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# A Rare Occurrence of Three Primary Malignancies: Renal Cell Carcinoma, Multiple Myeloma and Chronic Myeloid Leukaemia in the Same Patient: A Case Report

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**Abstract** **Case Report**

There is an increasing incidence of multiple primary malignancies over period with advent of better screening methods and newer diagnostic techniques. The prevalence of multiple primary tumours in the same patient at intervals is estimated to be between 0.7% and 11.7% with increasing age contributing to higher occurrence. The diagnosis is often an incidental finding when evaluating primary malignancies for further management.This is a case of a 53- year-old man with an incidental diagnosis of clear cell renal carcinoma of right kidney. Patient on follow up was diagnosed with chronic myeloid leukemia picture, subsequently confirmed on further investigations. Concomitant occurrence of multiple malignancies in same patient has been observed to have better prognosis which may be resulting from early diagnosis and management.

**Keywords:** RCC (Renal cell carcinoma), MM (Multiple myeloma) and CML (Chronic myeloid leukemia), myeloproliferative disorders, polycythaemia vera.



## INTRODUCTION

Multiple primary malignancies occurring in an individual is a rare phenomenon. These tumours can be either synchronous (less than 6months to diagnosis) or metachronous (more than 6 months of diagnosis) posing significant challenge in the sequence of diagnosis and treatment of the patient. Patient is at a 14% higher risk of developing a second primary malignancy (SPM) with past history of primary malignancy compared with the normal population [1]. The latest advents in the field of pathological and radiological diagnosis along with improved treatment modalities of cancers have resulted in prolonged life expectancy in individuals encountered with multiple primary cancers [2]. The most common sites with multiple primary cancers include the lung, breast, skin melanoma, and colon [1]. The prevalence of multiple primary tumours is between 0.7% and 11.7% with higher occurrence with increasing age [2]. Furthermore, multiple primary tumours have higher female preponderances than males. Some studies have reported higher incidence of second primary malignancy during the first 60 days following diagnosis and fall in incidence from 60 days to 1 year after diagnosis [3]. In the absence of a family history or specific genetic predisposition, the development of more than two primary unrelated malignancies is a rare phenomenon. However, two different primary cancers in a single patient have been widely reported even though low in incidence.

## CASE REPORT

A right renal mass was detected in a 53-year-old asymptomatic male patient on routine ultrasound sonography. CT urography detected well defined exophytic cystic lesion in upper pole of right kidney. CT renal angiogram suggested of Bosniak class IV renal cortical cystic lesion. He was a chronic smoker for the past 15 years, and hypertensive on medications since the past 7 years. Three years back, he underwent a right partial nephrectomy followed by local radiotherapy for a stage I (pT1bN0M0) renal cell carcinoma. Histopathology of the nephrectomy specimen revealed a conventional clear cell renal cell carcinoma (Fuhrman nuclear grade 2) with no lymphovascular emboli, no infiltration of perinephric fat and no renal capsular invasion. There was no

evidence of invasion of the renal vein, ureter and adrenal gland. Preoperative bone scan has revealed abnormal osteolytic activity involving left acetabular region which was biopsied and detected plasmacytoma with CD138 (+); kappa light chain restriction on in situ hybridization, CD20(-) and cytokeratin (-). Bone marrow biopsy was suggestive of normocellular bone marrow with 5% large plasma cells. Flow cytometry analysis suggested very small clonal plasma cell population of 0.5%. Abnormal plasma cells (APC) are 69% of total plasma cells. Normal plasma cells (NPC) are 30.9% of total plasma cells. Monoclonal M band was absent on serum electrophoresis as depicted in Figure 1.

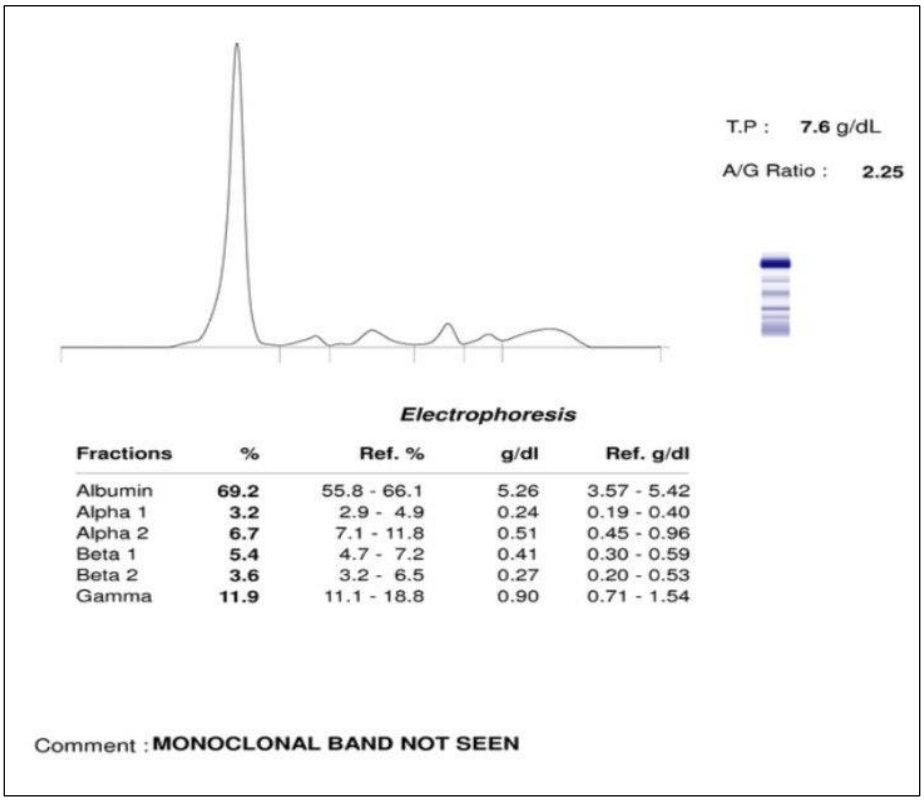


**Figure 1: Serum protein electrophoresis with absent M band**

Serum immune fixation electrophoresis confirmed it to be an IgG λ-type MM. His serum β2 microglobulin was 3.66 mg/L (ref. 0.6–2.28), M protein absent, albumin (4.91 g/dL, ref. 3.5–5 g/dL)) (International System Stage II). A routine laboratory evaluation revealed a normocytic normochromic anaemia with rouleaux formation, a raised erythrocyte sedimentation rate, a normal leucocyte and platelet count, a raised serum creatinine, uric acid and calcium, an altered albumin to globulin ratio and normal liver transaminases. Patient was started with chemotherapy with thalidomide which was continued for duration of 2 to 2.5 years and with consecutive follow-ups for monitoring multiple myeloma status.

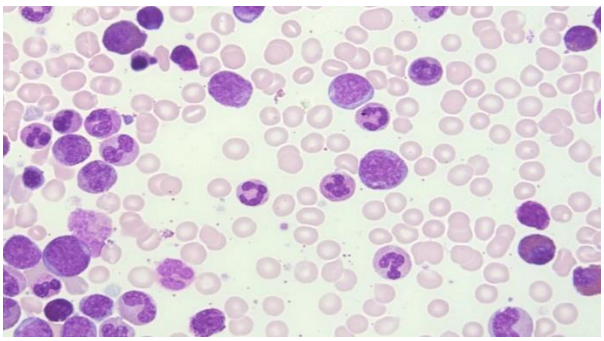

**Figure 2: Peripheral smear depicting chronic myeloid leukemia picture**

Peripheral blood analysis revealed white blood cell count of 1,61,760 cells/mm$^3$ (17% segmented neutrophils, 17% eosinophils, 15% basophils, 20% myelocytes, 14% metamyelocytes, 12% blast, 2% promyelocytes, 3% lymphocytes, and 0% monocytes). Haemoglobin was 10.1gm/dl, and platelets were 1224 x

$10^9$/µl (Figure 2). Neutrophil Alkaline Phosphatase (NAP) was 128, and Lactate Dehydrogenase (LDH) elevated (765U/L). Bone Marrow (BM) aspirate and biopsy were typical of CML with blast-6%, promyelocyte-3%, myelocyte-23%, metamyelocyte-12%, neutrophil-24%, lymphocyte-2%, monocytes-1%, eosinophils-11%, basophils-12%, plasma cells-0%, erythroid series were suppressed with normoblastic erythropoiesis with increased megakaryocytes; BM karyotype showed Philadelphia (Ph) chromosome in 10 out of 20 metaphases. Molecular analysis described below confirmed the diagnosis of CML. Karyotyping for haematological malignancies on bone marrow was abnormal with presence of 46, XY, {t (9; 22) (q34; q11)} [20]. FISH test for Philadelphia chromosome BCR-ABL1t (9; 22) on bone marrow was suggestive of BCR-ABL {t (9; 22) (q34; q11)} was present in 100% of the interphase cells studied as shown in the figure 3.

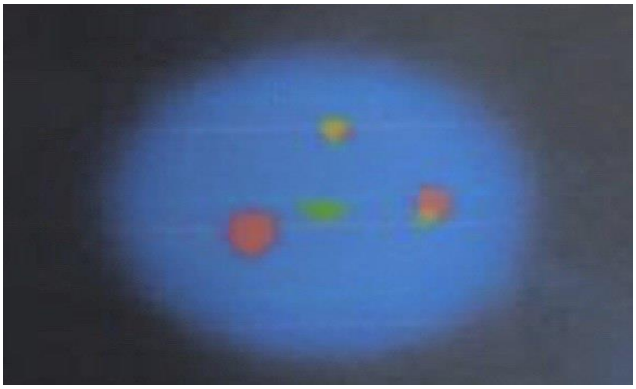

**Figure 3: FISH for BCR-ABL {t (9; 22) (q34; q11)} Note: BCR is green and ABL1 is orange**

BCR-ABL1 Quantitative International Scale [IS] with real time polymerase chain reaction (RT-PCR) on peripheral blood detected P210 (b3a2, b2a2) major transcript with19089 observed copies of BCR-ABL1 and BCR-ABL1 IS [International Scale] was high with 11.3417%. P190 (e1a2) minor transcript and P230 (c3a2) micro transcript were not detected. Germ line screening test did not detect any clinically relevant variant that is associated with elevated cancer risk. Variant of Uncertain Significance (VUS) was detected of CDKN1C (Cyclin dependent Kinase inhibitor 1C) in heterozygous state and with autosomal dominant inheritance pattern. Post chemotherapy PET scan detected lytic lesions involving left acetabulum, D11 and D12 vertebrae. Patient developed right lung pneumonia with subcentimeter sized ground glass opacities in upper and lower lobes of right lung associated with mild to moderate pleural effusion for which patient recovered satisfactorily after hospitalisation. Follow-up with clinicians were not significant with continuation of palliative care management.

## DISCUSSION

With increasing life expectancy due to advent of newer diagnostic techniques and successful treatment of primary malignancies, there rise in incidence of second primary malignancies. Although early intervention with early-stage diagnosis followed by appropriate treatment has increased the prognostic outcome, the risk of a secondary myelodysplastic syndrome or acute leukaemia in multiple myeloma cases is approximately 3% at 5 years and 9% at 10 years [4]. A rare case of metastatic prostatic cancer to bone marrow and multiple myeloma as secondary malignancy was reported by Sehgal *et al*. He suggested that probably bone marrow microenvironment play a crucial role in the development of myeloma [5]. Sporadic case reported by Bhandari *et al* have revealed dual malignancies occurring in renal cell carcinoma; such as prostate, bladder, lung, breast, colon and non-Hodgkin lymphoma which were the most common malignancies [6]. Ojha *et al* reported 69 case of renal cell carcinoma in 34,156 patients diagnosed with multiple myeloma in Dana-Farber Cancer Institute in Boston during 1973 and 2006. Ojha and his colleagues suggest that multiple myeloma was 1.51 times more likely to be found in renal cell carcinoma patients than in the general population [7]. The study of Bhandari *et al*, reported six cases of renal cell carcinoma in their 600 cases of plasma cell dyscrasia during ten years' period [6]. Dutcher and Wiernik have reported an increase incidence of hematologic malignancies in families of patients with renal cell carcinoma. Interestingly the large majority (94%) of these hematologic malignancies were B-cell origin [8]. The current patient was diagnosed with renal cell carcinoma initially followed by multiple myeloma and eventually on follow-up was diagnosed with chronic myeloid leukaemia. Sakai *et al* has hypothesized that one malignancy produces a tumour stimulating hormone like IL6 or TNFα which may increase the risk of second malignancy as many patients were having elevated serum IL6 and TNFα levels [9].

Badros *et al* reported other risk factors involved in pathogenesis of malignancies may be: environmental factors (tobacco, occupation and pollution, ultra-violate light), genetic factors, metabolic syndrome, previous medical treatment, sex and hormonal factors [10]. No common aetiology has been

established yet although various hypothesis has mentioned the same risk factors as above. Beside these risk factors; therapeutic strategies of multiple myeloma were tried for renal cell carcinoma with partial success which indicates the probable common pathophysiology [6]. Hov H *et al* suggested that c-met oncogene mutation, seen more commonly in hereditary papillary renal cell carcinoma, has recently been implicated in IL-6-induced myeloma cell proliferations. [12]. However, majority of renal cell carcinoma reported till date with multiple myeloma have been of clear cell phenotype, which is commonly associated with chromosome 3p abnormality although it has not been described in multiple myeloma as per Padhi S *et al* [11]. There are various reports of MM (multiple myeloma) coexistence with myeloproliferative disorders, which includes polycythemia vera, myelofibrosis, essential thrombocytosis, and chronic neutrophilic leukemia (CNL) [13]. There is theory which suggest that the existence of a common malignant pluripotent progenitor stem cell capable of differentiating into both myeloid and lymphoid cell lineages can result in development of CML (Chronic myeloid leukemia) and MM (multiple myeloma) in the same patient [14, 15, and 16]. Martin PJ *et al* reported that Ph+ B lymphoblastoid cells may be observed in patients with chronic phase CML (Chronic myeloid leukemia) which may be arising from the CML stem cell alone [17].

It is established fact that MM (multiple myeloma) is characterised by genomic instability and typically has no specific chromosomal abnormalities as of leukemias and lymphomas, there have been some reported cases of MM (multiple myeloma) patients associated with Philadelphia chromosomes [18, 19, and 20]. Another proposed theory is that the cytotoxic drugs or irradiation used to treat the first disease may cause secondary disease which could explain development of CML (Chronic myeloid leukemia) and MM (multiple myeloma) in same patients. Pandiella A *et al* reported in their study that Imatinib stimulate MM (multiple myeloma) cell proliferation through activation of the Erk1 and Erk2 Mitogen-Activated Protein Kinases (MAPKs) [21]. Moreover, Imatinib has shown to inhibit proliferation of MM cells by arresting cell-cycle progression *in vitro* suggesting its association with development of MM remains controversial. Holmberg et al suggested radiation exposure may induce t (9, 22) translocation explaining CML development in MM patient who received radiation therapy cannot be excluded [22]. In this case, we have reviewed the same patient for triple concomitant malignancies. The sequence of occurrence of malignancy is not clear as RCC was discovered incidentally followed by its workup, when multiple myeloma was detected. Along with routine workup and management of multiple myeloma; chronic myeloid leukaemia was detected after duration interval of 2-2.5 years and undergoing further management for it. This patient's RCC was in early stages and operable, he further underwent chemotherapy for his myeloma. Patient also responded very well for Dasatinib therapy for CML and achieved remission to resume his routine.

## CONCLUSIONS

There is a need for more awareness that a potential second malignancy in MM may be RCC and vice versa. Therefore, any new lytic bone lesion in a patient with prior renal cell carcinoma should be investigated for potential myeloma; especially when there is not any other metastatic lesion. Multiple myeloma-renal cell carcinoma (MM-RCC) have common risk factors like obesity, hypertension and smoking which may be useful for further evaluation. Both malignancies RCC and MM have similar pathogenesis of cytokine requirements like interleukin-6 (IL-6) for which may further guide IL-6 targeted therapy. The biological behaviour of MM following RCC has been very aggressive. This may be explained by high-grade myeloma cell morphology, advanced histological stage, possible underlying adverse cytogenetic alteration and poor response to chemotherapy. Any new lytic bone lesions in a patient with prior RCC should be carefully evaluated for possible myeloma; especially in the absence of pulmonary or visceral metastasis. Also it is recommended to follow-up regularly with lab investigation to observe remission of multiple myeloma which may lead to detection of another malignancy of chronic myeloid leukemia. This could help early detection and appropriate treatment in early stages of malignancies which could eventually lead to complete remission.

**Conflicts of Interest**

The authors declare that they have no conflict of interests. Informed written consent for publication was obtained from the patient prior to collecting data.

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