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Review Article

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A RARE CAUSE OF HYPERCALCAEMIA

Dr. Adel Ekladious* and Agbayani Evangeline

Medical School of Health and Medical Science, University of Western Australia.

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***Corresponding author: Adel Ekladious**
Associate Professor, Medical School of Health and Medical Science, University of Western Australia.
Email ID: ekladiou@gmail.com, agba0006@flinders.edu.au,
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ABSTRACT

A 50-year old female with hypercalcaemia has been diagnosed with sarcoidosis. She came with a history of anorexia and fatigue and investigations have shown extensive pulmonary fibrosis, lytic lesions on the skull and hips, along with hypercalcaemia, hypercalciuria, nephrocalcinosis and elevated 1,25 dihydroxyvitamin D levels. Both CT guided biopsy of the mediastinal lymph nodes and bronchial biopsy and washings confirmed non-caseating granulomas which is a hallmark of but not specific to sarcoidosis. She was treated with prednisolone 30mg daily which eventually resulted into normal metabolic activity on a PET-CT scan 2 months after the initiation of treatment. Raised 1,25 dihydroxyvitamin D level is common in sarcoidosis. Measuring 1-25 hydroxyvitamin D should be a part of the workup on patients who have hypercalcaemia because it can aid in ruling out or ruling in the possibility of non-malignant granulomatous diseases.

KEYWORDS: hypercalcaemia, hypercalciuria, nephrocalcinosis.

A 50-year old female presented for a preoperative workup for her upcoming elective cholecystectomy of two 3-centimetre gall bladder polyps. She has been complaining of dyspeptic symptoms and for the last 3 months, she reports anorexia and easy fatigability.

She has a background history of type 2 diabetes and had a low trauma fracture in her right thumb. Familial history revealed that her mother has been diagnosed with osteoporosis at the age of 40 while her dad has been diagnosed with multiple myeloma at the age of 50 which has been treated with stem cell transplantation and has been in remission since.

Investigations showed anaemia with a haemoglobin of 100g/L. Iron studies were normal. Urea, electrolytes are within normal range and creatinine is 170micromol/L. Liver function tests showed normal AST and bilirubin with a serum albumin of 40g/L and an elevated total protein of 80g/L. Serum calcium is elevated at 3mmol/L. CT chest showed mediastinal lymphadenopathy.

On examination, the patient has been found to be pale. Vital signs were within normal limits. The patient was afebrile. Cardiorespiratory exam was unremarkable. Abdominal exam was normal and there was no organomegaly. Limb, skin and joint examinations were also normal.

Metformin has been identified as the cause of dyspepsia. Gastrointestinal adverse events have been associated with metformin including indigestion or dyspepsia.[1]

The patient was assessed for eating disorders, multiple myeloma, lymphoma and gall bladder cancer. Urinary calcium has been looked at to investigate hypercalcaemia further and an abdominal ultrasound to rule out gall bladder cancer. Abdominal ultrasound showed no pathology but urinary calcium is elevated to 800mg/24 hours.

Possible causes for hypercalcuria including familial hypercalcuria has been ruled out. The patient was also investigated for multiple myeloma given the hypercalcaemia, kidney injury and anaemia however, test results have scratched it off the list of differentials.

A DEXA scan was performed which showed a T score of -4SD which corresponds to osteoporosis. Denosumab 120mg/1.7ml every 6 months was initiated. There was a suppression of the parathyroid hormone (PTH) 10pg/mL at that time. Alkaline phosphatase was normal while 25-hydroxyvitamin D which is about 20ng/ml was low and phosphate level was elevated to 3.5mg/dL.

Bone marrow biopsy and trephine biopsy showed 70% cellularity with 3% blast cells and some fat cells. No

clonal populations were found on flow cytometry and bone marrow and peripheral blood FISH was unremarkable. CT chest was done which showed extensive pulmonary fibrosis.

The patient has reported occasional headache without any nausea or vomiting. Neurological examination including fundi exam were unremarkable.

Hip x-ray and skull x-ray showed extensive lytic lesions which broadened the differentials to non-secretory multiple myeloma, hyperparathyroidism, lymphoma, sickle cell disease, paget's disease of the bone, thalassemia, disseminated malignancy, eosinophilic granuloma (histiocytosis X), osteomyelitis and metastatic breast cancer.

A repeat intact PTH was done and was low normal. 25-hydroxyvitamin D remains low and 1-25 dihydroxyvitamin D was elevated. Parathyroid related hormone peptide was detectable. Alkaline phosphatase was normal and tumour markers were negative.

The renal tract was imaged which showed nephrocalcinosis. Further investigations ruled out hyperthyroidism and adrenal insufficiency. The patient denies any herbal or over the counter medication use.

Consultation with an endocrinologist and respiratory physician was sought which resulted into a decision to do a multiple lymph node biopsy via bronchoscopy and repeat bone biopsy and flow cytometry.

CT guided biopsy of mediastinal lymph nodes showed non-caseating granulomas which is a histological characteristic of sarcoidosis.[2,10-11] There were no atypical cells or monoclonality on histological analysis and immunohistochemical staining. There was no evidence of amyloid deposit. Mycobacterial and fungal stains were negative. The bronchial biopsy and washings confirmed non-caseating granuloma which lead to the diagnosis of Sarcoidosis.

The patient has been started with prednisolone 30mg daily.[6-8] Steroid therapy is the standard treatment for sarcoidosis unless resistant and on that instance, a steroid-sparing agents can be used.[2,12-14] A PET-CT scan was done after 2 months which did not show any abnormal metabolic activity and haemoglobin was up to 150g/L. Adalimumab was added to the medication regime as a steroid-sparing agent.[12-14]

DISCUSSION

Calcium concentration in the serum is maintained by mechanisms involving the parathyroid glands, kidneys, bones and vitamin D hydroxylation. [19] Ninety percent (90%) of the cases of hypercalcaemia is caused by primary hyperparathyroidism and malignancy while the remaining 10% is due to other diseases such as phaeochromocytoma, hypervitaminosis D and non-malignant granulomatous disorders among others.[18-19, 21]

The current diagnostic approach to hypercalcaemia is towards differentiating if the calcium imbalance is due to primary hyperparathyroidism or malignancy and this involves testing for serum parathyroid hormone (PTH) which would differentiate if the hypercalcaemia is PTH or non PTH related.[21] Subsequently, 1,25 dihydroxyvitamin D is measured when PTH is normal to low normal to rule out lymphoma and granulomatous diseases.[21] 1,25 hydroxyvitamin D elevation makes the diagnosis of granulomatous disorders such as sarcoidosis highly probable.[10]

Sarcoidosis is a systemic disease that is characterised histologically by non-caseating granulomas and can affect different organ systems such as skin, liver and spleen but is mainly found in the lungs and mediastinal lymph nodes.[2,5] Only around 3-5% of those with sarcoidosis have bone disease with the small bones being more frequently affected whereas skull and pelvis involvement can be rare.[5] There is no particular standard in diagnosing sarcoidosis but is considered when other causes of granulomatous disorder has been ruled out.[2,10] The clinical presentation can vary from a patient being asymptomatic to a rapidly progressing disease which can lead to death.[2,5] It can also be characterised by relapses and recurrence after treatment is possible.[2,4]

Hypercalcaemia in sarcoidosis has been attributed to the ability of the macrophages to release 1-α hydroxylase which converts 25-hydroxyvitamin D to 1,25-hydroxyvitamin D.[16-18] A study which examined 101 cases of hypervitaminosis D mediated hypercalcaemia showed that 49% of these cases are caused by sarcoidosis.[18] With elevated 1,25 dihydroxyvitamin D, the expression of receptors that are involved in cell fusion and granuloma formation is increased, thus elucidating the presence noncaseating granulomas in sarcoidosis.[17]

Present guidelines for the investigation of hypercalcaemia does not include testing for 1,25 dihydroxyvitamin D. Its utility has not been supported because it is not comprehensively studied.[10] However, it is noted in the American Thoracic Society recommendations regarding sarcoidosis that 1,25 dihydroxyvitamin D levels can be an indicator of granuloma formation and possibly its magnitude.[10] Measurement of its levels should be part of the workup in investigating hypercalcaemia as it can rule in or rule out the possibility of granulomatous conditions in the list of differentials. Sarcoidosis is a rare cause of hypercalcaemia which can be treated with steroid and steroid-sparing agents.[2,14,20] Early detection could prevent progressive organ damage and reduce morbidity and mortality associated with it.

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