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Beyond Primary Hyperparathyroidism and Malignancy : A rare case of Humoral hypercalcemia of Benignancy

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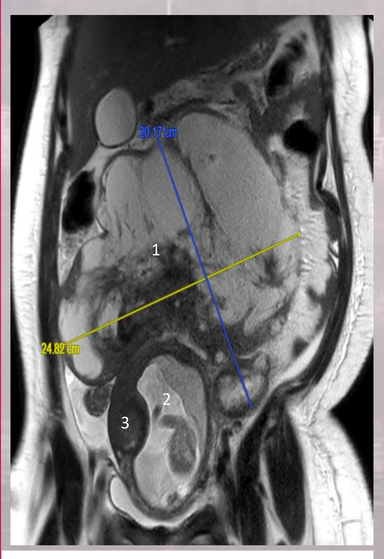
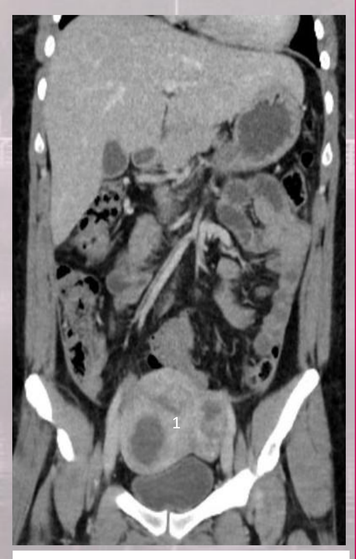
INTRODUCTION

Benign tumours, though rare contributors, can lead to hypercalcemia, as in this case, uterine leiomyoma. Hypercalcemia associated with uterine leiomyoma is a rare but important differential diagnosis to consider in women with unexplained hypercalcemia. The mechanism of hypercalcemia in uterine Leiomyoma is thought to be mediated by the production of PTHrP. The resolution of hypercalcemia following the removal of uterine fibroids in the handful of reported cases supports the association between uterine leiomyoma and PTHrP-mediated hypercalcemia. Uterine leiomyoma should be considered a potential cause of hypercalcemia in the absence of any other apparent malignancy in women presenting with parathyroid independent

Imaging



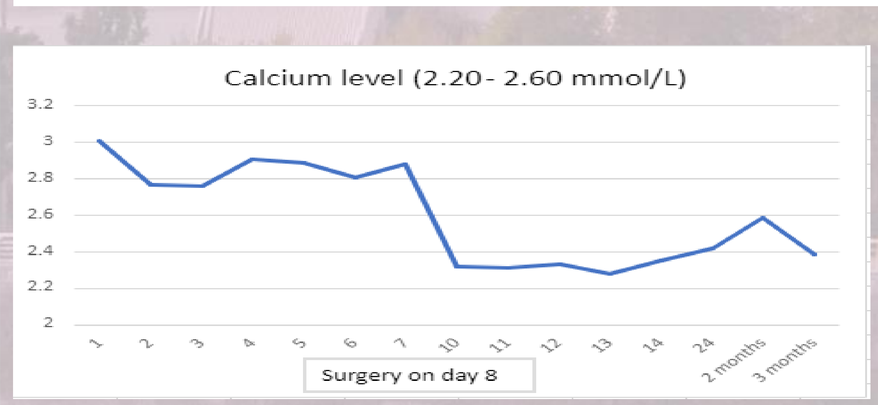
MRI before Surgery : (1) Large pedunculated torted necrotic fibroid (2) Gravid uterus (3) Smaller non-necrotic fibroid

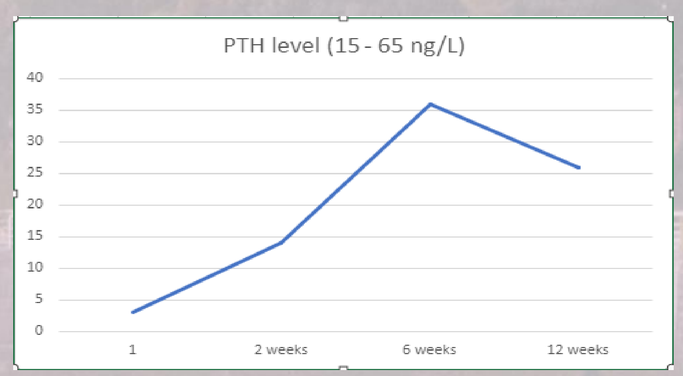


CT Post Surgery after one month : Large necrotic fibroid has been excised with (1) uterus left behind

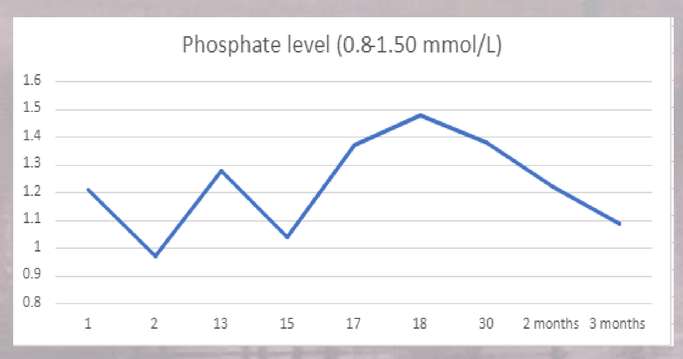
CASE

We report an interesting case of hypercalcemia in a 27-year-old pregnant woman with history of Uterine fibroids.The patient arrived at ED with two weeks history of worsening lower abdominal pain. There was no vaginal bleeding and bowels were not opened for four days. Physical examination revealed dehydration, tenderness in the lower abdomen with an abdomen larger than expected for her gestational age of 14 weeks.
Investigations revealed a calcium level of 3.01 mmom/L with normal kidney function. PTH was suppressed, and vitamin D was low. A subsequent renal ultrasound exhibited no significant abnormalities. Unfortunately assays for PTHrP were not available for testing in UK labs. Treatment continued with intravenous hydration. Initial low radiation imaging studies with a chest x-ray and a neck ultrasound demonstrated no remarkable findings prompting the decision to proceed with an abdominal and pelvic MRI (see image).
The MRI revealed a large necrotic uterine mass, likely to represent a fibroid with moderate volume ascites. Following discussion in the MDT, she underwent laparotomy, open myomectomy and partial subcolic omentectomy at 15 weeks of gestation. A 30 cm pedunculated fibroid was successfully, excised biopsy revealed leiomyoma.
Calcium levels rapidly normalised post-surgery accompanied by a rise in PTH. Sadly, three days after surgery, she had a miscarriage despite calcium remaining within the normal range. Repeat calcium and PTH levels 3 months after surgery have remained normal and cross sectional imaging showed no concerning findings.





Blood tests	Before removal of Uterine Leiomyoma	Post-Surgery	3 months After surgery
Calcium (2.20-2.60 mmol/L)	3.01	2.32	2.39
PTH (15 – 65 ng/L)	3	14	26
Phosphate (0.8 -1.50 mmol/L)	1.21	1.28	1.09



Discussion

In approximately 90% of cases, hypercalcemia can be attributed to primary Hyperparathyroidism or malignancy. However, when these factors are excluded, it becomes Imperative to investigate less conventional aetiologies. Hypercalcemia associated with malignancy is a well-established phenomenon, affecting around 20-30% of cancer patients, with a notable prevalence in bone and lung cancers due to the overproduction of PTHrP. PTHrP exhibits a PTH-like biological activity, particularly within its initial 34 amino acids, encompassing the receptor binding and activation domains. Both PTH and PTHrP share similar functions by promoting bone resorption and reducing calcium excretion. In the context of benign tumours, hypercalcemia is a rare occurrence and has been documented in conditions such as uterine leiomyoma, Giant pilomatricoma benign kidney tumours, benign pheochromocytomas, sarcoidosis, systemic lupus erythematosus, HIV-associated lymphadenopathy, and during pregnancy or lactation .While instances of hypercalcemia associated with uterine leiomyoma are infrequently reported, our case adds to the limited body of knowledge in this regard. It is believed to be associated with the production of PTHrP. Notably, PTHrP expression is elevated in uterine fibroids compared to normal myometrium. The resolution of hypercalcemia observed in our case following the removal of uterine fibroids underscores this association. Therefore, uterine Leiomyoma should be considered a potential cause of PTHrp-mediated hypercalcemia in the absence of any other apparent malignancy

Key Points

1. Malignancy is a frequent cause of parathyroid independent hypercalcemia.
2. Hypercalcemia originating from a benign tumor is exceedingly rare.
3. Uterine leiomyoma is a potential source of hypercalcemia, with a suspected mediator being parathyroid hormone-related peptide (PTHrP)
4. Uterine leiomyoma should be considered a potential cause of hypercalcemia in the absence of any other apparent malignancy in women presenting with parathyroid independent hypercalcaemia

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