

Urothelial Carcinoma With a Novel *MET* Exon 14 Skipping Alteration

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Abstract

Background/Aim: Urothelial cancer (UC) is the most common malignancy of the urinary tract, and outcomes in advanced disease remain poor. Comprehensive genomic profiling has revealed rare but potentially actionable alterations, including mesenchymal-epithelial transition factor (*MET*) exon 14 skipping events, which are well established in non-small cell lung cancer but rarely described in UC. We hereby report a case of high-grade plasmacytoid UC harboring a novel *MET* exon 14 skipping alteration and discuss its potential clinical relevance.

Case Report: A 78-year-old man presented with pelvic pain and hematuria. Imaging showed irregular thickening of the bladder wall with bilateral ureterovesical junction and distal ureter involvement and rectal invasion, consistent with unresectable stage IVA (cT4N0) plasmacytoid UC. He received carboplatin–gemcitabine followed by maintenance avelumab. Next-generation sequencing of tumor tissue identified a novel intronic *MET* splice-site alteration, NM_000245.4: c.2942-22_2942-19delCTTT, at high variant allele frequency, predicted to cause exon 14 skipping; this result was confirmed on an independent panel, and no additional driver variants were detected.

Conclusion: This case broadens the spectrum of *MET* exon 14 skipping events in UC by documenting a novel intronic c.2942-22_2942-19delCTTT alteration in plasmacytoid carcinoma. It underscores the importance of routine genomic profiling in advanced and histologically rare UC to uncover targetable alterations and supports consideration of *MET*-directed therapies or enrollment in tumor-agnostic trials for selected patients, while highlighting the need for further functional and clinical validation.

Keywords: Urothelial cancer, *MET* exon 14 skipping, targeted therapy.

Introduction

Urothelial cancer (UC) is the ninth most common malignancy worldwide for both sexes and the sixth for

men, with both incidence and mortality rates increasing, predominantly affecting the elderly population (1). UC primarily arises from the epithelial lining of the urinary tract and is the most prevalent type of bladder cancer. It



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also accounts for a significant proportion of cancers involving the renal pelvis, ureters, and urethra (2). Despite advances in surgical techniques, immunotherapy, and chemotherapy, the prognosis for patients with advanced or metastatic UC remains poor.

Comprehensive molecular profiling of urothelial tumours has revealed the heterogeneous nature of UC, leading to an increased focus on targeted therapies. The mutational landscape of UC includes alterations in various genes, such as FGFR3, PIK3CA, TP53, KDM6A, ARID1A and RB1. Among these, aberrations in the mesenchymal-epithelial transition factor (MET) proto-oncogene have gained attention due to their potential role in tumorigenesis and as therapeutic targets.

MET, located on chromosome 7 (7q21-q31), encodes for the receptor tyrosine kinase that plays an essential role in cellular proliferation survival and motility through activation of downstream signaling pathways, such as MAPK and PIK3/AKT. MET tyrosine kinase is expressed in epithelial cells of many organs, including the liver, pancreas, prostate and kidney (3, 4).

Exon 14 (out of 21) of MET encodes a portion of the juxtamembrane domain that includes a binding site for the c-Cbl protein, a multifunctional protein with E3 ubiquitin ligase activity, responsible for MET degradation. Skipping of exon 14, often caused by splice-site mutations or small insertions/deletions, results in the loss of the c-Cbl binding site, leading to impaired degradation and protein accumulation. This dysregulation enhances MET signaling, promoting uncontrolled cell growth and proliferation, which results in cancer development and progression (5, 6). MET exon 14 skipping has been most frequently detected in non-small cell lung cancer (NSCLC) – occurring in approximately 3% of cases and conferring sensitivity to MET inhibitors. It has also been reported, albeit rarely, in other types of cancer including nervous system cancers, gastrointestinal cancers and cancers of unknown primary origin (7, 8).

A few studies have identified MET exon 14 skipping in a small subset of UCs (7-9), with an estimated relatively low frequency of less than 1%. Despite its rarity, this alteration has highly significant implications for precision oncology. It

may contribute to oncogenesis in UC through enhanced MET signaling and resistance to conventional therapies (10). Emerging evidence suggests that solid cancer tissue samples harboring this alteration, including UC, may benefit from MET-targeted therapies, such as MET inhibitors (11, 12). However, due to its rarity, the clinical significance of MET exon 14 skipping in UCs remains to be fully elucidated, necessitating further research into its role as a prognostic biomarker and/or potential therapeutic target.

Case Report

A 78-year-old man from Greece was referred to our clinic with pelvic pain and hematuria. A pelvic positron emission tomography-computed tomography (PET/CT) scan revealed irregular thickening of the bladder wall, more pronounced on the posterior aspect, suggestive of a malignancy with Maximum Standardize Uptake Value (SUVmax) 5.1 (Figure 1A). Notably, the imaging also showed involvement of both ureterovesical junctions and the distal ureters, more prominent on the right side with SUVmax 4.7 (Figure 1B and C). Mild to moderate bilateral hydronephrosis was observed, along with concentric mural thickening of the mid-rectum and the presence of bilateral pig-tail nephrostomy catheters.

Immunohistochemical analysis demonstrated strong positivity for CK, AE1/AE3, CD138 and GATA3 indicative of urothelial carcinoma with plasmacytoid morphology. Subsequent histopathological examination of the bladder tissue biopsy confirmed high-grade urothelial plasmacytoid carcinoma [pT2 – American Joint Committee on Cancer (AJCC) 8th Edition] with invasion into the rectal wall. The tumor was clinically staged as cT4N0, corresponding to stage IVA disease. Based on the extent of local invasion, the tumor was deemed unresectable by the multidisciplinary tumor board. The patient was initiated first-line systemic chemotherapy with carboplatin and gemcitabine, followed by maintenance immunotherapy with avelumab (Bavencio).

To explore potential options for targeted therapy, molecular profiling was performed on formalin-fixed, paraffin-embedded (FFPE) tumor tissue using

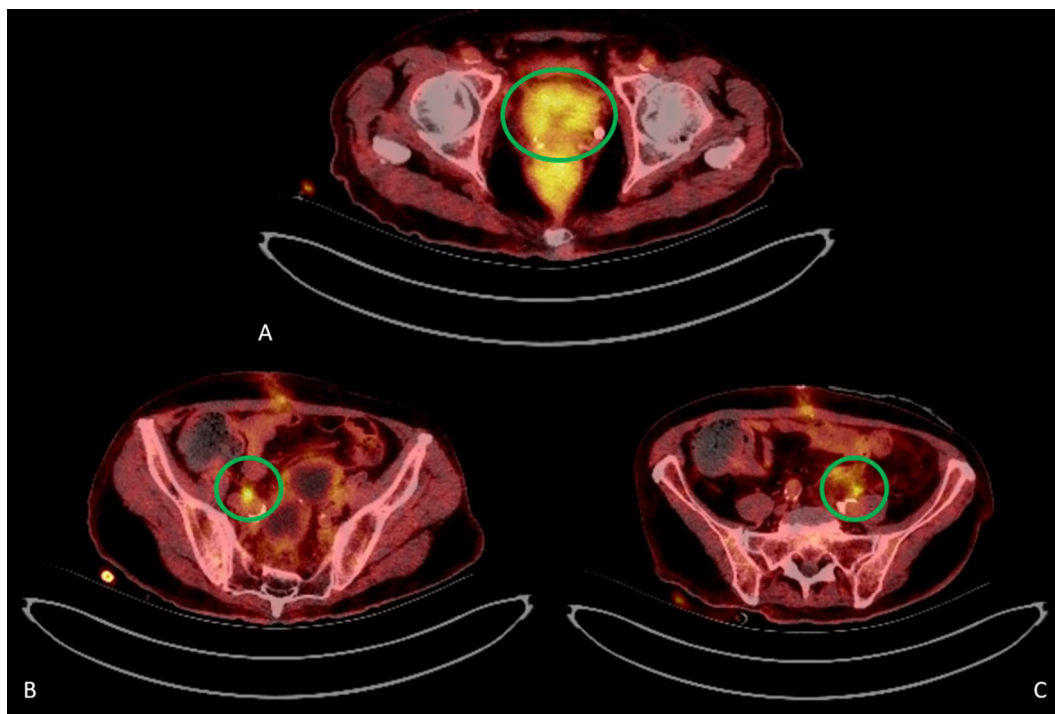


Figure 1. Positron emission tomography–computed tomography (PET/CT) imaging of urothelial carcinoma. (A) PET/CT scan showing increased radiotracer uptake (green circle; SUVmax: 5.1) consistent with urothelial carcinoma. (B, C) View of the same PET/CT scan highlighting increased radiotracer uptake along both ureters (green circle), more pronounced on the right side (B; SUVmax: 4.7), suggesting possible involvement.

comprehensive Next-Generation Sequencing (NGS). The 50-gene panel Oncomine™ Precision Assay (OPA, Thermo Fisher Scientific, Waltham, MA, USA) on the Ion Torrent Genexus System designed for detection of clinically relevant alterations was used. FFPE tissue sections, with 60% tumor cellularity, were processed per the manufacturer protocol. Library preparation, templating and sequencing were conducted using automated workflows. The average base coverage depth was approximately 5,000, with an average on-target percentage of >95%. For the amplicons covering the MET gene, the average base coverage depth was >3,000. No positive or negative FFPE controls were included in the sequencing run.

Data analysis was conducted using Ion Torrent Oncomine Variant Caller (OVC), version 5.16, integrated within the Genexus Software Suite. Variant calling was performed with default settings for the OPA, optimized for detection of low frequency somatic variants. The analysis revealed a novel

intronic alteration in the MET gene, resulting in exon 14 skipping (NM_000245.4: c.2942-22_2942-19delCTTT), with a variant allele frequency (VAF) of 69.62% (Figure 2). No other driving gene variants were found. The presence of the MET exon 14 skipping alteration was subsequently confirmed using an independent NGS panel that also included MET, which reported a VAF of 67.06%.

Discussion

In solid tumours, MET gene alterations– including amplifications and single nucleotide variants (SNVs), have emerged as critical oncogenic drivers with therapeutic implications. MET amplification leads to over-expression and constitutive activation of the MET receptor tyrosine kinase, resulting in the sustained activation of downstream signaling cascades such as PI3K/AKT, MAPK, and STAT3 pathways. These signaling events contribute to increase in

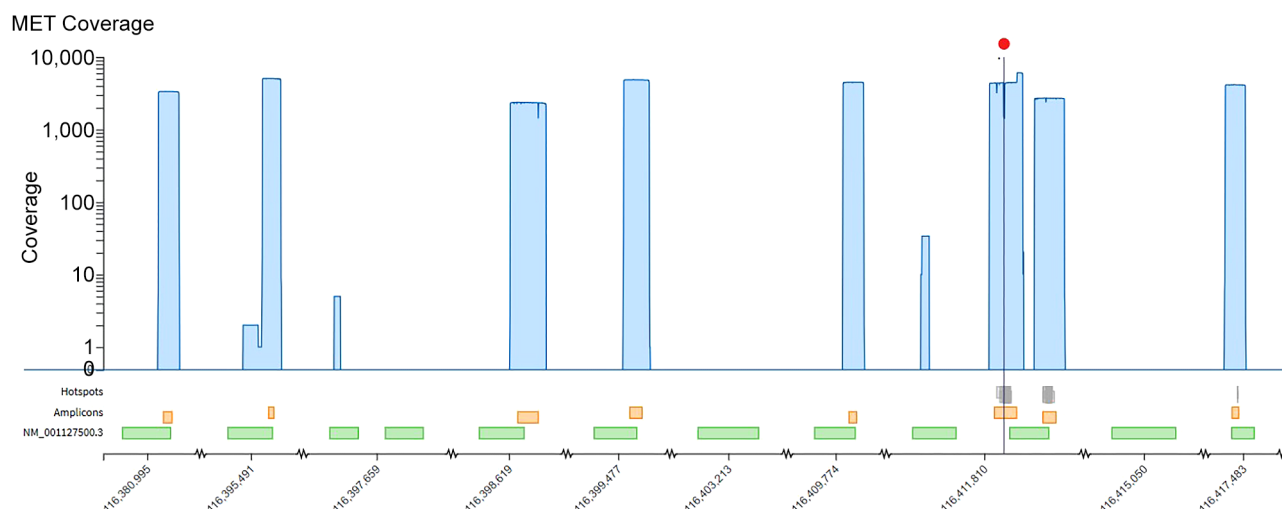


Figure 2. Identification of the mesenchymal-epithelial transition factor (MET) exon 14 skipping alteration. Coverage depth is shown on the graph, while the region of the alteration (vertical line) is highlighted with a red dot. The variant was detected with 69.62% variant allele frequency (VAF), supported by 91.95% reads on target.

cellular proliferation, survival, motility, and invasive potential. Activating MET SNVs, including those that lead to exon 14 skipping alteration, impair receptor degradation and prolong MET signaling. These alterations have been most extensively characterized in NSCLC, where MET exon 14 skipping alterations and amplifications serve as biomarkers for targeted therapy with MET inhibitors. Similarly, MET aberrations have been implicated in gastric, colorectal and hepatocellular carcinomas although their prevalence and therapeutic relevance vary across tumor types (13, 14).

The identification of MET overexpression in UC is synonymous to shorter overall survival or progression free survival (15). However, MET amplification and SNVs appear to occur at lower frequencies compared to those in other solid tumors, yet may still hold clinical significance in some patient subsets with UC. Data from genomic profiling studies indicate that MET alterations and amplifications, particularly exon 14 skipping events may contribute to disease progression and resistance to conventional therapies. While MET-targeted therapies have not yet become standard of care in UC, preliminary evidence from basket trials and early-phase studies

indicates potential benefit in MET-altered cases (16). These findings underscore the need for comprehensive molecular profiling in UC to identify patients who may derive therapeutic benefit from MET inhibition.

Here, we reported a case of a 78-year-old man suffering from UC who underwent comprehensive molecular testing, which revealed a novel MET exon 14 skipping alteration. This case illuminates the importance of molecular profiling in UC, particularly in patients with treatment-resistant or recurrent disease. The discovery of a novel MET exon 14 skipping alteration in this patient with advanced UC provides valuable insight into the potential role of targeted therapies for this malignancy. To date and to our knowledge, alterations leading to MET exon 14 skipping have been previously reported in only three other cases of UC, emphasizing the rarity of this genomic event in this specific type of cancer (7-9).

UC remains a relatively understudied malignancy with a number of genes involved in its prognosis and therapeutic approach still not fully understood. In light of recent findings, HOOK3 amplification in bladder UC has been associated with poorer prognosis, emphasizing the relevance of gene expression and survival analyses in

uncovering potential oncogenic prognostic drivers (17). In addition, the rising therapeutic option of DPP4 inhibitors in upper tract UC reinforces the need for comprehensive molecular profiling to guide precision oncology in UC (18). While further research and clinical trials are necessary to determine the efficacy of these emerging therapeutic alternatives in UC, this case provides promising evidence supporting personalized treatment approaches based on the tumor's molecular profiling. Targeted therapies, such as selective MET or DPP4 inhibitors, represent an exciting avenue for improving outcomes of patients with UC harboring this specific genetic alteration.

The clinical benefit observed in patients with lung cancer treated with selective tyrosine kinase inhibitors (TKIs) when their tumor exhibits a MET exon 14 skipping alteration is unquestionable. However, this benefit has not yet been replicated in other malignancies. This discrepancy may be attributed to the rarity of the alteration in non-pulmonary malignancies, differences in tumor biology, or uncertainty regarding the expression of the aberrant MET transcript resulting in diverse underlying function of the protein. Basket trials have been exploring the utility of targeted therapies across several tumor types that share actionable genomic variation. The recent Phase II trial by Kang *et al.*, investigated tepotinib in patients with diverse advanced solid tumours harboring MET exon 14 skipping alterations or amplifications, including NSCLC, gastric cancer and UC. The sample size for UC was limited. However, preliminary signals of efficacy were observed, supporting the broader application of MET-targeted therapies beyond NSCLC.

Study limitations. To date, clinical data on MET-targeted therapies in UC are limited. While MET exon 14 skipping alterations are well-established for NSCLC therapy management, their role in UC is less defined. A few early-phase clinical trials have explored the activity of TKIs in advanced solid tumours, including UC, but most did not specifically enrich for MET exon 14 skipping alterations. For example, the Phase II trial of capmatinib and tepotinib included small numbers of patients with bladder cancer,

though responses were primarily observed in MET-amplified or MET-dysregulated tumours rather than in *MET* exon 14 skipping cancers (12). Thus, further studies are needed to evaluate the predictive value of *MET* exon 14 skipping alterations for MET-TKI response in UC specifically. Another limitation is the absence of transcriptomic or proteomic validation of the *MET* exon 14 skipping alteration. Even though genomic sequencing identified the splice site variant, the absence of RNA or protein-level data raises a small but not negligible risk of an inaccurate prediction regarding exon 14 skipping. However, similar deletions within intron 13 (from -12 to -35 upstream of exon 14) are known to induce MET exon 14 skipping (7, 19). Furthermore, intratumor heterogeneity remains a concern in UC; it is possible the MET exon 14 alteration may not be present in all tumor subclones, which could impact therapeutic efficacy.

Conclusion

In summary, our case adds to the limited but growing body of evidence supporting the clinical relevance of MET exon 14 skipping in UC through comprehensive genomic profiling and highlights the need for continued investigation into its role as a therapeutic target. While MET alterations are more commonly studied in NSCLC, emerging evidence suggests that MET-targeted therapies might offer benefit across several tumor types. Overall, this report underscores the importance of precision oncology in guiding treatment decisions for rare molecular subsets.

Conflicts of Interest

The Authors declare no conflicts of interest regarding the present study.

Authors' Contributions

Clinical management of the patient: F.S.; Conceptualization: E.P.; Drafting of the manuscript: E.P.; Investigation: C.B., F.P.; Interpretation of molecular data: E.P.; Literature review: E.P., L.F.; Methodology: G.K.; Supervision: N.S.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (ChatGPT, OpenAI) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning-based image enhancement tools.

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