PRIMARY PULMONARY HYPERTENSION IN SYSTEMIC LUPUS ERYTHEMATOSUS

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SYNOPSIS

Five women with systemic lupus erythematosus (SLE) developed pulmonary hypertension which was found to be a late complication in our patients. The course and outcome did not appear to correlate with the activity of the systemic disease. Treatment of the primary disease did not influence the subsequent course of the pulmonary hypertension which was considered the cause of death in all the patients.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem disease in which the lungs are often involved (1-5). The relatively late occurrence of pulmonary hypertension in lupus has only recently been recognised (6). We report 5 such patients.

MATERIALS AND METHODS

An ongoing prospective study of patients with SLE was carried out from 1974. Patients suspected to have SLE were warded for clinical and laboratory workup, and the diagnosis was based on the criteria of the American Rheumatic Association (7). Following initiation of appropriate therapy the patients were followed up by one team at the SLE clinic.

The diagnosis of pulmonary hypertension was based on clinical features, chest x-rays, electrocardiogram, echocardiography, and in two of the patients by cardiac catheterisation. Other causes of pulmonary hypertension were excluded in all patients using in addition respiratory function tests and lung scans.

RESULTS

Five patients over 10 years of a total of 300 patients were found to have pulmonary hypertension not attributable to cardiac, pulmonary, thromboembolic or other disease. All five were young women. The most common initial symptoms of SLE were fever, arthralgia and rash, and there was an interval of 18 to 84 months (mean 45) before the diagnosis of SLE was made. Details of the initial clinical, serological features and therapy was shown in Table I. Prednisolone was given at diagnosis of SLE in three of the five and was not indicated till later in two.

Table II shows the onset, clinical features and the course of pulmonary hypertension in these patients. Symptoms due to pulmonary hypertension first occurred between 27 and 78 months (mean 60) after the initial symptoms of SLE. All patients had dyspnoea and fatigue. Two had hoarseness of voice; dysphagia, haemoptysis and angina occurred separately in one patient each. Survival after onset of symptoms of pulmonary hypertension ranged between 7 and 87 months (mean 39).

There was no consistent relationship found between the activity of SLE assessed clinically and serologically, the therapy given, and the development and progression of pulmonary hypertension. Table III gives details of these aspects at the time of confirmation of pulmonary hypertension. Patients 1 and 4 were well and had no other clinical manifestations of lupus activity when the pulmonary hypertension developed. Patient 2 was seen with active lupus and thrombocytopenia. Patient 3 was noticed to have vasculitic lesions and Raynaud's phenomenon after the onset of symptoms attributable to pulmonary hypertension. Patient 5 was seen with congestive cardiac failure preceded by many years of multiple symptoms of SLE. A representative case is described.

TABLE I
PRESENTING FEATURES OF SLE

Patients				Initial manifestations	Duration of symptoms at diagnosis of SLE (months)	Other systems involved during course of SLE	Serological findings at diagnosis of SLE	Treatment given
	Age at diagnosis	Sex	Race					
1.	28	F	Ch	Fever, arthralgia rash Pregnant 4 months at diagnosis of SLE	28	Nephritis	ANF 1/128 LE cells negative VDRL negative C3 33, and C4 7mg/dl	Initially none. Steroids 9 months after diagnosis of SLE for nephritis.
2.	23	F	Ind	Fever arthralgia	27	Thrombocytopenia Marrow hypoplasia	ANA 1/128 LE cells positive C3 88 C4 16 mg/dl	Steroids given at diagnosis of SLE for thrombocytopenia and bleeding
3.	29	F	Ch	Rash, oedema, arthralgia	18	Nephritis Vasculitis Psychosis	ANA 1/256 LE cells positive VDRL negative C3 32, C4 24 mg/dl	Steroids at diagnosis for nephritis for 87 months. Restarted 15 months later for reactivation.
4.	28	F	Ch	Arthritis, Raynaud's Rash	60	Coomb's positive haemolytic anaemia	LE negative High anti DNA and ANA Complement normal VDRL negative	Initially chloroquine, indomethacin. Steroids 6 years after diagnosis of SLE for joint pains, serological activity, dyspnoea.
5.	32	F	Ch	Fever, polyarthritis rash	84	Haemolytic anaemia	LE positive	Given steroids at diagnosis here.

Ch = Chinese
Ind = Indian

TABLE II
PULMONARY HYPERTENSION: ONSET, CLINICAL FEATURES AND COURSE

Patient	Interval from onset of SLE to first manifestations of pulmonary hypertension (months)	Findings	Survival after onset of symptoms of pulmonary hypertension (months)	Progress
1	46	Fatigue, dyspoea, hoarseness, haemoptysis, syncopal attacks Catheterisation: PA pressure 100/40 mmHg PVR = 936 dynes-sec-cm^{-5}	18	Severe hypotension following catheterisation. Symptoms progressive. Died elsewhere two months later with acute dyspnoea.
2	27	Fatigue, dyspnoea Catheterisation: PA pressure 70/30 mmHg PVR = 968 dynes-sec-cm^{-5}	7	Fever and increasing dyspnoea following catheterisation; died on the third day.
3	78	Dyspnoea	67	Progressive dyspnoea; died.
4	72	Hoarseness, dyspnoea, fatigue, angina	87	Found dead at home.
5	78	Dyspnoea, cardiac failure, dysphagia	18	Died suddenly elsewhere.

PA = pulmonary artery
PVR = pulmonary vascular resistance

TABLE III
SLE AT CONFIRMATION OF PULMONARY HYPERTENSION

Patient	Clinical features of other system involvement	LE cells	DNA-ab	A.N.A.	C_3 mg/dl	C_4 mg/dl	Therapy
1	Cough	Negative	Negative	Negative	48	10	Steroids given for nephritis a month beofre onset of features of pulmonary hypertension.
2	Hair loss, fever, anorexia, weight loss, rash, bleeding gums	Positive	—	1/128	88	16	Steroids for SLE 5 months prior to detecting pulmonary hypertension
3	Raynaud's, vasculitis	Negative	Negative	1/32	35	13	Had prolonged courses of steroids for nephritis and was on steroids at onset of dyspnoea
4	Asymptomatic	Positive	1/1024	1/2048	50	13	Not on steroids prior to symptoms of pulmonary hypertension
5	Fever, polyarthritis	Positive	—	—	—	—	SLE and pulmonary hypertension diagnosed at the same time, given steroids.

Patient 3

H.C., a 29 year old Chinese woman, presented in January 1972 with joint pains for eighteen months, malar rash and oedema for a year. She was admitted to another hospital, diagnosed to have SLE and given steroids for nephrotic syndrome. The proteinuria persisted and in January 1973 she became psychotic and was referred to the University Hospital. On admission, her heart and lungs were normal. She was grossly oedematous. The haemoglobin was 9.7 gm/dL, WBC 5,600 mm^3 abd ESR 72 mm/hr. There was heavy proteinuria (2.6 Gm/24 hours) with hypoalbuminaemia and urine microscopy showed 96 RBC and 90 WBC/ul. LE cells and ANA were both positive. Renal biopsy showed features compatible with severe active lupus nephritis. Respiratory function tests revealed: forced vital capacity (FVC) 2490 ml, forced expiratory volume in one second (FEV_1) 2050 ml, total lung capacity (TLC) 3030 ml and carbon monoxide transfer factor 15 ml/min/mmHg (predicted 17 ± 5). She was given steroids and recovered completely by 1974.

In 1977 she complained of exertional dyspnoea. There was a loud pulmonic closure sound. The ECG and chest x-ray showed changes compatible with pulmonary hypertension. By 1980 she had mild cardiomegaly, further decreasing effort tolerance, ECG changes of right ventricular hypertrophy (Fig. 1) and her chest x-ray showed enlarged pulmonary arteries with normal lung fields (Fig. 2). At this time, her vital capacity was 2096 ml, and the FEV_1 1990 ml. In 1982 she was hospitalised with Raynaud's phenomenon, vasculitic rash over her fingers and marked dyspnoea. Echocardiographic examination (Fig. 3) suggested right ventricular overload and pulmonary hypertension. Lung volumes showed little change; blood gases showed a pO_2 of 77 mmHg (10.3 kPa), pCO_2 33 mmHg (4.4 kPa). A lung scan did not show any focal defects. She deteriorated and died suddenly. Consent for post mortem could not be obtained.

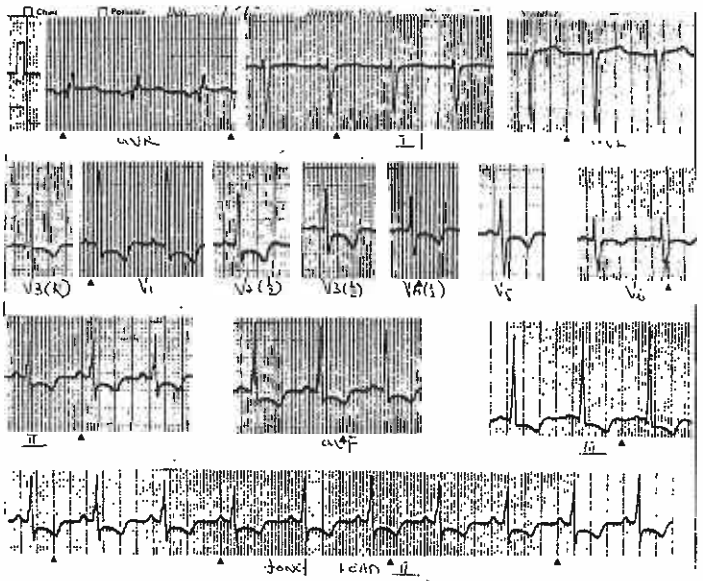

Figure 1 — ECG showing right ventricular hypertrophy and strain.

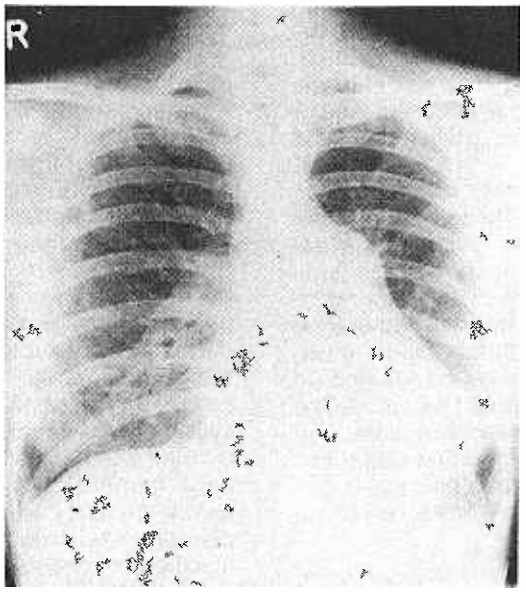

Figure 2 — Chest x-ray showing cardiomegaly and features of pulmonary hypertension.

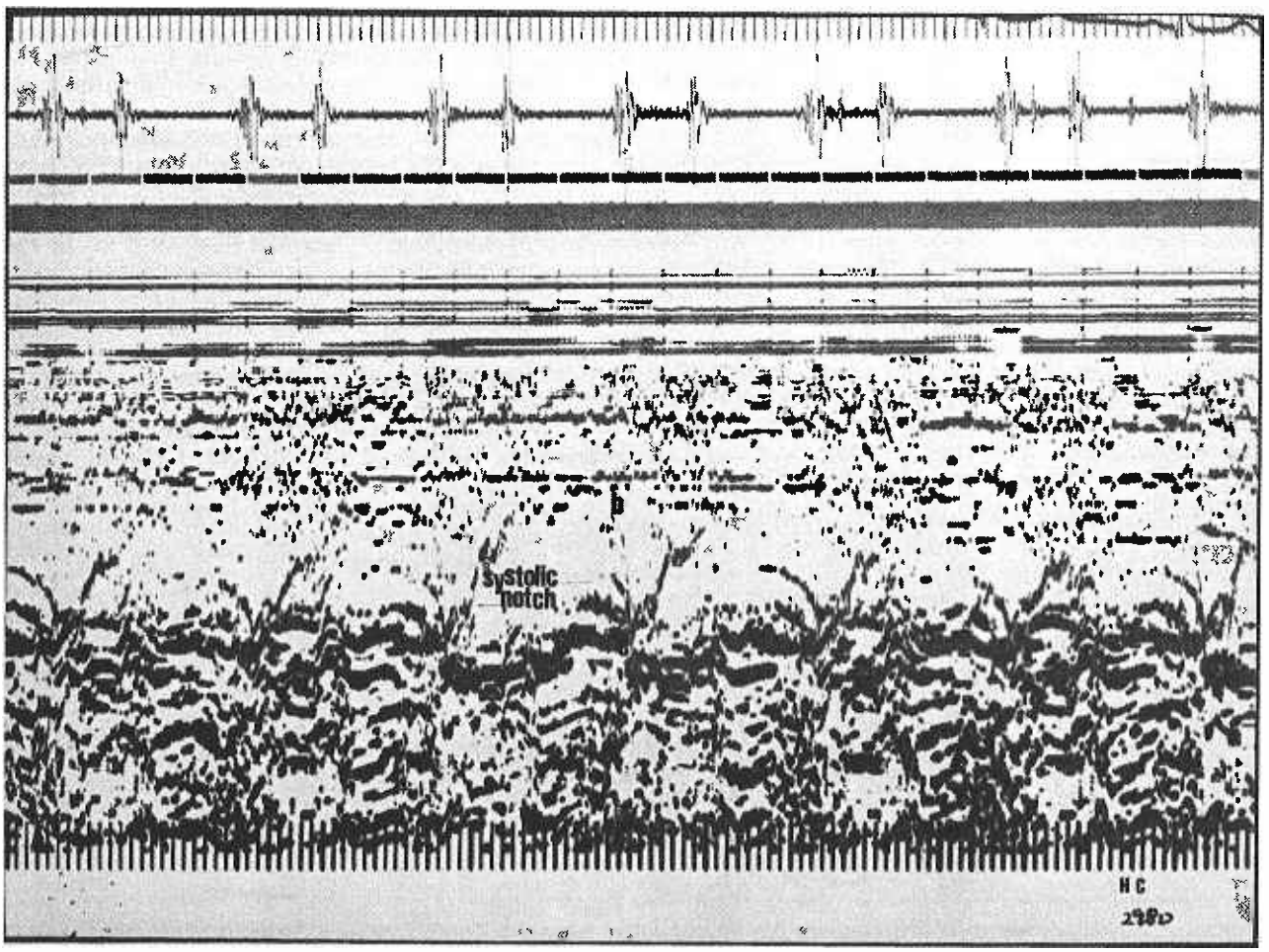

Figure 3 — M-mode echocardiogram of patient 3 showing features of pulmonary hypertension: namely mid-systolic notch and steep b-c slope (labelled).

DISCUSSION

Lung complications resulting from collagen vascular disease are seen most frequently in SLE, the reported incidence being 50-70% (4). Clinical manifestations include cough, dyspnoea and pleuritic pain. Radiographic features include pleuritis and/or effusion, acute lupus pneumonitis, atelectasis, and diffuse interstitial disease.

Pulmonary hypertension in patients with lupus has been described since 1973 (8-14). These patients had no underlying pulmonary disease. Our patients are considered to have primary pulmonary hypertension because of the history and absence of any features to suggest an underlying cause. We did not catheterise all of them. The risks of catheterisation in these patients are well known (15) and were manifested, in the two (patients 1 and 2) who had this procedure. The similarity in the findings and course of disease between those who underwent catheterisation and those who did not suggest a similar disease process in the two groups. Our patients appear similar to those described by other authors (8-14).

Other causes of pulmonary hypertension were carefully excluded by clinical, radiological, physiological and echocardiographic means. None of the patients had features of scleroderma or other connective tissue disease. Though some patients with interstitial lung disease may have no clinical or radiological changes (16) we do not think that interstitial lung disease was the cause of pulmonary hypertension in our patients.

There were no obvious difference between these patients and others with SLE at initial presentation. Asherson and Boey et al (6, 17) found circulating lupus anticoagulant in five of their six patients with pulmonary hypertension. This antibody was associated with a hypercoagulable state and venous thrombosis. Patients with circulating anticoagulant also had a higher risk of spontaneous abortions, thrombocytopenia, cerebral lupus and biological false positive tests for syphilis. In their series Raynaud's phenomenon and vasculitis were seen in three patients, two having both these features. We have no information about the presence of circulating anticoagulant in our patients but the serological tests for syphilis were negative in three of the five. Three were married and had children prior to having active clinical lupus (patients 1, 3 and 5). Thrombocytopenia was present in patient 2 while patients 3 and 4 had Raynaud's phenomena during the course of their illness; patient 3 also had psychosis and vasculitic skin lesions.

The marked delay between the initial manifestations of SLE and that of pulmonary hypertension is worthy of note. Those patients who had severe SLE improved with treatment (patients 1, 2 and 3) so that

the corticosteroids could be tapered off or discontinued completely (patient 3). Patients 2, 4 and 5 had no specific treatment till manifestations of pulmonary hypertension set in. Further, the manifestations of pulmonary hypertension were seen in the absence of signs of active systemic disease in patients 1, 3 and 4. These observations suggest early silent pulmonary vascular involvement with insidious progression and delayed clinical manifestations. Reactivation of SLE may aggravate pulmonary hypertension as appeared to be the case in patients 2, 3 and 4.

The recent recognition of the significance of lupus anticoagulant may be useful. Detection of this factor may identify patients likely to develop thrombotic complications and pulmonary hypertension so that vigorous therapy, including steroids and perhaps anticoagulants may be given to attempt prevention of this fatal complication.

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