



Histopathological and Immunohistochemical Analysis of Renal Cell Carcinomas At A Tertiary Care Hospital In Kashmir.

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Abstract

Objective: To study the histopathological and immunohistochemical features of Renal cell carcinoma (RCC) subtypes.

Method: A total of 62 cases of RCCs were studied prospectively at our centre, SKIMS Soura Kashmir. These included small biopsy and specimen samples. These tumours were analysed histopathologically and subtyped into Clear cell RCC, Papillary cell RCC, Chromophobe RCC and Sarcomatoid RCC. Immunohistochemical staining of these subtypes was done with CD 10, Vimentin, CK7, CD117 & P504s antibodies and positivity determined.

Results: This study focussed on the Renal cell carcinoma sub types. On histopathology most of the cases were Clear cell type followed by the papillary RCC, Chromophobe RCC and Sarcomatoid RCC. The mean age was approximately around 40 years and most of the tumors were left sided, majority were in the middle pole. On staining CD10 was positive in 80% of Clear cell RCC, 75% of Papillary RCC and 33% of Chromophobe RCC. Vimentin positivity was seen in 58% Clear cell RCC & 62% of Papillary RCC. CK7 staining was positive in 100% of Chromophobe RCC, 6% of clear cell RCC & 50% of papillary RCC. CD117 positivity was observed in all Chromophobe RCC, 4% Clear cell RCC and 13% Papillary RCC. P504s was seen positive in 62% of Papillary cell RCC & 4% of Clear cell RCC.

Conclusions: This histopathological study showed that major subtype of RCC diagnosed at our centre is Clear cell RCC followed by Papillary cell RCC. The ImmunoHistoChemical markers, CD 10 & Vimentin are the first line markers for diagnosis of these two subtypes. CD10 & Vimentin being more specific for Clear cell & Papillary cell RCC as compared to CK7 & CD117 who are more specific for Chromophobe RCC.

Keywords: Renal Cell Carcinomas(RCC), Clear cell RCC(CRCC), Papillary RCC(PRCC), Chromophobe RCC(CHRCC), Sarcomatoid RCC, ImmunoHistoChemistry, CD 10, Vimentin, CK7, CD117, P504s.

Introduction

Renal cell carcinoma is one of the most common & lethal renal cancers. Its origin is considered to be epithelial, originating from the cells of the renal tubules and are adenocarcinomas. It also known as Grawitz tumor or hypernephroma as based on the

concept of their origin from the adrenal rests in the kidney¹. Renal cell carcinoma (RCC) accounts for 2% of adult malignancies and 90-95% of neoplasms of the kidney².

RCC is classically divided into 5 main histologic subtypes: Clear cell, Papillary, Chromophobe, Collecting duct and unclassified RCC³. Out of this Clear cell & Papillary are the most common types, comprising 70-80% & 14-17% RCCs, respectively. Collecting duct (Bellini duct) carcinoma is the rarest type of RCC (<1%). Unclassified RCCs are those which do not fit into any of these 4 subtypes morphologically or cytogenetically⁴. Clear cell carcinomas (CRCC) histologically have a clear or granular cytoplasm and are mostly sporadic. Papillary carcinomas (PRCC) have a papillary growth pattern, multifocal in origin and are associated with dialysis linked cystic disease. Chromophobe RCCs (CHRCC) have an eosinophilic cytoplasm, distinct cell membranes and a halo around the nucleus. Collecting duct carcinomas arise from the collecting duct in the medulla and are nests of malignant cells surrounded by a fibrotic stroma.

The classic presentation of RCCs consists of hematuria, pain and flank mass⁵. However many patients lack all of these and present with systemic symptoms of weight loss, abdominal pain, and anorexia. These often invade the renal vein and grow in the vessel lumen and may extend through the inferior vena cava into the right side of the heart. Renal cell carcinoma occasionally causes paraneoplastic endocrine syndromes including pseudo hyperparathyroidism, erythrocytosis, hypertension, and gynecomastia⁶. RCC rarely occurs before 40 yrs of age, but its incidence increases from 4th decade to a peak in the sixth and seventh decades⁷.

Newer classification of renal cell tumours was proposed by WHO in 2016 based on cytoplasmic features, anatomic location of tumours and the alterations at molecular level. For grading and prognosis the most widely used system was proposed by Fuhrman and colleagues⁸. It includes nuclear grades based on nuclear size, irregularity of the nuclear membrane and nucleolar prominence⁹.

Immunohistochemistry is an important tool in our setup to differentiate between different subtypes of primary renal epithelial neoplasms and confirm the histopathological diagnosis. A number of antibodies like CD 10, Vimentin, CK7, CD117 & P504s are useful in determining the renal origin and in the differential diagnosis. In this study we aimed to identify the IHC panel which would correlate to

different subtype of RCCs determined on histopathological diagnosis.

MATERIALS AND METHODS

This study was conducted in the Department of Pathology at Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar. It was a prospective study of 2 years from September 2018 to September 2020. The study was conducted after taking permission from SKIMS Ethical Committee.

Complete clinical details, examination findings, and radiological investigations of all patients were studied. Both excised specimen and renal core biopsies were included. The excised tissue specimens were processed routinely and stained with Haematoxylin and Eosin. Only malignant tumours of kidney were taken up for immunohistochemistry and benign renal tumours were excluded from our study. Microscopic sections of all cases were used to select proper blocks for tissue microarray. Immunohistochemistry were performed on representative areas as identified on H&E slides. Tumor cells were taken positive only when the correct staining pattern was achieved. CD10 stains cell surface, Vimentin stains Cytoplasm, CK7 gives membranous & cytoplasmic staining CD117 stains cell membrane & P504s gives cytoplasmic staining. Immunoreactivity was taken positive only when greater than 10% cells got stained.

RESULTS

Out of a total of 62 biopsies received, 51 (82.3%) were large specimen while as only 11 (17.7%) were small biopsies. When relation of age with biopsy type was assessed, majority i.e. 4 (36.4%) of small biopsies belonged to patients aged 45-54 years while as majority i.e. 20 (39.2%) of large specimen belonged to patients aged 35-44 years. The mean age in small biopsy group was 44.8±11.52 years and that in large biopsy the mean age was 42.7±13.99 years as shown in figure 1.

Majority of small and large biopsy i.e. 9 (81.8%) and (36 70.6%) belonged to males while as 2 (18.2%) small biopsies and 15 (29.4%) large biopsies belonged to females. Out of a total of 11 small biopsies, 8 (72.7%) were clear cell type RCC, 2 (18.2%) were papillary type RCC and 1 (9.1%) was chromophobe RCC. Against a total of 51 large specimen, 42 (82.4%) were clear cell type RCC, 6 (11.8%) were papillary type RCC, 2 (3.9%) were chromophobe RCC and 1

(2%) was sarcomatoid RCC on histopathology as shown in Table 1. Tumor location was right sided in 11 (21.6%) and left sided in 40 (78.4%). Out of the total of 51 tumors, majority i.e. 22 (43.1%) were in middle pole followed by 17 (33.3%) in upper pole and 12 (23.5%) in lower pole. The size of majority of tumors i.e. 31 (60.8%) was 5-19cm, 16 (31.4%) tumors sized <5cm while as >10cm was the size of 4 (7.8%) tumors. There were 29 (56.9%) greyish white color, 18 (35.3%) were yellow brown and 4 (7.8%) were greyish brown. 31 (60.8%) tumors were hard in consistency, 12 (23.5%) were firm and 8(15.7%) were soft in consistency. As per Fuhrman's grade, 28 (54.9%) had Grade II, 17 (33.3%) had grade III, 4 (7.8%) had grade I while as 2 (3.9%) had grade IV as shown in Figure 2. There were 24 (47.1%) with stage II tumours, 18 (35.3%) with stage I, 6 (11.8%) with stage III and 3 (5.9%) with stage IV.

On immunohistochemistry CD10 was positive (Fig 3) in 80% of Clear cell RCC, 75% of Papillary RCC and 33% of Chromophobe RCC. Vimentin positivity (Fig 4) was seen in 58% Clear cell RCC & 62% of Papillary RCC. CK7 staining (Fig 5) was positive in 100% of Chromophobe RCC, 6% of clear cell RCC & 50% of papillary RCC. CD117 positivity was observed in all Chromophobe RCC, 4% Clear cell RCC and 13% Papillary RCC. P504s was seen positive in 62% of Papillary cell RCC & 4% of Clear cell RCC. These results are illustrated in Table 2.

DISCUSSION

Out of the total 62 samples received at our centre majority of patients were below the age of 45 years. The most common age group in our study was 35-44 and 45-54 years. This was comparable with Kumar D *et al*¹⁰, Agnihotri S *et al*¹¹ and Jun C *et al*¹². However data from West have revealed that approximately 3.4 to 5% of patients with renal tumors were less than 40 years and incidence increases with age and peaks at 60 to 70 years¹³.

In our study majority of cases belonged to males (72.6%) which was comparable with Verhoest G *et al*¹⁴ and Jun C *et al*¹².

We found out that out of a total of 11 small biopsies, 8 (72.7%) were clear cell type RCC, 2 (18.2%) were papillary type RCC and 1 (9.1%) was chromophobe RCC. Against a total of 51 large specimen, 42 (82.4%) were clear cell type RCC, 6 (11.8%) were papillary

type RCC, 2 (3.9%) were chromophobe RCC and 1 (2%) was sarcomatoid RCC on histopathology. Our findings were comparable with a study by Lopez JI¹⁵, according to which the renal tumors were classified as clear cell (50.7%), papillary (8.5%), chromophobe (14.6%), unclassified (16.9%) and clear cell papillary (9.3%).

On immunohistochemistry CD10 was positive in majority of Clear cell RCC & Papillary RCC and 33% of Chromophobe RCC. Vimentin positivity was seen in 58% Clear cell RCC & 62% of Papillary RCC. CK7 staining was significantly positive in all cases of Chromophobe RCC but negative in 94% of clear cell RCC. CD117 positivity was observed in all Chromophobe RCC & negative in 96% Clear cell RCC and 87% Papillary RCC. P504s was seen positive in 62% of Papillary cell RCC but negative in 96% of Clear cell RCC. This pattern of IHC staining for categorizing subtypes of RCC is well documented^{16,17,18,19}. Our results are in agreement with the studies of Bazille *et al*¹⁸ and Tretiakava *et al*²⁰ who found that Vimentin was positive in CRCC and negative in CHRCC & P504s was present in 88% of PRCC, 4% of CRCC and was absent in CHRCC, respectively.

CONCLUSION

We recommended using Vimentin, CK7, and CD10 as IHC markers in accordance to our results to confirm the RCC subtypes. Our study suggests specificity of P504s to confirm PRCC, CD117 for CHRCC & CD10 for CRCC. However according to the recent WHO classification of the renal cell carcinoma subtypes, genetic derangement is most appropriate to determine the RCC subtype²¹. So cytogenetic means should be the gold standard. But such methods are very costly and unavailable at our pathological laboratory. In our set up Immunohistochemical studies are still an appropriate technique for accurate categorization of the most cases of the renal cell carcinoma.

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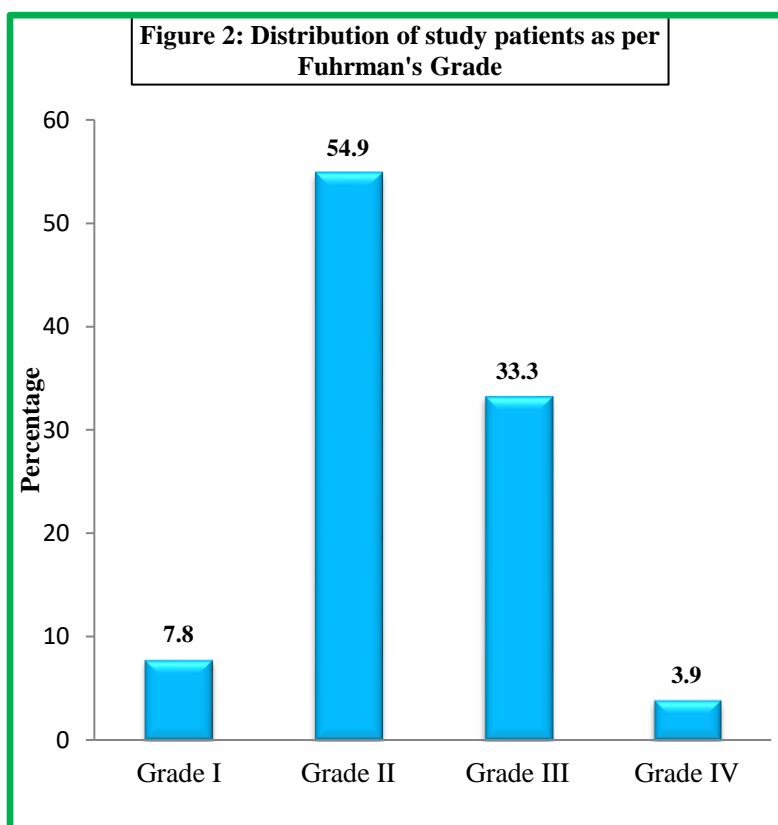
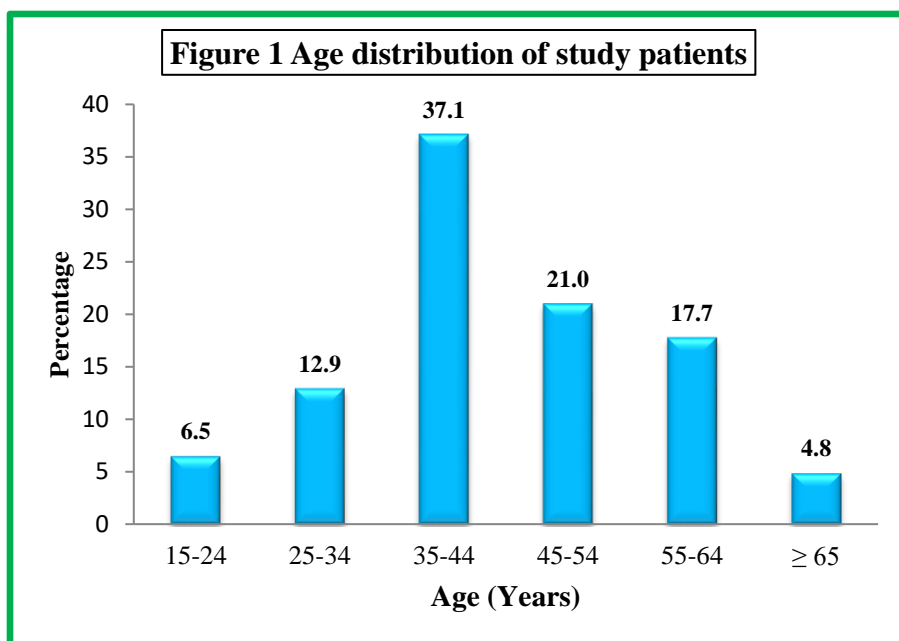


Figure 3: Photomicrograph showing positivity for CD 10

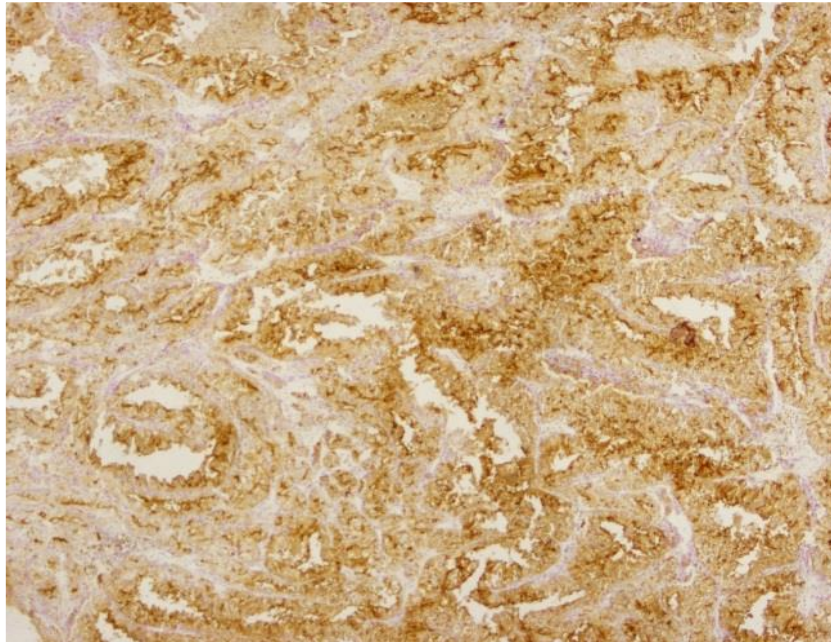


Figure 4: Photomicrograph showing positivity for Vimentin

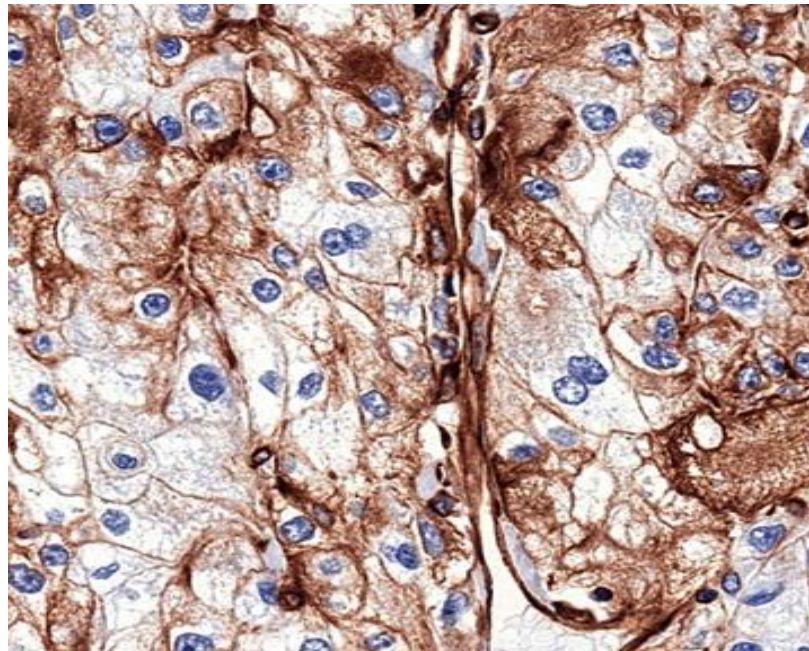


Figure 5: Photomicrograph showing positivity for CK-7

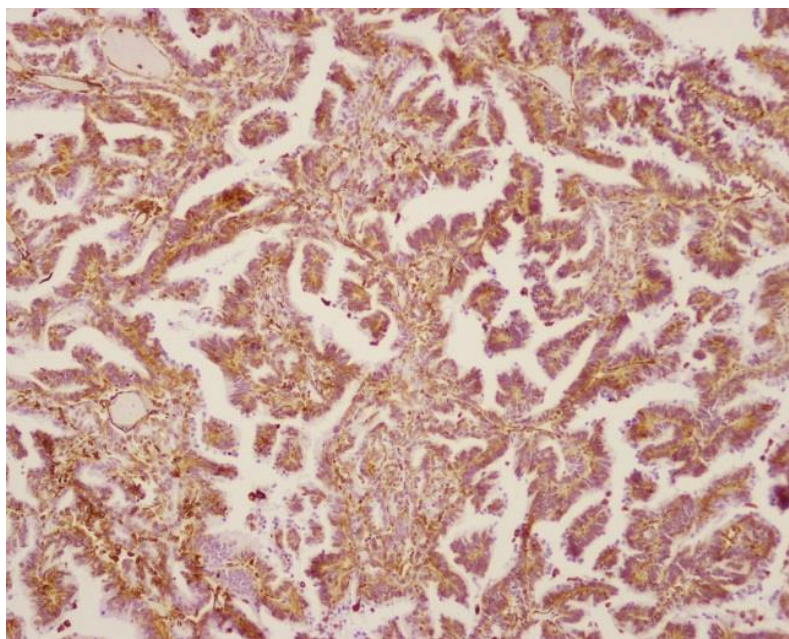


Table 1: Distribution of study patients as per histological type

Histological Type	Small Biopsy		Large Biopsy		Total	
	No.	%age	No.	%age	No.	%age
Clear cell type RCC	8	72.7	42	82.4	50	80.6
Papillary type RCC	2	18.2	6	11.8	8	12.9
Chromophobe RCC	1	9.1	2	3.9	3	4.8
Sarcomatid RCC	0	0.0	1	2.0	1	1.6
Total	11	100	51	100	62	100

Table 2.		Immunohistochemical Staining results				
RCC Subtype	Positivity	CD 10	Vimentin	CK7	CD117	P504s
CRCC N=50	Positive	40	29	3	2	2
	Negative	10	21	47	48	48
PRCC N=8	Positive	6	5	4	1	5
	Negative	2	3	4	7	3
CHRCC N=3	Positive	1	0	3	3	0
	Negative	2	3	0	0	3