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The Mutant Menage- Mit Family Translocation Renal Cell Carcinoma

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Abstract

Microphthalmia associated transcription factor (MiT) family translocation renal cell carcinoma is neoplasm which enunciates genetic fusions within members of MiT family of transcription factors, especially TFE3 gene and TFEB gene. Neoplasm frequently incriminates the adult population ≤ 35 years of age with an intense female predilection. Tumefaction exhibits a papillary, solid or alveolar pattern of tumour configuration and is composed of clear cells or non-cohesive, pseudo stratified, eosinophilic epithelial cells. Tumour cells are pervaded with voluminous cytoplasm and pleomorphic nuclei of advanced grade. Neoplastic cells are intensely immune reactive to TFE3 or TFEB, PAX8, cathepsin K, CD10, alpha methyacyl CoA racemase (AMACR), vimentin or E-cadherin. Tumour cells appear immune non-reactive to cytokeratin, epithelial membrane antigen (EMA), carbonic anhydrase IX(CAIX), CD45, calretinin and smooth muscle actin(SMA). MiT family translocation renal cell carcinoma requires segregation from neoplasms such as clear cell papillary renal cell carcinoma, clear cell renal cell carcinoma, epithelioid angiomyolipoma, chromophobe renal cell carcinoma or papillary renal cell carcinoma. Neoplasm may be appropriately alleviated by cogent manoeuvers as surgical extermination of the neoplasm.

Keywords: MiT Family Translocation; TFE3; TFEB

Abbreviations: TFEB: Transcription Factor EB; AMACR: Alpha Methyacyl CoA Racemase; EMA: Epithelial Membrane Antigen; SMA: Smooth Muscle Actin; FISH: Fluorescent in Situ Hybridization; SDH: Succinate Dehydrogenase; CAIX: Carbonic Anhydrase IX; CK: Cytokeratin.

Introduction

Microphthalmia associated transcription factor (MiT) family translocation renal cell carcinoma is neoplasm which enunciates genetic fusions within members of MiT family of transcription factors, especially TFE3 gene and TFEB gene. Generally, paediatric population or young adults are incriminated. Neoplasm is exclusively confined to renal parenchyma and manifests with a variable histological countenance. Papillary articulations and alveolar or nested tumour configuration is encountered. Tumefaction is comprised of clear cells or eosinophilic tumour cells. Calcific concretions as psammoma bodies are commonly observed. Precise immunohistochemistry and fluorescent in situ hybridization (FISH) can be beneficially adopted for discerning pertinent chromosomal translocations. Neoplasm is additionally denominated as renal cell carcinoma associated with Xp11 genetic translocation. Aforesaid neoplasm delineates genetic fusions within TFE3 gene in concurrence with multiple genetic partners. Besides, renal

cell carcinoma exemplifying chromosomal translocation t (6:11) may display co-existent MALAT1-TFEB genetic fusion [1,2].

TFE3 gene situated upon chromosome Xp11 may concur with several partner genes as the commonly discerned ASPL gene confined to chromosome 17q25 and PRCC gene confined to chromosome 1q21. Besides, genes such as NONO appearing upon chromosome Xq12, PSF/SFPQ emerging upon chromosome 1p34, CLTC situated upon chromosome 17q23 and genetic translocation (t (6:11)(p21;q12) along with translocation between TFEB and MALAT1 genes may engender overexpression of TFEB gene [1,2].

Chromosomal translocation t(X;17)(p11.2;q25) along with balanced translocation within TFE3 gene situated at chromosome Xp11.2 and ASPL gene located at chromosome 17q25 may occur within diverse renal neoplasms, in contrast to an unbalanced translocation der(17) t(X;17)(p11.2;q25) emerging within alveolar soft part sarcoma. Melanotic Xp11 renal cell carcinoma may concur with perivascular epithelioid cell tumour delineating PSF/SFPQ-TFE3 genetic anomaly and display identical clinical or histological manifestations.

MiT family translocation renal cell carcinoma configures ~3% of adult renal cell carcinomas wherein ~40% of paediatric renal cell carcinomas or neoplasms confined to young adults delineate immunoreactivity to TFE3+ [2,3]. Tumefaction exhibits overexpression of TFE3 gene or TFEB gene which activates multiple downstream targets, especially targets activated by MiT family of transcriptions factors. Therefore, expression of cysteine protease cathepsin K and melanocytic markers is frequent, in contrast to epithelial markers as cytokeratin [2,3]. MiT family translocation renal cell carcinoma frequently incriminates the adult population ≤ 35 years of age. An intense female predilection is observed. Tumours of advanced grade may be encountered upon initial disease representation. Factors contributing to disease emergence appear as exposure to cytotoxic chemotherapy [2,3].

Grossly, neoplasm demonstrates a tan or yellow hue and frequently enunciates foci of haemorrhage and tumour associated necrosis [3,4]. Upon microscopy, TFE3 rearranged renal cell carcinoma preponderantly exhibits a papillary, solid or alveolar pattern of tumour configuration. Neoplasm is composed of clear cells or non-cohesive, pseudostratified, eosinophilic epithelial cells. Tumour cells are pervaded with voluminous cytoplasm and pleomorphic nuclei of advanced grade. Frequently, TFE3 rearranged renal cell carcinoma exhibits psammoma bodies or disseminated melanin pigment, akin to pigmented perivascular epithelioid tumour (PEComa) [3,4].

Chromosomal translocation t(6:11) rearranged renal cell carcinoma characteristically demonstrates a biphasic configuration. Neoplasm is constituted of enlarged epithelioid cells commingled with aggregates of miniature cells circumscribing basement membrane-like material, a feature which simulates Call-Exner bodies discerned within adult granulosa cell tumour [3,4]. Ultrastructural examination exhibits tumour cells displaying features of clear cell carcinoma such as cellular junctions, innumerable mitochondria, microvilli, abundant intracellular glycogen and basement membrane [3-5] (Figures 1 & 2).

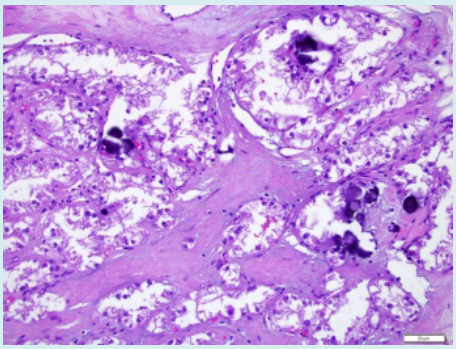

Figure 1: MiT family translocation renal cell carcinoma delineating papillary structures and alveolar configuration composed of clear cells imbued with voluminous cytoplasm and pleomorphic nuclei. Surrounding stroma exhibits psammoma bodies [6].

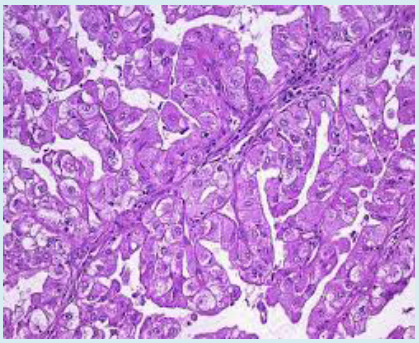

Figure 2: MiT family translocation renal cell carcinoma exhibiting papillary structures with fibro-vascular cores and alveolar articulations comprised of clear cells and eosinophilic cells pervaded with voluminous cytoplasm and pleomorphic nuclei [7].

Neoplastic cells are intensely immune reactive to TFE3 or TFEB, PAX8, cathepsin K, CD10, alpha methyacyl CoA racemase (AMACR), vimentin or E-cadherin. Renal cell carcinoma depicting genetic translocation t(6:11) is frequently immune reactive to human melanoma black

45 (HMB45) antigen and Melan A, in contrast to tumours delineating genomic alterations Xp11. Neoplasms confined to adults may be weakly immune reactive to TFE3. Tumour cells appear immune non-reactive to cytokeratin, epithelial membrane antigen (EMA), carbonic anhydrase IX(CAIX), CD45, calretinin and smooth muscle actin(SMA) [4,5] (Table 1).

	Hale	KIT	CK7	S100A1	VIM	CAIX	AMACR	SDH	TFE3
Chromo-phobe RCC	+++	+++	+++	-	-	-	-	+++	-
Clear cell RCC	-	-	-	-	+++	+++	-	+++	-
Oncocytoma	-	+++	rare	+++	-	-	-	+++	-
Papillary RCC	-	-	+++	-	+++	-	+++	+++	-
Translocation RCC							++	+++	+++
SDH deficient RCC	-	-	-	-	-	-	-	-	-

SDH: Succinate dehydrogenase, AMACR: Alpha methyacyl CoA racemase, CAIX: Carbonic anhydrase IX, VIM: Vimentin, HALE: Colloidal iron stain, CK: Cytokeratin, TFE3: Transcription Factor Binding To IGHM Enhancer 3, Hale: Hale's colloidal iron.
Table 1: Immuno-reactive profile of renal cell carcinomas [3,4].

Fluorescent in situ hybridization (FISH) employing TFE3 or TFEB break-apart probe emerges as a significantly sensitive and specific mechanism for cogent tumour categorization and may be beneficially adopted for classifying neoplasms which appear indeterminate upon morphological assessment or immunohistochemistry. MiT family translocation renal cell carcinoma requires segregation from neoplasms such as clear cell papillary renal cell carcinoma, clear cell renal cell carcinoma, epithelioid angiomyolipoma, chromophobe renal cell carcinoma or papillary renal cell carcinoma [4,5].

MiT family translocation renal cell carcinoma may be appropriately alleviated by cogent surgical manoeuvers as surgical extermination of the neoplasm. Besides, administration of chemotherapeutic agents as mTOR inhibitors or tyrosine kinase inhibitors may be advantageous. However, certain MET inhibitors may demonstrate moderate anti-tumour activity [4,5]. Tumefaction exhibits an aggressive clinical course. However, neoplasms depicting chromosomal translocation t(6;11)(p21;q12) enunciate minimal malignant potential, in contrast to various chromosomal translocation associated renal cell carcinomas [4,5].

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6. Image 1 Courtesy: Pathology outlines.

7. Image 2 Courtesy: MDPI.com.