Case report

Pulmonary hypertension in hydralazine induced systemic lupus erythematosus: association with C4 null allele

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SUMMARY A patient who developed pulmonary hypertension and systemic lupus erythematosus as a complication of hydralazine therapy is reported. She was a slow acetylator and in addition was found to have a null allele at the C4_A locus.

Key word: hydralazine.

This 52 year old Caucasian woman presented in March 1980 after collapsing. She was found to be in paroxysmal atrial fibrillation and hypotensive. Several months later hypertension was diagnosed and she was commenced on hydralazine 150 mg and atenolol 200 mg daily. Early in 1983 she first complained of arthralgias affecting her wrists, elbows, and knees followed by breathlessness on exertion, pleuritic chest pains, fever, mouth ulcers, and nailfold vasculitis. When examined she was found to have synovitis of her wrists, pedal oedema, and a raised jugular venous pressure.

Investigations showed a leucopenia of $2.8 \times 10^9/l$, haemoglobin of 8.9 g% (89 g/l), an erythrocyte sedimentation rate (ESR) of 55 mm/1st h, and positive LE cells. Antinuclear antibodies (ANA) were present at 800 units. Antibodies to double stranded deoxyribonucleic acid (dsDNA) were initially negative, and antibodies to single stranded deoxyribonucleic acid (ssDNA) were borderline at 28 (normal <28). The IgM was increased at 162 mg/dl (1.62 g/l) (normal <40 mg/dl (0.4 g/l)) and C4 diminished at 24 mg/dl (normal 25-45 mg/dl). A

chest x ray and V/Q lung perfusion scan suggested pulmonary embolism. The hydralazine was discontinued, and the fever abated.

When seen four weeks later she still complained of polyarthralgias affecting her wrists mainly, occasional pleuritic chest pains, and dyspnoea on exertion. On examination a loud P2 was audible; there was an atrial gallop. Antibodies to both dsDNA (16) (normal <10) and ssDNA (43) were now positive. The ANA test was still positive (400 units) but the Venereal Disease Research Laboratory test and 'lupus anticoagulant' were negative. The IgM levels had fallen to 75 mg/dl (0.75 g/l). Chest x ray showed areas of linear opacity and repeat V/Q lung scans showed similar matched defects as seen previously. An M mode echo was normal, as were bilateral ascending venograms. At cardiac catheterisation the pulmonary artery pressure was 38/22 mmHg.

The patient was anticoagulated with warfarin and treatment started with prednisone 20 mg daily. The ESR dropped to 26 mm/1st h and the ANA to 50 units. Prednisone was gradually reduced.

Four months later dsDNA, ssDNA, and ANA were negative. The haemoglobin had risen to 13.1 g% (131 g/l), white blood cell count to $6.5 \times 10^9/l$. In 1985 (approximately 18 months later) all immuno-

Table 1 Swan-Ganz catheter results

	27 Oct 1983	18 Oct 1985
Right auricle (mean)	6	6
Right ventricle	36/3	24/4
Pulmonary artery	38/22	24/18
Pulmonary artery wedge pressure	14	16

Values are in mmHg.

logical tests were negative with an ESR of 15 mm/1st h. Repeat chest x rays, apart from hypertensive changes, did not show any of the opacities visible in 1983. Repeat cardiac catheterisation showed the pulmonary artery pressure to be 24/18 mmHg. The patient was in hypertensive left ventricular failure at the time, which explains the increase in pulmonary artery wedge pressure (Table 1). She was found to be a slow acetylator, and the HLA typing of class I, II, and III antigens for the patient and her family was performed and she was found to have a null allele at the C4_A locus.

Discussion

Pulmonary hypertension is being reported with increasing frequency in systemic lupus erythematosus (SLE),¹⁻⁴ and serological markers such as the 'lupus anticoagulant',^{1,5} antibodies to ribonucleoprotein,⁶ the rheumatoid factor, and the anti-centromere antibody^{3,6,7} have been evident in several groups of patients. Although pulmonary hypertension is most common in progressive systemic sclerosis,⁸ particularly the CREST variant,⁹ its occurrence is also particularly common in the syndrome of mixed connective tissue disease.¹⁰ It has been infrequently reported with rheumatoid arthritis,^{11,12} discoid lupus,¹³ Sjögren's syndrome,¹⁴ dermatomyositis,¹⁵ and Whipple's disease.¹⁶ Often accompanied by Raynaud's phenomenon, the pulmonary hypertension seen in the connective tissue diseases most clearly resembles that seen in the 'primary' variety, but other pathogenetic mechanisms have been implicated in a minority of cases.⁶ Thromboembolism, most often seen in SLE and also in the syndrome of mixed connective tissue disease, which may be associated with the 'lupus' anticoagulant,^{6,17} immune complex deposition,^{3,18} and pulmonary vasculitis,^{19,20} have all been linked to its development. The incidence of a 'lupus-like' syndrome induced by hydralazine is dose dependent and is higher in women taking 200 mg/day.²¹ Patients receiving hydralazine who develop a 'lupus' syndrome are almost always slow acetylators and

an increased incidence of the HLA class II antigen DR4 has been found.^{22,23} More recently an association with null alleles coding for C4_A and C4_B has emerged.²⁴ The syndrome tends to develop after at least three months of therapy,²⁵ and often only after three years.²¹ Drug induced lupus is usually characterised by limited organ disease and a less severe clinical course than idiopathic SLE.²⁶

The clinical picture is dominated by prominent complaints of polyarthralgias and polyarthritis, as in our patient. Chest pain from pleurisy is also common. While vasculitis—including renal,²⁷ retinal,²⁸ and cutaneous^{21,29}—may also occur, central nervous system disease, hypocomplementaemia, and antibodies to double stranded natural DNA are infrequently encountered.²⁵ Antinuclear antibody test positivity occurs in about half of the patients receiving hydralazine therapy³⁰ and may be prolonged after discontinuation of therapy.

Our patient developed an SLE-like illness with pulmonary hypertension one and half years after the start of hydralazine 150 mg daily for treatment of hypertension. In view of the fact that her lupus anticoagulant test and venograms were negative it is presumed that the pulmonary shadowing seen radiologically occurred on the basis of a pulmonary vasculitis, though in the absence of histological evidence microthromboembolism and infarction cannot be definitively excluded.

This appears to be the first recorded case of pulmonary hypertension occurring as part of a drug induced SLE syndrome. Our patient, as well as being a slow acetylator, showed the HLA-DR4 antigen previously described in association with hydralazine SLE. Interestingly she also carried a null allele for C4_A in accordance with the more recently suggested association between C4 null alleles and this syndrome.²⁴ She differed, however, from other cases in that antibodies to dsDNA were present in addition to the demonstration of LE cells. Clinical and immunological evidence of the 'lupus-like' illness subsided after treatment was stopped.

The authors wish to thank Prof Richard Batchelor for his assistance and Dr Clein of Poole General Hospital for his permission to publish this case. We also wish to thank Mrs Celia Pritchard for the typing of the manuscript.

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