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# Novel treatment for refractory hypercalcaemia.

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## Introduction:

Hyperparathyroidism is the commonest cause of significant hypercalcaemia in older patients, but haematological disorders such as myeloma frequently present in this way also.

## Case history :

We present a 92-year-old lady who was found to have incidental hypercalcaemia (calcium 3.50 mmol/l) on routine testing. She was admitted with reduced mobility and was relatively asymptomatic at presentation with no cognitive impairment, thirst, polyuria, constipation or renal impairment. Biochemical investigations ( vitamin D, immunoglobulins, Bence Jones proteins) were normal except raised PTH of 34pl/L. US revealed the presence of widespread lymphadenopathy, no parathyroid mass and MIBI was negative. She underwent lymph node biopsy and histology confirmed a low grade B cell non Non-Hodgkin's lymphoma (Stage 3A marginal zone lymphoma). She had no B symptoms and her LDH was not elevated. Calcium levels failed to come down on initial hydration and repeated bisphosphanate therapy.

Chemotherapy was not immediately initiated, as this was a histologically low-grade disease with no B-symptoms, and was thought unlikely to account for her hypercalcaemia. She was commenced on cinacalcit with no response, so finally she was initiated on Ritxuimab and oral Chlorambucil and steroids (Prednisolone) and chemotherapy was continued to complete 6 full cycles. After 6 months, calcium came down to normal levels and repeat imaging with PET/CT confirmed good response to chemotherapy confirming complete metabolic remission. Repeat PTH levels following completion of treatment came down to normal levels.

| Test | Results on admission | Results after 6 months | Normal values |
|---|---|---|---|
| Parathyroid hormone(PTH) (pl/L) | 34 | 2.2 | 9-18pl/L |
| Sodium (mmol/L) | 130 | 135 | 133-146 |
| Potassium (mmol/L) | 4.2 | 4.5 | 3.5-5.3 |
| Urea(mmol/L) | 5.2 | 6 | 2.5-7.8 |
| Creatinine (mmol/L) | 66 | 88 | 50-120 |
| e-GFR (mL/min) | >60 | >60 | >60 |
| Po4(mmol/L) | 1.03 | 0.88 | 0.80 - 1.50 |
| Calcium (mmol/L) | 3.58 | 2.35 | 2.20-2.60 |
| LDH(U/L) | 396 | 270 | <500 |
| Serum ACE (U/L) | 20.8 | | 20 - 70 |
| Vitamin D(nmol/L) | 19 | | 75 - 200 |
| Myeloma screen | Negative | | |
| Haemoglobin(mg/dL) | 8.7 | 9.8 | (11.5-16.5) |

## Discussion:

This is a challenging case of hypercalcaemia in malignancy . Hypercalcaemia is relatively uncommon in lymphoma, but when it is seen it is generally a feature of histologically high grade disease with other aggressive clinical features, such as the presence of B symptoms and elevated lactate dehydrogenase (LDH). The mechanism of hypercalcaemia is unknown but there is strong evidence for humoral factors that may or may not be related to parathyroid hormone (PTH).

The majority of humoral hypercalcaemias are caused by tumour produced parathyroid hormone related protein (PTHrP). In lymphomas, tumour production of 1,25-dihydroxyvitamin D ( calcitriol) can also be responsible for this. Extremely rarely production of parathyroid hormone(PTH)itself by the tumour is possible but only a few cases of these are reported.

In this particular patient, PTHrP levels were undetectable. Studies of PTHrP assays revealed these assays (like all immunometric assays) are susceptible to false negative results at extremely high concentrations ("hooking") and also rare false positive results due to heterophile antibody interference.

In the presence of lymphoma , tumour cells producing 1,25-dihydroxyvitamin D (calcitriol) responds very well to steroids. Calcitriol levels were not measured in this particular patient, but expected to be undetectable. Laboratory studies have shown when 1,25-dihydroxyvitamin D (calcitriol) levels were high, PTH levels are undetectable.

In this case , hypercalcaemia could well be multifactorial. Although slandered imaging did not identify co-existing primary hyperthyroidism it can still be a possibility . And also ectopic production of PTH from lymphoma cells (although this is extremely rare) can be listed as a differential. It is equally fascinating that hypercalcaemia was very resistant to standard management and responded well to steroids and chemotherapy with PTH levels coming down to normal levels following completion of therapy.

## References:

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