Original Article

Is thrombocytosis a useful prognostic marker in renal cell carcinoma? Results of a single-center retrospective analysis

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ABSTRACT

Introduction: Our aim was to determine the correlation of platelet count with stage and grade of renal cell carcinoma (RCC) and to determine whether progression of disease was more likely in those with thrombocytosis.

Materials and Methods: A retrospective review of patients with RCC from January 2004 to December 2011 was undertaken. Patients with no preoperative platelet count and those with multiple tumors were excluded. Disease progression was defined as appearance of local recurrence or distant metastasis on follow-up. Thrombocytosis was defined as a platelet count of >400,000/cumm. Standard tests of significance and multivariate analysis using logistic regression were performed.

Results: A total of 322 cases were identified. The median follow-up was 7 months (range, 2-84 months). The platelet count correlated significantly with higher Fuhrmann grade, as well as increasing TNM stage at diagnosis. Patients with a platelet count of >400,000/cumm (n = 35) had a significantly higher mean tumor size and worse grade at diagnosis than those with a normal platelet count (n = 287). Patients with thrombocytosis also had a significantly worse stage at presentation. Progression of disease was seen more often in patients with thrombocytosis (28.6% vs 11.9%, P = 0.07). The median time to progression was significantly faster in patients with thrombocytosis (9 vs 18 months, P = 0.018). However, on multivariate analysis TNM stage was the only significant predictor of time to progression.

Conclusion: Rising platelet count correlated significantly with advancing stage and grade of disease. Patients with thrombocytosis were significantly more likely to have advanced tumors at presentation, poorer histological features, and rapid disease progression.

Key words: Prognostication, renal cell carcinoma, thrombocytosis

INTRODUCTION

Renal cell carcinoma (RCC) is referred to as the 'internists' tumor' due to its varied presentation and often unpredictable course. Every urologist has known patients with small renal masses but distant metastases, and at the other end of the spectrum, those who survive years with extensive disease. Some may even have seen spontaneous regression of metastatic RCC.

Prognostication of these cases has remained difficult, and a bewildering number of markers and prognostic systems have been used to better characterize prognosis in RCC.[1] The need for accurate prognostication became even more acute with the advent of targeted therapy for advanced RCC, and here too, new systems were devised.[2] Of these, the International Metastatic RCC Database Consortium prognostic model has proven accurate and has recently been externally validated.[3,4] There is now a growing body of the literature, suggesting that thrombocytosis could prove a simple, accurate and inexpensive prognostic marker in many malignancies, including RCC.[5] We, therefore, decided to review our experience to determine the prognostic significance of the platelet count in all stages of RCC.

MATERIALS AND METHODS

Ours is tertiary medical center in southern India with a large uro-oncology practice. We undertook a retrospective review

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of our electronic medical record database. All patients with biopsy or histopathologically proven RCC from January 2004 to June 2011 were eligible for inclusion. Patients undergoing either partial or radical nephrectomy were included. Patients with no record of a preoperative platelet count were excluded. Those with bilateral or multiple tumors [including von Hippel Lindau (vHL) disease] were also excluded from the study.

TNM staging was reviewed according to the American Joint Committee for Cancer 2009 revision of the International TNM classification. Tumor and nodal status were based on histopathology of the surgical specimen with radiological input. Metastases status was assessed using imaging studies, namely contrast-enhanced computed tomography (CECT) of the abdomen and chest X-ray, with CT chest in selected cases. Baseline data collected on all patients included demographic variables, laboratory parameters, TNM stage, pathological features, and available follow-up and survival data. The Fuhrmann system was used to assess tumor grade. Disease progression was defined as the new appearance of local recurrence or distant metastasis on a follow-up visit. Thrombocytosis was defined as a platelet count above 400,000/cubic milliliter (cuml).

Statistics

Initially, the correlation between baseline patient and tumor characteristics with the platelet count was studied. Patients were then classified into two arms: Those with and without thrombocytosis. These groups were then compared with respect to gross and microscopic tumor characteristics, TNM stage, and disease progression (as defined above). Standard statistical tests of significance were applied. Furthermore, multivariate analysis by logistic regression was performed using thrombocytosis, TNM stage, and tumor size as variables. A $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 16.

RESULTS

Figure 1 describes the derivation of the study group after applying the exclusion criteria. A total of 649 patients with RCC were identified during the study period. There was no record of a platelet count in 308. Of the remaining 341 patients, 11 were diagnosed cases of vHL disease, and a further 8 had bilateral tumors, leaving 322 in the study group.

Baseline demographic and tumor variables of the study population are represented in Table 1. The association of clinical and staging variables with the platelet count is represented in Table 2. We discovered that the platelet count was significantly higher in females and those with Fuhrmann grade 3-4 tumors. The platelet count also showed a significant progressive increase with TNM stage.

Patients were subsequently classified into those with thrombocytosis (n = 35) and compared with those with a normal platelet count (n = 287) [Table 3]. Both groups were similar with respect to age and gender. Patients with thrombocytosis had significantly larger tumors. Their tumors were also significantly more likely to have sarcomatoid and rhabdoid features, lymphovascular invasion, and capsular invasion at diagnosis. Patients with thrombocytosis had a significantly higher tumor stage; a significantly lower hematocrit and higher total leucocyte count than those with a normal platelet count. The rate of progression was higher in those with thrombocytosis with a significantly quicker median time to progression in this group.

Multivariate analysis of time to progression revealed TNM stage as the only significant predictor [Table 4]. The possible reason for this is the relatively short follow-up in our study.

DISCUSSION

Thrombocytosis has been implicated as an adverse prognostic factor in a number of malignancies including

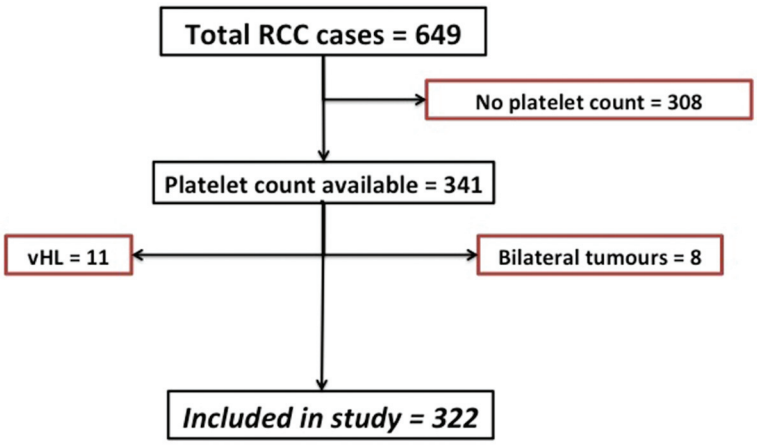

Figure 1: Flowchart depicting derivation of the study group

Table 1: Baseline demographic and tumor factors (*n*=322)

Age (years)	Mean: 52.33 (range: 14–84)
	SD: 11.93; SEM: 0.66
Male:female	3.3:1 (247:75)
Platelet count (/cumm)	Mean: 234,276.4
	SD: 114, 860.5; SEM: 6400.9
Follow-up (months)	Median: 7 (range: 3–84)
Tumor size (centimeters)	Mean: 7.49
	SD: 3.731; SEM: 0.208
Histological subtype (%)	
Clear cell	278 (86.4)
Papillary	21 (6.5)
Chromophobe	13 (4.1)
Collecting duct	8 (2.5)
Malignant oncocytoma	2 (0.6)
Fuhrmann grade (%)	
I	21 (6.5)
II	166 (51.6)
III	108 (33.5)
IV	27 (8.4)
T stage at diagnosis (%)	
I	151 (46.9)
II	60 (18.6)
III	102 (31.7)
IV	9 (2.8)
Node positive at diagnosis (%)	28 (8.7)
Metastases at diagnosis (%)	13 (4.0)
Final TNM stage	
I	150 (46.6)
II	54 (16.8)
III	100 (31.1)
IV	18 (5.6)

SD = Standard deviation, SEM = Standard error of mean, TNM = Tumour nodes metastasis

Table 2: Association of clinical and staging variables with the platelet count

Characteristics	Mean platelet count	*P* value
Sex		0.03
Male	229,878.5	
Female	248,760	
Age (years)		0.078
<55	244,951.9	
56-65	227,732.9	
66-75	207,222.2	
>75	147,857.1	
Grade		<0.001
1 and 2	210,497.2	
3 and 4	264,041.9	
Subtype		0.931
Clear cell	231,967.4	
Others	235,681.8	
T stage		<0.001
1	201,271.5	
2	232,932.2	
3	265,427.2	
4	380.333.3	
Nodal status		<0.001
N0	225,017	
N1	331,500	
Metastases		<0.001
M0	230,048.5	
M1	334,769.2	
TNM stage		<0.001
1	204,793.3	
2	228,722.2	
3	262,360	
4	340,611.1	

TNM = Tumour nodes metastasis

RCC.[6] In these situations, the exact cause of the secondary thrombocytosis is unclear, but it appears that circulating cytokines and growth factors play an important role.[6] Of these, interleukin (IL)-6 appears to be the most potent stimulator of megakaryocyte progenitors, and a raised level has been demonstrated in the majority of patients with malignancy-associated thrombocytosis.[7] Other cytokines that have been implicated include macrophage-colony stimulating factor, thrombopoietin, and IL-11.[7] Platelets have also been implicated in tumor growth as they can secrete large concentrations of vascular endothelial growth factor (VEGF) that is crucial for tumor angiogenesis, while also stimulating megakaryocyte maturation at the bone marrow level.[7,8] Activated platelets also secrete thrombopoietin, which reinforces platelet formation in the bone marrow.[8] Platelets and their secretory product thrombospondin have also been implicated in tumor metastasis. The purported mechanisms include allowing adhesion of tumor cells to the vascular endothelium, penetration through the endothelial barrier, and preventing malignant cells from being cleared from the circulation.[6]

Over the past decade, a few studies have studied the prognostic significance of thrombocytosis in RCC. In the largest study so far Bensalah *et al.* reported that a platelet count > 450,000/cuml positively correlated with worsening T stage, Fuhrman grade, tumor size, lymph node status, and distant metastasis in 804 patients with RCC.[8] Patients with thrombocytosis also had a significantly worse 5-year survival on both univariate and multivariate analyses.[8] This impact on prognosis was seen for both localized and metastatic disease.[8] Inoue *et al.* also showed a positive correlation between thrombocytosis and tumor size and stage.[7] In their study, thrombocytosis was associated with

Table 3: Results

Characteristics	Thrombocytosis, *N*=35	Normal platelets, *N*=287	*P* value
Mean platelet count (cumm)	478,342.9	204,512.2	
Mean age (years)	49.9	52.6	0.209
Male:Female	26:9	221:66	0.87
Mean size (cm)	10.4	7.1	<0.001
Grade			<0.001
1	1	20	
2	14	152	
3	11	97	
4	9	18	
Histology			0.782
Clear cell	30	248	
Papillary	3	18	
Chromophobe	2	11	
Oncocytoma	0	2	
Collecting duct	0	8	
Sarcomatoid or Rhabdoid features	14.29%	4.18%	0.003
Lymphovascular invasion	71.42%	39.55%	0.04
Capsular invasion	61.29%	33.05%	0.003
Tumor stage			<0.001
T1	9	142	
T2	3	56	
T3	19	84	
T4	4	5	
N0	25	269	<0.001
N1	10	18	
M0	30	279	<0.001
M1	5	8	
TNM stage			<0.001
I	8	142	
II	2	52	
III	18	82	
IV	7	11	
PCV (hematocrit)	30.66	36.76	<0.001
Total leukocyte count	14,900	8012.67	<0.001
Progression of disease	28.57%	11.88%	0.075
Median time to progression	9 months	18 months	0.018

TNM = Tumour nodes metastasis, PCV = Hematocrit

Table 4: Multivariate analysis

Factors	Odds ratio	95% CI for OR	*P* value
Platelet count (400,000)	0.92	0.31-2.76	0.88
Tumor size (cm)	1.01	0.91-1.13	0.84
TNM stage (1–4)	2.75	1.69-4.48	<0.001

OR = Odds ratio, CI = Confidence interval, TNM = Tumour nodes metastasis

a worse prognosis, but when adjusted for stage or tumor size, this was limited to pT1-2 tumors.[7] In the study by Cho *et al*., thrombocytosis significantly correlated with tumor size and metastasis.[9] It was a predictor of recurrence-free survival on univariate but not multivariate analysis.[9] Patel *et al*. reported a retrospective study on 237 patients who underwent radical nephrectomy for clinically localized disease.[5] They concluded that an increase in platelet count of >20% following radical nephrectomy could reliably predict recurrence and cancer-free survival.[5]

The need for prognostication in metastatic RCC has gained immense significance with the birth of targeted therapy, with accurate prognostication allowing individualization of therapy. In an early study, Symbas *et al*. studied 259 patients with metastatic RCC who received a variety of adjuvant therapies.[6] They discovered that those whose platelet count remained persistently normal had a 64% longer survival than those with thrombocytosis, even on multivariate analysis.[6] Perhaps the most important system for prognostication, the International Metastatic RCC Database Consortium prognostic model includes platelet count and neutrophil count above the upper limit of normal, as independent adverse factors.[3] The other components of this system are similar to those of the Memorial Sloan Kettering Cancer Centre (MSKCC) model and include hemoglobin less than the lower limit of normal, corrected calcium greater than the upper limit of normal, Karnofsky performance status <80%, and time from diagnosis to treatment of <1 year.[3] This model has recently been externally validated and has shown a concordance index of 0.68-0.73, which was better than other similar systems.[4] Other prognostic systems for metastatic RCC, including a revised model from the MSKCC (for patients treated with sunitinib), and one from the Cleveland Clinic also include the platelet count as one of the parameters.[10] While there is no doubt that a combination of factors will be most reliable in prognostication, the platelet count alone is a simple investigation that can give the clinician an indicator of the gravity of disease, and we believe that further prospective studies could help better establish its exact role.

The success of targeted therapy has also opened up the possibilities of neoadjuvant and adjuvant therapy for locally advanced RCC. Research in this area is underway and three randomized trials are ongoing to determine the efficacy of these drugs in the adjuvant setting.[11] The fact that thrombocytosis correlates well with adverse prognosis, even in patients with clinically nonmetastatic disease, may possibly be used to select patients who would benefit from further treatment.

Our study is limited by its retrospective nature and the relatively short follow-up of patients (median of 7 months). Only 18% (n = 58) of our patients had more than 3 years

follow-up, and only 6.8% (n = 22) had more than 5 years follow-up. This could be the reason that platelet count was not deemed significant on multivariate analysis of time to progression. However, platelet count correlated well with other adverse clinicopathological factors and was associated with a significantly shorter time to progression. Our study remains the first such study from the Indian subcontinent and has the second largest sample size from similar papers.

CONCLUSION

Rising platelet count correlated significantly with advancing stage and grade of disease in RCC. Patients with thrombocytosis were significantly more likely to have advanced tumors at presentation, poorer histological features, and more rapid disease progression. Multivariate analysis shows TNM stage to be the only reliable predictor of time to progression and further prospective studies are needed to establish the utility of the platelet count in this setting, and in potentially predicting the need for adjuvant therapy.

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