

ORIGINAL ARTICLE

ROLE OF IMMUNOHISTOCHEMISTRY IN SUBTYPING RENAL CELL CARCINOMAS WITH OVERLAPPING MORPHOLOGICAL FEATURES

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Background: Renal cell carcinoma (RCC), accounts for 2–3% of all new cancers diagnosed. Most renal tumours have characteristic histological features, which help in their sub classification. However, some cases do show overlapping morphology which pose a diagnostic challenge for the pathologists. Tumour ancillary studies such as immunohistochemistry (IHC) may play a significant role in segregation of these tumours. This study was undertaken to determine the role of IHC in diagnosing these tumours. **Methods:** It was a Cross-sectional, prospective study over a period of two years from 1st January 2014 to 30th December 2015. It was carried out in histopathology laboratory of Shifa International Hospital, Islamabad. A total of fifty-five (n=55) nephrectomy specimens having RCC subtypes were included. A specific morphological diagnosis was rendered in each case on H&E. A panel of six immunohistochemical markers CK7, CD10, CD117, CA IX, AMACR and Vimentin was then applied in each case and a final diagnosis considering both morphology and IHC was given. Statistical analysis was done using SPSS version 20.0. Mean and SD were calculated for quantitative variables where as frequencies and percentages were calculated for qualitative variables. **Results:** Out of a total of 55 cases, 36 (65.55%) were males whereas 19 (34.5%) were females. The mean age of patients was 54.04±14.40 years. Clear cell RCC comprised 70.9% (n=39), Papillary RCC 14.5% (n=8), Chromophobe RCC 10.9% (n=6) and clear cell papillary RCC 3.6% (n=2) of cases on morphology. After application of IHC stains in all cases, 83.6% (n=46) of cases were found to have correct diagnosis on H& E. However, 16.4% (n=9) of cases could not be correctly diagnosed on morphology alone and it was in these cases that IHC played a major role in reaching a final diagnosis. **Conclusion** Although most RCC subtypes display a characteristic morphology on H&E, in a significant proportion of the cases there are considerable overlapping morphological features. Our study shows that a correct diagnosis cannot be made on H & E alone in a notable number of cases. Therefore, IHC should be applied in all cases to reach a final diagnosis, which has both prognostic and therapeutic implications.

Keywords: Renal cell carcinoma; Immunohistochemistry; Clear cell papillary Renal cell carcinoma

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INTRODUCTION

Renal cell carcinoma (RCC), accounts for 2–3% of all new cancers diagnosed and 85% of all primary renal neoplasms in adults.¹ It is the most fatal urological cancer accounting for approximately 2% of all cancer deaths.² Renal cell carcinoma is divided into 5 main histologic subtypes: clear cell, papillary chromophobe, collecting duct and unclassified RCC. Of these clear cell RCC (70–80%), papillary RCC (14–17%) and chromophobe RCC (4–8%) are the most frequent. In the past few years many new types of RCC have been defined, of which most notable is clear cell papillary RCC having combined features of both clear cell and papillary RCC.³

Most of these tumour types manifest typical diagnostic histology on routine haematoxylin & Eosin (H&E) stain; however, overlapping morphological characteristics pose some difficulties even in the hands of experienced pathologists. Clear cell RCC usually has solid pattern with clear cells separated by thin septae, however high grade clear cell RCC has granular, eosinophilic cytoplasm making it difficult to distinguish from chromophobe RCC.^{3,4} Papillary RCC has discrete

papillary fronds lined by cells with eosinophilic cytoplasm, they must be differentiated from high grade clear cell RCC which demonstrate pseudo papillae and clear cell papillary RCC having papillae lined by clear cells.⁴ Chromophobe RCC is composed of sheets of large cells with voluminous cytoplasm and small cells with granular cytoplasm. Their main differential diagnosis is with clear cell RCC.³ Clear cell papillary RCC is comprised of papillae lined by clear cells making it difficult to differentiate from both clear cell RCC and papillary RCC.⁴ The prognostic factors along with treatment options, including neoadjuvant chemotherapy depends upon the specific subclass of renal cell carcinoma, therefore an accurate histopathological diagnosis has become increasingly important.⁵

To render an accurate diagnosis additional method such as electron microscopy and molecular genetics have been proposed however both these methods are time consuming, expensive and not available in most centres locally. Immunohistochemistry (IHC) in contrast is a fast and reliable method that is applicable in most pathological laboratories. To date numerous markers have

been studied in renal neoplasms; depending on morphological features a different panel of IHC markers can be applied. Al-Ahmedie *et al* showed that standard morphological evaluation in combination with the judicious use of 5 IHC markers (Ca IX, CD117, AMACR, CK7 and CD10) can produce correct diagnosis in >90% of cases.⁶

To date, not much research work has been done in Pakistan regarding IHC profile of RCC subtypes. As prognosis along with choice of neoadjuvant chemotherapy depends on specific subtype of RCC, it is therefore increasingly important to explore the role of immunohistochemistry in combination with morphology to reach a final diagnosis

MATERIAL AND METHODS

It was a prospective, cross sectional study conducted at histopathology department, Shifa International Hospital Islamabad, from 1st January 2014 to 30th December 2015 after approval from IRB and Ethics committee of the hospital. All malignant renal epithelial tumours belonging to subtypes clear cell RCC, papillary RCC, chromophobe RCC and clear cell papillary RCC were included in the study. Patients of all ages and both genders were considered. Poorly fixed samples and specimens with scanty tumour were excluded from the study.

Representative sections of the tumour were first embedded in paraffin and tissue blocks cut in 3–5 microns' sections. Slides were stained by H&E for light microscopy. A specific morphological diagnosis was rendered in each case on H&E. Blocks that were best representative of lesion were taken for IHC, for which sections will be cut at 4 microns from paraffin embedded blocks, deparaffinized and rehydrated. Later on, tissue sections were autoclaved at 121 °C for 15 min, after which they were treated with the diluted antibodies at 4 °C over-night.

Immunohistochemical staining was done using the IHC kits and results interpreted on light microscope using high power field objective. A panel of six immunohistochemical markers CK7, CD10, CD117, CA IX, AMACR and Vimentin was applied in each case and a final diagnosis considering both morphology and IHC was given. If a particular antibody gave brown precipitate on reaction with tumour cells, in specific distribution it was considered as a positive result for that specific antibody whereas very faint or no staining at all was considered as a negative result.

Results were verified by consultant histopathologist to minimize the bias.

Statistical analysis was done using SPSS version 20.0. Mean and SD were calculated for quantitative variables like, patients age. Frequencies and percentages were calculated for qualitative variables like gender of the patient, subtype of RCC on H & E and H& E + IHC.

RESULTS

A total of 55 cases of renal cell carcinomas were included in the study. Of these 36 (65.55%) were males whereas 19 (34.5%) were females. The age range of the patients varied from 26 to 76 years with a mean age of 54.04±14.40 years.

Frequencies of RCC subtypes including clear cell RCC, papillary RCC, clear cell papillary RCC and chromophobe RCC were calculated on H&E, i.e., morphology alone and on the basis of combined H & E + IHC. Clear cell RCC was the most frequent subtype in all cases. Results are shown in tables-1 and 2.

All 55 cases were subtyped on H&E. After application of IHC 46 (83.6%) cases were confirmed (Figure-1, 2 and 3) where as in 9 (16.4%) cases IHC results differed from morphological opinion. In these cases, IHC proved to be invaluable in rendering a final diagnosis. A breakdown of subtypes of RCC which could and could not be correctly diagnosed is given in table-3.

On morphology, a total of 39 cases of clear cell RCC were diagnosed. On application of immunohistochemistry it was seen that 36 were correctly diagnosed, whereas 3 were not. Out of 3 cases which were not correctly diagnosed, 2 were found to be clear cell papillary RCC (Figure-4), whereas 1 was found to be chromophobe RCC on application of IHC (Figure-5). On morphology 8 cases of papillary RCC were diagnosed. Of these 05 were found to be correct on application of IHC whereas 3 were not. Of the 3 cases, which were not correctly diagnosed all of them were found to be clear cell RCC (Figure-6) on application of IHC. Out of 6 cases of chromophobe RCC which were diagnosed on morphology, 5 were found to be correct on application of IHC.

One case which was not correctly diagnosed turned out to be eosinophilic variant of clear cell RCC (Figure-7) on application of IHC. Clear cell papillary RCC was the rarest subtype and only 2 cases were diagnosed on morphology, however both of them were found to be incorrect on application of IHC. On IHC one turned out to be papillary RCC and the other clear cell RCC (Figure-8).

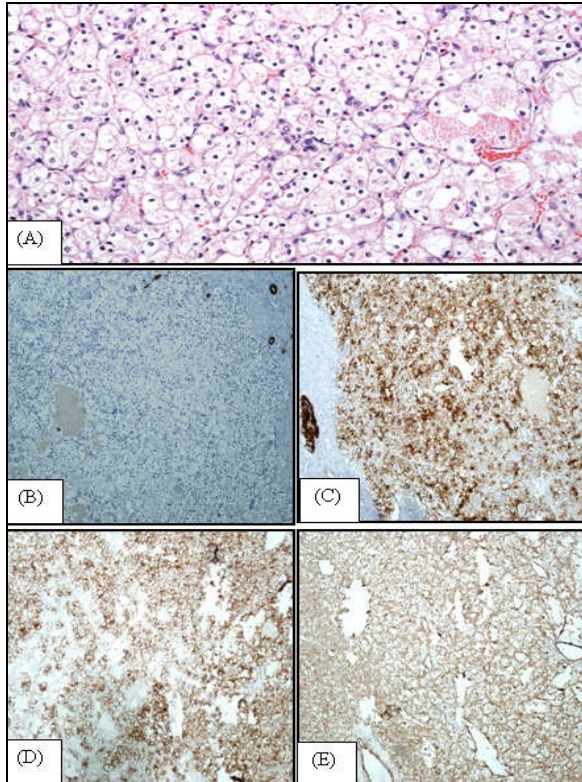


Figure-1: Morphology and IHC of clear cell RCC.
(A) Nests of clear cells separated by prominent intervening vessels. **(B)** Tumor showing CK7 negativity **(C)** membranous CAIX positivity **(D)** membranous & cytoplasmic CD10 positivity **(E)** weak cytoplasmic AMACR positivity (original magnifications X200[A])

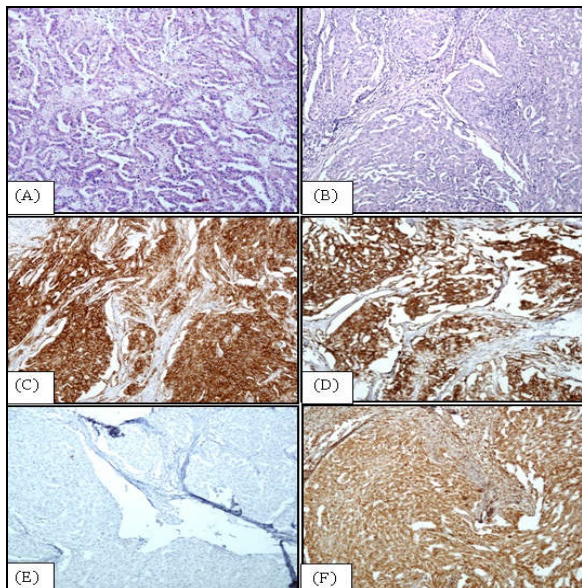


Figure-2: Morphology and IHC of papillary RCC.
(A,B) Tumor showing papillary architecture with multiple papillae lined by pseudo stratified columnar epithelial lining and cells exhibiting granular cytoplasm. **(C)** Tumor showing cytoplasmic AMACR positivity. **(D)** Diffuse membranous CK7 positivity. **(E)** CAIX negativity. **(F)** Vimentin positivity (Original magnifications X200[A], X100[B])

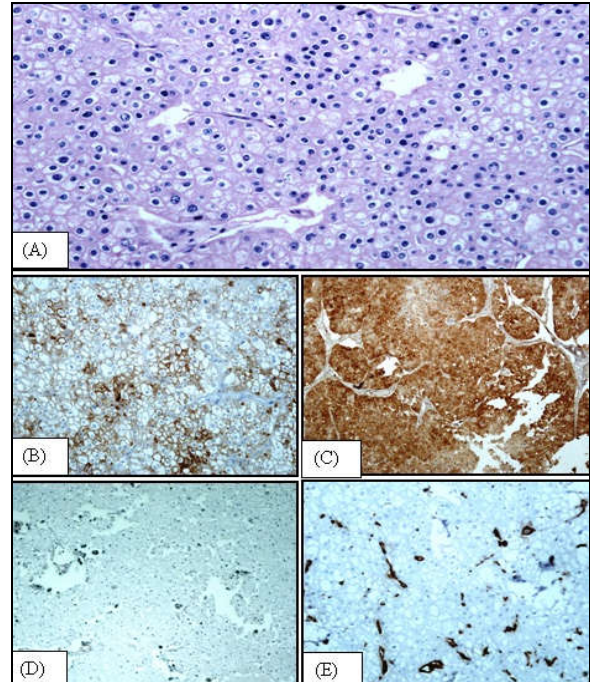


Figure-3: Morphology and IHC of chromophobe RCC. **(A)** Tumour showing nests of cells with perinuclear halo and granular cytoplasm. **(B)** Tumour showing membranous CK7 positivity. **(C)** Cytoplasmic and membranous CD117 positivity. **(D)** CAIX negativity. **(E)** Vimentin negativity (original magnifications X200[A])

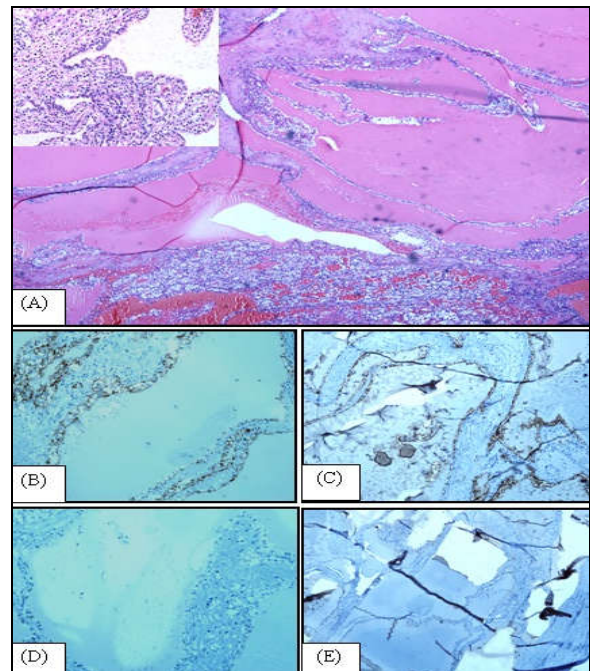


Figure-4: (A) Tumour with tubulocystic and focal papillary architecture (inset) lined by cells with clear cytoplasm. Morphological diagnosis: Clear Cell RCC **(B)** Tumour showing membranous CK7 positivity. **(C)** Cup like membranous CAIX positivity. **(D)** CD10 and **(E)** AMACR negativity. Final diagnosis: Clear cell papillary RCC (original magnifications X200[A])

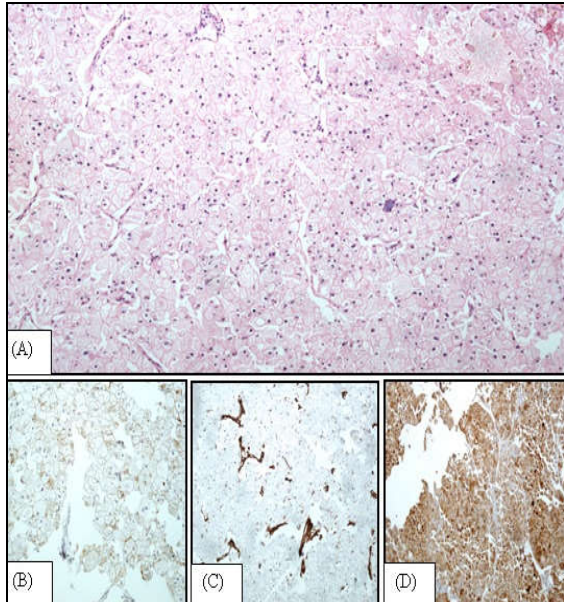


Figure-5: (A) Nests of cells with clear to granular cytoplasm and prominent sinusoids. Morphological diagnosis: Clear cell RCC (B) Tumour showing CK7 positivity (C) Vimentin negativity. (D) Diffuse CD117 positivity. Final diagnosis: Chromophobe RCC. (original magnifications X200[A])

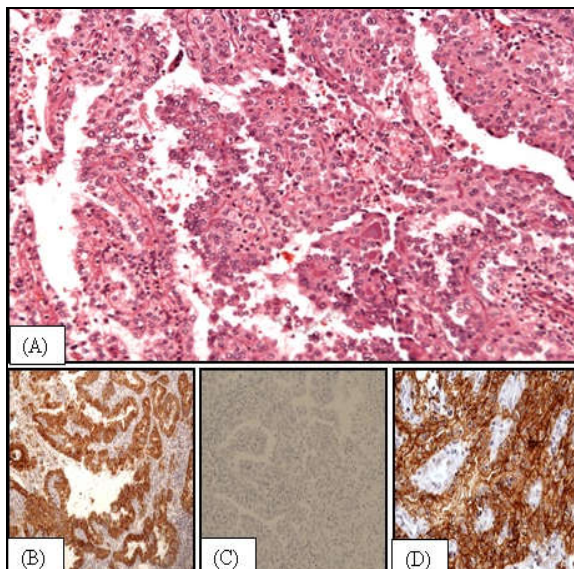


Figure-6: (A) Tumour showing papillary architecture lined by cells with granular eosinophilic cytoplasm. Morphological diagnosis: papillary RCC. (B) Tumour showing membranous CD10 positivity (C) CK7 negativity and (D) CA1X positivity. Final diagnosis: Clear cell RCC. (original magnifications X200[A])

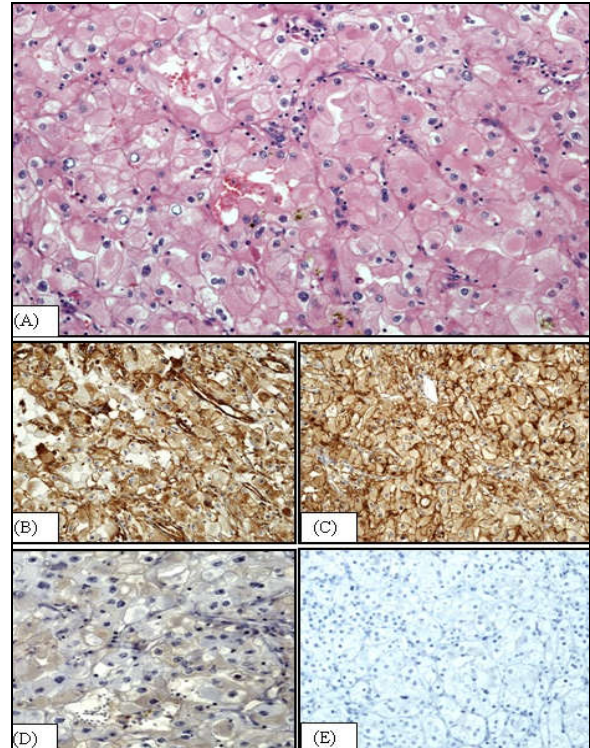


Figure-7: (A) Tumour showing nests of cells with perinuclear halo and granular eosinophilic cytoplasm. Morphological Diagnosis: Chromophobe RCC. (B) Tumour showing membranous CD10 and (C) CA1X positivity. (D) CK7 and (E) AMACR negativity. Final diagnosis: Eosinophilic variant of clear cell RCC (original magnifications X200[A])

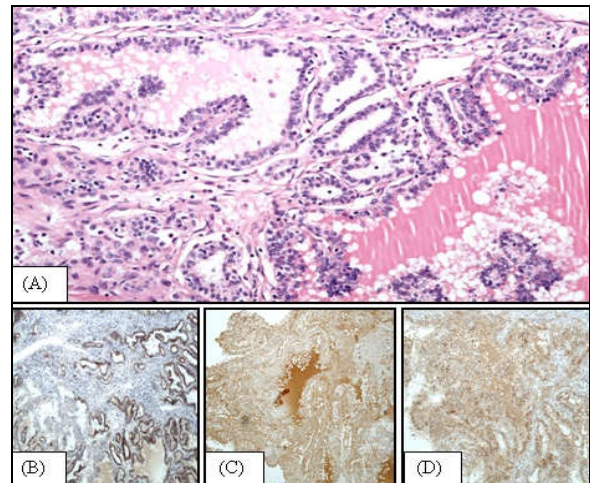


Figure-8: (A) Tumour showing papillae lined by cells with clear cytoplasm and apically placed nuclei. Morphological diagnosis: Clear cell papillary RCC. (B) Tumour showing membranous CK7 positivity (C) Diffuse cytoplasmic AMACR positivity (D) Membranous CD10 positivity. Final diagnosis: Papillary RCC (original magnifications X200[A])

Table-1: Subtypes of RCC on H&E (Morphology)

	Frequency	Percent	Valid Percent
Clear cell RCC	39	70.9	70.9
Papillary RCC	8	14.5	14.5
Chromophobe RCC	6	10.9	10.9
Clear cell papillary RCC	2	3.6	3.6
Total	55	100.0	100.0

Table-2: Subtypes of RCC on morphology +IHC

	Frequency	Percent	Valid Percent
Clear cell RCC	41	74.5	74.5
Papillary RCC	6	10.9	10.9
Chromophobe RCC	6	10.9	10.9
Clear cell papillary RCC	2	3.6	3.6
Total	55	100.0	100.0

Table-3: Frequency of RCC subtypes which could and could not be correctly diagnosed on morphology alone.

Subtypes of RCC as diagnosed on morphology (H&E) alone	Correct diagnosis (Morphology + IHC)		Total
	Yes	No	
Clear cell RCC	36 (65.45%)	3 (5.45%)	39
Papillary RCC	5 (9.09%)	3 (5.45%)	8
Chromophobe RCC	5 (9.09%)	1 (1.82%)	6
Clear cell papillary RCC	0 (0.00%)	2 (3.64%)	2
Total	46 (83.6%)	9 (16.4%)	55

DISCUSSION

This study was carried out to determine the role of immunohistochemistry in subtypes of renal cell carcinoma having overlapping morphological features on morphology and which are difficult to diagnose on morphology alone.

The age range of the patients in our study was from 26–76 years with a mean age of 54 years. In a study carried out in 14 different European centres of RCC patients the mean age of the patients was found to be 63 years, which is higher than our mean age.⁷ However this is based on western data and studies carried out in South Asia show a significantly younger age at diagnosis.^{8,9} Regarding gender distribution, our study showed that RCC was more common in males in contrast to females with a M:F ratio of 1.89:1. Other studies also support our results.^{10,11} In our study clear cell RCC was the most common subtype comprising 74.5% cases. A study carried out in America showed that clear cell RCC was the most prevalent subtype at 77%, followed by papillary 10% and chromophobe 5%.¹² In a recent study carried out in Jinnah post graduate medical centre, Karachi Clear cell RCC was again found to be the most frequent subtype at 70%.⁸

Immunohistochemistry plays a major role in diagnosis of renal cell carcinoma. Previous studies have shown that although diagnosis of renal cell carcinoma is usually straight forward on routine H&E staining specially in resection specimens, accurate subtyping requires additional special studies in order

to reach a definite diagnosis. Recently many new subtypes of renal cell carcinoma have been characterized which have overlapping morphological features with previously recognized categories. These subtypes have different prognosis and require different treatments hence the value of an accurate and confident diagnosis has become indispensable.³ Studies from different parts of the world have shown that morphology alone has a limited sensitivity and specificity. In separate studies by Gowrishankar¹³ and Barocas¹⁴ diagnostic accuracy of histology alone in subtyping of RCCs was found to be 80% and 83% respectively. Namnak *et al*¹⁵ showed that morphology in conjunction with IHC was able to complement the diagnosis given on morphology alone in more than 90% of cases. The results of our study show that correct diagnosis, defined as diagnosis in which morphological diagnosis complemented diagnosis made on immunohistochemistry could be achieved in 83.6% of cases. In 16.4% of cases histology showed considerable overlapping morphological features so much that a correct diagnosis could not be achieved. In these cases, immunohistochemistry proved to be imperative in reaching a final diagnosis.

The diagnostic accuracy of routine histopathology alone can be improved by combining with various techniques such as fluorescent insitu hybridization (FISH), electron microscopy and micro RNA based arrays.^{16,17} However all these methods are not only expensive but also time consuming, IHC in contrast is a fast and new method. It is readily available in most laboratories and is easy to interpret.

Different studies have utilized the role of different immunohistochemical markers in reaching a definite diagnosis.^{18,19} In a study by Ahmedie *et al* carried out in 2011, on needle core biopsies he showed that histology on routine H & E alone can correctly classify RCC in only about 81% of the cases where as if a panel of 05 immunohistochemical markers including CK7, AMACR, CA IX, CD 117 and CD10 were used the overall diagnostic accuracy improved to about 90% where as it improved upto 99% in common RCC subtypes. This study thus further highlights the increasing role of immunohistochemistry in subtyping of RCC and its importance in accurate classification of RCCs especially by amateur pathologists with limited experience.⁶

In our study, clear cell RCC was the most frequent subtype comprising 74.5% of the cases (n=41). On morphology, a total of 39 cases of clear cell RCC were diagnosed. On application of IHC, it was seen that 36 were correctly diagnosed, whereas 3 were not. Out of 3 cases which were not correctly diagnosed, 2 were found to be clear cell papillary RCC on application of IHC whereas 1 was found to

be chromophobe RCC. Most of the cases showed a classical morphology comprised of nests and sheets of polygonal cells. These nests were separated by prominent fibrovascular connective tissue septae. Individual cells had round nuclei with abundant clear cytoplasm and well-defined cell membranes. Few cases showed a granular/ eosinophilic cytoplasm where as some cases particularly those with a higher grade showed formation of papillae. On IHC, as is the classical profile²⁰ our results also showed CK7 to be -ve, CA IX showed strong membranous staining, Vimentin was +ve, CD 10 was +ve and CD117 was consistently -ve. AMACR showed mixed results in our study. Out of 41 cases in which a final diagnosis of clear cell RCC was rendered combining both morphology and IHC, 15 (36.5%) were positive whereas 26 (63.41%) were negative. However, all these cases which were positive for AMACR, showed weak, faint positivity. In a study by Hanan *et al*, he showed that although CK7 and AMACR are mostly -ve in tumour cells however a small proportion of cases may show faint weak positivity.¹⁸

Papillary RCC was next in number, with 06 cases (10.9%) diagnosed on morphology+IHC. Although initially 8 cases (14.5%) were diagnosed as papillary RCC on morphology alone, however on combining with IHC it was found that only 5 out of 8 cases were correctly labelled, whereas others were mislabelled. In all 3 cases which were misdiagnosed on morphology, it was later seen that their IHC profile matched that of clear cell RCC. This is most likely due to the fact that conventional RCC may also form papillae resulting in it mimicking papillary RCC. One of the cases which was interpreted as clear cell papillary RCC on routine H & E, proved to be papillary RCC when IHC was applied. For the purpose of study, no segregation was made between type 1 and type 2 papillary RCC, since many papillary RCCs show mixed features of both type 1 and 2 papillary RCC.²¹ All of our cases showed that the tumour was comprised predominantly of papillae with prominent fibrovascular cores. The papillae were lined by single or multiple layers of cells with small cuboidal nuclei and scant to abundant eosinophilic cytoplasm. On IHC our results showed that CK7, CD10, AMACR and Vimentin were consistently positive in all cases where as CAIX and CD117 were negative. Previous studies like that of Padhan have shown that a marked discordance (10/28 cases) among pathologists was seen in differentiating clear cell RCC with formation of papillae vs papillary RCC. IHC stain CK7 was helpful in this regard since it was found to be positive in most papillary RCCs and is negative in clear cell RCC.²¹ In our study too we found that conventional clear cell RCC was most likely to be misinterpreted as papillary RCC. In our

study we found that CK7 and CA IX were most useful in segregating between these two entities. Since CK7 was negative and CA IX was positive in clear cell RCC whereas papillary RCC showed the reverse pattern. AMACR although considered a useful marker by most for diagnosis of papillary RCC, however in our study we found much confusion regarding its interpretation. Since many cases of clear cell RCC also showed faint weak staining for AMACR, our experience suggests that only cases with diffuse strong cytoplasmic staining should be interpreted as papillary RCC.

Chromophobe RCC comprised 06 cases (10.9%) when both morphology and IHC were taken in account. Out of 6 cases of chromophobe RCC which were diagnosed on morphology, 5 were found to be correct on application of IHC. One case which was not correctly diagnosed turned out to be eosinophilic variant of clear cell RCC on application of IHC. On morphology most of our cases showed nests of cells with well-defined membranes and abundant granular cytoplasm. There was perinuclear halo along with raisinoid appearance of nuclei. In our study we found that chromophobe RCC was most likely to be misinterpreted as eosinophilic variant of clear cell RCC and vice versa. In a study by Pardhan *et al*¹ the highest number of discordant cases were seen between chromophobe RCC and eosinophilic variant of clear cell RCC. Similarly, other studies from various parts of the world have also reported difficulty in differentiating chromophobe RCC from clear cell RCC with eosinophilic cytoplasm.^{15,22,23} Yasir *et al* in 2012 proposed that a combination of positive CD10 and negative RON and CK7 is best suitable immunohistochemical panel in distinguishing clear cell RCC from chromophobe RCC.²⁴ In our study we found that chromophobe RCC was positive for CK7 and CD117 while negative for CAIX and Vimentin. This is in contrast with clear cell RCC which showed exactly the opposite staining pattern. A combination of CD117 which is seen to be positive in only chromophobe RCC amongst all other RCC subtypes along with any other afore mentioned markers is sufficient to reach a definite diagnosis.

Clear cell papillary RCC was found to be the rarest subtype of RCC amongst all four which we included in the study. It comprised a total of 2 cases (3.6%) when both morphology and IHC were considered. Although 2 cases were diagnosed on morphology, however both of them were found to be incorrect on application of IHC. On IHC 01 turned out to be papillary RCC and the other clear cell RCC. In our cases we saw that this tumour was found in otherwise normal kidney and not end stage kidney as was once thought.²⁵ In our cases the tumour was comprised mostly of multiple papillae with focal

tubocystic pattern. The papillae were lined by cells with clear cytoplasm and at least focal areas with nuclei polarized away from the basement membranes with a linear arrangement. The tumour lacked psammoma bodies and necrosis. In our study none of the cases could be correctly diagnosed on morphology alone. The two cases which were initially labelled as clear cell papillary RCC on morphology proved to clear cell RCC and papillary RCC. Similarly, another two cases which were labelled as clear cell RCC on morphology were found to be clear cell papillary RCC when IHC was applied. Previous studies have also shown difficulty in differentiating between clear cell RCC, papillary RCC and clear cell papillary RCC.^{5,26}

A study by Dhakal *et al* also in 2016 showed that there are few tumours which can show overlapping morphological and immunohistochemical features of clear cell RCC and clear cell papillary RCC.²⁷ In the recent ISUP consensus conference held at Vancouver it was recognized that conventional clear cell RCC may show areas that were typical for clear cell papillary RCC. Such tumours are best classified as clear cell RCC to date.²⁸ In our study we found that CK7, CA IX, CD 10 and AMACR comprised a suitable panel for differentiating between tumours having clear cells along with papillae. Clear cell papillary RCC in 02/02 cases diagnosed on IHC showed CK7 and CAIX positivity where as CD10 and AMACR were negative. CA IX in particular showed cup like staining pattern with absence of staining along the lumina which helps in differentiating from clear cell RCC which shows strong diffuse membranous staining. Similarly, CK7 positivity and CD 10 negativity also help in differentiating from clear cell RCC. AMACR is useful in differentiating clear cell papillary RCC from papillary RCC. Since papillary RCC shows strong diffuse AMACR staining whereas clear cell papillary RCC is typically negative.

Other studies have also employed these four markers and shown consistent results for differential diagnosis of renal tumours with clear cells and a papillary morphology.²⁹ An accurate diagnosis of clear cell papillary RCC is of crucial importance owing to its excellent prognosis reported in several studies.³⁰

CONCLUSION

Although most RCC subtypes display a characteristic morphology, on routine H& E, in a significant proportion of the cases there are considerable overlapping morphological features. Our study shows that a correct diagnosis cannot be made on H & E alone in a notable proportion. Therefore, IHC should be applied in all cases to reach a final diagnosis

which has both prognostic and therapeutic implications.

AUTHORS' CONTRIBUTION

NT & NM: Literature search, conceptualization of study design, data collection, data analysis, data interpretation, write-up, proof reading. AH, ZA & INA: Study design, data collection & data analysis, data interpretation, write-up, proof reading.

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