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Penicillamine induced lupus-like syndrome: a case report

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Several drugs have been suggested to cause lupus-like syndrome. However, penicillamine-induced lupus-like syndrome has only rarely been reported in patients with Wilson's disease. We describe a 6- year-old Taiwanese girl, with a diagnosis of Wilson's disease in November, 1997, who developed lupus-like syndrome 17 months after penicillamine treatment. After treatment with prednisolone and decrease in the dose of penicillamine, her symptoms subsided gradually. This is the first such case reported in a Taiwanese patient. Because the symptoms of drug-induced lupus (DIL) are nonspecific, subjective and variable, the diagnosis of DIL requires awareness of DIL-inducing potential of chronic medication.

Key words: Drug-induced lupus, penicillamine, Wilson's disease

Systemic lupus erythematosus (SLE) has been reported as one of the complications of penicillamine therapy in patients with Wilson disease[1-3]. Walshe first reported the condition in 1968 [2]. Specific criteria for the diagnosis of drug-induced lupus (DIL) have not been formally established. DIL usually occurs after several months or years of continuous therapy. Although the symptom onset can be rapid, patients frequently present with mild or few lupus-like symptoms, which typically worsen the longer the patient is maintained on the implicated drug. Serologic features are often useful in differential diagnosis because IgG anti-(H2A-H2B)-DNA antibodies have been detected in a high proportion of patients with lupus induced by a variety of drugs [4]. Herein we report a case of penicillamine induced SLE in which the patient had high levels of antibodies to histone determined by the Western blot assay.

Case Report

A 6-year-old Chinese girl initially presented with fever, diarrhea , hepatomegaly and impaired liver function. Wilson's disease was diagnosed based on the decreased serum ceruloplasmin level and increased urine copper secretion. Liver biopsy was performed and showed changes compatible with Wilson's disease. She received penicillamine treatment and the clinical course was smooth. However, she developed fever, oral ulcer, and arthralgia involving knees and ankles 17 months after penicillamine treatment. The erythrocyte sedimentation rate (ESR) was 24 mm/1h and 47 mm/2 h; C-reactive protein (CRP) was less than 0.01 (normal < 0.8 mg/dL); a complete blood count revealed WBC: 5.62 k/μL with N/L:50/48, RBC: 3.96 M/μL, Hb:10.8 g/dL, platelet: 370K/μL. Direct Coombs' test was positive and haptoglobin was 199 mg/dL (normal, 64.81-157.48 mg/dL). Urinalysis showed no hematuria and proteinuria. Serum complement level showed C3: 86.1 mg/dL; C4: 24 mg/dL (normal, C3: 81.61-118.41 mg/dL; normal C4: 27.45 ±10.72 mg/dL). Antinuclear antibodies (ANA) on HEp-2 cells showed a homogeneous pattern at 1/5210 dilution; anti-DNA by RIA was 10.4 IU/mL (normal, <12 IU/mL); autoantibodies to non-histone nuclear antigens (Sm, RNP, SS-A/Ro, SS-B/ La, Scl-70) were all negative; and antibodies to nucleohistone complex was demostrated by Western blot assay (Fig. 1) . DIL was highly suspected, and triethylene tetramine dihydrochloride (Trientine) was substituted for penicillamine. However, she suffered from epistaxis and arthralgia 7 days after treatment with Trientine. Prednisolone (20 mg/day) was then prescribed concurrently with a decreasing dose of penicillamine. Arthralgia subsided and 3 months later, follow-up antinuclear antibody showed a homogeneous pattern at 1/1280 dilution. She was on a decreased regimen of steroid (prednisolone 5 mg/day) and free of lupus

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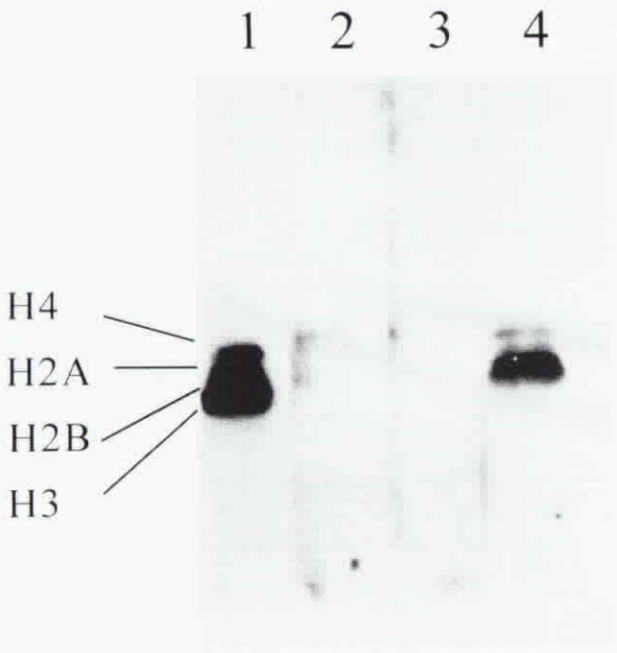

Fig.1. Western immunoblots of antibody to total histones in our patient, a healthy subject and our another patient with SLE, who fulfilled with the American College of Rheumatology criteria. Lane 1: Positive control (anti-histone monoclonal antibody); Lane 2: serum collected from our another SLE patient; Lane 3: serum of a healthy subject; Lane 4: our patient's serum. Antibody reactivity in our patient's serum sample showed obviously staining intensity at the (H2A-H2B)-DNA complex.

symptoms at 3-month-follow-up after the diagnosis of DIL.

Discussion

DIL was first recognized almost 50 years ago in association with hydralazine therapy [4]. Since then, numerous medications have been implicated in the induction of DIL. By far the most frequently associated drugs are procainamide and hydralazine, with approximately 20% incidence for procainamide and 5% to 8% for hydralazine during 1 year of therapy at currently used doses [4]. Quinidine can be considered moderate risk, whereas sulfasalazine, chlorpromazine, penicillamine, methyldopa, carbamazepine, acebutolol, isoniazid, captopril, propylthiouracil and minocycline are relatively low risk [4]. Penicillamine-induced lupus erythematicus was first reported by Walshe in 1968 in a patient with Wilson's disease [2]. The previously estimated frequency suggested by Washe in patients taking penicillamine for Wilson's disease was 0.4% [1]. To our knowledge, this is the first case reported in a Taiwanese patient.

Patients with DIL often do not fulfill criteria for SLE. In particular, symptoms common to SLE such as malar or discoid rash, photosensitivity, oral ulcer, alopecia, and renal or neurologic disorders are very unusual in DIL. Several features distinguish DIL from SLE. The high female-to-male predominance seen in SLE is not usually manifested in DIL. Multisystem involvement such as serious central nervous system (CNS) and kidney dysfunction are absent in DIL. Antibodies to dsDNA, generally regarded as highly specific for idiopathic SLE, are not found in patients with DIL [5,6]. The antibody specificity in DIL is largely restricted to histone-containing antigens [7,8]. It is still unknown why patients with DIL have antinucleo-histone-DNA complex antibodies but without the kidney involvement; it was suggested that these antibodies which are compared with anti-whole nucleosomes do not strongly bind to glomerular basement membrane [8]. Polyarthritis and poly-arthralgia are common manifestations of DIL and have been seen in patients receiving penicillamine for Wilson's disease and cystinuria [1,2]. Our patient developed polyarthralgia after taking penicillamine for 17 months. There was no skin, kidney and CNS involvement seen in our patient. These features are compatible with the previous reports. Other reports have suggested that most penicillamine-induced syndromes occurred between the sixth and the twelfth months of therapy [1]. However, lupus-like syndrome appeared as late as the seventeenth month of penicillamine therapy in our patient.

Specific criteria for the diagnosis of DIL have not been formally established. Diagnosis of DIL generally requires awareness of this risk of chronic medication, laboratory features and the characteristic full recovery after discontinuing treatment. Rubin *et al* suggested the following guidelines for identifying DIL: 1. continuous treatment with a suspected drug for at least 1 month and usually much longer; 2. common presenting symptoms including arthralgias. myalgias, malaise, fever, serositis; 3. anti-histone antibodies, especially IgG anti-(H2A-H2B)-DNA in the absence of other antinuclear antibody specificity; and 4. symptomatic improvement within days or a few weeks after discontinuation of suspected drugs [4]. Our patient developed severe arthralgia, mild anemia after a continuous17-month therapy of penicillamine. Laboratory studies showed positive ANA, positive antibodies specific to nucleohistone complex by Western blot, and normal serum complement levels (C3, C4). Such findings are typical in patients with DIL. Previous reports suggested that serologic test results improved as the lupus erythematosus abated after

penicillamine treatment was discontinued [3].

Although withdrawal of the offending drug is suggested in patients with DIL, our patient could not tolerate the alternative drug well. Decreased dose of penicillamine combined with low dose of prednisolone simultaneously was administered in our patient to treat DIL and to control the underlying Wilson's disease. The symptoms took 4 to 8 weeks to improve and serologic test results improved during the subsequent follow-up. Based on our findings we recommend that penicillamine should be reduced in dosage or discontinued, and steroids used if necessary. We have described a case of DIL induced by penicillamine, a common drug used in the treatment of Wilson's disease. The importance of recognizing the possible complication of DIL in patients receiving potentially DIL-inducing drugs should be emphasized.

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