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Case Report

Genomic Integration and Molecular Dysregulation in Aggressive Stage IV Bladder Cancer Following COVID-19 mRNA Vaccination

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Abstract

Background: Bladder cancer is rare in young women, and advanced presentations are exceptionally uncommon. We report a de-identified case of a previously healthy 31-year-old female who developed rapidly progressive stage IV bladder cancer within 12 months of completing a three-dose Moderna mRNA vaccination series (May 2021, June 2021, December 2021). ***Case Findings:*** Comprehensive multi-omic profiling was performed using PBIMA (Molecular Surveillance and Individualized Targeted Immunotherapy Peptide Editing) and REViSS (Spike-associated Transcription-al/Translational Instability Surveillance), incorporating analyses of plasma-derived circulating tumor DNA, whole-blood RNA, and urine exosome proteomics. Dysregulated gene expressions were identified across oncogenic driver genes (KRAS, ATM, MAPK1, NRAS, CHD4, PIK3CA, and SF3B1), auxiliary tumor-promoting signals (TOP1, PSIP1, and ERBB2), and broad evidence of genome instability with impaired DNA repair (ATM, MSH2). Within circulating tumor DNA, a host–vector chimeric read mapped to chr19:55,482,637–55,482,674 (GRCh38), in cytoband 19q13.42, positioned ~367 kb downstream of the canonical AAVS1 safe harbor and ~158 kb upstream of ZNF580 at the proximal edge of the zinc-finger (ZNF) gene cluster. This sequence aligned with perfect 20/20 bp identity to a segment (bases 5905–5924) within the Spike open reading frame (ORF) coding region (bases 3674–7480) of the Pfizer BNT162b2 DNA plasmid reference (GenBank accession OR134577.1), despite the patient only receiving Moderna vaccinations. This apparent paradox is best explained by shared Spike ORF sequences within the expression cassette across both vaccine platforms; because Moderna has not deposited its proprietary plasmid sequence in NCBI, BLAST defaults to Pfizer's published reference as the nearest available match. The integration site was located outside the canonical AAVS1 "safe harbor" and within a gene-dense, recombination-prone regulatory region, raising concern for transcriptional disruption, fusion transcript formation, and oncogenic potential. The probability of a random 20-base sequence perfectly matching a predefined target is approximately 1 in a trillion, making this alignment statistically compelling and highly unlikely to be an incidental artifact. ***Conclusions:*** This sentinel case report provides the first documented evidence of genomic integration of mRNA vaccine-derived genetic material in a human subject, documenting a temporal association between COVID-19 mRNA vaccination and aggressive malignancy, reproducible multi-omic evidence of oncogenic signaling, and a non–safe harbor host–vector integration event. While causality cannot be established from a single case, the con-vergence of (i) close temporal proximity to vaccination, (ii) genomic integration of a vaccine plasmid–derived spike gene fragment, and (iii) consistent transcriptomic and proteomic instability across biospecimens represents a highly unusual and biologically plausible pattern. These findings highlight an urgent need for systematic genomic sur-veillance, orthogonal validation with long-read sequencing, and larger cohort studies to rigorously define the im-pact of synthetic mRNA vaccine platforms on genome integrity and cancer risk.

Keywords: ***Bladder cancer; COVID-19 mRNA vaccine; multi-omic profiling; oncogenic driver genes; genomic inte-gration; genomic instability; precision oncology.***

1. Introduction

Bladder cancer is predominantly a disease of older adults, and its occurrence in young women is exceptionally uncommon [1-8]. When advanced disease is present in this demographic, it is typically aggressive and carries an unfavorable prognosis [9-17]. Such atypical presentations demand close examination of potential molecular drivers and external contributors [18-25].

Synthetic mRNA vaccines introduce heavily modified RNA molecules and lipid nanoparticle carriers that differ fundamentally from endogenous cellular transcripts. Residual plasmid DNA, stabilizing nucleotide analogs, and potential for reverse transcription raise concerns about genomic disruption, transcriptional dysregulation, and oncogenic activation [26-29]. Reports of plasmid DNA contamination, enhancer sequences, and persistence of spike protein expression have intensified scrutiny regarding the role of

mRNA vaccines in genomic instability and ma-lignant transformation [30,31].

We describe a 31-year-old previously healthy woman who developed rapidly progressive stage IV bladder cancer within 12 months of completing a three-dose Moderna mRNA vaccination series (May 2021, June 2021, December 2021). Given the rarity of advanced bladder cancer in this demographic, her case warranted in-depth molecular investigation. Multi-omic profiling identified reproducible oncogenic driver activation, DNA repair impairment, transcriptomic instability, and evidence of a vaccine-derived sequence integrated outside a genomic safe harbor [26,32]. This case illustrates a potential association between synthetic mRNA vaccination and the develop-ment of aggressive malignancy, underscoring the urgent need for systematic genomic surveillance and independ-ent investigation of the long-term oncogenic risks associated with mRNA vaccine platforms.

2. Case Presentation

A previously healthy 31-year-old female received three Moderna mRNA vaccinations (May 2021, June 2021, De-cember 2021) and, within 12 months, was diagnosed with rapidly progressive stage IV bladder cancer—an unusual and aggressive presentation for this age. The patient underwent comprehensive multi-omic profiling using PBIMA (Molecular Surveillance and Individualized Targeted Immunotherapy Peptide Editing) and REViSS (Spike-associated Transcriptional/Translational Instability Surveillance). Analyses incorporated circulating tumor DNA sequencing from plasma, whole-blood RNA transcriptomics, and urine exosome proteomics, enabling a multidimensional evaluation of genomic and transcriptional dysregulation.

Multi-omic analyses revealed dysregulated oncogenic drivers (KRAS, ATM, MAPK1, NRAS, CHD4, PIK3CA, SF3B1) and auxiliary tumor-promoting pathways (TOP1, PSIP1, ERBB2) across circulating tumor DNA, blood RNA, and urine exosome proteomics [11,33-36]. DNA repair deficiencies (ATM, MSH2) were also identified, consistent with enhanced susceptibility to genomic instability. The specific oncogenic drivers, auxiliary promoters, and DNA repair deficiencies identified through PBIMA multi-omic profiling are summarized in Table 1, highlighting their biospecimen presence and functional consequences.

Table 1: Dysregulated Oncogenic Drivers and Auxiliary Tumor-Promoting Pathways Identified by PBIMA Multi-Omic Profiling

Gene Target	Classification	Biospecimen Presence	Functional Implications
KRAS	Oncogenic Driver	ctDNA, blood RNA, urine	Constitutive RAS–RAF–MEK–ERK activation → uncontrolled proliferation, therapy resistance
ATM	Oncogenic Driver & DNA Repair	ctDNA, blood RNA, urine	Impaired DNA double-strand break recognition and checkpoint control → genomic instability
MAPK1	Oncogenic Driver	ctDNA, blood RNA, urine	MAPK effector hyperactivation → invasion, survival signaling
NRAS	Oncogenic Driver	ctDNA, blood RNA, urine	MAPK/PI3K signaling amplification → RAF1 dependence, malignant transformation
SF3B1	Oncogenic Driver	ctDNA, blood RNA	Spliceosome disruption → aberrant splicing, transcriptomic remodeling
CHD4	Oncogenic Driver	ctDNA, blood RNA, urine	NuRD chromatin remodeling dysfunction → impaired DNA repair, angiogenesis, immune evasion
PIK3CA	Oncogenic Driver	ctDNA, blood RNA	PI3K–AKT pathway activation → metabolic rewiring, angiogenesis, immune suppression
TOP1	Auxiliary Promoter	ctDNA, blood RNA, urine (variable)	DNA topology dysregulation → replicative stress, transcriptional collapse
PSIP1	Auxiliary Promoter	ctDNA, blood RNA, urine (variable)	Chromatin co-activator upregulation → immune suppression, angiogenesis
ERBB2 (HER2)	Auxiliary Promoter	ctDNA, blood RNA, urine	Receptor tyrosine kinase amplification → proliferative signaling, invasion, epigenetic reprogramming
MSH2	DNA Repair Gene	ctDNA, blood RNA	Mismatch repair deficiency → microsatellite instability, mutational burden

A particularly striking finding was the detection of a host–vector chimeric read mapping to chr19:55,482,637–55,482,674 (GRCh38), within cytogenetic band 19q13.42, located ~367 kb downstream of the canonical AAVS1 safe harbor locus and ~158 kb upstream of ZNF580 at the proximal edge of the zinc-finger (ZNF) gene cluster [37-39]. This sequence aligned with 100% identity to a segment (bases 5905 - 5924) within the Spike Open Reading Frame (ORF) coding region (bases 3674 - 7480) of the Pfizer BNT162b2 DNA plasmid reference (GenBank accession OR134577.1), despite the patient only receiving Moderna vaccinations. The probability of a random 20-base se-quence perfectly matching a predefined target is approximately 1 in a trillion, making this alignment statistically compelling and highly unlikely to be an incidental artifact. The integration site was located outside the canonical AAVS1 “safe harbor” and within a gene-dense, recombination-prone regulatory region, raising concern for tran-scriptional disruption, fusion transcript formation, and oncogenic potential [40,41].

Notably, the integrated fragment corresponded to a 20-nucleotide segment within the Spike ORF coding region of the engineered expression cassette. The apparent paradox is explained by (i) conservation of the Spike ORF across vaccine platforms and (ii) the absence of Moderna’s official proprietary plasmid reference in public databases. Be-cause Moderna has not deposited this sequence, BLAST alignments default to Pfizer’s published reference. Thus, the event represents a vaccine-derived Spike cassette fragment integrated into chr19q13.42, at the proximal edge of the ZNF cluster, with plausible regulatory impact. Supporting evidence is summarized in Table 2, which docu-ments the mapping parameters, alignment identity, genomic context, and functional implications of this integra-tion event.

Table 2. DNA Frag analysis of host–vector translocation in a Moderna-vaccinated patient, showing a chimeric read at chr19:55,482,637–55,482,674 (GRCh38), cytoband 19q13.42, with 100% alignment to a segment of the Pfizer BNT162b2 plasmid reference (OR134577.1). The integration site lies ~367 kb downstream of the canonical AAVS1 safe harbor and ~158 kb upstream of ZNF580, placing it within a gene-dense, transcriptionally active, recombination-prone region and raising concern for tran-scriptional disruption, fusion transcript generation, and genomic instability.

Parameter	Result
Sample Description	Aggressive bladder cancer (post–mRNA vaccination)
Vaccination History	Moderna (3 doses: May 2021, June 2021, December 2021)
Host Mapping	Human chromosome 19, positions 55,482,637 – 55,482,674 (GRCh38), cytoband 19q13.42
Viral Reference	OR134577.1 (Pfizer BNT162b2 expression vector)
Viral Alignment Range	Bases 5905 – 5924 (Spike ORF coding region of the engineered expression cassette)
Alignment Identity	20/20 bp (100%)
Overlap Type	Chimeric, "gap" alignment
Orientation	Host: forward (+); Viral: plus, orientation
Mapping Quality (MQ)	Host: 60 (high confidence), Viral: 6 (low confidence)
Edit Distance	Host: 4; Viral: 2; Total: 43
Integration Classification	Possible Host Translocation: TRUE; Vector Rearrangement: FALSE
Genomic Context	Located at 19q13.42, ~367 kb downstream of the AAVS1 safe harbor (chr19:55.09–55.12 Mb) and ~158 kb upstream of ZNF580.
Functional Relevance	Gene-dense, recombination-prone, transcriptionally active regulatory region; potential for transcriptional disruption, fusion transcripts, and genomic instability

3. Discussion

This case raises several mechanistic concerns regarding the potential role of synthetic mRNA vaccination in ma-lignant transformation. To our knowledge, it represents the first documented evidence of genomic integration of vaccine-derived genetic material in a human subject. Specifically, we identified a vaccine vector–derived sequence integrated at chr19:55,482,637–55,482,674 (GRCh38), within cytoband 19q13.42, positioned ~367 kb downstream of the canonical AAVS1 "safe harbor" and ~158 kb upstream of ZNF580 at the proximal edge of the zinc-finger (ZNF) gene cluster, providing direct molecular evidence of host–vector genomic interaction [42-44]. The integration site lies within a gene-dense, transcriptionally active, recombination-prone regulatory region, a context associated with increased risk of transcriptional disruption, fusion transcript formation, and genomic instability [45].

Second, the paradoxical alignment of the integrated sequence to the Pfizer BNT162b2 plasmid, despite the patient having received only Moderna vaccinations, highlights the issue of cross-platform plasmid homology and manu-facturing commonalities. The 100% identity to Pfizer's deposited vector sequence suggests the presence of shared plasmid backbone elements or spike-encoding motifs across vaccine platforms. Because Moderna has not disclosed its proprietary plasmid sequence, BLAST defaults to Pfizer's published reference as the nearest available match, further underscoring the need for independent disclosure and validation of proprietary vaccine constructs.

Third, several plausible mechanisms could underlie the observed integration event [26,46,47]. These include (i) persistence and carry-over of residual plasmid DNA fragments from the in vitro transcription template, (ii) reverse transcription of spike mRNA followed by insertion at double-strand DNA breaks, (iii) misrepair via non-homologous end joining (NHEJ) or microhomology-mediated end joining (MMEJ), (iv) homologous recombi-nation when stretches of sequence similarity exist, (v) LINE-1 retrotransposon activity generating cDNA interme-diates, and (vi) topoisomerase-mediated mis-ligation during DNA unwinding. Each of these routes is biologically feasible and consistent with the concurrent detection of DNA repair deficiencies (ATM, MSH2) in this patient, which would increase susceptibility to insertional mutagenesis. Such vulnerabilities may accelerate oncogenic transformation and malignant progression. Supporting this concern, Speicher et al. quantified billions of residual plasmid DNA fragments per vaccine dose, with levels in both bivalent and XBB.1.5 Pfizer-BioNTech and Moderna COVID-19 vaccine products exceeding regulatory safety thresholds by 36-627-fold, thereby providing a plausible source of template DNA for persistent chromosomal integration [28].

In addition to the host–vector integration event, the patient's multi-omic profile revealed a constellation of dysregulated oncogenic drivers and auxiliary tumor-promoting signals that together create a permissive landscape for aggressive malignancy [29,48,49]. Activating alterations in KRAS and NRAS converge on the MAPK signaling cascade, sustaining proliferative signaling and bypassing normal growth controls [9,50,51]. Concurrent dysregula-tion of MAPK1 amplifies downstream ERK-driven transcriptional programs that promote cell cycle progression and survival [1-3,35,52,53]. The chromatin remodeler CHD4 and the RNA splicing factor SF3B1 contribute to epigenetic reprogramming and aberrant transcript processing, fostering cellular plasticity and tumor adaptability [4,54-59]. PIK3CA activation drives PI3K/AKT signaling, enhancing metabolic fitness, invasion, and resistance to apoptosis, while auxiliary signals from TOP1, PSIP1, and ERBB2 further reinforce replication stress tolerance, transcriptional activation, and growth factor responsiveness [7,10,12,17,60,61]. Importantly, deficiencies in ATM and MSH2 com-promise DNA repair fidelity, predisposing to genomic instability, accumulation of mutations, and chromosomal rearrangements [17,22,25,62]. Together, this pattern of multi-pathway dysregulation provides a mechanistic basis for the patient's unusually rapid disease evolution, linking vaccine-associated genomic perturbations with a molecular environment primed for malignant transformation.

Emerging evidence supports a link between mRNA vaccination and oncogenesis [63,64]. A population-wide 30-month cohort study of nearly 300,000 residents of Pescara, Italy, found that receipt of ≥1 COVID-19 vaccine dose was associated with a 23% increased risk of cancer hospitalization overall (HR 1.23, 95% CI

1.11–1.37), with the strongest and statistically significant excess risks observed for breast cancer (HR 1.54), bladder cancer (HR 1.62), and colorectal cancer (HR 1.35) [61]. Complementing this epidemiologic evidence, Marik et al. formally defined the syndrome of COVID-19 mRNA vaccine-induced "turbo cancers," compiling clinical case reports, epidemiologic signals, and mechanistic pathways through which the spike protein may accelerate malignant transformation via metabolic reprogramming, apoptosis resistance, angiogenesis, and immune dysregulation [62]. Taken together, these reports provide convergent epidemiologic and mechanistic support for our present case, in which genomic integration and molecular dysregulation were directly documented.

Together, these observations support a biologically plausible framework in which synthetic mRNA vaccine expo-sure contributes to genomic instability, oncogenic signaling, and aggressive disease evolution. While causality cannot be inferred from a single case, the convergence of temporal proximity, vector sequence integration, and reproducible multi-omic dysregulation provides a strong hypothesis-generating signal. This warrants urgent sys-tematic genomic surveillance, orthogonal validation with long-read sequencing, and independent investigation of the long-term oncogenic risks associated with mRNA vaccine technologies. A schematic overview of the clinical course, host–vector integration, and multi-omic dysregulation is shown in Figure 1.

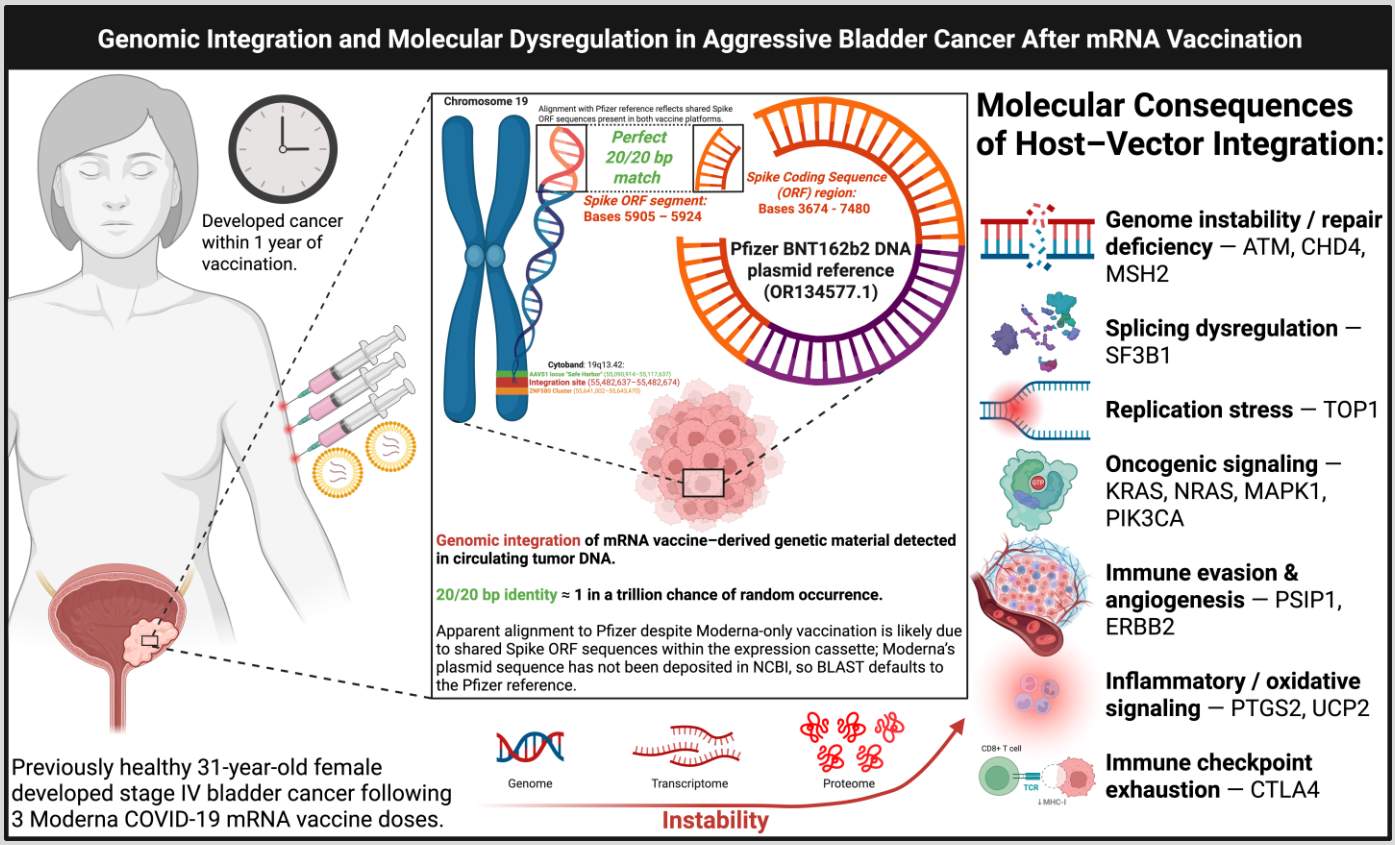

Figure 1: Genomic Integration and Molecular Dysregulation in Aggressive Bladder Cancer After mRNA Vaccination *Created with Biorender.com

4. Conclusions

This sentinel case report describes the rapid onset of aggressive stage IV bladder cancer in a young woman after a Moderna mRNA vaccination series, marked by direct evidence of genomic integration of vaccine-derived genetic material. Multi-omic profiling revealed reproducible oncogenic driver activation, DNA repair deficiencies, tran-scriptomic instability, and integration of a vaccine vector–derived sequence outside a genomic safe harbor[8,30,31,33,38,39,41,58,65]. While causality cannot be established from a single case, the convergence of tem-poral proximity, integration evidence, and multi-system molecular disruption raises serious concern regarding the oncogenic potential of synthetic mRNA vaccine platforms. These findings highlight the urgent need for systematic genomic surveillance, independent validation using orthogonal sequencing methods, and rigorous investigation into the long-term genomic and oncologic risks of mRNA vaccination.

5. Declaration

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Neo7Bioscience funded the case study and was involved in its design, data collection, analysis, and preparation of the manuscript.

Conflicts of Interest

This study was funded by Neo7Bioscience, which was involved in the study design, data collection, analysis, and manuscript preparation. John Catanzaro, who conceived the case study and served as Principal Investigator, is the CEO and a shareholder of Neo7Bioscience and also receives salary support from the company. Neo7Bioscience is a privately held biotechnology company specializing in the development of personalized therapeutic peptides. Ni-colas Hulscher, who provided

scientific input, receives salary support from the McCullough Foundation. Peter McCullough, who provided research oversight, is the founder of the McCullough Foundation but receives no compensation from the organization. The McCullough Foundation is a nonprofit entity dedicated to advancing independent public health research, medical ethics, and evidence-based policy.

Informed Consent

Informed consent was obtained from the subject involved in the study, and all data were de-identified before analysis.

Data Availability Statement

The sequencing datasets generated and analyzed in this study have been depos-ited in the NCBI databases under BioSample accession SAMN51401809 and Sequence Read Archive (SRA) accession SRS26533677. The data are publicly available at NCBI.

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