



Histological and immunohistochemically profiles of renal cell carcinoma in northern Nigeria

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Abstract

Introduction: Histologically, renal cell carcinoma (RCC) is classified into predominantly clear cell carcinoma, papillary carcinoma (PC), chromophobe carcinoma, collecting ducts of Bellini carcinoma and Xp11 carcinoma.

Objectives: This study aims to evaluate histological profile and staining patterns of RCC subtypes.

Materials and Method: All cases of RCC histologically diagnosed in the pathology department of a teaching hospital in northern Nigeria in 2015 were stained using a panel of 34βE12, CK7, RCC-ma and CD10 antibodies.

Results: Around 23 cases of RCC, at stage III, were diagnosed. Male: Female ratio was 1:1.9 with a mean age of 40±13 years. The tumors comprised of 11 (47.8%), cases of clear cell (CC) carcinoma, 7 (30.4%) cases of PC, 4 (17.4%) cases of chromophobe carcinoma and a case (4.4%) of Xp11.2-associated carcinoma. Eighty-eight percent of the CC carcinomas were RCC-ma+, 63% were CD10+ while 50% were CK7+. Seventy-five percent of the PCs were RCC-ma+ and 50% were CD10+. The chromophobe (CP) and the Xp11.2-associated carcinomas were only positive for RCC-ma and CD10. All cases of PCs, chromophobe and Xp11.2 related carcinomas were negative for CK7, and all were 34βE12 negative.

Conclusion: In contrast to populations with high incidence of RCC, our patients are predominantly female, younger, presented at higher stages and mostly presented with CC carcinoma.

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Introduction

Data from a population-based cancer registry in Nigeria put age-standardized incidence rates for cancer in the country at 66.4 per 100 000 men and 130.6 per 100 000 women (1). Globally, renal cell carcinoma (RCC) accounts for about 3% of all adult cancers while in Nigeria it has accounted for between 0.3% to 2.3% (2-7).

Histologically, RCC is classified into predominantly clear cell (CC) carcinoma, papillary carcinoma (PC), chromophobe carcinoma, collecting ducts of Bellini carcinoma and Xp11 carcinoma. However, morphological features are often not exact. CC carcinomas may demonstrate tubular, papillary and cystic patterns, while clear “chromophobic” cytoplasm may be seen in other lesions (8). Thus, immunohistochemical characterization for accurate diagnosis is necessary.

Objectives

This study aims to evaluate immunohisto-

Key point

In contrast to populations with high incidence of renal cell carcinoma, our renal cell carcinoma patients in Kano, Nigeria, are predominantly female, younger, presented at higher stages and mostly presented with clear cell carcinoma.

chemical characterization of RCC in patients in northern Nigeria.

Materials and Methods

Tissue blocks of all cases of RCC diagnosed in 2015 were subjected to immunohistochemical staining with CD10, CK7, 34βE12 and RCC-ma. Their histomorphological features including subtype, extent of necrosis, sarcomatoid change, nuclear grade (using the 4-tier system) and tumor, node and metastasis (TNM) staging were also documented.

Tissue sections for immunohistochemistry



(including positive and negative controls for each batch) were cut at three microns. The sections were then subjected to antigen retrieval technique using citrate buffer (pH 6.0) in a pressure cooker for 25 minutes. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 10 minutes, rinsed in phosphate buffer saline (PBS)/Tween 20 and then treated with ultraviolet protein block for 5 minutes.

Dako pre-diluted (RCC-ma and 34 β E12) primary antibodies, and concentrated Thermo Fisher Scientific Inc., (CD10 and CK7) 1:50 and 1:200 dilutions respectively were added to the respective slides for 45 minutes, rinsed thoroughly with PBS/Tween 20 and primary antibody enhancer added for 10 minutes.

Horseshradish peroxidase (HRP) polymer was applied for 10 minutes followed by rinsing in PBS/Tween and distilled water. This was followed by application of chromogenic substrate (3'3'Di-aminobenzidine-trahydrochloride) and immersion in 1% fresh copper sulphate solution for 5 minutes for each. The slides were washed under running tap water, counterstained in Hematoxylin, dehydrated, cleared and mounted.

Immunostaining was considered positive when over 10% of cells showed moderate to strong reaction with cell membrane antigen for CD10 and RCC-ma and cytoplasmic staining for CK7 and 34 β E12.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The research was approved by the institutional ethical committee of Aminu Kano Teaching Hospital, Kano, Nigeria.

Statistical analysis

While categorical data were presented as number and percentage, continuous data were shown as mean \pm standard deviation. Data were analyzed using SPSS

version 16 (IBM Inc.). *P* value <0.05 were considered to be statistically significant.

Results

The study found 23 cases of RCC. Females were more frequently affected than males (M: F ratio 1:1.9). The age range was between 8 and 65 years (mean age 40 \pm 13 years) with peak in the 21–40 year age range. Morphologically 76.5% of the tumors were left-sided but showed no statistically significant gender-related laterality even though all tumors found in males were left-sided (*P*= 0.205). No multifocal or bilateral tumor was recorded. The tumors had a mean diameter of 14.5 \pm 7 cm (range 3-30 cm) and mean weight of 1.1 \pm 0.9 kg (range 0.15-3.5 kg).

Microscopically 11 (47.8%) and 7 (30.4%) cases of CC carcinoma and papillary RCC were diagnosed respectively during the study period, while 4 (17.4%) cases of chromophobe carcinoma and a case (4.4%) of Xp11.2-associated carcinoma were detected (Table 1). The Xp11.2-associated carcinoma was diagnosed based on age of patient with suggestive morphology characterized by papillary architecture composed of voluminous CCs with focal nesting. Other histological features included varying degrees of necrosis in 61.5% of the tumors and sarcomatoid change in 2 cases of CC carcinoma.

Due to technical issues only 14 of the 23 cases were subjected to immunohistochemistry (8/11 CC; 4/7 PC; 1/4 chromophobe and 1/4 Xp). Of total CC carcinomas, 88% were RCC-ma+, 63% were CD10+ and 50% were CK7+. Seventy-five percent (75%) of the PC were RCC-ma+ while 50% were CD10+. The chromophobe carcinoma case showed negative staining for RCC-ma but positivity for CD10. The only case of Xp11.2-associated carcinoma was also positive for RCC-ma and CD10. All cases of PC, chromophobe carcinoma and Xp11.2 related carcinomas were negative for CK7 and similar to CC carcinoma were all 34 β E12 negative (Table 2; Figure 1A-C).

Table 1. Clinicopathologic characteristics of the renal cell carcinoma subtypes

	Clear cell	Papillary	Chromophobe	Xp-associated
Number	11	7	4	1
M: F	1:1	1:2.5	1:1	0:1
Mean age (y)	41 \pm 14	44 \pm 13	35 \pm 5	8
TNM (stage \geq III)	100%	100%	100%	100%
Nuclear grade 4	64%	57%	-	100%
Necrosis	46%	86%	50%	100%
Sarcomatoid change	18%	-	-	-

Abbreviation: TNM; tumor, node and metastasis.

Table 2. Immunohistochemical characteristics of the renal cell carcinoma subtypes

	N	RCC-ma+ (%)	CD10+ (%)	CK7+ (%)	34 β E12-(%)
Clear cell	8	7(88)	5(63)	4(50)	0
Papillary	4	3(75)	2(50)	0	0
Chromophobe	1	1(100)	1(100)	0	0
Xp11.2	1	1 (100)	1 (100)	0	0

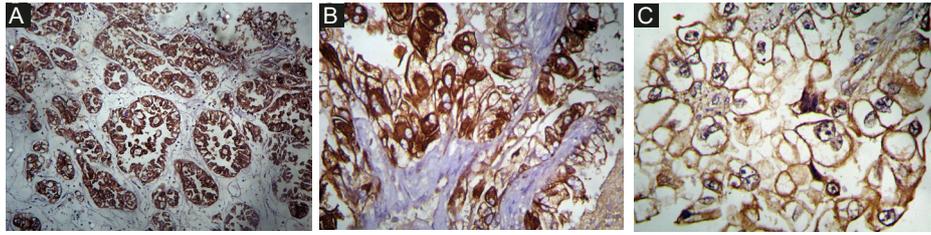


Figure 1. (A) Malignant cells disposed in tubule-papillary patterns and exhibiting complete and strong membrane staining with CD10 antibody ($\times 40$). (B) Strong cytoplasmic staining of malignant clear cell carcinoma with CK7 antibody ($\times 40$). (C) Complete and strong cell membrane staining of clear cell carcinoma for RCC-ma antibody ($\times 40$).

Discussion

The preponderance of female affectation observed in this study is in consonance with reports from a few other centers in the country, but contrasts with some other local and international data. The general trend observed in most studies worldwide, however, is of a male preponderance (9-11).

Excluding the outlier patient aged 8 years, the mean age from this study is 40 ± 13 years. This is within range of the national average of 45 ± 4 years (peak age in fifth decade) (2,4-7,12-19). This is about two decades earlier than the pattern described for western countries where the peak age incidence is in the seventh decade (11,20,21). Earlier age at onset was also documented in an analysis of data from a population-based cancer registry in Morocco, North Africa, Ghana in West Africa, Kenya in East Africa and in India (22-25). Reasons for this observed age-related variation is unclear but changing lifestyle and higher exposure to hazardous work environment among younger Africans may underlie this (26).

The gross morphology of our tumors revealed bulky lesions ranging between 3 cm and 30 cm and weights ranging between 0.15 kg and 3.5 kg. Various centers in the country have also documented very bulky tumors with weights ranging between 0.48 kg and 3.8 kg and tumor widths ranging between 15 and 56 cm (5-7,9-11). A study from Ghana, another West African country, also recorded tumor sizes with a mean diameter of 16.8 ± 4.0 cm (23). In contrast, a large population based study from Europe and a study from the United States showed that tumors ≤ 7 cm accounted for 58.3% and 89.7% of cases diagnosed respectively (27). Such bulky tumors as recorded among our patients support a tendency for late presentation for treatment and may also suggest that the tumors are aggressive. This is buttressed by observation of high frequency of significant necrosis in 61%, high nuclear grade in 57% and sarcomatoid change in 18% of our tumors. Frank et al (29) in their study have also observed that only 1% of all tumors less than 1 cm and 9.2% of all tumors less than 2 cm are usually high grade malignancies. The occurrence of CC carcinoma in patients in our setting (47.8%), even though the most common subtype, is lower than the range of between 60%–85.7% (12-18) documented in other centers in the country and worldwide (30-32). In contrast, even though there was a high frequency of PC

(30.4%), it was within the range of between 23.8% and 46.2% locally reported by others (5,12,17). This country-wide range is also higher than the 10%–15% reported in the western literature (32,33). This higher rate of papillary tumors highlights the need to more comprehensively investigate risk factors that may locally underlie this. The relative rarity of the Xp11.2-related subtypes may reflect not only their truly low incidence but also our inability to carry out genetic studies.

Immunohistochemically, the pattern of positivity of CC carcinoma for RCC-ma and CD10 antibodies in this study (RCC-ma: 88%, CD10: 65%) mirrors that described by Ortiz-Rey et al (34) (RCC: 50%; CD10: 75%) as well as that described by Lee and colleagues (35) (RCC-ma: 60%; CD10: 100%). Even though the latter study as well as that reported by Mi-Kyung et al (36) showed nil positivity for CK7, this study's finding in terms of positivity for the antibody is in consonance with the 75% positivity rate described by Williamson and colleagues (37).

PCs of the kidneys have shown variable staining reactions, especially to the cytokeratins. Cytokeratin 7 has been observed to fairly consistently stain this subtype, but as a consequence of further classification into types 1 and 2, with different staining reactions, the picture is far from unequivocal. The PCs in this study, similar to the CC carcinomas, were CD10+, just as described by Mi-Kyung & Seonwoo (36) and Avery et al (38). The uniform negativity for CK7 contrary to other reports may stem from the finding in this study that these tumors were classified as of type 2 sub-variant. This subtype of PC is wont to be CK7-.

Positivity of Xp11.2-associated carcinoma for CD10 and negativity for CK7 as was found in this study was also documented by Zou et al (39) and Alshenawy (40) respectively. Positivity for RCC-ma is also consistent with what was described by others (41). While other studies have identified strong staining for CK7 in $>70\%$ of chromophobe carcinomas, its negativity in the single case being reported in our study is insufficient as a ground for drawing conclusions. However, CD10 positivity and RCC-ma negativity by the tumor cells is consistent with established staining patterns noted for this subtype (42,43). Positivity of chromophobe carcinomas for CD10 has been shown by Martignoni et al (44) to be associated with greater clinical aggressiveness of this subtype. It also

useful in differentiating it from oncocytoma (CD10-) an important differential for chromophobe carcinoma.

Conclusion

We found, in contrast to populations with high incidence of RCC our patients are predominantly female, younger and present at higher tumor stages. Patients in this region of the world also present mostly with CC carcinomas; and even though of a smaller sample size, the papillary tumors demonstrate a propensity to be CK7-. It is also concluded that a combination of RCC-ma and CD10 are most useful for identification of RCC in our setting ($P=0.01$).

Limitations of the study

The major limitation of this study is small proportion of patients. We suggest further investigations in this regard.

Authors' contribution

ATA, AOJ and DTN were involved in care of patients, data collection, processing of renal biopsies, statistical analysis and the primary manuscript preparation. ATA detailed the initial framework of the study and began acquisition of data and was involved in all stages of the work. AOJ and DTN were involved with immunohistochemistry staining while all authors were involved with slide interpretation. AT did the write-up of the manuscript. All authors read, revised, and approved the final manuscript.

Conflicts of interest

There were no points of conflicts to declare.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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