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A chimeric bladder tumor in a renal transplant recipient: the oncogenic convergence of JC virus and PIK3CA mutation

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Dear editors,

Solid organ transplant recipients face a substantially elevated risk of post-transplant malignancies due to lifelong immunosuppression and impaired viral immune surveillance [1]. While most post-transplant tumors are *de novo*, donor-derived tumors (DDTs) represent a rare, highly informative biological model arising from engrafted donor-derived cells that behave as tumor-initiating cells (TICs) within the recipient host [2, 3]. Here, we report a unique case of donor-derived high-grade urothelial carcinoma originating in a two-time kidney transplant recipient with chronic JC polyomavirus (JCPyV) infection, highlighting a complex interplay between chronic viral inflammation, persistent immunosuppression, and donor-cell somatic mutation [4, 5].

A 59-year-old male with end-stage renal disease initially received a kidney transplant from a deceased male donor (karyotype XY) in 2006. Seven years post-transplantation, he developed JCPyV-associated nephropathy, leading to graft failure. In 2021, he received a second kidney transplant from a deceased female donor (karyotype XX). Despite immunosuppressive adjustment with everolimus, JCPyV replication persisted at high levels in plasma, urine, and cerebrospinal fluid. Two years after the second transplant, the patient presented with macrohematuria. Work-up revealed a high-grade invasive urothelial carcinoma of the bladder involving the left ureteral orifice, requiring bilateral native and graft nephroureterectomy with radical cystectomy. To elucidate the cellular origin and oncogenic drivers of the lesion, six fresh tissue specimens were collected from native and transplanted structures. Multiplex QF-PCR short tandem repeat (STR) analysis (Elucigene QST*Rplusv2) and *in vitro* primary tissue culture in Chang medium were conducted. Targeted Next-Generation Sequencing (NGS) covering 67 cancer-related genes (Archer VariantPlex Solid Tumor Kit) was performed on both the neoplastic lesion and macroscopically normal tissues (Figure 1).

STR profiling revealed that non-neoplastic native tissues (native bladder and native ureters) shared an identical recipient haplotype (XY). In contrast, the left transplanted ureter and the hyperemic bladder carcinoma displayed a distinct XX donor genotype, interspersed with recipient-derived allelic peaks indicative of local cellular chimerism. Primary cells isolated from the hyperemic bladder area and the left transplanted ureter

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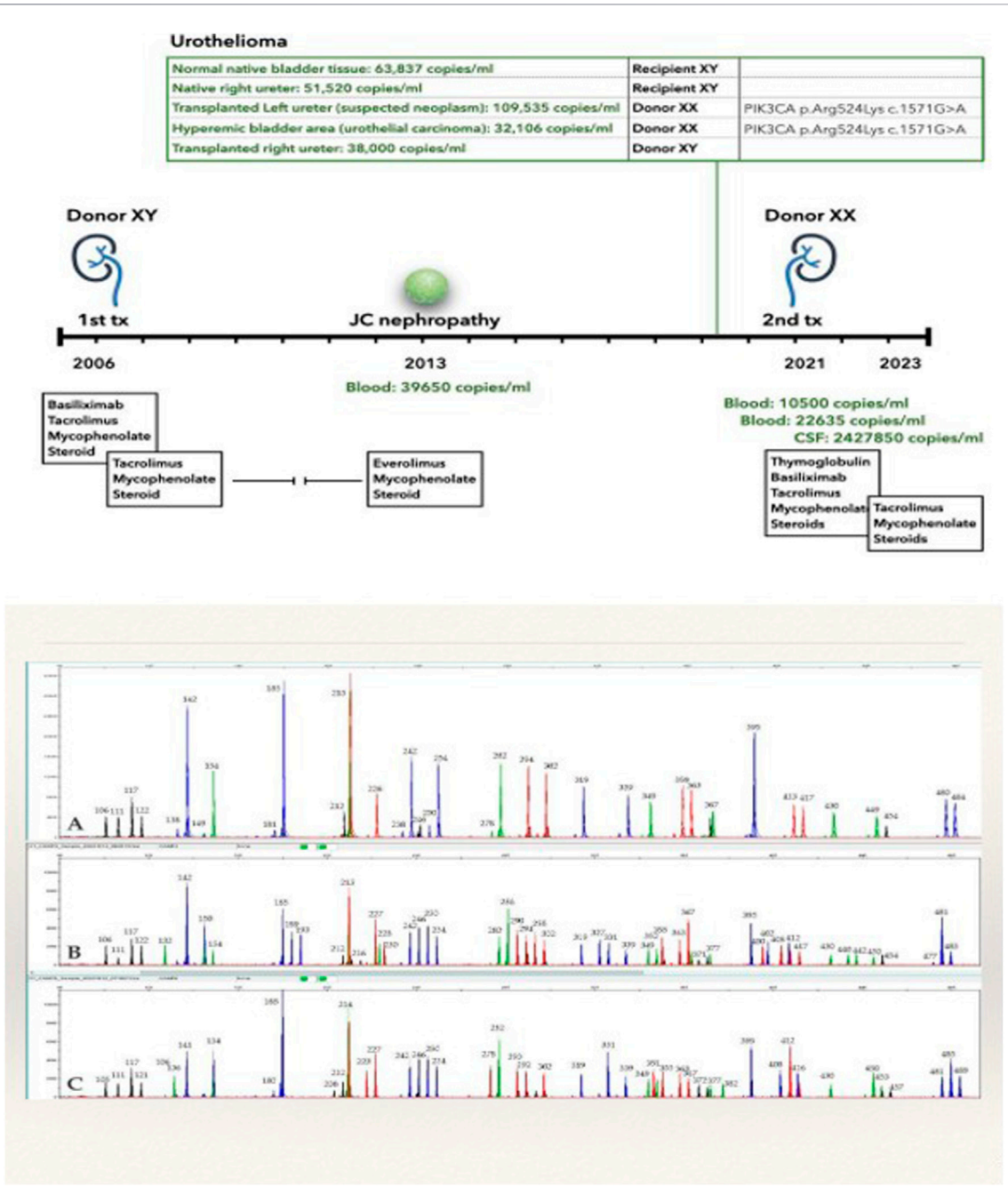


FIGURE 1
Integrated Clinical Timeline, Tissue Virological/Mutational Mapping, and Molecular Chimerism Analysis. **(A)** Clinical Timeline and Tissue-Specific Profile: Chronological overview of the patient's clinical trajectory from first kidney transplantation (2006, male donor XY) through JCPyV nephropathy (2013), second transplantation (2021, female donor XX), and diagnosis of donor-derived urothelial carcinoma (2023). Integrated table summarizes JCPyV DNA viral loads, donor/recipient genetic origin, and somatic *PIK3CA* (p.Arg524Lys, c.1571G>A) mutation status across native and transplanted tissues. **(B)** Capillary Electrophoresis STR Haplotype Profiles: Short Tandem Repeat (STR) profiles obtained via QF-PCR multiplex assay. Panel **A**: Recipient baseline haplotype (XY) shared by normal native bladder tissue and native ureters. Panel **B**: Chimeric profile from the transplanted left ureter and hyperemic bladder carcinoma, displaying a predominant XX donor genotype with persistent recipient allelic peaks. Panel **C**: Haplotype from the first transplanted right ureter (XY donor genotype with recipient-derived peaks).

were successfully expanded over five passages in culture, acquiring an immortalized phenotype with a homogeneous XX donor karyotype.

Targeted NGS identified a specific *PIK3CA* mutation (c.1571G>A, p.Arg524Lys) in both the hyperemic bladder carcinoma and the macroscopically normal left transplanted ureter. No other pathogenic variants were detected across the 67-gene panel. Real-time PCR confirmed JCPyV DNA persistence across all tissue specimens (range: 3.2 × 104 to 1.1 × 105 copies/mL), although viral DNA was absent in the expanded *in vitro* cellular pellets, excluding direct ongoing viral integration within the cultured neoplastic clone.

The concordant STR profiles obtained from tumor tissue and cultured cells, together with the clonal expansion of XX cells *in vitro* and the detection of the same PIK3CA mutation in both ureteral and bladder lesions, strongly support a donor-derived origin of the tumor-initiating cells rather than a secondary infiltration or mosaic event. Rather than a late passenger event, this *PIK3CA* substitution—located within the helical domain of the PI3K/AKT/mTOR pathway—appears to represent an early somatic alteration present in engrafted donor cells [6, 7]. We hypothesize a model wherein donor-derived TICs harboring the *PIK3CA* variant migrated from the transplanted ureter to the bladder mucosa.

Importantly, JCPyV likely contributed to tumor development indirectly via a "field effect" mechanism [8]. Chronic viral infection induced localized, severe chronic cystitis, establishing an inflamed microenvironment. Synergizing with systemic immunosuppression, this permissive inflammatory niche favored the engraftment, survival, and subsequent clonal expansion of donor-derived TICs.

This case is more than a rare oncologic curiosity—it provides a living model of early carcinogenesis. In a scenario where donor and recipient cells are genomically distinguishable, chimerism could enable the tracking of tumor initiation from its earliest steps, allowing the isolation of the first altered cells, those that silently pave the way for clinical cancer long before dysplasia becomes evident.

Current sequencing efforts focus largely on late-stage tumors, where all cancer cells share the same set of "public mutations," masking the founding event of transformation. Here, we had the rare opportunity to detect that founding event in a context where the neoplastic population emerged from a known origin and timeline, offering an unparalleled view of tumor initiation *in vivo*.

This case demonstrates that molecular chimerism analysis combined with targeted genomic profiling of non-neoplastic tissues can track the earliest stages of donor-derived oncogenesis *in vivo*. Extending genomic surveillance beyond traditional clinical timelines may improve cancer risk stratification and early detection in solid organ transplant recipients [9,10].

Data availability statement

The datasets presented in this study are available from the corresponding author upon reasonable request.

Ethics statement

Ethical approval was not required for the studies involving humans because this study reports a single retrospective clinical case managed according to standard medical practice, without any experimental intervention or deviation from routine care. All analyses were performed on samples collected for diagnostic and therapeutic purposes, and the manuscript was prepared using fully anonymized patient data in accordance with institutional policies. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

GI, DD, MG, PB, SL, DF, and AB contributed to data collection and experimental procedures; GC, DD, SL supervised the project and provided critical resources; GI and AB drafted the manuscript; and all authors read and approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

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