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A case of pulmonary veno-occlusive disease responding to treatment with azathioprine

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Sanderson, J. E., Spiro, S. G., Hendry, A. T., and Turner-Warwick, M. (1977). *Thorax*, **32**, 140–148. **A case of pulmonary veno-occlusive disease responding to treatment with azathioprine.** Histological features of a lung biopsy specimen from a 46-year-old woman showed all the characteristics described in veno-occlusive disease. The clinical features, however, were distinctive in that in addition to the lung involvement there was alopecia, digital vasculitic ulcers, Raynaud's phenomenon, polyarthritis, and muscle weakness. Treatment with azathioprine resulted in a progressive improvement in her condition. It is suggested that pulmonary small vein occlusion may occur as a pattern of tissue response in more than one situation and that it is sometimes more amenable to therapy than has been previously reported.

Narrowing or obliteration of the small pulmonary veins and venules is the characteristic histological pattern of pulmonary 'veno-occlusive disease' (Rosenthal *et al.*, 1973; Thadani *et al.*, 1975) and this is now a well-recognised but still rare cause of pulmonary hypertension. Previous reports have noted a poor prognosis and a disappointing or negligible response to various therapeutic measures. We wish to report a patient who is currently making a good response to treatment and shows several features not previously described in association with this disease.

Case report

The patient, a 46-year-old housewife, was quite well until December 1972 when she first noted bilateral painful swelling of the terminal interphalangeal and wrist joints. In February 1973 she developed weakness and stiffness of the proximal muscles of both legs and experienced difficulty in climbing stairs. In April 1973 she first complained of dyspnoea on exertion which rapidly deteriorated over five weeks. In May 1973 she was admitted to hospital: she was cyanosed, there was an audible gallop rhythm, and crepitations were heard over both mid and lower zones of the lungs. She had swelling and tenderness of the terminal interphalangeal joints of both hands but no clubbing. The electrocardiogram showed depression of the T waves in all chest leads. A chest radiograph showed patchy shadowing in the right mid and lower zones and in the left lower zone. Pulmonary function tests showed small lungs with a restrictive defect and a gas transfer factor for carbon monoxide reduced to 29% of the predicted normal value. A clinical diagnosis of fibrosing alveolitis was made and treatment with prednisone (40 mg daily) was started. There was some clearing of the lung base, but the mid zone shadows persisted. Two months later she spontaneously developed subcutaneous emphysema and she was transferred for further assessment.

On admission (August 1973) she complained of shortness of breath and was limited by dyspnoea to 5 yards (4·6 metres). She was orthopnoeic, had weakness of both legs, progressive loss of hair for two months, and also showed Raynaud's phenomenon. She had lost 3·6 kg in weight since starting steroid therapy. On examination there was gross interstitial emphysema of the face, neck, thorax, and arms with central cyanosis. There was diffuse alopecia. The blood pressure was 140/70 mmHg. On auscultation the pulmonary component of the second heart sound was accentuated; a third heart sound was heard but there were no murmurs. There was marked weakness of the

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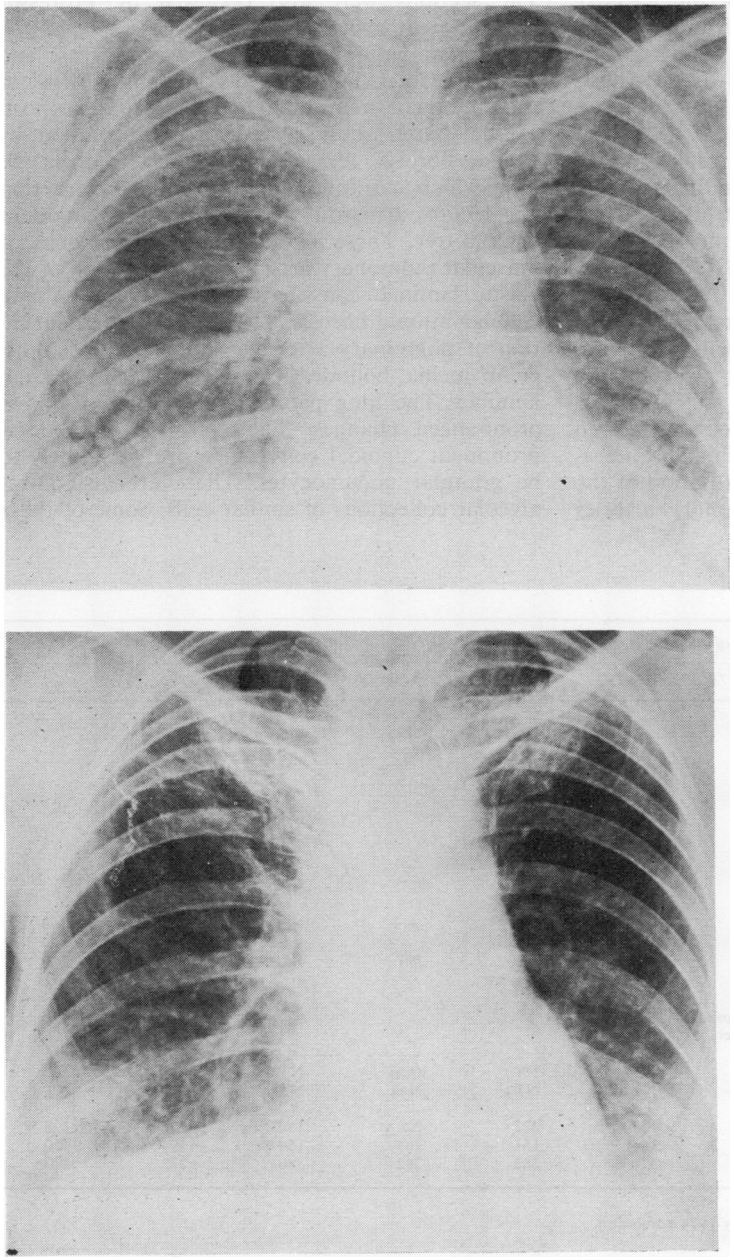
quadriceps muscles but no active arthritis. Her hands, apart from being cool, with poor capillary circulation in all fingers, were unremarkable at this stage of the illness. The chest radiograph showed diffuse, persistent shadows throughout both lung fields predominantly at the bases and in the left upper zone with prominence of the right hilum (Fig. 1). An electrocardiogram showed a normal axis but a P wave of 3 mm in lead II, suggesting right atrial hypertrophy.

The blood count, electrolytes, blood urea, and liver function tests were normal and the ESR was 12 mm in the first hour. Antinuclear antibody by immunofluorescence and LE cells studied on two



(*a*)

(*b*)

Fig. 1 *Chest radiograph (a) on admission (August 1973) after clearing of the subcutaneous emphysema, and (b) after treatment with azathioprine showing partial clearing of the shadows (Feb. 1975) (wiring at biopsy site seen in right upper zone).*

occasions were not found. Rheumatoid factor (differential agglutination test and Latex) was absent. Antibodies to mitochondria were also absent, but thyroid cytoplasmic and smooth muscle antibodies were present. The latter showed a polygonal pattern using liver as a substrate in the standard double layer immunofluorescent test. Aspergillus, Candida, pigeon, and budgerigar serum precipitins were absent. Serum electrophoresis was normal. IgA 151 IU/l and IgG 156 IU/l were normal: IgM was 351 IU/l (normal 58–196 IU/l) (see Table 1). Thyroid function tests were normal. The toxoplasma dye test titre was negative.

Radiographs of the skull, sacroiliac joints, hands, and oesophagus (Gastro-grafin swallow) were all normal. Blood gases at rest breathing air were: pH 7·46, Po_2 6·9 kPa (52 mmHg), Pco_2 4·25 kPa (32 mmHg), Hco_3 22 mmol/l (22 mEq/l), and O_2 saturation 87%. Pulmonary function tests (Table 3) performed after the interstitial emphysema had cleared confirmed reduced lung volumes with a low gas transfer factor for carbon monoxide.

An open lung biopsy was performed and showed the histological appearance of 'intimal proliferation leading to occlusion and recanalisation of the pulmonary veins. The small pulmonary arteries show medial hypertrophy with intimal proliferation and fibrosis. Fibrinoid change was not apparent. There was no haemosiderosis. The alveolar walls had some degree of fibrocellular thickening associated with a mononuclear exudation. This is not the pattern of fibrosing alveolitis with pulmonary hypertension but has the features as described in veno-occlusive disease' (Figs 2 and 3). The sections were also reviewed by Professor Donald Heath who agreed that these showed the features of pulmonary veno-occlusive disease and made the following detailed comments: 'Most of the pulmonary veins and venules, as small as post-capillary size, show considerable obstruction by intimal fibrosis. The capillary hypertension in the lung which has followed this venous obstruction has led to structural changes in the pulmonary arterial tree. These include medial hypertrophy of muscular pulmonary arteries with crenation of the elastic laminae consistent with constriction and cellular intimal fibrosis. There is also muscularisation of pulmonary arterioles with a distinct muscular media bounded by internal and external laminae. The lung parenchyma itself also shows pronounced changes. The alveoli are lined by prominent cuboidal cells which are very likely to be granular pneumocytes. There are also intra-alveolar collections of similar cells. Some of these

Table 1 *Immunological data*

Test	*Date of admission*						
	Aug. '73	*Sep. '73*	*Jan. '74*	*May '74*	*Nov. '74*	*Feb. '75*	*Apl. '76*
Antinuclear antibody titre	–	–	+ (weak) 1/20	++ 1/80	+ (weak) 1/20	+ 1/10	++
Rheumatoid factor							
(a) Differential agglutination titre (rabbit globulin)	–	–	–	–	–	–	–
(b) Latex (human globulin)	±	–	–	–	–	–	–
Tissue antibodies[1]							
Kidney							
(a) Basement membrane	–	–	–	–	–	–	–
(b) Mitochondria	–	–	–	–	–	–	–
Thyroid							
(a) Cytoplasm	++	++	++	++	++	++	++
(b) Tanned red cell agglutination titre (thyroglobulin)	1/20	1/20	1/20	NT	1/20	NT	NT
Smooth muscle (stomach wall)	++ (also polygonal on liver)	+	–	–	–	–	±
Gastric parietal cell	–	–	–	–	–	–	–
Anticomplementary titre	NT	NT	NT	Neg.	NT	NT	NT
C_3 conversion (C_3-C_3b)	NT	NT	NT	Neg.	NT	NT	NT
Immunoglobulins (IU/l)							
IgG (normal 57–172)	156	157	222	226	180	226	198
IgA (normal 75–268)	151	164	151	205	154	194	150
IgM (normal 58–196)	351	321	282	282	380	232	179

[1]Tested by double layer immunofluorescence.
Azathioprine treatment was started during the May 1974 admission.
NT=not tested.

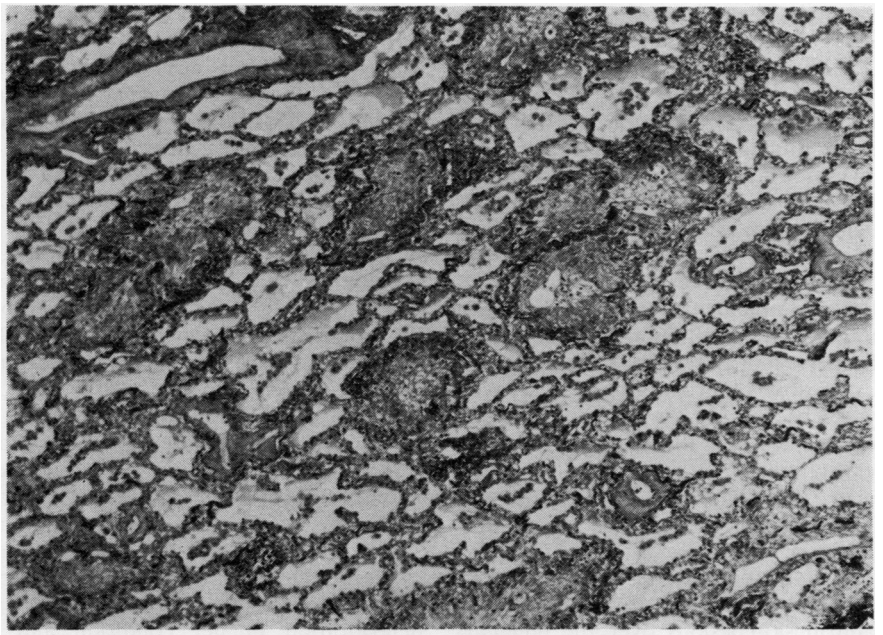


Fig. 2 *Histology of lung biopsy specimen showing pulmonary veins with considerable intimal fibrosis and narrowing of the lumen. There is also patchy fibrosis. Elastic van Gieson* ×52

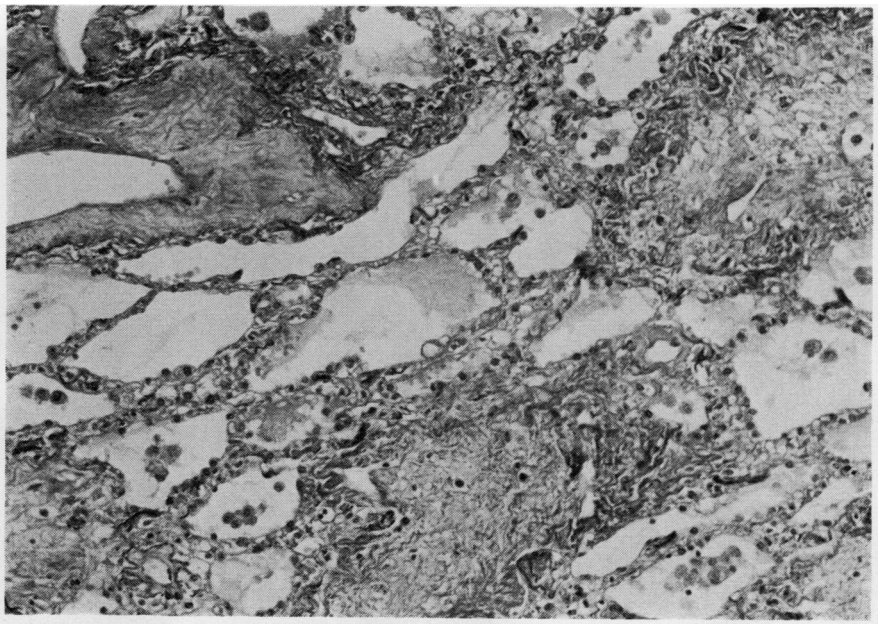


Fig. 3 *Histology of the same specimen* ×175 *showing the details of the concentric thickening of small veins and the thickening of the alveolar walls with interstitial and intra-alveolar cellular infiltration.*

have disintegrated. There is extensive intra-alveolar fibrosis'. Electron microscopy kindly undertaken by Dr. Brian Corrin confirmed that the alveolar lining cells were granular pneumocytes. The majority of the cells free in the alveolar lumen were macrophages. Apart from arteriolar thickening by smooth muscle proliferation there were no other abnormalities of the blood vessels and in particular there was no evidence of electron dense deposits in the basement membrane. Immunofluorescent microscopy failed to show immunoglobulin or complement deposits on the basement membrane of the small pulmonary vessels.

During the period of slowly resolving surgical emphysema, the dose of prednisone was reduced without any relapse of her lung condition. She was discharged able to walk only 10–20 yards (9–18 metres) taking prednisone, 10 mg daily. However, over the following six months she noticed an increase in joint pains with early morning stiffness of the knees, elbows, and interphalangeal joints of both hands, although her breathing remained unchanged. Subsequently she developed painful skin lesions over the metacarpophalangeal joints and the finger tips of both hands which progressed to painful ulceration.

On readmission in May 1974, although she felt that her breathing was a little improved, she had evidence of severe Raynaud's phenomenon with ulcers on the fingers of both hands (Fig. 4) and also on the heels and some toes. She had an active arthritis with effusions in both knees and weakness of the proximal muscle groups. Tenderness of the deltoids and quadriceps was also present. On examination the blood pressure was 130/75 mmHg; the jugular venous pressure was normal but there was a right ventricular impulse. On auscultation the pulmonary component of the second heart sound was loud and delayed. There was also a pulmonary ejection click. Bilateral basal crepitations were heard. The chest radiograph and electrocardiogram were unchanged. The resting Po_2 was 7·3 kPa (55 mmHg), breathing air. The IgG was raised to greater than 226 IU/l (normal 57–172 IU/l) and the IgM was 282 IU/l (normal 58–196 IU/l). The antinuclear antibody (ANA) was positive (Table 1). The rheumatoid factor remained negative and the serum creatinine phosphokinase was normal. Her pulmonary function showed a further small decrease in the total lung capacity, but an increase in the single breath transfer factor (Table 2). In view of the general deterioration in her condition and the severe digital vasculitis, azathioprine, 150 mg daily, was added to the maintenance dose of prednisone. Over the next six months she noticed a marked improvement of her symptoms. On readmission (November 1974) her exercise tolerance had in-

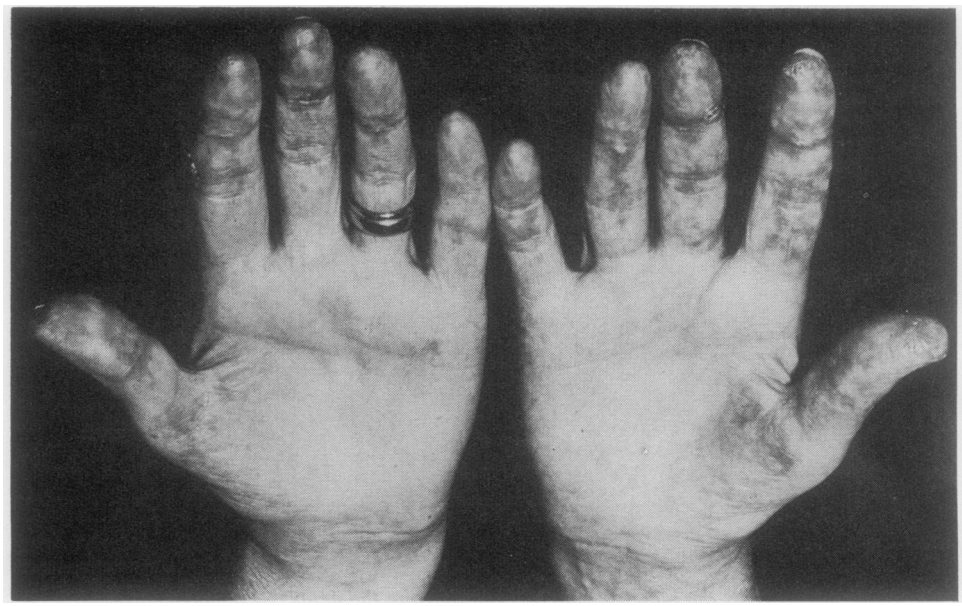


Fig. 4 *Hands before treatment with azathioprine, showing extensive vasculitis with ulceration of the fingers.*

Table 2 *Pulmonary function test data*

	Predicted	*20 Sept. '73*	*22 May '74*	*7 Nov. '74*	*5 Feb. '75*
Forced expiratory volume in 1 sec (FEV_1) (ml)	2410	1100	1050	1450	1630
Vital capacity (VC) (ml)	3050	1250	1375	1600	2150
FEV_1/FVC (%)	79·0	80·2	82·0	82·9	77·6
Functional residual capacity (FRC) (ml)	2670	2110	1730	1920	1830
Total lung capacity (TLC) (ml)	4620	2710	2280	2720	3080
Residual volume/Total lung capacity (RV/TLC) (%)	33·9	54·0	39·7	41·2	32
Gas transfer factor (TF) (mmol min^{-1} kPa^{-1})	6·3	2·3	3·4	3·0	3·8
(ml min^{-1} $mmHg^{-1}$)	18·3	6·7	9·7	8·7	11·0
Transfer coefficient (Kco) (mmol min^{-1} kPa^{-1} l^{-1})	1·8	0·83	1·58	1·1	1·42
(ml min^{-1} $mmHg^{-1}$ l^{-1})	5·2	2·4	4·6	3·2	4·1

creased, and she was able to walk over a quarter of a mile (0·4 km), and climb about 15 stairs. In addition she was able to do housework and shopping. The ulcers on the hands had almost healed. She had no arthralgia, her muscle power had improved considerably, and her hair had regrown.

Azathioprine was continued at the same dose, and when seen in February 1975 the patient's improvement was continuing. She felt well and was able to walk around the local shops and manage three flights of stairs slowly without stopping. There was still some early morning stiffness in her hands, although she could now knit with ease. Her digital ulcers were healed (Fig. 5) and the Raynaud's phenomenon was confined to only the tips of all fingers. Her appetite was good, and she had gained 7 lb (3·1 kg) in weight since starting azathioprine.

On examination she was no longer cyanosed; the Po_2 was 9·8 kPa (74 mmHg) and Pco_2 4·8 kPa (36 mmHg) at rest. There were a few basal crepitations in both lung fields. The pulmonary second sound was still accentuated. There was no evidence of active arthritis, joint deformity or weakness. Her hair had fully regrown. The ECG was normal with a P wave of only 1 mm in lead II. The chest radiograph showed considerable clearing of the shadowing in both lungs compared with the initial film (Fig. 1b). The ANA was reported as only weakly positive (Table 1). Pulmonary function (Table 2) had also continued to improve. A progressive exercise test was performed at each

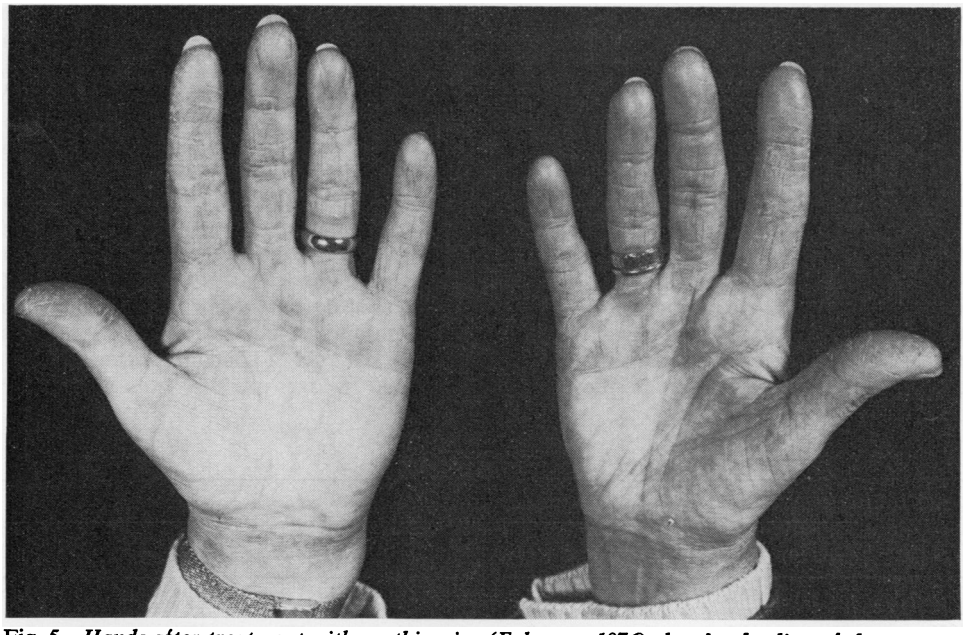


Fig. 5 *Hands after treatment with azathioprine (February 1976) showing healing of the finger ulcers.*

assessment (Table 3). The patient sat at rest on a mechanically braked cycle ergometer, and on starting exercise, the work rate was increased by 16·7 Watts (100 kpm min^{-1}) each minute until she was no longer able to continue. Initially both the heart rate and minute ventilation were excessive at rest and during exercise. In the later studies the resting heart rate became normal, but the increases during exercise remained excessive. The heart rates and ventilation at the end of each test were abnormally high for the work rate achieved. The test was stopped on each occasion because of dyspnoea and general fatigue, and although there was an improvement in exercise tolerance, the final work rate achieved was approximately 50% of that expected for her age and sex. The resting Pao_2 improved with time, and the tendency for the Pao_2 to fall during exercise diminished.

Treatment was continued with azathioprine (150 mg daily) and prednisone (10 mg daily). She was reassessed in April 1976 and the improvement noted in 1975 was maintained.

Discussion

Pulmonary veno-occlusive disease (PVOD) is now a well-recognised condition. Although the original description is credited to Höra (1934), it was Heath *et al.* (1966) who recognised that the histological features in the lung are distinctive and that the condition should be separated from the main group of patients with clinical pulmonary hypertension and be referred to as 'pulmonary veno-occlusive disease'. It is the histological appearance which is characteristic, and in the previously reported cases diagnosis was not made until lung biopsy (Stovin and Mitchinson, 1965; Brown and Harrison, 1966; Corrin *et al.*, 1974) or, more usually, necropsy had been performed. The feature common to all the reported cases is a fibrous narrowing or obliteration of the lumen of many small veins and venules. In some venules, the fibrous tissue thickening appears concentric while in others it is eccentric or nodular. This characteristic intimal fibrosis was well seen in the biopsy specimen from our patient (Fig. 2). Liebow *et al.* (1967) suggested that the venous lesions represent organised or recanalised thrombi, although evidence for recent thrombi has not been convincing in the reported cases (Carrington and Liebow, 1970).

The venous obstruction produces capillary hypertension and consequent structural changes in the pulmonary arterial tree which include medial hypertrophy of the small arteries and arterioles, sometimes with intimal thickening (Carrington and Liebow, 1970). These arterial changes were present in our case. The recent review by Wagenvoort *et al.* (1971) of the histology of seven patients noted additional parenchymal changes. In all of his patients, interstitial fibrosis was present in addition to pulmonary venous obstruction and in four of the seven cases there was an infiltration of the alveolar walls by inflammatory cells. The lung biopsy of our patient also showed extensive intra-alveolar fibrosis and a mononuclear exudation. A further feature noted previously is the presence of haemosiderosis which is due to iron encrustation in the elastic lamina of the occluded vessels and which suggests a post-capillary origin of the hypertension (Liebow *et al.*, 1973). It was not seen in the biopsy specimen of the patient reported here. The clinical features of previous cases have been dominated by the presence of severe pulmonary hypertension and progressive exertional dyspnoea. However, in contrast to primary pulmonary hypertension, orthopnoea seems common in PVOD (Brewer and Humphreys, 1960; Massachusetts General Hospital, 1937; Weisser *et al.*, 1967) and was noted by our patient.

The electrocardiographic findings are similar to those seen in pulmonary hypertension, and in previous reports included right axis deviation with right ventricular hypertrophy and strain (Brown and Harrison, 1966) and right atrial hypertrophy (Clinicopathological Conference, 1968). Cardiac catheterisation data have confirmed the presence of pulmonary hypertension in 15 previously reported patients (Thadani *et al.*, 1975). The measured wedge pressure was normal in eight

Table 3 Exercise test data: increasing work rate exercise test

Date	*Rest*					*Final minute of exercise*			
	HR (*bt* min^{-1})	*Ventilation* (*l* min^{-1})	PaO_2 (*kPa*)	$PaCO_2$ (*kPa*)	*Work rate* (*Watts*)	*HR* (*bt* min^{-1})	*Ventilation* (*l* min^{-1})	PaO_2 (*kPa*)	$PaCO_2$ (*kPa*)
June 1974	126	15·3	7·0	4·2	50	152	30·5	6·9	4·0
August 1974	120	19·9	9·8	4·6	50	162	37·8	8·1	4·7
November 1974	85	13·2	9·8	4·9	50	155	33·4	8·9	4·65
February 1975	78	15·0	9·6	4·4	66·7	168	38·0	9·6	4·5

cases and slightly raised in another five. Thadani *et al.* (1975) have summarised the detailed findings.

Catheterisation data were not obtained in our patient as the diagnosis was made on lung biopsy. However, the histology of the biopsy specimen showed marked structural changes in the pulmonary arteries consistent with pulmonary hypertension. Furthermore, the signs of pulmonary hypertension subsequently developed with the appearance of a right ventricular impulse and a pulmonary ejection click with obvious delay of the pulmonary component of a second heart sound. After treatment with azathioprine these physical signs have improved with loss of the right ventricular impulse and the pulmonary ejection click.

Two further features were noted in our patient which can be of diagnostic value in separating PVOD from idiopathic pulmonary hypertension. First, the presence of crepitations in the lungs has been a common finding in PVOD (Massachusetts General Hospital, 1937; Crane and Grimes, 1960; Heath *et al.*, 1966; Liebow *et al.*, 1967; Rosenthal *et al.*, 1973). Secondly, the chest radiograph in PVOD shows, in addition to the features of pulmonary hypertension, pulmonary infiltrates and interstitial shadows with occasional Kerley B lines (Grainger, 1958; Brown and Harrison, 1966; Weisser *et al.*, 1967; Liebow *et al.*, 1973; Rosenthal *et al.*, 1973). There is no evidence of upper lobe blood diversion, which is usually due to left atrial hypertension.

In the patient reported here, there were clinical features which have not been previously noted in association with PVOD. Arthritis, muscle weakness, alopecia, Raynaud's phenomenon, and vasculitic ulcers on the hands and feet were prominent and distressing features. Although the rheumatoid factor was persistently absent, the positive ANA and markedly raised IgG and IgM levels suggested an underlying immunological disorder. Pulmonary fibrosis in association with systemic disorders is well recognised. In a series of 130 patients with cryptogenic fibrosing alveolitis reported by Turner-Warwick (1974), 30% had polyarthritis of some form. Raynaud's phenomenon was noted in three of the 130 patients and polymyositis occurred in one. It is possible that the muscle weakness and tenderness in our patient was due to polymyositis although a muscle biopsy was not done. The normal creatinine phosphokinase is difficult to evaluate as the patient was taking prednisone at the time. In addition to her dyspnoea and hair loss, the patient complained of severe and painful ulcers on the hands which were very slow to heal. The exact cause of these vasculitic lesions remains speculative.

The most striking feature of the present case is the good response to azathioprine. It is unlikely that the continued prednisone therapy has contributed signficantly to her improvement as she was clinically deteriorating on this drug alone, and her improvement coincided with the addition of azathioprine. The prognosis for PVOD is very poor (Rosenthal *et al.*, 1973; Thadani *et al.*, 1975) and all the previous cases in the literature died within two years of the onset of symptoms. One patient reported by Brown and Harrison (1966) with increased platelet 'stickiness' made an initial improvement on heparin, digitalis, and diuretics. However, it was not possible to control the pulmonary hypertension and the patient deteriorated soon afterwards and died 15 months after the initial presentation (Clinicopathological Conference, 1968). Corticosteroids alone have been tried without success (Stovin and Mitchinson, 1965; Weisser *et al.*, 1967). Diuretics and digoxin have not produced any significant effect on the progressive downhill course (Rosenthal *et al.*, 1973). In our patient, there was evidence of a marked improvement not only of her symptoms and signs, but also of her exercise capacity. Furthermore, her resting Po_2 had increased and the fall in Po_2 during progressive exercise was less.

The response obtained using an immunosuppressive agent may throw some light on the aetiology of this condition. The disease is acquired and until now has been steadily progressive despite all attempts at therapy. A few cases have suggested an infective aetiology (Brewer and Humphries, 1960; Crane and Grimes, 1960; Wagenvoort *et al.*, 1971) including toxoplasmosis (Stovin and Mitchinson, 1965) and a virus (Liebow *et al.*, 1967). However, attempts to isolate a causative organism or show a rising titre of antibodies to microbial agents have been unsuccessful.

A recent report (Corrin *et al.*, 1974) of PVOD in a 33-year-old woman, diagnosed by lung biopsy and confirmed at necropsy, has suggested that immune complexes may be important. Electron microscopy of the lung biopsy specimen showed electron-dense deposits in the capillary basement membranes, and immunoglobulin and complement were demonstrated in a corresponding position by immunofluorescent microscopy. It was suggested that immune complexes may have initiated thrombotic occlusion of the small pulmonary veins.

An immunological abnormality is suggested in our patient by the response to immunosuppressive therapy, by the high IgG and IgM levels which fell

to normal, the antibodies demonstrated to smooth muscle, thyroid, and nuclear antigens, and by the systemic symptoms. However, all these features also make our patient distinctive when compared to all the previous reported cases, although the histology was characteristic of 'veno-occlusive disease'. It is, of course, impossible at present to know if the histological features which are common to all the reported cases represent a particular pathological response to a particular type of injury or are merely the pathological end result of multiple and differing types of tissue injuries inflicted upon the lung. The distinctiveness of our patient would suggest that the latter is possible.

We are grateful to Dr. K. W. F. Hinson, Professor Donald Heath, and Dr. Brian Corrin for advice on the interpretation of the histological material and to Dr. I. Dowdeswell for the exercise tests.

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