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Hypercalcemia in a Seminoma

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Abstract

Background: The association of seminoma with malignant hypercalcemia is extremely rare. Case findings: We present a 32-year-old male with hypercalcemia. Subsequently, a metastatic seminoma was discovered according to computed tomography and biopsy testing. Elevated 1,25-dihydroxyvitamin D levels were identified as the cause of hypercalcemia. Conclusion: Hypercalcemia is a rare but possible scenario in seminoma and therefore it is important to consider this uncommon cause in the differential diagnosis.

Subject Areas

Oncology

Keywords

Paraneoplasic Hypercalcemia, Seminoma, 1,25-dihydroxyvitamin D

1. Introduction

Hyperparathyroidism and malignancy are the two most common causes of hypercalcemia (90%). Paraneoplastic hypercalcemia affects about 20% of all cancer patients [1] [2]. The pathophysiology of hypercalcemia of malignancy is primarily explained by four mechanisms—excessive secretion of Parathyroid Hormone (PTH)-related protein (PTHrP), bony metastases leading to the release of osteoclast-activating factors, the production of 1,25-dihydroxyvitamin D (calcitriol), and ectopic secretion of PTH [3] [4]. Almost all cases of Hodgkin lymphoma, about one-third of non-Hodgkin lymphoma cases, and granulomatous diseases such as sarcoidosis and tuberculosis may cause hypercalcemia by increasing 1,25-dihydroxyvitamin

D (calcitriol) production. Excessive production of calcitriol is responsible for less than 1% of hypercalcemia of malignancy cases overall [5]. The tumor cells or surrounding lymphocytes overexpress 1α-hydroxylase, which causes ectopic conversion of 25 hydroxyvitamin D to 1,25-dihydroxyvitamin D. The hypercalcemia of excess calcitriol production is caused by increased intestinal and bone resorption of calcium. Unlike other forms of hypercalcemia of malignancy, calcitriol-mediated hypercalcemia of malignancy tends to be associated with normal to high phosphorus levels [5]. This subset of patients (increased extrarenal 1,25-dihydroxyvitamin D production independent of PTH, which is low) typically responds well to steroid treatment. It reduces vitamin D production by lowering the 1α-hydroxylase, which is known to convert 25(OH)D (calcidiol) into 1,25$(OH)_2$D (calcitriol), and decreases calcium absorption from the intestines [6] [7].

2. Case Presentation

A 32-year-old male who underwent right orchiectomy ten years ago in a different hospital with histopathological diagnosis of seminoma, was referred to our Clinic for assessment and management of severe hypercalcemia. The patient complained of nausea with intermittent vomiting (about 2- to 3 times daily), anorexia, apathy, fatigue and back pain. At the time of admission to the hospital the patient exhibited severe hypercalcemia, unmeasurable levels of parathyroid hormone, low 25-hydroxyvitamin D levels and high 1,25-dihydroxyvitamin D levels. All laboratory tests are shown in **Table 1**. These results raised the suspicion of paraneoplastic hypercalcemia [8]. A computed tomography study of the chest, abdomen and pelvis showed a large retroperitoneal mass, with no evidence of bony metastases (**Figures 1-3**). A targeted biopsy was performed and revealed metastasis of the seminoma

Table 1. Laboratory measures.

Parameter	Value	Normal ranges
Calcium	4.38 mmol/L	2.20 - 2.65
Phosphorus	1.68 mmol/L	0.81 - 1.45
Magnesium	0.76 mmol/L	0.73 - 1.06
Creatinine	116 µmol/L	64.0 - 104.0
Albumin	44.8 g/L	35.0 - 52.0
AFP	1.1 µg/L	<9.0
β-hCG	218 U/L	<5.0
PTH	<0.58 pmol/L	1.58 - 6.03
25$(OH)D_3$	52.3 nmol/L	75.0 - 250.0
1,25$(OH)_2D_3$	96.3 ng/L	18.9 - 79.3

AFP, alpha-fetoprotein; β-hCG, human chorionic gonadotrophin; PTH, biointact parathyroid hormone (1-84) ECLIA; 25$(OH)D_3$, 25-hydroxyvitamin D; 1,25$(OH)_2D_3$, 1,25-dihydroxyvitamin D, CLIA.

(Figure 4, Figure 5). We did not perform immunochemical tests for 1α-hydroxylase and PTHrP testing. This presents some limitations in our case. Severe hypercalcemia was lowered to 2.66 mmol/L, after one week of intravenous hydration with saline, furosemide and prednisone at a daily dose of 50 mg. The patient's α-fetoprotein levels were normal and β-human chorionic gonadotropin was moderately elevated; therefore, the actual status was categorized as good-risk seminoma (International Germ Cell Consensus Classification). After normalization of hypercalcemia, the patient was started on chemotherapy with three cycles of bleomycin/cisplatin/etoposid, which is still ongoing at the time of writing this report.

3. Discussion

Hypercalcemia associated with malignancy due to $1,25(OH)_2D_3$ accounts for less than 1% of cases [4]. This type of hypercalcemia is usually associated with granulomatous diseases (sarcoidosis, tuberculosis, fungal infections), less frequently with lymphomas and rarely with dysgerminomas. Seminoma with malignant hypercalcemia was first described by King *et al.* in 1972 [9]. Grote and Hainsword reported the first case of a seminoma with malignant hypercalcemia mediated by calcitriol [10]. Granulomatous conditions have enhanced 1α-hydroxylation of vitamin D in macrophages and mRNA for 1α-hydroxylase was

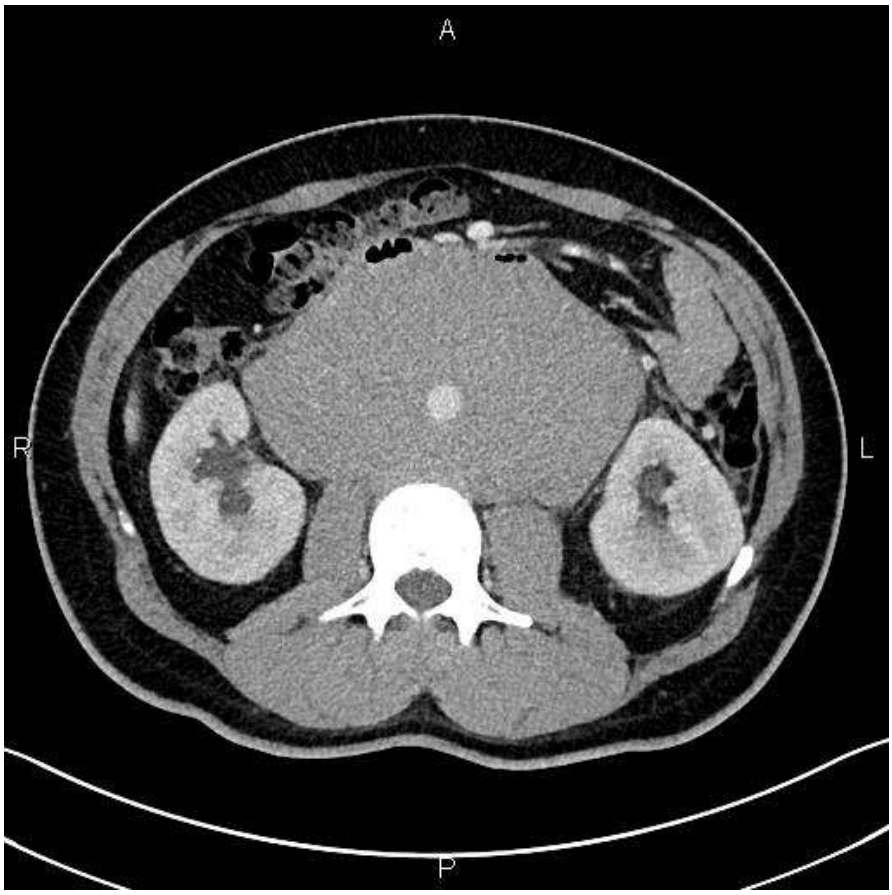

Figure 1. CT transversal.

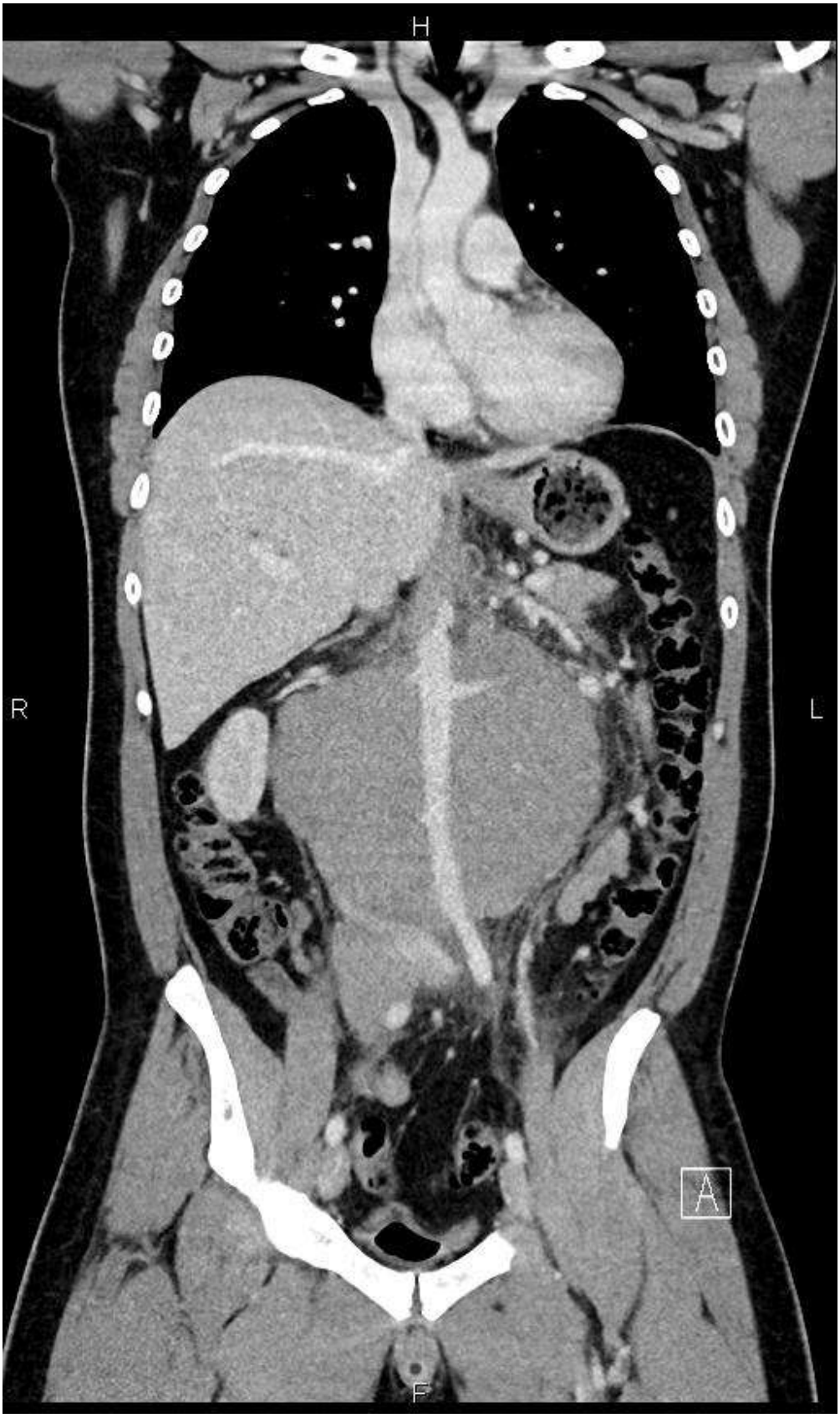

Figure 2. CT frontal.

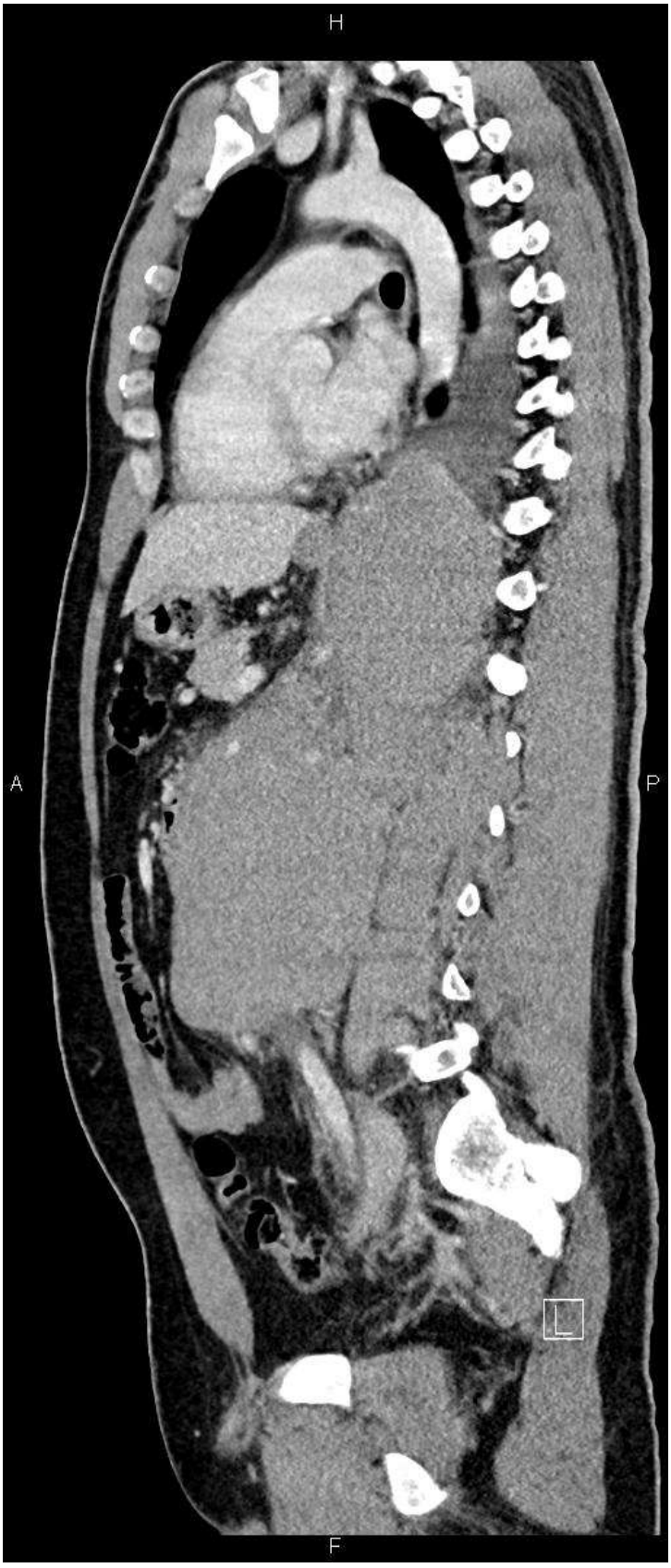

Figure 3. CT sagital.

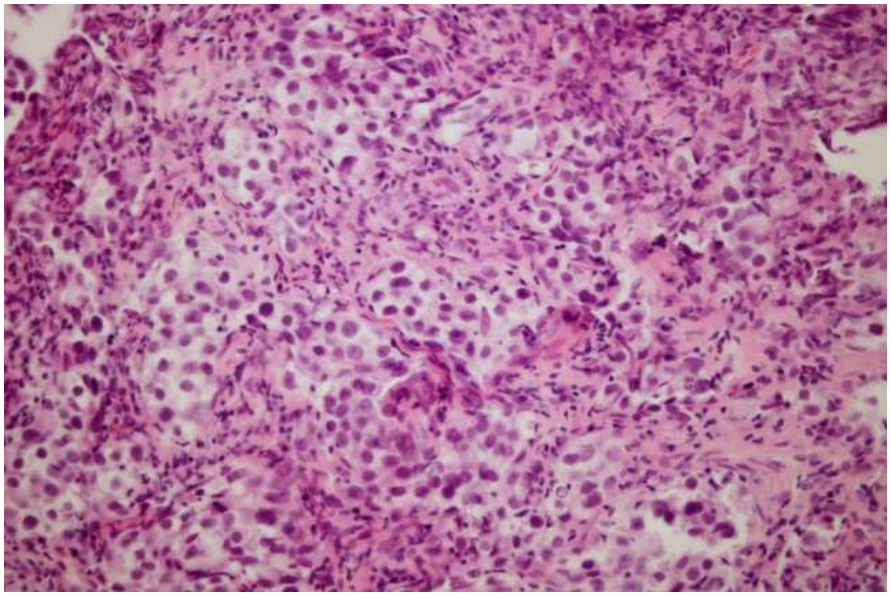

Figure 4. Biopsy Hematoxilin eosin staining.

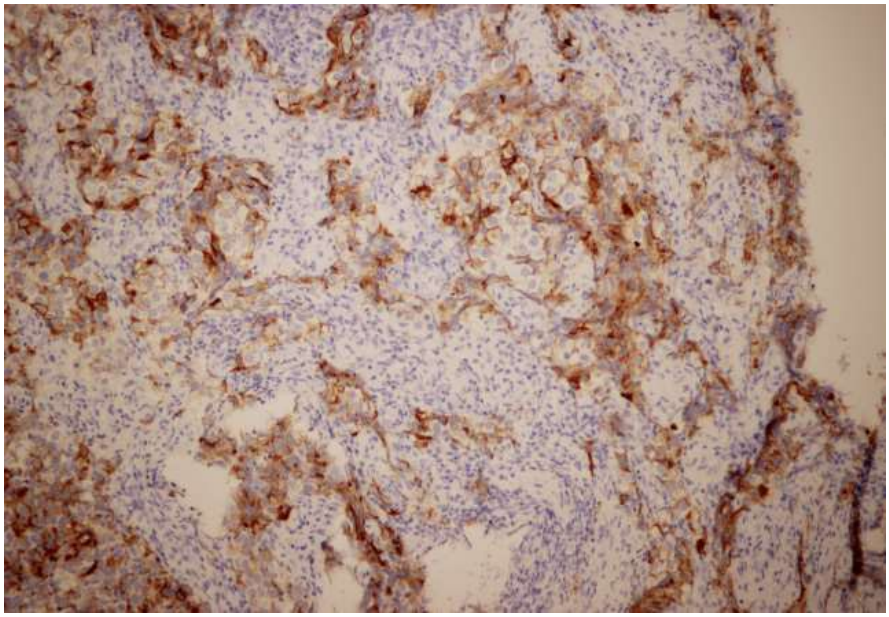

Figure 5. Biopsy Placental alkaline phosphatase staining.

increased in dysgerminoma cells [11] [12]. Seminomas have seldomly been associated with malignant hypercalcemia. Similarly hypercalcemia associated with dysgerminoma and elevation of calcitriol are very rare and have been reported in 14 cases in literature reviews [13]. These solid tumors with increased 1,25-dihydroxyvitamin D production showed a good response when treated with glucocorticoids. In our case, we used furosemide for heavy hypercalcemia, which promotes urinary calcium excretion by inhibiting calcium reabsorption at the loop of Henle. They should only be administered after adequate intravenous hydration has been achieved. Second-line therapy with denosunab and bisphosphonates is recommended

in hypercalcemia due to high 1,25-dihydroxyvitamin D levels despite glucocorticoid treatment. In contrast to many other forms of malignancy, the development of hypercalcemia did not adversely affect the prognosis of patients with seminoma [14] [15].

Hypercalcemia in seminoma has been reported in 12 cases in literature [15] [16] [17] before this report. Common characteristics are no evidence of skeletal metastases, elevated calcium levels and normal or elevated phosphorus levels. Mean age at time of diagnosis was 44.1 years (range 35 - 59) [17]. Of those 12 cases, 5 reports measured calcitriol levels and in all 5, calcitriol levels were elevated.

The exact pathophysiological mechanism by which calcitriol is produced in seminomas is not well understood. Ectopic overexpression of 1α-hydroxylase has been reported to play a major role, but the full and complete mechanism still awaits elucidation [18].

4. Conclusion

Seminomas are the most common germ cell tumors in men, so it is important to be aware of them and not ignore rarely reported symptoms such as hypercalcemia.

Statement of Ethics

Ethical approval was not required for this study in accordance with local or national guidelines. Written informed consent for publication on this case report, and any accompanying images, was obtained from the patient.

Autor Contributions Statement

Alexander Kreze conceived the study, Alexander Kreze, Quynh Vu, Oliver Kuchař and Jason Joachim Kolesár reviewed the literature, analysed data and wrote manuscript. Kristina Klemperová contributed to biochemistry and hormonal analysis and interpretation. Zuzana Špůrková worked on biopsy exams and results. Lenka Balážová was an in-patient treating oncologist. All contributors approved the final version of the manuscript.

Data Availability Statement

All data generalized or analyzed during this study are included in this article. Further inquiries can be directed to corresponding author.

Conflicts of Interest

The authors declare no conflicts of interest.

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