Concomitant Anti-GBM Glomerulonephritis and Acute Interstitial Nephritis Following Programmed Death Receptor-1 Blockade With Nivolumab

To the Editor: We report a case of necrotic crescentic glomerulonephritis (GN) and tubular interstitial nephritis (TIN) with antiglomerular basement membrane (GBM) antibodies following immune checkpoint inhibitor, nivolumab, administration.

A 74-year-old man was diagnosed with stage IB nonsmall cell lung cancer and underwent surgery 4 years prior to admission, followed by recurrence after 3 years. Nivolumab (3.75 mg/kg) was administrated for a total of 6 cycles over 3 months. The patient presented with general fatigue, fever, microscopic hematuria, and renal function decline with elevated anti-GBM antibody levels (>350 IU/l) (Supplementary Table S1).

Renal biopsy revealed diffuse necrotizing crescentic GN with linear deposition of IgG (IgG1 > IgG3) and C3 along the GBM and concomitant acute TIN (Figure 1a–f, Supplementary Figure S1 and S2). Immunosuppressive therapy was initiated with intravenous methylprednisolone (1000 mg/day) for 3 days, followed by daily doses of prednisolone (60 mg), intravenous cyclophosphamide pulse (500 mg), and plasmapheresis. Despite therapy, the patient developed end-stage kidney disease and needed maintenance hemodialysis. Despite treatment, the patient died of cytomegalovirus pneumonia on the fifty-fifth day of hospitalization.

As previously reported in immune checkpoint inhibitor-associated GN, including anti-GBM GN,[1–4, S1–S4] (Supplementary Table S2), concomitant TIN was observed in our case. Anti-GBM GN itself is known to cause TIN due to the presence of antibodies against collagen IVα3 on the distal tubular basement membrane, in which neutrophils and predominantly CD4 lymphocyte infiltrations are mainly observed.[5] In this case, mononuclear cells and eosinophils were observed, with predominantly CD8 lymphocytes colocalized with CD20-positive B cells and CD68-positive macrophages in the tubulointerstitial lesion (Figure 1e–j). Therefore, TIN, in this case, was considered drug-induced nephropathy due to nivolumab rather than a complication of idiopathic anti-GBM GN itself. Immune checkpoint inhibitor-associated anti-GBM GN is rare, and only 4 cases have previously been reported (cases 1–4 in Supplementary Table S2),[2,S1–S3]. There are also 2 cases of atypical anti-GBM GN without circulating anti-GBM antibody (cases 5–6 in Supplementary Table S2).[4,S4] In such cases, the renal outcome and mortality rate seemed worse than typical immune checkpoint inhibitor-related acute TIN without GN, despite more aggressive treatments in cases of immune checkpoint inhibitor-associated anti-GBM GN.[1-3, S1–S3]

PATIENT CONSENT

Consent was received from the patient.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

Supplementary Article Text.

Figure S1. Immunofluorescence staining of glomeruli reveals linear deposition of IgG and C3 along the glomerular basement membrane (GBM).

Figure S2. Immunofluorescence staining of glomeruli reveals polyclonal deposition of IgG1 and IgG3 along the glomerular basement membrane (GBM) with a linear pattern.

Table S1. Initial laboratory data and urinalysis at presentation.

Table S2. Clinical features of patients with immune checkpoint inhibitors (ICPis)-associated antiglomerular basement membrane (GBM) nephritis.

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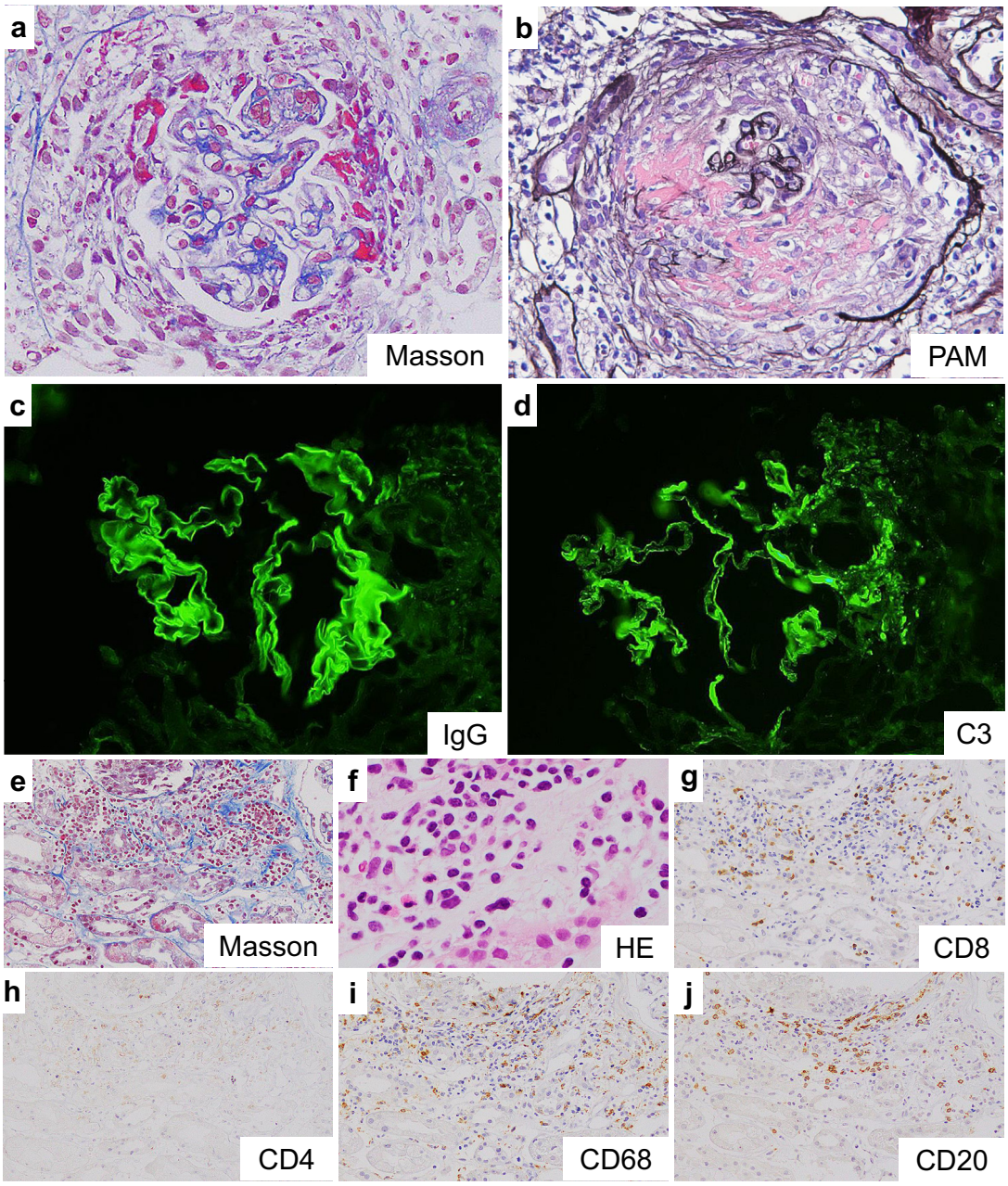

Figure 1. Kidney biopsy findings reveal necrotizing crescentic glomerulonephritis with linear IgG and C3 distribution along the GBM and TIN with infiltration of inflammatory cells. (a,b) Glomerulus revealed diffuse necrotizing crescentic glomerulonephritis characterized by cellular crescents with GBM ruptures and fibrin deposition (a, Masson stain; b, PAM stain, 400x). (c,d) Immunofluorescence of the glomeruli staining for IgG and C3 reveals linear distribution along the GBM (FITC, 400x). (e, f) TIN with interstitial infiltrating inflammatory cells, mainly eosinophils and mononuclear cells, was noted. (e, Masson stain, 100x; f, HE stain, 400x) (g–j) CD4-positive and CD8-positive lymphocytes (CD8>CD4) were colocalized with CD20-positive B cells and CD68-positive macrophages in the tubule stroma, which indicates that both T cells and B cells played a role. Immunohistochemical staining, 100x. GBM, glomerular basement membrane; HE, hematoxylin and eosin; Masson, Masson's trichrome; PAM, periodic acid-methenamine-silver; TIN, tubulointerstitial nephritis; Masson, Masson's trichrome.

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