CASE REPORT

Twist on a classic: vitamin D and hypercalcaemia of malignancy

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SUMMARY

Malignancy is the most common cause of hypercalcaemia in the inpatient setting. Most cases are caused by tumour production of parathyroid hormone-related protein and osseous metastases. In less than 1% of cases, hypercalcaemia is driven by increased production of 1,25-dihydroxyvitamin D (1,25(OH)₂D), a mechanism most commonly seen in haematological malignancies. Here, we describe a woman with metastatic small cell cervical carcinoma who developed hypercalcaemia secondary to paraneoplastic overproduction of 1,25(OH)₂D, a finding that, to our knowledge, has not been previously associated with this cancer. We also review the current cases of solid tumours reported to have this mechanism of hypercalcaemia and the evidence behind multiple therapeutic approaches.

BACKGROUND

Hypercalcaemia is a common complication in patients with cancer, occurring in up to 30% of patients and is associated with poor prognosis. Despite being described as a single entity, there are several mechanisms that could mediate its development. Therefore, understanding the pathophysiology of each mechanism is crucial for diagnosis and for treatment.

Ectopic production of parathyroid hormone-related protein (PTHrP) is the most common cause of malignancy-associated hypercalcaemia in solid tumours, followed by the presence of osteolytic metastases. Here, we describe a unique case of a solid malignancy that developed resistant hypercalcaemia mediated by overproduction of 1,25-dihydroxyvitamin D (1,25(OH)₂D), which is a rare aetiology and is primarily associated with haematological malignancies. We also review the evidence behind the diagnostic tools available to measure calcium as well as the current therapeutic approaches to this entity.

CASE PRESENTATION

A 75-year-old woman with recently diagnosed metastatic small cell cervical cancer was transferred from an outside hospital with refractory hypercalcaemia. She initially presented with abdominal pain, postmenopausal bleeding and 35 lb weight loss. A CT of the chest, abdomen and pelvis showed a large pelvic mass involving the cervix, uterus, vagina and bilateral adnexa as well as mild left hydronephrosis related to bulky retroperitoneal adenopathy (figure 1A). A biopsy demonstrated a high-grade

neuroendocrine neoplasm positive for Ki-67 (80%–90%), p16-INK4a, synaptophysin, chromogranin A (focal) and CD56 with features of small cell carcinoma (figure 1B). Soon after her diagnosis, she became somnolent and was admitted to an outside hospital where she was found to have a calcium level of 14.6 mg/dL. She was treated with intravenous fluids, calcitonin and pamidronate and discharged 1 week later with a calcium of 10.0 mg/dL. The following week, the patient again became lethargic and was readmitted with a calcium of 14.5 mg/dL. She received intravenous fluids and calcitonin but remained persistently hypercalcaemic. She received another dose of pamidronate and was transferred to our hospital for further management.

On arrival at our institution, the patient reported feeling well aside from mild abdominal pain and constipation. Other medical history was significant for type 2 diabetes mellitus, hypertension and coronary artery disease. She reported taking several vitamin supplements which included calcium sulfate 5 mg and D3 cholecalciferol 5000 IU daily but not calcitriol (1,25(OH)₂D). She denied personal or family history of sarcoid or other autoimmune diseases. She was born in Guyana and moved to the USA 15 years ago. She had no known tuberculosis exposure.

On physical examination, the patient was lethargic but arousable to voice. Vital signs were within normal limits except for blood pressure of 159/68 mm Hg. Abdominal examination was notable for a large palpable pelvic mass and mild diffuse tenderness to palpation. Cardiopulmonary examination was unremarkable.

INVESTIGATIONS

On arrival to our institution, laboratory results showed a calcium level of 11.1 mg/dL (reference range: 8.9–10.3 mg/dL) which, when adjusted for albumin 2.9 g/dL, resulted in a corrected calcium level of 12.0 mg/dL. The ionised calcium level was 1.46 mmol/L (reference range: 1.12–1.32 mmol/L) and phosphorus level was normal (table 1). In this case, work-up revealed an inappropriately normal intact parathyroid hormone (PTH) level of 15 pg/mL (reference range: 12–88 pg/mL), undetectable PTHrP, 25-hydroxyvitamin D (25(OH)D) level of 30.7 ng/mL (reference range: 30–80 ng/mL) and 1,25(OH)₂D level of 183 pg/mL (reference range: 19.9–79.3 pg/mL). Serum and urine protein electrophoresis, ACE level, purified protein derivative skin test and Quantiferon-TB Gold tests were normal. Positron emission tomography CT revealed

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Figure 1 Radiological and pathological findings of metastatic small cell cervical carcinoma (A) Axial CT image of the abdomen and pelvis demonstrating a large pelvic mass involving the cervix, uterus, vagina and bilateral adnexa. (B) H&E stain at 400× magnification demonstrates highly cellular sheets of small to medium-sized cells with high nuclear to cytoplasmic ratio, nuclear moulding, hyperchromatic nuclei, mitoses and apoptotic bodies. Crush artefact, characterised by cellular smearing, can be readily appreciated.

small fludeoxyglucose-avid osseous lesions without definite CT correlate in the T4 and L1 vertebral bodies, ileum and right femur (figure 2A,B).

DIFFERENTIAL DIAGNOSIS

In this case, malignant hypercalcaemia was thought to be secondary to paraneoplastic $1,25(\text{OH})_2\text{D}$ overproduction related to metastatic neuroendocrine cervical cancer. Careful review of her vitamins and supplements showed no evidence of exogenous ingestion of calcitriol ($1,25(\text{OH})_2\text{D}$). The patient had no prior tuberculosis (TB) exposures, no chest X-ray findings suggestive of TB and negative Quantiferon-TB Gold test. Sarcoidosis was unlikely given normal levels of ACE and no other clinical findings associated with sarcoidosis. Her CT scans were not suggestive of lymphoproliferative disorders.

TREATMENT

The patient received calcitonin, aggressive intravenous hydration and furosemide while awaiting response to the pamidronate dose she received the day prior to transfer. However, calcium levels remained persistently elevated. On hospital day 5, she was treated with denosumab 120 mg subcutaneously and her calcium levels normalised over the following days (figure 3). Markers of bone turnover also improved, including C-terminal telopeptide from 1173 pg/mL to 563 pg/mL (reference range for postmenopausal women: 104–1008 pg/mL), N-terminal telopeptide from 21.3 nM bone collagen equivalents (BCE) to 11.9 nM BCE (goal range for treated postmenopausal women: 6.2–19.0 nM BCE) and bone alkaline phosphatase from 6.9 µg/L to 6.7 µg/L (reference range for postmenopausal woman: 7.0–22.4 µg/L). However, 2 weeks later, hypercalcaemia recurred and was difficult to control with intravenous fluids and furosemide. Repeat $1,25(\text{OH})_2\text{D}$ level was persistently elevated at 125 pg/mL. Prednisone 40 mg daily was initiated with a plan for a slow taper.

OUTCOME AND FOLLOW-UP

The patient's hospital course was complicated by worsening hydronephrosis secondary to malignant obstruction for which she underwent placement of a left ureteral stent and right percutaneous nephroureterostomy with improvement in renal function. She developed a urinary tract infection and bacteraemia due to multidrug-resistant *Enterobacter cloacae*, for which she was treated with meropenem and levofloxacin. The patient

Table 1 Patient laboratory results at the time of admission

	Patient results	Reference range
Serum chemistries		
Sodium (mmol/L)	136	136–144
Potassium (mmol/L)	3.7	3.2–5.2
Chloride (mmol/L)	102	101–111
Bicarbonate (mmol/L)	23	22–32
Urea nitrogen (mg/dL)	13	8–20
Creatinine (mg/dL)	1.59	0.44–1.03
Glucose (mg/dL)	173	74–118
Calcium (mg/dL)	11.1	8.9–10.3
Ionised calcium (mmol/L)	1.46	1.12–1.32
Magnesium (mEq/L)	1.0	1.5–2.1
Phosphorus (mg/dL)	3.2	2.4–4.7
Endocrine		
Parathyroid hormone (pg/mL)	15	12–88
Parathyroid hormone-related protein (pg/mL)	<10	14–27
25-hydroxyvitamin D (ng/mL)	30.7	30–80
1,25-dihydroxyvitamin D (pg/mL)	183	19.9–79.3
Liver function tests		
Total protein (g/dL)	6.4	6.1–7.9
Albumin (g/dL)	2.9	3.5–4.8
AST (IU/L)	93	15–41
ALT (IU/L)	14	14–54
Alkaline phosphatase (IU/L)	60	32–91
Total bilirubin (mg/dL)	0.5	0.3–1.2
Direct bilirubin (mg/dL)	0.1	0.1–0.5
Indirect bilirubin (mg/dL)	0.4	0.1–0.8
Globulin (g/dL)	3.5	1.8–3.3
Haematology		
White blood cells ($\times 10^9/\text{L}$)	5.0	3.4–11.2
Haemoglobin (g/dL)	9.1	11.7–15.3
Haematocrit (%)	26.2	35.0–45.0
Platelets ($\times 10^9/\text{L}$)	318	150–450
Mean corpuscular volume (fL)	84.8	81–100
Mean corpuscular haemoglobin (pg)	29.4	27–34
Coagulation studies		
Prothrombin time (s)	13.0	10.2–12.9
International normalised ratio	1.1	0.9–1.1
Partial thromboplastin time (s)	29.5	27.2–36.2

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Figure 2 PET-CT of metastatic small cell cervical carcinoma. (A) Representative PET-CT image demonstrating large intensely FDG-avid lobulated pelvic mass (17×15 cm, SUV max 17.9) with involvement of adjacent bladder. FDG avidity in right femoral neck and right ilium adjacent to sacroiliac joint. (B) Representative PET-CT image demonstrating FDG-avid retrocaval and retroperitoneal lymphadenopathy. FDG, 18F-fluorodeoxyglucose; PET, positron emission tomography; SUV, standardized uptake values.

Figure 3 Corrected calcium and ionised calcium levels before and during hospital stay. Total calcium level corrected for albumin, that is, 'corrected calcium' (red line) and ionised calcium (blue line) during the patient's hospitalisation. Treatments received are indicated with arrows or brackets. Dotted lines represent normal reference values for total calcium (8.9–10.3 mg/dL) and ionised calcium (1.12–1.32 mmol/L). Negative days represent laboratory values at outside hospital, day zero (0) represents day of admission to our institution. Gaps in the measurement of ionised calcium levels represent absence of its measurement during the days prior to the admission to our institution.

was offered palliative chemotherapy and palliative radiation. However, given her multiple complications and progressively declining functional status, the patient elected to transition to hospice care.

DISCUSSION

Production of $1,25(\text{OH})_2\text{D}$ accounts for less than 1% of cases of hypercalcaemia of malignancy and is primarily associated with Hodgkin lymphoma and other haematological malignancies.^{1,2} In this report, we describe a unique case of hypercalcaemia associated with $1,25(\text{OH})_2\text{D}$ overproduction in a woman with metastatic neuroendocrine cervical cancer as well as the clinical implications of different therapeutic approaches. The histomorphology of her biopsy (figure 1B) is compatible with small cell carcinoma, a type of poorly differentiated neuroendocrine carcinoma that is typically positive for at least one neuroendocrine marker (synaptophysin, chromogranin or CD56) and is often positive for pan-cytokeratin immunostains.³ Ectopic production of corticotropin, vasopressin, serotonin, PTH and PTHrP by neuroendocrine tumours has been described previously⁴; however, to our knowledge, this is the first reported case of small cell cervical carcinoma with symptomatic hypercalcaemia mediated by overproduction of $1,25(\text{OH})_2\text{D}$. This patient's $1,25(\text{OH})_2\text{D}$ level was persistently more than twice the upper limit of normal despite multiple therapeutic approaches, and her evaluation did not reveal any evidence of granulomatous disease. Thus, we postulate that paraneoplastic overactivity of 1- α -hydroxylase was responsible for excess conversion of $25(\text{OH})\text{D}$ to $1,25(\text{OH})_2\text{D}$. The neuroendocrine characteristics of the tumour may make this mechanism more likely. Consideration was given to stain tumour samples for 1- α -hydroxylase; unfortunately, this assay was not available at our institution or affiliated institutions. Furthermore, immunohistochemistry of neuroendocrine tumours has been historically unreliable for determining whether tumours are truly functional. The patient's inappropriately normal PTH level suggests that some degree of primary hyperparathyroidism, along with bony metastases, were contributing factors. However, given the unimpressive degree of

these abnormalities, they were felt to be unlikely as the primary aetiology of her refractory hypercalcaemia.

Our review of the literature found few case reports of this mechanism associated with solid tumours (table 2). Of those reported, only one was a neuroendocrine tumour.⁵ Nonetheless, an Australian retrospective case series of patients with calcitriol-mediated hypercalcaemia found that 5% of cases were associated with solid tumours.² This evidence suggests that overproduction of $1,25(\text{OH})_2\text{D}$ may be an under-reported cause of hypercalcaemia in patients with solid malignancies and a comprehensive work-up should be performed for these patients, especially as this could have implications for management.

Treatment of hypercalcaemia is indicated when calcium levels exceed 14 mg/dL or when patients become symptomatic, typically from neurological or renal manifestations.⁶ Aggressive volume repletion with isotonic fluid is essential to correct hypovolaemia secondary to anorexia and renal losses.⁷ Once euvoalaemia is achieved, loop diuretics may be considered to increase calcium excretion. Calcitonin both inhibits bone resorption and augments calcium excretion and is effective in lowering calcium levels. However, due to rapid tachyphylaxis typically within

Table 2 Reported cases of hypercalcaemia of malignancy secondary to vitamin D production in solid tumours

Primary malignancy	PTH	PTHrP	$1,25(\text{OH})_2\text{D}$	Reference
Clear cell renal cell carcinoma	Low	Slightly above normal	Elevated	Shivnani <i>et al.</i> ¹⁹
Pancreatic neuroendocrine	Normal	Normal	Elevated	Zhu <i>et al.</i> ⁵
Ovarian dysgerminoma	Low	Low	Elevated	Hibi <i>et al.</i> ²⁶
Ovarian dysgerminoma	Elevated	Not available	Elevated	Allbery <i>et al.</i> ²⁷
Seminoma	Normal	Not available	Elevated	Grote <i>et al.</i> ²⁸

$1,25(\text{OH})_2\text{D}$, 1,25-dihydroxyvitamin D; DPTH, parathyroid hormone; PTHrP, PTH-related peptide.

48 hours, its use is helpful primarily as a temporising agent.⁸ Therapies with a more durable response include bisphosphonates, receptor activator of nuclear factor-kappa B (RANKL) inhibitors and glucocorticoids. Regardless of the strategy, it is important to note that treatment of malignancy-associated hypercalcaemia has not been associated with improvement in survival. Initiation of antitumour therapy, when indicated, is necessary to improve overall prognosis.^{9 10}

Intravenous bisphosphonates are the most well-studied agents in the treatment of malignancy-related hypercalcaemia, with pamidronate¹¹ and zoledronate¹² being the two drugs approved by the Food and Drug Administration (FDA) in the USA. They inhibit osteoclast activity and therefore decrease bone resorption, with calcium lowering effects usually occurring 2 to 4 days after administration.¹³ Zoledronate has been shown to be more potent than pamidronate specifically in the treatment of malignancy-related hypercalcaemia and has a similar safety profile.¹⁴

In 2014, denosumab was approved as an alternative therapy for hypercalcaemia of malignancy. Denosumab is a human monoclonal antibody that inhibits osteoclast maturation by targeting RANKL.¹⁵ FDA approval came after a single-arm study demonstrated efficacy in patients with hypercalcaemia of malignancy refractory to bisphosphonates. Interestingly, of the patients who responded to therapy, more than 60% had elevated PTHrP and one-third had bone metastases.¹⁶ The greatest advantage of denosumab over bisphosphonates is its safe use in patients with renal impairment. Furthermore, recent data suggest that denosumab may be more effective than bisphosphonates in decreasing the risk of developing malignancy-related hypercalcaemia as well as in delaying the time of onset of this complication.¹⁷

Glucocorticoid use in the treatment of hypercalcaemia is most efficacious in granulomatous diseases and lymphomas.¹ Glucocorticoids inhibit 1-alpha-hydroxylase in malignant lymphocytes and active macrophages, decrease intestinal calcium absorption and decrease osteoclastic activity.¹⁸ One case report also reported efficacy for calcitriol-induced hypercalcaemia in a patient with renal cell carcinoma.¹⁹ Importantly, prolonged corticosteroid use is associated with toxicity including immunosuppression, hyperglycaemia and psychiatric effects which must be weighed carefully in patients with hypercalcaemia driven by incurable cancers.

Lastly, we bring attention to the diagnostic value of measuring total versus ionised calcium in the management hypercalcaemia. Only half of circulating calcium is biologically active as ionised (or free) calcium, with the rest bound to albumin and various other organic and inorganic anions. Before modern laboratory advances, direct measurement of ionised calcium was not feasible, so formulas were derived to estimate ionised calcium levels based on serum albumin levels. However, a number of additional factors influence ionisation, including pH, citrate and magnesium levels.²⁰ Not surprisingly, patients who are critically ill or have renal dysfunction have worse correlation between total and ionised calcium levels, presumably due to dynamic changes in these other factors.^{21 22} Studies also suggest that ionised calcium may have better accuracy in the setting of malignancy compared with total calcium^{23 24} or total calcium corrected for albumin.²⁵ Interestingly, our patient demonstrated discordance of total and ionised calcium levels 26% of the time (6 of 23 data sets), with ionised calcium levels within the normal range and falsely high albumin-adjusted total calcium levels in all cases (figure 3). Therefore, we advocate for increased use of ionised calcium when actively managing hypercalcaemia in these high-risk populations.

In conclusion, hypercalcaemia of malignancy is a very common complication in cancer. The mechanisms that drive this entity are multiple and a thorough work-up is necessary to elucidate the cause of this complication, especially because this may have implications for treatment. Here, we describe the uncommon case of hypercalcaemia driven by paraneoplastic production of calcitriol, where standard management with intravenous fluids, diuretics, calcitonin and bisphosphonates was not effective. Steroids or recently approved medications such as denosumab could be potential therapeutic options in these types of cases. Importantly, treatment of the underlying malignancy is the definitive treatment for lasting control of hypercalcaemia and all other medical approaches are temporising and will not change survival in these patients.

Learning points

- Hypercalcaemia of malignancy is a common complication in cancer that requires a thorough work-up to elucidate the underlying mechanisms due to its implications for treatment.
- Overproduction of 1,25-dihydroxyvitamin D may be an under-reported cause of hypercalcaemia in patients with solid malignancies.
- Despite multiple approaches available to treat malignancy-associated hypercalcaemia, the primary and definitive management is treatment of the underlying malignancy.
- Ionised calcium measurements may be more accurate than total calcium or total calcium corrected for albumin in patients with hypercalcaemia of malignancy.

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REFERENCES

- 1 Seymour JF, Gagel RF. Calcitriol: the major humoral mediator of hypercalcaemia in Hodgkin's disease and non-Hodgkin's lymphomas. *Blood* 1993;82:1383–94.
- 2 Donovan PJ, Sundac L, Pretorius CJ, et al. Calcitriol-mediated hypercalcaemia: causes and course in 101 patients. *J Clin Endocrinol Metab* 2013;98:4023–9.
- 3 Chun YK. Neuroendocrine tumors of the female reproductive tract: a literature review. *J Pathol Transl Med* 2015;450–61.
- 4 Kaltsas G, Androulakis IJ, de Herder W, et al. In: De Groot LJ, Chrousos G, Dungan K, *Paraneoplastic Syndromes related to Neuroendocrine Tumours*. South Dartmouth, 2000.
- 5 Zhu V, de Las Morenas A, Janicek M, et al. Hypercalcaemia from metastatic pancreatic neuroendocrine tumor secreting 1,25-dihydroxyvitamin D. *J Gastrointest Oncol* 2014;5:E84–7.
- 6 Bilezikian JP. Management of acute hypercalcaemia. *N Engl J Med* 1992;326:1196–203.
- 7 Hosking DJ, Cowley A, Bucknall CA. Rehydration in the treatment of severe hypercalcaemia. *Q J Med* 1981;50:473–81.
- 8 Wisneski LA. Salmon calcitonin in the acute management of hypercalcaemia. *Calcif Tissue Int* 1990;46:S26–S30.
- 9 Ralston SH, Gallacher SJ, Patel U, et al. Cancer-associated hypercalcaemia: morbidity and mortality. Clinical experience in 126 treated patients. *Ann Intern Med* 1990;112:499–504.
- 10 Wright JD, Tergas AI, Ananth CV, et al. Quality and outcomes of treatment of hypercalcaemia of malignancy. *Cancer Invest* 2015;33:331–9.

- 11 Nussbaum SR, Warrell RP, Rude R, *et al.* Dose-response study of alendronate sodium for the treatment of cancer-associated hypercalcemia. *J Clin Oncol* 1993;11:1618–23.
- 12 Body JJ, Lortholary A, Romieu G, *et al.* A dose-finding study of zoledronate in hypercalcemic cancer patients. *J Bone Miner Res* 1999;14:1557–61.
- 13 Carano A, Teitelbaum SL, Konsek JD, *et al.* Bisphosphonates directly inhibit the bone resorption activity of isolated avian osteoclasts in vitro. *J Clin Invest* 1990;85:456–61.
- 14 Major P, Lortholary A, Hon J, *et al.* Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001;19:558–67.
- 15 McClung MR, Lewiecki EM, Cohen SB, *et al.* Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med* 2006;354:821–31.
- 16 Hu MI, Glezerman IG, Leboulleux S, *et al.* Denosumab for treatment of hypercalcemia of malignancy. *J Clin Endocrinol Metab* 2014;99:3144–52.
- 17 Diel IJ, Body JJ, Stopeck AT, *et al.* The role of denosumab in the prevention of hypercalcaemia of malignancy in cancer patients with metastatic bone disease. *Eur J Cancer* 2015;51:1467–75.
- 18 Sandler LM, Winearls CG, Fraher LJ, *et al.* Studies of the hypercalcaemia of sarcoidosis: effect of steroids and exogenous vitamin D3 on the circulating concentrations of 1,25-dihydroxy vitamin D3. *Q J Med* 1984;53:165–80.
- 19 Shivnani SB, Shelton JM, Richardson JA, *et al.* Hypercalcemia of malignancy with simultaneous elevation in serum parathyroid hormone--related peptide and 1,25-dihydroxyvitamin D in a patient with metastatic renal cell carcinoma. *Endocr Pract* 2009;15:234–9.
- 20 Franklin C, McLean A. The classic: the state of calcium in the fluids of the body. I. The conditions affecting the ionization of calcium. Franklin C. McLean and A. Baird Hastings. *Clin Orthop Relat Res* 1970;69:4–27.
- 21 Drop LJ, Laver MB. Low plasma ionized calcium and response to calcium therapy in critically ill man. *Anesthesiology* 1975;43:300–5.
- 22 Zaloga GP, Chernow B, Cook D, *et al.* Assessment of calcium homeostasis in the critically ill surgical patient. The diagnostic pitfalls of the McLean-Hastings nomogram. *Ann Surg* 1985;202:587–94.
- 23 Bowers GN, Brassard C, Sena SF. Measurement of ionized calcium in serum with ion-selective electrodes: a mature technology that can meet the daily service needs. *Clin Chem* 1986;32:1437–47.
- 24 Ladenson JH, Lewis JW, McDonald JM, *et al.* Relationship of free and total calcium in hypercalcemic conditions. *J Clin Endocrinol Metab* 1979;48:393–7.
- 25 Ijaz A, Mehmood T, Qureshi AH, *et al.* Estimation of ionized calcium, total calcium and albumin corrected calcium for the diagnosis of hypercalcaemia of malignancy. *J Coll Physicians Surg Pak* 2006;16:49–52.
- 26 Hibi M, Masahito H, Hara F, *et al.* 1,25-dihydroxyvitamin D-mediated hypercalcemia in ovarian dysgerminoma. *Pediatr Hematol Oncol* 2008;25:73–8.
- 27 Allbery SM, Swischuk LE, John SD. Hypercalcemia associated with dysgerminoma: case report and imaging findings. *Pediatr Radiol* 1998;28:183–5.
- 28 Grote TH, Hainsworth JD. Hypercalcemia and elevated serum calcitriol in a patient with seminoma. *Arch Intern Med* 1987;147:2212–3.

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