Case Report

Renal cell carcinoma and plasma cell myeloma: Unique association and clinical implications

Somanath Padhi, Pradyumna Kumar Sahoo[1], Debashis Banerjee[2], Rabindra Nath Ghosh[3]

Department of Pathology, Pondicherry Institute of Medical Sciences, Ganapathychettykulam, Kalapet, Puducherry, [1]Surgical Oncology, [2]Urology, and [3]Hemato-Oncology, Cancer Center Welfare Home and Research Institute, Thakurpukur, Kolkata, West Bengal, India

Abstract

Several case series, in the recent past, have postulated an association between plasma cell myeloma (MM) and renal cell carcinoma (RCC). Population-based data have revealed a bi-directional association between these two malignancies, which points to shared risk factors, similar cytokine (Interleukin-6, IL-6) requirements for growth and survival, and overlapping clinical presentation. The presence of lytic lesions in a patient with prior RCC may simulate bone metastasis; thus, leading to a diagnostic pitfall with potentially adverse clinical implications. Besides these, therapeutic strategies employed for MM have been tried for RCCs with partial success. We aimed to describe two patients, aged 64 and 54 years, with RCC-MM association, with review of relevant literature; and create awareness among pathologists/hematologists, and oncologists. Elucidating a common genetic basis might throw some light in understanding the pathobiology of these tumors and development of newer targeted therapies.

Key Words: IL-6, metastasis, plasma cell myeloma, renal cell carcinoma

Address for correspondence:
Dr. Somanath Padhi, Department of Pathology, Pondicherry Institute of Medical Sciences, Ganapathychettykulam, Kalapet, Puducherry - 605 014, India.
E-mail: somanath.padhi@gmail.com
Received: 13.09.2012, **Accepted:** 10.02.2013

INTRODUCTION

Survivors of a primary malignancy have an increased risk of developing a second primary malignancy (SPM), which is attributed more commonly to antecedent chemotherapeutic agents (alkylators) as well as genetic, life style, or environmental factors.[1] Although patients of syndromic renal cell carcinomas (RCCs) are at increased risk of second primary tumors, sporadic RCCs are rarely associated with other malignancies.[2] Specifically, an association between RCC and plasma cell myeloma (MM) is extremely rare, and only sporadically reported in the literature. Recent epidemiological data have shown that RCC-MM link is bi-directional with shared risk factors. The risk of development of one with a prior history of the other is more than expected in the general population, for which further in-depth studies are necessary.[3-9]

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/0974-7796.134292

We aimed to describe two patients with RCC and MM for the first time from India, with a review of existing literature and create awareness among clinicians regarding such association.

CASE REPORT

The clinical presentation (both past and present), lab investigations, radiological characteristics, management, and follow-up data of two patients are presented in Table 1.

DISCUSSION

Renal cell carcinoma and MM are more frequently diagnosed among older adults, constituting 3% and 1%

Table 1: Clinical presentation, laboratory findings, and management of two patients of plasma cell myeloma with prior history of renal cell carcinoma

Features	Case 1	Case 2
Age/gender	64 years/male	54 years/male
Risk factors	Obesity	Chronic smoker
Presentation	Low back pain, fatigue ×9 months, altered sensorium, and pedal edema ×4 months	Fatigue and fever ×1 month, decreased urinary output ×1 month
Past medical history (time gap)	CT[¶] scan: S/o of left-sided RCC[†] Management: Left radical nephrectomy+radiotherapy+Int erferon-α Pathology: Clear cell RCC, Fuhrman grade 2, infiltration of perinephric fat; +, lymphovascular invasion; –, invasion of inferior vena cava, ureter, and adrenal; –, stage III ($pT_3N_0M_0$) (44 months) No evidence of recurrence or metastasis till date	CT scan: S/o of right-sided RCC [Figure 1] Management: Right radical nephrectomy+radiotherapy. Pathology: Clear cell RCC, Fuhrman grade 2, infiltration of perinephric fat +, lymphovascular emboli +, no inferior vena cava, ureter, or adrenal invasion; stage III ($pT_3N_0M_0$) (36 months) No evidence of recurrence or metastasis till date
Routine laboratory investigations[‡]	Hb; 66 g/L, TLC; 7×10^9/L, TPC; 150×109/L, ESR; 60 mm/1st hr, PBS; NCNC RBCs and rouleaux Ur; 107 mg/dL, Cr; 2.3 mg/dL, TSP; 8.0 g/dL, Albumin; 2.5 g/dL, Globulin; 5.5 g/dL, A: G; 0.45, Ca^{2+}; 11.0 mg/dL, PO_4^{3-}; 3.7 mg/dL, Uric acid; 8.9 mg/dL, LDH; 659 IU/L, liver transaminases; within normal range	Hb; 77 g/L, TLC; 4.8×10^9/L, TPC; 150×10^9/L, ESR; 120 mm/1st hour Ur=87 mg/dL, Cr=3.1 mg/dL, TSP=15.2 g/L, Albumin=1.6 g/dL, Globulin=13.6 g/dL, A: G; 0.2; Uric acid=17.8 mg/dL, Ca^{2+}=10.4 mg/dL, liver transaminases; within normal limits
Myeloma work up[ǁ] [Figures 2a-c, 3a-b]	SPE; M– band+ BMA; pleomorphic myeloma cells (50%), BMBx; nodular and diffuse infiltrate of myeloma cells, CD 138 and kappa (k)+ Serum light chain assay (nephelometry); k; [> 14,640 mg/L (3.30-19.40)], lambda (λ); 1.89 mg/L (5.71-26.30), markedly elevated IgD Interleukin-6 (IL-6); 27.1 pg/mL (<50, ELISA), $ß_2$ microglobulin; 1.88 mg/L (0.6-2.28) Lateral skull X-ray; lytic lesions +, MRI LS spine; L1-L4 Vertebral body lesions, Bone scan; increased uptake at L1	SPE; M- band+(8.76 g/dL) BMA and BMB_x; diffuse infiltrate of myeloma cells IFE; IgG; 9960 mg/dL (700-1600), suppressed IgA, IgD, and IgM, lambda (λ); 245 mg/L (5.71-26.3), k; 11.7 mg/L (3.3-19.4) Interleukin-6 (IL-6); 2464 pg/mL (<50, ELISA), $ß_2$ microglobulin; 3.66 mg/L (0.6-2.28) Lateral skull X-ray; multiple punched out lytic lesions +
Staging	Durie salmon (IIB)/ISS[ϒ] (I/II)	Durie salmon (IIB)/ISS (II)
Management	Vincristine+Doxorubicin+Dexamethasone	Lenalidomide+Bortezomib+Dexamethasone
Follow-up	Myeloma cells reduced to 10% at 3 month post-chemotherapy, stable disease, on follow-up	Lost to follow-up

[¶]Contrast-enhanced computerized tomogram scan of abdomen, [†]RCC: Renal cell carcinoma, [‡]Hb: Hemoglobin, TLC: Total leukocyte count, TPC: Total platelet count, ESR: Erythrocyte sedimentation rate (Westergren), PBS: Peripheral blood smear, NCNC: Normocytic normochromic, RBC: Red blood cells, Ur: Serum urea, Cr: Serum creatinine, TSP: Total serum protein, A: G: Albumin to globulin ratio, Ca^{2+}: Corrected serum calcium, PO_4^{3-}: Serum phosphate, LDH: Serum lactate dehydrogenase, [ǁ]SPE: Serum protein electrophoresis (cellulose acetate, pH=8.6), BMA: Bone marrow aspiration, BMB_x: Bone marrow trephine biopsy, IFE: Immune fixation electrophoresis, MRI: Magnetic resonance imaging, LS: Lumbo-sacral spine, [ϒ]International system staging for myeloma

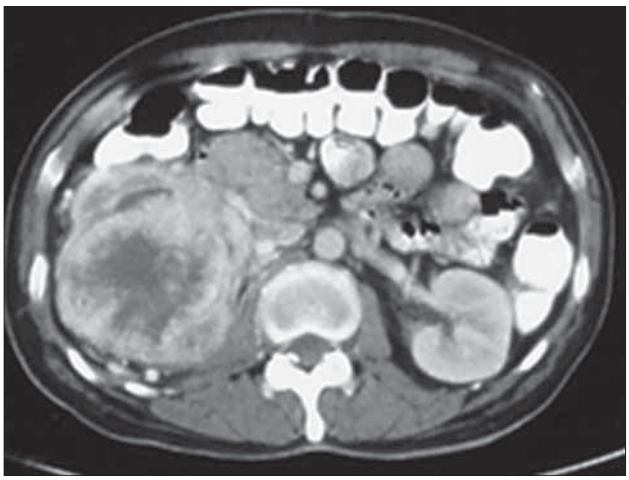

Figure 1: Contrast-enhanced computerized scan of abdomen from case two showing a heterogeneously enhancing mass with central necrosis in the right kidney, highly suggestive of renal cell carcinoma

of malignancies, respectively.[10] A recent population-based study (1973-2006) analyzed data from 57,190 primary RCCs (62.2% males; mean age = 61.2 years; SD = 16.4) and 34,156 primary MMs (52.6% males; mean age = 67.9 years; SD 12.3).[3] Patients with RCCs had a higher overall relative risk (51%) of secondary MMs (n = 88) than in the general population (median follow-up = 2.5 years), whereas that of RCCs was 89% higher among MM patients compared to the general population (n = 69, median follow-up = 1.83 years). Thirty five percent (31/88) of secondary MMs and 55% (38/69) of secondary RCCs were observed within the first year of diagnosis of primary malignancy. Women had a remarkably higher relative risk of MM incidence within one year after RCC diagnosis compared to men. A bimodal age distribution (50-59 and >80 years) of increased risk was observed for MMs following RCC diagnosis, whereas age-specific relative risk of secondary RCCs followed a constant pattern across the age groups. Throughout the whole study period (33 years), only two patients were found to have MM associated with metastatic RCCs. As majority of SPMs occurred within first year of the diagnosis of first malignancy, the authors postulated a complex interplay between genetic, environmental, or lifestyle factors rather than

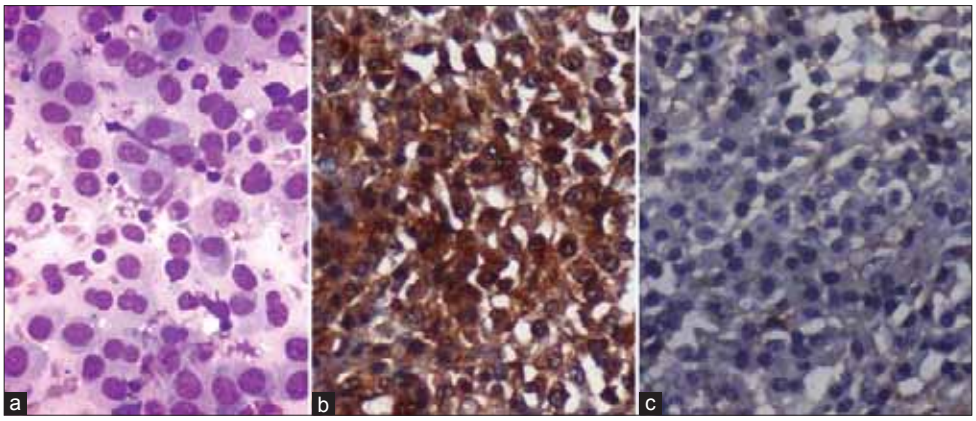

Figure 2: Bone marrow aspirate smears (case 1) (a) showing immature myeloma cells (plasmablasts) with polylobated nuclei and conspicuous nucleoli (Wright Giemsa, ×400), which on trephine biopsy, showed diffuse sheets of myeloma cells with intense cytoplasmic positivity for kappa (b), and negativity for lambda (c) monoclonal antibody (Peroxidase-anti-peroxidase method, ×400)

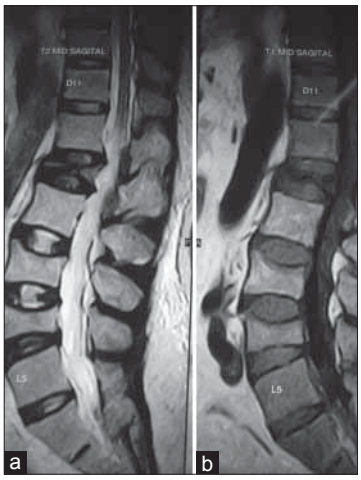

Figure 3: T_2W (a) and T_1W (b) mid sagital magnetic resonance imaging (MRI) of spine from case 1 showing wedge compression fracture with altered signal at L_1-L_3 vertebral bodies, suggestive of osteoporosis or metastasis

treatment-related consequences, which is consistent with other reported SPMs among patients with RCC. Furthermore, surgery rather than chemoradiotherapy is the treatment of choice of RCC, which also decreases the potential of therapy-induced carcinogenesis in MM.[2]

A systematic review of 21 patients with RCC and MM, including those reported by Cooper *et al*.,[8] (1991-2008), and their comparison with our cases is presented in Table 2. As described by Ojha *et al*. [3] and others, majority of cases were observed in males (M:F = 13:8) with a predilection for the whites (11/21) as opposed to the Afro-Americans in whom MM is known to be more common.[10] The mean age at diagnosis of RCCs and MMs was 61 years (38-70) and 63 years (49-78), respectively. In 13/21 (52%), MM occurred as a SPM after a time gap ranging from 11 months to 26 years, comparatively longer than RCC as SPM (9/21, 42.8%, 20-24 months). Synchronous RCC and MM were reported in three patients (two by Ozturk *et al*., one by Sakai *et al*.).[4,9] Of interest is the fact that right-sided RCCs outnumbered the left [11 (52%) vs. 8 (38%)]; bilateral in one, and majority were of clear cell phenotype. Baring three patients (two pulmonary, one para-aortic lymph node metastases), all presented at early stage (I/II) (stage III in our cases) and were managed by curative resection without any evidence of local recurrence or distant metastases on follow-up. In contrast, patients with MM presented at an advanced stage with multiple lytic bone lesions; three had plasmacytoma (rib/sternum/right kidney), and one had monoclonal gammopathy of undetermined significance (MGUS).[6,7] Sixteen of 21 (76%) (including case one, present series) had a kappa (κ) chain phenotype. When RCC was diagnosed first, the finding of lytic bone lesions could have raised the possibility of metastatic RCC especially that the incidence of bone metastases is reported to be 26-31% in the metastatic setting.[6] However, in the absence of visceral or pulmonary metastases, these lytic lesions were unlikely to be from an early stage RCC. The morbidity and mortality of patients were due, mostly, to MMs (4/13 expired), whereas none of the patients had RCC-related mortalities.

Interleukin-6 is one of the most important proliferation and survival factors in myeloma.[10] Sakai *et al*.,[9] for the first time, described a case of synchronous RCC and MM in an elderly female where serum levels of IL-6 decreased from 240 ng/L to 19 ng/L following nephrectomy which, in turn, had a dramatic impact on therapy for MM. On the other hand, when stimulated with recombinant IL-6 *in vitro*, cultured myeloma cells started proliferating. Based on this, the authors hypothesized that IL-6 produced by RCC cells acted in a paracrine fashion for the survival, proliferation, and progression of MM.

Though both MM and RCC are dependent upon on the same cytokines such as IL-6, tumor necrosis factor- α (TNF- α)

Table 2: Association between renal cell carcinoma and plasma cell myeloma: Comparison between present two cases with those published in literature (1991-2008)

Features	Badros *et al*.,[5] 2007	Choueiri *et al*.,[6] 2007	Bhandari *et al*.,[7] 2008	Sakai *et al*.,[9] 1991	Present series 2012
No. of cases; M/F*	5; 4/1	8; 6/2	6; 3/3	1; Female	2; Males (2/2)
Ethnicity	4; Caucasian, 1; Afro-American	7; Caucasian, 1; Afro-American	-	Japanese	Indian
Mean age at diagnosis[$] (years)	RCC: 57 (39-70) MM: 69 (63-78)	RCC: 57 (46-66) MM: 58 (49-66)	RCC: 58 (38-64) MM: 61 (55-65)	67	RCC: 61, 51 MM: 64, 54
Secondary MM[†] (*n*) (time gap)	4/5 (12-300 months) (mean; 129 months)	4/8 (1-108 months) (mean; 39 months)	2/6 (11 months, 26 years)	Synchronous	2 (44 and 36 months)
Secondary RCC[^] (*n*) (time gap)	1/5 (24 months)	4/8 (3-46 months) (mean; 20 months)	4/6 (11-48 months) (mean; 20 months)	-	-
Pathology of RCC	4/5 LK[‡], 1/5 RK[¥], 4/5 clear cell, 1/5 transitional cell, early stage (I/II)	1/8 LK, 6/8 RK, 5/8 clear cell, 3/8 unknown, 6/8 stage I/II	2/6 LK, 3/6 RK, 1/6 bilateral, 4/6 clear cell (1 granular cell variant), 1 chromophobe, 1 papillary; 5/6 stage I/II, 1/6 stage IV	Fever, fatigue, anemia, stage III RCC (LK), raised IL-6[#] (240 ng/L; normal<5 ng/L), raised CRP[¶]	1 LK, 1 RK, 2/2 clear cell, 2/2 stage III, lymphovascular invasion (1/2), IVC invasion; 0/2
Management of RCC, outcome	Nephrectomy (4), Toremifene (1), remission (4), LN[ϒ] metastasis (1, from LK), no systemic metastasis	Laparoscopic cryoablation (1), hemi (1)/radical (1)/partial (2)/nephrectomy (3), 7/8 RCC free, 1/8 pulmonary metastasis, stable with therapy	Partial nephrectomy (2/6), radical nephrectomy (4/6, bilateral in 1), thalidomide (1/6), 1/6 pulmonary metastasis from RK- RCC (CT[≠]scan)	Left nephrectomy, IL-6; 19 ng/L, decreased CRP (post nephrectomy)	Radical nephrectomy+RT (2/2), Interferon-α (1/2), no recurrence or metastasis, till date
Pathology of MM	Lytic lesions (spine, 2/5), renal failure (2/5), asymptomatic (1/5), kappa+(5/5), 3/5 IgG+, 2/5 IgA+	Multiple bony lytic lesions (6/8 spine), 2 plasmacytomas (1 sternum, 1 RK), anemia (1), pancytopenia (1), abdominal mass (1) (RK plasmacytoma), 4/8 kappa+, 3/8 lambda+, 5/8 IgG+, unknown (1)	1/6 solitary plasmacytoma (rib), 1/6 MGUS[±], 5/6 kappa+, 3/6 stage IIIA, 1 stage IIA, 1 stage IA (none with creatinine >2 mg %) (Durie Salmon)	Stage IIIA, IgG Kappa+	Lytic lesions in skull (2/2) and spine (1/2), renal impairment 2/2; 1 IgD kappa, 1 IgG lambda, 2/2 Durie Salmon IIIB, 2/2 ISS[!] I/II, IL-6; 27 pg/mL (case 1), 2464 pg/mL (case 2) (upto 50)
Management of MM, outcome	CT/RT[ǁ], SCT[€], 4/5 CR[£], 1/5 PR[ת]	Radical nephrectomy (RK plasmacytoma), CT/RT	RT/thalidomide/ dexamethasone	Vincristine/ melphalan/methyl prdnisolone	Vincristine, adriamycin, dexamethasone (case 1); Lenalidomide, bortezomib, dexamethasone (case 2)
Follow-up	All alive till 2007	4/8 died of MM, 3/8 alive, 1/8 lost to follow-up, till 2007	Not documented	Dramatic response to therapy following nephrectomy	Myeloma cells reduced from 50% to 10%, on follow-up (case 1), lost to follow-up (case 2)
Suggested hypotheses	?genetic/immune dysregulation/ environmental	?genetic/environmental/ immune dysregulation/ therapy-related	?genetic/epigenetic/ environmental	Possible role of IL-6 as an autocrine and paracrine factor	Obesity, smoking common to RCC and MM, ?genetic/immune dysregulation

Abbreviations: *Male/female, [$]Pathological diagnosis after nephrectomy (in some cases, retrospective review showed abnormal radiological findings even before the actual diagnosis), [†]Plasma cell myeloma, [^]Renal cell carcinoma, [‡]Left kidney, [¥]Right kidney, [ϒ]Para-aortic lymph node, [ǁ]Chemotherapy (vincristine, adriamycin (doxorubicin), dexamethasone, thalidomide, bortezomib, melphalan, methyl prednisone, lenalidomide, arsenic trioxide, rituximab, in varying combinations) and radiotherapy, [€]Autologous stem cell transplantation, [£]Complete remission, [ת]Partial remission, [≠]Computerized tomogram scan, [±]Monoclonal gammopathies of undetermined significance, [#]Interleukin-6, [¶]C-reactive protein, [!]International system staging for myeloma

etc., this seems highly unlikely in our cases as the second malignancy occurred years after the first. On the other hand, the cumulative effect of IL-6, produced by prior RCC, caused osteoclast activation, which possibly led to advanced lytic bone lesions in our second patient (very high IL-6, Table 1). A high proportion of patients with MM had a 'κ' phenotype rather than lambda (λ) (16κ, 5λ, including our series). This probably explained the lack of renal insufficiency (more common with 'λ') as a dominant presentation and the overall favorable prognosis seen in all MMs (2/4 deaths were of λ phenotype).

C-met oncogene mutation, seen more commonly in hereditary papillary RCCs, has recently been implicated in IL-6-induced myeloma cell proliferations.[11] However, majority of RCCs reported till date with MMs have been of clear cell phenotype, which commonly harbors Chromosome 3p abnormality. However, this abnormality has not been described in MMs.

Besides this, a probable genetic basis for the 'κ' light chain preponderance needs to be explored.

CONCLUSION

RCC-MM association has certain unique characteristics such as; (i) shared risk factors like obesity (increased IL-6 production by adipose tissue),[3] hypertension, smoking; (ii) similar cytokine requirements; and (iii) lytic bone lesions. Both myeloma and RCC appear to benefit from therapies such as those directed against cytokines (TNF-α receptor blocker), immunomodulators drugs like thalidomide/lenalidomide, proteosome inhibitor (bortezomib), and autologous stem cell transplantation, although results have been more satisfying for MMs than metastatic RCCs.[6] Therefore, 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 metastases. Similarly, all patients of MM should be carefully evaluated for complex mass lesion in the kidneys, more specifically in the right side.

ACKNOWLEDGMENT

The authors sincerely thank Dr. Saumyaranjan Mallick, M.D., Department of Pathology, and Dr. Chinmay Kumar Pani, M.D., Department of Pediatrics, at All India Institute of Medical Sciences (AIIMS), New Delhi, India for their contribution in review of literature in this manuscript.

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How to cite this article: Padhi S, Sahoo PK, Banerjee D, Ghosh RN. Renal cell carcinoma and plasma cell myeloma: Unique association and clinical implications. Urol Ann 2014;6:252-6.

Source of Support: Nil, **Conflict of Interest:** None.