



EXCEPTIONAL CASE

Relapse of membranous nephropathy with cancer immunotherapy

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Correspondence and offprint requests to: Youngho Kim; E-mail: ablapia@gmail.com**ABSTRACT**

Advances in monoclonal antibody technology have enabled the application of engineered antibodies to interfere with specific immune pathways. Checkpoint inhibitors have shown promising results in treating certain cancers by employing patients' own immune systems to attack cancer cells. Checkpoint inhibitors release the brake on the immune system and can cause immune-related diseases. Theoretically this could be disadvantageous in patients with autoimmune diseases. Here I describe a case of nephrotic syndrome relapse in a patient with a history of membranous nephropathy during programmed death-ligand 1 inhibitor therapy for lung cancer. It is postulated that enhancement of the immune system triggered the relapse of nephrotic syndrome by leading to an escape of immune tolerance and increased susceptibility.

Keywords: checkpoint inhibitors, durvalumab, lung cancer, membranous nephropathy, nephrotic syndrome

INTRODUCTION

Advances in monoclonal antibody technology have enabled the application of engineered antibodies to interfere with specific immune pathways. Checkpoint inhibitors such as anti-programmed death 1 (PD-1), anti-PD ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibodies have proved to be promising options in treating certain cancers by employing patients' own immune systems to attack cancer cells. Checkpoint inhibitors release the brake on the immune system and can cause immune-related diseases. Theoretically this could be disadvantageous in patients with autoimmune diseases. Here I describe a case of nephrotic syndrome (NS) relapse in a patient with a history of membranous nephropathy (MN) during PD-L1 inhibitor therapy.

CASE REPORT

A 55-year-old male with non-small cell lung cancer (NSCLC) was found to have severe generalized swelling while

undergoing durvalumab therapy. His urinalysis showed major proteinuria, which prompted nephrology referral.

Eight years prior to the diagnosis of NSCLC, the patient developed NS. His medical history included hypertension, tobacco-use disorder, chronic obstructive pulmonary disease and depression. Physical examination revealed moderate pitting edema of the lower extremities. The initial laboratory evaluation was significant for serum albumin 2.2 g/dL, low-density lipoprotein (LDL) 316 mg/dL, creatinine 0.9 mg/dL, 24-h urine protein 11 190 mg and hepatitis C virus (HCV) RNA viral load of 6.2 log IU/mL with genotype 3a. Serum protein electrophoresis showed no monoclonal proteins and no other serological test results were significant. Chest X-ray showed no active disease. Renal biopsy was performed and ~48 glomeruli were examined. Light microscopy revealed patent glomeruli that had a subtle accumulation of eosinophilic material along the subepithelial surfaces of the silver-staining glomerular basement membranes, with rare and subtle evidence of silver-positive spike formation. The tubular parenchyma showed no obvious abnormalities and there was no significant sclerosis or hyalinosis in

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the arterial vessels. Granular glomerular basement staining for immunoglobulin G (IgG; 3⁺), IgA (2–3⁺), complement 3 (C3; 1⁺), kappa light chain (3⁺) and lambda light chain (3⁺) was demonstrated by immunofluorescence (IF). Staining for the HCV immune complex was not performed. Electron microscopy revealed thickened capillary basement membranes due to the accumulation of numerous subepithelial discrete electron-dense deposits, along with diffuse podocyte foot process effacement. These findings were compatible with MN. An anti-phospholipase A2 receptor (PLA2R) antibody was not available at the time. The patient was started on an angiotensin receptor blocker and no immunosuppressive therapy was attempted afterward. Treatment for the HCV infection was with pegylated interferon once a week and oral ribavirin. The viral load became undetectable 6 months after biopsy and proteinuria became subnephrotic within 2 years after biopsy, with subsequent normalization of serum albumin 6 months later. He showed complete remission over the following 8 years with preserved renal function.

After being in a stable condition for 8 years, the patient presented with shortness of breath and productive cough. Imaging studies showed postobstructive pneumonia in the right lung, pleural effusion and mediastinal lymphadenopathy. Tissue diagnosis was made by right main bronchus biopsy, which revealed invasive squamous cell cancer. Due to the development of empyema, he underwent right thoracotomy with complete decortication. Positron emission tomography (PET) scanning confirmed N3 lymph node metastasis, and there was a normal distribution of fluorodeoxyglucose (FDG) throughout the abdomen and pelvis. His chemotherapy regimen consisted of cisplatin and taxol followed by radiation therapy. He opted for durvalumab maintenance at a dose of 10 mg/kg of body weight every 2 weeks for 12 months.

He developed severe anasarca 9 months into durvalumab therapy. Urinalysis and sediment examination revealed 3⁺ proteinuria with occasional oval fat bodies. Laboratory tests showed 24-h urine protein of 11 230 mg, creatinine 0.98 mg/dL, albumin 1.3 mg/dL and LDL 374 mg/dL. Serological tests were all negative, including undetectable HCV RNA. Serum anti-PLA2R antibody, as detected by enzyme-linked immunosorbent assay, was elevated to 51 RU/mL (reference range <14 RU/mL). Follow-up PET showed a marked decrease in FDG in an area of the right lung and thoracic lymph nodes consistent with a positive response to interval therapy. Angiotensin-converting enzyme inhibitor (ACEI) treatment along with diuretics for volume control were initiated. Due to the augmented risk of hypercoagulability, the patient was also started on coumadin.

The patient remained relatively stable until the completion of 12 months of durvalumab therapy, although mild fluctuations in serum creatinine were observed with ongoing diuretic therapy. His proteinuria had improved, but remained significant in the nephrotic range, with a urine protein:creatinine ratio (UPCR) between 7 and 8 and persistence of severe hypoalbuminemia. The patient agreed to kidney biopsy at this time. Light microscope examination revealed glomerular basement membrane thickening, with an accumulation of eosinophilic material along the subepithelial surface of the glomerular basement membrane. The parenchyma showed focal tubular atrophy and interstitial fibrosis, and there were no findings suggestive of active inflammatory processes. IgA was no longer found and capillary wall staining for IgG (4⁺), C3 (trace), kappa light chains (4⁺) and lambda light chains (3⁺) was demonstrated. Indirect IF staining for PLA2R was positive (1–2⁺) in the glomerular immune deposits. Electron microscopy revealed numerous

subepithelial and intramembranous immune-type electron-dense deposits, with extensive basement membrane remodeling and extensive foot process effacement of overlying epithelial cells.

One month after the completion of durvalumab therapy and 7 months after the relapse of NS, the patient's UPCR started to decrease and followed a downward trend over the next 4 months while the patient was on low-dose ACEI, the dose of which had been limited due to intermittent hyperkalemia. Serum albumin had improved to 2.8 mg/dL and creatinine had remained stable at 1.2 mg/dL. Repeated anti-PLA2R antibody titer was 48 RU/mL, similar to the previously recorded value.

DISCUSSION

After histological examination determines a membranous pattern of kidney injury, one is said to have primary MN if no secondary causes can be identified. The patient's first biopsy findings represented MN, with the only unusual features being positive staining for both IgG and IgA. Prominent deposits of IgM and IgA are features of systemic lupus nephritis, but small amounts can be found in primary cases. The HCV viremia found at the time of the first biopsy may have contributed to the development of MN. Although HCV infection is most commonly associated with membranoproliferative glomerulonephritis and cryoglobulinemic vasculitis, several studies have shown that MN may be induced by chronic HCV infection. HCV treatment in this case was quite successful, in that the patient achieved serological remission early in interferon-based therapy that was sustained until the final presentation. It is not certain that HCV infection was the culprit behind the first incidence of NS, as the HCV immune complex was not sought in the IF study and would have had a variable time course regarding clinical and histological recovery after the initial treatment of HCV infection. It is arguable that the patient's remission of MN could have been due to spontaneous remission of the disease, as it occurred within 2 years of disease onset, when most spontaneous remission cases occur.

The relapse of the patient's NS over the clinical course suggests a number of different potential diagnoses. Primary nephrotic glomerulonephritis could be considered, including a recurrence of previous MN. Furthermore, the history of HCV infection, lung cancer and concurrent durvalumab therapy complicates assessment. Paraneoplastic MN and kidney disease related to chronic viral infection and immune checkpoint inhibitors should be taken into consideration.

Relapse of MN is not uncommon and relapse can develop with a significant interval. Laluck *et al.* [1] reported 29% relapse in 82 biopsy-proven MN patients after complete remission during a postremission period of ≤10 years. Solid tumors, especially lung cancers, have a well-described association with NS regarding the histological pattern of MN. The diagnosis of MN can precede, coincide with or follow the diagnosis of an associated malignancy by variable periods of time. It is not clear whether the relapse of the patient's NS was due to paraneoplastic disease or a recurrence of primary MN, and differentiation could be challenging even with histological examination. There are no defined histological features that allow the differentiation of primary and paraneoplastic MN. Nevertheless, immunohistochemistry for certain tumor antigens and subclass determination of IgG in deposits could be useful in some cases.

Novel discovery of PLA2R as a culprit antigen for Heymann nephritis, although it has limitations, has made a significant contribution to the diagnosis, management and monitoring of

MN. The clinical significance of anti-PLA2R status was analyzed in 91 subjects with biopsy-proven MN for a medial follow-up period of 10.7 years. Hazard ratios for malignancy were 9.705 and 0.103 for negative and positive anti-PLA2R test results, respectively, and malignancy-free survival was significantly shorter among patients with undetectable anti-PLA2R [2]. Patients are unlikely to have an associated malignancy if they have detectable anti-PLA2R at the time of MN diagnosis, and it is likely that malignancies developing during an extended follow-up period would be coincidental in an aging population.

At the time of referral, the patient was 9 months into a course of durvalumab therapy and follow-up PET around this time showed a marked decrease in FDG avidity, suggesting reduced cancer activity. Paraneoplastic MN in general shows a parallel correlation of proteinuria and cancer activity. The magnitude of the patient's proteinuria developing inversely to his cancer activity leads to questions regarding his cancer as an etiology for NS. Serum HCV RNA was undetectable, thus his HCV status was unlikely related to the relapse of his NS. Meanwhile, his positive anti-PLA2R antibody status in the absence of other secondary etiologies suggests that his NS relapse was a form of primary disease, and the time frame of the illness suggests that durvalumab therapy may have played a role in some way.

Checkpoint inhibitors target two immune checkpoints, PD-1 and CTLA-4, that certain cancers use to evade the immune surveillance and defense systems. Durvalumab, one of the immune checkpoint inhibitors approved by the US Food and Drug Administration, boosts the immune system by inhibiting the self-regulatory function of PD-1/PD-L1 signals. PD-L1 was originally discovered as a B7 family member and is a transmembrane molecule that negatively regulates the cell-mediated immune response. Malignancies including lung cancer and melanoma are known to express PD-L1. When combined with PD-1 on T lymphocytes, it leads to the inhibition of T cell functions, allowing the malignant cells to escape immune surveillance. Theoretically, enhancement of the immune system by checkpoint inhibitors could be disadvantageous in patients with autoimmune diseases, as these regulatory systems have important roles in immune tolerance and the prevention of autoimmunity in healthy individuals. Indeed, immune-mediated organ dysfunctions have been observed, including pneumonitis, colitis, hepatitis, endocrinopathies and nephritis. With the increasing use of checkpoint inhibitors, there have been reports of kidney disease related to these agents and a variety of renal toxicities have been described.

Wanchoo et al. [3] conducted a review of the published literature and reported several types of renal adverse events associated with checkpoint inhibitors, including acute kidney injury, nephritis, proteinuria and various electrolyte abnormalities. Most biopsy-proven cases showed acute interstitial nephritis, which often developed several months after the initiation of therapy. Although NS was a rare finding overall, anti-CTLA-4 therapy was associated with podocytopathy in some forms of MN and minimal change disease. Two cases of NS were

reported recently with podocytopathy mimicking minimal change disease, where anti-PD-1 and anti-CTLA-4 antibodies were used for lymphoma and melanoma, respectively.

The exact mechanism of podocyte injury during checkpoint inhibitor therapy is unknown. PD-1L is expressed in parenchymal cells in kidneys and significantly higher expression has been noted in kidneys with type IV lupus nephritis. Experiments using PD-L1- or PD-L2-deficient mice have shown that both PD-Ls provide distinct negative regulatory checkpoints that are poised to suppress autoimmune renal disease [4]. Intact PD-L signals would prevent interaction with and, importantly, the presentation of antigens between parenchymal cells and T cells in the kidneys. Grywalska et al. [5] conducted a case-control study of 20 glomerulonephritis patients and suggested that deregulation of the PD-1–PD-L1 axis may contribute to the development of glomerular inflammation and injury. Important roles of T cells in the development of autoimmune kidney diseases including MN have been well described. These findings could suggest that, in our case, the interruption of regulatory PD-1 and PD-L1 signaling by durvalumab may have caused the activation and proliferation of T cells, leading to recognition of the embedded antigenicity of PLA2R.

I suggest that the most probable etiology for the patient's recurring NS was relapse of primary MN. It is speculated that prolonged durvalumab therapy may have triggered a relapse of the patient's MN by leading to an escape of immune tolerance and increased susceptibility. With the increasing use of checkpoint inhibitors, clinicians should be aware of potential complications and remain vigilant in monitoring renal function, electrolytes and urinary abnormalities, especially when these agents are used for patients with preexisting glomerular diseases with autoimmunity.

CONFLICT OF INTEREST STATEMENT

None declared.

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