Systemic lupus erythematosus induced by isoniazid

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Abstract

The case is described of a 73 year old man who presented with a lupus-like syndrome related to treatment with isoniazid and had IgG antinuclear antibodies against the nucleohistone complex (H2A–H2B)–DNA. After a short course of treatment with prednisone and discontinuation of isoniazid the patient's lupus symptoms resolved and a gradual decrease in antibodies to (H2A–H2B)–DNA occurred. This case suggests that isoniazid is capable of inducing an autoantibody specificity associated with drug related lupus.

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Several drugs have been suggested to cause a lupus-like syndrome. Procainamide and hydralazine are the most common and have been shown by prospective studies to induce a mild form of a systemic lupus erythematosus (SLE)-like disease in 5–20% of patients treated.^{1,2} Isoniazid rarely induced this syndrome, with an incidence considerably less than 1%. Drug induced autoantibody production has been found to occur in 20% of patients receiving isoniazid, however.³ We report here a case of isoniazid induced SLE in which the patient had high levels of antibodies to histone determined by an enzyme linked immunosorbent assay (ELISA).

Case report

A 73 year old Mexican man was admitted to the Hospital General de Occidente in April 1989 with a seven day history of fever (39°C), chills, malaise, increased sweating, hyporexia, and mild dyspnoea. One year before admission he had been diagnosed as having pulmonary tuberculosis and was treated with a regimen of drugs including isoniazid (300 mg/day), streptomycin (1 g/day), and pyrazinamide (600 mg/day). The physical examination at admission showed blood pressure 80/50 mmHg, a mild increase in respiratory rate, mild jaundice, erythematous and descamative plaques on the malar region, non-tender cervical lymphadenopathy, and bilateral pleural effusions. At this time he did not report the presence of myalgias, arthralgias, arthritis, mouth ulcers, seizures, nor other symptoms related to SLE. An initial chest radiograph showed moderate bilateral pleural effusions without pulmonary infiltrates.

Laboratory studies showed normocytic-normochromic anaemia (haemoglobin 95 g/l), leucopenia ($1.7 \times 10^9/l$), with lymphocytopenia ($0.55 \times 10^9/l$), neutropenia ($0.47 \times 10^9/l$), and

thrombocytopenia ($80 \times 10^9/l$). The erythrocyte sedimentation rate (Westergren) was 125 mm/hour (normal 0–20 mm/hour). Results of liver function tests were abnormal: serum aspartate transaminase (AST) 144 mU/ml (normal 2–19 mU/ml), serum alanine transaminase 168 mU/ml (normal 3–17 mU/ml), and total bilirubins 41.0 $\mu\text{mol/l}$ (normal 6.8–25.7 $\mu\text{mol/l}$). Determinations of glucose, urea, creatinine, coagulation studies, urine analysis, rheumatoid factor, Venereal Diseases Research Laboratory (VDRL) test, serum complement levels, direct Coomb's test, cryoglobulins, serum protein electrophoresis, and an HIV test were normal or negative. There was no evidence of acid alcohol resistant bacilli in samples of sputum. Aspirated serosanguineous pleural fluid had a protein concentration of 31 g/l; cultures for mycobacteria were negative and no tumour cells were found.

Antinuclear antibodies in this fluid were positive with a homogeneous pattern. Immunological abnormalities included a positive test for antinuclear antibodies on HEp-2 cells showing a homogeneous pattern at 1/256 dilution. Antibodies to nDNA were negative by indirect immunofluorescence using *Crithidia luciliae* as a substrate at 1/10 dilution and by an ELISA. Antibodies to non-histone nuclear antigens (Sm, n-ribonucleoprotein), SS-B/La, Scl-70, PCNA) by a double immunodiffusion method were negative. Serial serum samples were examined for antibodies to total histones and histone complexes by an ELISA as described previously;⁴ increased antibody activity to total histones especially of the IgA class was detected. When the specificity of the antibodies to histone was studied in more detail IgG and IgA reactivity was detected against the H2A–H2B (dimer) complex, especially when bound to DNA ((H2A–H2B)–DNA) (table).

With all these features we believed that our patient had signs and symptoms of a lupus-like disease related to the drugs used to treat his tuberculosis. These were then discontinued. The patient was treated with prednisone (20 mg/day) and he showed symptomatic improvement with resolution of the jaundice, lymphadenopathy, pleural effusions, and malaise. The patient was discharged and followed up as an outpatient. In July 1989 the dose of prednisone was tapered to 10 mg/day and one month later discontinued. The antinuclear antibodies remained positive at all times with the same pattern but the titre decreased from 1/256 to 1/16. After discontinuation of isoniazid a gradual decrease in IgG antibodies to (H2A–H2B)–DNA occurred with only negligible activity detectable nine months later. No

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Activity of antibodies to histone after discontinuation of treatment with isoniazid

Antigen	Ig class	Antibody binding activity in serum sample ^a			
		10 May 1989	12 May 1989	9 June 1989	7 February 1990
Total histone	IgG	0.15 (0.07)	1.02 (0.40)	0.40 (0.10)	1.30 (0.43)
	IgA	3.41 (0.23)	4.34 (0.31)	1.65 (0.11)	4.64 (0.53)
	IgM	0.54 (0.03)	0.30 (0.04)	0.17 (0.04)	0.10 (0.03)
H2A-H2B	IgG	0.25 (0.03)	0.31 (0.18)	0.02 (0.01)	0.08 (0.08)
	IgA	1.27 (0.22)	0.93 (0.13)	0.75 (0.09)	1.08 (0.07)
	IgM	0.12 (0.03)	0.04 (0.03)	0.10 (0.03)	0.02 (0.01)
(H2A-H2B)-DNA	IgG	4.90 (0.44)	2.87 (0.66)	2.09 (0.52)	0.17 (0.09)
	IgA	0.46 (0.11)	0.04 (0.04)	0.01 (0.01)	0.01 (0.00)
	IgM	0.06 (0.01)	0.01 (0.00)	0.00 (0.00)	0.01 (0.00)

^aValues were determined by enzyme linked immunosorbent assay (ELISA) using class specific detecting reagents (Caltag Inc, Burlingame, CA, USA) and are expressed as mean (SD) units of absorbance (triplicate determinations). Normal serum binding was <0.10 absorbance units on all antigens.

reactivity with DNA bound to methylated albumin⁴ was detected at any time (data not shown). Antibodies to total histone of all three classes suddenly decreased between May and June 1989 but IgG and IgA binding to total histones returned to the original level after another eight months (table). In February 1990 the patient was readmitted due to persistent leucopenia and neutropenia. A bone marrow aspirate was taken and the findings were consistent with acute myelogenous leukaemia. Chemotherapy was begun.

Discussion

Isoniazid has previously been implicated in drug induced lupus.⁵ The lupus-like illness induced by this drug is rare but positivity for antinuclear antibodies is seen in approximately 22% of patients treated for a mean of six months.³ No formal diagnostic criteria for drug induced lupus have been developed but the criteria for idiopathic SLE⁶ have generally applied. Our patient had lupus-like symptoms and a positive test for antinuclear antibodies with a homogeneous pattern. The haematological malignancy was probably present since the onset of his disease, but features such as an erythematous rash, pleural effusions and a positive test for antinuclear antibodies cannot be explained by the leukaemia. Moreover, since the discontinuation of isoniazid the symptoms of the SLE-like syndrome have not recurred and the titre of antinuclear antibodies has decreased. Antibodies to histone, especially with specificity for the (H2A-H2B)-DNA complex, support the diagnosis of isoniazid induced lupus.

In patients with procainamide induced lupus the antinuclear antibodies have been shown to be directed primarily against histone components of the nucleus.⁷ Our patient had a similar serology: a positive titre for antinuclear antibodies with specific antibodies to histone, and without antibodies to nDNA and non-histone nuclear proteins. A predominant specificity in this patient was directed at the histone H2A-H2B dimer, similar to that observed in procainamide induced lupus.^{8,9} Antibody binding was enhanced when DNA was com-

plexed to the H2A-H2B antigen. Increased reactivity with the (H2A-H2B)-DNA complex has been observed in serum samples from patients with lupus induced by procainamide and quinidine, but these serum samples were not reactive with DNA alone.¹⁰ DNA apparently stabilises a protein epitope in the H2A-H2B complex, or the complete epitope is generated by the juxtaposition of histone and DNA.

Interestingly in our patient antibody activity to total histones was unusual in being predominantly IgA and fluctuated during the illness, suggesting that another population of antibodies to histone existed and behaved independently of the treatment with isoniazid. The sudden decrease in the activity of antibodies to total histone may have been the result of the immunosuppressive effect of prednisone, followed by a rebound to pretreatment levels when treatment was discontinued. It is possible that antibodies to histone in this patient are related to idiopathic SLE rather than isoniazid induced lupus. Systemic lupus erythematosus, however, is often associated with renal and neurological disease, antibodies to native DNA, Sm or SS-A/Ro, or both, and low complement levels. None of these features was present in this patient. The highly unusual IgA predominance of the activity of antibodies to total histone might reflect a mono- or oligoclonal antibody related to the underlying leukaemia.

In contrast to the activity of antibodies to total histone, antibodies to (H2A-H2B)-DNA were predominantly IgG and continued to decrease after the withdrawal of treatment with isoniazid. Antibodies to (H2A-H2B)-DNA were not detected in 25 patients with tuberculosis receiving long term treatment with isoniazid while remaining free of lupus-like symptoms (García-De La Torre and Rubin, unpublished observations). The correlation of IgG antibodies to (H2A-H2B)-DNA with symptomatic lupus-like disease appears convincing, however, and these results suggest that isoniazid is capable of inducing this auto-antibody specificity. The mechanism by which drugs induce clinical and serological manifestations of SLE is not known, but several hypotheses have been offered to explain the aetiology of autoantibodies in drug induced lupus.¹¹ The correct mechanism will need to explain how a variety of structurally diverse pharmacological agents^{1,2,5} induce a similar spectrum of symptoms and signs including a characteristic specificity of antibodies to histone.

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- 1 Lee S L, Chase P H. Drug-induced systemic lupus erythematosus: a critical review. *Semin Arthritis Rheum* 1975; 5: 83-103.
- 2 Weinstein A. Drug-induced lupus erythematosus. *Prog Clin Immunol* 1980; 4: 1-21.
- 3 Rothfield N F, Bierer W F, Garfield J F. Isoniazid induction of antinuclear antibodies. *Ann Intern Med* 1978; 88: 650-2.

- 4 Rubin R L. Enzyme linked immunosorbent assay for anti-DNA and anti-histone antibodies. In: Rose N R, Friedman H, Fahey J L, eds. *Manual of clinical immunology*. Washington: American Society of Medicine 1986: 744-9.
- 5 Hess E. Drug-related lupus. *N Engl J Med* 1988; **318**: 1460-2.
- 6 Tan E M, Cohen A S, Fries J F, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 1271-7.
- 7 Rubin R L, Reimer G, McNally E M. Procainamide elicits a selective autoantibody immune response. *Clin Exp Immunol* 1986; **63**: 58-67.
- 8 Totoritis M C, Tan E M, McNally E M. Association of antibody to histone complex H2A-H2B with symptomatic procainamide-induced lupus. *N Engl J Med* 1988; **318**: 1431-6.
- 9 Portanova J P, Arndt R P, Tan E M. Anti-histone antibodies in idiopathic and drug-induced lupus recognize distinct intrahistone regions. *J Immunol* 1987; **138**: 446-51.
- 10 Burlingame R W, Rubin R L. Antihistone antibody induction by drugs implicates autoimmunization with nucleohistone. *Arthritis Rheum* 1989; **32**: S22.
- 11 Solinger A M. Drug-related lupus. Clinical and etiologic considerations. *Clin Rheum Dis* 1988; **14**: 187-200.