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Case report

Pulmonary hypertension in connective tissue disease

Report of three cases and review of the literature

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Summary. Patients with connective tissue disease (CTD) who are prone to developed isolated pulmonary hypertension (PH) are primarily young females with a history of Raynaud's phenomenon associated with an exertional dyspnoea. From the start of the disease, pulmonary function tests show a decreased diffusing capacity for carbon monoxide, while X-ray examination shows no obvious abnormalities such as interstitial fibrosis. All patients show, on electrocardiographic examination, evidence of right axis deviation and right ventricular hypertrophy. It has been suggested that PH is found mostly in patients with systemic scerlosis characterized by the CREST syndrome. The histopathological findings are intimal proliferation, narrowing of the vessel lumen and medial fibrosis. These are not specific for CTD. One would expect more signs of vasculitis. Neither signs of lung fibrosis, nor signs of pulmonary emboli are described.

Key words: Pulmonary hypertension – Connective tissue disease – Diffusing capacity for carbon monoxide

Introduction

Between 1977 and 1989 a diagnosis of isolated pulmonary hypertension (PH) was made before death in only three patients who visited our outpatient clinic for connective tissue diseases (CTD). Becaue PH is a rather uncommon complication of CTD, we reviewed the literature on different aspects of PH such as sex, age of disease onset and clinical and laboratory characteristics. The purpose of this study was to determine the characteristics of patients with CTD who develop PH, and to decide whether or not they form a separate entity.

Case reports (Table 1)

Patient A was a forty-year-old woman who presented with a 2-year history of fatigue, polyarthritis, Raynaud's phenomenon and a butterfly rash on the face. Anti-dsDNA was doubtfully positive and anti-ENA was positive. A diagnosis of Systemic Lupus Erythematosus (SLE) was made and treatment with hydroxychloro-quinesulfate was initiated.

Six months later the patient presented with pleuropericarditis, which was treated with corticosteroids. Two years later she developed severe dyspnoea. Examination revealed a heart rate of 72 beats per minute, a blood pressure of 120/80 and an elevated jugular venous pressure. There was acrocyanosis, a butterfly rash on the face, purpura of the face and the extremities and an accentuated pulmonary second sound.

A lung scan showed no evidence of pulmonary emboli. Cardiac catheterization revealed a systolic pulmonary artery pressure of 75 mm Hg, and a diastolic pulmonary artery pressure of 43 mm Hg. No cardiac or pulmonary conditions were found that might have been responsible for the PH. Shortly after cardiac catheterization the patient developed severe cardiac failure from which she died.

An autopsy revealed right ventricular hypertrophy, dilatation of the right atrium and arteritis necroticans of the lungs. There were no signs of lung fibrosis or pulmonary emboli that could account for the existence of PH.

Patient B was a 56-year-old woman who presented with exertional dyspnoea, fatigue and Raynaud's phenomenon. She was examined initially by a pulmonologist. Physical examination revealed a heart rate of 140 beats per minute, a blood pressure of 130/80 and oedema of the ankles. There were no abnormalities of the heart or the lungs. Laboratory investigations showed an elevated erythrocyte sedimentation rate; Latex and Waaler-Rose tests were positive.

Table 1. See text

	Age	Sex	Clinical symptoms	Serologic abnormalities
Patient A	40	Female	Raynaud, polyarthritis, butterfly rash, pleuro-pericarditis, dyspnoea	Anti ds DNA pos, ENA pos
Patient B	56	Female	Raynaud, dyspnoea	ANA pos Anticentromere antibodies pos Rose test pos
Patient C	30	Female	Raynaud, arthritis, dyspnoea	ANA pos Anti RNP pos Rose test pos

Pulmonary function tests showed normal spirometry, but the diffusing capacity for carbon monoxide was markedly reduced (<50% of predicted). No treatment was initiated.

A few months later physical examination revealed a dry and "tight" skin and facial telangiectasias. Laboratory investigations revealed a creatinine clearance of 42 ml/min; anticentromere antibodies were positive to a titre of 10240. An X-ray of the oesophagus showed decreased motility. It was assumed that the patient suffered from systemic sclerosis.

One month later physical examination revealed acrocyanosis, the murmur of tricuspid incomptence was heard, and there was oedema of the ankles. Electrocardiography showed right axis deviation and signs of right ventricular hypertrophy.

Two months later she was admitted to hospital because of severe exertional dyspnoea, orthopnoea, palpitations and dizziness on effort. Physical examination revealed a heart rate of 80 beats per minute, a blood pressure of 100/60, an elevated jugular venous pressure, cyanosis of the lips and the acra, a tricuspid incompetence murmur, pitting oedema of the ankles and a "tight" skin. Chest X-ray showed cardiomegaly. A lung scan was normal. Echocardiography revealed a pericardial effusion and incompetence of the tricuspid and pulmonary valves. Cardiac catheterization revealed a systolic pulmonary artery pressure of 55 mm Hg and a diastolic pulmonary artery pressure of 20 mm Hg. Pulmonary wedge pressure was normal. Pulmonary function tests were unchanged.

Treatment with diuretics, ACE-inhibitors and isosorbide-dinitrate was started. Her complaints of severe exertional dyspnoea, orthopnoea, fatigue and dizziness on effort continued. Treatment was started therefore with corticosteroids, cyclophosphamide, vasodilators, digitalis and diuretics. Nevertheless a rapidly progressive cardiac failure developed with severe hypoxemia from which the patient died.

An autopsy revealed right ventricular hypertrophy, dilatation of the right atrium and the right ventricle and there were no signs of pulmonary emboli, infarctions or fibrosis. The pulmonary arteries showed extensive, partly obliterative, intimal fibrosis.

Patient C is a 30-year-old women who presented with pain in the hands, feet and neck, fatigue, a 1-year history on Raynaud's phenomenon, atypical chest pain and exertional dyspnoea. Physical examination revealed a heart rate of 76 beats per minute, a blood pressure of 110/80 and a normal venous pressure. The heart seemed enlarged and a loud pulmonary second sound and a systolic murmur were heard. The palms of the hands were swollen.

Laboratory investigations revealed a positive Waaler-Rose test, positive ANA, a positive anti-RNP and an elevated CPK. Chest X-ray showed cardiomegaly; the lungs were normal. Electrocardiography showed right axis deviation and a pattern of right ventricular hypertrophy. Echocardiography revealed dilatation of the right atrium and the right ventricle and imcompetence of the tricuspid valve. Cardiac catheterization revealed a systolic pulmonary artery pressure of 68 mm Hg and a diastolic pulmonary artery pressure of 24 mm Hg. The severe tricuspid incompetence was confirmed. Pulmonary function tests showed a normal diffusing capacity for carbon monoxide. Treatment was started with corticosteroids, cyclophosphamide and vasodilators. To date, the clinical condition of the patient has been quite good. Some of the clinical and laboratory characteristics of the three patients are summarized in Table 1.

Review of the literature

PH is a serious complication of CTD, which has been reported with increasing frequency during the last decade. PH until now, has been described mostly in progressive systemic sclerosis (PSS), particularly in the CREST syndrome variety. SLE and the closely related mixed connective tissue disease (MCTD) account for the majority of cases in the other CTD groups. PH is rarely seen in rheumatoid arthritis (RA). In this review a description will be given of the clinical and laboratory characteristics of PH in PSS, the CREST syndrome variety of PSS, SLE and RA.

Table 2. Isolated pulmonary hypertension in the CREST syndrome [1]

	CREST-PH ($n=20$)	CREST-noPH ($n=287$)
Incidence	±4.5%	–
Mean age at disease onset	42 years	41 years
Sex % female	80%	83%
Raynaud's phenomenon	100%	68%
ANA positive	44%	37%
Anticentromere antibodies	53%	46%
Rheuma factor positive	13%	13%
DLCO <45% of predicted	65%	13%

Progressive systemic sclerosis

A large-scale study of 673 systemic sclerosis patients has been performed by Stupi et al. [1]. In 59 patients (9%) PH occurred during the disease course. In 30 patients, all with the CREST syndrome, the PH was isolated, i.e. independent of other pulmonary or cardiac conditions. Because PH is one of the main causes of death among patients with the CREST variant, the investigators tried to identify clinical and laboratory characteristics that might severe as predictors of this complication. Twenty patients with isolated PH and 287 patients without PH could be described in detail. Some of the clinical and laboratory characteristics are summarized in Table 2. At the time of diagnosis of PH, the most common cardiopulmonary symptom in the 20 patients was exertional dyspnoea. In 17 of the 20 patients this symptom was present for less than 1 year prior to the diagnosis of PH. Orthopnoea was noted in 35% of the patients.

Electrocardiographic evidence of right axis deviation was noted in all 20 PH patients, and 19 patients and evidence of right ventricular hypertrophy. In 18 of the 20 PH patients, chest X-rays showed right ventricular enlargement, as well as prominent enlargement of the pulmonary arteries. However, no signs of pulmonary interstitial fibrosis were observed. The diffusing capacity for carbon monoxide was strikingly reduced in the group of patients with PH. Six PH patients underwent pulmonary function testing 1 to 6 years before confirmation of PH. All six had a severely reduced DLCO. Of the 20 patients, only one remained alive; death was in general attributed to cor pulmonale. The most common vascular changes in PH at autopsy were smooth muscle hyperplasia and intimal fibrosis.

Salerni et al. [2] have described 10 patients with severe PH without pulmonary fibrosis in the CREST syndrome. Some of the main clinical and laboratory characteristics are summarized in Table 3. The characteristic histological finding they have described was intimal proliferation with narrowing of the vessel lumen in the small and medium sized pulmonary arteries and arterioles. They

have also found immunoglobulin IgG and complement component C1q in the pulmonary vessels.

Owens et al. [3, 4] have reported dyspnoea on exertion and at rest, pleuritic chest pain and a chronic nonproductive cough as the main clinical symptoms. Summarizing the above reports [1–4] the most important histopathological findings in PH patients indicate a vascular disease rather than a disease of pulmonary (interstitial fibrosis) origin [5]. Furthermore the disease seems to be restricted to the CREST variant of PSS.

Systemic lupus erythematosis (SLE). Cases of PH in SLE have been documented by different authors. Some of the characteristics are summarized in Table 4 [6–10]. In all documented case reports the clinical and laboratory characteristics of PH are similar to those described in systemic sclerosis and the CREST variant. Pulmonary function tests show a decreased diffusion capacity for carbon monoxide in the majority of cases. The occurrence of PH appears unrelated to the severity of SLE activity [8]. It always appears suddenly in the disease course with a steady down-hill progression, despite therapy. Serologically some features are noteworthy. The incidence of RNP positivity, often in high titres, is greater than the 25% average occurring in SLE [8]. Quismorio et al. [9] has described a high frequency of rheumatoid factors; i.e. in 9 of 11 patients. A high incidence of the "lupus anticoagulant" has been reported by others [10].

Pathological studies of the pulmonary vasculature have revealed intimal fibrosis with occasional obliteration of the lumen, medial fibrosis and in few occasions fibrinoid necrosis and signs of vasculitis [6, 8, 9]. Again there are no signs of lung fibrosis or pulmonary emboli that could account for the existence of PH.

Table 3. Pulmonary hypertension in the CREST syndrome ($n=10$) [2]

Reported incidence (CREST)	8%
Mean age at disease onset	54 years
Sex % female	80%
Raynaud's phenomenon	100%
DLCO ($n=5$) decreased	100%

Multiple etiological factors have been suggested in the pathogenesis of PH in SLE. The association between Raynaud's phenomenon and PH in SLE has been reported by different authors [9, 11].

In conclusion, it appears that in cases of PH in SLE, the clinical signs and the course of the disease are similar to systemic sclerosis.

Rheumatoid arthritis. PH is uncommon in RA and has been infrequently reported in the literature. Between 1971 and 1983, three patients with classical RA who developed PH have been described by Asherson et al. [12].

All patients were female and developed PH late in the course of their rheumatoid disease. Raynaud's phenomenon was present in only one patient. One patient had established pulmonary disease with mild pulmonary fibrosis; another may have had thromboembolic disease, while in the third patient there were no obvious pathogenetic factors for PH. Definitive histological diagnosis of the type of PH could not be made because of absence of pathological data.

Discussion

PH is a serious complication of CTD that is being increasingly reported in the literature, but fortunately it is relatively uncommon. We were able to diagnose PH before death in three patients who visited our outpatient clinic or rheumatic diseases. This clinic is a referral centre for the southwest of The Netherlands which has a population of 2.5 million. Annually, 1500 new patients are referred to our outpatient clinic. A rough calculation suggests that the incidence of PH is 1:6000 new referred patients.

Patient A suffered from SLE and developed PH, independent of pulmonary or cardiac conditions. In patient B and C it was not possible to make a firm diagnosis. patient B did not meet all the criteria of systemic sclerosis nor of the CREST syndrome variant. To date, patient C does not fulfill the criteria for SLE or MCTD, nor for PSS. Also, in these two patients the PH was isolated. Although a common diagnosis could not be made in these three patients, they showed similar clinical and lab-

Table 4. Pulmonary hypertension in SLE. –=not reported

Authors (year) (number of patients)	Reference	Incidence in SLE (%)	Age range (X)	Sex % female	Raynaud's phenomenon (%)
Perez and Kramer (1981) ($n=4$)	[6]	9	17–53 years (38)	100	75
Hodson et al. (1983) ($n=4$)	[7]	3	21–31 years (27)	100	100
Asheron and Oakley (1986) ($n=6$)	[8]	–	19–47 years (30)	66	50
Quismorio et al. (1984) ($n=20$)	[9]	0.5	21–45 years (30.9)	95	73
Asheron et al. (1986) ($n=64$)	[10]	–	18–49 years	90	75

oratory characteristics. All patients were female and relatively young at disease onset. There was a history of Raynaud's phenomenon and dyspnoea. Serologically ANA were positive in all patients and patient B and C had a positive Waaler-Rose test. Furthermore, the three patients showed the same clinical and laboratory characteristics that are associated with PH.

Evaluation of the literature on different aspects of PH in CTD shows that nearly all the patients are females. The age of disease onset varies from 18 to 50 years and is mostly around 30 years. Raynaud's phenomenon is present in all the patients with systemic sclerosis. In SLE, Raynaud's phenomenon is present in 75% of the patients with PH. The most important clinical symptom associated with PH is dyspnoea on exertion.

In most patients with PH, electrocardiographic evidence of right axis deviation and right ventricular hypertrophy is noted. Chest X-rays show right ventricular enlargement and prominent pulmonary arteries, while there are no signs of pulmonary interstitial fibrosis. Pulmonary function tests show only mild abnormalities, with the exception of the diffusion capacity for carbon monoxide which is strikingly reduced in patients with isolated PH in the CREST syndrome as well as in SLE. It has been emphasized by Stupi et al. that the diffusing capacity for carbon monoxide might be of predictive value in the development of PH [1]. They conclude that patients with a decreased diffusing capacity should be considered to be at risk for the development of PH.

There are no serologic abnormalities that predict, or correlat with the development of PH. However, some serologic features are noteworthy. The incidence of RNP positivity in patients with PH is greater than the average of 25% occurring in SLE [8]. A high frequency of rheumatoid factors has been described by Quismorio et al. [9], while a high incidence of the lupus anticoagulant has been reported by Asherson et al. [10].

In the cases we reported, patient B and C had a positive Waaler-Rose test. The characteristic histological findings in patients with PH are similar to those found in systemic sclerosis, the CREST syndrome and in SLE. The histopathological changes involving the small and medium sized arteries and arterioles consist of intimal fibrosis with narrowing of the vessel lumen, smooth muscle hyperplasia and medial fibrosis. These histopathological findings are also characteristic of isolated or primary PH, as has been described by Wagenvoort and Wagenvoort [13, 14], and seems to be the consequence of PH itself. In none of the cases of PH that were described in this article were there signs of interstitial fibrosis or pulmonary emboli that could account for the existence of PH.

Although multiple etiological factors have been suggested in the pathogenesis of PH, the etiology remains unclear. We can only conclude that patients who develop PH in CTD are young females with a history of Raynaud's phenomenon and dyspnoea on exertion. RNP positivity as well as positive rheumatoid factors and the lupus anticoagulant may be present. Pulmonary function tests show a strikingly decreased diffusing capacity for carbon monoxide. The histopathological changes consist of intimal proliferation, narrowing of the vessel lumen and medial fibrosis. These characteristics are independent of the type of CTD that has been diagnosed. Therefore we conclude that PH forms a distinct syndrome within the group of patients with CTD.

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References

1. Stupi A, Steen V, Owens G, Barnes E, Rodhan G, Medsger T (1986) Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. Arthritis Rheum 29: 515–524
2. Salerni R, Rodhan G, Leon D, Shaver J (1977) Pulmonary hypertension in the CREST syndrome variant of progressive systemic sclerosis (scleroderma). Ann Intern med 86: 394–399
3. Owens G, Follansbee W (1987) Cardiopulmonary manifestations of systemic sclerosis. Chest 91: 118–127
4. Owens G, Fino G, Herbert D et al. (1983) Pulmonary function in progressive systemic sclerosis: comparison of CREST syndrome variant with diffuse scleroderma. Chest 84: 546–550
5. Young R, Mark G (1978) Pulmonary vascular changes in scleroderma. Am J Med 64: 998–1004
6. Perez H, Kramer N (1981) Pulmonary hypertension in systemic lupus erythematosus: report of four cases and review of the literature. Semin Arthritis Rheum 11: 177–181
7. Hodson P, Klemp P, Meijers O (1983) Pulmonary hypertension in systemic lupus erythematosus: a report of four cases. Clin Exp Rheumatol 1: 241–245
8. Asherson R, Oakley C (1986) Pulmonary hypertension and systemic lupus erythematosus. J Rheumatol 13: 1–5
9. Quismorio F, Sharama O, Koss M et al. (1984) Immunopathologic and clinical studies in pulmonary hypertension associated with systemic lupus erythematosus. Semin Arthritis Rheum 13: 349–359
10. Asherson R, Mackworth-Young C, Boey M et al. (1983) Pulmonary hypertension in systemic lupus erythematosus. Br Med J 287: 1024–1025
11. Ito M, Kagiyuama Y, Omura I et al. (1979) Cardiovascular manifestations of systemic lupus erythematosus. Jpn Circ J 43: 985
12. Asherson A, Morgan S, Hackett D, Montanes P, Oakley C, Hughes G (1985) Rheumatoid arthritis and pulmonary hypertension. A report of three cases. J Rheumatol 12: 154–159
13. Wagenvoort C, Wagenvoort N (1977) In: Pathology of pulmonary hypertension. Wiley, New York, pp 127–130
14. Wagenvoort C, Wagenvoort N (1977) In: Pathology of pulmonary hypertension. Wiley, New York, pp 50–153