A Review of Translocation T(6;11) Renal Cell Carcinoma Tumors in the Adult Patient

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Key Words

Translocation renal cell carcinoma • t(6;11) RCC •
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Abstract

Historically, T(6;11) renal cell carcinoma (RCC) has been associated with the pediatric and adolescent populations and documentation of this tumor in adults has been rare. However, the frequency of translocation renal cell carcinoma (TRCC) may be widely underestimated in the adult population due to an inadequate immunohistochemical workup or misdiagnosis from similar gross and histological findings to other RCC. A subset of MiT family translocation carcinomas, t(6;11) (p21;q12) translocation tumors cause an *alpha*-TFEB gene fusion. Morphologically, this neoplasm tends to mimic the various types of RCC's, including clear cell, papillary, and even epithelioid angiomyolipomas. Adult cases of TRCC have shown to behave more aggressively than their indolent pediatric counterpart, but due to the limited number of reported cases the true nature of these tumors has yet to be determined. The aim of this review is to bring an awareness of translocation RCC to better understand its diagnoses, treatment and prognosis, and, in turn, to allow for new cases to further highlight the behavior of this rare variant.

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Introduction

T(6;11) translocation renal cell carcinoma (TRCC) is an extremely rare variant and accounts for 0.02% of all renal carcinomas [1]. Approximately 50 cases have been documented in the literature, the majority of which occurring in children and adolescents, however, more recent literature has demonstrated that these neoplasms can present in adults as well [2]. The mean and median age of presentation is 31 years, with a wide reported range of 3–68 years [2]. The only identified risk factor has been previous treatment with cytotoxic chemotherapy [2].

First described in 2001 by Argani et al, TRCC was not recognized as a new clinical entity by the International Society of Urological Pathology until 2012, where it was determined to be a subtype of the MiT family translocation carcinomas, which includes the more common Xp11 TRCC [3, 4].

Genetically, the t(6;11) translocation is a fusion of the 5' portion of the *Alpha* gene, an un-translated gene of unknown function, mapped at 11q12 with the transcription factor EB (TFEB) gene located at 6p21 [4]. This fusion results in the overexpression of native TFEB proteins that can be specifically identified on immunohistochemistry [5]. Although the mechanisms through which these fusions contribute to oncogenesis remains unclear, several studies suggest that the translocation factor E3 fusion

proteins seen in other MiT family RCC are transcription activators [6]. Similarly to Xp11.2 TRCC, the origin of t(6;11) RCC is suggested to be from the proximal tubules of the nephron based on the ultrastructural identification of the rudimentary microvilli [7, 8].

Pathologic Evaluation

Since MiT RCCs appear grossly similar to clear cell RCC and immunohistochemistry is not routinely performed as standard pathologic practice for adult renal tumors, adult MiT family translocation carcinomas are often misclassified as clear cell RCC in daily practice [2]. This specific subtype is not identifiable on pre-operative imaging, and reports demonstrate that these neoplasms are distinctive only at the morphological, immunohistochemical, and cytogenetic levels [9]. T(6;11) TRCC harbors a specific *alpha-TFEB* gene fusion which can be detected by reverse transcriptase polymerase chain reaction or by fluorescence *in situ* hybridization [2, 10]. While TRCCs do not have a distinctive gross appearance, reports indicate that these tumors have generally been un-encapsulated and exhibited a mahogany color and soft texture [2]. Histologically, these tumors are biphasic consisting of large and small epithelioid cells, which often form nests of rosettes clustered around the basement membrane [4].

The immunohistologic features are most distinctive and helpful in enabling an accurate diagnosis. Previous literature reports that most t(6;11) RCCs melanocytic markers are homatropine methylbromide 45 (HMB45) and Melan-A are positive and traditionally TRCC immunostains negative for translocation factor E3 as well as cytokeratins and epithelial membrane antigen [9, 11, 12]. Smith et al demonstrated t(6;11) RCC labeled diffusely for cathepsin K (83% mean labeling) and Melan A (92% mean labeling), and less extensively for HMB45 [3]. A report from John Hopkins demonstrated immunohistochemical labeling for paired box 8, cathepsin K, and Melan A in absence of cytokeratine AE1/3 is suggestive of t(6;11) RCC [3]. While these characteristics aid in accurate diagnosis, it is noteworthy that immunoreactivity for melanocytic markers HMB45 and Melan A and immune negativity for epithelial markers pan cytokeratin and epithelial membrane antigen may lead to another misdiagnosis of angiomyolipoma [12]. Ultimately, the identification of these neoplasms as TRCC should be confirmed definitively by TFEB fluorescence *in situ* hybridization (FISH) studies [3, 12].

Outcomes

T(6;11) RCC is recognized mostly as low-grade non-aggressive tumor. There are no well-established prognostic markers or protocols predicting biological behavior that are applicable for t(6;11) RCC. Recommendations from the International Society of Urological Pathology Consensus Conference, state that behavior of these tumors is yet to be fully characterized, although 10% of the 30 reported cases have developed fatal metastatic disease [13]. Some adult cases have presented with metastasis or pursued an aggressive clinical course causing death [6, 7, 14]. While most cases affecting children and young adults seem to be rather indolent, recurrence occurs in 17% of these patients [6]. In a comparative study of 6 cases of t(6;11) RCC, Peckova et al. [5] found that age and necrosis could potentially be taken as independent adverse prognostic factors. On multivariate analysis, demonstrated that more aggressive t(6;11) RCC appeared to affect the older (mean 45.2 years) rather than younger patients (mean 31.5 years) [5]. Additionally, grossly visible necrosis was present in aggressive t(6;11) RCC only [5]. There are currently no well-established prognostic models predicting biological behavior that are applicable for t(6;11) TRCC [5].

Postoperative Surveillance

The behavior of t(6;11) RCC remains unestablished due to the limited number cases in the literature. Extirpative surgery remains the lone therapeutic strategy as no proven neoadjuvant or adjuvant therapies exist. The recommendation for follow-up in adult patients is undetermined at this time. However, given the more aggressive behavior in adult populations as well as the potential for recurrence and metastasis, a more aggressive post-operative follow-up may be warranted [5, 10, 15].

Future Research

Future cases of t(6;11) RCC will further delineate the incidence, epidemiology, and nature of this tumor. Studies utilizing emerging genomic technologies will help identify prognostic factors and therapeutic targets in these neoplasms [2]. Some case reports on the MiT translocation family have shown varied responses to mammalian target of rapamycin (mTOR) inhibitors [16]. Lastly whole genome DNA and RNA sequencing studies

have recently been performed on a small number of cases of the MiT family translocation RCCs and hoped that these studies will identify therapeutic targets [17].

Currently there are a few clinical trials evaluating response and survival rates of different therapeutic agents. Underway, is a phase 2 trial evaluating MiT family cancers overall response to treatment with ARQ 197, a drug directed at blocking the c-Met pathway [18]. Another study at MD Anderson Cancer Center is assessing the progression free survival time of all non-clear cell renal cancers, including TRCC, in patients treated with Everolimus as compared to Sunitinib [19]. The results of these clinical trials will help direct the care of patients with these atypical tumors.

Conclusion

T(6;11) RCC is an uncommon tumor, found predominantly in children and adolescents. It is now clear that this tumor presents in adults as well, often with a worse prognosis [15]. Awareness and knowledge of this rare tumor and its unique immunohistological and morphological features will help to establish an accurate diagnosis to help delineate aggressive follow up. Future studies are needed to better understand tumor biology to create multispecialty guidelines to optimize patient care.

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