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Membranous nephropathy with dual PLA2R and THSD7A positivity in kidney and prostate cancer tissues: a case report highlighting the diagnostic value of paired renal– tumour antigen staining

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Case Report

Keywords: Membranous nephropathy, PLA2R, THSD7A, Prostate cancer, Case report

Posted Date: November 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11313378/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Membranous nephropathy (MN) is increasingly classified according to the target antigens. Phospholipase A2 receptor (PLA2R) is the major target antigen in primary MN, whereas thrombospondin type-1 domain-containing 7A (THSD7A) is frequently associated with malignancy. However, the significance of dual PLA2R/THSD7A positivity and the role of PLA2R positivity in malignancy-associated MN remains unclear.

Case presentation:

We report a 70-year-old Japanese man with nephrotic syndrome and metastatic prostate cancer. Renal biopsy revealed early-stage MN with enhanced glomerular staining for both PLA2R and THSD7A, whereas NELL-1 and EXT1/2 were negative. Immunofluorescence demonstrated granular IgG deposition along the capillary walls, with an IgG1-dominant and minimal IgG4-positive pattern. Prostate needle biopsy revealed acinar adenocarcinoma with perineural invasion (Gleason score, 4 + 5 = 9). Immunohistochemistry showed PLA2R positivity in perineural invasive tumour-associated areas and THSD7A positivity in tumour cells with high nuclear-to-cytoplasmic ratios. The patient was treated with combined androgen blockade followed by docetaxel-based chemotherapy. Urinary protein excretion gradually improved in parallel with a decrease in serum prostate-specific antigen levels.

Conclusions

This case supports a malignancy-associated mechanism of MN despite PLA2R positivity. To our knowledge, this is the first reported case in which both kidney and tumour tissues were evaluated and tested positive for both PLA2R and THSD7A. Paired renal–tumour antigen staining may provide clinically useful information for aetiological classification and treatment prioritisation in selected patients with MN and concurrent malignancies.

Background

Membranous nephropathy (MN) is a major cause of nephrotic syndrome in adults and has traditionally been classified as primary or secondary according to the presence of associated conditions, such as autoimmune disease, infection, drug exposure, or malignancy. More recently, however, the discovery of target antigens has led to an antigen-based reappraisal of MN [1, 2]. Major known target antigens include phospholipase A2 receptor (PLA2R), thrombospondin type-1 domain-containing 7A (THSD7A), neural epidermal growth factor-like 1 protein (NELL1), semaphorin 3B (SEMA3B), protocadherin 7 (PCDH7), and exostosin 1/2 (EXT1/2), among others [2, 4]. Among these, PLA2R is the most common target antigen,

accounting for approximately 60–80% of adult primary MN, whereas THSD7A is detected in a smaller subset, generally around 3–10% of cases [1–3].

PLA2R and THSD7A are important not only because they are diagnostically useful but also because they provide biological insights into underlying disease mechanisms. Both are large single-pass transmembrane proteins expressed on podocyte foot processes and are accessible to circulating autoantibodies [3, 5]. PLA2R is the major antigen in primary MN, whereas THSD7A has been more consistently linked to malignancy-associated MN [3, 4]. Nonetheless, recent epidemiological and pathological observations suggest that PLA2R positivity does not exclude the presence of underlying malignancies [4, 6]. This distinction is clinically important because overreliance on PLA2R positivity as evidence of primary disease may lead to underrecognition of a tumour-associated process.

Simultaneous positivity for PLA2R1 and THSD7A is rare, and its clinical and pathogenetic significance remains uncertain at present [7]. Moreover, the interpretation of PLA2R positivity in patients with concurrent malignancy remains challenging.

Here, we report a rare case of MN in which both PLA2R and THSD7A showed positive staining in the renal and prostate tumour tissues. We believe that this paired-antigen staining approach may provide an informative clue to the potential etiological relationship between MN and malignancy.

Case presentation

A 70-year-old Japanese man with bilateral leg oedema and nephrotic-range proteinuria was referred to our nephrology department. Approximately one month earlier, he had visited a urology clinic because of dysuria and urinary incontinence and was diagnosed with prostate cancer with lymph node and bone metastases. He had an unremarkable medical history and had received no prior treatment. His family history was notable for his mother initiating maintenance haemodialysis at 72 years of age. Occupationally, he was as an acupuncturist.

At admission, his blood pressure was 132/79 mmHg, heart rate 109 beats/min, body temperature 37.2°C, and oxygen saturation 98% on room air. Bilateral lower extremity pitting oedema was present. Laboratory testing demonstrated severe nephrotic syndrome, with serum albumin 1.1 g/dL, total protein 5.0 g/dL, spot urinary protein-to-creatinine ratio 19.09 g/gCr, and 24-hour urinary protein excretion 12.5 g/day. Serum creatinine was 1.01 mg/dL and estimated glomerular filtration rate was 56.9 mL/min/1.73 m². The antinuclear antibody was positive at a titer of 1:160 with a speckled pattern; however, other autoimmune markers were negative, complement levels were within the normal range, and no convincing alternative secondary autoimmune causes were identified [Table 1]. Renin–angiotensin system inhibitors were not administered. Serum anti-PLA2R antibody levels could not be measured because they were unavailable at our institution.

Table 1
Laboratory findings at the initial nephrology evaluation

Category	Parameter	Result
Hematology / coagulation	White blood cell count	7,400 /μL
	Red blood cell count	3.61 × 10^6^ /μL
	Hemoglobin	11.1 g/dL
	Hematocrit	32.7%
	Platelet count	3.1 × 10^5^ /μL
	MCV / MCH / MCHC	90.6 fL / 30.7 pg / 33.9%
	Reticulocyte count	0.9%
	APTT / PT-INR	30.7 s / 0.88
	Fibrinogen / D-dimer / Antithrombin III	955 mg/dL / 11.3 μg/mL / 92%
Serum biochemistry	Total protein / Albumin	5.0 / 1.1 g/dL
	Total bilirubin	0.3 mg/dL
	AST / ALT / LDH / ALP / CK / Amylase	18 / 12 / 277 / 158 / 162 / 86 U/L
	Blood urea nitrogen / Creatinine	26.4 / 1.01 mg/dL
	eGFR / eGFR based on cystatin C	56.9 / 41.5 mL/min/1.73 m²
	Cystatin C	1.58 mg/L
	Uric acid / HbA1c	6.7 mg/dL / 5.9%
	Triglycerides / HDL-C / LDL-C	133 / 96 / 169 mg/dL
	Sodium / Potassium / Chloride	141 / 4.8 / 110 mmol/L
	Magnesium / Calcium / Inorganic phosphorus	1.9 / 7.8 / 3.3 mg/dL
	C-reactive protein / Brain natriuretic peptide	2.31 mg/dL / 63.4 pg/mL
	Prostate-specific antigen	53.64 ng/mL
Immunology / serology	IgG / IgA / IgM	1,033 / 250 / 51 mg/dL
	κ/λ ratio	1.05
	Cryoglobulin	Negative

Category	Parameter	Result
	CH50 / C3 / C4	65.8 CH50/mL / 183 / 55 mg/dL*
	Antinuclear antibody	1:160, speckled pattern
	C-ANCA / P-ANCA / ASO	Negative / Negative / 25 IU/mL
	HBsAg / HBsAb / HBcAb / HCV antibody / Treponema pallidum antibody	Negative / Negative / Negative / Negative / Negative
Urinalysis	Protein / occult blood / leukocyte esterase / nitrite / glucose	4+ / 2+ / negative / positive / negative
	Red blood cells / White blood cells	20–29 /HPF / 30–49 /HPF
	Granular casts / Bacteria	1–4 /WF / 2+
	Spot urinary protein-to-creatinine ratio	19.09 g/gCr
	24-hour urinary protein excretion	12.5 g/day
Urinary protein fraction / tubular markers	Selectivity index	0.27
	α1-microglobulin / β2-microglobulin	114.2 mg/dL / 978 μg/L
	Bence Jones protein	Below detection sensitivity

Renal biopsy revealed 54 glomeruli, of which 5 were globally sclerosed. Light microscopy showed diffuse thickening of the glomerular capillary walls without significant mesangial hypercellularity. Immunofluorescence demonstrated granular IgG staining along the glomerular capillary walls, with IgG1 predominance and minimal IgG4 staining. C3c staining was weakly positive, whereas C1q staining was negative. Both kappa and lambda light chains showed a polyclonal pattern. Enhanced staining for PLA2R and THSD7A was observed along the glomerular basement membrane. In contrast, NELL-1 and EXT1/2 staining results were negative. Electron microscopy showed subepithelial electron-dense deposits with diffuse foot process effacement and no significant subendothelial or mesangial deposits, consistent with early-stage MN [Figure 1].

Prostate needle biopsy revealed acinar adenocarcinoma with perineural invasion and a Gleason score of 4 + 5 = 9. Immunohistochemical examination revealed PLA2R positivity in perineural invasive tumour-associated areas and THSD7A positivity in tumour cells with high nuclear-to-cytoplasmic ratios [Figure 2].

The patient was treated with combined androgen blockade followed by docetaxel-based chemotherapy. Low-dose prednisolone was administered as part of the oncological regimen; however, no high-dose immunosuppressive treatment specifically targeting MN was given. During follow-up, the prostate-

specific antigen (PSA) decreased from 314.7 ng/mL at the initial urologic evaluation to 53.64 ng/mL at nephrology admission and continued to decline thereafter. Urinary protein excretion gradually improved in parallel, eventually approaching partial remission [Figure 3]. Medication adherence was good, and the treatment was well tolerated without any treatment-related adverse events.

Discussion and conclusions

The most distinctive feature of the present case was the concordant detection of both PLA2R and THSD7A in the kidney and prostate tumour tissue. This finding is unusual and provides a stronger pathophysiological link between MN and underlying malignancy than clinical coexistence alone. In previously reported malignancy-associated MN, concordance between renal and tumour antigen staining has not been universal, indicating that paired staining is not merely confirmatory, but may offer additional etiological information in selected cases [6]. In this context, our case is notable because the same two target antigens were identified at both sites, supporting a shared tumour-related immune process rather than incidental coexistence.

PLA2R and THSD7A are not simply “renal markers” but membrane proteins with biological relevance beyond the kidney. Current reviews describe both molecules as large single-pass transmembrane proteins expressed on podocyte foot processes, where their extracellular domains are accessible to circulating autoantibodies [3, 5]. THSD7A was initially characterised in the endothelial and placental vascular tissues before being established as a target antigen in MN [3]. Public gene expression resources indicate that PLA2R and THSD7A are not kidney-specific and are also expressed in nonrenal tissues [8]. These observations make a tumour-associated immune mechanism biologically plausible: if these antigens are expressed in tumour tissue, the resulting immune response could secondarily target podocyte antigens and induce MN.

The tumour-staining pattern in our patient therefore deserves particular attention. To our knowledge, reports of PLA2R positivity in both renal and tumour tissues remain extremely limited, having been previously described only in thyroid and renal cell carcinomas [6, 9]. In the present case, PLA2R staining was observed in the perineural invasive tumour-associated areas of prostate cancer, and THSD7A was detected in tumour cells with high nuclear-to-cytoplasmic ratios. Because perineural invasion by carcinoma cells was histologically confirmed, it is reasonable to interpret PLA2R positivity as a tumour-associated signal rather than an incidental signal from benign neural tissue. More importantly, to the best of our knowledge, cases in which both kidney and tumour tissues were evaluated for PLA2R and THSD7A and showed positive results at both sites are extremely rare. This appears to represent the principal novelty of the present report.

The clinical and pathological findings of the present case further support the possibility that MN develops through a tumour-related immune mechanism rather than representing an incidental coexistence. Most importantly, proteinuria improved in parallel with tumour control after cancer-directed therapy despite the absence of disease-specific high-dose immunosuppressive treatment for MN. This

temporal association supports the paraneoplastic process. In addition, the glomerular immune deposits showed an IgG1-dominant rather than an IgG4-dominant pattern, which may be considered a supportive clue, although not definitive evidence, for malignancy-associated MN.

IgG subclass findings, however, should be interpreted with caution. Earlier clinicopathological studies have suggested that primary MN is often associated with IgG4-dominant deposits, whereas malignancy-associated MN often lacks IgG4 or shows non-IgG4-predominant patterns [10]. More recent antigen-specific analyses, however, indicate that IgG subclass profiles are not sufficiently specific to distinguish primary MN from malignancy-associated MN on their own. In particular, von Haxthausen et al. reported that antigen-specific IgG subclasses against PLA2R1 or THSD7A do not reliably differentiate primary MN from malignancy-associated MN [11]. Moreover, exceptions clearly exist; IgG4-dominant glomerular deposits have been reported in THSD7A-associated MN with malignancy and in PLA2R-positive MN with associated malignancy [6, 12]. Taken together, these observations suggest that IgG subclass findings may provide supportive clinicopathological information but are not sufficiently specific to establish the etiological classification of MN.

Although dual PLA2R/THSD7A positivity is rare and its independent clinical significance remains uncertain, it may be mentioned as a secondary feature, suggesting that multiple antigenic pathways may have been activated simultaneously [7]. However, in clinical practice, dual positivity may also complicate etiological classification because it can blur the distinction between primary and secondary MN. Such diagnostic uncertainty may delay appropriate therapeutic decision-making, particularly if malignancy-associated MN is not adequately considered before immunosuppressive therapy is prioritized [13].

Taken together, these observations suggest a possible immunopathogenic model. One plausible explanation is that the tumour cells aberrantly express PLA2R1 and THSD7A, either quantitatively or qualitatively, leading to immune sensitisation and subsequent injury to podocyte antigens. In dual positive cases, this process may be amplified by cross-reactivity or epitope spreading. Structural studies have suggested a shared motif between the CysR domain of PLA2R and the TSR1 domain of THSD7A, providing a possible molecular basis for broader immune recognition once one pathway is triggered [14]. However, this proposed mechanism remains hypothetical from the present case alone.

Within this framework, our case contributes to an important clinical point: PLA2R positivity does not exclude malignancy-associated MN. Recent epidemiological data strongly support this view. In a 2026 cohort study of adults with PLA2R-associated MN, the cancer incidence was higher than expected compared to that in the general population, and prostate cancer was the most common malignancy diagnosed during follow-up [15]. Older age and tobacco exposure were independent predictors of malignancy, whereas PLA2R antibody titers over time, antibody positivity at diagnosis, and remission status were not associated with cancer occurrence [15]. These findings are highly relevant to our patient, who had PLA2R-positive MN, prostate cancer, and clinicopathological evidence supporting a paraneoplastic link. They also suggest that serological PLA2R status alone may be insufficient for etiological classification.

From a practical standpoint, the main implication of this report is not simply that malignancy screening should be considered in PLA2R-positive MN. A serology-based approach has been proposed for antigen-specific MN, in which positivity for anti-PLA2R or anti-THSD7A antibodies may support a diagnosis of primary MN and guide the use of immunosuppressive therapy in selected patients [13]. However, our case suggests that such an approach should be applied cautiously when an underlying malignancy is present or suspected. Even if antigen-specific serological or glomerular findings appear to support primary MN, careful evaluation for occult malignancy remains essential, because premature prioritisation of immunosuppression may delay appropriate tumour-directed therapy [13, 15]. In this regard, paired antigen staining of the kidney and tumour tissues may provide clinically actionable diagnostic information. Demonstration of concordant target-antigen expression at both sites may strengthen the inference that MN is truly associated with malignancy, and this distinction may influence treatment strategies by supporting the prioritisation of tumour-directed therapy over upfront immunosuppression.

This report has several limitations. First, serum levels of anti-PLA2R and anti-THSD7A antibodies were not measured because these assays were unavailable at our institution. Accordingly, although the clinicopathological findings were compatible with a tumour-related immune mechanism, we could not directly confirm the presence of circulating antigen-specific autoantibodies. Second, this was a single-case report, which limited the generalisability of our findings. Third, while concordant antigen staining in the kidney and tumour tissues strongly supports a pathogenic link, it does not determine whether the immune response was initiated by tumour-associated antigen expression and subsequently targeted podocytes, or whether a kidney-initiated autoimmune response secondarily recognised a shared antigen in the tumour tissue. A more direct distinction between these possibilities would require evidence linking the tumour, serum, and kidneys. In particular, the demonstration that circulating patient antibodies recognise the tumour-associated PLA2R/THSD7A epitope and that this reactivity parallels glomerular binding and disease activity strongly supports a tumour-origin mechanism. By contrast, if the dominant antibody response were shown to target glomerular antigens independently of tumour reactivity, a kidney-origin mechanism would remain more plausible. Thus, concordant tumour–kidney staining, even when combined with parallel improvement in cancer burden and proteinuria, should be interpreted as strong supportive evidence rather than definitive proof of the direction of immune initiation.[15, 16]

In conclusion, we report a rare case of MN in which PLA2R and THSD7A were positive in both the kidney and prostate cancer tissues. The combination of concordant renal–tumour antigen staining, an IgG1-dominant pattern, and parallel improvement in proteinuria and tumour burden supports a paraneoplastic mechanism. In selected patients with MN and malignancy, evaluation of both renal and tumour tissues may help refine the etiologic classification and guide therapeutic decision-making.

Abbreviations

MN
membranous nephropathy

PLA2R1
phospholipase A2 receptor 1
THSD7A
thrombospondin type-1 domain-containing 7A
NELL1
neural epidermal growth factor-like 1 protein
EXT1/2
exostosin 1/2
PSA
prostate-specific antigen
eGFR
estimated glomerular filtration rate
RAS
renin–angiotensin system

Declarations

Ethics approval and consent to participate

This case report involved a single patient and was conducted in accordance with the institutional and national ethical standards. Ethics committee approval was not required for this case report, in accordance with the policy of our institution.

Consent for publication

Written informed consent for publication of this case report and any accompanying images was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

Authors’ information

Not applicable.

Funding

Not applicable.

Author Contribution

SF generated the table and figures and was a major contributor to writing the manuscript. TT also generated the figures and revised the manuscript accordingly. All authors read and approved the final manuscript.

Acknowledgement

We thank the urologists and pathologists in Ichikawa general hospital. We would like to thank Editage(www.editage.jp) for English language editing.

Data Availability

All data generated or analysed during this study are included in this published article.

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Figures

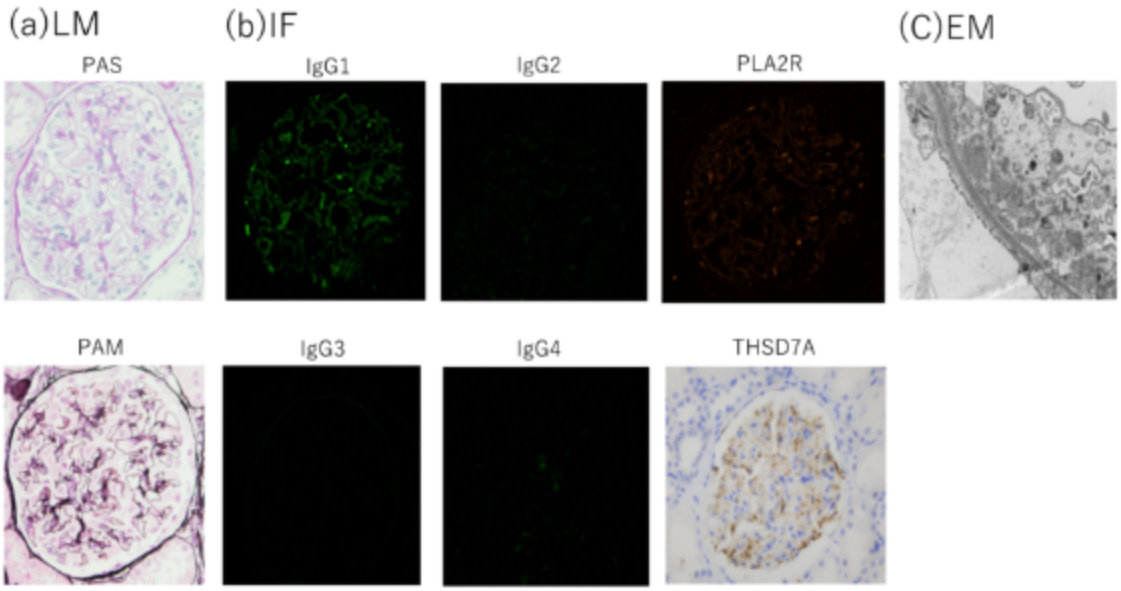


Figure 1

Renal biopsy findings.

(a) Light microscopy (LM): Periodic acid–Schiff (PAS) and periodic acid methenamine silver (PAM) staining showed diffuse thickening of the glomerular capillary walls without significant mesangial hypercellularity.
(b) Immunofluorescence and antigen staining (IF): Immunofluorescence demonstrated granular capillary wall staining for IgG, with predominance of IgG1 and only minimal staining for IgG2, IgG3, and IgG4. Enhanced staining for PLA2R and THSD7A was observed along the glomerular basement membrane.
(c) Electron microscopy (EM): Electron microscopy revealed subepithelial electron-dense deposits with diffuse foot process effacement, consistent with early-stage membranous nephropathy.

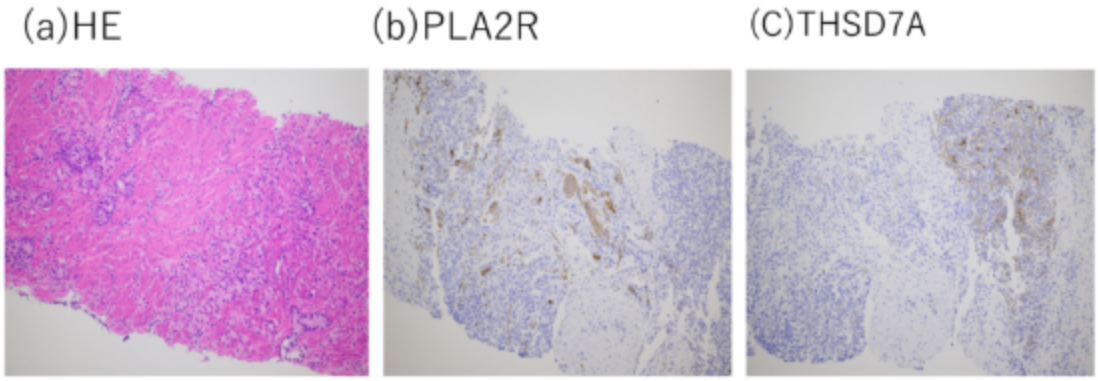


Figure 2

Prostate biopsy findings and tumor antigen staining.

(a) Prostate needle biopsy revealed acinar adenocarcinoma with perineural invasion and a Gleason score of 4 + 5 = 9.

(b) PLA2R expression was detected in cancer cells invading perineural tissue.
(c) THSD7A expression was detected in tumor cells with high nuclear-to-cytoplasmic ratios.

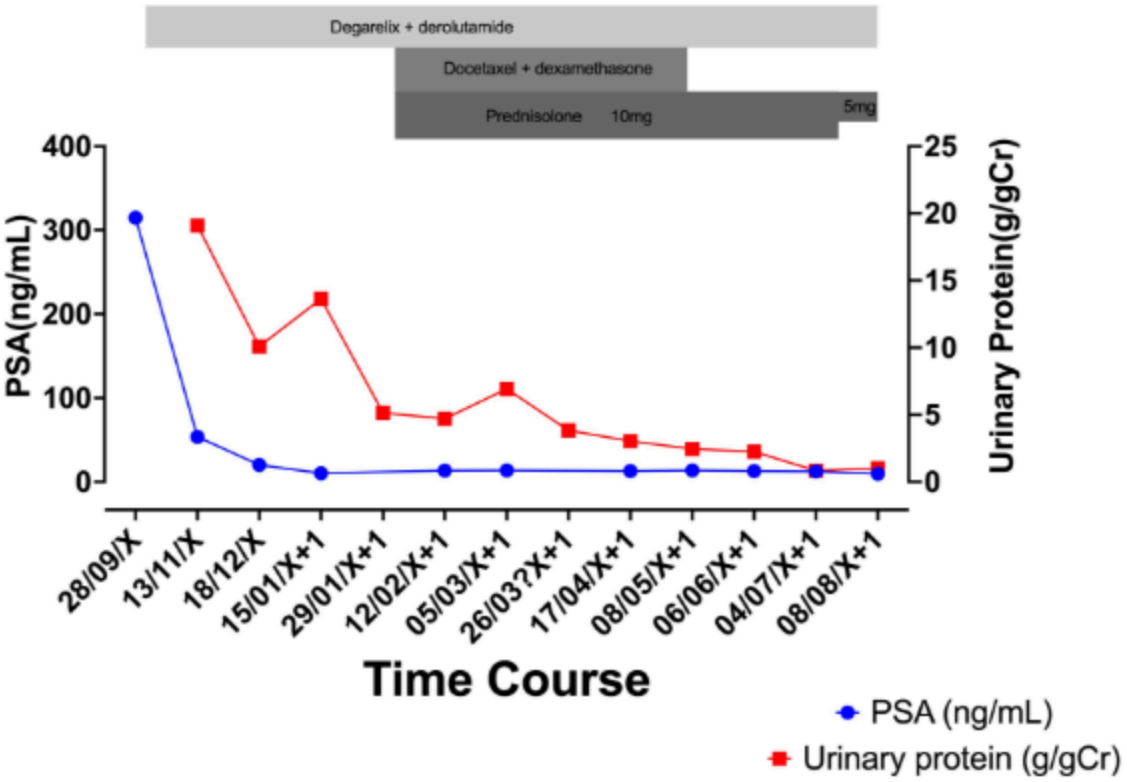


Figure 3

Temporal changes in urinary protein excretion and serum prostate-specific antigen during cancer-directed therapy.

Combined androgen blockade therapy with degarelix (80 mg monthly) and darolutamide (1200 mg daily) was initiated on October 17, year X. From January 30, year X+1, the patient received docetaxel-based chemotherapy consisting of docetaxel (75 mg/m², 126.8 mg) plus dexamethasone (6.6 mg) every month for six cycles. Oral prednisolone was started at 10 mg/day on January 30, year X+1 and tapered to 5 mg/day from August 1, year X+1. Following initiation of cancer-directed therapy, serum PSA levels decreased in parallel with gradual improvement in urinary protein excretion.