

Drug-induced systemic lupus erythematosus after 7 years of treatment with carbamazepine

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Abstract. Aim of this work is to describe a late-onset of carbamazepine-induced systemic lupus erythematosus (SLE) in a 38-year-old female patient who had been treated with daily carbamazepine (CBZ) for 7 years because of a bipolar I disorder. When CBZ was discontinued, symptoms rapidly improved and anti-nuclear antibodies (ANA) disappeared. So far, only few cases have been reported of CBZ-induced SLE within months after the beginning of treatment. This is the second (first Italian) case report in literature about CBZ-induced SLE with serological confirmation after years of treatment without previous side effects. (www.actabiomedica.it)

Key words: Carbamazepine, systemic lupus erythematosus, bipolar disorder, epilepsy

Introduction

Carbamazepine (CBZ) is an anticonvulsive drug that is commonly employed for the treatment of seizure disorders, chronic pain syndromes, trigeminal neuralgia, and psychiatric illness (i.e., bipolar disorders, resistant major depression and borderline states) (1). Although CBZ is usually well tolerated by most patients, its potential side effects can vary from mild symptoms to severe systemic hypersensitivity reactions. Common side effects include drowsiness, ataxia, diplopia, nausea, and vomiting; more serious adverse reactions include drug-induced systemic lupus erythematosus (SLE), pseudolymphoma syndrome, aplastic anemia, and agranulocytosis (1, 2).

CBZ-induced SLE within months after the beginning of treatment has also been described (3-12), but this adverse drug reaction remains allocated in the category of "isolated cases", because its frequency appears to be far below the natural prevalence rates for the disease (less than 0.001% of the treated patients) (13). Herein, we report on a case of late-onset SLE in-

duced by CBZ after 7 years of treatment which rapidly resolved after the discontinuation of the drug. Clinical manifestations included rash, enlarged lymph nodes, joint involvement, myalgia, fever, lymphopenia, and positive antinuclear antibodies (ANA). Clinical symptoms, lymphopenia, and ANA titers normalized after the discontinuation of CBZ.

Case report

The 38-year-old female patient presented a three-week history of multiple arthralgia with tenderness and stiffness mainly affecting wrists, elbows, ankles and knees. She noticed a blotchy rash on her hands, legs, and forearms as well as a facial erythema (particularly on cheekbones); photosensitivity of light-exposed skin was also described. The patient reported fever (temperature > 38.5° C), lower back pain, and complained of general weakness with multiple myalgia. She had been treated daily with 1.2 g CBZ for more than 7 years because of a bipolar I disorder.

Throughout CBZ therapy, she did not report any adverse reactions. On admission, serum levels of CBZ were within therapeutic limits (9.5 µg/ml) (1, 2).

The clinical examination revealed a vasculitic rash (erythematous raised patches with follicular plugging) on her hands, knees, and forearms as well as a fixed facial erythema raised on the cheekbones prominences, sparing the nasolabial folds. Joint swelling and tenderness was seen in wrists, elbows, knees, and ankles; muscle weakness (particularly of neck flexors and iliopsoas) was also noticed with an elevation of CK serum concentration (175 U/L). The patient showed mild collar, armpit, and groin adenopathy, but no neurological deficits and no laboratory findings of liver and renal involvement.

Laboratory investigations revealed a hemoglobin concentration of 10.3 g/dl, a hematocrit of 29.5%, a white cell count of 7100 cells per ml (84% neutrophils, 11% lymphocytes, 4% monocytes, and 1% eosinophils), a lymphopenia of 700 cells per ml, a platelet count of 315.000 cells per ml, and an erythrocyte sedimentation rate of 78 mm in the first hour. Creatinine, urea, and electrolyte levels were normal; liver function values were also within the normal range. ANA titer was positive (at a dilution of 1:320) as well as the anti-histone (H2A-DNA) antibody test (at a dilution of 1:640), while anti-Ro-SSA and anti-double-stranded DNA antibodies were negative. Complement C3 and C4 were reduced and immunoglobulins were over the normal range (23%). Chest X-ray appearance was normal and ECG showed no pathological findings, while an abdominal ultrasound examination revealed slight splenomegaly.

In view of the above findings (i.e., polyarthritis, cutaneous vasculitis, photosensitivity, lymphopenia, positive ANA and anti-histone antibody tests), a diagnosis of SLE was made. CBZ was withdrawn and replaced with sodium valproate; at the same time, prednisolone (40 mg daily) and ibuprofen (2x400 mg daily) were added. The patient rapidly improved and the clinical signs of SLE disappeared. Prednisolone and ibuprofen were gradually reduced and stopped after 3 months. The results of ANA and anti-histone antibody tests return at normal values 12 weeks after the discontinuation of CBZ. Subsequently, the patient remained in good clinical conditions for 10 months

without further antiphlogistic or immunosuppressive treatment.

Discussion

Although CBZ-induced SLE within months after the beginning of treatment has also been described (3-10), only one case was reported in literature about CBZ-induced SLE with serological confirmation after years (8 years) of therapy without previous side effects (11). Several major criteria have been used in the diagnosis of drug-induced SLE (12,13). These criteria include the following: (a) the development of SLE-like symptoms during CBZ treatment, (b) the rapid resolution of the clinical and serological features of SLE within weeks after discontinuation of drug therapy, (c) the lack of disease recurrence over the next 10 months and (d) no clinical and laboratory evidence of SLE prior to the beginning CBZ administration. Furthermore, no preceding infection or other SLE-inducing events had to be shown and the presence of anti-histone antibodies is a strong evidence that the symptoms were due to drug-induced SLE (14, 15). In this connection, anti-histone antibodies are present in only 50% of patients with idiopathic SLE, but in 95% of patients with drug-induced SLE; while anti-dsDNA antibodies are usually absent in drug-induced SLE and present in 85% of patients by idiopathic SLE. ANA are not helpful in making this distinction, since they are present in more than 85% of patients affected with either idiopathic or drug-induced SLE.

This case report shows that drug-induced SLE may start even after 7 years of high dose CBZ therapy without previous side effects, and how its symptoms may subside after the discontinuation of CBZ and after treatment with anti-inflammatory drugs (the persistence of symptoms supports the diagnosis of idiopathic SLE). Moreover, in differentiating between idiopathic and drug-induced SLE, this article reaffirms that ANA and anti-dsDNA antibody tests are not helpful, but anti-histone antibodies in the absence of high titers of anti-dsDNA antibodies is a reliable test in confirming the diagnosis of drug-induced SLE.

In conclusion, according to the case report described by Toepfer et al. (1998) (11) - which showed

no significant differences in clinical and serological terms - this article (the second [first Italian] reported in literature about a CBZ-induced SLE after years of treatment) underlines that drug-induced SLE may be an important side effect after long-term CBZ therapy, and how an early diagnosis of this syndrome is crucial, because it usually resolves after the discontinuation of the offending drug and after the administration of anti-inflammatory or immunosuppressive treatment.

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