Autoimmune Pitfalls of Anti-Tumor Necrosis Factor-Alpha Therapy

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Biological therapy refers to the use of medication tailored to specifically target an immune or genetic mediator of disease. It has revolutionized the treatment of chronic inflammatory diseases, such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and inflammatory bowel diseases (IBD) [1,2]. Most medications are directed against tumor necrosis factor-alpha (TNFα) (infliximab, adalimumab, etanercept, golimumab, certolizumab pegol) and others against interleukin (IL)-1 (anakinra), IL-6 (tocilizumab), CD20 (rituximab), and CD28-CD80/86-mediated T cell co-stimulation (abatacept). The most extensive clinical experience was gathered from treating RA patients with anti-TNF agents. Since their introduction in 1998, over a million patients have been treated.

However, increasing clinical data warn us of the potential dangers of disabling TNF-mediated immunological signaling – namely, increased incidence of infections, solid and hematological tumors, demyelinizing disease, cardiovascular incidents, and induction of autoimmunity [1,2]. Induction of autoantibodies (antinuclear antibody, anti-dsDNA) under biological therapy is well recognized: elevated titers were found in 11–13% of patients treated with etanercept and 3–98% treated with infliximab, depending on the indication and type of antibodies determined [1,3]. Most of these patients had no clinical manifestations, but some of them developed autoimmune syndromes: vasculitis, systemic lupus erythematosus (SLE), interstitial lung disease, inflammatory myopathies, antiphospholipid syndrome, etc. [4].

We present the case of a patient who developed drug-induced lupus erythematosus (DIL) after etanercept was introduced into his treatment for severe RA. Etanercept is a soluble p75 TNF-receptor fusion protein conjugated to the Fc region of human immunoglobulin (Ig) G used since 1998 to treat RA, AS, PsA and juvenile idiopathic arthritis. It is given by self-injection under the skin once or twice a week (50 mg/week). DIL is generally a milder version of the idiopathic disorder that is traditionally associated with production of antihistone antibodies. This pattern is now changing, in part due to the many new drugs – both conventional and biological – that have been introduced into clinical practice for treating autoimmune diseases [4]. DIL has been recognized as a side effect of more than 80 drugs since its first description in association with sulfadiazine. Despite frequent induction of autoantibodies in treated patients, development of DIL under anti-TNF therapy is uncommon; De Bandt et al. [5] reported a 0.19% prevalence for infliximab and 0.18% for etanercept.

PATIENT DESCRIPTION

A 45 year old man presented at the emergency room complaining of fever (41.6° CF), dry cough and left-sided chest pain of 2 weeks duration, with no improvement following a prescribed course of antibiotics. He had been diagnosed with rheumatoid arthritis 2 years previously and was initially treated with leflunomide and methotrexate, which were switched to etanercept and methotrexate 2 months before the present admission. Pre-treatment PPD and Quantiferon test were negative. After 2 weeks of treatment, he developed erythema on the trunk and extremities, but the treatment was continued since the joint symptoms abated significantly. Other medications included low dose prednisone (5 mg), folic acid, pantoprazol and occasional non-steroidal anti-inflammatory drugs (NSAID). The patient is allergic to sulfasalasine and is a former smoker.

Upon arrival he appeared ill, diaphoretic, with resting rate 130/80 mmHg, pulse 130/min and respiratory rate 22/min. His skin was covered with a maculopapular scaling rash in centripetal distribution. Head and neck examination revealed "moon face" aspect, without palpable lymph nodes. Lung auscultation on the lower left field showed no breathing sounds. Metacarpophalangeal and proximal interphalangeal joints were symmetrically swollen and tender on palpation. The rest of the physical examination was unremarkable. Chest X-ray showed left-sided

pleural effusion without infiltrate. Based on the patient's general appearance, iatrogenic immunosuppression and laboratory findings of neutrophilia with left shift, elevated C-reactive protein (CRP, 243.3 mg/L) and procalcitonin (1.97 μg/L), a regimen of broad-spectrum antibiotic and antifungal treatment was started. Other findings included mild normocytic normochromic anemia (lowest hemoglobin level 109 g/L) and positive direct Coomb's test without hemolysis. Despite antibiotics and antifungal medication the patient remained febrile without clinical improvement. Extensive microbiological and imaging workup (repeated blood, sputum, pleural effusion and swab cultures, computed tomography scan of brain and chest, transesophageal echocardiogram, abdominal ultrasound) failed to show any source of infection. CT scan showed bilateral pleural effusion and small pericardial effusion. Pleural fluid biochemistry and cytology showed exudates with abundant lymphocytes, repeated cultures for *Mycobacterium tuberculosis* returned negative. PPD and Quantiferon test were repeated and were also negative.

A diagnosis of drug-induced lupus (DIL) was assumed, considering the preexisting rash correlating with etanercept therapy, pericardial and pleural effusions, fever of unknown origin and other general symptoms. Further testing included ultrasound of hands and wrist joints (minimal joint effusion, improvement compared to the pre-etanercept period), skin biopsy with direct immunofluorescence assay (granular C3 and IgM deposits on epidermodermal junction) and battery of autoantibodies (ANA, antinucleasome and antihistone antibodies were positive while the other antibodies were negative).

After 3 weeks, antimicrobial therapy was stopped and prednisone 20 mg/day was introduced leading to gradual improvement. Fever and general symptoms abated completely; the rash and joint stiffness remained but subsided significantly. The patient was discharged with gradual tapering of corticosteroids; no other biological agent was prescribed.

COMMENT

Clinical experience with anti-TNF biological therapy is rapidly increasing, and we are becoming aware of potential risks from altering the complex and incompletely understood cytokine network. Side effects can be cumbersome leading to treatment cessation and serious morbidity, which prevents their wide use as first-line medications. Most articles on anti-TNF (particularly etanercept)-induced lupus are reports on individual cases, with only two larger retrospective studies of 32 and 7 patients respectively [4,5]. Since the first description of etanercept-induced lupus erythematosus in 2002, fewer than 50 cases have been published and, to our knowledge, this is the first described case in Croatia. In the previous reports, timing of the onset and cessation of the SLE features also strongly support a drug-related effect of etanercept. SLE developed after a mean of 7.7 months (range 3–24 months) of commencing etanercept therapy [4,5]. Our patient's symptoms began only 2 weeks after initiating therapy. The most common clinical feature of DIL is skin rash, and skin biopsy was not performed in most of the published cases while in our patient it showed granular IgG and complement deposits. There was no significant life-threatening organ involvement such as kidney, lung (interstitial lung disease), heart, or central nervous system. Our patient's clinical presentation is consistent with the typical clinical features previously described in DIL, including severe general and joint symptoms and rash; however, he also had serositis which has been described in only 3% of cases (in the largest series of 37 patients) [4].

Serologic and clinical manifestations of DIL differ from those in idiopathic SLE, but there is also a difference between "classic" DIL (e.g., procainamide) and anti-TNF DIL. Patients with anti-TNF DIL generally have a milder clinical picture, with higher prevalence of rash than those with classic DIL, more inconsistent elevation of positive ANA, anti-dsDNA and antihistone antibodies [4]. The pathophysiology of DIL is controversial. Induction of antibodies is the first step and occurs in all described cases. In RA patients treated with infliximab, ANA developed in 29–76.7% and anti-dsDNA in 10–29%. Also, in etanercept-treated RA patients, 11–36.3% had developed ANA and 5–15% developed anti-dsDNA [3,4].

The question remains: why does anti-TNF therapy decrease titers of rheumatoid factor and anti-CCP antibodies, concurrently inducing ANA and anti-dsDNA. TNF might up-regulate the cellular expression of the adhesion molecule CD44, which has a role in the clearance of apoptotic material by phagocyte. Reduced CD44 expression by anti-TNF can potentially induce SLE by abnormal clearance of apoptotic materials. Experimental models also show that agents or events that modify T cell DNA methylation may induce autoimmunity by causing over-expression of T cell LFA-1 (lymphocyte function-associated antigen 1, CD11a/CD18).

Cytokine imbalance is another attractive hypothesis: TNF, overexpressed in RA, exerts inhibitory effects on plasmatocytoid dendritic cell expansion and systemic release of interferon-alpha (IFNα), a culprit of SLE. Therefore, blocking TNF function may cause DIL by inducing IFNα secretion.

There are no consensual diagnostic criteria for DIL, but most authors use the following: i) a temporal relationship between clinical manifestations and anti-TNF therapy, ii) at least one serologic American Congress of Rheumatology (ACR) criterion of SLE (e.g., ANA, anti-dsDNA), and iii) at least one non-serologic ACR criterion (e.g., arthritis, serositis, hematologic disorder, malar rash) [5]. Our patient fulfilled 5 of 11 ACR criteria.

The mainstay of DIL treatment is cessation of the incriminating drug, which is sufficient in most cases [4,5]. Some patients require glucocorticoid therapy and only in rare instances another immunosuppressant. There are reports of successful treatment with rituximab. The prognosis is good, with the vast majority of patients suffering no permanent damage and recovering completely, although recovery can be prolonged (median 8 weeks, range 3–16 weeks, in one case 6 months) [5].

DIL is a relatively novel side effect of anti-TNF biological therapy. In fact, it might be a logical consequence of altering immune system signaling, considering the high frequency of autoantibody induction during anti-TNF therapy.

Recognizing patients who are likely to develop clinical manifestations is a future challenge, and early recognition of this potentially harmful condition is mandatory. It is also prudent to check baseline autoantibody levels before initiating biological therapy and not to prescribe it to patients with SLE.

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