Commentary Article

Journal of Surgery and Surgical Procedures

The Transmuting Tier-Transitional Cell Carcinoma

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Submitted : 04 Jun 2022 ; Published : 21 Jun 2022

Citation: Bajaj, A. (2022). The Transmuting Tier-Transitional Cell Carcinoma. J Sur & Surgic Proce , 2022; 1(1): 1-3.

Abstract

Transitional cell carcinoma emerges from malignant transmutation of transitional epithelium layering intrinsic surface of urinary bladder, ureter, urethra and urachus. Classically, carcinoma of urinary bladder exhibits painless, episodic, intermittent, gross or microscopic haematuria. Transitional cell carcinoma predominantly expounds papillary lesions (70%) whereas nearly 30% neoplasms are non papillary. Transitional cell carcinoma enunciates somatic mutations with genomic deletions in chromosome 9q,9p,11p,17p,13q,14q along with overexpression of RAS oncogene and epidermal growth factor receptor (EGFR). Localized transitional cell carcinoma is aptly subjected to surgical resection.

Keywords: Urothelial carcinoma, papillary variant, carcinoma bladder.

Introduction

Transitional cell carcinoma emerges from malignant metamorphosis of transitional epithelium layering intrinsic surface of urinary tract comprised of urinary bladder, ureter, urethra and urachus. Additionally designated as urothelial carcinoma, majority (95%) of urinary bladder carcinomas are constituted of transitional cell carcinoma. Transitional cell carcinoma contributes to ~10% of malignant primary renal neoplasms (Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022). Clinical symptoms of transitional cell carcinoma appear contingent to location and extent of carcinoma. Characteristically, carcinoma of urinary bladder exhibits painless haematuria. The commonly discerned, gross or microscopic haematuria is episodic and intermittent. Cogent urinary analysis is required to assess microscopic haematuria (Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022). Carcinoma bladder manifests with gross haematuria as an initial disease representation in ~ 90% instances. Although non specific to transitional cell carcinoma urinary bladder, symptoms such as pain during micturition, polyuria or incomplete evacuation of bladder with vesicle tenesmus may ensue (Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022).

Exceptional variants of carcinoma bladder such as urachal adenocarcinoma secrete mucin with consequent excretion of thickened urine (Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022).

Advanced transitional cell carcinoma of urinary bladder delineates pelvic, bony or flank pain or lower limb oedema. Exceptionally, tumefaction appears palpable on physical examination (Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022).

Factors contributing to occurrence of transitional cell carcinoma are environmental carcinogens as cigarette smoking, exposure to chemicals as petroleum products, paints and pigments as aniline dyes or agrochemicals (Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022).

Physical irritation predisposes to emerging transitional cell carcinoma with possible malignant metamorphosis of the urothelium. Thus, transitional cell carcinoma is commonly discerned in association with conditions such as chronic calculi of urinary tract, chronic catheterization adopted in parapIegia or multiple sclerosis or chronic urinary tract infections (Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022).

Chemotherapeutic agents such as cyclophosphamide or exposure to radiation predisposes to urothelial carcinoma (Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022).

Transitional cell carcinoma enunciates somatic mutations with genomic deletions in chromosome 9q,9p,11p,17p,13q,14q along with overexpression of RAS oncogene and epidermal growth factor receptor (EGFR) (Dobruch & Oszczudłowski,

2021; Kaseb & Aeddula, 2022).

Tumour cells exhibit an anomalous extra chromosome designated as small supernumerary marker chromosome (sSMC). Transitional cell carcinomas of urinary bladder demonstrating small supernumerary marker chromosome (sSMC) are aggressive and infiltrative (Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022).

Thus, "sSMC i(5)(p10)" is a frequently delineated, repetitive structural chromosomal anomaly discernible in transitional cell carcinoma(Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022).

World Health Organization (WHO) has categorized transitional cell carcinoma into papillary neoplasms of low malignant potential (PNLMP), low grade papillary carcinoma or high grade papillary carcinoma (Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022).

Nevertheless, grading system of transitional cell carcinoma expounded by World Health Organization (WHO) as a papilloma, grade I, grade II or grade III neoplasms is frequently adopted (Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022).

Around ~40% of transitional cell bladder carcinomas appear as multifocal lesions. The neoplasm can depict distinct configurations as papillary, sessile or carcinoma in situ (Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022).

Transitional cell carcinoma predominantly expounds papillary lesions (70%) whereas nearly 30% neoplasms are non papillary (Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022).

Non papillary carcinoma of urinary bladder is comprised of carcinoma in situ (Cis) demonstrating high grade tumour cells with significant cytological atypia and nuclear pleomorphism, micro-invasive carcinoma and frankly invasive transitional cell carcinoma (Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022).

Transitional cell carcinoma can exemplify differentiation into diverse variants. Papillary transitional cell carcinoma can represent typically as transitional cell or micro-papillary variant (Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022).

Additionally, differentiation with squamous or glandular epithelium, sarcomatoid, urothelial carcinoma with small tubules and microcystic form, lymphoepithelioma –like carcinoma, lymphoma-like and plasmacytoid variant, nested variant, urothelial carcinoma with giant cells, trophoblastic differentiation, clear cell variant, plasmacytoid and unusual stromal reactions can be exemplified (Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022).

Non transitional cell carcinomas of urinary bladder configure ~5% of malignant lesions and are expounded as squamous cell carcinoma, adenocarcinoma, sarcoma, small cell carcinoma and secondary metastatic carcinomas arising from primary tumefaction confined to distant sites (Dobruch & Oszczudłowski, 2021; Kaseb & Aeddula, 2022).

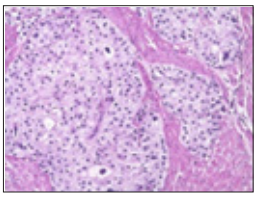

Figure 1: Transitional cell carcinoma depicting cellular nests with cytological atypia, cells with anisonucleosis and mitotic figures surrounded by desmoplastic reaction
Courtesy: Nature.com .

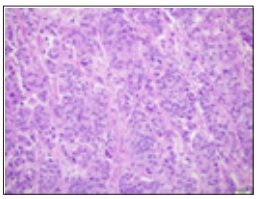

Figure 2: Transitional cells carcinoma with significant stromal invasion of nests of atypical epithelial cells with cellular and nuclear pleomorphism, mitotic figures and minimally fibrotic stroma.
Courtesy: Pathology Outlines

Tumour	Node	Metastasis
TX: Primary tumour cannot be assessed		
T_0: Primary tumour is non discernible	N_0: Lymph node deposits are absent	M_0: Distant metastasis are absent
Ta: Non invasive papillary carcinoma		
Tis: Flat, non invasive carcinoma or carcinoma in situ		
T1:Tumour extends to lamina propria	N1:Tumour extends to one regional or pelvic lymph node	M1a: Tumour spreads to distant lymph nodes M1b:Tumour spreads to distant sites as bones, lungs, liver
T2a: Tumour extends to inner muscle layer T2b: Tumour extends to outer muscle layer	N2:Tumour extends to ≥2 regional lymph nodes	
T3a: Tumour infiltrates the muscle T3b:Tumour extends to serosa	N3:Tumour extends to lymph nodes along common iliac artery	
T4a: Tumour extends to prostate, seminal vesicles, uterus, vagina T4b: Tumour extends through the bladder to abdomino-pelvic wall		

Table 1: TNM classification of Urothelial Carcinoma(1,2).

Commonly, extra pelvic metastasis of transitional cell carcinoma occurs within bone wherein the vertebral column is a frequent site of disease emergence (Teoh el al., 2020; Lopez-Beltran el al., 2022).

Cogent and efficacious therapeutic approach towards transitional cell carcinoma can be challenging to ascertain. Localized transitional cell carcinoma is aptly subjected to surgical resection although tumour reoccurrence is frequent (Teoh el al., 2020; Lopez-Beltran el al., 2022).

Additionally, chemotherapeutic agents such as mitomycin can be injected into urinary bladder as a singular dose following surgery or administered sequentially within few weeks (Teoh el al., 2020; Lopez-Beltran el al., 2022).

Localized or antecedent transitional cell carcinoma can be treated with bladder infusion of Bacille Calmette- Geurin (BGG) (Teoh el al., 2020; Lopez-Beltran el al., 2022).

Neoplasms with preliminary tumour invasion into muscularis propria can be treated with radical surgical manoeuvers as a cysto-prostatectomy with tissue sampling of regional lymph nodes (Teoh el al., 2020; Lopez-Beltran el al., 2022).

Advanced or metastatic transitional cell carcinoma can be administered chemotherapeutic agents as gemcitabine or cisplatin or combined chemotherapy with methotrexate, vinblastine, adriamycin or cisplatin. Taxanes or vinflunine are second line agents adopted following progressive platinum-based chemotherapy (Teoh el al., 2020; Lopez-Beltran el al., 2022).

Immunotherapy with agents as pembrolizumab appear efficacious in treating metastatic urothelial carcinoma (Teoh el al., 2020; Lopez-Beltran el al., 2022).

Agents such atezolizumab appear beneficial in treating locally advanced or metastatic urothelial carcinomas non responsive to cisplatin-based chemotherapy. Sacituzumab govitecan is employed for locally advanced or metastatic urothelial cancer (mUC) previously treated with platinum-based chemotherapy and programmed death receptor -1(PD-1) or programmed death –ligand 1(PD-L1) inhibitor (Teoh el al., 2020; Lopez-Beltran el al., 2022).

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