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Novel Insights from Research Practice

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Molecularly Confirmed Female Donor-Transmitted Lobular Breast Cancer to Male following Renal Transplantation

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Established Facts

- Cancers in the post-transplant setting include transplant associated, donor transmitted, and donor-derived cancers.
- When a single person donates multiple organs, he could potentially transmit an occult malignancy to more than one recipient.
- The strongest evidence for the origin of a post-transplant cancer is HLA typing.

Novel Insights

- Alternative molecular testing may be used when HLA typing is not feasible or unnecessary, such as sex discordance between donor and recipient (in which X and Y chromosome typing is sufficient).
- The metastatic donor-transmitted estrogen receptor-positive breast cancer behaved more indolently in the present male patient than is generally seen in the female population, presenting a potential area for research.

Keywords
Male lobular breast cancer · Renal transplantation · Donor-transmitted · Breast cancer · Fluorescent in situ hybridization

Abstract
Introduction: Lobular breast cancer represents 10%–15% of breast cancers in women but is virtually nonexistent in men, related to the typical absence of the anatomic breast lobule structure in male breast tissue. We describe donor-transmitted metastatic lobular carcinoma to a male after kidney transplantation. Determining whether a post-transplant cancer is transplant associated, donor transmitted, or donor

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derived is significant for treatment, prognosis, and possibly management of other organ recipients. ***Case Report:*** A 74-year-old Caucasian male presented to the emergency department with lower abdominal pain and macro-hematuria. Past medical history included two renal transplantations. Computed tomography identified a 4–5-cm space-occupying lesion in the native left kidney. A left native nephrectomy was performed. Histology pathologic examination demonstrated lobular (as opposed to ductal) breast carcinoma. Fluorescent in situ hybridization probes to identify X- and Y-chromosomes showed tumor cells with an XX genotype, whereas the surrounding host cells were of XY genotype. These findings confirmed the female-sex origin (donor) of the tumor within the XY native male (current patient) tissues. ***Discussion/Conclusion:*** Due to discordance between the donor and recipient sex, fluorescent in situ hybridization as a molecular technique correctly identified the origin of an individual's cancer in the post-transplant setting. The metastatic breast cancer behaved more indolently than usually seen. Expanded criteria donors (ECD) are those who cannot donate under standard criteria for organ transplantation; expanded criteria widen the potential organ donor pool at the expense of increased risk for post-transplant complications (e.g., graft failure, the transmission of malignancy). The case provides a potential area of future research into considering allowing ECDs with a distant history of cancer with very low transmission risk when the biochemical environment of the recipient would, in the unlikely event of transmission, induce the tumor to pursue an indolent clinical course.

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Introduction

While breast cancer is the most common malignancy in females, accounting for almost 1 in 4 cancers in women [1], it is uncommon in men, accounting for only 1% of cancers in this population [2]. In both men and women, most breast cancers are estrogen receptor (ER)-positive and human epidermal growth factor receptor 2 negative [2]. The two most common histologic types of breast cancer in order are ductal and lobular, with lobular breast cancer representing 10%–15% of breast cancers in women but virtually nonexistent in men, related to the fact that the anatomic breast lobule is rarely present in male breast tissue [3, 4]. In this manuscript, we describe a donor-transmitted metastatic lobular carcinoma to a male after kidney transplant. While donor-transmitted breast cancer has been previously reported, to the best of our knowledge the present case represents the first case of the lobular subtype being diagnosed in a male.

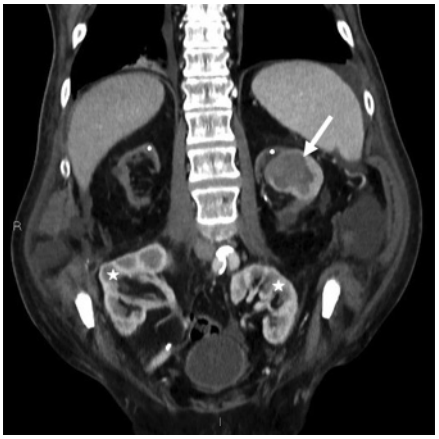

Fig. 1. Coronal view of contrast-enhanced CT showing transplanted kidneys (asterisks) in the lower abdomen and native atrophied kidneys (dots). Heterogenous mass is shown in the upper pole of the left native kidney (arrow).

Various classes of malignancies that arise in a transplant recipient have been noted [5]; these include (1) transplant-associated malignancies that arise from the patient's native tissues in the context of immunosuppression; (2) donor-transmitted cancers, in which malignant cells are transferred during the transplantation; and (3) donor-derived cancers, in which de-novo malignancy arises within a transplant at a later time. The treatment options vary for each of the three aforementioned classifications. For example, in the case of recipient-derived transplant-associated malignancy, immunosuppression may be withheld to allow the patient's natural defenses to take over. As treatments vary across transplant-related cancers, their determination has a significant impact on patient outcomes.

Case Report

In 2018, a 74-year-old Caucasian man presented with lower abdominal pain and macro-hematuria. Patient past medical history included two renal transplantations (discussed below), ischemic heart disease, coronary artery bypass grafting (2008), type 2 diabetes mellitus, paroxysmal atrial fibrillation, arterial hypertension, and hypothyroidism. The patient had a 20 pack-year history before quitting smoking almost 40 years prior to his current presentation.

In 2012, an initial right kidney transplant was performed due to end-stage renal disease associated with glomerular sclerosis. The patient experienced an episode of acute rejection 2 days after the transplantation. In 2013, the patient underwent a second suc-

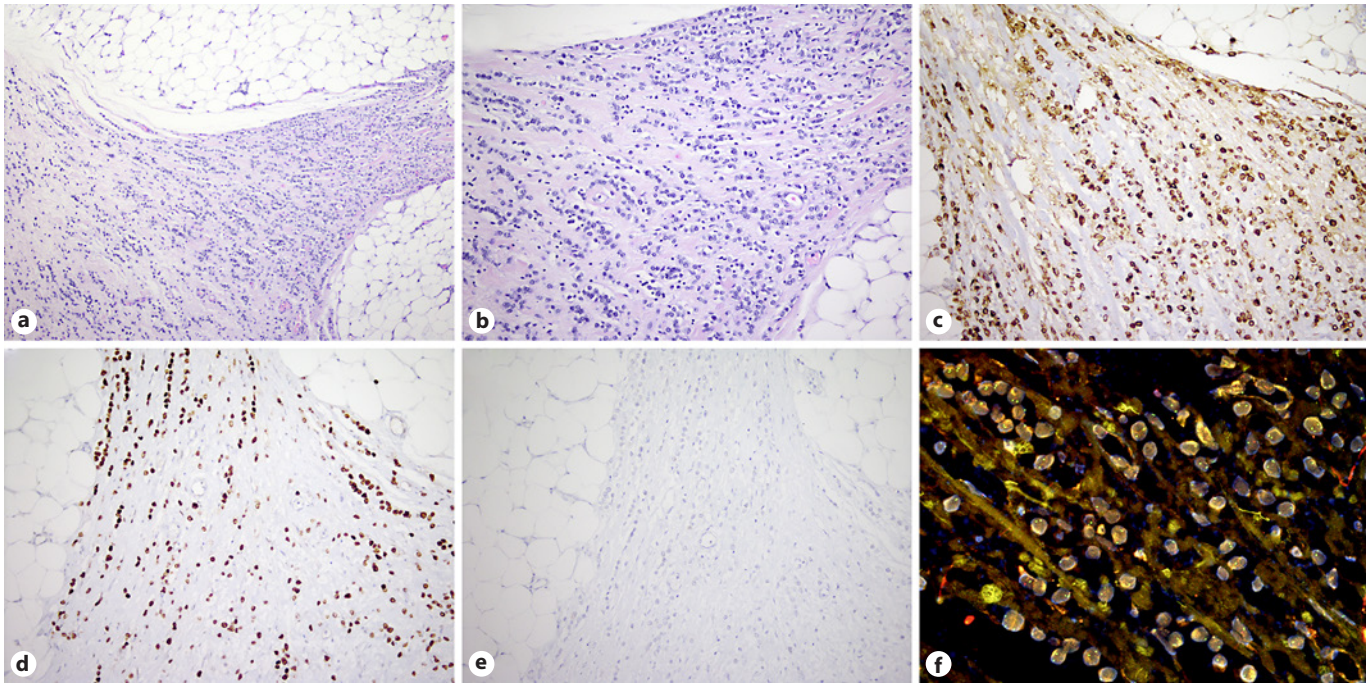

Fig. 2. Pathological examination of the tumor. H&E stain at ×100 (**a**) and ×200 (**b**) magnification. Immunostains were positive for cytokeratin 7 (**c**) and ER (**d**), consistent with breast origin, with loss of E-cadherin (**e**), characteristic of lobular breast carcinoma (all at ×200 magnification). FISH (**f**) for X chromosome (green signal) and Y chromosome (red signal) demonstrates XX tumor cells embedded in an XY stroma. H&E, hematoxylin and eosin.

cessful left lower quadrant kidney transplant. Bilateral native kidneys and the rejected right transplanted kidney remained in place.

Five years after the second kidney transplantation, a patient arrived at the emergency room with abdominal pain and macrohematuria. A contrast-enhanced computed tomography (CT) scan identified a 4–5-cm space-occupying lesion in the native left kidney with heterogenic content occupying the calyxes that were partially hemorrhagic (Fig. 1). Systemic workup, including positron-emission tomography-CT, identified bilateral pleural effusion, ascites, and an infiltration of mesenterial fat. The lesion was non-F-fluorodeoxyglucose avid.

Subsequently, a left native kidney nephrectomy was performed. Upon microscopic evaluation of the peri-renal fibroadipose tissue (Fig. 2a, b), there was an infiltrate of small, somewhat hyperchromatic cells with slightly vesicular nuclei which form single-file lines of cells. Scattered smaller cells with closed nuclei represent reactive lymphocytes. The tumor cells were positive for cytokeratin 7 (Fig. 2c) and negative for vimentin, consistent with carcinoma. Further elucidation of the immune profile of the tumor cells showed positivity for ER (Fig. 2d) and GATA3, consistent with breast origin. Positive immunostains also highlighted the linear formation of the tumor cells, characteristic of lobular breast carcinoma. The loss of e-cadherin expression (Fig. 2e) supported lobular (as opposed to ductal) breast carcinoma. Further extensive panel stains excluded various organs as the primary site.

Further investigation into the origin of the malignant cells was supported by a fluorescent in situ hybridization (FISH) study. A triple color probe (ZytoLight Spec 18/CEN X/Y) clearly identified the centromeres of X and Y chromosomes (Fig. 2f). FISH Probes for the X-chromosome (green signal) and Y-chromosome (red signal) demonstrate linear tumor cells with an XX genotype (some are XXXX, representing either mitotic or tetraploid cells), whereas the surrounding host cells are of XY genotype. These findings confirm the female-sex origin (donor) of the tumor within the XY native male (current patient) tissues.

After confirmation of cancer's origin, tamoxifen was initiated in April 2019. The patient was switched from tacrolimus to everolimus for immunosuppression. A clinical oncologic workup was performed concurrently with the pathological examination above. Bilateral breast ultrasound mammography was reported as BI-RADS 2 (benign) and a breast MRI was normal. Due to treatment intolerance, tamoxifen was withdrawn and replaced with letrozole and goserelin. The patient is presently clinically stable, with no evidence of illness on positron-emission tomography-CT, 39 months after his initial presentation in the emergency department, and tumor markers are stable.

Discussion

The Impact of Screenings, Expanded Criteria Donors, and Religion on Cancer Transmission

For both living and deceased donors, there is an increased risk of cancer transmission from donated organs

Table 1. Molecular analysis of donor-transmitted cancer in the literature

Reference	Donor-transmitted cancer type	Technique to determine origin	Time to diagnoses (relative to transplant)	Outcomes (time relative to cancer diagnosis)
Matser et al. [12]	Breast (ER+/PR+) adenocarcinoma	DNA microsatellite	16 months to 6 years	Death of 3 recipients after 1 month to 3 years; 1 patient in follow-up as of 6 years
Zhang et al. [13]	Monophasic synovial sarcoma	DNA microsatellite	3–9 months	One recipient died after 16 months; two recipients in follow-up as of 2 years
Lipshutz et al. [15]	Ovarian mucinous adenocarcinoma	FISH	6 months[1]	Death after 5 months
Zelinkova et al. [16]	Colorectal adenocarcinoma	STR analysis and FISH	18 months	Not a surgical candidate; death after several months
Michel Ortega et al. [17]	Urothelial carcinoma	FISH	9 years	In follow-up as of 12 months
Xiong et al. [18]	Malignant rhabdoid tumor	STR analysis and FISH	4 months	In follow-up as of 10 months
Yilmaz et al. [19]	Renal cell carcinoma	FISH and karyotyping[2]	2 years	In follow-up as of 7 months
Present case	Breast (ER+/PR+) lobular carcinoma	FISH	5 or 6 years[3]	In follow-up as of 39 months

ER, estrogen-receptor; PR, progesterone-receptor; FISH, fluorescent in-situ hybridization; STR, short tandem repeat. [1] Two recipients are mentioned in the article; for one the timeline is clearly delineated, and for the second both diagnosis and death together are implied to be shortly after death of the first patient. [2] On FISH, there was a combination of XY and XX cells, whereas on cultured cell karyotyping all cells were XX; the authors postulate hybridization of the hematopoietic transplant DNA with the tumor cells, and that only XX cells happened to be cultured. [3] The patient underwent two previous renal transplants from female donors.

of older donors [6]. Facing the growing demand for donor transplants, a transplant's quality is often sacrificed. This scarcity of donor organs necessitates broader transplantation criterium, unfortunately resulting in increased transmission of occult diseases [7, 8]. In the UK, from 2010 to 2011, 53% of donors were over the age of 50, compared to 60% in 2019–2020 [9]. With the widening donor criterium, several organizations have collaborated in order to render consistent the definition of expanded criteria donors [10]. In countries with higher rates of organ donations, such as the United States, the use of older donors is less of a concern as there are many listed organ donors in the country [11]. In Israel, the country of the presented case, 9.1 kidney transplants from deceased donors occur per million of the population (pmp), in comparison to the United States with 34.1 donations pmp [11].

Using FISH and Sex to Determine a Cancer's Origin

With the confirmation of cancer's origin, attempts were made to gather additional information from the hospital at which the transplant took place as well as the National Transplant Center (Ministry of Health) about the two deceased kidney donors and their respective additional recipients. Previous studies reported donor-transmitted breast cancer and synovial sarcoma, which were occult at the time of transplant, to several recipients; the authors in both reports used DNA microsatellite imaging to identify cancers' origin [12, 13]. The strongest evidence for transplanted-related cancer originates from HLA typing of the cancerous cells and cross-referencing with donor HLA typing, along with identifying the same cancer in another recipient or in the donor after death [5].

There were two reasons that the origin of cancer was of interest. First, treatments for donor transmitted malignancies differ from de novo cancers, and obtaining information that could help determine the source of cancer (such as HLA typing) could aid the current patient. Second, identifying additional recipients from the same donor could lead to a focused oncological screening of those patients with appropriate treatment. Information that was collected led to the revelation that both deceased donors were female, as were all 5 additional recipients (2 and 3 recipients from each donor).

The tricolor 18/CEN X/Y FISH probe is indicated to identify trisomies and sex chromosome aneusomies [14]. However, in this report and several more recent studies, FISH was used to identify donor-transmitted cancer ori-

gins, specifically when donors and recipients were of the opposite sex [15–19]. In the present case, both of the recipient's kidneys had come from female donors. Hence, determining the origin of cancer itself was impossible without further information about the donors. However, because all the co-recipients were already deceased, any desire to specify the donor and learn about the causes of death from such donor's recipients was purely academic, as there would be no diagnostic, prognostic, or therapeutic indication for obtaining such information at this point. Despite several methodological uses by pathologists in donor-transmitted and donor-derived cancers, the use of FISH probes to identify X and Y chromosomes remains an off-label usage [15–19]. In this case, it assisted in explaining the extremely rare occurrence of metastatic lobular carcinoma in a male patient. This case offers validation to using the XY FISH probes when there is discordance between the sex of donor and recipient, and the source of cancer needs to be determined.

Previous reports that employed non-HLA typing molecular techniques to identify the origin of cancer in a post-transplant setting are summarized in Table 1. Five of the reports used XY FISH probes in a similar manner to that reported presently; four used more traditional DNA analysis techniques for matching tissue samples (DNA microsatellite and short tandem repeat [STR] analysis alone or in conjunction with FISH). These techniques may also be cost-efficient in the correct setting but require more viable tumor and non-neoplastic cells, as well as the ability to supply for analysis a tumor cell-rich region to compare to non-neoplastic cells (i.e., via microdissection or repeat biopsy). FISH can be performed with less material and without the need for micro-dissection, but the presented probes only yield XY genotyping; STR and microsatellite analysis can provide more genetic information if needed to match to a specific donor.

The Impact of Estrogen-Dependent Cancer and Its Impact on Future Research

The case presented represents metastatic ER+ lobular breast carcinoma. Stage-IV breast cancer with these characteristics has a median overall survival of 30 months [20]. Given the fact cancer in this man presents only in the perirenal fat of the man's native kidney without other distant metastases together with favorable tumor characteristics, the indolent nature of its disease so far is not surprising. This finding presents a possible area of further research in terms of the factors limiting an organ's transplantation. As per widening donor criterium, there is a growing need for safely expanding the availability of organs for transplantation. One area of potential research would be to allow a female donor with a distant history of low-grade, low-stage, and low-grade ER+ breast carcinoma to donate to a male recipient under expanded criteria donor criteria. It is important to note that kidney transplant recipients often possess several co-morbidities and diseases that the transplanted kidneys provided benefits outweigh the low risk of potential latent malignancies. The present case demonstrated the second-longest progression-free survival of any of the cases presented in Table 1.

Limitations

Researchers were unsuccessful in attaining further information about the donor or about other organ recipients from the same donor. Within Israel, if physicians were able to attain more information regarding the donor in the future, it may be possible to learn more about donor transmitted malignancies in general, and about our posited pathogenesis of the behavior of low-grade ER+ cancers in men versus women (e.g., if female co-recipients had more dismal prognoses than the male co-recipients).

Conclusion

This article presents a unique case of a male, status post renal plant, with metastatic lobular carcinoma. We have highlighted the importance that FISH and specific X- and Y-chromosome probes may play in correctly identifying the origin of an individual's cancer in the transplant setting. Furthermore, this report uncovers a possible area of further research into the expansion of donor criterium to include organs with a very low risk of transmitting a malignancy that could behave considerably more indolently in a recipient with a fundamentally different internal biochemical environment.

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Statement of Ethics

Ethics approval was not required because the Soroka University Medical Center IRB does not require review for case reports of single patients. Written and signed consent was obtained by Dr. Waleed Kian. The patient agreed to the publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jonah M. Cooper: writing – original draft, visualization, and investigation; Benzion Samueli: conceptualization, methodology, resources, visualization, and writing – review & editing; Elad Mazor: resources; Waleed Kian: review & editing, Hadar Goldvaser: review & editing; and Gal Ben-Arie: resources and visualization.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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