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Case Report

Morphologic heterogeneity and markers of renal cell carcinoma with t(6; 11)(p21; q12): a case report and literature review

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Abstract: Objective: Renal cell carcinoma (RCC) with t(6; 11)(p21; q12) case report and review to explore its pathology morphologic heterogeneity and diagnostic criteria. Methods: A female patient is 46 years old, who was admitted to hospital due to tumor of kidney. The gross and histological morphology of tumor were observed. Fluorescence in situ hybridization and immunohistochemistry were used to analyze the molecular markers, and the related literatures were reviewed. Results: Grossly, the tumor was a 6 cm×5.5 cm×4.5 cm mass locating at the lower lobe of the right kidney. The tumor was poorly circumscribed, gray to tan cut surface with focal hemorrhage and cystic change. Histologically, the tumor was predominantly composed of alveolar architecture of polygonal tumor cells with well-defined cell borders, separated by thin capillaries. The tumor cells were positive for TFEB, Cathepsin-K, HMB45, Melan-A, E-cadherin and Vimentin. Gene rearrangement of TFEB was found. These markers showed that the tumor is a RCC with t(6; 11)(p21; q12). Conclusion: The morphology of RCC with t(6; 11)(p21; q12) is not entirely distinctive. Differential diagnosis of RCC with t(6; 11)(p21; q12), high-grade clear cell RCC and papillary RCC was necessary. For cases morphologically suspicious for t(6; 11)(p21; q12) RCC, FISH and IHC may be helpful for pathological diagnosis.

Keywords: t(6; 11)(p21; q12) RCC, TFEB, pathological diagnosis

Introduction

RCC with t(6; 11)(p21; q12) chromosome translocation was initially described in 2011 [1]. It is low-grade RCC and extremely rare. The t(6; 11)(p21; q12) translocation fuses the Alpha (MALAT1) gene with the TFEB transcription factor gene [2]. Histologically, the tumor presents a biphasic pattern which is large epithelioid cells with voluminous clear to slightly eosinophilic cytoplasm and clusters of small cells, usually clustered around basement membrane-like material. However, there has been increasing evidence showed that the t(6; 11)(p21; q12) RCC may demonstrate unusual morphological structures, such as papillary, tubular and clear cell RCC-like structures. Sometimes, the t(6; 11)(p21; q12) RCC may present the same morphology as Xp11 RCC. As mentioned above, differential diagnosis of clear cell RCC, Papillary RCC (PRCC) and other RCC with a papillary architecture and clear to eosinophilic cytoplasm cells is necessary and difficult.

In this paper, a case of t(6; 11)(p21; q12) RCC was reported and the differential diagnosis of high-grade clear cell RCC, PRCC and Xp11 RCC was reviewed.

Materials and methods

Patient

A female patient, 46 years old, who was admitted to hospital due to fatigue and low back pain for 2 months. A tumor locating at the lower pole of the right kidney was been found by CT. The CT showed us the tumor has abnormal blood vessels and a slight blurring in the perirenal fat space (**Figure 1A**), which was considered as a malignant tumor. The MRI showed an ovoid mixed density mass at the lower pole of the right kidney. The tumor appears unclear edge

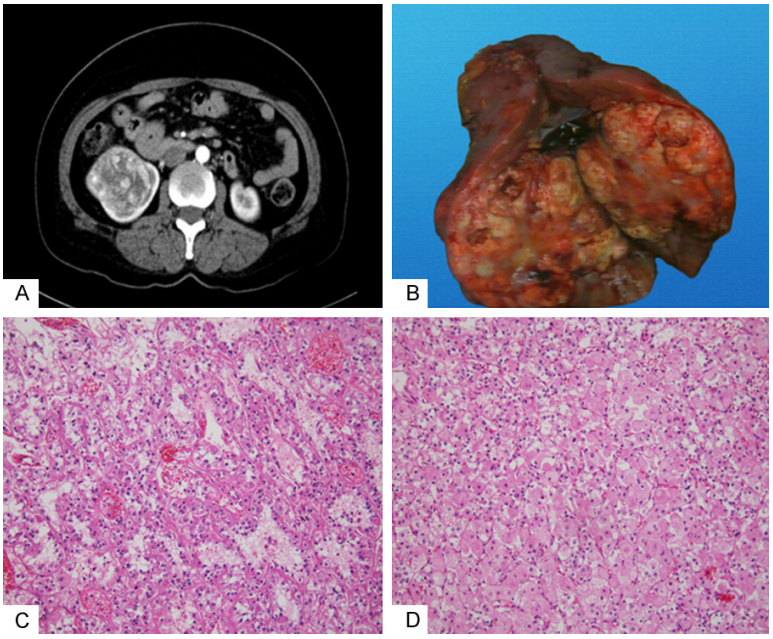

Figure 1. A. The CT showed us the tumor has abnormal blood vessels and a slight blurring in the perirenal fat space, which was considered as a malignant tumor. B. Grossly, the tumor was located at the lower pole of the right kidney. The size of tumor was 6 cm×5.5 cm×4.5 cm. The tumor was poorly circumscribed, and displayed gray to tan cut surface with focal hemorrhage and cystic change. C. H&E staining of alveolar architecture (magnification, ×200). D. H&E staining shows in other areas, the tumor was comprised of nests (magnification, ×200).

and infiltration of adjacent calyces. The patient underwent a radical nephrectomy.

Hematoxylin and eosin (H&E) staining

Tumor tissues were fixed in 10% formalin and embedded in paraffin. Sections of 4 μm thickness were stained by H&E, observed by light microscopy.

Immunohistochemistry (IHC)

IHC was performed using EnVision method. The following primary antibodies were used: TFEB, TFE3, HMB45, Melan-A, Cathepsin-K, RCC, E-cadherin, CD10, CD117, CK, EMA, CA9 and Vimentin. Appropriate positive controls were used.

Fluorescence in situ hybridization (FISH)

The FISH assay was performed for paraffinembedded tissues. It was a method to detect TFEB gene rearrangements by centromeric (green 5-fluorescein dUTP) and telomeric (red 5-ROX dUTP) labelled probes. Green and red combinated signals were observed in normal cells and separated signals in cells with gene rearrangements.

Results

Gross findings

Grossly, the tumor was located at the lower pole of the right kidney. The size of tumor was 6 cm×5.5 cm×4.5 cm. The tumor was poorly circumscribed, and displayed gray to tan cut surface with focal hemorrhage and cystic change (**Figure 1B**).

Histological findings

Pathological characteristics were of typical polygonal tumor cells with well-defined borders aggregation to form nests or alveolar structures, separated by thin capillaries (**Figure 1C**, **1D**). Some cytoplasms of polygonal cells were pink clear, sparsely granular, whereas others were eosinophilic densely granular. Nuclei were generally rounded. Occasionally atypia and small central nucleoli were appeared. In addition, significant bleeding, necrosis and cystic changes were seen in some areas.

Immunohistochemical findings

The tumor cells demonstrated focal immunoreactivity for vimentin and melanocytic markers (HMB45, Melan-A and Cathepsin-K), moderately positive staining for TFEB (**Figure 2A-C**), strong positive expression of RCC and E-cadherin. TFE3, CA9, CK, CD10, CD117 and EMA were negative expression. A few Ki-67-positive nuclei occur, demonstrated a low proliferation rate.

TFEB FISH analysis

The result showed clear split signals, and gene rearrangement of TFEB was found (**Figure 2D**).

Discussion

RCC with t(6; 11)(p21; q12) is exceedingly rare subset of renal translocation tumors. The fu-

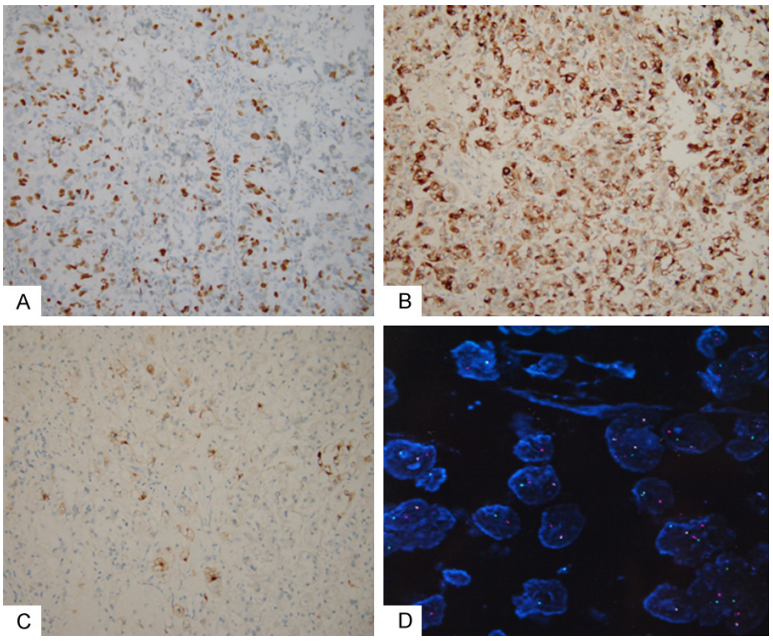

Figure 2. A-C. Immunohistochemical staining positive expression of TFEB, Melan-A and HMB45 respectively (magnification, ×200). D. The FISH assay results showed that there were several pairs of red and green split signals, and this means the presence of TFEB gene rearrangement.

sion of Alpha gene and TFEB gene is caused by translocation of t(6; 11). It is mostly common in children and young adults, a few of patients being older adults. The patient of our case is 46 years old.

The most typical histologic patterns of t(6; 11)(p21; q12) RCC is pseudorosettes which is large epithelioid cells with voluminous clear to slightly eosinophilic cytoplasm and clusters of small cells, usually clustered around hyaline material [3, 4]. However, there has been increasing evidence that the t(6; 11)(p21; q12) RCC demonstrate atypical morphological features which are similar to other RCC [5, 6]. In this case, the tumor was predominantly composed of nests and alveolar architecture, consistent with the literature, but there was no typical pseudorosette structure and small cells [7].

The t(6; 11)(p21; q12) RCC is negative for a wide range of epithelial markers, while is positive for renal tubular epithelial markers. In this case, the tumor cells demonstrated strongly positive staining for E-cadherin and RCC but negative for EMA, CK and CD10. In addition, immunoreactivity for TFEB is highly sensitive and specific for this tumor [8]. Our results showed the tumor cells were moderately positive for TFEB. It is noteworthy that focal positive staining of melanocytic markers, including HMB45, Melan-A and Cathepsin-K could be detected in tumor cells of most cases. The possible cause of that may be the TFEB is involved in melanocytic differentiation, and gene rearrangement of TFEB.

For the cases with typical morphology, t(6; 11)(p21; q12) RCC can be initially diagnosed with the help of ancillary studies. However, it is necessary to differential diagnosis of t(6; 11)(p21; q12) RCC, Xp11 RCC, high-grade clear cell RCC and PRCC for most cases with atypical morphological features.

Both of TFE3 and TFEB are members of the microphthalmia transcription factor (MiT) family. TFE3 gene is located on the short arm of the X chromosome (Xp11) and may fuse to many translocation partners [9]. Microscopically, the Xp11 RCC is composed of large, epithelioid cells with abundant clear to eosinophilic cytoplasm, and papillary structures were formed. The typical histologic patterns of t(6; 11)(p21; q12) RCC could rarely be seen in Xp11 RCC. The differential diagnosis between them is difficult when the morphology is not typical. Melanocytic markers were also expression in t(6; 11)(p21; q12) RCC and Xp11 RCC, therefore, TFE3 and TFEB detecting were important by IHC and FISH for differential diagnosis. Xp11 RCC would be negative for TFEB expression, amplification and gene rearrangements [10].

The differential diagnosis between MiT family RCC and high-grade clear cell RCC with papillary architecture was important. When the morphological features were atypical, IHC and FISH are helpful for differential diagnosis. TFE3 or TFEB was positive in MiT family RCC. Epithelial markers (EMA and CK) were strongly expression in the clear cell RCC, but melanocytic markers (Melan-A, HMB-45, and Cathepsin-K) were negative. By contrast, melanocytic markers were positive for t(6; 11)(p21; q12) RCC. In

addition, CA9 is normally negative for t(6; 11)(p21; q12) RCC, but strong and diffuse expression for clear cell RCC. TFE3 or TFEB split signals would be detected by FISH in MiT family RCC, but would not be detected in clear cell RCC.

PRCC is needed to identify. Microscopically, the tumor cells were polygonal, abundant cytoplasm, eosinophilic and arranged in papillary structure. EMA and pancytokeratins were strongly expression in PRCC, cytokeratin 7 expression was generally positive but might be variable, but Melan-A, HMB-45 and Cathepsin-K were negative. Cytogenetic analysis showed that t(6; 11)(p21; q12) RCC is typically characterized by trisomy 7 and/or 17 and the TFEB split signals and gene rearrangements would not be seen in PRCC.

In a word, the histologic patterns of t(6; 11)(p21; q12) RCC were complex and changeable, so differential diagnosis is challenged for some cases. IHC and FISH were very helpful for differential diagnosis, Xp11 RCC, high-grade clear cell RCC and PRCC. Most scholars even believe that FISH should be the gold standard for the diagnosis of the disease, because of its specificity, accurate positioning, easy to implement [11, 12].

Disclosure of conflict of interest

None.

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References

[1] Argani P, Hawkins A, Griffin CA, Goldstein JD, Haas M, Beckwith JB, Mankinen CB, Perlman EJ. A distinctive pediatric renal neoplasm characterized by epithelioid morphology, basement membrane production, focal HMB45 immunoreactivity, and t(6; 11)(p21.1; q12) chromosome translocation. Am J Pathol 2001; 158: 2089-2096.

[2] Argani P, Reuter VE, Zhang L, Sung YS, Ning Y, Epstein JI, Netto GJ, Antonescu CR. TFEB-amplified renal cell carcinomas: an aggressive molecular subset demonstrating variable melanocytic marker expression and morphologic heterogeneity. Am J Surg Pathol 2016; 40: 1484-1495.

[3] Argani P, Yonescu R, Morsberger L, Morris K, Netto GJ, Smith N, Gonzalez N, IIlei PB, Ladanyi M, Griffin CA. Molecular confirmation of t(6; 11)(p21; q12) renal cell carcinoma in archival paraffin-embedded material using a break-apart TFEB FISH assay expands its clinicopathologic Spectrum. Am J Surg Pathol 2012; 36: 1516-1526.

[4] Argani P, Laé M, Hutchinson B, Reuter VE, Collins MH, Perentesis J, Tomaszewski JE, Brooks JS, Acs G, Bridge JA, Vargas SO, Davis IJ, Fisher DE, Ladanyi M. Renal carcinomas with the t(6; 11)(p21; q12): clinicopathologic features and demonstration of the specific alpha-TFEB gene fusion by immunohistochemistry, RT-PCR, and DNA PCR. Am J Surg Pathol 2005; 29: 230-240.

[5] Xia Q, Shi S, Shen Q, Wei X, Wang X, Ma H, Lu Z, Zhou X, Rao Q. Renal cell carcinoma with t(6; 11)(p21.2; q13)/MALAT1-TFEB fusion: a clinical and pathological analysis. Zhonghua Bing Li Xue Za Zhi 2015; 44: 895-899.

[6] Rao Q, Liu B, Cheng L, Zhu Y, Shi QL, Wu B, Jiang SJ, Wang Y, Wang X, Yu B, Zhang RS, Ma HH, Lu ZF, Tu P, Wang JD, Zhou XJ. Renal cell carcinomas with t(6; 11)(p21; q12): a clinicopathologic study emphasizing unusual morphology, novel alpha-TFEB gene fusion point, immunobiomarkers, and ultrastructural features, as well as detection of the gene fusion by fluorescence in situ hybridization. Am J Surg Pathol 2012; 36: 1327-1338.

[7] Zhong M, De Angelo P, Osborne L, Paniz-Mondolfi AE, Geller M, Yang Y, Linehan WM, Merino MJ, Cordon-Cardo C, Cai D. Translocation renal cell carcinomas in adults: a single-institution experience. Am J Surg Pathol 2012; 36: 654-662.

[8] Inamura K, Fujiwara M, Togashi Y, Nomura K, Mukai H, Fujii Y, Yamamoto S, Yonese J, Fukui I, Ishikawa Y. Diverse fusion patterns and heterogeneous clinicopathologic features of renal cell carcinoma with t(6; 11) translocation. Am J Surg Pathol 2012; 36: 35-42.

[9] Magers MJ, Udager A, Mehra R. MiT family translocation-associated renal cell carcinoma: a contemporary update with emphasis on morphologic, immunophenotypic, and molecular mimics. Arch Pathol Lab Med 2015; 139: 1224-1233.

[10] Argani P. MiT family translocation renal cell carcinoma. Semin Diagn Pathol 2015; 32: 103-113.

[11] Kuroda N, Tanaka A, Sasaki N, Ishihara A, Matsuura K, Moriyama M, Nagashima Y, Inoue K, Petersson F, Martignoni G, Michal M, Hes O. Review of renal carcinoma with t(6; 11)(p21;

q12) with focus on clinical and pathobiological aspects. Histol Histopathol 2013; 28: 685-690.

[12] Peckova K, Vanecek T, Martinek P, Spagnolo D, Kuroda N, Brunelli M, Vranic S, Djuricic S, Rotterova P, Daum O, Kokoskova B, Vesela P, Pivovarcikova K, Bauleth K, Dubova M, Kalusova K, Hora M, Michal M, Hes O. Aggressive and nonaggressive translocation t(6; 11) renal cell carcinoma: comparative study of 6 cases and review of the literature. Ann Diagn Pathol 2014; 18: 351-357.