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# Thrombotic Microangiopathy From Peptide Receptor Radionuclide Therapy



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**Received 1 October 2024; accepted 7 November 2024; published online 13 November 2024**

*Kidney Int Rep* (2025) **10,** 610–613; https://doi.org/10.1016/j.ekir.2024.11.009


## INTRODUCTION

Lutetium-177 prostate-specific membrane antigen (Lu-PSMA) is a peptide receptor radionuclide therapy recently approved by the US Food and Drug Administration and the European Medicines Agency, for PSMA-positive metastatic castration resistant prostate cancer.[1] The recommended dose is 7.4 gigabecquerels i.v. every 6 weeks for up to 6 doses, until disease progression or unacceptable toxicity.[2] However extended therapy has not been associated with increase in grade 3 to 4 toxicity.[3] This treatment targets the PSMA-expressing cells to deliver radiotherapy on specific tissues. The PSMA is expressed in physiological prostate tissue; however, it is significantly more expressed in prostate adenocarcinoma and lymph nodes metastases,[4] and its expression is correlated with aggressive phenotype.[5]

In 2023, Schäfer *et al.*[6] reported 3 cases of kidney failure after an overexposure to Lu-PSMA (8 to 10 cycles) because of renal-limited thrombotic microangiopathy (TMA). The outcome was poor because all of them had end-stage-kidney disease. However, the diagnostic work-up for TMA was limited (no genetic testing, no bone marrow examination, and no complement pathway evaluation), and no anti-C5 blockers were used.

In the present report, we describe 3 new patients who developed acute kidney injury (AKI) associated with hematuria, new onset hypertension, and hematological evidence of TMA confirmed by kidney biopsy after a normal exposure to Lu-PMSA (5 to 6 cycles). They had a comprehensive diagnostic work-up (including genetic evaluation in 1 patient), and 2 of them were treated by eculizumab.

## CASE PRESENTATION

### Patient 1

In 2016, a 70-year-old man was diagnosed with locally advanced prostate adenocarcinoma. Despite hormone therapy and chemotherapy, lymph nodes and bone metastases occurred. He was treated by Lu-PSMA in February 2023. One month after the sixth Lu-PSMA injection, the patient presented with mild AKI (Kidney Disease Improving Global Outcomes stage 1) with macroscopic hematuria, severe hypertension, and evidence of hematological TMA (Table 1).

No abnormalities were found regarding complement alternative pathway (factor H, factor I, anti–factor H antibodies, and CD46 membrane cofactor). Exome sequencing did not identify pathological variants. ADAMTS13 activity was at 79%. Bone marrow examination exhibited no metastatic cells (Table 2).

Kidney biopsy was delayed, because of high bleeding risk (estimated at 17%),[S1] but eventually performed after 3 months. Severe lesions of glomerular TMA were found; however, no arteriolar TMA were observed. Interstitial fibrosis and tubular atrophy were severe (75%) (Table 1).

**Table 1.** Clinical and biological parameters, treatment, and evaluation

| | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| Previous therapies | Bicalutamide - enantone, enzalutamide - enantone, abiraterone acetate - enantone, docetaxel, apalutamide - enantone | Taxotere - enantone, cabazitaxel, enzalutamide – apalutamide | Triptoreline - bicalutamide, abiraterone, docetaxel, enzalutamide, cabazitaxel, taxotere |
| 177-Lu-PSMA characteristics | | | |
| Number of cycles | 6 | 5 | 6 |
| Cumulative dose (GBq) | 44 | 37 | 44 |
| Ligand | 177-Lu-PSMA 617 | 177-Lu-PSMA 617 | 177-Lu-PSMA 617 |
| Time from start (mo) | 9 | 7 | 11 |
| Patient characteristics | | | |
| Comorbid conditions | Hypertension, diabetes mellitus | - | Hypertension |
| Baseline sCr (μmol/l) | 100 | 110 | 88 |
| Clinical and biological parameters at admission | | | |
| Blood pressure (mm Hg) | 180/90 | 220/100 | 185/90 |
| Hemoglobin (g/dl) | 106 | 72 | 86 |
| Number of RBC units transfused | 6 | 2 | 2 |
| Platelet count (x$10^9$/L) | 74 | 59 | 81 |
| Schistocytes (%) | 0.7 | 0 | 0.8 |
| Lactate dehydrogenase (xULN) | 2.2 | 2.2 | 1.9 |
| Haptoglobin (g/l) | < 0.3 | < 0.1 | < 0.1 |
| SCr (μmol/l) | 150 | 347 | 2582 |
| Hematuria | Macroscopic | Microscopic | Macroscopic |
| Proteinuria (g/g) | 4.1 | 0.7 | 1.4 |
| Kidney biopsy | | | |
| Glomerular TMA | Mesangiolysis / endothelosis<br>No microthrombi | Mesangiolysis / endothelosis<br>No microthrombi | - |
| Glomerular proliferation | No | No | - |
| Arteriolar TMA | No | Yes | - |
| ATN | Yes | Yes | - |
| IF-TA | 75% | 25% | - |
| If deposit | No | No | - |
| Etiological evaluation | | | |
| ADAMTS13 (%) | 79 | - | 43 |
| CAP assessment | C3 high, C4 normal<br>Factor H, I, MCP: normal<br>Anti-FH: normal<br>C5b9: normal | C3 normal, C4 high<br>Factor H, I: normal<br>Anti-FH: normal | - |
| Myelogram | No metastatic infiltration | - | - |
| Exome sequencing | No pathogenic variant | - | - |
| PSA (ng/ml) | 3.3 | 1.1 | 500 |
| Eculizumab treatment | | | |
| Treatment | Yes | Yes | No |
| Initiation after diagnosis (d) | 14 | 5 | - |
| Duration (mo) | 6 | 1 | - |
| Plasmapheresis | | | |
| | No | No | No |
| Evaluation at 6 mo | | | |
| Death | No | No | Yes |
| Blood pressure (mm Hg) | 143/75 | 100/80 | - |
| Hemoglobin (g/dl) | 11.8 | 9.2 | - |
| Platelets (x$10^9$/L) | 130 | 150 | - |
| SCr (μmol/l) | 417 | 295 | - |

anti-FH, anti-factor H; ATN, acute tubular necrosis; CAP, complement alternative pathway; GBq, gigabecquerels; If, immunofluorescence; IF-TA, interstitial fibrosis and tubular atrophy; Lu-PSMA, Lutetium-177 prostate-specific membrane antigen; MCP, membrane cofactor protein; PSA, prostate-specific antigen; RBC, red blood cell; SCr, serum creatinine; TMA, thrombotic microangiopathy; xULN, x upper limit of normal.

The patient received eculizumab starting 14 days after admission. After 6 months of eculizumab treatment, hematological TMA resolved; however, renal function deteriorated up to end-stage-kidney disease (Table 1).

## Patient 2

In 2016, a 71-year-old man was diagnosed with metastatic prostate cancer. After treatment with chemotherapy and hormonotherapy, cancer progression was observed and administration of Lu-PSMA was started

**Table 2.** Teaching points

| | |
|---|---|
| What do we know? | • Lu-PSMA could induce hematological and renal TMA even when using recommended doses.<br>• An exhaustive exploration of other causes for TMA is required, including bone narrow examination and evaluation of complement alternative pathway.<br>• Lu-PSMA TMA is a late complication (occurred several months after initiation).<br>• Lu-PSMA TMA is a severe complication responsible for ESKD or death. |
| What do we have to study? | • Pathological mechanisms are unknown.<br>• We do not know the risk factors to developing Lu-PSMA TMA.<br>• C5 blockers seem to be effective on hematological TMA; however, the effects on kidney improving are unclear. |

ESKD, end-stage kidney disease; Lu-PSMA, lutetium-177 prostate-specific membrane antigen; TMA, thrombotic microangiopathy.

in January 2023. After the fifth injection, he presented with dyspnea, anemia, and evidence of hematological TMA. At admission, he displayed severe AKI (Kidney Disease Improving Global Outcomes stage 3) associated with microscopic hematuria and proteinuria. He needed continuous i.v. perfusion of urapidil for severe hypertension. Kidney biopsy revealed glomerular and arteriolar TMA, interstitial fibrosis and mild tubular atrophy (25%) (Table 1).

Eculizumab was started 5 days after admission and was stopped 1 month after stabilization of kidney function. At a follow-up at 6 months, serum creatinine remained stable, and the patient was normotensive without any medication. The last injection of Lu-PSMA was administered and was well-tolerated.

### Patient 3

In 2014, a 71-year-old man was diagnosed with metastatic prostate adenocarcinoma. Despite treatment by hormone therapy and chemotherapy, the cancer progressed and administration of Lu-PSMA was started in May 2022. After 11 months of treatment, he was admitted for a severe obstructive AKI (Kidney Disease Improving Global Outcomes stage 3) along with clotting macroscopic hematuria. Kidney function partially improved after bladder catheterization (serum creatinine decreased from 2582 to 120 μmol/l) (Table 1). He also presented with concomitant severe hypertension and hematological TMA. Palliative care was decided due to cancer progression and the patient died after 6 months.

## DISCUSSION

To the best of our knowledge, these cases are the first description of TMA associated with Lu-PSMA despite the recommended treatment duration of 6 cycles. In contrast to Schäfer *et al.*[6]'s findings,[6] these patients had an earlier AKI (5–6 cycles vs. 8–10 cycles), hematuria, new-onset severe hypertension, and hematological TMA (Supplementary Table S1).

In the present study, 2 patients were treated with eculizumab for Lu-PSMA-associated TMA; the effect on renal function was favorable in 1 patient with stabilization of renal function but not in the other one who reached end-stage-kidney disease at 6 months. Interestingly, eculizumab was started earlier (5 days in patient 2 vs. 14 days after admission in patient 1) and exposure to Lu-PSMA was lower (37 gigabecquerels by 5 cycles in patient 2 vs. 44 gigabecquerels by 6 cycles in patient 1).

Our results indicate that usual exposure to Lu-PSMA can result in TMA, and it occurred after a few cycles of treatment, implicating a need for careful evaluation of renal function and proper assessment of hematological TMA. Whether very early use anti-C5 blockers could be effective on renal TMA is debatable because it was associated with stabilization of renal function in 1 patient, highlighting the need for optimal management of these patients. However, this hypothesis must be confirmed.

Interestingly, the 2 patients treated with eculizumab had a remission of both hematological TMA and severe hypertension. These findings are important because they suggest that the pathophysiology of hematological and renal TMA may be partly different. This hypothesis is strengthened by the observation that eculizumab was effective on hematological TMA and reduced the transfusion requirement in patients with TMA associated with gemcitabine; however, its effect on renal function was less frequently effective.[7] According to the conclusions from the Kidney Disease Improving Global Outcomes Controversies Conference, several drugs that target the complement system will be available, and their effect may vary "depending on the underlying disease process and patient-specific factors."[S2] Whether such medications may prove useful in patients with Lu-PSMA-induced TMA is unsure and should be tested.[S3]

In the report by Schäfer *et al.*,[6] PSMA was expressed in tubular renal cells, providing more evidence that this radioligand is probably the cause of TMA.[6] Other radioligands such as 90-Yttrium-DOTATOC treatment can also result in renal TMA with poor renal outcome.[8] Whether this radioligand is also expressed in renal cells is presently unknown. TMA induced by radiation is not well-known but described since 1964 by Luxon and Kunkler.[S4]

TMAs are relatively often associated with malignancies and their treatment, and their incidence is up to 20% among the different cohorts.[S2,S5] Bone marrow examination is essential to exclude infiltration by metastatic cells which may be responsible for TMA.[S6]

The frequent implication of drugs in the development of TMA has been largely described[S5]; however, a worldwide explosion of TMA resulting from recently marketed immune system targeting and anticancer drugs has been reported.[9] The pathophysiology of TMA associated with these newly developed drugs is usually unknown.[9] In such patients, diagnostic work-up, including evaluation of complement alternative pathway and genetic testing should be systematically performed to identify the pathophysiology of these causes of TMA.

## CONCLUSION

Our findings indicate that hematological and renal TMA associated with Lu-PSMA may occur, even after a treatment duration of 6 cycles or less (Table 2). The pathophysiology is unclear, and no specific treatment is recommended. Anti-C5 blockers may be effective on hematological TMA, and its effects on renal function are unclear.

## DISCLOSURE

The authors declared no conflicting interests.

## PATIENT CONSENT

The authors declared that they have obtained consent from the patients discussed in the report.

## ACKNOWLEDGMENTS

The authors thank Dr. Chevalier Thomas (oncologist) and Dr. Taieb David (nuclear medecine physician) for their help with this report.

## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Table S1.** Comparison with Schäfer *et al.*[6]'s report.

**Supplementary References.**

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