invasive moderately differentiated adenocarcinoma. Depth of involvement cannot be determined.

Figure 4: Liver core biopsy showing high grade malignant neoplasm consistent with epithelioid mesothelioma. Immunoperoxidase stain for inhibin, CAM 5.2, CK7, calretinin, WT1 were positive. This malignant neoplasm is histologically distinct from his rectal adenocarcinoma and represents a synchronous secondary primary neoplasm.

DISCUSSION:

Our patient had excessive 1,25 OH vitamin D producing hypercalcemia as evident by normal PTHrP, lack of osteolytic lesions, low PTH and elevated 1,25 OH vitamin D.

Hypercalcemia resulting from calcium homeostasis imbalance is seen in one third of malignancies commonly through increased synthesis of PTHrP or metastatic osteolytic bone lesions. 1,25 OH vitamin elevation causes hypercalcemia by increased vitamin D absorption. Elevated 1,25 OH vitamin D mediated hypercalcemia has been established in granulomatous diseases and lymphomas. This mechanism occurs through elevated extra renal hydroxylation of 25 OH vitamin D. Extra-renal 1-hydroxylase was found in tumor adjacent tissue macrophages[1] and is resistant to normal feedback controls leading to uncontrolled hypercalcemia.

There are very few case reports identifying elevations of 1,25 OH vitamin D causing hypercalcemia in other malignancies. Among these neoplasms, dysgerminomas of ovary leading to hypercalcemia have been reported in twelve patients.[2] Resection of the dygerminoma resulted in normalization of serum calcium and 1,25 OH vitamin D.[2] A case of inflammatory myofibroblastic tumor on surgical pathology showing abundant macrophage infiltration has been described to be associated with hypercalcemia with 1,25 OH vitamin D elevation.[3] Abundant mRNA encoding for 1-alpha-hydroxylase in this tumoral tissue was demonstrated.[3]

A patient with gastrointestinal stromal tumour with 1,25 OH vitamin D associated hypercalcemia who transiently responded to tyrosine kinase inhibitor and bisphosphonates has been reported.[4] Similar to our patient, a patient with pleural mesothelioma had elevated calcium from this mechanism.[5] Pleural mesothelioma resection resulted in normalization of calcium and 1,25 OH vitamin D.5 Ex vivo upregulation of mRNA encoding for 1-hydroxylase has been described in colon cancer[6,7] but there are no colon cancer case reports of 1,25 OH vitamin D mediated hypercalcemia. Due to the patients underlying septicemia and deterioration, we could not establish which malignancy caused elevation of 1,25 OH vitamin D in this patient. However this case reports the rare occurrence of 1,25 OH vitamin D mediated hypercalcemia in patient with malignancy without lymphoma.

CONCLUSION:

Elevated 1,25 OH vitamin D could be a hypercalcemia etiology in non lymphoma malignancies. This case shows two different malignancies associated with this mechanism, neither of which has been well reported in the literature. Future investigation should be considered when work up for elevated PTHrP and osteolytic hypercalcemia is negative.

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