Adalimumab-Induced Lupus Erythematosus with Central Nervous System Involvement in a Patient with Crohn’s Disease

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Abstract

The anti-tumor necrosis factor (TNF) agents are drugs that in recent years turned out to be a mainstay of therapy for the treatment of inflammatory bowel disease. Nevertheless, they have several adverse effects such as infectious complications and immunogenicity. One of the most common immunogenic effects is the development of autoantibodies, mainly anti-nuclear antibodies and anti-double-stranded DNA antibodies, only rarely associated with overt clinical manifestations of systemic lupus erythematosus. Adalimumab is a fully humanized monoclonal antibody widely used for the treatment of Crohn’s disease and supposed to have less immunogenic activity and a safer profile than other anti-TNF agents. The occurrence of systemic lupus erythematosus with involvement of the central nervous system appears to be a very rare complication of such drugs, and no cases have been reported in the medical literature in patients treated with adalimumab. We report a case of a 53 years-old woman with ileo-colic Crohn’s disease where the treatment with adalimumab was complicated by systemic lupus erythematosus with central nervous system vasculitis.

Key words


Introduction

Anti-tumour necrosis factor (TNF) agents are now widely used in the management of patients with inflammatory bowel disease and the efficacy and safety profile of these agents has led to their increasing use in clinical practice. Infectious complications and immunogenicity are the main drawbacks of these drugs. One of the most common side effects is the development of autoantibodies, mainly anti-nuclear antibodies (ANA) and anti-double-stranded DNA (ds-DNA) antibodies, only rarely associated with overt clinical manifestations. Adalimumab is a fully humanized monoclonal antibody, recently introduced on the market for the treatment of Crohn’s disease (CD) and supposed to have less immunogenic activity and a safer profile than other anti-TNF agents. Adalimumab-induced systemic lupus erythematosus (SLE) is a rare but well described syndrome, however in the literature there are no reported cases of SLE with central nervous system (CNS) involvement. We report a case of CD treated with adalimumab and complicated by SLE with CNS vasculitis.

Case report

A Caucasian 53 years old woman with ileo-colic CD was admitted to our unit in July 2009 for the onset of nuchal headache, dizziness and right superior quadrantopsy. She was a non smoker, her past medical history was insignificant except for CD diagnosed in 2003 and complicated by intermittent knee and wrist arthralgias. She was on treatment with corticosteroids, and during the last 10 months there had been four episodes of severe relapses along with reactivation of arthralgias requiring escalation of corticosteroid treatment. Four months before admission her referral gastroenterologist decided to start treatment with anti-TNF agent adalimumab at the dosage of 40 mg s.c. every 14 days; at that time search for autoantibodies was negative (Table I).

On hospital admission the patient was alert, mildly drowsy, afebrile. Along with nuchal headache and a visual defect in her right eye, she reported the onset of prolonged chest pain with pleuritic pain and increasing abdominal volume during the past week.

On clinical examination, there were no signs of meningeal irritation; the remaining neurologic examination was normal except for the presence of a right superior quadrantopsy. On physical examination there was a suspicion of ascites and right basal pleural effusion. Heart rate was 80 bpm in
sinus rhythm, blood pressure was 110/60 mmHg, oxygen saturation was 98% on room air.

On admission, a direct head CT scan showed an occipital cortical-subcortical hypodense lesion of the left hemisphere. On the same day the MRI of the brain with a complete angiographic study showed bilateral occipital serpiginous lesions and an ischemic area of the right cerebellar hemisphere (Fig. 1A). There was no extra and intra-cranial vascular disease. A spinal tap was performed showing normal findings on chemical-physical and cultural examination. An electroencephalography showed normal electrical activity and there were no signs of encephalitis. A complete thoracic and abdominal CT scan showed splenomegaly (15 cm) and diffuse mild pleural, pericardial and peritoneal effusions.

Anticoagulant were negative (Table I). Based on clinical and laboratory findings this case was consistent with a diagnosis of SLE, according to the American College of Rheumatology (ACR) criteria [1].

After the infusion of high-dose pulse steroids, the patient progressively ameliorated during the following week, with complete resolution of headache and drowsiness; there was an improvement in visual defects, even if a complete resolution was not achieved. Pleural, peritoneal and pericardial effusions completely disappeared.

A brain MRI at 15 days showed marked improvement of the aforementioned lesions (Fig. 1B).

At one year follow-up on treatment with prednisone 12.5 mg/day the patient had no neurological and gastrointestinal relapses; the autoantibody pattern normalized.

Discussion

TNF-α is a cytokine that plays a crucial role in inflammation by means of predominantly T-cell-mediated tissue damage. Inhibition of TNF-α has recently emerged as an effective therapy for treating an expanding number of rheumatic and autoimmune disorders, including CD. With the increasing number of treated patients with anti-TNF and availability of long-term data, a new spectrum of relevant adverse events is emerging. Well known adverse effects include serious and opportunistic infections, mainly tuberculosis [2-3]. An association with demyelinating disorders and lymphoproliferative diseases has been described [4-5]. More recently, the use of anti-TNF agents has been associated with autoimmune disorders ranging from asymptomatic immunological laboratory alterations to life-threatening systemic autoimmune disease [6]. The most common autoimmune manifestation associated with anti-TNF therapy is the development of ANA and ds-DNA autoantibodies without related clinical syndrome [7]. Overt autoimmune diseases are very rare. Among these, undifferentiated vasculitis, SLE/lupus-like syndrome and interstitial lung disease are the most frequent.

The clinical syndrome of SLE/lupus-like in patients receiving anti-TNF drugs is a distinct syndrome of drug-induced lupus, recently named “anti-TNF-induced lupus” (ATIL) [8]. This syndrome is characterized by a laboratory autoantibody profile different from classical drug-induced SLE. The high prevalence of anti-dsDNA antibodies (>90%) and a low prevalence of anti-histones antibodies (57%) is a distinct pattern of this syndrome with respect to the classical form, suggesting a different pathogenic mechanism [9-10]. It is worth noting that there are no strictly defined criteria for diagnosing drug-induced lupus. A widely accepted definition is the presence of definite SLE, according to ACR criteria [1], concomitant with exposure to a lupus-inducing drug [11].

In a recent review on autoimmune diseases induced by TNF-targeted therapies [10], 233 cases of related immunological diseases were identified in the period 1990-2006. Among these, the prevalence of vasculitis and ATIL was 48% and 39%, respectively. ATIL was associated with

Table I. Autoantibody pattern before, during and after treatment with adalimumab.

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Before treatment with adalimumab</th>
<th>On admission</th>
<th>6 months follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>Negative</td>
<td>Title 1:320</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-Ds-DNA</td>
<td>Negative</td>
<td>Title 1:320</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-Histones</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-cardiolipin IgM</td>
<td>-</td>
<td>Positive</td>
<td>-</td>
</tr>
<tr>
<td>Anti-phospholipid IgM antibodies</td>
<td>-</td>
<td>Positive</td>
<td>-</td>
</tr>
<tr>
<td>Lupus Anticoagulant</td>
<td>-</td>
<td>Negative</td>
<td>Negative</td>
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</tbody>
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![Fig 1. A) MRI (T2Flair) of the brain on admission showing bilateral occipital ischemic lesions (arrows). B) MRI (T2Flair) of the brain at 15 days showing advanced resolution of the previously described lesions.](image-url)
infliximab in 44%, etanercept in 40% and adalimumab in 16% of cases. Among 92 patients with ATIL, a CNS involvement was documented only in 2 cases (infliximab and etanercept therapy). Of note, neither in that case series nor in the review of current literature, cases of ATIL with CNS involvement associated with adalimumab have been found.

In our case, the involvement of the central nervous system, the polyserositis and positivity of ANA and ds-DNA autoantibodies occurring during treatment with adalimumab allowed the diagnosis of ATIL. This was supported by the absence of autoantibodies before the initiation of treatment with adalimumab and their disappearance 6 months after withdrawal of the drug. Thus, clinical and radiologic findings were consistent with a diagnosis of neuropsychiatric SLE with CNS involvement according to the American College of Rheumatology criteria [11].

In conclusion, the use of adalimumab has been associated with an increasing number of cases of autoimmune disease, mainly vasculitis, SLE and lupus-like syndrome. The clinical case reported above is consistent with a diagnosis of adalimumab-induced SLE with CNS vasculitis. To our knowledge, this is the first case of such a complication in a patient with Crohn’s disease treated with this anti-TNF agent.

Conflicts of interest

Nothing to declare.

References