CASE REPORT

Plasmablastic multiple myeloma following clear cell renal cell carcinoma

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SUMMARY

We aim to describe the clinicohaematological profile of an elderly male with plasmablastic multiple myeloma (MM) (IgG λ , International System Stage II) with an unfavourable outcome following chemotherapy. The serum interleukin-6 level was found to be markedly elevated (2464 pg/mL, reference; <50 pg/mL). Thirty-six months prior to MM diagnosis, he underwent left radical nephrectomy for a stage III (pT3N0M0) clear cell renal cell carcinoma (RCC, Fuhrman grade 2). The unique MM-RCC association, shared risk factors, myeloma pathobiology and clinical implications are discussed with a brief literature review.

BACKGROUND

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, lifestyle or environmental factors.¹ Several case series in the recent past have postulated an association between multiple myeloma (MM) and renal cell carcinoma (RCC). Population-based data have revealed a bidirectional 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.² 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.^{2–8} In this manuscript, we have aimed to describe the clinicohaematological profile of a high-grade MM with a prior history of RCC, and review the relevant literature.

CASE PRESENTATION

A 64-year-old male patient presented to the outpatient department of our Institute in 2012 with persistent low-grade fever and fatigue for 1 month, decreased urinary output and low backache for the past 20 days. He was a chronic smoker for the past 15 years, and a hypertensive on medications since the past 7 years. Thirty-six months previously, he underwent a right radical nephrectomy followed by local radiotherapy for a stage III (pT₃N₀M₀) RCC. Histopathology of the nephrectomy specimen revealed a clear cell RCC (Fuhrman nuclear grade 2) with lymphovascular emboli and infiltration of perinephric fat. There was no evidence of invasion

of the renal vein, ureter and adrenal gland. His periodic clinicoradiological follow-up to date was negative for any recurrence or metastasis from RCC.

A routine physical examination revealed an overweight male (body mass index=28 kg/m², reference; <25) with significant conjunctival pallor, a distended abdomen and bilateral pedal oedema, but no organomegaly. His right arm blood pressure (supine) was 150/100 mm Hg, with a heart rate of 75/min and regular rhythm. A routine systemic examination was unremarkable except for mild cardiomegaly, ascites and tenderness over the lumbar spine (L1–L5). A CT of the brain, thorax and abdomen was unremarkable except for ascites, a shrunken kidney with altered echo texture on the left side and an absent kidney on the right. T2-weighted (A) and T1-weighted (B) mid-sagittal MRI of spine showed wedge compression fracture with altered signal at L1–L3 vertebral bodies, suggestive of osteoporosis or metastasis, or MM (figure 1A, B).

INVESTIGATIONS

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. Cellulose acetate serum electrophoresis (pH=8.4) revealed a thick, sharp monoclonal (M) band at the γ -globulin region. Bone marrow aspiration and trephine biopsy findings were consistent with a plasmablastic MM (Bartl histological grade 3) with diffuse sheets of myeloma cells (packed marrow (>50% myeloma cells), Bartl histological stage 3) (figure 2A–C). Serum immune fixation electrophoresis confirmed it to be an IgG λ -type MM. Cyclin D1 immunohistochemistry (IHC) on trephine sections of the bone marrow revealed a weak positivity among 10–20% tumour cell nuclei (grade 1) compared to another case (figure 2D, E).⁹ His serum β_2 microglobulin was 3.66 mg/L (ref. 0.6–2.28), M protein of 7.5 g/L, albumin (1.5 g/dL, ref. 3.5–5 g/dL) (International System Stage II). His serum IL-6 was markedly elevated (2464 pg/mL, reference; <50, ELISA). He was started on lenalidomide, bortezomib and a dexamethasone-based regimen at a referral oncology centre along with maintenance haemodialysis (HD) and then subsequently lost to follow-up.

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Figure 1 T2-weighted (A) and T1-weighted (B) mid-sagittal MRI of the spine showing a wedge compression fracture with altered signal at the L1–L3 vertebral bodies, suggestive of osteoporosis or metastasis.

One year later, in December 2013, he presented again with worsening uraemic symptoms, low back pain and increasing fatigue. On enquiry, he was found to be on irregular treatment, and later switched to thalidomide and a dexamethasone-based regimen with maintenance HD before coming to our centre. A follow-up bone marrow evaluation revealed persistence of MM with similar plasmablastic morphology (Bartl histological stage 3, grade 3). He was continued on thalidomide and dexamethasone-based therapy with maintenance HD, along with supportive therapy, but finally succumbed to worsening hyperkalemia, sepsis and cardiorespiratory compromise. A comparison of laboratory parameters of the patient at first admission and at 1 year follow-up is presented in [table 1](#).

DISCUSSION

MM and RCCs are more frequently diagnosed among older adults, constituting 3% and 1%, respectively, of malignancies.¹⁰ Recently, a large population-based² study (1973–2006) involving patients with primary RCCs (n=57, 190) and primary MMs (n=34, 156) has reported a strong bidirectional association between these two malignancies. Patients with RCCs had a higher overall relative risk (51%) of secondary MMs (n=88) than those in the general population (median follow-up=2.5 years), whereas that of RCCs was 89% higher among patients with MM compared to the general population (n=69, median follow-up=1.83 years). Thirty-five per cent (31/88) of secondary MMs and 55% (38/69) of secondary RCCs were observed within the first year of diagnosis of primary malignancy. Only

two patients were found to have MM associated with metastatic RCCs. As surgery, rather chemo radiotherapy, is the treatment of choice for RCC, the possibility of therapy-induced MM carcinogenesis seems highly unlikely.

A systematic review of 21 patients with an RCC-MM association, including those reported by Cooper *et al*⁷ (1991–2008), and their comparison with our case is presented in [table 2](#). As described by Ojha *et al*² and others, the majority of cases were observed in males (M:F=13:8) with a predilection for the whites (11/21) as opposed to the African-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%) patients, MM occurred as an SPM after a time gap ranging from 11 months to 26 years, comparatively longer than RCC as an SPM (9/21, 42.8%, 20–24 months). Synchronous RCC and MM were reported in three patients (2 by Ozturk *et al*³, 1 by Sakai *et al*).⁸ Of interest is the fact that right-sided RCCs outnumbered the left-sided ones (11 (52%) vs 8 (38%)); one had bilateral tumours, and the majority were of clear cell phenotype. Barring three patients (2 pulmonary, 1 para-aortic lymph node metastases), all presented at an early stage (I/II) (stage III in our case) 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.^{5 6} Fifteen of 21(71.4%) patients had a κ chain phenotype. When

Figure 2 Bone marrow aspirate smears (A) showing plasmablastic myeloma cells (Bartl grade 3) with polylobated nuclei and conspicuous nucleoli (Wright Giemsa, $\times 400$). Bone marrow trephine biopsy (B and C) showed diffuse sheets of plasmablastic myeloma cells filling entirely the intertrabecular space (packed marrow, Bartl histological stage 3) (H&E, B; $\times 100$, C; $\times 400$). Cyclin D1 immunohistochemistry (D), in the present case, showing weak grade 1 positivity (10–20%) among the tumour cell nuclei. Note the intense grade 2 nuclear positivity (20–50%) among tumour cell nuclei in another case of multiple myeloma (E) for comparison (peroxidase antiperoxidase, $\times 100$).⁹

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 in RCC is reported to be 26–31% in the metastatic setting.⁵ 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 mostly due to MMs (5/13 expired, including the present case), whereas none of the patients had RCC-related mortalities.

IL-6 is one of the most important proliferation and survival factors in myeloma.^{8–10} Sakai *et al*,⁸ for the first time, described the paracrine role of IL-6 in MM carcinogenesis. In their case of synchronous RCC and MM, serum IL-6 levels decreased from 240 to 19 ng/L following nephrectomy, which in turn had a dramatic impact on therapy for MM. Furthermore, when stimulated with recombinant IL-6 in vitro, cultured myeloma cells started proliferating, which led to the hypothesis that IL-6 produced by RCC cells acted in a paracrine fashion for the survival, proliferation and progression of MM. Although MM and RCC are both dependent on the same cytokines such as IL-6, tumour necrosis factor- α (TNF- α) etc, this seems highly unlikely in our case as the second malignancy occurred years after the first. On the other hand, the cumulative effect of IL-6 from the prior

RCC might have caused osteoclast activation, which possibly explains the lytic lesions, advanced histological stage (packed marrow) and overall poor response to chemotherapy in our case. Furthermore, the increased production of IL-6 by the adipocytes (our patient was overweight) might have been the added cause for RCC as well as the aggressive MM following RCC.²

A high proportion of patients with MM-RCC had a 'κ' phenotype rather than λ (16κ, 5λ, including our patient). This probably explained the lack of renal insufficiency (more commonly associated with the 'λ' phenotype) as a dominant presentation, and the overall favourable prognosis seen in all MMs (3/4 deaths were of λ phenotype, including the present case). The exact genetic mechanism underlying this 'κ' chain preponderance in the MM-RCC setting is still not known and needs further exploration in future studies. C-met oncogene mutation, seen more commonly in hereditary papillary RCCs, has recently been implicated in IL-6-induced myeloma cell proliferations.¹¹ However, the majority of RCCs reported to date with MMs have been of clear cell phenotype, which commonly harbours Chromosome 3p abnormality, which has not been described in MM.

Cyclin D1 overexpression is an early and unifying event in myeloma pathogenesis, although the prognostic significance has

Table 1 Clinicolaboratory parameters of the patient at the time of first admission (2012) and at 1-year follow-up (2013)

Laboratory parameters	2012	2013	Reference range
Haemoglobin (g/L)	77	57	120–140
Haematocrit (%)	23	16	45–50
Total leucocyte count ($\times 10^9/L$)	4.8	3.0	4–11
Total platelet count ($\times 10^9/L$)	177	150	150–450
Erythrocyte sedimentation rate (mm/1st hour Westergren)	120	Not done	<50
Serum urea (mg/dL)	87	123	20–40
Serum creatinine (mg/dL)	3.1	10.7	0.5–1.2
Serum total protein (g/dL)	15.2	13.4	6–8
Serum albumin (g/dL)	1.6	2.0	3.5–5
Albumin: globulin ratio	0.2	0.3	0.8–2
Serum uric acid (mg/dL)	17.8	–	3.4–7
Corrected calcium (mg/dL)	10.4	10.8	8.5–11
Serum protein electrophoresis (cellulose acetate, pH=8.4)	Thick M band	Thick M-band	Absent
Serum immune fixation electrophoresis	IgG (9960 mg/L)	Not done	700–1600
Serum light chain assay	λ (245 mg/L)	Not done	5.71–26.3
Serum β_2 microglobulin (mg/L)	3.66	Not done	0.6–2.28
Serum interleukin-6 (pg/mL)	2466	Not done	<50
Bone marrow morphology ⁹ (figure 2A–C)	3 (plasmablastic)	3 (plasmablasti c)	–
Bartl histological grade	3 (plasmablastic)	3 (plasmablastic)	–
Bartl histological stage	III (>50%)	III (>50%)	–
Pattern of infiltration	Diffuse sheet	Diffuse sheet	–
Cyclin D1 expression (immunohistochemistry) ⁹	Grade 1 (10–20% nuclear positivity)	Not done	–
Management	Lenalidomide, bortezomib, dexamethasone, maintenance haemodialysis	Thalidomide, dexamethasone, maintenance haemodialysis	
Outcome	Lost to follow-up	Expired (12 months)	

been shown to be controversial in several studies. Cyclin D1 overexpression results either due to translocation t (11; 14) (q13; q32) or gene amplification.⁹ Patients with myeloma who harbour t (11; 14) are categorised as the standard risk group, whereas those with t (4; 14) and deletion (del) 17p are regarded as the poor risk group.¹⁰ Recently, we studied the prognostic utility of cyclin D1 expression in 14 newly diagnosed patients with MM by IHC (8 positive, 6 negative) and correlated that with various histomorphological features.⁹ Six of eight cyclin D1 positive patients showed a better response to bortezomib, lenalidomide or the thalidomide-based chemotherapeutic regimen than did the cyclin D1 negative group, although the outcome did not show any statistical significance. Compared to other positive patients, the present case had a weak, grade 1 cyclin D1 positivity (10–19% nuclei), which might have been responsible for the aggressive behaviour and poor outcome. Besides these, other adverse cytogenetic markers in MM such as t (4; 14) and del 17p were not tested in our case due to the non-availability of these tests at our centre as well as financial constraints. Whether it is the prior RCC or the underlying de novo adverse cytogenetic/molecular events per se that might have explained the adverse myeloma biology in the present case

is still a matter of speculation. More in-depth studies in the future are required to substantiate this underlying mechanism.

Learning points

- ▶ Multiple myeloma-renal cell carcinoma (MM-RCC) has shared risk factors like obesity, hypertension and smoking.
- ▶ Both RCC and MM share similar cytokine requirements like interleukin-6 (IL-6) for which IL-6 targeted therapy may be useful in both.
- ▶ 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 metastases.

Table 2 Association between renal cell carcinoma and plasma cell myeloma: comparison between present case with those published in the literature (1991–2008)

Features	Badros <i>et al</i> ⁴	Choueiri <i>et al</i> ⁵	Bhandari <i>et al</i> ⁶	Sakai <i>et al</i> ⁸	Present case (2012–2013)
No. of cases; M/F	5; 4/1	8; 6/2	6; 3/3	1; Female	1; Male
Ethnicity	4; Caucasian, 1; African-American	7; Caucasian, 1; African-American	–	Japanese	Indian
Mean age at diagnosis ^{3*} (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 MM: 64
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	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, anaemia, stage III RCC (LK), raised IL-6 (240 ng/L; normal <5 ng/L), raised CRP	RK, clear cell, stage III, lymphovascular invasion present. Inferior vena cava invasion: absent
Management of RCC, outcome	Nephrectomy (4), Toremifene (1), remission (4), LN 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 (postnephrectomy)	Radical nephrectomy+RT, no recurrence or metastasis, till date
Pathology of MM	Lytic lesions (spine, 2/5), renal failure (2/5), asymptomatic (1/5), κ + (5/5), 3/5 IgG+, 2/5 IgA+	Multiple bony lytic lesions (6/8 spine), 2 plasmacytomas (1 sternum, 1 RK), anaemia (1), pancytopenia (1), abdominal mass (1) (RK plasmacytoma), 4/8 κ +, 3/8 λ +, 5/8 IgG+, unknown (1)	1/6 solitary plasmacytoma (rib), 1/6 MGUS, 5/6 κ +, 3/6 stage IIIA, 1 stage IIA, 1 stage IA (none with creatinine >2 mg %) (Durie Salmon)	Stage IIIA, IgG κ +	Lytic lesions in spine, renal impairment present; IgG λ , Durie Salmon IIIB, ISS II, IL-6; 2464 pg/mL (upto 50)
Management of MM, outcome	CT/RT†, SCT, 4/5 CR, 1/5 PR	Radical nephrectomy (RK plasmacytoma), CT/RT	RT/thalidomide/dexamethasone	Vincristine/melphalan/methyl prednisolone	Lenalidomide, bortezomib, dexamethasone; thalidomide, dexamethasone, haemodialysis
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	Persistence of the disease and expired at 12 months post-MM diagnosis
Suggested hypotheses	?genetic/immune dysregulation/ environmental	?genetic/environmental/immune dysregulation/ therapy related	Possibly genetic/epigenetic/environmental	Possible role of IL-6 as an autocrine and paracrine factor	Obesity, smoking, IL-6

*Pathological diagnosis after nephrectomy (in some cases, the retrospective review showed abnormal radiological findings even before the actual diagnosis).

†Chemotherapy (vincristine, adriamycin (doxorubicin), dexamethasone, thalidomide, bortezomib, melphalan, methyl prednisone, lenalidomide, arsenic trioxide, rituximab, in varying combinations) and radiotherapy.

CR, complete remission; CRP, C reactive protein; IL-6, interleukin-6; ISS, International System Staging for myeloma; LK, left kidney; LN, para-aortic lymph node; M/F, male/female; MGUS, monoclonal gammopathies of undetermined significance; MM, plasma cell myeloma; PR, partial remission; RCC, renal cell carcinoma; RK, right kidney; SCT, autologous stem cell transplantation.

Contributors SP and SM were involved in the conceptual design, acquisition and interpretation of the data, as well as the writing and editing of the manuscript. RG'BV reviewed the manuscript for intellectual content. IV provided the patient management and follow-up data, and also read and reviewed the manuscript. All the authors agreed to the final content of the manuscript to be published.

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