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Advanced Leiomyosarcoma of the Retroperitoneal Space in a Kidney Transplant Recipient with a History of Peritoneal Dialysis: A Case Report

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Data Collection B
Statistical Analysis C
Data Interpretation D
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Patient: Female, 44-year-old
Final Diagnosis: Leiomyosarcoma • liver metastases
Symptoms: Abdominal pain
Medication: —
Clinical Procedure: Biopsy
Specialty: Nephrology • Oncology • Transplantology

Objective: Rare disease

Background: Leiomyosarcoma frequently occurs in patients who are on immunosuppressive therapy. It is the second most common sarcoma in this population and is often associated with Epstein-Barr virus (EBV) infection. We present a case of advanced leiomyosarcoma of the retroperitoneal space in a kidney transplant recipient and discuss additional risk factors for oncogenesis.

Case Report: A 44-year-old woman with a history of peritoneal dialysis and kidney transplantation was diagnosed with multiple liver lesions. PET-CT scanning showed a metabolically active tumor in the left lumbar region with numerous liver focal lesions. The histological examination of the liver lesion biopsy identified advanced retroperitoneal leiomyosarcoma with a high proliferative index and liver involvement. Unexpectedly, the relation with EBV infection was not proven. The patient was treated with first-line doxorubicin, with the simultaneous reduction of immunosuppression. Owing to disease progression after 6 cycles, the patient received second-line chemotherapy based on gemcitabine and docetaxel, which was terminated owing to unacceptable toxicity, despite an observed response. Third-line trabectedin-based therapy with good tolerance and stabilization of disease after 20 months was being maintained at the time of this report.

Conclusions: The increased cancer mortality in solid-organ transplant recipients requires an individualized approach and increased post-transplantation screening according to additional specific cancer risk factors. A further consideration is the hypothetical relevance of long-term peritoneal membrane irritation in peritoneal dialysis patients.

Keywords: Case Reports • Immunosuppression • Kidney Transplantation • Leiomyosarcoma • Peritoneal Dialysis

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/933267

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Background

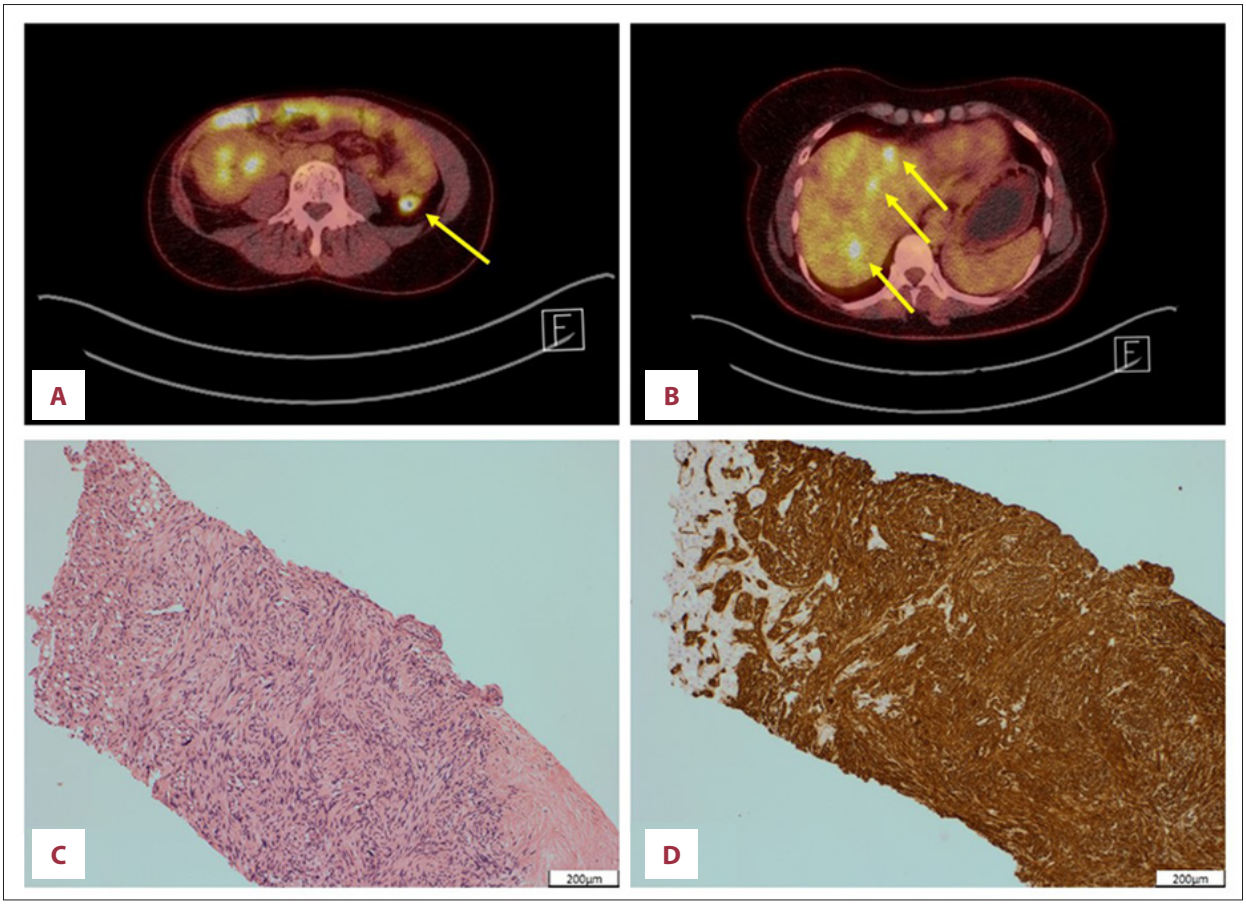
Leiomyosarcoma is the second most common sarcoma after Kaposi sarcoma in patients undergoing maintenance of immunosuppressive treatment [1] and is one of the most common soft-tissue sarcomas in the general population [2]. It derives from smooth muscle cells of large veins or mesenchymal stem cells and is usually located in the retroperitoneal space. Of note, Epstein-Barr virus (EBV) infection in immunocompromised patients (including HIV-infected and organ transplant recipients) has been widely discussed as a potential risk factor for leiomyosarcoma [2,3] and its multifocal development [4]. Immunohistochemical assays fail to confirm the presence of viral genetic material in only 12% of cases [1].

It has been shown that the overall length and the net effect of immunosuppressive therapy increase the risk of carcinogenesis [5]. It is believed that increased gene expression for transforming growth factor beta-1 and vascular endothelial growth factor during therapy with certain immunosuppressive drugs, such as cyclosporine A and tacrolimus, can promote tumor invasiveness and metastatic dissemination [6].

Case Report

A 44-year-old woman was admitted to the nephrology department with multiple liver lesions of unknown origin, which were identified during an abdominal ultrasound in January 2019. She had a Zubrod performance status of 0 and had a history of kidney transplantation (KTx) from a deceased donor, with basiliximab induction in May 2016 on a 3-drug maintenance immunosuppressive regimen (tacrolimus, mycophenolate sodium, and prednisone). She had experienced mild right upper abdominal pain for a few months prior to her presentation, which did not require painkillers.

The patient had a medical history of right-sided nephrectomy and systemic therapy for nephroblastoma at the age of 6 years. She had chronic interstitial pyelonephritis of the remaining kidney, not associated with ureterovesical reflux and without confirmed immune deficiencies, which eventually led to end-stage kidney failure, with the initiation of automated peritoneal dialysis for 27 months before KTx. Comorbidity included type 2 diabetes and subtotal thyroidectomy, with parathyroidectomy performed in October 2015 owing to secondary hyperparathyroidism and a colloid goiter.



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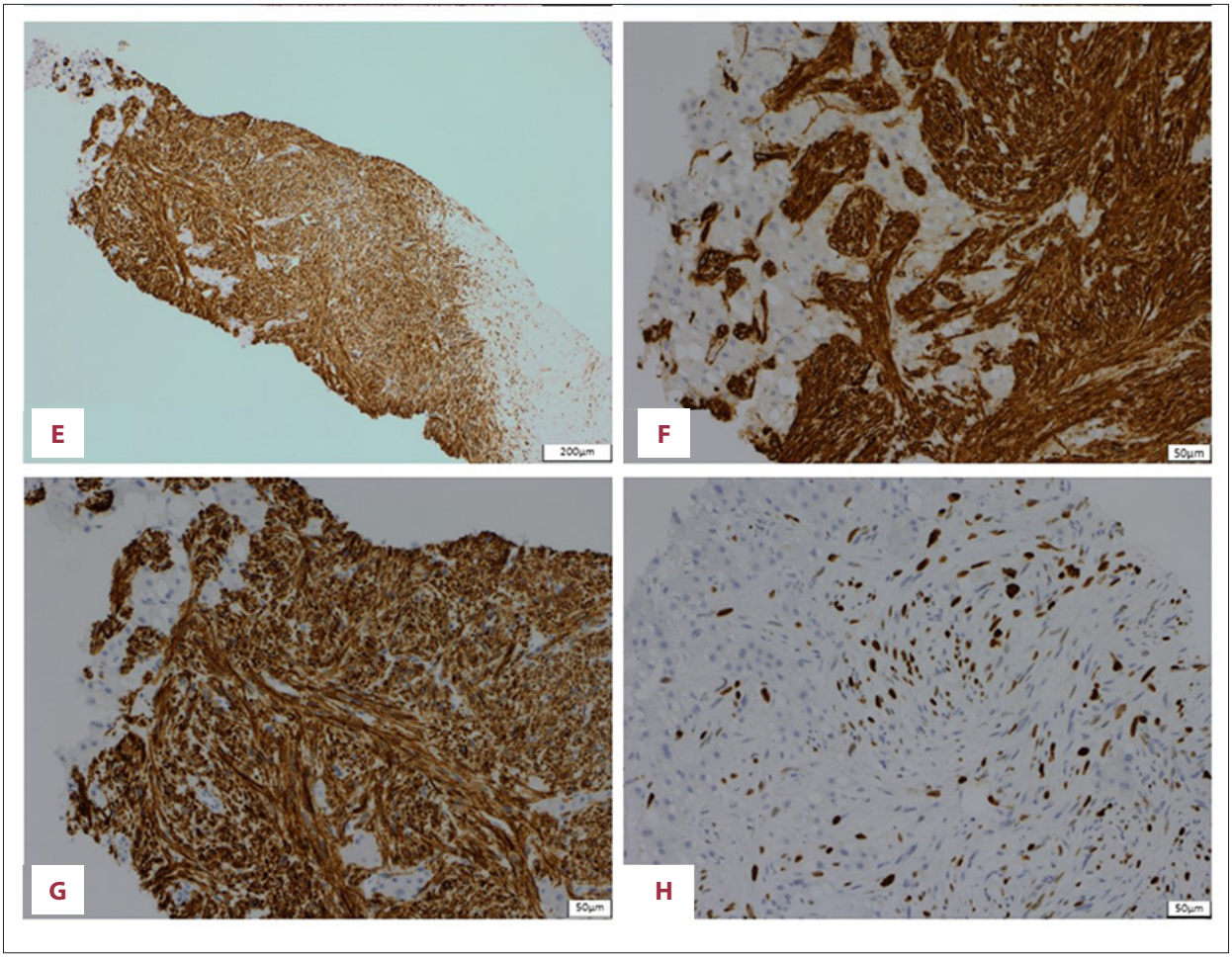

Figure 1. PET-CT with 18^{F}-FDG showing a metabolically active tumor in the left lumbar region of 49×41×44 mm size (**A**) and numerous liver focal lesions up to 22 mm large (**B**). The histopathology of the tumor. Hematoxylin-eosin staining ×50 (**C**) showing metastasis of sarcoma to liver tissue (hepatocytes can be seen in the upper left corner) composed of large atypical, spindle cells with abundant, fibrillary cytoplasm and blunt-ended nuclei forming irregular chaotically arranged cellular fascicles. Immunohistochemical staining ×50 for SMA (**D**) and desmin (**E**). In the upper left corner, normal liver tissue can be seen between tumor cells. Tumor cells positively stained for SMA (**D**) and desmin (**E**). High-magnification images (×100) of immunohistochemical staining showing sarcoma cells spreading into the normal liver tissue and staining positively for SMA (**F**) and desmin (**G**). Ki-67 staining ×100 reflects a high proliferative index in sarcoma cells (**H**).

The patient's laboratory tests performed on admission were within the reference range with optimal kidney graft function (serum creatinine concentration of 1.1 mg/dL; normal urinalysis).

She underwent an abdominal and pelvic computed tomography (CT) scan, which showed more than 25 poorly vascularized metastatic lesions in the liver. The lesions were an average diameter of 10 mm to 25 mm, and there was a 38-mm tumor in the small pelvis next to the left iliac vessel (adhered to the larger lumbar muscle on the left side, left iliac artery, and the small intestinal loop), with heterogeneous gaining after administration of contrast media. A similar lesion of 25×30 mm was found in the fundus of the uterus. We performed a PET-CT scan with 18^{F}-FDG in search of the primary lesion. The scan revealed a metabolically active tumor in the left lumbar region, sized 49×41×44 mm (**Figure 1A**), and numerous liver focal lesions up to 22 mm (**Figure 1B**).

The patient underwent an ultrasound-guided core biopsy of the liver lesions.

Histological examination revealed metastasis of sarcoma, which was composed of large atypical, elongated cells with abundant, fibrillary cytoplasm forming irregular cellular fascicles (**Figure 1C**). Immunohistochemical staining revealed extensive expression of smooth muscle actin (**Figure 1D, 1F**), desmin (**Figure 1E, 1G**), and high Ki67 proliferative index (**Figure 1H**)

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but did not detect any expression of ALK-1 protein, HMB45, neuron-specific enolase, DOG-1, S-100 protein, or cytokeratines 34 and 117. The specimens also stained negative for EBV.

Therefore, a diagnosis of advanced retroperitoneal leiomyosarcoma with liver involvement was established (cT1N0M1 CS IV).

The patient started chemotherapy with doxorubicin 50 mg/m^2 every 21 days. The dosage of mycophenolate sodium was reduced from 1260 to 540 mg daily, and trough levels of tacrolimus were maintained at approximately 6 ng/mL. The patient's tolerance of the first-line chemotherapy was good and she received subsequent cycles without delay. She did not experience any adverse events, including infectious complications and neutropenic fever.

Unfortunately, CT imaging after administration of 6 cycles showed progression in the primary retroperitoneal lesion and in the liver, with metastasis merging into a conglomerate of 64×51×50 mm. Owing to disease progression, the patient received a second-line chemotherapy based on gemcitabine (900 mg/m^2 on days 1 and 8) and docetaxel (100 mg/m^2 on day 8) every 3 weeks. Despite the use of adequate premedication, she presented significant toxicity that was aggravated with every administration of docetaxel, including subcutaneous edema of the upper and lower extremities, generalized sensory neuropathy (CTCAE G3), and erythematous-desquamative lesions on the face and neck. Despite a mild size reduction of the primary lesion (by 19%) and metastatic lesions in the liver (stable disease, according to RECIST 1.1), we terminated the second-line chemotherapy owing to unacceptable toxicity. The patient was referred to another oncology center with access to trabectedin-based therapy. Since January 2020, the patient has been continuing courses of trabectedin (1.5 mg/m^2 every 21 days) with good tolerance and maintenance of stable disease status, reaching over 31 months of overall survival since the initial diagnosis. The kidney graft function is still excellent, despite a mycophenolate dosage reduction to 360 mg daily.

Discussion

Soft-tissue sarcomas in patients after solid-organ transplantation usually have higher histological grading, and about 40% of patients are diagnosed in the metastatic phase of the disease [7]. Oncological treatment in patients with KTx should include all conventional pharmacological approaches, along with the concomitant consideration of the reduction of immunosuppression dosage. The median overall survival for advanced disease does not exceed 15 months [7].

Increased cancer risk is one of the major concerns in solid-organ transplant recipients. The 10-year risk of de novo cancer is twice as great in transplant recipients than in the general population [8]. De novo malignancies have tremendous impact on survival after solid-organ transplantation, as they have been reported as a leading cause of late mortality after transplantation [9]. One of the main causes of increased cancer incidence among patients with transplants is the common use of more intensive immunosuppressive therapies [10]. In KTx recipients, the use of tacrolimus and induction antibodies was proven to increase the risk of de novo post-transplantation malignancy [11]. It is worth noting that increased oncogenesis is observed already at the stage of chronic kidney disease and dialysis therapy [11,12]. Furthermore, the increasing age of the transplant population, longer organ survival, and exposure to oncogenic viruses also contribute to increased malignancy rates after transplantation [13,14].

Although soft-tissue sarcomas remain a rare type of cancer in KTx recipients, soft-tissue sarcomas are significantly more common in KTx recipients than in the general population: the standardized incidence ratio is 14.4 (95% CI: 9.2-19.5) in male patients and 4.5 (95% CI: 0.6-8.5) in female patients [15]. The diagnosis of leiomyosarcoma is often accidental and can occur at any point after transplantation. Interestingly, a different pattern of the primary location has been observed in patients with KTx, with 33% occurring in the head and neck, compared with only 5% in the head and neck in the general population [7,16].

In the present case, the specimen derived from the tumor did not demonstrate EBV activity. However, pre-transplantation EBV-positive recipient status in itself has been demonstrated to increase the risk of post-transplantation malignancy [13]. Nevertheless, several circumstances can be identified as potential factors that were conducive to the development of sarcoma in our patient. Above all, was the immunosuppressive therapy she received. Second, we cannot exclude a hypothetical relevance of the long-term exposure to dialysis fluid as an additional risk factor for carcinogenesis. It has been demonstrated that the high-glucose load in peritoneal dialysis fluid increases the formation of advanced glycation end-products (AGEs). AGEs then exert cancer-promoting effects, mediated by an interaction with the receptor for AGEs and increased oxidative stress, in addition to chronic inflammatory responses [17], which have been shown to be strong contributors of carcinogenesis [18,19]. Moreover, metabolic complications such as insulin resistance and low plasma adiponectin levels have been associated with the increased risk of malignancy, even in nondiabetic peritoneal dialysis patients [20]. Hence, we cannot exclude that, in our patient, peritoneal dialysis treatment and diabetes alongside immunosuppression might have been involved in the pathogenesis of the retroperitoneal sarcoma.

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Conclusions

Certainly, substantially prolonged survival after KTx increases the cancer incidence and mortality in this cohort. According to a recent report, mortality attributable to cancer steadily increases after transplantation, reaching 15.7% of deaths in recipients that are more than 10 years past transplantation [21]. Despite regular ambulatory monitoring, cancers in KTx recipients are diagnosed in a more advanced stage as compared with those in the general population [22]. Importantly, imaging during this period is focused mainly on assessment of the graft and cirrhotic kidneys, and the guidelines for cancer screening vary greatly, depending on the screened organ, except for skin cancer [23]. Because patients after KTx present a markedly increased risk of malignancy complications, we strongly suggest individualizing post-transplantation screening, considering individual cancer risk, comorbidities, overall prognosis, and screening preferences.

Department and Institution Where Work Was Performed

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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