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Research Article

Evaluation of renal cell carcinomas using TFE3 immunohistochemistry

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Abstract. Introduction: Evaluation of renal cell carcinomas (RCC) with Xp 11.2 translocation is a little explored topic, probably due to the low incidence of this type of renal cell carcinoma. At present, the incidence of RCCs with Xp 11.2 translocation in Romania is unknown. Objective: Through this study we aim to identify the existence of these carcinomas in a chosen case series and to encourage more detailed research and study through molecular biology techniques. The importance of diagnosing these carcinomas results from the fact that they have an increased potential for aggressive behaviour and from the fact that those carcinomas are frequently diagnosed as other types of RCC such as clear cell or papillary RCC. Material and method: We analyzed 191 patients diagnosed with RCC, out of which 47 patients met the histological criteria for Xp 11.2 translocation RCCs. On these tumors we performed immunohistochemical staining for TFE3 and established staining positivity. Results: Out of the 47 cases for TFE3 immunohistochemistry, 7 were considered to have positive staining. Therefore, most of the cases selected for immunolabeling with TFE3 were negative, therefore excluding the diagnosis of RCC with Xp 11.2 translocation in these situations. Conclusion: The importance of including TFE3 immunolabeling in the antibody panels of pathology departments lies on reducing the rate of underdiagnosis of RCC with Xp 11.2 translocation. Cases that show positivity on immunohistochemistry can further undergo fluorescent in situ hybridization Polymerase Chain Reaction for confirmation.

Key Words: renal cell carcinoma, TFE3, immunohistochemistry

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Introduction

Renal cell carcinoma (RCC) is the most common kidney malignancy in adult population, being responsible for more than 85% of all kidney malignancies (Oya 2017).

According to the latest WHO Classification of Tumors of the Urinary System and Male Genital Organs, RCC presents several histopathological forms, one of them being MiT family translocation RCCs (Moch et al 2016). RCC with various translocations on the Xp 11.2 chromosome are included in this family (Moch et al 2016). They result from the fusion of TFE3 transcription factor genes (Argani et al 2001, 2002; Clark et al 1997; Pradhan et al 2015). Although the incidence of RCCs with Xp 11.2 translocation of all RCCs is low, their importance results from the tumors' increased potential for aggression (Ma et al 2014; Pflueger et al 2013). Another key factor defining these types of tumors is the fact that, the higher the aggressiveness, the lower the age of onset (Komai et al 2009; Pradhan et al 2015). The actual incidence of these neoplasms may be higher because it is a recently discovered subtype that is of interest and has been extensively studied over the last decade.

The aim of this paper is to evaluate renal carcinomas with histological features suggestive of carcinoma with translocation Xp 11.2 by TFE3 immunolabeling. The current importance lies in the underdiagnosis of RCC with Xp 11.2 translocation, which can be avoided by practicing TFE3 immunohistochemistry. Usually, they are diagnosed as clear cell or as papillary RCC, due to the similar morphological characteristics of these types of renal malignancies. The more precise the histological classification is, the bigger the significance on the prognosis and on the targeted therapeutic approach is (Moch et al 2016). From a microscopic point of view, Xp 11.2 translocation RCC is a carcinoma composed of eosinophilic cells with solid, alveolar or papillary architecture (Argani et al 2001, 2002; Moch et al 2016). It may have an intensely eosinophilic or clear cytoplasm, discrete cell margins, chromatin vesicles and prominent nucleoli. Psammoma bodies and hyaline nodules can be seen in the stroma (Argani et al 2001, 2002; Moch et al 2016). Those tumors resemble clear cell carcinoma with clear cell variant, papillary RCC, renal multilocular cystic neoplasm with low malignancy potential, oncocytoma or epithelioid angiomyolipoma (Argani et al 2005, 2012; Green et al 2013a; Xu et al 2015). Some RCCs with Xp 11.2 translocation contain melanin pigment (Argani et al 2009, 2010a; Moch et al 2016).

Histopathological examination may be followed by additional tests, such as immunohistochemistry or in situ hybridization tests. It is important to note that immunohistochemistry has diagnostic relevance only in the context of the histopathological aspect of the analysed specimen.

On routine immunohistochemistry, a high sensitivity and specificity of the TFE3 protein was observed for neoplasms with Xp 11.2 translocation (Argani et al 2003). Other immunohistochemical features are under expression of polyclonal cytokeratins, inconsistent expression to PAX8, vimentin, AMACR or epithelial markers (Argani et al 2010b; Smith et al 2014). Some carcinomas may have expression in melanocyte markers. 60% may be positive for cathepsin K and rarely for CD10 (Argani et al 2010b; Smith et al 2014). The definite diagnosis of RCC with Xp 11.2 translocation is made using immunohistochemistry with the specific antibody TFE3 which is completed by detecting the mutation using molecular biology techniques (Oya 2017; Xu et al 2015).

Tumor grading is made according to the size and shape of the nucleoli and is represented by the WHO / International Society of Urological Pathology (ISUP) system.

According to the latest European Association of Urology from 2020, the treatment of choice for localized RCCs is partial nephrectomy. Partial nephrectomy is associated with a lower risk of developing chronic kidney disease. However, there are situations where it is not feasible, for example in the case of locally advanced tumors or unfavorable tumor localization (Professionals). Cryo-ablation and radiofrequency ablation are suitable for small, locally accessible tumors and are recommended for elderly patients with comorbidities, multiple or bilateral tumors, and patients with single kidneys. The oncological results of these methods are comparable to those of partial nephrectomy (Ramirez et al 2013; Tanagho et al 2013). Histological assessment of tumor tissue as well as the surgical margins is not possible when using treatment options that destroy the tissue.

Material and Methods

A number of 191 patients diagnosed with RCC at the Cluj-Napoca Municipal Clinical Hospital, between January 2012 and January 2017, were introduced in this retrospective population analytical study.

This study included patients who underwent partial nephrectomies and radical nephrectomies and who met the following histopathological criteria: clear cell or papillary RCC. The reason for choosing these inclusion criteria consists in the fact that RCC with Xp 11.2 translocation has morphological characteristics superimposable with RCC variant with clear cells and papillary RCC, therefore it is often confused with these types of malignancies. Immunohistochemistry and molecular biology are not practiced on routine examination of RCCs, which is why in the chosen cases we did not have a definite diagnosis of RCC with Xp 11.2 translocation. Consequently, we included in the study all clear cell and papillary RCCs with the purpose of identifying Xp 11.2 carcinomas that were missed during the first examination.

We excluded from the study patients who did not sign the informed consent.

Processing method

Histopathological examination of the selected cases was performed according to the steps described below.

The specimens of partial or radical nephrectomy were described from a macroscopic and microscopic point of view, respecting the protocols of the American College of Pathologists (CAP).

Macroscopically, the size, the location of the tumor, the number of tumors, extrarenal and intrarenal extension of the tumor, weight of necrosis, macroscopic venous extension, number of macroscopically positive lymph nodes or total number of lymph nodes detected in the received material were described. The piece was sectioned in a bivalve manner (Fig.1.) and fixed in a buffered formaldehyde solution 4-10% for at least 24 hours. After that, the resection edges are marked with ink for their identification under microscopy. Then fragments of tissue measuring approximately 15/15/ 2 mm were taken. Those were than processed histologically and examined microscopically. Histological sections are cut to 3 microns and stained with the usual strain, hematoxylin eosin.

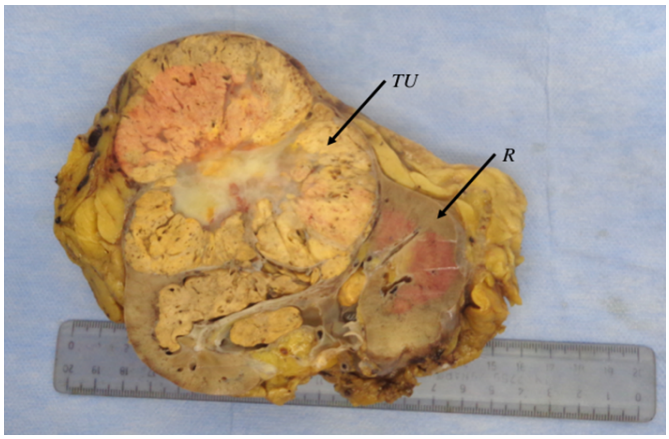

Fig. 1. Radical nephrectomy specimen – cross section (TU – tumor; R – non-tumoral renal parenchyma)

Microscopic examination was performed by optical microscopy at 100x, 200x, and 400x magnification. Sampling sites were chosen to provide relationships related to tumor staging (sinus or perirenal fat infiltration, invasion of the pyelocaliceal apparatus, venous extension) and the most accurate determination of tumor aggression (degree of differentiation, extent of necrosis). The histopathological report of renal tumors, according to CAP recommendations, includes: determination of the histological type of the tumor, assessment of the presence or absence of the sarcomatoid or of rhabdoid features, as well as quantification of their percentage if present; establishing the ISUP degree, evaluation of tumor necrosis and its percentage if present, establishing the condition of the resection margins: parenchymal, capsular and perirenal fat for partial nephrectomies; fascial, ureteral and renal vein for radical nephrectomies, evaluation of microscopic tumor extension: invasion of perirenal fat, invasion of renal sinus, extra fascial extension, direct invasion of adrenal (T4) or metastatic (M1), venous extension, invasion of the pyelocaliceal apparatus and invasion of other organs; the existence of the invasion of lymphatic vessels, evaluation of the number of positive lymph nodes / total number of lymph nodes examined; determination of pathological staging, pTNM; the existence of some changes of the non-tumor parenchyma: glomerulopathies, tubulo-interstitial nephropathy, vasculopathies, cystic disease; the existence of other benign tumors or "tumor-like" lesions.

Next step was slides selection. We selected slides (and their corresponding paraffin embedded block) which meet the following morphological criteria: solid architecture; clear cell and/or papillary architecture, presence of hyaline globules and/or calcifications and/or necrosis, ISUP grade ≥2.

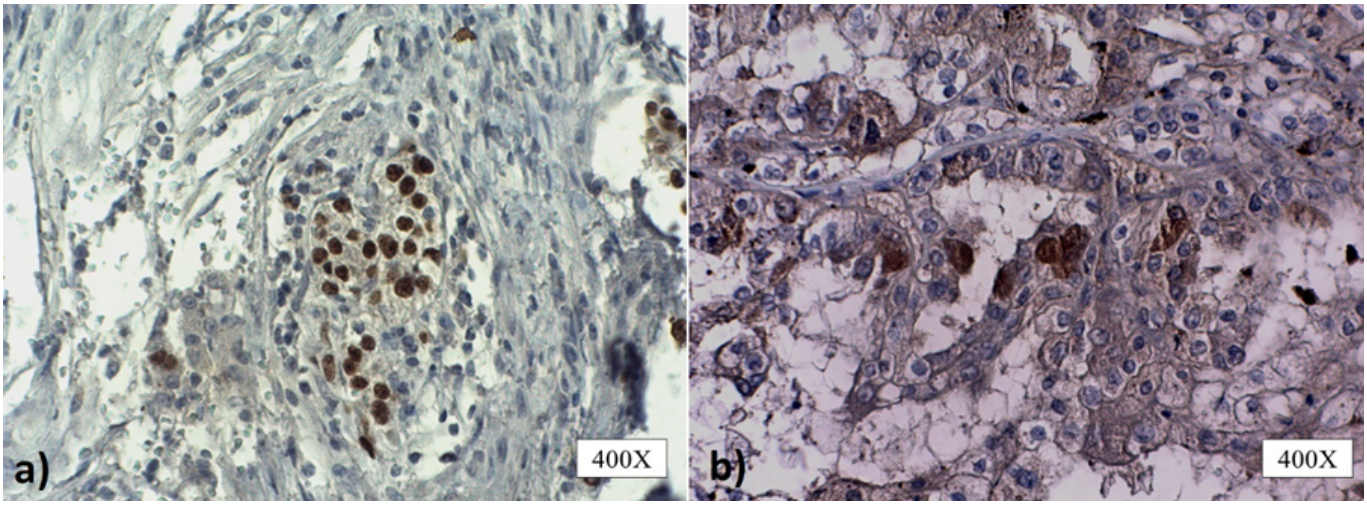

Fig. 2. Optical microscopy, 400x magnification, TTF3 immunohistochemistry: a) intense nuclear staining; b) intense cytoplasmatic and low intensity nuclear staining

Implementation of the immunohistochemistry technique with TFE3

The TFE3 monoclonal antibody (MRQ-37) from A. Menarini Diagnostics, EMERGO EUROPE Molenstraat 15, 2513 BH The Hague, The Netherlands, was used for the immunolabeling technique. This antibody is intended for in vitro diagnosis. It is used for the qualitative identification, by optical microscopy, of the presence of the associated antigen in the specimens prepared according to the previous description. The use of this antibody is recommended for the identification of RCC with Xp 11.2 translocation and soft tissue alveolar sarcoma. A.Menarini Diagnostics indicates the interpretation of this antibody in the context of the morphology determined by examination by light microscopy in hematoxylin eosin staining, together with other immunolabels (CD10, Vimentin, AMACR) and the patient's clinical history. The following materials were then used: positive and negative control, silane blades for microscopy, thermostat for histology set at 60 ° C ± 5 ° C, graduated cylinders for the laboratory, stopwatch, xylene, ethanol for analysis, distilled water, kettle electric under pressure for tissue pre-treatment and unmasking, PolyVue Plus HRP / DAB detection kit, PBS wash solutions, hematoxylin, antibody dilution solution, mounting medium and slides.

The selected blocks were sectioned at 3 microns. The entire immunolabeling procedure with the TFE3 monoclonal antibody was performed manually. Initially, the specimens were deparaffined in xylene for 30 minutes, then dehydrated and the antigen was exposed by heat treatment at 99 ° C for one hour. Subsequently, the immunohistochemistry technique with mouse monoclonal antibody TFE3 in 1:50 dilution was implemented. Subsequently, the slides were examined in 100x, 200x and 400x optical microscopy with the Olympus CX31 microscope. The acquisition of the microscopic image was done with an Optika B5 microscope with a 5-megapixel camera. The following features of the immunolabeling have been identified: intensity, homogeneity and extranuclear positioning.

TFE3 expression was considered positive in cases where nuclear and cytoplasmic immunolabeling was present in over 80% of cells. The expression was considered negative in the absence of immunohistochemical labelling with TFE3 of the preparation. Control was used.

Statistical analysis

Statistical analysis was performed using the MedCalc® Statistical Software version 20 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021). Quantitative data were expressed as median and 25-75 percentiles. Qualitative data were characterized by frequency and percentage. Comparisons between groups were performed using the Mann-Whitney or chi-square test, whenever appropriate. The differences were considered statistically significant if $p < 0.05$.

Results

We studied a number of 191 patients diagnosed with clear cell RCC and papillary RCC out of which 47 patients met the historical criteria mentioned in the previous chapter (solid architecture, clear cell papillae, hyaline globules, calcifications, necrosis, Fuhrman grade ≥2). These patients have had the TFE3 immunolabeling technique implemented. Seven cases had intense positive nuclear immunolabeling or intense positive cytoplasmic immunolabeling of over 80% of tumor cells (Fig.2.). They were considered to belong to the "RCC TFE3 +" group. Those who did not have a positive immunolabeling and those who did not meet the historical criteria were considered to belong to the group "Clear cell and papillary RCC".

Of the 191 total cases, 47 were selected for TTF3 immunohistochemistry, out of which 7 were considered to have positive immunohistochemistry. They represent a percentage of 15% and had a positive nuclear or cytoplasmic immunolabel. Therefore, most of the cases selected for immunolabeling with TFE3 were negative, being able to exclude the diagnosis of RCC with Xp 11.2 translocation in these situations. Reporting the number of positive cases to the total number of cases studied their share is 3.6%. We mention the fact that most of our cases presented with positivity the cytoplasmic level. We considered positive only the cytoplasmic immunolabeling of tumor cells, not that of the accompanying inflammatory cells.

Of all the cases included in the study, the ones that met the histological criteria (Table 1.) and then followed the immunolabeling procedure with the TFE3 monoclonal antibody was 21%. We emphasize again the histological criteria, noting that the explanation of their choice is detailed a: solid architecture, papillae with clear cells, hyaline globules, calcifications, necrosis,

Table 1. Classification of cases included in the study by each histological criterion required

Histological criteria	Number of cases that meet histological criteria:
Solid architecture	44
Papillae with clear cells	37
Hyaline globules	18
Calcifications	7
ISUP grade ≥2	47

Table 2. Comparison between the two study groups

Criteria	TFE3+ RCCs (n=7)	Clear cell and papillary RCCs (n=40)	P
Age (years)	66 (64; 68)	60.5 (53; 68)	0.04
Male %	5 (71.4%)	31 (77.5%)	1
Female %	2 (28.6%)	9 (22.5%)	
Radical nephrectomy	5(71.4%)	34 (85%)	0.5
Partial nephrectomy	2 (28.6%)	6 (15%	
pT1a	2 (28.6%)	5 (12.5%)	
pT1b	3 (42.9%)	10 (25%)	
pT2a	-	8 (20%)	0.6
pT2b	-	1 (2.5%)	
pT3a	2 (28.6%)	15 (37.5%)	
pT4	-	1 (2.5%)	
V0	5 (71.4%)	18 (45%)	
V1	1 (14.3%)	16 (40%)	0.3
V2	1 (14.3%)	6 (15%)	
Histologic Grade (ISUP) 2	2 (28.6%)	18 (45%)	
Histologic Grade (ISUP) 3	3 (42.9%)	16 (40%)	0.5
Histologic Grade (ISUP) 4	2 (28.6%)	6 (15%)	

(pT = primary tumor according to AJCC 8th Edition, V= Venous extension, ISUP= International Society of Urological Pathology)

ISUP grade ≥2. Please note that each of the selected cases met at least two of the criteria described. All selected tumors showed solid and papillary architecture in various proportions, some of them associating hyaline globules and fewer psammoma bodies. Age was significantly higher in patients with TFE3+ (table 2). The rest of variables did not differ significantly between groups. From the ISUP grading point of view, we considered the grading greater than or equal to 2, because by definition RCCs with Xp 11.2 translocation excludes ISUP grade 1. According to Table 1, in the case of TFE3+ RCCs the percentage of high-grade tumors is higher than in the other study group. However, tumors with ISUP grade of 2 have the highest frequency in both groups studied.

The non-tumor renal parenchyma was evaluated in the two groups. The predominance of renal cysts is observed in the case of TFE3 + RCC and the predominance of parenchyma without changes is higher in the case of clear cell and papillary RCCs (Table 3.). No secondary tumors, other tumors, preneoplastic lesions or angiolymphatic invasion distant from the tumor were found in either of the study groups. Also, in the case of TFE3+ RCCs there were no cases of chronic pyelonephritis, lymphoid infiltration or atrophy, post-dialysis changes.

Table 3. Non-tumoral renal parenchyma in the two study groups

Non-tumor renal parenchyma	TFE3+ RCCs	Clear cell and papillary RCCs
Renal cyst	3 (7.5%)	3 (42.9%)
Atrophy	4 (10%)	-
Chronic pyelonephritis	11 (27.5%)	-
Parenchyma without important changes	19 (47.5)	4 (57.1%)
Lymphoid infiltration	7 (17.5)	-

In the clear cell and papillary RCC group clear cell RCCs were more frequently encountered, predominant, with 91% of all cases being clear cell variant. Clear cell RCCs may also have a focal papillary architecture, but the characters differ from those of renal papillary RCCs of type 1 and 2. On the other hand there is also the variant of papillary carcinoma with solid architecture, although in this study we did not encounter this scenario.

Discussion

The main objective of the study was to identify positive TFE3 cases diagnosed as clear cell and papillary RCCs, given that there was no case diagnosed as RCC with translocation, due to the lack of TFE3 antibody in the immunohistochemistry antibody palette used at the Cluj-Napoca Municipal Clinical Hospital.

According to the latest WHO Classification of Tumors of the Urinary System and Male Genital Organs, the incidence of TFE3 positive RCCs, out of the total RCC, is 1.6-4% in adults and 40% in pediatric patients (Moch et al 2016). In the present study, there were 5 pediatric patients and they were diagnosed with nephroblastoma, therefore they did not meet the criteria for inclusion in the study. Of all RCCs included in this study, 3.6% had TFE3-positive immunolabeling. These data are superimposable with the literature.

In 2016, worldwide there were 150 cases of RCC with Xp 11.2 translocation that were diagnosed both by immunolabeling with TFE3 and by completing the diagnosis with FISH (Fluorescent in situ hybridization) or PCR (Polymerase Chain Reaction) technique (Green et al 2013b; Zhong et al 2010).Hirobe, Masumori and collaborators, postulate that the incidence of this type of carcinoma is underestimated, which leads to the classification of several RCCs with Xp 11.2 translocation as the most common clear cell variant of RCC (Hirobe - 2016).

Most studies in the literature on TFE3-positive RCC are performed on young populations, with an average age below 45 years: average age 24.5 years (Pradhan et al 2015), 44.5 years (Ma et al 2014), 24.6 years (Camparo et al 2008), 12.9 years (Geller et al 2015) or 27 years (Xu et al 2015).

In our study, the mean age of patients with TFE3-positive RCC was 66 years. We consider that the interpretation of this average age must be made in the context of the general average age of the study, 58.7 years. We believe that through this, our

study can bring a perspective on a little studied age group. One of the limitations of the study comes from the fact that the age groups to which the literature refers are not as well represented in our case studies.

In a study of 28 cases diagnosed as RCC with Xp 11.2 translocation of Argani and collaborators, a predominance of females is observed (22 cases, 79%) (Argani et al 2003). Choueiri et al identify in their study 15 cases of RCC with Xp 11.2 translocation representing 80% of the case study (Choueiri et al 2010). Gorin and Ball studied 4 patients in the study, and the share by sex was equal (Ma et al 2014). In the present study, the share of males was higher than that of females. A possible explanation for this is that in the case of the Cluj-Napoca Municipal Clinical Hospital, the cases of renal cell carcinomas that underwent surgery had a marked male predominance (65.8%), thus TFE3-positive carcinomas kept the same trend.

Being a rare tumor, in the case of patients treated by partial nephrectomy, both doctors and patients are faced with a dilemma regarding the postoperative attitude: the choice between completing the surgery with total nephrectomy or active surveillance. Multiple studies have addressed this dilemma. Liam and You retrospectively analysed 8 cases of RCC with Xp 11.2 translocation that underwent partial nephrectomy and followed them for 48 months, during which there was no tumor recurrence (Renal Cell Carcinoma Associated with Xp11.2 Translocation/TFE3 Gene Fusions: Clinical Features, Treatments and Prognosis). Gorin and Ball followed 4 such patients for 37 months and had similar results (Ma et al 2014). However, several authors such as Hirobe, Masumori (Hirobe et al 2016) and Argani (Argani et al 2003) believe that it is necessary to follow these patients for a much longer period to conclude which attitude is correct, even if these short-term studies seem to show that partial nephrectomy is sufficient. We did not have access to the follow-up information for the patients included.

From the point of view of tumor gradation, there is a similarity between our results and those in the literature (Camparo et al 2008; Geller et al 2015; Ma et al 2014; Pradhan et al 2015; Xu et al 2015), the percentage of high-grade tumors being higher in TFE3-positive cases, compared to total clear cell and papillary renal cell carcinomas. Hirobe, Masumori and co-workers recommend using the TFE3 antibody as a screening test for the detection of RCC with Xp 11.2 translocation and completing the diagnosis using the FISH (Fluorescent in situ hybridization) technique.

A limitation of the study comes from the fact that the immunolabeling is cytoplasmic positive in most of our cases, a pattern that is not detailed in the literature, therefore does not allow a definite interpretation. Given the small number of positive cases compared to the large number of cases studied, we believe that positive cytoplasmic immunolabeling should not be disregarded.

Immunolabeling with TFE3 has not been performed in our geographical area so far, which is why, although we have a positive nuclear control confirmed by the FISH technique, our immunolabeling technique may not be ideal, as it is overly sensitive to many variables: pH of the fixative (unknown), poor control of room temperature, half-life of the unknown antibody, different ages of the biological material and others.

We mention that in order to develop the technique we contacted laboratories abroad (United States of America: University of California, Los Angeles and UC Davis School of Medicine, Sacramento), the optimization of the technique being in progress even in these centres.

Another limitation is the impossibility of following the patients to be able to compare the evolution of the TFE3 RCCs positively with those of the other patients.

Surprisingly, we did not have cases with intense nuclear positive labelling of over 80% of the cells. We wonder if this is a population genetic peculiarity or is a shortcoming of the insufficient experience of immunolabeling with TFE3.

From a practical point of view, TFE3 positive RCC is useful to be better known and diagnosed as being more aggressive tumors and require a more appropriate therapeutic attitude in these cases. The results obtained are encouraging to extend the study to a wider range of cases including more hospitals and possibly a longer period of the case collection.

Conclusion

In the present study, out of the 191 cases, 7 showed positive cytoplasmic and weak nuclear immunolabeling with TFE3. These cases were initially diagnosed as clear cell or papillary RCCs, although some were suspected to be TFE3 positive, this could not be demonstrated due to the lack of TFE3 immunohistochemistry in our country's laboratories.

It is justified to introduce the immunolabeling with TFE3 in the range of antibodies used in the diagnosis of RCC, in cases with histological characters assigned to RCC with Xp 11.2 translocation.

Given that this is a pilot study in Romania, its results encourage the organization of a larger population study.

The current importance lies in demonstrating the usefulness of including TFE3 immunolabeling in the diagnosis of RCCs in order to reduce the rate of underdiagnosis of RCC with Xp 11.2 translocation.

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