HUMORAL HYPERCALCEMIA IN ENDOMETRIAL CARCINOMA - A RARE COMPLICATION

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ABSTRACT

Humoral Hypercalcemia of Malignancy is rarely associated with endometrial carcinoma. We report a case of a 75 year old female who presented with increasing drowsiness. A detailed blood biochemical evaluation revealed Hypercalcemia. MRI abdomen and pelvis revealed the underlying endometrial carcinoma. Detailed evaluation revealed Humoral Hypercalcemia of Malignancy as the cause of encephalopathy. Patient was started on vigorous hydration and loop diuretics to induce calciuresis for which the patient responded and consciousness normalized by the next 2 days. This report throws light into paraneoplastic entity and its management.

Key-words: Humoral Hypercalcemia of Malignancy, Paraneoplastic syndrome, Endometrial Carcinoma

Key Messages: Humoral Hypercalcemia of malignancy as paraneoplastic manifestation gynaecological malignancies should be borne in mind in view of frequent association in recent years.

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INTRODUCTION

Hypercalcemia has been reported to occur in 20% - 30% of patients with cancer sometime during the course of illness. [1] It could be either due to direct invasion of bone by the malignancy or due to humoral factors. [2] Humoral hypercalcemia of malignancy (HHM) caused by endometrial cancer is very rare. [3, 4] In this report, we report a case of poorly differentiated endometrial carcinoma with no bony metastasis presenting as hypercalcemic encephalopathy.

CASE HISTORY:

A 75 year old female presented with increasing drowsiness of 4 days duration. She was a known diabetic and hypertensive on regular treatment. Patient was diagnosed as having urinary tract infection a week ago and was treated with parenteral levofloxacin. Menstrual history, family history and personal history were non-contributory.

On examination, patient was pale. Vitals were stable. No abnormality was detected on systemic examination. No localizing sign found on central nervous system (CNS) examination. Baseline investigations revealed anaemia (Hb-10.5 g/dl, Peripheral smear- normocytic normochromic blood picture) with high white cell count (TC-22.2 x10^9 cells/mm^3, Neutrophils-85%, Lymphocytes-12%, monocytes-1%, Basophils-2%). Random blood sugar was 3.5mmol/L. Routine urine examination showed no abnormality. Renal function test showed raised serum creatinine (203.3 µmol/L). Thyroid profile was normal. Serum electrolytes (Sodium, Potassium and Chloride) and Arterial Blood Gases were in the normal range. Blood and Urine culture showed no growth. CT brain (plain) and CSF (routine, TB-PCR, HSV-PCR) were normal. A provisional diagnosis of metabolic encephalopathy was made and was continued on parenteral antibiotics for the treatment of urinary tract infection.

When there was no symptomatic improvement, further investigations were ensued. Serum calcium was high (3.8 mmol/L). The patient was evaluated for the aetiology of Hypercalcemia. Serum phosphorus was normal (0.8 mmol/L). Intact Parathyroid Hormone (PTH) was low (6.10 pg/ml). Serum cortisol, Serum Angiotensin Converting Enzyme level and vitamin D level were normal. Test for serum Anti-Nuclear Antibody was negative. Serum electrophoresis showed mild hypoalbuminaemia, otherwise normal.

Ultrasonography of abdomen and pelvis showed enlarged uterus with heterogenous echotexture with thickened endometrium. MRI abdomen and pelvis showed bulky uterus with irregular lobulated surface with loss of endomyometrial junction. Extensive paraaortic and bilateral iliac lymphadenopathy was seen. Moderate hydronephrosis on right side due to infiltration of mid-ureter by para-aortic nodes was noted. MRI brain, spine and thorax were normal.
Excision biopsy of endometrium was done. A differential diagnosis of undifferentiated carcinoma or angiosarcoma was made. CD 31, the pathognomonic marker of angiosarcoma was negative. Further cytogenetic studies for the differentiation (CD30, CD34, Lymphocyte Common Antigen, HMB-45, S100 protein, Smooth Muscle Antigen and Cytokeratin) were negative. The malignancy was confirmed as poorly differentiated endometrial carcinoma and diagnosis of HHM with hypercalcemic encephalopathy was made.

Since the tumour was aggressive, the patient was started on palliative treatment. The patient was started on calcium reducing measures for which the patient responded well. Two days later, the patient suffered massive myocardial infarction from which the patient could not be revived.

**DISCUSSION**

Hypercalcemia is known to present with a wide range of symptoms. [5] CNS symptoms include apathy, altered cognition, drowsiness, obtundation and coma. Whenever hypercalcemia is confirmed, a definitive diagnosis must be established. The most common cause of hypercalcemia in adults is primary hyperparathyroidism followed by malignancy. Hypercalcemia due to hyperparathyroidism manifests with elevated serum calcium, low or normal phosphate level and elevated PTH. [6]

Hypercalcemia in malignancy is the most common paraneoplastic syndrome. The prognosis of the condition is very poor- survival is less than 6 months if hypercalcemia is apparent at the time of presentation. [7]

The primary cause of Hypercalcemia in malignancy is from bone resorption. There are two distinct mechanisms causing tumour induced bone resorption- either by local autocrine or paracrine effects by tumour cells following bone metastasis or by Humoral effect of tumour derived factors. The latter is the most common cause of Hypercalcemia in malignancy even in malignancies with bone metastasis such as breast cancer or prostate cancer. [7]

The concept of HHM was first reported by Boyd and Lodenson in a case of uterine cancer in 1956. [8] It is common in solid tumours but otherwise uncommon in patients with gynaecological malignancies. Recently gynaecological malignancies are frequently being reported with manifestations of Hypercalcemia. [9] A series of gynaecological malignancies manifesting with Hypercalcemia studied by Stewart et al, reported that humoral mechanisms were responsible for Hypercalcemia in all cases in the series. [10]

Ovarian carcinoma is the most common gynaecological cancer manifesting as HHM. Endometrial cancers are also reported with HHM but as a rare phenomenon. Kinugasa et al reported a case of Parathyroid hormone related protein (PTHrP) producing endometroid adenocarcinoma in a 32 year old nulliparous woman. [3] Buller and co-workers reported paraneoplastic
Hypercalcemia associated with endometrial adenocarcinoma with PTHrP production. [11]

The criteria for HHM are 1) Malignancy without any bone metastasis; 2) Hypercalcemia ranging from 3.20 to 3.52 mg/dl; 3) normal or low serum parathyroid hormone levels; 4) reduced tubular resorption of phosphate; and 5) reduced serum albumin levels. [7]

The major etiological factor causing HHM is PTHrP. The amino terminal of PTHrP is homologous to PTH. Binding of PTHrP to bone and kidney PTH receptors results in hyperparathyroid picture-increased bone resorption, decreased calcium excretion and increased phosphate excretion in kidneys. The other factors speculated to cause HHM are tumour derived interleukins-interleukin-1 or 6. [6]

There are presently no guidelines available for the treatment of hypercalcemia associated with malignancy. Once the other probable co-existing causes of hypercalcemia are ruled out, the treatment is directed to reduce the serum calcium level. Vigorous rehydration depending on the patient’s cardiovascular and renal status, aggressive calciuresis and inhibition of bone resorption form the major lines of treatment. Serum calcium begins to fall within 12 hours after initiating the treatment and reaches plateau by four to seven days. It remains in the same levels for about two to three weeks by which time measures are taken to tackle the source of hypercalcemia.

CONCLUSION

We present a case of poorly differentiated endometrial carcinoma presenting with encephalopathy. The patient condition improved following calcium reducing measures. Raised serum calcium, with reduced PTH, malignancy without any bony metastasis or parathyroid pathology indicated the diagnosis of HHM. Hypercalcemia should be considered as a differential diagnosis when the usual causes of altered sensorium are ruled out, especially in a malignancy background.

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