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Renal Cell Carcinoma Associated with Xp11.2 Translocation/*TFE*3 Gene Fusion: A Case Report with Immunohistochemical and Cytological Features

Takuji Tanaka[1*], Kuniaki Hirai[2], Fumimasa Etori[1], Masashi Matsuyama[1], Naoki Watanabe[1], Hiromi Kondo[3], Masayoshi Tamaki[3], Tatsuya Yamashita[4], Shiho Yasue[4], Mika Noda[4], Kunihiro Shinoda[4], Hisao Komeda[3]

[1]Department of Diagnostic Pathology (DDP) & Research Center of Diagnostic Pathology (RC-DiP), Gifu Municipal Hospital, Gifu, Japan
[2]Department of Radiology, Ehime University Graduate School of Medicine, Ehime, Japan
[3]Department of Urology, Gifu Municipal Hospital, Gifu, Japan
[4]Department of Pediatrics, Gifu Municipal Hospital, Gifu, Japan
Email: *takutt@toukaisaibou.co.jp

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Abstract

Gene fusions involving two of the MiT subfamily factors, such as *TFE*3, *TFEB*, *TFC* and *MiTF*, have been identified in renal cell carcinoma (RCC). Xp11.2 translocation RCC is a rare pediatric neoplasm that harbors gene fusions involving *TFE*3, which plays an important role in cell proliferation and survival. We herein present a case of RCC associated with Xp11.2 translocation/*TFE*3 gene fusion in a 14-year-old Japanese boy presenting gross hematuria and body weight loss. The tumor was characterized by histopathology, cytology and *TFE*3-immunohistochemistry/immunocytochemistry. Knowledge of distinctive morphological and immunostaining features of this tumor can help to accurately diagnose this rare subset of translocation associated RCC in routine pathological diagnostic procedures.

Keywords

Renal Cell Carcinoma, Xp11.2 Translocation, *TFE*3, Cytology, Immunohistochemistry, Immunocytochemistry

*Corresponding author.

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1. Introduction

Gene fusions involving two of the MiT subfamily factors [1], such as transcription factor E3 (*TFE*3), transcription factor EB (*TFEB*), *TFC* and *MiTF*, have been identified in renal cell carcinoma (RCC) [2] [3]. An extremely rare RCC associated with Xp11.2 translocations and *TFE*3 fusions (Xp11.2 RCC) was recognized as a distinct entity in the WHO classification of kidney tumors in 2004 [4]. The first pediatric case of this distinct tumor was reported by Tomlinson *et al.* [5]. This RCC subtype is defined by different translocations involving chromosome Xp11.2, all of which result in *TFE*3 gene fusions. Fusions of the *TFE*3 gene with different genes includes ASPL(17q25), PRCC(1q21), PSF(1q34), NonO(Xq12) and CLTC(17q23) [6] [7]. PRCC-*TFE*3 RCCs [8] and ASPL-*TFE*3 RCCs [9] are the most frequent types of Xp11.2 translocation RCCs. The incidence of Xp11.2 translocation RCC is low: one-third of pediatric RCCs are estimated to be Xp11.2 translocation RCCs associated with *TFE*3 gene fusion [10], 0.9% in adult RCCs [11], 15% in young adult RCCs [12], and 54% in child RCCs [3]. Another subset of RCC is associated with *TFEB* resulting from t(6;11) (p21; q12).

For an accurate diagnosis, identification of the nuclear over expression of *TFE*3 protein by immunohistochemistry [13] is needed. We herein present a case report of this rare malignancy which was developed in a 14-year-old Japanese boy, highlighting its histopathological, immunohistochemical and immunocytochemical features [6] [13] [14].

2. Case Report

Patient: A 14-year-old Japanese boy presented at our hospital with complaints of acuteabdominal pain (right side) and macrohematuria. He also complained of a fever. Because he noticed a 10 kg body weight loss over the previous year, the patient and his family wanted further examinations. No history of trauma or any other significant past history was reported. At admission, complete blood counts except for the white blood cell count (12, 210/μL) were within normal limits. A blood biochemistry analysis showed elevated abnormalities in C-reactive protein (CRP, 2.23 mg/dL) and neuron-specific enolase (NSE, 51.5 ng/mL) levels. A urinalysis reported protein (3+) and occult blood in the urine (3+). Abdominal computed tomography (CT, **Figure 1**), abdominal magnetic resonance imaging (MRI, **Figure 2(A)**) and a positron emission tomography (PET)-CT scan (**Figure 2(B)**) showed a large mass lesion (78 × 73 × 112 mm) with calcification in the right kidney, compressing the vena cava inferior and metastasis to the renal hilar lymph nodes (**Figure 1** and **Figure 2(B)**). A bone scintigram revealed no distant metastases.

Pathology: Right radical nephrectomy was performed according to the clinical diagnosis of RCC or Wilms' tumor. A frozen section diagnosis during the operation reported papillary RCC. However, cytology of imprint touch smears from the cut surface of the tumor led us to suspect Xp11.2 translocation RCC, because epithelial cancer cells showing a positive reaction for *TFE*3 in the nuclei of neoplastic cells (**Figure 3**) proliferated with a papillary pattern. The removed kidney grossly had yellowish multi-nodular tumors with partly hemorrhagic and small cysts; the largest nodular tumor measured 7.2 × 7.2 × 6.8 cm in size (**Figure 4**). The tumor almost completely replaced the normal renal parenchyma. After a macroscopic examination, the removed tissue was fixed in 10% neutral buffered formalin and embedded in paraffin for the histopathological diagnosis. Histopathology revealed a biphasic population of neoplastic cells, large epithelioid cells with voluminous eosinophilic cytoplasm and severe nuclear atypia (**Figure 5(A)**) and smaller cells with clear cytoplasm and small round nuclei (**Figure 5(B)**). There were a few psammoma bodies. Necrotic areas were scattered throughout the tumor tissue. Invasion and infiltration of cancer cells into the fibrous capsule of the kidney and vessels (**Figure 5(C)**) were prominent. Immunohistochemistry showed strongly positive nuclear staining of *TFE*3 protein in the cancer cells (**Figure 5(D)**). Other immunohistochemical findings included negativity for cytokeratin (AE1/AE3) and SMA and focally positivity for CD10 and vimentin. Brown pigments in the cytoplasm were positive for HMB45. A RT-PCR analysis of an unfixed and fresh tumor sample showed SFPQ/PSF-*TFE*3 (+), ASPL-*TFE*3 (−) and PRCC-*TFE*3 (−). Five months after nephrectomy, metastases in the lymph nodes, bone and liver were found. Thereafter, the patient received anti-angiogenic tyrosine kinase inhibitor, pazopanib (Novartis Pharma K.K., Tokyo, Japan) [15], and a long-term intensive follow-up.

3. Discussion

Xp11.2 RCC is a rare malignancy that generally occurs in children and young adults [6]. This incidence is underestimated in adults because of its morphological similarities with clear cell and papillary RCCs. In addition,

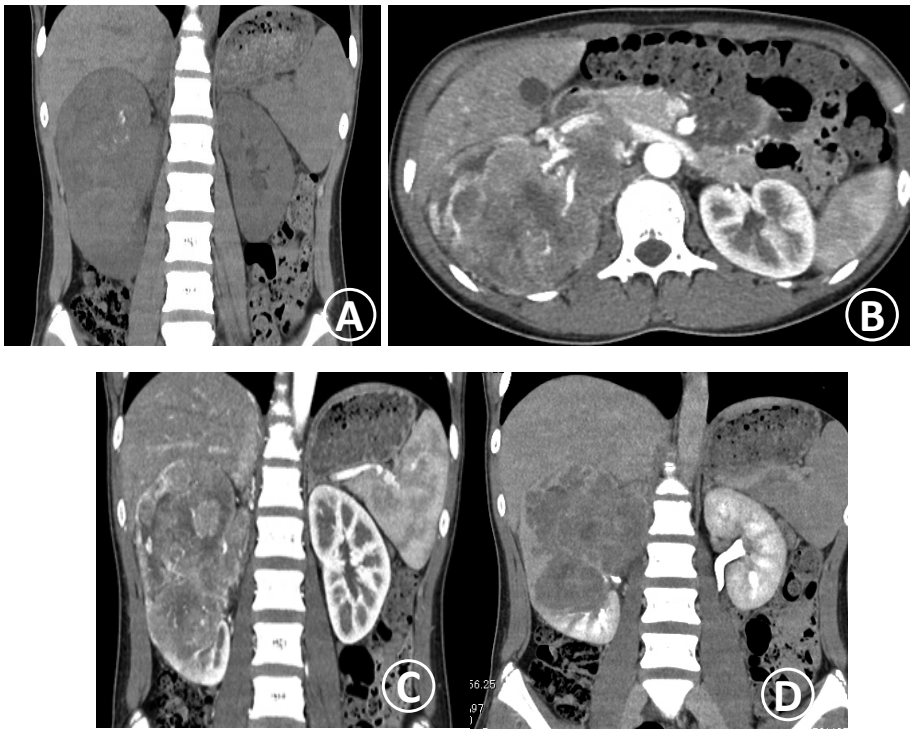

Figure 1. CT images of translocation RCC.CT scans of the abdomen and pelvis in the patient with (A) a coronal section showing a large right renal mass and an axial section (B) demonstrating heterogeneous and prolonged enhancement of the mass, measuring 7.8 × 7.3 × 11.2 cm with microcystic areas and mottling calcification. Intravenous dynamic contrast-enhanced images (C) and (D) showing the delayed enhancement of the mass.

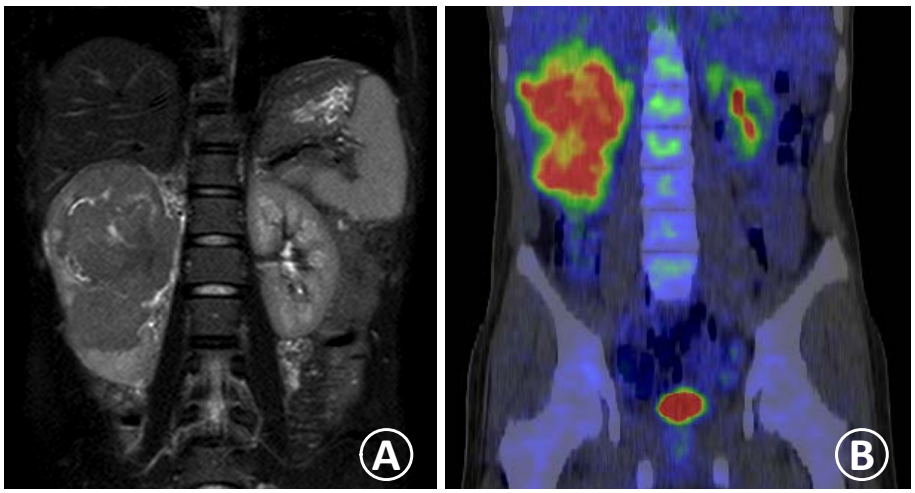

Figure 2. A coronal T2WI MRI image (A) showing an irregular ill-defined right renal mass with a heterogeneous and slightly high signal intensity. A PET-CT image (B) showing abnormal uptakes on FDG-PETin the right kidney and hilar lymph nodes

immunohistochemical and cytogenetic analyses are not carried out systematically in adults. The presence of the PSF-*TFE*3 fusion has only been described in a very limited number of cases [16]. We herein presented a novel case of SFPQ/PSF-*TFE*3-associated RCC in a 14-year-old Japanese boy.

The MiT subfamily of transcription factors includes *TFE*3, *TFEB*, *TFC*, and *MiTF*. Gene fusions involving two of these transcription factors were identified in RCC: Xp11.2 and t(6;11) translocation RCC [2]. Both

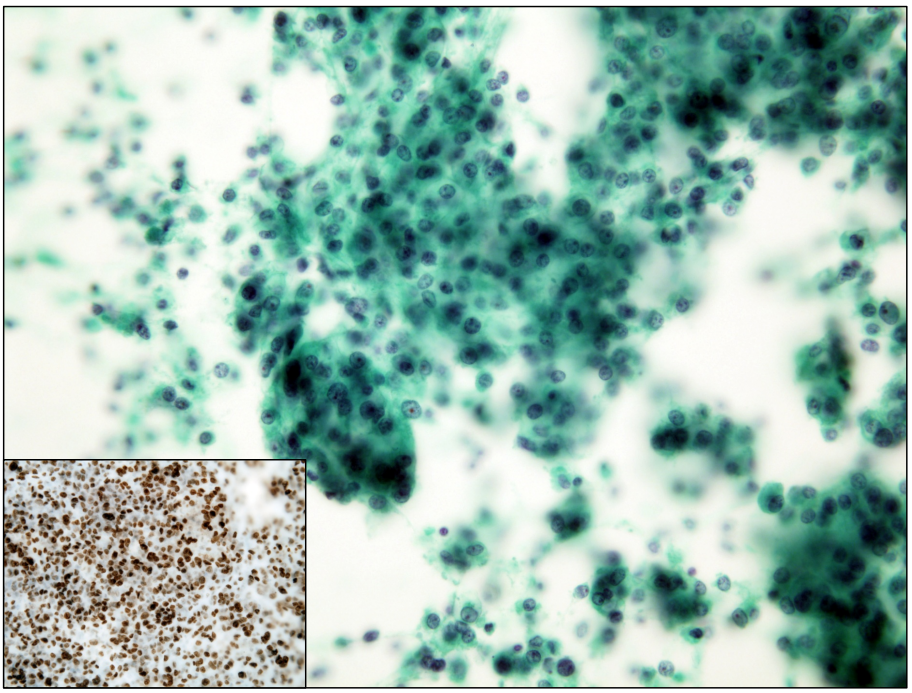

Figure 3. Imprint touch smear showing papillary clusters of cancer cells (Papanicolaou stain, 400×). Note: strong nuclear positive reaction against *TFE*3 antibody (insert, *TFE*3 immunocytochemistry, 200×).

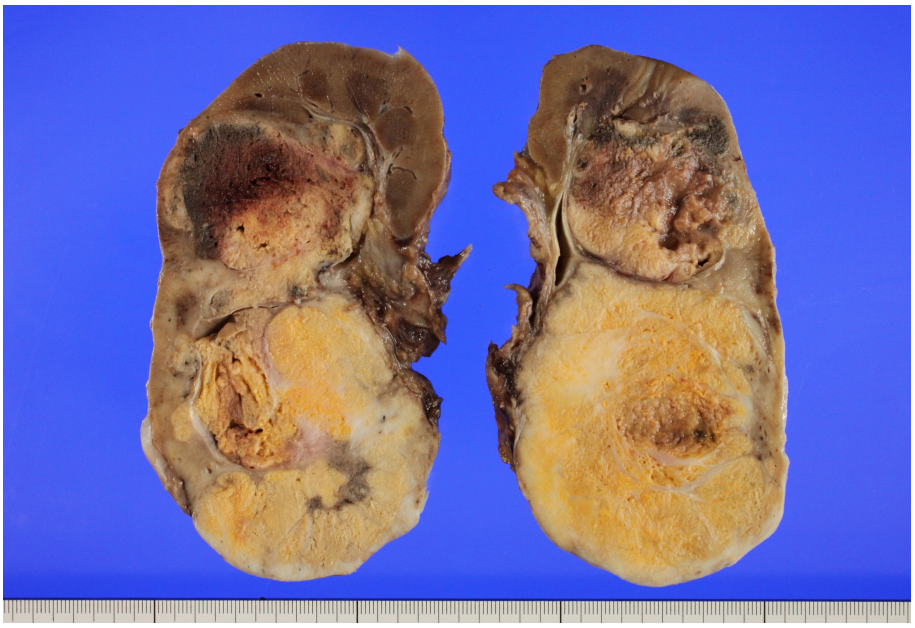

Figure 4. Cut surface showing yellowish multi-nodular tumors with partly hemorrhagic and small cysts. The tumor almost completely replaced the normal renal parenchyma.

neoplasms, grouped under the heading of "MiT family translocation RCC" [17], have a tendency toward young age at presentation. Specific immunohistochemistry analyses for nuclear proteins produced by both translocations are useful for an accurate diagnosis [13] [18]. Xp11 translocation RCC was first officially recognized in the 2004 WHO renal tumor classification [4], harboring gene fusions involving *TFE*3. The official recognition of the t(6; 11) RCC, harboring a specific *alpha-TFEB* gene fusion, was made in the 2013 International Society

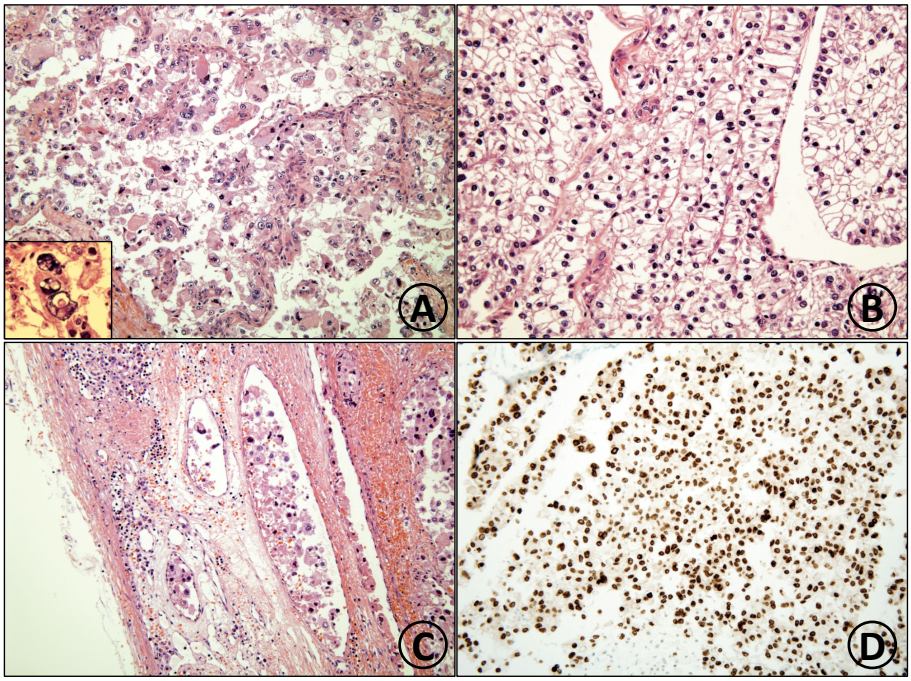

Figure 5. Histopathology of the resected right renal tumor. The tumor composed of (A) papillary growth of cancer cells with severe atypia and eosinophilic cytoplasm and (B) sheets of cancer cells with slight atypia and clear cytoplasm, the former predominating. (C) Cancer cells infiltrating into venous and lymphatic vessels. (D) A strong positive reaction against *TFE*3 antibody in the nuclei of cancer cells. Note: insert in (A), apsammoma body. (A)–(C); H & E stain, 200×. (D) *TFE*3 immunohistochemistry, 200×. Insert, H & E stain, 400×.

of Urologic Pathology (ISUP) Vancouver classification of renal neoplasia [17]. Histologically, the lesion is characterized by papillary architecture lined by clear and eosinophilic cells with abundant psammoma bodies [6] [18]. On the other hand, t(6;11) RCC has a biphasic appearance with both large and small epithelioid cells.

The morphology of these two neoplasms can overlap, thus the differential diagnosis is not simple. Histopathology of our case was similar to Xp11.2 translocation RCC, however, a few psammomatous bodies were observed on the tissue and smear samples. Immunohistochemistry of our case showed that the cancer cells were positive for *TFE*3 and HMB45, while negative for cytokeratin (AE1/AE3), SMA, CD10 and vimentin. The immunohistochemical marker for the diagnosis of Xp11.2 RCC is antibody against *TFE*3 protein [13] [19]. Immunocytochemistry also showed nuclear positivity of *TFE*3 in our case. Thus, the immunohistochemical/immuno- cytochemical marker for the diagnosis of Xp11.2 RCC is antibody against *TFE*3 protein [13] [19].

There are only a few reports on the cytological features of Xp11.2 RCC [14] [20]-[23]. Cytological samples included two fine needle aspirations, two touch imprint smears, and one voided/catheterized urine [14]. Kuwamoto *et al.* [14] strengthen the concept that the presence of sheets or clusters of cells with abundant clear or granular cytoplasm, round to oval nuclei, prominent nucleoli, occasional papillary clusters with fibrovascular/hyalinized cores, and psammoma bodies in the background is characteristics of RCC associated with Xp11.2 translocations/*TFE*3 gene fusions. In our case, we noted a papillary pattern of atypical cell clusters with psammoma bodies on the touch imprint smears during operation. When considering the age of patient, we decided to perform *TFE*3-immunocytochemistry for the diagnosis of Xp11.2 RCC.

Xp11.2 RCC should be considered when a child or young adult patient presents with a renal tumor with heterogeneous features such as hemorrhaging, necrosis, cystic changes, and calcification on CT and MRI and/or is accompanied by metastatic evidence. A radiologic examination may be valuable for the diagnosis of Xp11.2 RCC [24], although only a few case reports focusing on its imaging features are available due to the rarity of Xp11.2 RCC. MRI is suggested to be superior to CT due to the increased soft-tissue contrast and multiple imaging weights of MRI, which better reveal the heterogeneous composition (such as hemorrhaging or necrosis) of this type of tumor [25]. However, the non-invasive diagnosis of this type of tumor is difficult, especially at the early stage.

Treatments for Xp11.2 RCC include surgery, immunotherapy and molecular-targeted therapy. Surgical resection can achieve a favorable outcome for early stage Xp11.2 RCC. Recently, the assessment of the clinical efficacy of targeted agents, such as sunitinib (multikinase inhibitor), sorafenib (multikinase inhibitor) and everolimus (mTOR inhibitor), in patients with Xp11.2 RCC has been published [26]. At present, our patient is receiving treatment with an anti-angiogenic tyrosine kinase inhibitor, pazopanib, for metastatic tumors in the liver and bone. Xp11.2 RCC tends to develop in young patients with lymphnode metastasis. Further studies are needed to assess systemic therapy and the long-term prognosis.

In conclusion, when the patient's age and imaging findings are taken into account, the histopathological or cytological diagnosis may indicate this rare tumor as part of the differential diagnosis, and further investigations using immunohistochemistry and/or immunocytochemistry against *TFE*3 for accurate diagnosis are warranted.

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