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【 CASE REPORT 】

IgA Vasculitis Developed as an Adverse Effect of Tofacitinib Taken for Rheumatoid Arthritis

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Abstract:
Tofacitinib is a new small-molecule inhibitor of the JAK/STAT signaling pathway used to treat rheumatoid arthritis. We herein report a case of IgA vasculitis apparently caused by tofacitinib. A 67-year-old woman with rheumatoid arthritis developed IgA vasculitis after taking tofacitinib for 6 months. She presented with proteinuria and purpura of the lower extremities. Biopsy specimens from her skin and kidney were compatible with IgA vasculitis. Following termination of tofacitinib, the patient completely recovered from the IgA vasculitis. Drug-induced IgA vasculitis has been previously described for anti-tumor necrosis factor-(TNF)α therapies, but this is the first report of this adverse effect with anti-JAK therapy.

Key words: IgA vasculitis, tofacitinib, JAK inhibitor, rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease. A wide range of inflammatory cytokines are involved in the pathogenesis of RA, many of which are involved in the tumor necrosis factor (TNF)-α and/or JAK/STAT signaling pathways (1, 2). Treatments targeting these inflammatory mediators (e.g., TNFα inhibitors) are now widely used in the treatment of RA. However, various adverse events, including nephropathy, have been reported with these drugs.

Nephropathy is a common extra-articular complication of RA itself, appearing as mesangial proliferative glomerulonephritis (most often caused by IgA nephropathy), membranous nephropathy, renal amyloidosis, malignant rheumatoid arthritis, ANCA-associated vasculitis, or thin basement membrane disease. In addition, nephrotoxicity is a major side effect of the nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARDs) used to treat RA. NSAIDs cause tubulointerstitial nephritis, while the DMARDs methotrexate, bucillamine, penicillamine, gold salts, and lobenzarit disodium can cause tubular obstruction, membranous nephropathy, and interstitial nephritis. In addition, biologics such as TNFα, interleukin-6, and CD80/86 inhibitors can reportedly cause proliferative glomerulonephritis or crescentic glomerulonephritis.

A new group of synthetic inhibitory small molecules targeting JAK tyrosine kinase is reported to be as effective as biologics against RA. Among these, tofacitinib is available for oral administration. We herein report for the first time a case of IgA vasculitis arising as an adverse effect of the JAK inhibitor tofacitinib.

Case Report

A 67-year-old woman was admitted to our hospital with proteinuria and purpura of the lower extremities that had developed 2 weeks earlier. Her medical history included a diagnosis of RA, which had manifested as ankle pain when the patient was 51 years of age. There was no prior infection associated with this nephritis. In the previous year, the patient had also received methotrexate and NSAIDs, and in the distant past, she had received prednisolone, bucillamine, slazosulfapyridine, infliximab, and golimumab, all without any side effects. She had been taking tofacitinib for six

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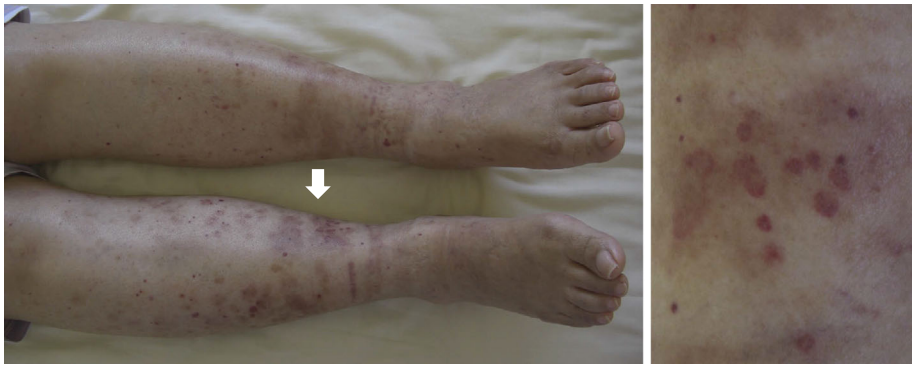

Figure 1. **Macroscopic findings of purpura on both lower extremities. The right panel shows a closer view of the lesion indicated by the arrow in the left panel.**

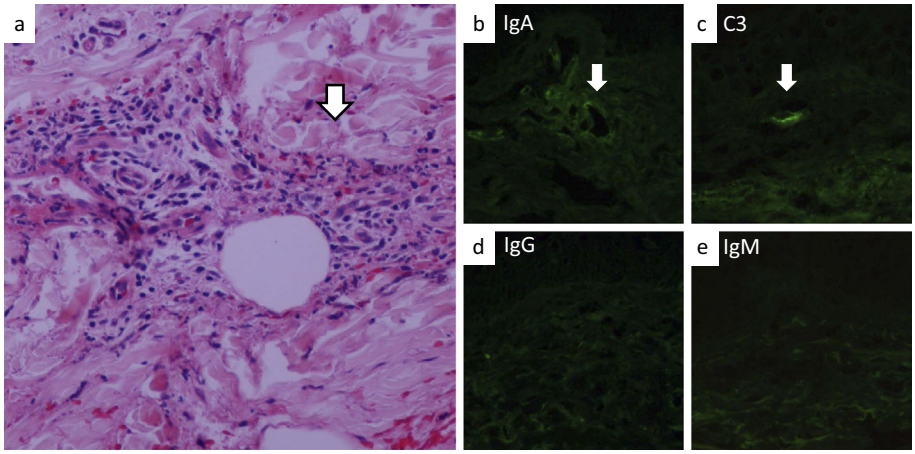

Figure 2. **Histology of the skin biopsy specimen showing IgA vasculitis. (a) Hematoxylin and eosin-stained section showing leukocytoclastic vasculitis. The arrow indicates inflammatory cells infiltrating around the blood vessels (original magnification, 200×). (b-e) Immunofluorescence images showing superficial dermal vascular deposition of IgA (b) and C3 (c). Arrows indicate positive lesions around the vessel. Staining for both IgG (d) and IgM (e) as controls was negative.**

months prior to the development of the proteinuria.

At the time of her first visit, other medications being taken included famotidine, amlodipine besilate, and pregabalin. However, drug lymphocyte stimulation tests (DLSTs) for tofacitinib, amlodipine besilate, and pregabalin were all negative. A physical examination revealed purpura and edema of the lower extremities and ankle pain (Fig. 1). Regarding the laboratory data, the rheumatoid factor level was 45.3 IU/mL (normal, <15). A urinalysis revealed massive and continuous proteinuria (18.89 g/gCre), and 24-h urine collection contained 8 g of protein with hematuria [30-49 RBCs per high-power field (HPF)] and numerous granular casts. The selectivity index indicated low selectivity (0.24). Despite the massive proteinuria, the levels of serum albumin (3.2 g/dL), total protein (6.2 g/dL), and total cholesterol (281 mg/dL) did not meet the diagnostic criteria for nephrotic syndrome. The serum IgA level was 466 mg/dL (normal, 90-400 mg/dL), which was compatible with IgA vasculitis. Collagen diseases other than IgA vasculitis were excluded based on the serologic results. The levels of complements (Cs) were nearly within the normal range: C3, 116 mg/dL (normal, 80-140); C4, 28 mg/dL (normal, 11-34); and CH50, 46 U/mL (normal, 30-45). Anti-nuclear antibodies, PR3-antineutrophilic antibodies (ANCA), and MPO-ANCA were all negative. The serum amyloid A level was 5.9 μg/mL (normal, 0-10.0 μg/mL). Serum cryoglobulin was negative, as was Bence Jones Protein. Liver enzymes were elevated due to fatty liver. Upper and lower gastrointestinal endoscopy and computed tomography (CT) revealed no evidence of a malignant tumor. In a skin biopsy specimen, leukocytoclastic vasculitis was observed in the upper dermis (Fig. 2a), and immunofluorescence studies revealed IgA and C3 deposition (Fig. 2b, c), which were not considered non-specific staining, since IgG and IgM were negative in the same specimen (Fig. 2d, e).

In response to those findings, tofacitinib was discontinued, and a renal biopsy was performed on the patient's first hospital day. Because of the sustained massive proteinuria, oral prednisolone 50 mg/day and additional intravenous methylprednisolone pulse therapy (500 mg/day×3) were initiated before the renal biopsy report was received. Prednisolone was tapered by 10 mg every 2-4 weeks. In the renal bi-

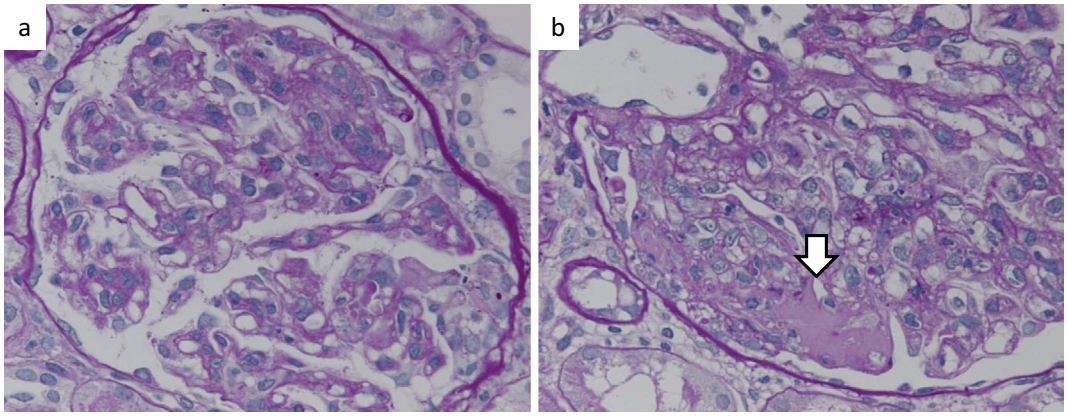

Figure 3. **Histology of the renal biopsy specimen. (a) Photomicrograph of a periodic acid-Schiff-stained section showing cellular crescents with segmental endocapillary proliferation (original magnification, 400×). (b) Photomicrograph providing a closer view of a periodic acid-Schiff-stained section (original magnification, 400×). The arrow indicates an area showing fibrinoid necrosis of the glomerular tuft.**

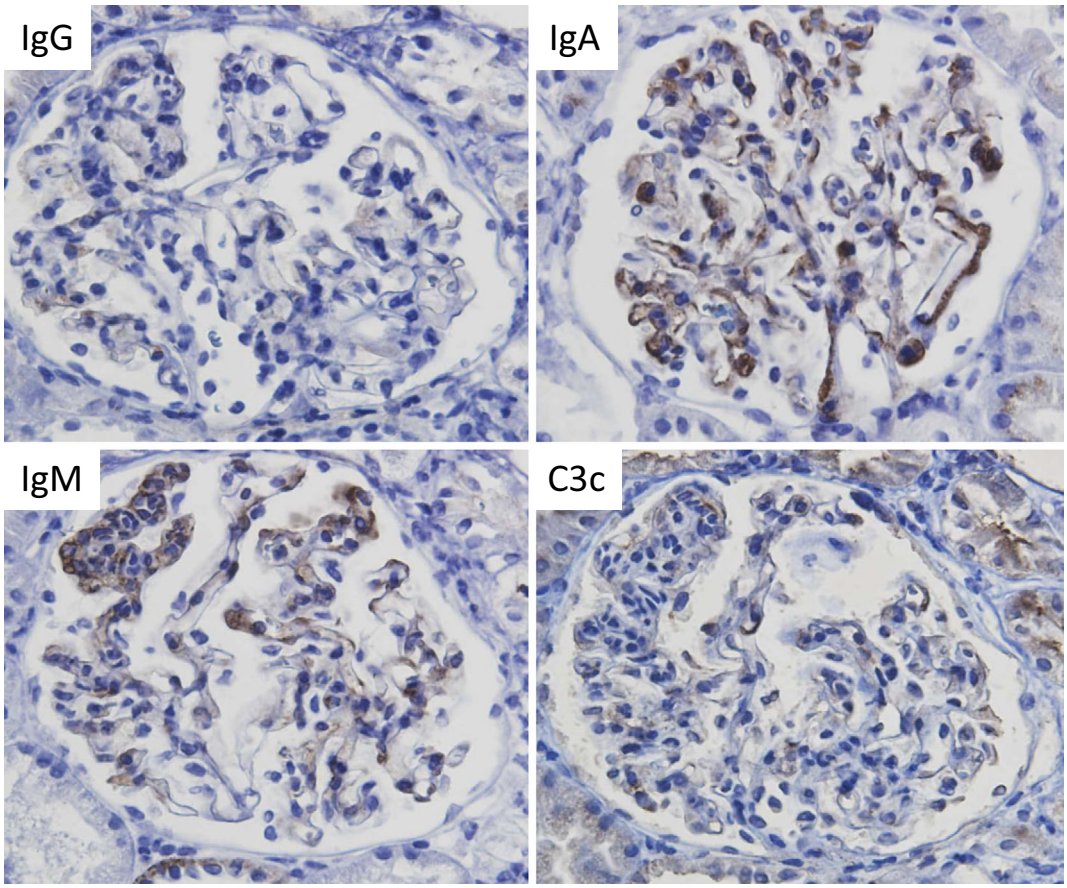

Figure 4. **Immunohistochemistry of the renal biopsy specimen. Shown are photomicrographs stained with polyclonal antibodies against IgG, IgA, IgM and C3c. Positive staining for IgA and IgM was observed in the glomerular mesangium (original magnification, 400×).**

opsy, the pathological findings were compatible with IgA vasculitis. Under light microscopy, 3 of 41 glomeruli showed global sclerosis. Most glomeruli in the most serious lesion in the specimen exhibited endocapillary proliferation (Fig. 3). Cellular crescents were observed in five glomeruli. There were no granulomas or active interstitial inflammation. No features of amyloidosis were noted. Immunohistochemistry showed a granular pattern for IgA, IgM, and C3c in the mesangium (Fig. 4). Electron microscopy revealed electron-dense deposits in the mesangial, paramesangial, and subendothelial areas (Fig. 5).

Given the proteinuria and renal biopsy results showing

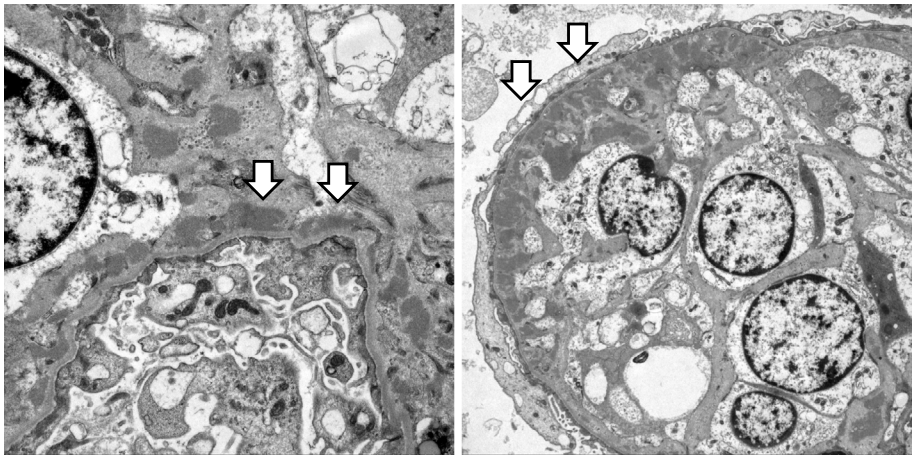

Figure 5. Electron micrographs of the renal biopsy specimen. Dense deposits were observed in mesangial, paramesangial, and subendothelial lesions (arrows).

cellular crescent formation, a second round of methylprednisolone pulse therapy was added on the 51st hospital day. These treatments successfully reduced the proteinuria to less than 1 g/day by the 61st hospital day. The patient was discharged on the 74th hospital day and was prescribed oral prednisolone at a dose of 30 mg/day. Because she achieved complete remission of her proteinuria and showed a psychiatric side effect, prednisolone was tapered off in the outpatient department beginning on day 284 (i.e., after 9 months and 11 days). Since then, the patient has had no recurrence of the proteinuria, and her serum IgA level has decreased to 211 mg/dL. Because this patient has remained in remission since the discontinuation of tofacitinib, ethical considerations have precluded re-challenging this patient.

Discussion

Glomerular diseases are frequently noted in RA patients receiving biological drug therapy. For example, Piga et al. reported 29 patients with glomerulonephritis during treatment with biologics. The biologics most frequently associated with glomerulonephritis are TNFα inhibitors, including Etanercept (15 cases), Adalimumab (9 cases), and Infiximab (3 cases); interleukin (IL)-6 receptor antagonists, including Tocizumab (1 case); and the selective T-cell costimulation modulator Abatacept (1 case). More than 90% of these nephrotoxic biologics are TNFα inhibitors. The most frequent histopathological finding in these glomerulonephritis cases is mesangial proliferative nephritis (41%), which is IgA vasculitis or IgA nephropathy in half of cases (3). Glomerulonephritis induced by a JAK inhibitor has not been reported before, and our case is the first report of a JAK inhibitor inducing IgA vasculitis.

Tofacitinib is a JAK inhibitor that suppresses multiple signaling molecules involved in RA, including interferon-α and IL-6. Tofacitinib is not a biologic but a targeted synthetic small molecule. Unlike biologics, which target individual extracellular mediators, such as soluble cytokines, cytokine receptors, or other cell surface receptors, tofacitinib works intracellularly to inhibit multiple cytokines, thereby suppressing inflammation to a degree similar to biologics (4, 5).

The mechanism by which TNFα inhibitors or tofacitinib causes nephritis is unknown. An earlier paper described the beneficial effects of tofacitinib against IgA nephropathy (6). Conversely, tofacitinib induced IgA vasculitis in our case. This suggests that while some biologics may be used to effectively treat systemic vasculitis, the same drug paradoxically causes development of vasculitis in other patients. The negative DLST result for tofacitinib in our case suggests this IgA vasculitis is not an adverse effect induced by an allergic reaction. More likely it reflects molecular signaling related to the TNF pathway. Regarding the onset of glomerulonephritis, including IgA nephropathy, the balance between Th1-type and Th2-type immune responses is thought to greatly affect the glomerulonephritis phenotype (7). Furthermore, differences in the effects of TNFα inhibitors are reportedly due to differences in sensitivity to individual drugs, which reflect the patients' genetic predisposition (8). Tofacitinib suppresses various cytokines, thereby disturbing the Th1/Th2 balance. Consequently, tofacitinib may be therapeutic in one person but induce nephritis in another.

Both TNF inhibitors and tofacitinib may cause nephritis through the same mechanism. TNFα inhibitors suppress the TNF signaling pathway, which includes p38MAPK, NF-kB, JNK, and/or caspases, whereas tofacitinib suppresses JAK/STAT, which is activated by extracellular interleukins and acts directly as a nuclear transcriptional factor. Although there does not appear to be a direct association between the TNFα pathway and JAK/STAT, the type 1 TNF receptor (TNFR1) is reported to directly interact with JAK kinase to form a signaling complex, which suggests that TNF activates a JAK/STAT signal transduction cascade via TNFR 1 (9). Thus, TNF blockers likely affect the same intracellular signaling pathway as JAK inhibitors, including tofacitinib. In the present case, therefore, JAK inhibition-induced IgA vasculitis may have been caused by direct interaction between

TNFR1 and JAK/STAT. This means that reported cases of IgA vasculitis induced by TNFα blockade may also be caused by the interaction of TNFR1 and JAK/STAT.

More than half of the incidents of nephritis mentioned above appeared within 12 months of beginning treatment (3, 10), and most were resolved within 1 year after the termination of the responsible drug (8, 10, 11). In the present case, IgA vasculitis developed 6 months after the patient started taking tofacitinib, and complete remission was achieved after 9 months and 11 days through termination of the drug, which suggests a clinical course similar to that reported for drug-induced glomerulonephritis. Secondary IgA vasculitis has been reported in patients with malignancies or infections and in those taking nivolumab, cilostazol, vancomycin, carbamazepine, ceftriaxone, cyclosporine, or metronidazole (12-14). However, our patient had no malignancy or infection and was not taking any of the aforementioned drugs. Serological and renal biopsy results were negative for ANCA-associated vasculitis and amyloidosis. Malignant RA was excluded based on the low titer of rheumatoid factor. We therefore conclude that our patient's IgA vasculitis is attributable to tofacitinib, as there was no other clear trigger. The patterns of IgA staining and deposition of the dense deposit were unique in our case. Immune complex deposits were detected within capillary areas as well as mesangial areas, which may be a characteristic feature of this drug-induced nephritis. Because this is the first report of tofacitinib-induced nephritis and there are few case reports that include electron microscopic analyses, future reports of such cases are awaited.

JAK inhibitors are expected to become a common treatment for RA, especially for patients who have difficulty with injections or do not respond to conventional anti-TNFα drugs. When administering a JAK inhibitor, a regular urinalysis should be performed in order to promptly detect the occurrence of glomerulonephritis. Once an adverse effect is suspected, the JAK inhibitor should be stopped or switched to another medication as soon as possible.

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

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