

Recovery from pulmonary hypertension in an adolescent with mixed connective tissue disease

Deborah M Friedman, Hal J Mitnick, Delores Danilowicz

Abstract

This paper describes the case of an 11 year old girl who presented with mixed connective tissue disease which was complicated by the development of pulmonary hypertension. This case is unique with respect to the young age of onset, the serial non-invasive method used to follow the disease process, and the favourable response to treatment with vasodilator and anti-inflammatory drugs.

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Pulmonary hypertension is a serious and baffling clinical problem, the optimum evaluation of which still eludes definition and the treatment of which is largely empirical. Secondary pulmonary hypertension may result from a variety of cardiac, pulmonary, or systemic diseases, or may present as an apparently primary disease with a predominantly arteriopathic, veno-occlusive or thromboembolic nature. Often life threatening in severity, the disease begins subtly in a poorly accessible site so that optimum diagnostic evaluation is delayed and difficult and treatment is still not fully defined. This problem has now become more widely recognised in children.¹

Mixed connective tissue disease is an autoimmune disease rarely seen in children,² but which is known to be associated with the development of pulmonary hypertension,³⁻⁵ which usually carries an unfavourable prognosis. This paper describes an 11 year old girl with mixed connective tissue disease who developed well documented pulmonary hypertension and who responded to aggressive treatment with apparent pulmonary vascular recovery.

Case report

An 11 year old Asian girl presented with mixed connective tissue disease, including fever, swollen hands, Raynaud's phenomenon, pleuro/pericarditis, Coombs' positive anaemia, lymphadenitis and parotitis, circulating anti-coagulant, restrictive lung disease, and intermittent changes in urinary sediment. The representative serological profile early in her course included an antinuclear antibody titre of 1/640 in a diffuse and speckled pattern, a positive ribonucleoprotein (RNP) titre of $1/4 \times 10^6$, an SM titre positive at 1/64, a latex fixation of 1/320, a negative titre for antibodies to double stranded DNA, a normal initial C3, but C4 markedly reduced at 75 mg/l. She was treated with salicylates and steroids, which resulted in clinical improvement despite a delay

in growth with vertebral fractures and aseptic necrosis of the femoral head. Azathioprine was later added for disease control.

At 15 years of age an asymptomatic murmur was attributed to mitral valve prolapse, but no other abnormalities were seen by echocardiography. When she was 16 years old, one year after discontinuing azathioprine treatment and decreasing the dose of steroids, an intercurrent respiratory infection indicated pulmonary hypertension, for which the steroid dose was increased.

Physical examination showed a small girl with an immature appearance and Cushingoid features, weighing 34 kg and with a blood pressure of 105/85 mmHg. Her skin was taut and dry and she had small tapered fingers and toes. There was an area of chronic ischaemic changes on her right foot and ankle. There was no Homan's sign, no lymphadenopathy, and no hepatosplenomegaly. There was no jugular venous distension, clubbing, cyanosis or oedema. Her lungs were clear and pulses strong. The right ventricular impulse was increased; the second heart sound was palpable at the left upper sternal border and was loud and single. There was an early systolic apical click and an intermittent grade 2/6 apical mid to late systolic 'whooping' murmur, but no diastolic murmur.

An electrocardiogram showed a right axis deviation of $+120^\circ$ and non-specific T wave changes, but no definite chamber hypertrophy. A chest radiograph showed a normal heart size but a dilated main pulmonary artery shadow and an enlarged right ventricle. The lung fields were clear. An echocardiogram showed a dilated right ventricle and pulmonary artery with evidence of pulmonary hypertension by time intervals and pulmonary flow velocity timing (table 1). There was holosystolic mitral valve prolapse without regurgitation.

Cardiac catheterisation (table 2) showed pulmonary hypertension at one third of systemic levels (aortic systolic pressure 115 mmHg, pulmonary 37 mmHg) and a low cardiac index (2 l/min/m^2), resulting in a pulmonary vascular resistance of 6 U/m^2 . The pulmonary artery pressure increased with exercise. Trials with oxygen, isoprenaline hydrochloride, and hydralazine showed that the last drug was the most efficacious and best tolerated vasodilator.

Further evaluation at the time of catheterisation showed a haemoglobin concentration of 91 g/l, an erythrocyte sedimentation rate of 120-140 mm/hour, white blood cell count $4-10 \times 10^9/\text{l}$, and platelet count $101 \times 10^9/\text{l}$. The protime was normal, but the partial thrombo-

Division of
Pediatric Cardiology,
New York University
Medical Center,
New York, NY, USA
D M Friedman
D Danilowicz

Division of
Rheumatology,
New York University
Medical Center,
New York, NY, USA
H J Mitnick

Correspondence to:
Dr Deborah M Friedman,
Division of
Pediatric Cardiology,
New York University
Medical Center,
550 First Avenue,
New York, NY 10016, USA.

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Table 1 Clinical data

Measured parameter	March 1984	May 1984*	July 1984	August 1984	October 1984†	January 1985	March 1985	July 1985
Right systolic time interval	0.44	0.44	0.34	0.40	—	0.44	0.38	0.40
Pulmonary artery acceleration time (ms)	80	80	80	128	—	85	130	100
Erythrocyte sedimentation rate (mm/hour)	130	25	100	96	62	95	40	52
Haemoglobin (g/l)	99	133	—	—	114	—	104	—
Weight (kg)	34	40	43.5	41.5	43.5	—	43.5	42.3
Platelets ($\times 10^9/l$)	137	—	—	100	168	177	198	168
C3 (mg/l)	—	—	—	—	—	—	—	—
C4 (mg/l)	13	—	24	—	—	—	—	—
RNP	1/40 960	—	—	—	—	—	—	—
Treatment:								
Prednisone qod‡ 5 mg	↑ 15 qd‡	↑ 20 tid‡	↓ 40 qod	—	↓ 35 qod	↓ 20 qod	—	↓ 12.5 qod
Hydralazine		Begin 25 mg qid‡						
Cyclophosphamide			Begin 37.5 mg qd	→	Stop for low white blood cell count	Restart 25 qd		

*Date of first catheterisation.

†Date of second catheterisation.

‡qod=every other day; qd=every day; tid=three times a day; bid=twice a day; qid=four times a day.

Table 2 Catheterisation data

	10 May 1984					9 October 1984	
	Rest	100% oxygen	Isoprenaline hydrochloride*	Hydralazine	Exercise	Rest without drugs	Hydralazine
Heart rate (beats/min)	70	74	94	94	120	85	115
Aortic pressure (mmHg)	115/75, 95	105/75, 88	105/68, 75	95/70, 82	110/88, 102	125/85, 100	100/72, 85
Aortic saturation (%)	96	99	97	97	96	98	98
Aortic Po ₂ (mmHg)	89	430	95	96	—	98	95
Pulmonary pressure (mmHg)	37/10, 20	42/20, 30	45/25, 35	35/12, 24	48/30, 40	50/28, 34	45/25, 34
Pulmonary saturation (%)	60	70	63	68	75	69	75
Pulmonary Po ₂ (mmHg)	32	40	36	35	—	45	50
Mean right atrial pressure (mmHg)	3	3	8	3	—	3	3
Mean pulmonary capillary pressure (mmHg)	5	4	5	6	—	7	5
Oxygen consumption (ml/min/m ²)	124	—	206	181	—	145	128
Arteriovenous oxygen difference (ml/dl)	4.5	4.5	4.4	3.9	2.8	4.1	3.2
Cardiac output (l/min)	2.4	—	4.7	4.7	—	4.9	5.4
Pulmonary vascular resistance (U/m ²)	6	—	6	3/8	—	5.5	4.9
Systemic vascular resistance (U/m ²)	38	—	14	17	—	20	16
PVR/SVR	0.2	—	0.4	0.2	—	0.3	0.3
Right systolic time interval (M mode)	0.23	—	0.38	0.29	—	0.40	—
Doppler acceleration time (ms)	80	—	—	80	—	128	—

*Patient developed nausea, hypertension, and bradycardia.

plastin time was increased 43.9 s (control 32 s), and a circulating anticoagulant was shown. A single urine sample revealed 4+ proteinuria with 5–10 red blood cells and white blood cells per high power field. Subsequent urine analysis, however, was normal and nephritis was not seen. Pulmonary function tests showed a moderate restrictive abnormality with normal diffusion, and gallium and ventilation/perfusion lung scans, and peripheral venous Doppler examination ruled out pulmonary emboli and deep vein thrombosis. A lung biopsy sample was not taken. Nailfold capillary microscopy showed dilatatory changes of the scleroderma type. Serologies remained positive as before, with a low C4 and a positive titre for antiSSA (Ro). In the presence of pulmonary hypertension and active serologies, she was treated again with high dose prednisone, hydralazine was begun at 25 mg four times a day by mouth, and cyclophosphamide was added for further immunosuppression.

Over the next four months she showed subjective and objective improvement on this drug regimen. The Doppler pulmonary artery acceleration time was still prolonged, but the M mode right sided systolic time intervals decreased. Her sedimentation rate decreased from 120 to 25 mm/hour, and the steroid dose was tapered.

A repeat cardiac catheterisation five months after the first (table 2) showed persistent pulmonary hypertension (aortic systolic pressure 125 mmHg, pulmonary 50 mmHg) with a stable pulmonary vascular resistance of 5.5 U/m². Acute drug testing showed persistent responsiveness to hydralazine with an increase in the cardiac index from 3.5 to 3.9 l/min/m². Therefore the regimen of corticosteroids, cyclophosphamide, and hydralazine was continued, in tapering doses, over the next four years. The course was complicated only by transient neutropenia and thrombocytopenia, associated with antibodies to platelets.

October 1985	February 1986	May 1986	June 1986	July 1986	April 1987	March 1988	May 1988	May 1989
0.28	0.29	—	—	0.30	—	—	—	—
140	140	—	—	120	—	—	110	—
70	53	60	46	—	46	73	69	—
115	115	120	128	—	—	—	130	—
42.7	44	—	—	42.5	—	—	43	—
140	134	—	380	—	—	62	—	111
—	—	—	73	—	79	29	43	34
—	—	—	22	—	9	17	23	19
—	—	—	—	0	1/1280	1/10,240	—	1/2560
↓ 7.5 qod	↓ 5 qod	—	—	—	—	↑ 40 qd	—	↓ 25 qd
—————→					25 bid†	—	—	—
—————→					Discontinued	—	—	—

Within three years of the recognition of pulmonary hypertension, the patient was completely asymptomatic. Her cardiac examination returned entirely to normal, and her electrocardiogram became normal with an axis of $+80^\circ$. The echocardiogram was normal without mitral valve prolapse, the pulmonary acceleration time was 110 ms, and the right systolic time interval was 0.30. Her haemoglobin increased to 130 g/l, and her weight to 43 kg, but the sedimentation rate remained at 45 mm/hour and the platelet count $118 \times 10^9/l$. She currently receives only a maintenance dose of steroids for autoimmune thrombocytopenia and has no evidence of pulmonary hypertension. When first measured at the age of 20 years, her anticardiolipin antibody titre was borderline for IgG and negative in other subclasses; the titres were all negative at 21 years of age.

Methods

Cardiac catheterisation was performed using the Fick method with measured oxygen consumption. A pulmonary vascular resistance greater than 3 U/m^2 was considered abnormal, as was a systolic pulmonary artery pressure greater than 35 mmHg (mean 22).

Echocardiography was performed with a duplex pulsed Doppler unit using a 3.0 MHz transducer. From a cross sectional parasternal view, the cursor was placed along the axis of the main pulmonary artery with the Doppler sample volume just distal to the valve leaflets. An M mode tracing of the pulmonary valve allowed direct measurement of the pre-ejection period (onset of QRS to valve opening) and systolic ejection time (valve opening to closure) and a ratio greater than 0.30 was considered abnormal. From the pulmonary artery Doppler flow waveforms, the acceleration time was taken as the interval from onset to the peak velocity of flow. An acceleration time of less than 100 ms was considered abnormal; 100 to 120 ms was borderline, and an acceleration time over 120 was considered normal.^{6,7}

Discussion

Mixed connective tissue disease is an overlap syndrome of autoimmune disease with features resembling systemic lupus erythematosus, scleroderma, and dermatomyositis, but with a characteristic serological picture.² Our patient showed various findings over a period of time, but her disease never evolved clearly into any of the other collagen vascular disease categories. Although some may argue that the intermittently positive titre for antiSm favours a diagnosis of lupus erythematosus, we felt her overall pattern best fitted the diagnosis of mixed connective tissue disease. This disease has a known tendency towards the development of pulmonary hypertension.³⁻⁵ The pathophysiology is not fully known, but may be similar to that in primary pulmonary hypertension, a disease in which there is a high incidence of positive serologies for collagen vascular disease.⁸ Limited pathological studies in mixed connective tissue disease³ have shown features which are characteristic of pulmonary hypertension in general, including right ventricular hypertrophy, marked intimal proliferation, and medial hypertrophy of pulmonary arteries and arterioles. The part played by in situ thrombosis, as shown in pulmonary hypertension,^{9,10} has not been well defined in mixed connective tissue disease.⁵ This suggests, however, a possible role for the lupus anticoagulant,¹¹ such as in our patient, in the origin or progression of this process. Although anticardiolipin antibodies may theoretically affect thrombosis, we were unable to measure them in our patient until 1988, when they were normal.

Several additional clinical features deserve comment. During aggressive treatment, the cardiopulmonary improvement seemed to parallel the improved serological data and resolution of thrombocytopenia. Despite later serological and haematological relapses, which occurred as the drugs were tapered to less toxic levels, the pulmonary vascular remission was maintained.

Secondly, dilated nailfold capillary microscopy changes of the scleroderma type were seen in this patient. These findings are associated with pulmonary hypertension in mixed connective tissue disease.³ Finally, the patient had a well documented mitral valve prolapse, which disappeared as the disease came under control. This finding underlines the observed association between mitral valve prolapse and collagen vascular disease.¹²

Clinical evaluation of patients with pulmonary hypertension has generally required the use of serial invasive cardiac catheterisations to measure pulmonary artery pressure and flow. This is clearly not ideal for a sick child owing to its morbidity, discomfort, and cost. Improvements in the technology of ultrasound have provided a non-invasive serially applicable means of assessing the pulmonary pressure. The use of two dimensional echocardiography has shown the predictive value of flattening and posterior displacement of the interventricular septum toward the lumen of the left ventricle, indicating right ventricular hypertension.^{13,14} This finding is seen only with the more severe

disease, however, and is difficult to quantitate. Although right sided systolic time intervals measured by M mode echocardiography to assess pulmonary pressures are non-invasive, they are not accurate. When combined with Doppler derived time intervals of pulmonary flow velocity, such as the acceleration time, however, the predictive accuracy is improved, and a useful non-invasive assessment tool for pulmonary hypertension is available.⁶⁻⁷ These methods were used in this patient, and allowed less frequent invasive catheterisations to measure pulmonary pressure and resistance. This case is unique in that a new non-invasive technology was the key to diagnosis and serial evaluation of pulmonary hypertension in mixed connective tissue disease.

Treatment for pulmonary hypertension is empirical and usually unsuccessful. The underlying disease, if present, is treated, and in this instance included the vigorous use of steroids and antimetabolites. If thromboembolism is felt to play a part, then anticoagulants may be used.⁹⁻¹⁰ Attention has recently focused on the use of vasodilator drugs for short term clinical benefit, and perhaps for long term reversal of the underlying process. Classes of drugs include the direct vasodilators such as hydralazine,¹⁵⁻¹⁶ calcium channel blockers such as nifedipine,¹⁷ and prostaglandins such as prostacyclin.¹⁸ These drugs have had variable results. The patient in this study was treated with hydralazine, which during acute invasive drug testing was effective and was the better tolerated drug.

The prognosis of pulmonary hypertension is generally poor in most natural history studies,³ and not much improved even with the use of long term vasodilatation.¹⁹ Therefore, this patient is unusual in that, with aggressive vasodilatation and treatment of the underlying disease, subjective and objective evidence of recovery from pulmonary hypertension was achieved.

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