CASE REPORT

Drug-induced systemic lupus erythematosus in interferon beta-1b therapy

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Abstract

Drug-induced systemic lupus erythematosus (SLE) is a rare complication of therapies with some drugs. Breaking out after months or years of therapy with a certain drug, its occurrence is likely to increase with the duration of the medication and the cumulative quantity of the drug. The symptoms of this syndrome include, in particular, arthralgia, myalgia, fever, serositis, skin exanthema and production of antinuclear (ANA) antibodies. In contrast to SLE, its symptoms gradually abate after discontinuation of the inducing agent.

The authors describe the case of a 43-year-old patient suffering from multiple sclerosis who experienced drug-induced SLE after 8-year application of interferon (IFN) beta-1b.

INTRODUCTION

The current first-line therapy for the relapsing-remitting form of multiple sclerosis (RRMS) involves disease-modifying drugs (DMD), which reduce disease activity by immune system modulation. The first drug of this group introduced into MS therapy is IFN beta-1b, its administration may rarely lead to exacerbation of autoimmune diseases, e.g., autoimmune thyroiditis, autoimmune hepatitis or systemic lupus erythematosus (SLE). A rare and very serious adverse effect is the development of drug-induced SLE syndrome (Havrdova *et al.* 2001; Javed *et al.* 2006).

Our report aims to draw attention to the possibility of development of drug-induced SLE syndrome in MS patients treated with IFN beta-1b.

CASE REPORT

A 43-year-old woman has been treated for RRMS since 1990. From February 1998 she used IFN beta-1b, 8 million IU s.c. every other day. No clinical activity was apparent, except exacerbation in 2001. Abnormal neurological findings included left-sided lateralization of stretch reflexes and minimal palleo-cerebellar symptoms, with the Kurtzke (Expanded Disability Status Scale) score of 1.5. Medical history included mild sideropenic anaemia and low-back pain. In March 2006, she experienced severe flu-like symptoms and strong local skin reaction after IFN beta-1b administration. High erythrocyte sedimentation rate (ESR) 110–135 per hour, and rheumatologic screening revealed presence of antinuclear antibodies includ-

ing anti-Ro and anti-La antibodies. She was hospitalized in the medical department for worsening renal insufficiency with creatinine values reaching up to 223 mmol/l (norm 53–124 mmol/l), considerably reduced glomerular filtration 0.97 ml/s (norm 1.25–2.2 ml/s) and tubular resorption of 0.96 (norm 0.983–1), glycosuria up to 22.5 mmol/l with normal glycaemia, and also albuminuria (166.1 mg/l per day, norm 0–20 mg/l/24 hour), slight proteinuria (0.64 g/l, norm 0–0.1 g/l) and haematuria. Histological examination of kidney biopsy showed active tubulointerstitial nephritis. The patient developed secondary arterial hypertension which responded to a small dose of beta-blocker. Due to xerophthalmia confirmed by Schirmer's test (left eye: 3 mm, right eye: 2 mm), the diagnosis of Sjögren's syndrome within drug-induced SLE was made. Administration of IFN beta-1b was terminated and the patient switched to small dose of corticosteroids. Renal functions normalized and ESR dropped to 22/56. Despite repeated advice of the causal relationship between the renal affection and the application of IFNbeta-1b, the patient insisted on its continuation and therapy was restarted. Regular rheumatologic examinations did not reveal any activity of drug-induced SLE. In October 2006, local skin reactions after IFN application became aggravated again and even a haematoma developed in m. rectus abdominis. Administration of IFN was discontinued but on the patient's demand the therapy was re-started again in January 2007. The examination in March 2007 demonstrated relapse of tubulointerstitial nephritis with glycosuria and proteinuria. Therapy with IFNbeta-1b was definitely terminated and the patient began treatment with glatiramer acetate. However, the preparation had to be discontinued because of adverse effects (chest oppression, breathlessness). In November 2007, she experienced another relaps of MS manifested with quadrupyramidal syndrome, and bilateral neocerebellar symptoms completely regressing after treatment with intravenous corticosteroids. Due to intolerance of first-choice therapy, treatment with natalizumab was initiated in December 2007, with no adverse effects. Patient has not had MS attacks, the repeat brain MRI in 2008 showed no new MS lesions. Rheumatologic tests did not reveal any signs of disease activity either.

Tab. 1. Diagnostic criteria of SLE (10).

Diagnostic criteria of SLE	
1. Butterfly erythema	
2. Discoid erythema	Keratosis
3. Fotosensitivity	In medical history and at presence
4. Oral ulcers	Often painful
5. Arthritis	Nonerosive, affecting more joints
6. Serositis	Pleuritis, endocarditis
7. Renal impairment	Proteinuria more than 3+/ or 0,5g
8. Neurological signs	Convulsions, psychosis
9. Haematology	Haemolytic anaemia, leukopenia, lymphopenia, trombocytopenia
10. Imunology	LE cells., anti-DNA, anti-Sm antibodies, falsely positive BWR
11. ANA	Antinuclear antibodies

DISCUSSION

SLE is an autoimmune disease of unclear aetiology mediated by B-lymphocytes producing a number of antibodies that cause vasculitis affecting various internal organs. It is also associated with a change of rheologic blood properties. A characteristic feature is production of antinuclear antibodies (ANA)(Havrdova *et al.* 2001). Several types of these antibodies can be demonstrated, namely histone antibodies, double-stranded (anti-dsDNA) or single-stranded denatured DNA antibodies (anti-ssDNA) and a group of extractable nuclear antigen (ENA) antibodies – ribonucleoprotein antibodies (anti-RNP), anti-Sm (Smith), anti-Scl-70, anti-Jo-1, anti-SS-A/Ro and anti-SS-B/La (https://zdravcentra.cz/).

Drug-induced SLE, or lupus-like syndrome, is a rare complication of therapy with some drugs and clinically imitates SLE. Developing after weeks or years, its occurrence is likely to increase with the duration of the treatment and the cumulative quantity of the inducing agent (Borchers *et al.* 2007). Generally recognized diagnostic criteria of lupus-like syndrome are: a) continual exposure to the inducing drug, b) occurrence of at least 1 symptom typical for SLE (Table 1), c) absence of SLE symptoms before initiation of the therapy with a suspected drug, and d) regression of symptoms within weeks or months after discontinuation of the inducing drug (Borchers *et al.* 2007).

The first case of drug-induced SLE was described in 1945 in a patient treated with sulfasalazine. Subsequently the phenomenon was detected in association with treatment with hydralazine in 1953 (Robert *et al.* 2005; Puttini *et al.* 2005). At present there are approximately 80 drugs known to induce the syndrome, inluding procainamide, chlorpromazine, captopril, methyldopa, acebutol, isoniazid, carbamazepine, penicilamine and sulphasalazine (Puttini *et al.* 2005).

The most frequent symptoms of drug-induced SLE are arthralgia or arthritis, myalgia, serositis, fever, hepatosplenomegalia, skin efflorescence and presence of ANA antibodies for the whole time of administration of the inducing agent (Puttini *et al.* 2005). Nervous system and kidneys are affected less frequently, in contrast to SLE (Beth *et al.* 2003). The age of the affected patients also differs: the typical age of the patients suffering from drug-induced SLE is 50–70 years, in contrast to SLE patients whose average age is approximately 30. Half of the patients with drug-induced SLE are women, whereas the proportion of women in SLE

is 90 %. Impairment of renal functions, which also contributes to mortality, dominates in SLE disease. However, death of a patient with drug-induced SLE is extremely rare. According to the literature, up to 10 % of the U.S. patients diagnosed with SLE actually suffer from drug-induced SLE (http://en.wikipedia.org/wiki/Drug-induced lupus erythemtosus).

Therapy of drug-induced SLE consists in termination of the therapy with the inducing drug, followed by gradual regression of clinical and laboratory abnormalities (Puttini *et al.* 2005).

Exacerbation of diagnosed SLE after exposure to certain substances, e.g. antibiotics, non-steroidal anti-inflammatory drugs (piroxicam, diclofenac) or dermatologics is known. Literature describes development of aseptic meningitis in a SLE patient after administration of ibuprofen (Robert *et al.* 2005).

CONCLUSION

Although treatment of MS patients with IFN beta is very beneficial and improves the prognosis, it may have adverse effects. Induction of "lupus-like syndrome" ranks among relatively rare and serious complications. Confirmation of this diagnosis is an indication for immediate termination of IFN therapy.

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