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Hypercalcemia and Acute Kidney Injury in Malignancy

Authors
Dr Sameena Hussainy[1], Dr Pradeep Shenoy[2]
[1]PG Resident, Department of General Medicine, K.S. Hegde Medical Academy, Nitte University, Mangalore
[2]Assistant Professor, Department of Nephrology, K.S. Hegde Medical Academy, Nitte University, Mangalore, India

Abstract
Introduction: *Acute kidney injury (AKI) refers to an abrupt decrease in kidney function, resulting in the retention of urea and other nitrogenous waste products and in the dysregulation of extracellular volume and electrolytes. It is associated with increased morbidity and mortality.*
Case Presentation: *A 37 year old male presented with progressive sswelling and recurrent ulceration over right side of neck and malaise with extreme fatigability. He also consumes gutka very frequently since 8 years. On examination he was found to have large ulcer over the right supraclavicular region along with generalised lymphadenopathy, and hepatosplenomegaly. He was found to have anaemia (Haemoglobin -11 g/dl) acute renal failure (Serum creatinine - 2.54 mg/dl) and hypercalcemia (Serum calcium-17.1 mg/dl) and Vitamin D deficiency (Vitamin D – 5.37 ng/ml). Urine examination and PTH was normal. Ultrasound showed bilateral normal sized kidneys. On further evaluation, Ultrasound guided FNAC of the right axillary lymph node was done which revealed metastatic deposits favouring poorly differentiated squamous cell carcinoma. He was found to have a lesion in the right lung from which CT guided Biopsy was taken and he was diagnosed to have Non small cell lung carcinoma. Following management of hypercalcemia and AKI patient's renal function improved and was started upon chemotherapy for lung cancer.*
Conclusion: *Pulmonary carcinoma is the most common solid tumor to metastasize to the kidneys, followed by gastric and breast carcinomas. Although rare, few cases of Aacute renal failure resulting from metastatic solid tumor with widespread renal parenchymal infiltration have been reported in the literature. Hypercalcemia secondary to malignancy can also present with AKI. This is a case of Lung malignancy which presented with AKI secondary to hypercalcemia.*

Introduction

Acute kidney injury is common in patients with cancer. The incidence and severity vary, depending on the type and stage of cancer, the treatment regimen, and coexisting conditions. Patients with cancer who are critically ill have the highest risk of acute kidney injury (incidence 54%), particularly patients who have hematologic cancers or multiple myeloma and those with septic shock[1].

Hypercalcemia has been reported to occur in up to 20 to 30 percent of patients with cancer at some time during the course of their disease. This incidence may be falling owing to the wide use of bisphosphonates in patients with either multiple myeloma or breast cancer, although data are lacking. Hypercalcemia leads to progressive mental impairment, including coma, as well as renal failure. These complications are particularly common terminal events among patients with

cancer. The detection of hypercalcemia in a patient with cancer signifies a very poor prognosis; approximately 50 percent of such patients die within 30 days[2].

Here we present a case of severe hypercalcemia causing acute kidney injury due to underlying lung malignancy.

Case presentation

A 37 year old male presented with progressive swelling and recurrent ulceration over right side of neck and malaise with extreme fatigability. He consumes gutka very frequently since 8 years. On examination he was found to have large ulcer over the right supraclavicular region along with generalised lymphadenopathy and hepatosplenomegaly. Vitals were normal. He was found to acute renal failure (Serum creatinine - 2.54 mg/dl) and hypercalcemia (Serum calcium- 17.1 mg/dl) and Vitamin D deficiency (Vitamin D – 5.37 ng/ml). Urine examination and PTH was normal Ultrasound showed bilateral normal sized kidneys. On further evaluation, Ultrasound guided FNAC of the right axillary lymph node was done which revealed metastatic deposits favouring poorly differentiated squamous cell carcinoma. He was found to have a lesion in the right lung from which CT guided Biopsy was taken and he was diagnosed to have Non small cell lung carcinoma. His serum phosphorus level was 3.8 mg per deciliter, serum creatinine level was 2.54 mg per deciliter and serum albumin was 3.6 g per deciliter. Following management of hypercalcemia and AKI, Patient's renal function improved and was started upon chemotherapy for lung cancer.

Investigations

TEST NAME	OBSERVED VALUE (BEFORE TREATMENT)	OBSERVED VALUE (AFTER TREATMENT	UNIT	REFERENCE NORMAL RANGE
Haemoglobin	**12.1**	6.7	g/dl	12 – 18
Total Leucocyte Count (TLC)	**35000**	15800	c/cumm	4000 – 11000
Differential Count/DC				
Neutrophils	**92**	**85**	%	40 – 75
Lymphocytes	**04**	**13**	%	20 – 40
Eosinophils	**04**	**02**	%	1- 6
Erythrocyte Sedimentation Rate	**86**	32	mm/hr	0 – 10
Platelet Count	**306000**	442000	c/cumm	150000 – 400000
UREA	**74.3**	20.8	mg/dL	16.6-48.5
CREATININE	**2.54**	0.61	mg/dL	0.7-1.4
URIC ACID	**6.8**	3.7	mg/dL	3.4-7
CALCIUM	**17.1**	9.6	mg/dL	8.6-10
PHOSPHORUS	**3.8**	-	mg/dL	2.5-4.5
VIT D	**5.37**	-	ng/ml	30-70
LDH	**225**	-	U/L	UPTO 250
Total Protein	**7.4**	-	g/dL	6.4 - 8.3
Albumin	**3.6**	-	g/dL	3.5 - 5.2
Globulin	**3.80**	-	g/dL	2.3 - 3.5
Bilirubin Total	**0.48**	-	mg/dL	Upto 1.2
Bilirubin Direct	**0.19**	-	mg/dL	≤ 0.2
Bilrubin Indirect	**0.29**	-	mg/dL	0 - 0.75
SGOT	**22**	-	U/L	0 – 40
SGPT	**41**	-	U/L	0 – 41
Alkaline Phosphatase	**215**	-	U/L	60 – 170

Fig 1: Ulcer over the Right supraclavicular region

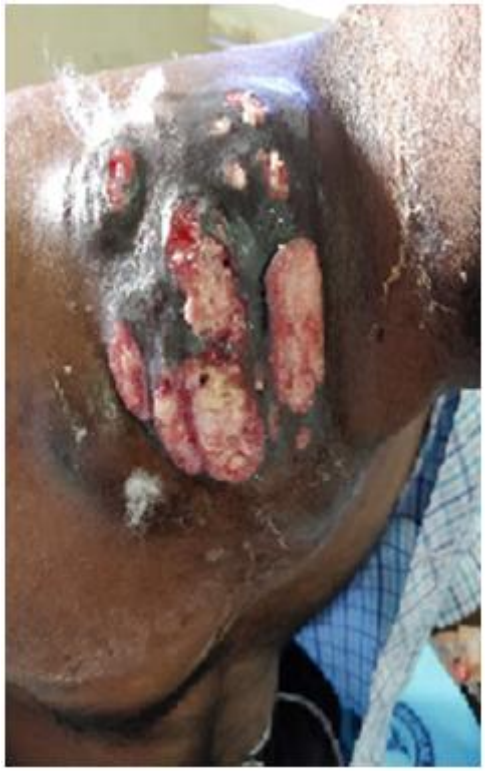

Fig 2: CECT Thorax showing lesion in the Right Lung

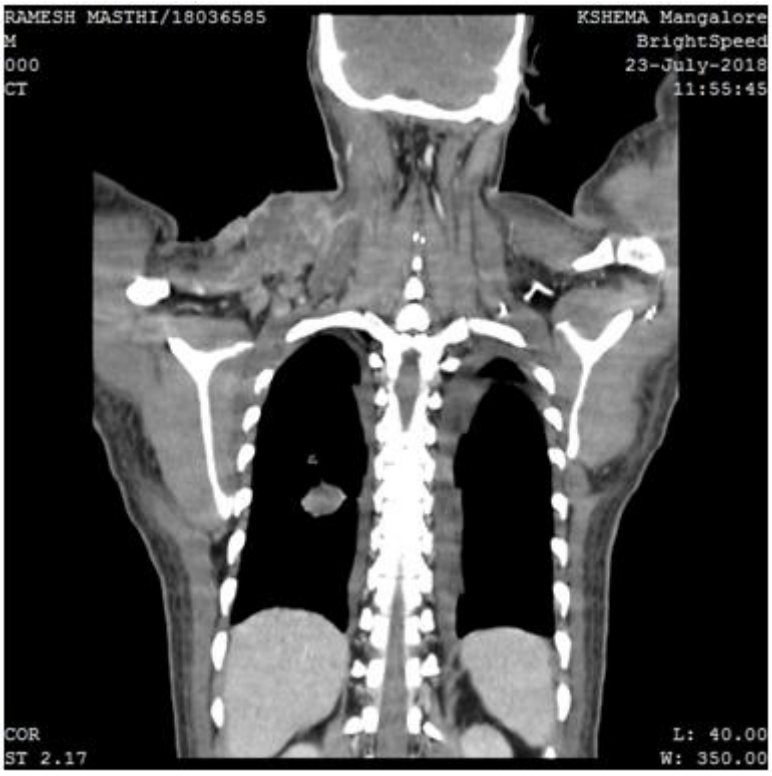

Fig 3: CECT Thorax showing Right Axillary and Mediastinal Lymphadenopathy

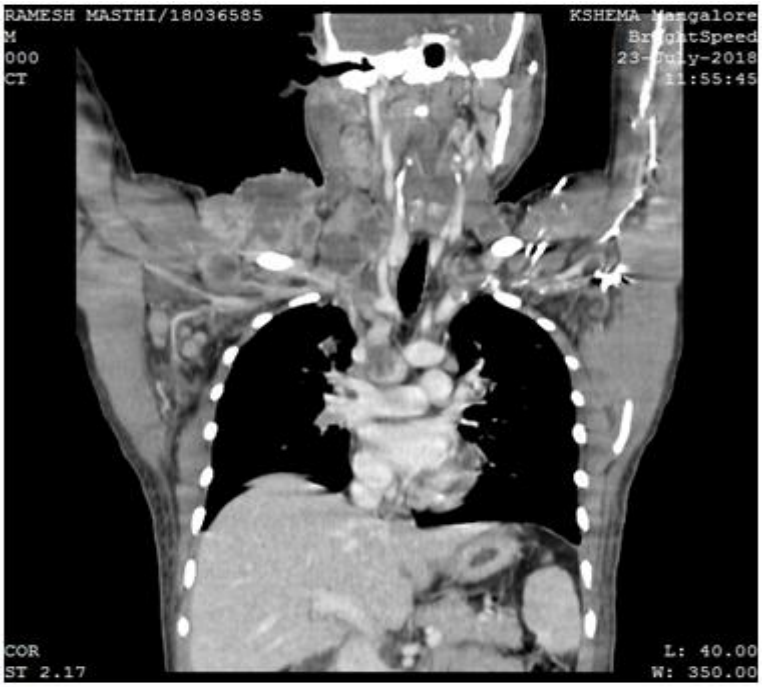

Fig 4: Urine routine examination

CLINICAL PATHOLOGY

Test Name	Observed Value	Unit	Reference Range
Urine Analysis Complete			
Specific Gravity	**1.010**	-	1.003 - 1.03
PH.	**6.0**		
Protein	**NIL**		
Glucose	**NIL**		
Ketone Bodies	**NIL**		
Urobilinogen	**Normal**		
Bilepigment	**NIL**		
Bile Salt	**NIL**		
Blood	**NIL**		
Erythrocytes	**NIL**		
Leucocytes	**1-2/hpf**		
Epithelial Cells	**1 - 2/HPF**		
Casts	**NIL**		
Crystals	**NIL**		

Fig 5: Peripheral smear

HAEMATOLOGY

Peripheral Smear

RBCs show anisopoikilocytosis.
RBCs are both macrocytic and microcytic hypochromic.

WBCs are increased in number with increase in neutrophils and eosinophils.
Neutrophils appear reactive.
Few hypersegmented neutrophils are seen.
DC = Neutrophils 78%, Lymphocytes 04%, Eosinophils 18%.

Platelets are adequate.

No abnormal cells.

No hemoparasites.

Impression :

DIMORPHIC ANEMIA WITH NEUTROPHILIC AND EOSINOPHILIC LEUCOCYTOSIS AND LYMPHOPENIA.

Fig 6: Biopsy from right supraclavicular ulcer

CLINICAL PATHOLOGY

Histopathology

CLINICAL DETAILS : Swelling with ulceration over left shoulder.
Ulcerated lesion over right side of neck.

GROSS :
Received 2 pale white tissue masses.
Larger tissue mass is skin covered and measuring 0.8x0.5x0.5cms with skin measuring 0.8x0.5cms. Cut surface - Pale white areas noted. Cut into 2. All embedded in - 5952.
Smaller tissue mass measuring 0.6x0.5x0.3cms with skin measuring 0.5x0.3cms. Outer surface - Pale white to pale brown. All embedded in - A.

MICROSCOPY:
Multiple sections studied show ulcerated skin with invasive tumor and fragment of tumor tissue. The floor of the ulcer show tumor containing polygonal to pleomorphic tumor cells having pleomorphic vesicular to hyperchromatic nucleus and moderate amount of cytoplasm with keratinisation. Keratin pearls is also seen at places. Tumor cells are seen in the deep surgical resected margin. One lateral resected margin is free from tumor. Small bit of tissue show similar features that of ulcerated invasive tumor.

Impression :

Histological features are those of Moderately differentiated Squamous Cell Carcinoma.
- Tumor clusters are seen in the deeper surgical margins.
- One lateral margin is free from tumor

Fig 7: Lung biopsy

Histopathology

CLINICAL DETAILS :
Ulcer over left shoulder since 4 months + Generalised lymphadenopathy.
Multiple necrotic lymph nodes with multiple lung necrotic lesions with unknown primary.
Biopsy from right hilar lesion of lung.

GROSS :
Received 4 linear pale white linear tissue bits largest measuring 1.5cm in length. All embedded in 6177.

MICROSCOPY :
Multiple sections studied from the lesional tissue shows tumor cells situated amidst the stroma. The tumor cells appear to be dissociated and shows nuclear plepmorphism, hyperchromatism and an irregular nuclear membrane. Dyskeratotic cells and single cell keratinisation is seen. Some cells are seen displaying a pulled out cytoplasm.

Impression :

Features are suggestive of Non small cell carcinoma lung - Moderately differentiated squamous cell carcinoma.

Fig 8: Axillary lymph node FNAC

CYTOPATHOLOGY

U.S GUIDED FNAC GRADE I

Right axillary lymphnode

Smears studied are moderately cellular and show pleomorphic tumour cells arranged in clusters, sheets and singles. They display marked pleomorphism like hyperchromatic nuclei, irregular nuclear margins, prominent nucleoli, coarse chromatin, dyskeratosis, atypical mitosis and tadpoling of the cytoplasm.

Background shows mixed inflammatory cells and haemorrhage.

Impression :

FEATURES ARE SUGGESTIVE OF METASTATIC DEPOSITS FAVOURING POORLY DIFFERENTIATED SQUAMOUS CELL CARCINOMA.

Treatment

IV hydration using normal saline was given at a rate of 150ml/hr and serial monitoring of calcium was done. Patient was also given one dose of zoledronic injection 4 mg . Patient was evaluated for malignant hypercalcemia and was diagnosed with non small cell carcinoma of lung. He was later started on chemotherapy and radiotherapy.

Discussion

Pulmonary carcinoma is the most common solid tumor to metastasize to the kidneys, followed by gastric and breast carcinomas. Although rare, few cases of Acute renal failure resulting from metastatic solid tumor with widespread renal parenchymal infiltration have been reported in the literature. Occult tumor infiltration of the kidneys clinically mimick renal medical disease and

oftentimes escape detection in the routine imaging investigations including ultrasonography and CT[3]. The clinical silent event constitutes a diagnostic challenge to the nephrologists and radiologists. In this situation, infiltrative processes are usually suggested by radiological finding of bilateral renal enlargement accompanied with progressive renal failure.

The reversible decrease in glomerular filtration rate in severe hypercalcemia is thought to be mediated in part by direct renal vasoconstriction. In addition, volume depletion can occur through several different mechanisms, contributing to worsening of kidney function[4]. A defect in urinary concentrating ability, leading to polyuria and polydipsia, is an important mechanism. This is thought to be due to down regulation of aquaporin 2 (AQP2) water channels in the collecting tubules and tubulointerstitial injury caused by calcium deposition in the medulla. In addition, activation of the calcium sensing receptors present on the basolateral membrane of the thick ascending limb of the loop of Henle reduces calcium reabsorption. In addition, generation of prostaglandin E2 by hypercalcemia is thought to reduce sodium chloride reabsorption in the loop of Henle[5]. AKI caused by hypercalcemia is usually reversible with volume expansion with saline solution and lowering of serum calcium concentration. In this case, serum creatinine concentrations gradually improved from 2.54 mg/dl to 0.61 mg/dl. Hypercalcemia in malignancy may be due to PTH-related peptides (PTHrPs) and osteolytic metastases, but it can also be caused by ectopic activity of 1a-hydroxylase, leading to the formation of 1,25-dihydroxycholecalciferol and ectopic PTH production[6]. The history of gutka consumption, extensive lymphadenopathy and lesion in the hilum of right lung on computed tomography prompted the diagnosis of lung carcinoma in this patient. Also Hypercalcemia occurs in 10% of patients with lymphoma[7].

Hypercalcemia associated with cancer can be classified into four types.In patients with local osteolytic hypercalcemia, the hypercalcemia results from the marked increase in osteoclastic bone resorption in areas surrounding the malignant cells within the marrow space. The condition known as humoral hypercalcemia of malignancy (HHM) is caused by systemic secretion of parathyroid hormone (PTH)related protein (PTHrP) by malignant tumors. PTHrP causes increased bone resorption and enhances renal retention of calcium. The tumors that most commonly cause HHM are listed in, but essentially any tumor may cause this syndrome. Some lymphomas secrete the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25(OH), causing hypercalcemia as a result of the combination of enhanced osteoclastic bone resorption and enhanced intestinal absorption of calcium. Finally, ectopic secretion of authentic PTH is a rare cause of hypercalcemia[8].

Table 1. Types of Hypercalcemia Associated with Cancer.*

Type	Frequency (%)	Bone Metastases	Causal Agent	Typical Tumors
Local osteolytic hypercalcemia	20	Common, extensive	Cytokines, chemokines, PTHrP	Breast cancer, multiple myeloma, lymphoma
Humoral hypercalcemia of malignancy	80	Minimal or absent	PTHrP	Squamous-cell cancer, (e.g., of head and neck, esophagus, cervix, or lung), renal cancer, ovarian cancer, endometrial cancer, HTLV-associated lymphoma, breast cancer
$1,25(OH)_2D$-secreting lymphomas	<1	Variable	$1,25(OH)_2D$	Lymphoma (all types)
Ectopic hyperparathyroidism	<1	Variable	PTH	Variable

* PTH denotes parathyroid hormone, PTHrP PTH-related protein, $1,25(OH)_2D$ 1,25-dihydroxyvitamin D, and HTLV human T-cell lymphotrophic virus.

In planning therapy for patients with hypercalcemia associated with malignant disease, anti hypercalcemia therapy should be considered an interim measure, one with no ultimate effect on survival. Treatment of hypercalcemia induced acute kidney injury relies on restoration of intravascular volume and renal perfusion, an increase in the glomerular filtration rate, and rapid lowering of the serum calcium level, followed by a sustained therapeutic phase focused on maintaining a normal serum calcium level. The first step in therapy is aggressive intravenous hydration with 0.9% normal saline (200 to 250 ml per hour)[9]. Loop diuretics are of little benefit, since they increase excretion of renal calcium, which may precipitate in the kidney, and also confer a risk of hypovolemia. Thus, diuretics should be used only in patients with hypervolemia. Severe cases of acute kidney injury, which are often characterized by oligoanuria, may not be amenable to intravenous hydration, whereas hemodialysis with a low calcium dialysate effectively corrects hypercalcemia. After this initial therapeutic stage, medications that diminish bone calcium release (bisphosphonates, calcitonin, or both) are used to maintain normocalcemia. If pamidronate is used for bisphosphonate therapy, the dose must be adjusted for kidney function. A newer therapeutic option that does not require dosing modification is denosumab, a humanized monoclonal antibody that neutralizes the receptor activator of nuclear factor-κ β ligand and reduces osteoblast activity and bone calcium release[10].

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