

Neurological disorders with demyelinating brain white matter lesions in a patient with rheumatoid arthritis treated with etanercept

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Abstract: We present the case of a 37-year-old woman with severe, drug-resistant rheumatoid arthritis. The patient has been previously treated with several disease-modifying anti-rheumatic drugs as well as infliximab alone and in combination therapy. Despite the treatment, a high disease activity persisted. For this reason, the patient was qualified to etanercept therapy. During the therapy, a gradual joint condition improvement was demonstrated, including arthritis remission. From the fourth month of etanercept administration, neurological disorders such as sight and speech disorders, confusion and muscle weakening were reported. The symptoms aggravated with therapy continuation. The patient reported her complaints to her leading rheumatologist after 8 months of their duration. Optic fundus and visual field examination, as well as in the neurological examination no significant abnormalities were found. Magnetic resonance imaging of the head demonstrated single, small hyperintensive lesions in the T2w images located in the white matter of the frontal and parietal lobes of the left cerebral hemisphere, which could be identical with demyelination. Based on the clinical and laboratory findings, drug-induced neurological disorders associated with etanercept administration were suspected. After discontinuation of etanercept therapy, the complaints gradually subsided. The confusion episodes, concentration disorders and speech disorders were less frequent. There was no relapse of muscle weakening. Within 6 months of the drug discontinuation, neurological symptoms resolved completely.

Key words: demyelinating white matter lesions, etanercept, neurological disorders, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by the occurrence of polyarthritis, extra-articular manifestations and systemic complications, lower life quality, high morbidity, disability and premature mortality [1,2].

The main treatment for RA is the classical disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate used alone or in combination early at effective doses [2]. At the end of the 90s of the 20th century, new drugs aimed against one of the inflammatory mediators were introduced. Agents against tumor necrosis factor α (TNF- α) were termed anticytokine drugs [3]. This brought new therapeutic opportunities for RA patients, especially those with a severe and drug-resistant disease, or with contraindications to DMARDs [2,4]. Currently, three drugs of this class have been approved,

namely, infliximab, etanercept and adalimumab [3,5]. Short and long term studies have demonstrated their effectiveness, especially when combined with traditional DMARDs [6]. They diminish the disease activity, improve life quality, reduce the formation and progression of radiological lesions, prevent from the disability or at least delay it [6,7]. In the pre-registration clinical trials the anticytokine drugs were well tolerated and safe [3,7]. The most common adverse events reported during these initial studies were drug-induced allergic reactions and upper respiratory tract infections [2,7].

A longer administration of TNF- α inhibitors in clinical practice demonstrated that they may cause various complications not reported previously that might be related to the TNF- α blockade. However, this relationship has not been proved yet [1,3,5-7]. These adverse events include severe, opportunistic infections, eg, tuberculosis, lymphoproliferative diseases, cancer, lupus-like syndrome, pancytopenia, cardiac insufficiency exacerbation, and neurological disorders with demyelination [1-6,8].

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CASE REPORT

We present a case of a 37-year-old woman diagnosed at the age of 15 with severe, aggressive and treatment-resistant RA.

The patient had no history of other chronic diseases. Previously she has been taking only the RA drugs. In the past, various DMARDs group drugs were administered in monotherapy and in combination, including chloroquine, gold, sulfasalazine, cyclosporine, cyclophosphamide and methotrexate. In 2002 infliximab was added to methotrexate treatment, however, the drug had to be discontinued for fever episodes and an allergic skin reaction occurring after the third drug infusion. Because of the treatment failure or adverse reactions to the previously administered drugs and unavailability of other drugs, ie leflunomide and etanercept, since 2004 the patient started taking methylprednisolone and cyclophosphamide at doses ranged from 50 to 100 mg/24h. Due to high inflammation process activity (DAS28 = 5.3) in February 2006, etanercept treatment was introduced twice a week at the dose of 25 mg *s.c.* Concurrently, cyclophosphamide therapy was continued at the dose of 100 mg/24h, *p.o.*, and methylprednisolone therapy at the dose of 8 mg/24h. A gradual joint improvement was demonstrated from the 12th week of treatment manifested by a decrease in the number of painful and swollen joints and inflammatory markers until disease remission was reached. In the 5th and 10th treatment month DAS28 was 2.5 and 1.72, respectively. In June 2006, a short-term confusion episode and left-sided hemianopia was observed. The patient reported to an ophthalmologist who did not find any significant abnormalities, including the fundoscopy. Vision area examination and neurological consultation has been recommended. Because of rapid symptom resolution the patient did not undergo these examinations, she did not report her signs and symptoms to the leading rheumatologist either. During further etanercept treatment, several short term speech disorders and cognitive impairment occurred. Furthermore, from the 10th month of treatment, after drug administration the patient reported muscle weakening in the upper and lower limbs, which would not resolve until several or several dozens of hours. The patient reported her symptoms to her leading rheumatologist not earlier than in February 2007. Assuming that neurological disorders were induced in the patient by etanercept therapy, the drug was discontinued and the patient was hospitalized for additional diagnostic tests. On admission, her general condition was good. The following abnormalities were reported, i.e., immobilization of carpal joints, swan neck deformities of the fingers of both hands, visible scarring of both hands as a result of correction surgery performed. Laboratory findings did not demonstrate important abnormalities – the inflammatory markers were low, the complete blood count, renal and hepatic function markers were normal, antinuclear antibodies, antiphospholipid antibodies and anti-double stranded DNA antibodies were absent. The ophthalmologic examination, including the fundoscopy and visual field, did not demonstrate important abnormalities. On echocardiography, only negligible mitral and tricuspid valves regurgitations were demonstrated. On Doppler ultrasound, no abnormalities in the carotid vessel wall or carotid or vertebral arterial flow disorders were

observed. The electroencephalography examination and visual evoked potentials were normal. Magnetic resonance (MR) of the brain demonstrated single, small hiperintensive lesions in the T2-weighted images, located in the white matter of the frontal and parietal lobes of the left cerebral hemisphere, which could be identical with demyelination. The angio-MR of the brain demonstrated normal intracranial arteries. The patient was consulted by a neurologist who did not report any abnormalities in the neurological examination. Based on the clinical and laboratory findings, drug-induced neurological disorders associated with etanercept therapy were suspected. Etanercept was permanently discontinued. Methotrexate at the dose of 15 mg/week was introduced, and cyclophosphamide therapy at the dose of 50 mg/24h, as well as methylprednisolone therapy at the dose of 8 mg/24h was continued. With etanercept discontinuation, the patient reported a gradual resolution of symptoms. Concentration and speech disorders occurred less frequently, confusion (the last episode took place three weeks after the drug discontinuation), muscle weakening did not relapse. After 2 months, in April 2007 the methotrexate dose was increased to 20 mg/week, while cyclophosphamide was discontinued.

At 6 months from etanercept therapy discontinuation the complaints resolved completely. During follow-up, MR of the brain, performed in October 2007, no lesions were reported compared with the results of the examination performed 8 months earlier.

DISCUSSION

White matter lesions are a frequent abnormality demonstrated in the imaging of the nervous system [9,10]. They may occur in healthy subjects and their incidence increases with age [9,10]. They may also be associated with several neurological and psychiatric symptoms, i.e. with cognitive function disorders, dementia syndromes, psychoses, depression, motor coordination disorders, headache [9,10]. The risk factors associated with the development of white matter lesions include age, diabetes, hypertension, large vessel atherosclerotic lesions, coronary artery disease, a previous stroke, endothelial function disorders [9,10]. They also occur in the course of various psychiatric, neurological diseases, including primary demyelinating diseases, systemic connective tissue diseases, during the administration of some drugs, including anticytokine and immunosuppressive drugs [3,4,9]. White matter lesions, located mainly in the occipital and parietal lobes, with accompanying specific clinical symptoms, i.e. headaches, consciousness disorders, visual disturbances and epilepsy, may occur in patients treated with various immunosuppressive drugs, especially cyclosporine and also cyclophosphamide [11]. Reversible posterior leukoencephalopathy occurs mainly in patients with hypertension or acute renal failure and is characterized by the above mentioned localization of cerebral lesions, by certain symptoms and by clinical and radiological abnor-

CASE REPORTS

malities resolution with causative factor elimination [11]. In the present case the neurological symptoms and white cerebral matter lesions demonstrated in MR occurred in a young woman, with no medical burden, who had been treated for RA with glucocorticosteroids and several DMARDs, including cyclophosphamide taken for over 2 years, and etanercept for 4 months. Considering the time relation between the symptoms onset, initiation of etanercept treatment and the symptoms resolution after drug discontinuation, the most probable cause is etanercept-associated, drug-induced neurological disorders in our patient.

Neurological disorders have been reported during treatment with all TNF- α inhibitors, most commonly with etanercept [5,6]. Twenty cases have been reported so far, 18 with etanercept and 2 with infliximab treatment [1,3-5,8]. The most frequent were paresthesias (65% of patients), visual disturbances associated with optic nerve inflammation (40% of patients) and confusion (25% of patients) [1,2,8]. Other reported disorders include multiple sclerosis, multiple sclerosis-like syndrome and transverse spinal cord inflammation [1,2,5,6,8]. The present patient demonstrated visual disturbances, confusion episodes and muscle weakening. In most of the reported patients to date, including our patient, these disorders were accompanied by white matter demyelinating lesions demonstrated with brain MR [3,4]. Apart from that, during anti-TNF- α drug treatment, there have been over 15 cases of optic nerve inflammation reported in the literature [8]. Visual disturbances occurred within 2–18 months from treatment initiation and were not always accompanied by ophthalmological examination and head MR abnormalities [8]. In the current case visual disturbances, being the first symptom, occurred after 4 months of etanercept therapy. They were not accompanied by abnormalities in ophthalmological examination. In most cases of drug-induced demyelination, neurological and ophthalmologic symptoms resolved partly or totally with TNF- α inhibitor discontinuation [4-6]. Maintaining or reintroducing the treatment was associated with the relapse [5,8]. Also in our patient, the neurological symptoms increased with etanercept therapy continuation, and resolved completely with drug discontinuation. Moreover, awe-inspiring information regarding the effect of TNF- α inhibitors on the formation of demyelinating lesions has been reported in multiple sclerosis patients, treated with infliximab and lenercept. These drugs, contrary to expectations, exacerbated the disease course [1,4,8].

Long-term clinical studies assessing the safety of anti-TNF- α drugs administration and post registration observations have not confirmed the above mentioned data as yet [4,6,7]. They demonstrated that neurological disorders and demyelinating lesions in TNF- α inhibitors treated patients do not occur more often than in the general population [4-7]. It remains unknown whether anticytokine drugs induce neurological disorders with white matter demyelinating lesions, or rather reveal the secret demyelinating disease, or at last do the two diseases just happen to coexist with one

another [1,4,6]. It cannot be excluded that the neurological symptoms may be associated with a chronic progressive leukoencephalopathy, a disorder reported in one patient treated with TNF- α inhibitor so far, and in patients treated with another drug of this class, natalizumab [3,12]. These concerns require further studies to validate these observations [3,7]. Until now the TNF- α inhibitors have been contraindicated in patients with demyelinating diseases or with a history of optic nerve inflammation [1,6,8]. In patients with a long family history of demyelinating diseases it is necessary to be cautious [1,6,8]. Strict monitoring of TNF- α patients treated with inhibitors, regarding the ophthalmologic and neurological symptoms occurrence, is necessary [4,8]. The occurrence of neurological demyelinating disorders in the brain MR during treatment is an indication to drug discontinuation [1,6,8]. Following these recommendations, in the present case, immediately after the patient had reported her neurological symptoms and visual disturbances, etanercept was discontinued.

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