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CASE REPORT

Calcitriol-mediated hypercalcemia in a patient with bilateral adrenal non-Hodgkin's B-cell lymphoma case report

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Calcitriol-mediated hypercalcemia is a frequent manifestation of hematological malignancies. However, there are a few reports of cases presenting with increased angiotensin-converting enzyme (ACE) level, which suggests a possible mechanism similar to that of granulomatous diseases. We present a patient with hypercalcemia, normal parathyroid hormone, and parathyroid hormone-related protein levels but high calcitriol and ACE levels that, after further investigation, was diagnosed with bilateral adrenal non-Hodgkin's B-cell lymphoma. Primary adrenal lymphoma represents only 1% of all non-Hodgkin's lymphomas and is usually asymptomatic but should be considered by clinicians among the malignancies that cause calcitriol-mediated hypercalcemia.

Keywords: *non-Hodgkin's lymphoma*; *primary adrenal lymphoma*; *calcitriol-mediated hypercalcemia*

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As a result of the increased use of computed tomography (CT) and magnetic resonance imaging (MRI) in clinical practice, there has been a reported increase of adrenal incidentalomas, with the latest data indicating a prevalence range between 0.4 and 4.4% (1). These incidentalomas can be benign cortical adenomas, endocrine tumors, metastases from malignant tumors, or lymphomatous involvement from widespread lymphoma. However, primary adrenal lymphoma (PAL) is a very rare entity. PAL represents less than 1% of all non-Hodgkin's lymphomas with a total of approximately 100 cases reported in the literature. The initial clinical presentation can be subclinical or range from non-specific symptoms like abdominal pain, back pain, or fever to more specific symptoms related to adrenal insufficiency (2–6).

To date, of the 100 cases of PAL in the literature, only four cases of adrenal lymphoma with hypercalcemia have been reported. Of these four cases, postmortem reassessment revealed the etiology to be an increased parathyroid hormone–related protein (PTH-RP). In this report, we present a patient with PAL and calcitriol-mediated hypercalcemia with increased angiotensin-converting enzyme (ACE) level (7, 8).

Case

An 81-year-old man with past medical history of hypertension, chronic kidney disease, and chronic back pain presented with weight loss, decreased appetite, and abdominal pain of 4 weeks duration. Supplemental history provided by the family indicated that he had become more withdrawn and lethargic over a poorly defined but recent time course. He was not on vitamin D, calcium supplements, or diuretics. After evaluation, it was found that he was hemodynamically stable, and his cardiovascular and abdominal analyses were unremarkable, but his neurological analysis revealed a new unsteadiness of his gait, mild confusion, and a tangential thought process. Laboratory evaluation revealed significant hypercalcemia, an elevated creatinine from baseline, normal 25-hydroxyvitamin D but elevated 1,25-dihydroxyvitamin D, elevated ACE level but normal PTH and PTH-RP (Table 1).

In the emergency department, due to the change in mental status, the patient received CT scans of the brain and chest which were normal, but CT of the abdomen revealed a 1.5×4 cm right adrenal mass and a $10 \times 8.4 \times 7.4$ cm heterogeneous left adrenal mass with no other positive findings in pelvis (Fig. 1). Bone nuclear medicine

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Table 1. Laboratory results: endocrine workup for adrenal incidentaloma

Lab	Value	Reference value
Corrected calcium	11.8 and 14 mg/dl	8.5–10.5 mg/dl
Creatinine	2.41 mg/dl	0.5–1.5 mg/dl
Phosphorous	3.7 mg/dl	2.5–4.6 mg/dl
PTH	34 pg/ml	15–88 pg/ml
PTH-RP	0.7 pmol/Lt	<2 pmol/Lt
25-Hydroxyvitamin D	34 ng/ml	25–80 ng/ml
1,25-Dihydroxyvitamin D	90 pg/ml	18–78 pn/ml
Angiotensin-converting enzyme	100 U/L	8–53 U/L
Cortisol	10.3 mcg/dl	8.7–22.4 mcg/dl
ACTH	50 pg/ml	10–60 pg/ml
DHEA-S	33.5 μg/dl	5–253 μg/dl
Metanephrine free	<0.20 nmol/L	<50 nmol/L
Testosterone	3.9 ng/dl	9–30 ng/dl
Estradiol	<20 pg/ml	20–75 pg/ml

scan with technetium (Tc-99m) showed no osseous evidence of metastatic disease, and skeletal bone survey did not identify any lytic lesions. The rest of the endocrine workup was normal including cortisol, thyroid hormones, Adrenocorticotropic hormone (ACTH), Dehydroepiandrosterone sulfate (DHEA-S), metanephrines, testosterone, and estradiol (Table 1). Flow cytometry showed mixed phenotype and immature monocyte population A left adrenal mass core biopsy was reported as large B-cell lymphoma with non-germinal center and diffuses reactivity for CD20 and for CD43 (Figs. 2 and 3).

The patient's hypercalcemia was treated with IV fluids, calcitonin, and pamidronate with good response, and serum calcium normalized by day 4 to 10.5 mg/dL. The patient began rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP), but he died after 3 months.

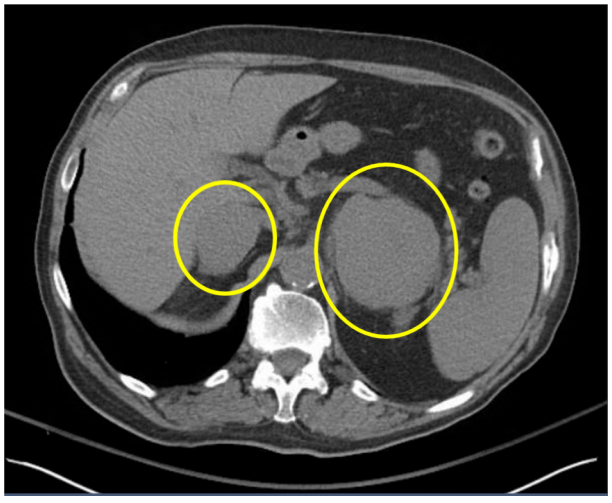

Fig. 1. CT findings: 5 × 4 cm right adrenal mass and 10 × 8.4 × 7.4 cm left adrenal mass with minimal surrounding inflammation.

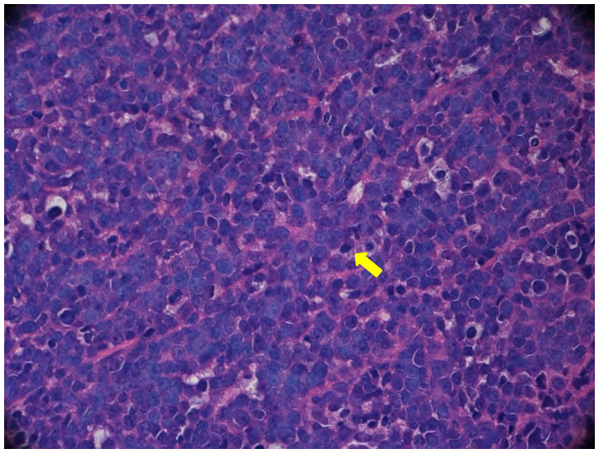

Fig. 2. Pathology report high-power view – positive for neoplastic lymphoma cells. High volume of lymphocytes showing high nuclear-cytoplasmic ratios (arrow).

Discussion

Within the last decade, the increase in abdominal imaging studies has raised the rate of discovery of incidental anomalies in the adrenal glands. The majority are just incidentalomas, also known as benign anatomical mistakes, and, most frequently, they do not have any clinical consequences. However, the appropriate workup has been under discussion for some years because the extensive evaluation performed in some patients can lead to unnecessary testing and treatment while trying to find extremely unlikely diagnoses (5, 9).

The most feared diagnosis of adrenal cancer is always a concern and the prevalence of malignancy in adrenal masses varies from 4.2 to 25% according to different

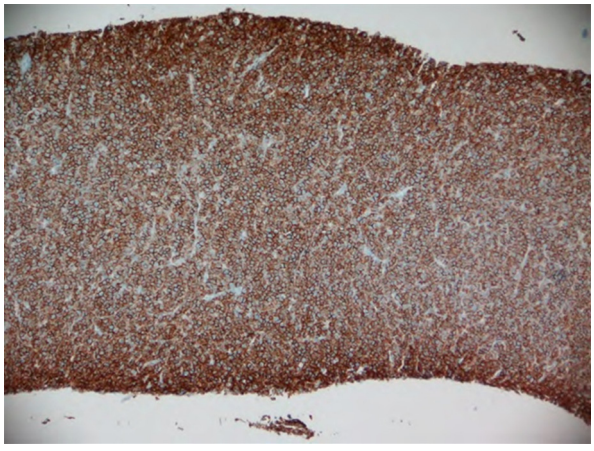

Fig. 3. Pathology report: Large B-cell lymphoma non-germinal center type. Neoplastic cells show diffuse reactivity for CD20 and for CD43. Background T cells are reactive for CD3. No reactivity for pan-cytokeratin, CD56, S-100 protein, chromogranin, synaptophysin, or TTF-1.

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series (10). Therefore, the internal medicine physician should guide further workup according to clinical and general laboratory findings.

In our case, the patient presented with abdominal and back pain accompanied by hypercalcemia, which is often noted in patients with malignancies. This hypercalcemia can be a consequence of metastatic bone lesions or humoral hypercalcemia of malignancy (HHM) caused by different agents produced by neoplastic cells. Among patients with hematological malignancies and hypercalcemia, lymphoma is the cause in approximately 5.6% of the cases, but this is usually related to PTH-RP production; in our patient, the values of PTH and PTH-RP were completely normal while there were increased calcitriol and ACE levels, inconsistent with HHM (11).

Previous reports of non-Hodgkin's lymphoma associated with hypercalcemia and increased serum ACE have speculated about a mechanism akin to that of sarcoidosis, in which production of lymphokines activate macrophages to produce 1,25-dihydroxyvitamin D3 (calcitriol) (12). Elevated levels of calcitriol were demonstrated in our patient, suggestive of a similar etiology.

Our patient did have bilateral adrenal masses which is a common finding (70%) in PAL, and the pathology report was consistent with the most common histology finding of diffuse large B-cell lymphoma (13). Men are the most affected, with an age interval between 39 and 89 years, and the most common symptoms at presentation include abdominal or back pain, fever and signs of adrenal insufficiency, some of which were present in our patient, but he did not ably have a normal cortisol level (13, 14).

The pathophysiology of PAL has not yet been well elucidated. Some of the theories include viral infections, for example, Epstein–Barr virus, or autoimmune-related infections (15). Unfortunately, PAL has a very poor prognosis, even with active treatment with chemotherapy. Some studies have tried to use rituximab-containing chemotherapy with initial better results, but the best treatment is still to be determined (6). In this reported case, the patient had a fatal outcome within 3 months, even with the initiation of chemotherapy.

Conclusions

Patients with PAL, despite its poor prognosis, can be asymptomatic for long periods of time and are sometimes only found during autopsy. With the increased usage of abdominal imaging, adrenal incidentalomas should be worked up according to clinical and laboratory findings for different causes, including lymphoma and metastases. This is especially the case if the patient is elderly and/or has a bilateral presentation because of the high prevalence of malignancy.

Hypercalcemia should be evaluated initially with renal function, medication reconciliation, and PTH as first step that will guide the diagnosis between PTH-dependent or PTH-independent causes, thereby limiting further studies to those appropriate to the mechanism. Early diagnosis of this type of non-Hodgkin's lymphoma may impact the poor prognosis and extend life expectancy. Further research may improve the options for future treatments.

Conflict of interest and funding

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