Kidney Medicine

Pembrolizumab-Mediated Complete Remission of a PLA2R-Positive Paraneoplastic Membranous Nephropathy: A Case Report

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Management of paraneoplastic membranous nephropathy (MN) is directed toward the underlying malignancy, and prescriptions of immune checkpoint inhibitors (ICIs) are skyrocketing in the field of oncology. However, this drug category is usually discouraged for patients with autoimmune disorders (AIDs) because it might trigger immune-related adverse events (irAEs) in the form of flare-ups or even genesis of AID. Yet, nothing is known about the efficacy and safety of ICIs for cancers associated with paraneoplastic MN. Here, we report a rare case of PLA2R-positive MN related to a PDL1-positive locally advanced lung adenocarcinoma. Antineoplastic treatment with the anti-PD1 pembrolizumab as a first-line, single-drug therapy allowed for both cancer and nephropathy remissions. To date, to our knowledge, this is the first description of a (PLA2R-positive) paraneoplastic MN that was put into remission via an ICI monotherapy successfully targeting the associated neoplasia only, without additional immunosuppressive agents.

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Membranous nephropathy (MN) is the commonest etiology of nephrotic syndrome in adulthood. In total, 10% of MN cases are related to cancer, and management of paraneoplastic MN is based on treatment of the underlying malignancy. On the contrary, "primary" MN appears as a renal-limited disease often associated with autoantibodies directed against phospholipase A2 receptor (PLA2R) or newly identified target antigens, and treatment in this case may require immunosuppressive agents.[1-3]

Here, we report a rare case of PLA2R-positive MN related to a programmed death-ligand 1 (PDL1)-positive, locally advanced lung adenocarcinoma. Interestingly, antineoplastic treatment with the antiprogrammed cell death 1 protein (PD1) pembrolizumab as a first-line, single-drug therapy allowed for both cancer and nephropathy remissions synchronously. Yet, immune checkpoint inhibitors (ICIs) are often contraindicated for patients with pre-existing autoimmunity. To the best of our knowledge, this is the first description of a (PLA2R-positive) paraneoplastic MN that was put into remission via an ICI monotherapy successfully targeting the associated malignancy only.

CASE REPORT

A 49-year-old male patient was evaluated for pitting edema of lower extremities. Routine laboratory tests showed a nephrotic syndrome with urinary protein-creatinine ratio (uPCR) at 5 g/g and serum albumin level at 8 g/L, associated with microscopic hematuria and acute kidney failure (peak creatininemia 182 μmol/L vs baseline level 65 μmol/L). The patient had a prior history of familial hypercholesterolemia and 35 pack-year active smoking. Viral and immunologic blood workup (including anti-PLA2R enzyme-linked immunosorbent assay test) was negative. Kidney ultrasound and renal vein Doppler sonography were unremarkable. On light microscopy, kidney biopsy showed characteristic "spikes" of the glomerular basal membrane (Fig S1). Immunostaining of these immune deposits proved positive for IgG, IgA, C3, C1q, κ light chains, and λ light chains. IgG subtyping study showed IgG4 +++, IgG3 +, and IgG2 + staining. Overall, diagnosis of in situ PLA2R-positive MN was made. Screening for secondary cause uncovered one positron emission tomography (PET)-positive nodule of the right lower lobe, combined with mediastinal and left hilar lymphadenopathies. Percutaneous lymph node fine-needle aspiration led to the diagnosis of a 100% PDL1-positive, thyroid transcription factor-1–positive lung adenocarcinoma with regional node involvement (stage IIIB). In-depth genotyping analysis was not possible because of material exhaustion.

Platinum salts and pemetrexed were contraindicated because of the impaired kidney function, so the ICI pembrolizumab (200 mg IV at D1, D1 = 22) was chosen as a first-line, single-drug therapy. Interim PET scans performed after the third and the sixth treatment cycles both concluded that partial metabolic response was achieved according to the PET response evaluation criteria for immunotherapy (PERCIMT criteria).[4] Stereotaxic radiotherapy was performed during the ninth cycle, and pembrolizumab was continued only once every 6 weeks after the 14th cycle. Complete remission was reached and sustained for almost 2 years according to close radiologic follow-up examinations, which allowed ICI discontinuation after 2 years of well-tolerated immunotherapy.

In the meantime, the patient only received conservative treatments for his nephropathy, including diuretics, sartan, therapeutic-dose anticoagulation, and erythropoietin-stimulating agent. Serum creatinine level stabilized around

170 μmol/L for almost 1 year before slowly decreasing to approximately 110 μmol/L (estimated glomerular filtration rate between 60 and 65 mL/min/1.73 m^2 according to the Chronic Kidney Disease Epidemiology Collaboration formula). Partial remission of nephrotic syndrome (ie, 50% reduction in baseline uPCR and uPCR < 3.5 g/g) was reached after 11 months of antitumor immunotherapy, whereas serum albumin concentrations eventually exceeded 30 g/L. Normalization of uPCR (<0.5 g/g) was achieved > 3 years after the first cycle of pembrolizumab (Fig 1). No kidney flare-up nor positive anti-PLA2R test was reported throughout the patient's follow-up.

Two years after the last infusion of pembrolizumab, both the lung cancer and the kidney disease are still in remission.

DISCUSSION

In a setting of nephrotic syndrome that stems from immune complex deposition outside the glomerular basal membrane, the main arguments supporting the diagnosis of "primary" MN comprises the absence of active neoplasia (or other causes of secondary MN) and the presence of anti-PLA2R antibodies in the patient's serum or kidney tissue. The semantical dichotomy between "primary MN" and "paraneoplastic MN" does not always tally with real-life experience.[5] For instance, cases of PLA2R-positive cancer-related MN are not exceptional anymore.[6] On the other hand, treating the underlying malignancy proves sometimes insufficient to extinguish the nephropathy without sequelae.[7] These examples are some of the reasons why the antigen-driven classification paradigm is currently spreading in the field of MN.[5]

In our case, the diagnosis of paraneoplastic MN was assumed despite anti-PLA2R antibody deposits, notably because a lung adenocarcinoma was concomitantly discovered. Consequently, management focused on the associated cancer. No adverse event was observed, and the last radiologic workup 2 years after the ultimate infusion

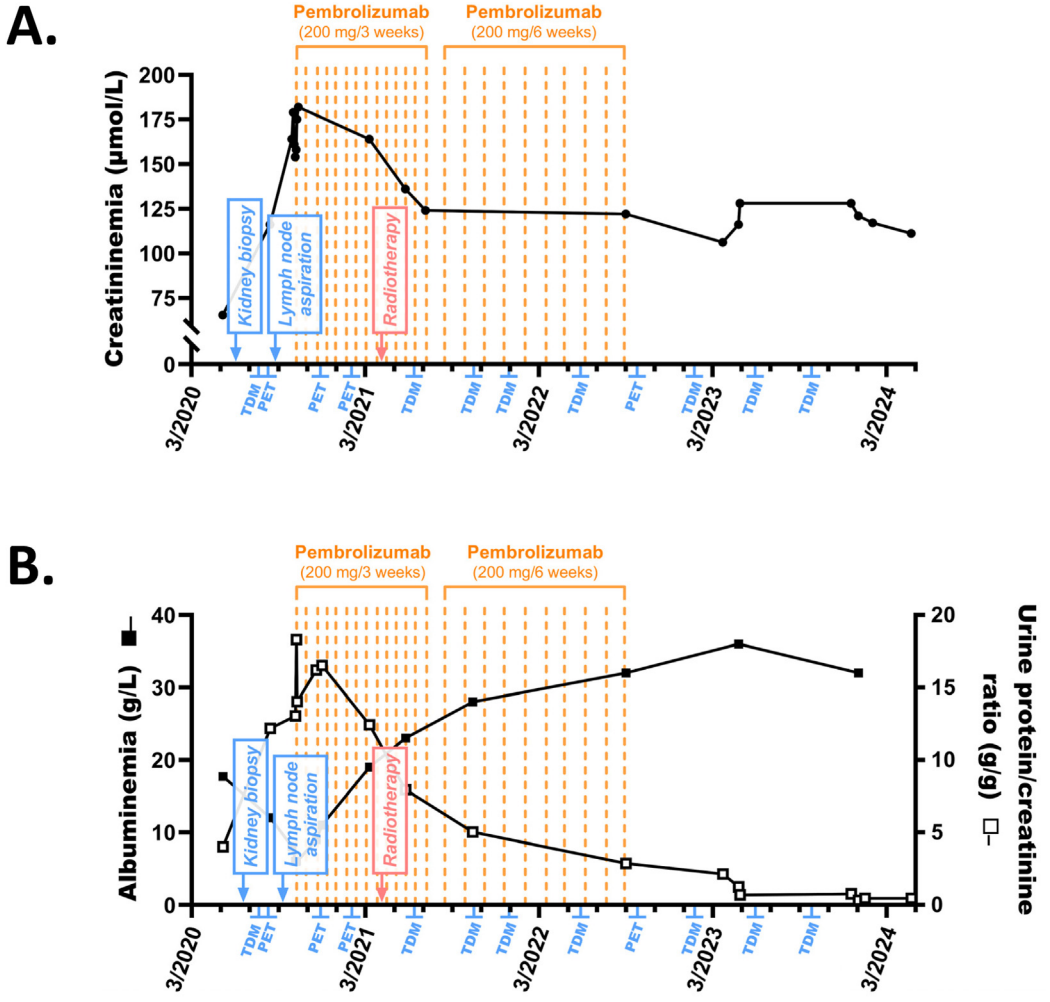

Figure 1. Evolution of kidney function over time. (A) Serum creatinine concentration (μmol/L) over time. (B) Urinary protein-creatinine ratio (g/g) and serum albumin concentration (g/L) over time. Abbreviations: PET, positron emission tomography; TDM, tomodensitometry.

of pembrolizumab confirmed sustained cancer remission. Normalization of kidney function and proteinuria took over 2 years since the first ICI infusion. Favorable renal outcome and absence of MN relapse after cancer remission furtherly gave credence to the paraneoplastic origin of this MN. Staining of other MN-related antigens was not performed because kidney biopsy material was exhausted, and dual positivity of MN antigens is extremely rare anyway.[8] Unfortunately, expression of PLA2R in cancer cells was impossible to assess also because of tissue material exhaustion (lymph node fine-needle aspiration). The idea that a common surface protein shared by both tumoral tissue and kidney parenchyma could trigger the production of autoantibodies—ultimately leading to MN lesions—has been already well-discussed in the literature.[9] Despite some interesting data to support this hypothesis,[10,11] MN with tumoral expression of PLA2R remains a rarity.[12]

To date, to our knowledge, this is the first report of a successful treatment of both an active neoplasia and a related MN with an ICI as an antineoplastic monotherapy. Through CTLA4 or PD(L)1 inhibition, ICI agents promote T-cell activation and reverse T-cell exhaustion, reinvigorating the antitumoral immunity. One concern however is that downstream production of cytokines may generate off-target inflammation. Moreover, B-cell autoreactivity could be triggered or boosted through T-cell modulation. These are some of the main hypotheses whereby many authors explain how immune-related adverse events (irAEs) arise.[13,14] Genesis or relapse of thyroiditis,[15] lupus erythematosus,[16] and even MN,[17] are some of the irAEs that have been documented so far. Thus, ICI are often not recommended for patients with already-known AID or inflammatory diseases.[18] In our case, positive anti-PLA2R antibodies could reflect autoreactive mechanisms involved in the development of this paraneoplastic MN. As such, particular attention was paid to detect any possible flare-up of the patient's nephropathy after immunotherapy initiation, which did not seem to happen. Previous cohorts have already suggested that ICI might be safely administrated to patients with pre-existing AID.[19-21] However, renal AID are scarcely reported, with only 1 MN found in the cohort of Cortellini et al,[21] as dermatologic, rheumatologic, endocrinal, and gastrointestinal pathologies dominate the field. In addition, assuming that our patient did not have MN before the neoplastic outbreak but as a synchronous paraneoplastic syndrome, his clinical trajectory might not be strictly comparable with the ones of patients suffering from both cancer and primary AID. One could argue that the state of this MN at diagnosis is questionable, because discrepancy between the absence of circulating anti-PLA2R antibodies and the presence of renal PLA2R deposits may reflect ongoing spontaneous remission. In contrast, the disease could be at an early stage during which a very high affinity between anti-PLA2R autoantibodies and their glomerular target could account for an abrupt depletion of circulating antibodies.[22] Nevertheless, pembrolizumab does not seem to have worsened the kidney prognosis.

As a case report, this work cannot make definitive conclusions about the safety of ICI agents for paraneoplastic MN; it also does not provide any evidence that malignancy-related PLA2R-negative MN may react differently. Nonetheless, this experience fuels the idea that ICI-based therapies should not be systematically discarded for patients with pre-existing or concomitant autoimmune nephropathy. In our case, despite its renal risk, pembrolizumab was tested because of the patient's young age and the aggressiveness of this PDL1-positive lung cancer. Obviously, a careful evaluation of the benefit–risk ratio should always be carried out in every individual through a multidisciplinary process.

CONCLUSION

We report the successful treatment of a locally advanced lung adenocarcinoma with pembrolizumab, despite paraneoplastic PLA2R-positive MN. No flare-up of the kidney disease was detected during the course of the antineoplastic protocol or the 2-year follow-up after therapy. This case supports previous works suggesting that ICI agents remain valid options for patients despite paraneoplastic-related autoimmunity; it advocates for the efficacy and safety of ICI-based regimens in the particular frame of an active cancer with paraneoplastic MN, pushing forward personalization of kidney management strategies.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Figure S1: Kidney histology.

ARTICLE INFORMATION

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