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Pembrolizumab-Induced Anti-GBM Glomerulonephritis: A Case Report

Nidal El Yamani, Gabrielle Cote, Julie Riopel, Nicolas Marcoux, Fabrice Mac-Way, David Philibert, and Mohsen Agharazii

Immune checkpoint inhibitors are known to have a wide range of autoimmune toxicities, such as acute interstitial nephritis. Immunotherapy induced glomerulonephritis has been described, but anti-glomerular basement membrane disease (anti-GBM) is rarely reported. We present a case report of a 60-year-old woman with squamous cell carcinoma of the cervix who was treated with pembrolizumab, an anti-programmed cell death protein 1, and who developed severe acute kidney injury 4 months after therapy initiation. The immune workup showed a positive serum anti-GBM antibody (24 U/mL). The kidney biopsy showed crescentic glomerulonephritis with linear immunoglobulin G2 glomerular basement membrane staining, compatible with anti-GBM glomerulonephritis. The patient was treated with plasmapheresis, IV steroids, and cyclophosphamide, but she developed kidney failure, necessitating dialysis. Few case reports, such as the present case, provide a possible link between anti-GBM glomerulonephritis and immune checkpoint inhibitors, warranting early clinical suspicion and investigation in patients who are treated with these agents and subsequently develop acute kidney injury.

Complete author and article information provided before references.

Correspondence to M. Agharazii (Mohsen.Agharazii@crchudequebec.ulaval.ca)

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INTRODUCTION

Immune checkpoint inhibitors, which are used to enhance the immune system, have substantially improved the prognosis for patients with advanced malignancies. However, these agents are associated with a wide spectrum of autoimmune toxicity that can affect any organ. Kidney toxicity is relatively rare and occurs in 2%-5% of patients who are treated with checkpoint inhibitors.[1] The most common kidney disease is acute interstitial nephritis that is usually responsive to steroids. Case reports have shown that checkpoint inhibitors can also cause a wide range of kidney injuries, such as pauci-immune glomerulonephritis, C3 glomerulonephritis, lupus nephritis, immunoglobulin (Ig)A nephropathy, minimal change disease, and thrombotic microangiopathy.[1]

In this case report, we present a case of pembrolizumab-induced anti-glomerular basement membrane disease (anti-GBM) glomerulonephritis in a patient with squamous cell carcinoma of the cervix.

CASE REPORT

A 60-year-old woman was referred to the nephrology department for an acute kidney injury. Her medical history included hypertension and a metastatic squamous cell carcinoma of the cervix. At the time of her cancer diagnosis, she presented with urosepsis and bilateral hydronephrosis caused by neoplastic compression; her serum creatinine level had increased from 49-451 μmol/L. Bilateral nephrostomies stabilized the serum creatinine level to ∼80 μmol/L. She was treated with pembrolizumab, carboplatin, and paclitaxel. Bevacizumab was added 3 weeks later, at the beginning of the second cycle.

Four months after initiating therapy and after completing 4 cycles, the patient was referred to the nephrology department for a serum creatinine level of 271 μmol/L on a routine blood test. The patient only reported a decrease in appetite and water intake in the past week because of gastrointestinal intolerance to antibiotics for a possible urinary tract infection. She did not report any diarrhea. She had received piperacillin-tazobactam for 2 days, followed by amoxicillin/ciprofloxacin for 10 days. She did not report any exposure to non-steroidal anti-inflammatory drugs or contrast agents. She did not present with hemoptysis, arthritis, or purpura. Her blood pressure was 108/74 mm Hg, and she reported no peripheral edema. Her urinalysis showed 4-10 red blood cells and >50 white blood cells per high-power field. Kidney ultrasound showed bilateral nephrostomies without hydronephrosis, with the right and left kidneys measuring 12.5 and 11.5 cm, respectively. The 24-hour proteinuria was 0.845 g/d. There was no thrombocytopenia or hemolysis. The main biochemical parameters are summarized in Table 1. The patient was a nonsmoker, and the chest computed tomography was normal.

After intravenous hydration, serum creatinine level decreased to 230 μmol/L before increasing again. Given the high degree of suspicion of acute interstitial nephritis, prednisone (1 mg/kg) was started empirically. After a few days without any signs of kidney recovery, a kidney biopsy was performed. Serologic studies were positive for anti-GBM antibody (24 U/mL, normal range of <7), negative for antinuclear antibody and antineutrophil cytoplasmic antibody and showed normal complement levels.

A kidney biopsy (Fig 1) was performed on day 6 and showed 49 glomeruli: 2 were globally sclerotic (4%), 32 had crescents (30 cellular and 2 fibrocellular), and 3 additional glomeruli showed foci of fibrinoid necrosis. Crescents were often fibrin-rich or associated with

Table 1. Biochemical Parameters at the Time of Acute Kidney Injury

Parameters	Result	Reference Range
Hemoglobin, g/L	89	120-160
White blood cell count × 10^9 /L	8.8	4.8-10.8
Platelets × 10^{12} /L	586	150-400
Creatinine, μmol/L	271	45-85
Albumin, g/L	19	35-50
Lactate dehydrogenase, U/L	186	<225
Haptoglobin, g/L	5.66	0.34-2.00
ANA	1/160	NA
Anti-DsDNA, UI/mL	<0.5	<10
Anti-GBM, U/mL	24	<7
C-ANCA	Negative	NA
P-ANCA	Negative	NA
C3, g/L	1.67	0.90-1.80
C4, g/L	0.26	0.10-0.40
Hepatitis B	Negative	NA
Hepatitis C	Negative	NA
HIV	Negative	NA
Rheumatoid factor, KUI/L	<10	0-15
Serum protein electrophoresis And immunofixation	Normal	
Serum free light chain ratio	1.50	0.26-1.65
Urine analysis	NA	NA
Red blood cell/hpf	4-10	0-3
White blood cell/hpf	>50	0-4
Bacteria	Presence	Absence
Proteinuria, g/24 h	0.845	<0.150

Abbreviations: Anti-GBM, anti-glomerular basement membrane disease; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; DsDNA, double-stranded DNA.

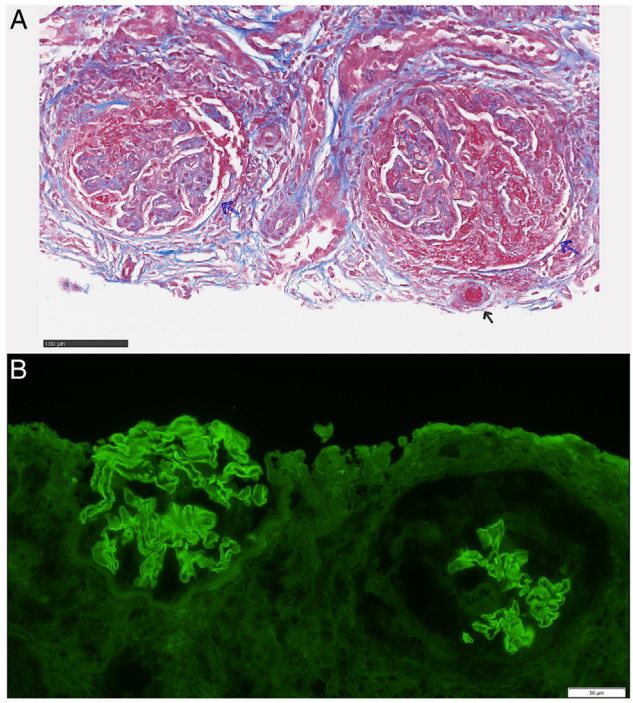

Figure 1. Kidney biopsy. (A) The upper panel (Masson's Trichrome stain) shows glomeruli with fibrin-rich cellular crescents (blue arrows) and fibrinoid material in the lumen of a periglomerular arteriole (black arrow). (B) The lower panel shows immunoglobulin G immunofluorescence with linear glomerular basement membrane staining.

abundant fibrinoid necrosis. Fibrinoid material even extended to the lumen of 5 periglomerular arterioles. There were numerous red blood cell casts, mild-to-moderate acute tubular injury, and moderate-to-severe tubulointerstitial inflammation (lymphoplasmacytic with eosinophils and neutrophils). Tubular atrophy and interstitial fibrosis were moderate. Immunofluorescence showed moderate linear polytypic (λ > κ) diffuse and global glomerular basement membrane staining for IgG (IgG2 > IgG3 subclass). Weak staining of glomerular basement membranes in the same distribution was also observed for IgM, IgA, and albumin. There was mild-segmental mesangial and peripheral granular staining for C3. The pathologic findings and the positive serum anti-GBM antibody test were consistent with anti-GBM glomerulonephritis. A cellular crescent was found in one of the 2 glomeruli examined under the electron microscope, with signs of basement membrane rupture in both glomeruli. Multifocal glomerular basement membrane thinning was also noted, but the distribution of the α5 chain of collagen IV was normal by immunofluorescence.

On day 7, the plasma exchange was started, along with pulse methylprednisolone (1.1 g for days 7-9) and cyclophosphamide (150 mg oral daily × 3 days and 75 mg oral daily). Oral prednisone (60 mg daily) was resumed after pulse methylprednisolone, but the kidney function worsened within a few days. A renal MAG-3 scan showed poor kidney perfusion and severe parenchymal dysfunction without any urine production, suggesting a poor prognosis. Hemodialysis was then started. Two weeks later, the patient reported flank pain and fever; piperacillin-tazobactam was then initiated for suspected pyelonephritis. Because there were no signs of improvement in kidney function, plasma exchange and immunosuppression were stopped by the fourth week of hospitalization. Hemodialysis was later discontinued when the patient and her family wished for comfort measures.

DISCUSSION

In this article, we present a case of anti-GBM glomerulonephritis that was likely induced by pembrolizumab. Although there is no clear association in the literature, 6 case reports describe similar presentations after checkpoint inhibitor therapy (Table 2).[2-7] However, 2 cases presented with atypical anti-GBM glomerulonephritis with no detectable serum anti-GBM antibodies and few crescents on kidney biopsy.[5,6] In our case, despite anti-GBM antibodies being positive, the titer (24 U/mL) was lower than expected with such an extensive disease on kidney biopsy (65% crescents). Although in classical anti-GBM glomerulonephritis

Table 2. Summary of Case Reports of Checkpoint Inhibitors Induced Anti-GBM Glomerulonephritis

	Sammartino et al,[2] (2010)	Takahashi et al,[3] (2018)	Hultin et al,[4] (2020)	Kyriazis et al,[5] (2021)	Javaugue et al,[6] (2022)	Tani et al,[7] (2022)	Present case
N of patients	1	1	1	1	1	1	1
Age, y	50	74	NA	58	74	74	65
Sex	M	M	M	M	M	M	F
Type of cancer	Melanoma	Lung adenocarcinoma	Melanoma	Melanoma	Lung squamous cell carcinoma	Non–small cell lung cancer	Cervical squamous cell carcinoma
Checkpoint inhibitor therapy	Tremelimumab	Nivolumab	Ipilimumab + nivolumab	Ipilimumab + nivolumab	Pembrolizumab	Nivolumab	Pembrolizumab
Checkpoint inhibitor's target	Anti-CTLA-4	Anti-PD-1	Anti-CTLA-4 + Anti-PD-1	Anti-CTLA-4 + Anti-PD-1	Anti-PD-1	Anti-PD-1	Anti-PD-1
Onset of AKI after CI initiation, mo	13.5	4	12	16	2	3	3
Creatinine at presentation, mg/Dl	3.3	1.98	15.6	2.4	5.6	2.97	3.07
Hematuria	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Proteinuria	NA	2+ dipstick	NA	2 g/g	12 g/d	0.78 g/g	0.845 g/d
Anti-GBM antibody	>200 U/mL	>350 U/mL	614	Negative	Negative	>350 IU/L	24 U/mL
ANCA	Negative	NA	NA	Negative	Negative	1 EU	Negative
Pulmonary hemorrhage	No	Yes	NA	No	No	No	No
Kidney Biopsy							
% Crescents	71	NA	>95	13	23	NA	65
% Global sclerosis	6	NA	NA	0	45	NA	4
IgG subclass predominance	NA	NA	NA	NA	IgG2	IgG1	IgG2
Treatment	Plasma exchange steroids cyclophosphamide	Plasma exchange steroids	Plasma exchange steroids cyclophosphamide	Steroids cyclophosphamide	Plasma exchange rituximab	Plasma exchange steroids cyclophosphamide	Plasma exchange steroids cyclophosphamide
Outcome	Kidney failure	Kidney failure, death because of respiratory failure	Partial response with persistent CKD stage 4	Partial response with a relapse of kidney failure after reinitiation of nivolumab	Kidney failure	Kidney failure, death after respiratory failure because of cytomegalovirus pneumonia	Kidney failure

Abbreviation: Anti-GBM, anti-glomerular basement membrane disease; ANCA, antineutrophil cytoplasmic antibody; AKI, acute kidney injury; Anti-CTLA-4, anti-cytotoxic T-lymphocyte–associated antigen 4; anti-PD-1, anti-programmed cell death protein 1; CKD, chronic kidney disease; NA, not available.

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there is predominance of IgG1 or IgG4+, our case showed a predominance of IgG2 in glomerular basement membrane immunofluorescence staining. This observation is similar to the case reported by Javaugue et al,[6] suggesting that the IgG subclass might be useful in differentiating these 2 entities.

In the present case, the glomerulonephritis occurred after 4 months of pembrolizumab introduction. The onset of the disease after checkpoint inhibitor initiation varied in case reports between 2 and 16 months, with a median time of 3 months.[3]

The pathophysiology of checkpoint inhibitor-induced anti-GBM glomerulonephritis is not fully understood. We know that anti-GBM glomerulonephritis is caused by autoantibodies mainly directed against the noncollagenous1 domain of the α3 chains of type IV collagen, a gene found in basement membrane collagen.[6] However, in many patients, serum antibody titers failed to correlate with the severity of the disease, suggesting that there may be another mechanism involved in the pathogenesis of anti-GBM glomerulonephritis. Growing data suggest that autoreactive T cells may also contribute to the inflammatory state. In fact, experimental transfer of antigen-specific autoreactive T cells to naïve rats has been shown to induce glomerulonephritis.[8] By contrast, regulatory T cells are believed to play a protective role by inhibiting the autoimmune response. This was tested in animal models with anti-GBM glomerulonephritis, in which the transfer of regulatory T cells reduced glomerular damage and decreased $CD4^+$ T cell, $CD8^+$ T cell, and macrophage infiltration.[9] Checkpoint inhibitors, through different mechanisms, stimulate the immune system to fight cancerous cells and alter the regulatory T cells function. This leads to the loss of immune homeostasis and promotes autoimmunity against, among others, GBM antigens. Concurrently with the glomerulonephritis, our case also reported a moderate-to-severe acute tubulointerstitial inflammation, a typical finding in patients treated with checkpoint inhibitors.[10]

The standard treatment for idiopathic anti-GBM disease, as per Kidney Disease: Improving Global Outcomes 2021 recommendations, includes plasma exchange for 2-3 weeks until anti-GBM titers are no longer detectable, glucocorticoids, and cyclophosphamide.[11] Because checkpoint inhibitors induced anti-GBM disease is very rare, there are no official recommendations concerning this entity. The actual practice follows the same treatment approach as for idiopathic anti-GBM disease when there are typical findings, such as crescentic glomerulonephritis in biopsy and high serum anti-GBM titers, in addition to suspending the offending immunotherapy agent. In this case, despite the early and comprehensive treatment, kidney function kept worsening until kidney failure, a predominant outcome as noted in 6 of the 7 known anti-GBM post checkpoint inhibitors cases (Table 2).[2-7] This suggests that either checkpoint inhibitors induced anti-GBM disease has a worse outcome than the idiopathic form or that the current therapeutic strategies may not be sufficient in managing the extent of inflammation.

There are also some confounding factors that should be considered. First, anti-GBM glomerulonephritis has rarely been described as a paraneoplastic disease, but in the reported cases, serum antineutrophil cytoplasmic antibody levels are positive.[12,13] Second, there has been a case report of anti-GBM glomerulonephritis associated with nintedanib,[14] but not with bevacizumab. Whereas nintedanib is a small molecule that targets vascular endothelial growth factor receptors-1,2,3, platelet-derived growth factor receptors-α/β, and fibroblast growth factor receptors-1,2,3 pathways, bevacizumab is a recombinant humanized monoclonal antibody that binds to vascular endothelial growth factor-A.[15,16] Given the timing of the AKI and the extent of interstitial nephritis, we believe that pembrolizumab is the most likely culprit in the present case report.

In conclusion, checkpoint inhibitors are mostly known to induce acute interstitial nephritis, but growing data report a range of glomerulonephritis after this therapy, such as anti-GBM disease. Routine urinary sedimentation is recommended to help raise suspicion for this morbid disease and allow for early biopsy and management, particularly for patients who do not improve with empirical steroids.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Nidal El Yamani, MD, MSc, Gabrielle Cote, MD, Julie Riopel, MD, Nicolas Marcoux, MD, Fabrice Mac-Way, MD, David Philibert, MD, Mohsen Agharazii, MD

Authors' Affiliations: CHU de Québec Research Center- L'Hôtel-Dieu de Québec Hospital, Québec City, Québec, Canada (NEY, FMW, MA); Division of Nephrology, Department of Medicine (GC, MA, DP), Division of Pathology, Department of Molecular Biology, Medical Biology and Pathology, (JR), and Division of Hematology and Oncology, Department of Medicine, Faculty of Medicine (NM), Université Laval, Québec City, Québec, Canada.

Address for Correspondence: Address to Mohsen Agharazii, MD, CHU de Québec Research Center–L'Hôtel-Dieu de Québec Hospital, 11, Côte du Palais, Québec, Quebec, Canada, G1R 2J6. Email: Mohsen.Agharazii@crchudequebec.ulaval.ca

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