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Xp11 Translocation Renal Cell Carcinoma: Unusual Variant Masquerading as Upper Tract Urothelial Cell Carcinoma

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ABSTRACT

Xp11 translocation renal cell carcinoma (TRCC) is a rare subtype of renal cell carcinoma characterized by chromosomal translocations involving the *TFE3* gene located at the Xp11.2 locus. Initial cases were more common in children, but cases in older adults have begun to accrue and suggest a relatively more aggressive course. We report a case of Xp11 TRCC in a 63-year-old female patient with initial presentation mimicking upper urinary tract urothelial cell carcinoma, with biopsy proving TRCC. She underwent a radical nephrectomy and paracaval lymph node dissection and is followed up with the intent to initiate vascular endothelial growth factor–targeted therapy in case of recurrence.

Introduction

Initially thought to be a malignancy affecting the pediatric and young adult population, recent studies have identified Xp11 translocation renal cell carcinoma (TRCC) in older adults. Incidence ranges from 0.95% to 5% of all adult renal cell carcinomas (RCCs).[1] Considering that RCC is more prevalent in adults than children, Xp11 TRCC in adults represents a greater number of tumors as a whole than Xp11 TRCC in children. Compared with its more indolent presentation in the pediatric population, older adults usually present with advanced stage and distant metastasis.[2] Prognosis is generally poor, and adult patients often succumb to a rapid terminal course despite aggressive surgical intervention.[3] Although the most favorable outcomes have been reported with patients who undergo a radical nephrectomy and lymph node dissection before the development of metastasis, successful and reliable treatment regimens are lacking.[4] For the patients who undergo radical nephrectomy, the challenge then lies in follow-up. A unique surveillance protocol has yet to be developed, although many agree that these patients should be categorized as high risk.[2,3] Clinicians should be aware of this rare variant and various presentations to ensure appropriate patient management and surveillance.

Case presentation

A 63-year-old woman was referred to us for a right renal pelvic mass detected on ultrasound during a gross hematuria and flank pain evaluation. Urine cytology was negative for malignancy, and computed tomography (CT) showed high-grade obstruction of the right kidney secondary to a 3.5-cm infiltrative lesion involving the proximal collecting system with infiltration into the superior renal pole parenchyma. The patient also had diffuse retroperitoneal and pelvic lymphadenopathy and splenomegaly, which were attributed to her chronic lymphocytic leukemia (CLL) currently in remission on the basis of comparison with previous imaging. In addition to CLL, past medical history included Moyamoya disease, transient ischemic attacks, hypertension, diabetes mellitus type 2, fibromyalgia, seizure disorder, asthma, and hypothyroidism due to thyroidectomy for papillary thyroid cancer. She remained highly functional despite her medical comorbidities. Chest CT revealed no evidence of metastasis, and the patient was counseled on the need for ureteroscopic biopsy for tissue diagnosis.

Cystoscopy showed no abnormal findings. Retrograde ureteropyelogram identified a large filling defect within the right renal pelvis extending all the way to the mid ureter. Flexible ureteroscopy revealed a large, elongated, and pale fleshy-appearing mass that did not appear to be consistent with urothelial carcinoma, but rather resembling a necrotic fibroepithelial polyp. The non-necrotic parts of tumor were biopsied despite extensive clot surrounding this mass which made visualization extremely challenging. Two large

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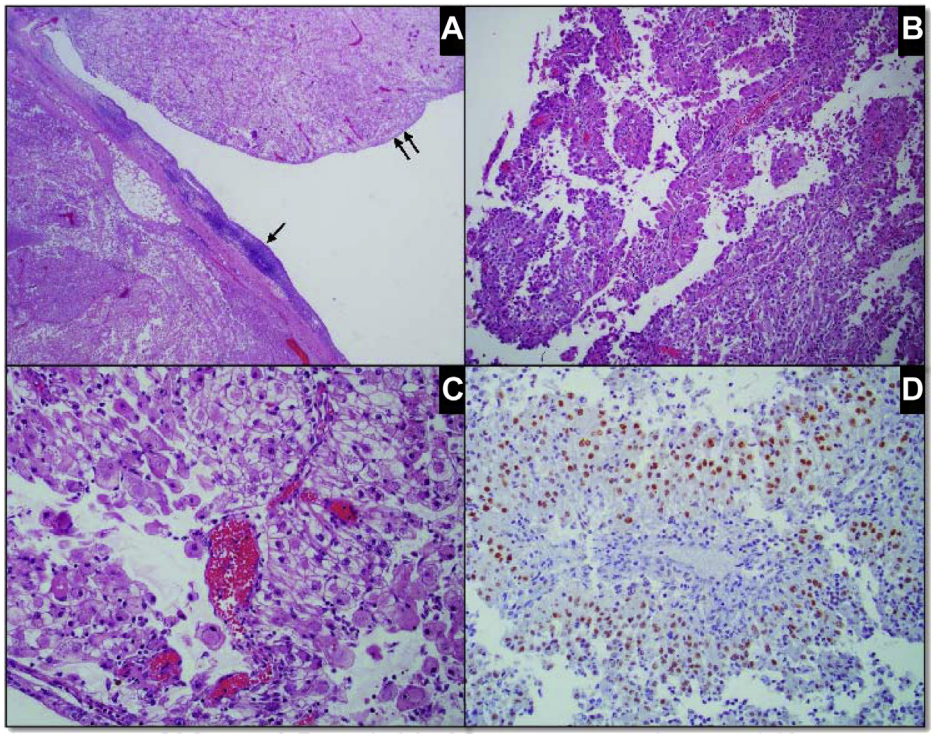

Figure 1. Composite photomicrograph showing the characteristic features of Xp11 translocation renal cell carcinoma. (**A**) Low power view (40×) showing an exophytic tumor (double arrows) in the renal pelvis (arrow). The tumor has a papillary growth pattern (**B**; 40×) and is composed of voluminous cells (**C**, 200×) with clear and eosinophilic cytoplasm. Note the delicate blood vessels inside the papillae. Immunohistochemistry for *TEF3* shows nuclear immunoreactivity (200×).

fragments were sent for permanent pathologic analysis. Immunohistochemical studies showed that the tumor cells were partially *PAX8*(+), CD10(+), CK7(−), *p63*(−), *GATA3*(−), and *MiTF*(−) with strong immunoreactivity for *TFE3*, excluding urothelial carcinoma. Considering the aggressive nature of Xp11 TRCC, the decision was made with the patient and family to promptly undergo a right laparoscopic radical nephrectomy and regional lymphadenectomy, which were performed without complications.

Surgical pathology revealed pT3aN1Mx, Xp11.2-associated clear cell RCC, with Fuhrman nuclear grade 4 and negative margins (Fig. 1). One of 4 lymph nodes was positive for metastatic carcinoma, and the lymph nodes were effaced by a diffuse lymphocytic

Table 1
Case reports in the literature of Xp11 TRCC in patients older than 55 years

Author	Demographics	Presentation	Treatment	Outcome
Haudebourg et al[5]	57-y-old female patient	4.5-cm solid right, inferior pole renal mass with calcifications seen on CT. Biopsy showed solid and alveolar growth pattern composed of clear cells, consistent with clear cell RCC.	Emergency nephrectomy because of retroperitoneal hemorrhage, pT1bNxMx, grade 3. Immunohistochemistry and FISH positive for *TFE3*, cytogenetic analysis showed t(X;1)(p11.2;p34). Additional karyotypic alterations were monosomy 18, monosomy 21, and trisomy 20.	No evidence of disease at follow-up period of 13 mo
Salles et al[6]	58-y-old female patient	4.8-cm mass in middle, third of right kidney on MRI. Presented with infrequent nephritic colic for 6 mo, no findings on physical examination or urine sediment and culture.	Radical nephrectomy, pT1bN2MX, Immunochemistry positive for *TFE3*.	No evidence of disease at 6 mo of follow-up.
LaGrange et al[7]	63-y-old female patient	3-cm right renal mass seen incidentally on CT during evaluation for left lower quadrant abdominal pain.	Hand-assisted laparoscopic partial nephrectomy, pT1aNxMx. Immunohistochemistry positive for *TFE3* and vimentin, negative for cytokeratin and epithelial membrane antigens.	No evidence of disease at 24 mo of follow-up.
Franzini et al[8]	79-y-old male patient	Presented with gross intermittent hematuria. Sonography showed spherical left kidney with increased total size, without evidence of cortiocomedullary differentiation because of parenchymal dyshomogeneity with neoplasm aspect, confirmed by CT, which also showed gross nodal involvement. Angiography showed massive thrombotic involvement of renal vein.	Radical nephrectomy with thrombectomy and staging lymphadenectomy. Pathology showed kidney parenchyma substituted by white firm tissue and multiple node metastases. Immunhistochemistry positive for *TFE3* and CD10 and negative for cytokeratin and epithelial membrane antigens.	Postoperative time uneventful except for lymphorrhea, discharged on postoperative day 14. One month later develops massive thrombosis of the portal vein and dies.

CT, computed tomography; MRI, magnetic resonance imaging; RCC, renal cell carcinoma.

infiltrate with a phenotype consistent with B-cell CLL. Owing to the aggressive course of Xp11 TRCC, she was referred to the medical oncology service for consideration of adjuvant chemotherapy or targeted therapy. Because of the lack of evidence for any benefit with these treatment modalities on this unique pathologic entity and no other foci of disease found on the patient's postoperative positron emission tomography-CT, adjuvant therapy was deferred to the time of possible future recurrence.

Discussion

Data regarding older adults are limited, and a review of the literature identified only 4 reports discussing Xp11 TRCC in patients older than 55 years, [5–8] as summarized in Table 1. However, the incidence of this rare neoplasm may be underestimated with the true frequency unknown in patients older than 40 years because of its histologic features that often mimic clear cell and papillary RCC.[9] Misdiagnoses may be further compounded by the fact that *TFE3* immunohistochemistry and cytogenetic studies are not routinely done and there is significant histologic overlap with *TFE3* negative and *TFE3* positive RCC. Our case illustrates the importance of performing immunohistochemical analyses in suspicious cases, as the distinction of Xp11 TRCC is crucial in providing appropriate counseling and determining surveillance protocol and management. Cytogenetic analyses are another helpful modality to diagnose Xp11 TRCC and should be used alongside immunohistochemistry.

Despite the literature suggesting the propensity of adult Xp11 TRCC to progress rapidly, 3 reports in adults older than 55 years with final pathologic stages pT1aN0Mx, pT1bN0Mx, and pT1bN2Mx disease found no evidence of disease at 24, 13, and 6 months, respectively.[5–7] The fourth case involved the oldest patient of 79 years with pT3a disease and multiple positive lymph nodes without distant metastasis.[8] The patient underwent a radical nephrectomy without adjuvant chemotherapy but passed away approximately 44 days after the operation from massive thrombosis of the portal vein. Our case presents an elderly patient with advanced T3aN1Mx disease, more consistent with the existing literature that suggests a relatively aggressive clinical course in adults. The patient was referred to medical oncology for evaluation of adjuvant chemotherapy, as there are emerging data suggesting efficacy of agents that target vascular endothelial growth factor and mammalian target of rapamycin pathways.[10] These agents have been shown to have modest effects in the setting of metastatic disease and appear to be the optimal agents for management of metastatic Xp11 TRCC.

Conclusion

Considering the rising incidence of RCC with the increased use of cross-sectional imaging, clinicians should be aware of Xp11 TRCC as a unique tumor and its propensity for rapid progression in adults to facilitate appropriate patient management. Considering histologic overlap of Xp11 TRCC with other RCC subtypes, it is imperative to perform immunohistochemistry and cytogenetics to prevent misdiagnoses in borderline or suspicious cases. There is no successful and reliable treatment regimen for Xp11 TRCC; however, the most favorable outcomes have been associated with curative surgical excision with radical nephrectomy and lymph node dissection. Literature in the older adult population is limited, and outcomes data are still premature, making long-term follow-up data necessary.

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