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【 CASE REPORT 】

Overlap of Thrombotic Microangiopathy and Mesangial Proliferative Glomerulonephritis Caused by Combination Therapy with Atezolizumab and Bevacizumab

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Abstract:

Vascular endothelial growth factor inhibitors and checkpoint inhibitors are effective treatments for solid tumors. These new classes of anti-cancer agents frequently cause kidney-related side effects. Although their anti-cancer effects may be enhanced when used in combination, the severity of their kidney-related side effects is unknown. We herein report the first case of thrombotic microangiopathy and mesangial proliferative glomerulonephritis caused by combined treatment with atezolizumab and bevacizumab in a 74-year-old man with hepatocellular carcinoma. The combination therapy was discontinued and replaced with intravenous methylprednisolone followed by oral prednisolone. Subsequently, the urinary protein excretion levels declined.

Key words: anti-VEGF inhibitor, atezolizumab, bevacizumab, checkpoint inhibitor, mesangial proliferative glomerulonephritis, thrombotic microangiopathy

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Introduction

Anti-vascular endothelial growth factor inhibitors and checkpoint inhibitors are effective in treating solid tumors. Although their anti-cancer effects may be enhanced when used in combination, these new classes of anti-cancer agents frequently cause kidney-related side effects, the severity of which remains unknown.

We herein report the first case of thrombotic microangiopathy (TMA) and mesangial proliferative glomerulonephritis (MsPGN) caused by combination therapy with atezolizumab and bevacizumab.

Case Report

A 74-year-old man with a 5-year history of hepatocellular carcinoma (HCC) presented with progressive proteinuria. He received several treatments of transarterial chemoembolization but experienced repeated HCC recurrence. Combination therapy with atezolizumab and bevacizumab was initiated; 1 month later, it led to massive proteinuria with microhematuria [20 red blood cells (RBCs)/high-power field (HPF); normal range, <5 RBCs/HPF].

A physical examination revealed pretibial edema. Laboratory tests showed that the serum creatinine (SCr) level was elevated from 0.98 mg/dL (baseline SCr at 6 months before) to 1.81 mg/dL (normal range, 0.65-1.07 mg/dL), whereas serum albumin levels were as low as 2.5 g/dL (normal range, 4.1-5.1 g/dL). CH50, C3, and C4 levels were 60.0 U/mL (normal range, 31.6 U/mL), 131.5 mg/dL (normal range, 73-138 mg/dL), and 34.7 mg/dL (normal range, 11-31 mg/dL), respectively. The results of serological testing, including tests for antinuclear, anti-ds-DNA, anti-SSA, anti-SSB, anti-RNP, and anti-Sm antibodies, were all negative. HCV antibody was positive, but all other infectious diseases tested

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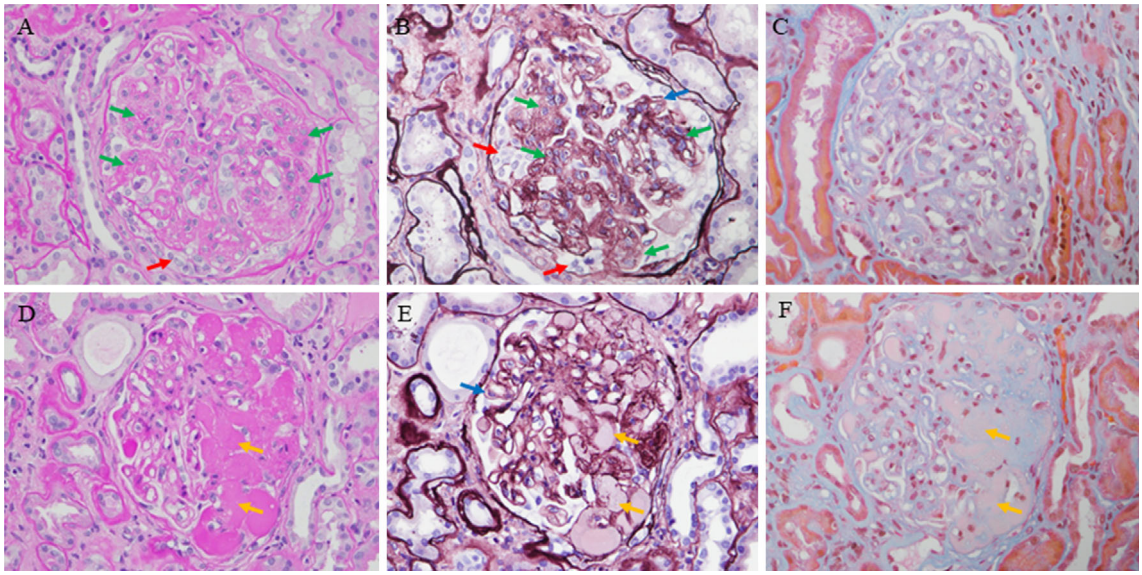

Figure 1. **Findings on light microscopy of renal biopsy specimens. Light microscopy findings revealed fibrin thrombi (yellow arrows) in the glomerular capillaries, endothelial swelling (blue arrows), mesangial proliferation (green arrows), and cellular crescent formation (red arrows) (A, D: periodic acid Schiff stain; B, E: periodic acid methenamine-silver stain; C, F: Masson's trichrome stain; original magnification, ×200).**

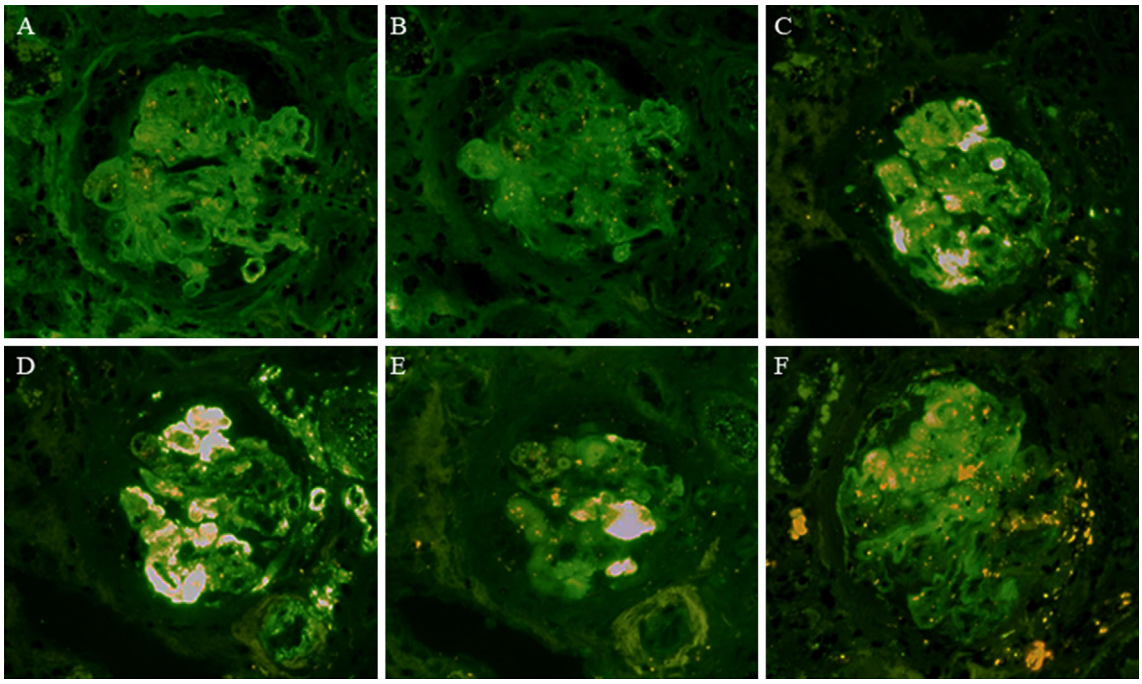

Figure 2. **Findings of immunofluorescence staining of renal biopsy specimens. Immunofluorescence staining showed deposits of IgM, C3, and C4 in the glomerular vessels and mesangial area and no deposition of IgG, IgA, or C1q (A: IgG; B: IgA; C: IgM; D: C3; E: C4; F: C1q; original magnification, ×200).**

negative. IgG, IgA, and IgM levels were 843 mg/dL (normal range, 861-1,747 mg/dL), 230 mg/dL (normal range, 93-393 mg/dL), and 38 mg/dL (normal range, 33-183 mg/dL), respectively. Cryoglobulinemia was negative. Urinary protein excretion was 10.5 g/gCr (normal range, <0.3 g/gCr).

A renal biopsy revealed fibrin thrombi in the glomerular capillaries, endothelial swelling, mesangial proliferation, and cellular crescent formation (Fig. 1). Immunofluorescence staining showed deposits of IgM, C3, and C4 in the glomerular vessels and mesangial area, with no deposits of IgG, IgA, and C1q (Fig. 2). Electron microscopy revealed electron-dense deposits in the subendothelial area of the

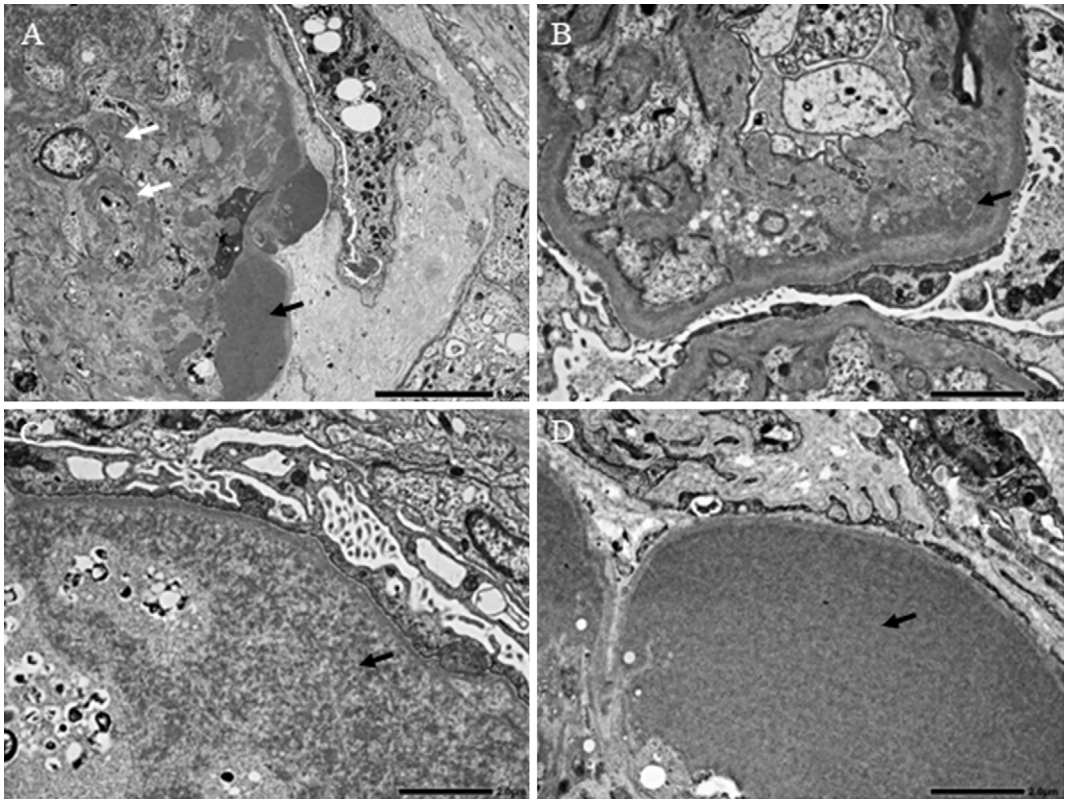

Figure 3. **Findings on electron microscopy of renal biopsy specimens. Electron microscopy revealed electron-dense deposits in the subendothelial area of the glomerular vessel wall (black arrows) and mesangial area (white arrows) (Original magnification, A: ×2,000; B-D: ×5,000).**

glomerular vessel wall and mesangial area (Fig. 3). Based on the above findings, the patient was diagnosed with TMA and MsPGN caused by combined treatment with atezolizumab and bevacizumab.

The combination therapy was discontinued, and intravenous methylprednisolone (1 g/day for 3 days) was initiated, followed by oral prednisolone (30 mg/day). His symptoms and microhematuria improved (<5 RBCs/HPF), and the SCr level and proteinuria decreased to 1.31 mg/dL and 2.7 g/day, respectively; however, these changes did not result in complete remission.

Discussion

Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, is an anti-cancer drug that blocks the activation of VEGF receptors that promote angiogenesis (1). VEGF is indispensable for the proliferation, differentiation, and survival of mesangial and endothelial cells (2). Local, continuous VEGF production by podocytes is necessary for the functioning of the adult glomerular filtration barrier (2). The use of VEGF inhibitors increases the incidence of proteinuria (3). According to pathological findings, TMA is the main type of renal damage caused by VEGF inhibitors (3).

Atezolizumab is a checkpoint inhibitor, a new class of anti-cancer drugs that has recently gained therapeutic prominence. Checkpoint inhibitors are humanized antibodies that inhibit down-regulatory receptors on T cells; therefore, they are known to cause immune-related adverse events (irAEs). Kidney irAEs are now widely understood, with their incidence ranging from 2-5% (4). Most of the initial studies on kidney irAEs focused on acute interstitial nephritis (4). However, a small number of cases of glomerulonephritis have also been reported (5). In our case study, renal TMA and MsPGN with immune deposits in the mesangial region to the subendothelial area of glomerular vessels were observed. In patients treated with bevacizumab, TMA is often found, but MsPGN is rare. Therefore, it was suspected that both of these side-effects were observed because of the atezolizumab treatment.

In the future, we suspect that the pathophysiology of renal damage will become more complicated with the use of multiple new classes of medications in combination. Clinicians should make appropriate diagnoses and treat renal disorders based on a thorough understanding of the mechanisms of action of drugs and their effects on pathological conditions.

The authors state that they have no Conflict of Interest (COI).

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