Severe lupus induced by the tumor necrosis factor-alpha inhibitor Anbainuo: a case report

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Abstract
In rare cases, clinical inhibitors of the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) can induce symptoms of lupus erythematosus (drug-induced lupus, DIL), but this adverse response usually resolves rapidly upon drug withdrawal. We report the case of a 25-year-old Asian woman with rheumatoid arthritis exhibiting severe prolonged DIL even after the termination of TNF-α inhibitor treatment. The patient had been treated intermittently using Traditional Chinese Medicine for 11 years, but this therapy failed to effectively control her clinical symptoms. Subsequently, methotrexate and hydroxychloroquine were prescribed, but a reduced white blood cell count was detected. Finally, the TNF-α inhibitor Anbainuo was prescribed. However, after 2 months of treatment, the patient exhibited elevated serum creatinine, anti-double-stranded DNA (++)+, anti-nuclear antibody (1:1000), and urine protein (+++++) accompanied by buccal erythema, hair loss, and hand shaking, consistent with Anbainuo-induced lupus, lupus nephritis, and lupus encephalopathy. Moreover, her serum creatinine level remained high after Anbainuo withdrawal and prolonged steroid and immunosuppressive therapy. Careful and sustained monitoring for adverse reactions to Anbainuo (and other TNF-α inhibitors) is recommended.

Keywords
TNF-α inhibitor, Anbainuo, drug-induced lupus, rheumatoid arthritis, biologic disease-modifying anti-rheumatic drug, case report

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Introduction
Rheumatoid arthritis (RA) is a relatively common disease in China, with an estimated prevalence of 0.28% to 0.42%. Although possibly less frequent than in Europe and North America (0.5%–1.0% estimated prevalence), China has the highest number of patients with RA worldwide, many of whom have limited access to modern treatments.1,2 Traditional disease-modifying anti-rheumatic drugs (DMARDs) are still the first choice for RA, whereas biologic or targeted DMARDs are recommended for patients unresponsive to traditional DMARDs.3 Tumor necrosis factor-alpha (TNF-α) inhibitors are commonly prescribed and well-studied biological DMARDs for RA. However, TNF-α inhibitors can induce auto-antibody generation. In most cases, these complications disappear shortly after medication withdrawal.4 However, in the rare case reported here, the extent of organ damage was more severe, and the clinical symptoms were not fully relieved for months after TNF-α inhibitor withdrawal. Notably, creatinine and proteinuria had not fully recovered at 14 months post-withdrawal.

Drug-induced lupus (DIL) resembles systemic lupus erythematosus but can be distinguished by several unique laboratory findings, clinical signs, and symptoms,5,6 including positivity for antinuclear antibody (ANA) and at least one lupus clinical criterion (e.g., arthritis, serositis, or rash).5 In most cases of TNF-α inhibitor-induced lupus, suspension of the drug will rapidly alleviate adverse reactions and lead to a full recovery.4 The TNF-α inhibitor infliximab, a human-mouse chimeric monoclonal antibody, is associated with the greatest risk of DIL among this class of drugs (0.19%–0.22% vs. 0.18% for etanercept and 0.10% for adalimumab).7 Anbainuo (ABN) is an injectable recombinant human TNF-α receptor II: IgG Fc fusion protein produced by Haizheng Pharmaceutical Co, Ltd, Zhejiang, China. It is biosimilar to etanercept, but ABN-induced DIL has not been documented. To our knowledge, this is the first report of ABN-induced severe lupus.

Case report
The reporting of this study conforms to CARE guidelines,8 and the patient consented in writing to all treatment procedures described. A 25-year-old female patient with RA receiving intermittent treatment using Traditional Chinese Medicine (TCM) was admitted to the Department of Rheumatology of our hospital in June 2018 with swelling and tenderness of bilateral proximal interphalangeal, metacarpophalangeal, and wrist joints. In addition, the right ring finger exhibited a swan-neck deformity. Auxiliary examinations revealed elevated rheumatoid factor (RF = 329 IU/mL, reference range < 20 IU/mL), anti-cyclic citrullinated peptide (CCP > 500 U/mL, reference range < 17 U/mL), erythrocyte sedimentation rate (ESR = 65 mm/hour, reference range < 21 mm/hour), and C-reactive protein (CRP = 58 mg/dL, reference range 0.068–8.2 mg/dL) but seronegativity for ANA and ANA spectrum (ANAs). The patient had no history of allergies, oral ulcers, drinking, smoking, or drug abuse and no relevant family history. After exclusion of infectious diseases, such as hepatitis B and tuberculosis, we prescribed methotrexate (MTX) 10 mg once per week and hydroxychloroquine (HCQ) 200 mg twice per day for immunomodulation and etoricoxib 120 mg once per day for analgesia. On 15 June 2018, her white blood cell (WBC) count had decreased to 1.86×10^9/L, indicating drug-induced leukopenia. Therefore, MTX and HCQ were stopped immediately. Next, we administered ABN 25 mg twice per week
after normal treatment to increase leukocytes, and this rapidly relieved joint pain without impacting the WBC count. However, the patient gradually developed systemic edema and involuntary hand trembling during the 2 months of regular ABN treatment.

Physical examination revealed mild hair loss, body edema, cheek erythema, and involuntary hand shaking without oral ulcers or goiter. Auxiliary examinations revealed markedly elevated urinary protein (+++) and total 24-hour urine protein content (6 g), reduced platelet count (68 \times 10^9/L, reference range 100–300 \times 10^9/L), ANA positivity (1:1000), anti-double-stranded DNA (anti-dsDNA) positivity (+), low C3 (0.34 g/L, reference range 0.79–1.52 g/L), elevated creatinine (268 \mu mol/L, reference range 30–90 \mu mol/L), high lumbar puncture brain pressure (320 mmH2O, reference range 80–180 mmH2O), slightly elevated cerebrospinal fluid protein (428 mg/L, reference range 200–400 mg/L), and elevated ESR (55 mm/hour) and CRP (62 mg/dL). Furthermore, anti-neutrophil cytoplasmic antibody, thyroid hormone, and head magnetic resonance imaging manifestations were normal, but kidney biopsy revealed lupus nephritis (Figure 1). Based on these clinical signs and symptoms, the patient was tentatively diagnosed with ABN-induced lupus, lupus encephalopathy, and lupus nephritis, and ABN treatment was stopped immediately.

Subsequently, we administered dehydration and intracranial pressure reduction treatment, switched to methylprednisolone (MP) 500 mg intravenous infusion (ivgtt) for 3 days followed by 80 mg for the next 2 days, administered prednisone (pred) 40 mg for maintenance treatment, and added HCQ 200 mg twice per day and mycophenolate mofetil (MMF) 0.75 g twice per day. These systematic treatments improved the patient’s hand-shaking symptoms, and pred was gradually reduced to 10 mg once per day. On re-examination in April 2019, joint swelling and pain were reduced. In addition, anti-dsDNA and ANAs were negative, although C3 was still low (0.56 g/L), and ANA (1:100), urinary protein (++), and creatinine (165 \mu mol/L) remained elevated. By September 2019, edema, hand trembling, joint swelling, and pain had disappeared, and C3 was normal, but urinary protein (+), creatinine (117 \mu mol/L), and titers for RF and anti-CCP antibodies remained elevated. However, ANA was negative, and the WBC count, ESR, and CRP were all normal. Thus, the patient had almost fully

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**Figure 1.** Renal pathology associated with Anbainuo-induced lupus in the 25-year-old woman reported in this case. a) Periodic Acid-Schiff staining of renal tissue (×200); b) Hematoxylin–eosin staining of renal tissue (×200). Scale bar = 100 \mu m. Diffuse mesangial cells and glomerular stromal cells showed moderate proliferation. Endothelial cells also proliferated and filled the loop cavity, resulting in crescent formation.
recovered by this time, but recovery was slow compared with most cases of ABN-induced lupus.

**Discussion**

Since Hoffman first reported sulfadiazine-induced DIL in 1945, more than 90 drugs have been reported to induce DIL, including pyridazine, procainamide, quinidine, isoniazid, interferon, and minocycline. Among these, TNF-\(\alpha\) receptor inhibitors commonly used in rheumatology account for only 0.18% to 0.22% of DIL cases, and symptoms are rapidly mitigated by drug withdrawal in most cases. This current case suggests that in rare instances, DIL caused by the TNF-\(\alpha\) receptor inhibitor Anbainuo can be maintained even after drug withdrawal, emphasizing the importance of carefully sustained monitoring for signs of DIL.

There are currently three clinically approved TNF-\(\alpha\) inhibitors widely used globally: infliximab, etanercept, and adalimumab. Infliximab is a chimeric mouse-derived monoclonal antibody against TNF-\(\alpha\) containing an Fc fragment of human IgG and the variable chains of IgG1k. Infliximab neutralizes biological activity by binding soluble TNF-\(\alpha\) (monomers and trimers) and membrane-bound TNF-\(\alpha\). Etanercept is a fusion protein consisting of two subunits: the membrane p75 TNF-\(\alpha\) receptor and the Fc part of IgG1. It binds two molecules of TNF-\(\alpha\), thereby acting as a false receptor. Moreover, it binds to TNF-\(\beta\). Adalimumab is the first fully human monoclonal IgG1k antibody against TNF-\(\alpha\). Adalimumab selectively neutralizes TNF-\(\alpha\), thereby inhibiting its binding to p55 and p75 receptors. Among these three TNF-\(\alpha\) inhibitors, etanercept has been linked to the highest number of DIL events. With the same pharmacological mechanism as etanercept, the most frequently reported adverse events for ABN are injection site reactions, infection, allergy, itching, and fever.

Because the current case exhibited severe joint pain and a reduced WBC count after receiving traditional DMARDs, we administered ABN for treatment. Although the WBC count was normal and joint pain significantly reduced, hair loss, cheek erythema, systemic edema, and involuntary hand shaking gradually developed. In addition, auxiliary examination revealed severe proteinuria, high ANA and anti-dsDNA antibody positivity, low C3, moderately low platelet count, high serum creatinine, lupus nephritis (crescent formation), elevated brain pressure, and slightly elevated cerebrospinal fluid protein. Although the patient had been treated using TCM methods for over a decade, ANA and ANAs were negative before receiving TNF-\(\alpha\) inhibitors. Thus, it is unlikely that DIL was caused by TCM. The patient was ultimately diagnosed with ABN-induced lupus, lupus encephalopathy, and lupus nephritis because the patient had no history of lupus with ANA or anti-dsDNA positivity prior to ABN, and rash, hair loss, nervous system dysfunction, and kidney damage occurred only after taking ABN.

After the DIL diagnosis was established, ABN was stopped immediately. Given that the patient’s condition was serious, treatment was changed to MP 500 mg ivgtt for 3 days and gradually switched to pred 10 mg for maintenance treatment, with the addition of HCQ 200 mg twice daily and MMF 0.75 g twice daily. After 12 weeks of ABN withdrawal, edema, hand shaking, and joint pain subsided, and serum ANA, anti-dsDNA, and C3 returned to normal by 14 months, whereas creatinine and urinary protein remained slightly elevated.

TNF-\(\alpha\) inhibitor-induced lupus is characterized primarily by joint pain, polyarthritis, mucosal skin manifestations, and serositis and differs from traditional DIL.
in clinical manifestations and serological characteristics. According to previous clinical reports and the adverse reactions database of the United States Food and Drug Administration, the incubation period for etanercept-induced lupus erythematosus is approximately 4 to 5 months, and it ultimately manifests as acute cutaneous lupus erythematosus but with no kidney or nervous system damage. However, in the current case, the patient developed lupus with kidney and nervous system involvement after only 2 months of ABN administration. After ABN withdrawal and combined treatment with MP, HCQ, and MMF for more than 1 year, her clinical condition markedly improved, but creatinine and proteinuria did not return to normal. The symptoms and serology of most patients with DIL gradually improve or recover within a short period after terminating the causative drug treatment and initiating low-dose pred and HCQ. We speculate that the prolonged recovery of clinical symptoms and serological abnormalities resulted from severe damage to the kidneys and nervous system.

The mechanisms underlying TNF inhibitor-induced lupus remain unclear. It is possible that TNF inhibition leads to the upregulation of interleukin-10 and B cell hyperactivity or T helper 2 cell hyperactivity concomitant with B cell activation. Common infections in patients treated with TNF inhibitors may activate this immune cell activity. It has also been suggested that a possible overlap of RA and underlying lupus pathology might be exacerbated by TNF inhibitors, leading to clinical lupus.

This case has important implications for rheumatologists. In cases of DIL with severe clinical manifestations, it is critical not only to consider withdrawing the causative medication immediately but also to actively monitor and treat the condition over a sustained period.

Ethics statement
The patient agreed in writing to the publication of this article, and the study protocol was approved by the Medical Ethics Committee of the Affiliated Hospital of Zunyi Medical University (approval no.: KLL-2020-306).

Declaration of conflicting interest
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