Kidney Medicine

# Pegylated Liposomal Doxorubicin and Kidney-Limited Thrombotic Microangiopathy in a Kidney Transplant Recipient: A Case Report

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A 64-year-old man with Kaposi sarcoma in clinical remission after treatment with pegylated liposomal doxorubicin and a history of deceased-donor kidney transplantation 4 years prior presented with a slowly progressive increase in his serum creatinine level, well-controlled hypertension, stable subnephrotic-range proteinuria, and bland urinary sediment. An allograft kidney biopsy demonstrated thrombotic microangiopathy, without clinical or laboratory features of systemic involvement. Based on the timing of drug initiation preceding thrombotic microangiopathy, complete recovery after drug withdrawal, and the absence of other etiologies, it was concluded that pegylated liposomal doxorubicin was the likely cause of kidney-limited thrombotic microangiopathy. When pegylated liposomal doxorubicin was resumed, the patient developed hypertension and kidney allograft dysfunction. A new kidney biopsy was not performed because of the overall risk benefit. The case highlights the importance of recognizing novel etiologies of thrombotic microangiopathy in kidney transplant patients with malignancy. Although Kaposi sarcoma has not been linked to thrombotic microangiopathy, pegylated liposomal doxorubicin has been increasingly associated with drug-induced thrombotic microangiopathy. To our knowledge, this is the first case report that etiologically links pegylated liposomal doxorubicin to kidney-limited thrombotic microangiopathy in a kidney transplant patient.

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## INTRODUCTION

Thrombotic microangiopathy (TMA) is a spectrum of disorders characterized by occlusive microvascular thrombosis, microangiopathic hemolytic anemia, thrombocytopenia, and potentially fatal end-organ damage.[1-3] TMA in patients with cancer is a rare but often devastating complication that may be directly related to an underlying malignancy, chemotherapeutic treatment,[4,5] or a separate incidental diagnosis.[6-8] Cancer-associated TMA is clinically indistinguishable from other TMA syndromes.[3,9] A sudden decrease in hemoglobin levels, acute kidney injury, uncontrolled hypertension, and thrombocytopenia may alert clinicians to the possibility of TMA. In patients with malignancy, kidney-limited TMA is not unusual, particularly with exposure to anti-vascular endothelial growth factor (VEGF) agents.[10,11] In drug-induced TMA, the most common clinical presentations are slowly progressive kidney failure, new or worsening hypertension, and a bland urinary sediment, often in the absence of a clinically apparent tumor.[1]

Doxorubicin is an anthracycline, antineoplastic agent commonly used to treat breast cancer, bladder cancer, Kaposi sarcoma, and recurrent ovarian cancer.[5,12] Doxorubicin has been associated with acute interstitial nephritis and cardiotoxicity.[4,5] Its pegylated liposomal formulation reduces its uptake in the myocardium and markedly prolongs its half-life in the vascular compartment, thereby attenuating myelosuppression and cardiotoxicity. However, pegylated liposomal doxorubicin (PLD) has been linked to TMA in small case series.[12] To the best of our knowledge, we presented the first case of kidney-limited TMA related to PLD in a kidney transplant patient with Kaposi sarcoma.

## CASE REPORT

A 64-year-old man with a history of Kaposi sarcoma and deceased-donor kidney transplantation 4 years prior was seen for a slowly progressive increase in his serum creatinine (sCr) level. He had a history of chronic kidney failure of unknown etiology and had undergone hemodialysis for 8 years before receiving the kidney transplant.

His past medical history included hypertension, dyslipidemia, and moderate aortic stenosis. His medications included extended-release tacrolimus 5 mg daily, mycophenolic acid 360 mg twice a day, prednisone at 5 mg daily, acetylsalicylic acid at 81 mg daily, bisoprolol 5 mg daily, ramipril 10 mg daily, and pravastatin 40 mg daily. He was a lifelong nonsmoker, had minimal alcohol intake, and did not use recreational drugs.

A kidney allograft biopsy performed 10 months after transplantation because of allograft dysfunction revealed acute tubular necrosis, unremarkable glomeruli, and moderate chronic vascular disease. One and a half years after transplantation, the patient developed nonpainful, nonpruritic, confluent, violaceous papules bilaterally on the medial surfaces of his feet as well as macules on the dorsum of the left metatarsophalangeal joints. A skin biopsy revealed Kaposi sarcoma. He was treated with PLD at

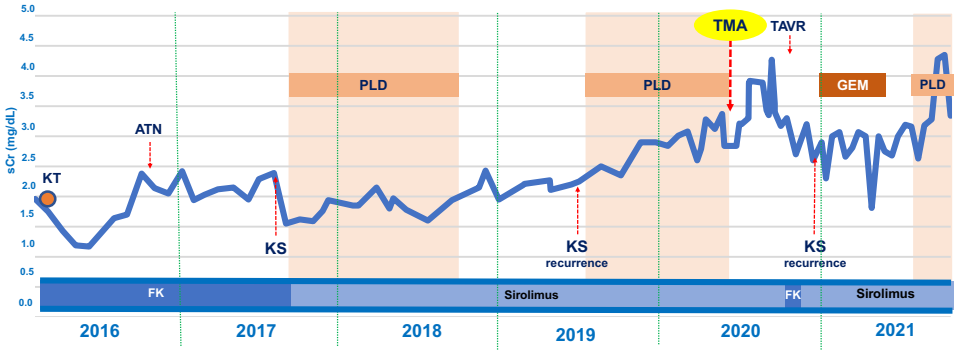


**Figure 1.** Evolution of kidney function during follow-up, immunosuppressive therapy, and chemotherapy. Conversion factor for units: serum creatinine in mg/dL to μmol/L, ×88.4. Abbreviations: ATN, acute tubular necrosis; FK, tacrolimus; GEM, gemcitabine; KS, Kaposi sarcoma; KT, kidney transplantation; PLD, pegylated liposomal doxorubicin; TMA, thrombotic microangiopathy; TAVR, transcatheter aorta valve.

20 mg/m$^2$ every 3 weeks for 13 months; clinical remission was achieved, with good drug tolerance. At the time of Kaposi sarcoma diagnosis, tacrolimus was replaced with sirolimus with the goal of improving cancer control,[13,14] and the mycophenolic acid dose was decreased. The patient presented with Kaposi sarcoma recurrence 8 months later, and therefore, the PLD treatment was resumed at the previous dose and frequency, with good clinical response.

Over the subsequent few months, the patient developed worsening dyspnea on exertion and mild peripheral edema. A transthoracic echocardiogram showed the worsening of his previously documented aortic stenosis with the aortic valve area reduced to 0.9 cm$^2$. The patient developed a slow but progressive increase in the sCr level from his baseline level of 2.2 mg/dL to 3.4 mg/dL (Fig 1), with stable subnephrotic proteinuria. The patient did not report any drug abuse or medication noncompliance. His blood pressure remained adequately controlled, with no modifications in his antihypertensive regimen. The patient had no weight loss, new skin lesions or masses, headache, cough, or diarrhea, and his physical examination was unremarkable.

Laboratory investigations showed stable, normocytic anemia, without evidence of hemolysis and mild thrombocytopenia. Donor-specific antibodies were absent (Table 1). The urinary sediment was bland, the albumin-to-creatinine ratio was 470 mg/g, and 24-hour urine collection demonstrated 1.2 g of protein. A kidney ultrasound ruled out any obstructive etiology or vascular abnormality. A kidney allograft biopsy was performed to further evaluate the patient's worsening kidney function. The biopsy findings were consistent with subacute TMA with diffuse mesangiolysis, red cell fragments, and capillary wall double contouring; without glomerulitis, peritubular capillaritis, or tubulointerstitial inflammation; and a negative C4d staining result. There were no viral cytopathic changes, and immunostaining for simian vacuolating virus 40 yielded a negative result (Fig 2). The patient had a stable Kaposi sarcoma. In light of case reports associating PLD treatment with TMA, the PLD treatment was discontinued.

Two months after the diagnosis of PLD-induced, kidney-limited TMA, the patient was scheduled for a transcatheter aortic valve replacement for the treatment of his aortic stenosis. At that time, sirolimus was switched to extended-release tacrolimus to ensure optimal surgical wound healing after the procedure (Fig 1). The patient's posttranscatheter aortic valve replacement course was complicated by pneumonia, heart failure, and acute or chronic kidney injury (maximum sCr level, 4.3 mg/dL). Thereafter, the sCr level returned to baseline, and sirolimus was resumed 3 months later, with no evidence of TMA. Seven months after the discontinuation of PLD, the patient presented with localized Kaposi sarcoma recurrence. He received gemcitabine for 4 months, with poor tolerance (pancytopenia, febrile neutropenia, and mucositis) despite dose reductions, whereas his kidney function remained stable.

Because of the history of clinical response to PLD and after a thorough multidisciplinary discussion with the patient, PLD was resumed at the previous dose and frequency. Three months later (cumulative dose, 800 mg/m$^2$), the patient developed worsening kidney function (sCr level, 4.2 mg/dL); hypertension (blood pressure, 170/60 mm Hg); stable normocytic anemia, without evidence of hemolysis; and mild thrombocytopenia (hemoglobin level, 8.1 g/dL; reticulocyte count, 92 × 10$^9$/L; negative direct antiglobulin test result; no schistocytes on peripheral blood smear test; and platelet count, 115 × 10$^9$/L), suggestive of recurrent kidney-limited TMA, leading to PLD withdrawal. Furthermore, persistent subnephrotic proteinuria (albumin-to-creatinine ratio, 1,504 mg/g) and a bland urinary sediment were observed. A repeat kidney biopsy was not performed because of the overall risk benefit. No other causes of TMA were identified, and donor-specific antibodies were absent. A plan to

**Table 1.** Laboratory Investigations

| Laboratory Tests | Result | Reference Range |
|---|---|---|
| Hemoglobin, g/dL | 10.5 | 14-18 |
| WBC count, ×10$^9$/L | 4.3 | 4.0-11.0 |
| Platelet count, ×10$^9$/L | 131 | 150-400 |
| Reticulocyte count, ×10$^9$/L | 93 | 30-110 |
| Peripheral blood smear | No schistocytes | — |
| Sodium, mmol/L | 137 | 135-145 |
| Potassium, mmol/L | 4.9 | 3.2-5.0 |
| Bicarbonate, mmol/L | 21 | 23-29 |
| sCr, mg/dL | 3.4 | 0.72-1.2 |
| BUN, mg/dL | 79.2 | 7.0-20 |
| Calcium, mg/dL | 8.82 | 8.5-10.5 |
| Phosphate, mg/dL | 3.1 | 3-4.5 |
| Albumin, g/dL | 3.6 | 3.8-5.0 |
| AST, U/L | 23 | 5-34 |
| ALT, U/L | 26 | 7-40 |
| ALP, U/L | 59 | 40-150 |
| Total bilirubin, mg/dL | 0.35 | 0.3-1 |
| Triglycerides, mmol/L | 1.32 | <1.7 |
| C3, g/L | 1 | 0.98-1.96 |
| C4, g/L | 0.28 | 0.1-0.4 |
| ADAMTS13 antibody, IU/mL | 0 | <12 |
| ADAMTS13 activity | 0.5 | 0.40-1.30 |
| ANA | Negative | Negative |
| Anticardiolipin, lupus anticoagulant, anti-β2 microglobulin antibodies | Negative | Negative |
| Anti-PR3 antibodies | <0.2 | ≤0.9 |
| Anti-MPO antibodies | <0.2 | ≤0.9 |
| Anti-GBM | <0.2 | ≤0.9 |
| INR | 1.1 | 0.9-1.2 |
| PTT, s | 28.3 | 23.0-30.0 |
| Ferritin, μg/L | 1,191 | 30-250 |
| Iron saturation, % | 15 | 25-50 |
| B12 vitamin, pmol/L | 455 | 222-652 |
| Sirolimus trough level, μg/L | 4.7 | — |
| CMV PCR | Negative | — |
| BK virus PCR | Negative | — |
| EBV PCR | Negative | — |
| SARS-CoV2-2 PCR | Negative | — |
| HIV ELISA | Negative | — |
| Hepatitis s antigen | Negative | — |
| Hepatitis B core antibodies | Negative | — |
| Hepatitis B DNA | Negative | — |
| Hepatitis C antibody | Negative | — |
| Donor-specific antibodies | Negative | — |
| Urinalysis | Negative blood, trace protein | — |
| Urinary sediment | Bland | — |
| Albumin-to-creatinine ratio, mg/g | 470 | <30 |
| Urine culture | Negative | — |
| Blood culture | Negative | — |

Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88; urea nitrogen in mg/dL to mmol/L, ×0.357.
Abbreviations: ADAMTS13, disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; anti-GBM, antiglomerular basement membrane; anti-MPO, anti–myeloperoxidase antibodies; anti-PR3, anti-proteinase 3 antibodies; AST, aspartate aminotransferase; BK virus; BUN, blood urea nitrogen; CMV, cytomegalovirus; EBV, Epstein-Barr virus; ELISA, enzyme-linked immunosorbent assay; HIV, human immunodeficiency virus; INR, international normalized ratio; PCR, polymerase chain reaction; PTT, partial thromboplastin time; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sCr, serum creatinine; WBC, white blood cell.

begin paclitaxel was made to treat Kaposi sarcoma recurrence.

## DISCUSSION

This case describes a 64-year-old man with a remote history of kidney transplantation; Kaposi sarcoma in clinical remission after 2 courses of PLD; and biopsy-proven, kidney-limited TMA attributed to PLD.

Transplant-associated TMA may result from multiple risk factors, including the use of calcineurin inhibitors or mammalian target of rapamycin inhibitors, graft-vs-host disease, previous transplantations, human leukocyte antigen mismatch, and opportunistic infections.[1,3,9] The common pathogenetic pathway includes endothelial cell injury, potential complement activation, and end-organ damage.

Calcineurin inhibitors likely have direct toxic effects on the kidney allograft, leading to endothelial dysfunction and increased platelet aggregation, possibly through prostacyclin inhibition.[3] Patients with sirolimus-induced TMA have significantly lower kidney VEGF expression compared with those with normal transplanted kidneys. The inhibition of VEGF function in glomerular endothelial cells appears to be the cause of TMA.[8,14,15] In this case, a secondary workup for TMA yielded negative results, with no active infections, acute rejection, connective tissue or autoimmune diseases, exposure to radiation, or exposure to other toxins.

TMA is a well-described complication of both cancer and its treatment.[1-3] Cancer-related TMA usually occurs in the context of advanced or metastatic cancer, resembling thrombotic thrombocytopenic purpura, and is more commonly seen in mucin-producing adenocarcinomas.[1] There are no reported cases of TMA associated with Kaposi sarcoma, and the patient's clinical remission at the time of TMA diagnosis makes Kaposi sarcoma an unlikely etiology.[1,2]

Chemotherapy-induced TMA is more common than cancer-related TMA. However, the evidence supporting its causal role is limited. PLD has been linked to TMA.[16,17] Shavit et al[16] reported 3 patients with biopsy-proven, kidney-limited TMA after several years of high

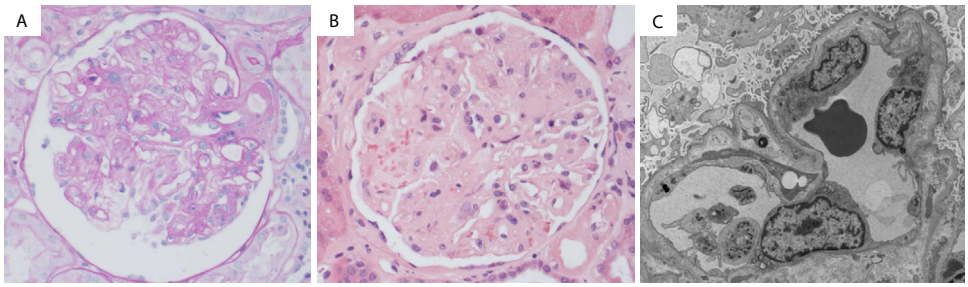


**Figure 2.** Subacute thrombotic microangiopathy. (A) Global mesangiolysis and capillary wall double contouring (periodic acid–Schiff stain; original magnification, ×20). (B) Global mesangiolysis and segmental red cell fragmentation (hematoxylin and eosin stain; original magnification, ×20). (C) Endothelial cell swelling and subendothelial lucent expansion (electron microscopy; original magnification, ×6,000).

cumulative doses of PLD (range, 880-1,445 mg/m$^2$), including 1 who also received bevacizumab (ie, VEGF inhibition).[12] These patients experienced increases in their sCr levels (up to 5.5 mg/dL), hypertension, and subnephrotic-range proteinuria, which improved partially upon PLD withdrawal. Of note, thrombocytopenia or hemolytic anemia was not observed. In another series, 56 patients were treated with PLD alone or other chemotherapeutic drugs, and it was found that 23% of the patients developed stage 3-4 chronic kidney disease and hypertension. The authors suggested that kidney-limited TMA should be considered a potential long-term complication of PLD treatment, although causal inferences were limited because kidney biopsies were not performed.[12,16,18] The proposed mechanisms of PLD-associated TMA include direct, drug-induced endothelial injury; increased platelet aggregation; and genetic factors.

The clinical presentation of our case is similar to that described in previous case series: the gradual onset of kidney failure, prolonged and iterative exposure to PLD, subnephrotic-range proteinuria, kidney-limited TMA, and the stabilization of kidney function after PLD discontinuation.

The temporal association between the use of PLD and worsening kidney function, improvement after PLD discontinuation despite continued exposure to sirolimus or tacrolimus, a high cumulative PLD dose, recurrent kidney dysfunction when PLD was resumed, and clinically overt or progressing metastatic malignancy support the notion that PLD-induced TMA was the probable etiologic factor. This is further supported by use of the World Health Organization-Uppsala Monitoring Center System and the Naranjo causality assessment scale in this case.[19,20] A potential contributing role for the patient's immunosuppressive therapy and gemcitabine cannot be ruled out.[1]

In conclusion, we described the first case of kidney-limited TMA due to PLD in a kidney transplant patient. Kidney transplant patients are at increased risk of malignancy, and it is important to recognize PLD-associated TMA as an entity that is frequently insidious and limited to the kidney. Patients receiving PLD should be monitored for new or worsening hypertension, hematuria, proteinuria, and decreased kidney function.

## ARTICLE INFORMATION

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