Acute Kidney Injury due to Renal Sarcoidosis during Etanercept Therapy: A Case Report and Literature Review

Mitsuhiro Akiyama, Yuko Kaneko, Hironari Hanaoka, Masataka Kuwana and Tsutomu Takeuchi

Abstract

We herein report a case of renal sarcoidosis presenting as acute kidney injury (AKI) during treatment with etanercept for rheumatoid arthritis. Blood tests showed a high level of angiotensin-converting enzyme and a renal biopsy demonstrated non-caseating granulomatous tubulointerstitial nephritis. The administration of high-dose steroid therapy (1 mg/kg) and discontinuation of etanercept resulted in an improvement in the patient’s renal function. Although renal sarcoidosis induced by anti-tumor necrosis factor (TNF) therapy is an extremely rare manifestation, this case suggests that renal sarcoidosis should be considered in the differential diagnosis of AKI in patients receiving anti-TNF therapy, as providing an early diagnosis and treatment is important for preventing irreversible renal impairment.

Key words: renal sarcoidosis, acute kidney injury, anti-tumor necrosis factor, rheumatoid arthritis


DOI: 10.2169/internalmedicine.54.4188)

Introduction

Sarcoidosis is a multisystem disease characterized by the presence of non-caseating granulomas in involved organs (1). The pathophysiology of sarcoidosis is not well understood, although it is known that tumor necrosis factor (TNF)-α plays a major role in the development of the disease, and anti-TNF therapy is used for to treat refractory sarcoidosis (2). However, previous case reports have described a paradoxical effect in which anti-TNF therapy has resulted in the onset of sarcoidosis (3).

We herein report a case of renal sarcoidosis presenting as acute kidney injury (AKI) during treatment with etanercept. The onset of renal sarcoidosis induced by anti-TNF therapy is extremely unusual. However, considering the increasing number of sarcoid granuloma cases secondary to anti-TNF therapy, primarily involving the lungs and/or skin, this case suggests that renal sarcoidosis should be considered in the differential diagnosis of AKI in patients receiving anti-TNF therapy, as providing an early diagnosis and treatment can lead to recovery of the renal function and prevent irreversible interstitial fibrosis.

Case Report

An 81-year-old woman with a history of rheumatoid arthritis (RA) was admitted to our hospital for treatment of AKI in November 2013. She had been diagnosed with RA in 1994 and subsequently treated with 6 mg/week of methotrexate (MTX). In 2007, she developed pneumocystis pneumonia, and MTX administration was discontinued. She subsequently received low-dose prednisolone and minocycline; however, weekly injections of 50 mg of etanercept were added in May 2010 due to exacerbation of the arthritis. The prednisolone and minocycline treatment was then discontinued, and she remained in remission under therapy with etanercept alone. In November 2013, an outpatient clinic blood test indicated a high level of serum creatinine (2.3 mg/dL), whereas a previous blood test performed three months earlier had demonstrated a normal level (0.81 mg/dL), and she was therefore admitted to our hospital.
A physical examination revealed a normal blood pressure (130/54 mmHg) and temperature of 37.4°C. The findings of ocular, lung, cardiovascular, abdominal, neurological and skin examinations were normal, and no swelling and/or tenderness of the joints were detected.

Laboratory tests revealed moderate anemia (hemoglobin: 10.2 g/dL) and a severely impaired renal function (serum creatinine: 2.98 mg/dL). The serum electrolyte levels were as follows: sodium=133.3 mEq/L, potassium=4.2 mEq/L, chloride=101 mEq/L and calcium=9.0 mg/dL. Other blood parameters, including the levels of liver enzymes, C-reactive protein and blood glucose, were within the normal ranges. QuantiFERON TB-2 G testing was negative, and a urinalysis showed no proteinuria, occult blood, white blood cells, casts or elevation of the calcium or N-acetylglucosaminidase levels, although the β2-microglobulin level was elevated at 85,256 μg/L (normal range: 0-230 μg/L).

A chest X-ray revealed swollen bilateral hilar lymph nodes; however, no signs of interstitial shadows were apparent. Gallium-67 scintigraphy demonstrated an increased uptake in the hilar lymph nodes and bilateral kidneys (Fig. 1a), and additional blood tests disclosed elevation of the angiotensin-converting enzyme (ACE) and lysozyme levels at 48.6 IU/L (normal range: 7.7-29.4 IU/L) and 27.0 μg/mL (normal range: 5.0-10.2 μg/mL), respectively.

A kidney biopsy was performed to determine the etiology of the AKI. Consequently, the specimen for light microscopy was found to contain 10 glomeruli, two of which exhibited global sclerosis, while the other eight remained almost intact. In addition, tubular atrophy and fibrotic lesions were noted in approximately 10-20% of the observed area, and severe non-caseating granulomatous tubulointerstitial nephritis was apparent in several foci (Fig. 2a); the affected lesions consisted of multinucleated giant and inflammatory cells (Fig. 2b). The diagnosis of renal sarcoidosis was made after excluding the presence of infection.

The etanercept therapy was discontinued, and treatment with 40 mg/day (1 mg/kg) of prednisolone was started. Three months later, the abnormal uptake in the bilateral kidneys and hilar lymph nodes previously noted on gallium scintigraphy had nearly disappeared (Fig. 1b). The creatinine level decreased to 1.58 mg/dL, the urine β2-microglobulin level decreased to 18,065 μg/L and the angiotensin-converting enzyme level normalized to 9 IU/L.

**Discussion**

The development of sarcoidosis triggered by anti-TNF therapy has increasingly been reported in recent years (4), with an estimated prevalence of 0.04% in a single study in France (5). Etanercept is the most frequently offending drug, although some cases have been also ascribed to infliximab or adalimumab (3). To our knowledge, a total of 50 cases involving the development of sarcoidosis after anti-TNF treatment have been reported (Supplementary material), including seven cases (14%) associated with IFX, 10 cases associated with ADA and 33 cases associated with ETN. We identified the cases reported in 2013 and summarized them...
rent case constitutes the first report of a patient presenting with the eyes being an infrequently involved site. The cur-
anti-TNF therapy predominantly include the lungs and skin, in Table. The organs involved in sarcoidosis induced by 
tribute to granuloma formation. Whereas anti-TNF-
cept remains unclear, a few possible mechanisms may con-
though the pathogenesis of sarcoidosis induced by etaner-
receiving infliximab or adalimumab, as shown in Table. Al-
quently seen in patients treated with etanercept than in those 
(Infliximab and adalimumab) and soluble TNF receptors 
the mechanism of action: anti-TNF-

Table. Clinical Features of Sarcoidosis that Developed during Anti-TNF Therapy: Review of the Literature

<table>
<thead>
<tr>
<th>References</th>
<th>Age/Sex/Disease</th>
<th>Drugs/Months</th>
<th>Affected organs</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present case</td>
<td>81/F/RA</td>
<td>ETN/42</td>
<td>Kidneys and hilar lymph nodes</td>
<td>ETN discontinuation, PSL</td>
<td>Resolution</td>
</tr>
<tr>
<td>9</td>
<td>40/F/RA</td>
<td>ETN/84</td>
<td>Central nerve systems, eyes and hilar lymph nodes</td>
<td>ETN discontinuation, PSL</td>
<td>Resolution</td>
</tr>
<tr>
<td>10</td>
<td>50/F/RA</td>
<td>ETN/12</td>
<td>Skins and hilar lymph nodes</td>
<td>ETN discontinuation, PSL</td>
<td>Resolution</td>
</tr>
<tr>
<td>11</td>
<td>54/F/RA</td>
<td>ETN/8</td>
<td>Eyes</td>
<td>ETN discontinuation</td>
<td>Resolution</td>
</tr>
<tr>
<td>12</td>
<td>9/F/RA</td>
<td>ETN/24</td>
<td>Lungs and skins</td>
<td>ETN discontinuation, PSL</td>
<td>Resolution</td>
</tr>
</tbody>
</table>


in Table. The organs involved in sarcoidosis induced by anti-TNF therapy predominantly include the lungs and skin, with the eyes being an infrequently involved site. The current case constitutes the first report of a patient presenting with AKI who was diagnosed with renal sarcoidosis on a kidney biopsy under etanercept therapy. This case suggests that the possibility of renal sarcoidosis should be considered in RA patients treated with anti-TNF therapy manifesting symptoms of AKI, as the differential diagnoses in such cases usually include non-steroidal anti-inflammatory drug use, secondary Sjögren’s syndrome and secondary amyloi-
dosis.

Anti-TNF therapy is classified into two types based on the mechanism of action: anti-TNF-α monoclonal antibodies (infliximab and adalimumab) and soluble TNF receptors (etanercept). The development of sarcoidosis is more fre-

trations, such as the kidneys (5). In fact, while infliximab is reported to be an effective treatment for sarcoidosis (2), etanercept is considered to be less effective or even worsen sarcoidosis (7). These observations may explain the greater tendency of etanercept to induce sarcoidosis than infliximab or adalimumab.

The incidence of renal sarcoidosis remains unclear, although sarcoidosis is associated with a broad spectrum of renal manifestations, including disordered calcium metabolism, granulomatous interstitial nephritis and glomerulopathy (8); the most common cause of AKI is disordered cal-
cium metabolism. The present patient did not exhibit hyper-
calcemia or hypercalciuria, and a kidney specimen revealed that granulomatous interstitial nephritis had caused the AKI.

Most patients with granulomatous interstitial nephritis as-
sociated with sarcoidosis respond well to glucocorticoid treat-
ment; however, full recovery of the renal function de-
pends on the degree of interstitial fibrosis (8). It is important to initiate therapy as soon as possible in order to prevent worsening of the fibrosis. In addition, anti-TNF therapy should be discontinued, as disease progression may be re-
versed after discontinuation; the improvement may be partial and transient despite the use of steroid treatment if anti-TNF therapy is not stopped (5).

The development of sarcoidosis during treatment with anti-TNF therapy may be accidental. However, since the number of observations reporting paradoxical adverse events of sarcoidosis has increased, there is likely a plausible mechanism(s) underlying this complication. Therefore, more
cases should be accumulated and the mechanisms researched further. Importantly, physicians should also consider the possibility of sarcoidosis in the differential diagnosis of patients who develop AKI during anti-TNF therapy. The ACE level exhibits a sensitivity of 90% and may aid in making the diagnosis, as observed in the current case (3).

In summary, we herein described a case of renal sarcoidosis presenting as AKI during treatment with etanercept in a patient with RA. Although uncommon, the possibility of renal sarcoidosis should be considered in the differential diagnosis of AKI in patients receiving anti-TNF therapy, as providing an early diagnosis and treatment may result in recovery of the renal function and prevent irreversible interstitial fibrosis.

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

References


