ACUTE DIFFUSE INTERSTITIAL FIBROSIS OF THE LUNGS

By S. C. Poh, E. H. Monteiro and T. C. Chao

SYNOPSIS

Whilst diffuse interstitial fibrosis of the lungs in the sub-acute and chronic forms have been extensively studied and reported, the acute form as first described by Hamman and Rich is comparatively rare. Only twenty-one cases have been recorded in the literature. A case of this syndrome with its rapid downhill course resulting in death from cor pulmonale 36 days after the onset of the illness is described. The response to steroid therapy was only temporary. Investigations for an autoimmune process, viral and ricketsial infections as a possible aetiological factor were all negative.

In 1944 Hamman and Rich published an account of a syndrome which they termed "acute diffuse interstitial fibrosis of the lungs." The four cases described were all in adults; they presented the clinical features of fever with marked dyspnoea and cyanosis and ran an acute course, the total duration of the disease from onset to death from heart failure ranging from four weeks to six months.

Of unknown aetiology, the condition is characterised by an extensive diffuse and progressive interstitial proliferation of fibrous tissue throughout all lobes of both lungs and unassociated with any changes in other organs. Whilst a more chronic and commoner form of the condition has been extensively studied and described (Livingstone, Lewis, Reid and Jefferson, 1964; Scadding and Hinson, 1967; Grant, Hillis and Davidson, 1956; Rubin and Lubliner, 1957), the acute form as originally described by Hamman and Rich has been rarely reported (Hamman and Rich, 1944; Eder, Hawn and Thorn 1945; Pokorny and Hellwig, 1955; Peabody, Buechner and Anderson, 1953; Chernoff and Hartcroft, 1956; Cross, 1957). We report here a case of the syndrome which ran an acute course terminating in death from cor pulmonale 36 days after the onset of the illness. This is the first case of the Hamman Rich Syndrome reported in the local literature.

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CASE REPORT

A 24 year old Chinese woman was first admitted to the Middleton Hospital on 30th September, 1970, with a history of fever, cough and sore throat of 5 days' duration. She had been well prior to her present illness and there was no significant past history of note. The main clinical finding at the time of admission was a membrane over both tonsils and pharynx. She was treated as a case of diphtheria with antidiphtheritic serum and erythromycin although the throat swab failed to show C. diphtheriae. Two days after admission she coughed out about 100 mls. of fresh blood. The membrane in her throat had cleared. Three days later she was noticed to be cyanosed with petechiae over her trunk and limbs. She was then transferred to the Tan Tock Seng Hospital for further management.

On admission she appeared dyspnoeic and was cyanosed; her temperature was 102°F, pulse rate 150 per min. and respiratory rate 26 per min. Her B.P. was 120/70 mm. Hg. and there were petechiae over her trunk and limbs. There was no clubbing of the fingers. The jugular veins were slightly engorged and the liver was enlarged 3 cms. below the costal margin. No cardiac murmurs were heard. There were crepitations over both lung bases.

Course in Hospital

She was given digoxin, nasal oxygen and ampicillin; her general condition improved and the fever gradually settled over the next few days. The petechial spots subsided. The lung signs, however, persisted. She remained dyspnoeic and cyanotic and had to be nursed in an oxygen tent continuously. Her respiratory rate varied from 25 to 40 per min. and her minute ventilation from 23 to 32 litres. With the oxygen concentration in the tent at 57 per cent, her arterial blood pH was 7·48, carbon dioxide tension 32 mm. Hg. and oxygen saturation 79 per cent. Prednisolone 60 mg. daily was started

12 days after her admission. Her general condition improved over the next few days (her blood pH was 7·43, pCO_2 32 mm. Hg. and saturation 92 per cent) but the extreme dyspnoea persisted, and she could not bear even a short period out of the oxygen tent. Two days before her demise, the blood pH had dropped to 7·38, the pCO_2 was 52 mm. Hg. and oxygen saturation 84 per cent. Her pulse gradually became more rapid and feeble, and she finally succumbed 31 days after entering the hospital and 36 days after the onset of her illness.

Investigations Done

The haemoglobin was 12·0 Gm. per 100 ml. and the total white count was 12,800 per cu. mm. with 87 per cent polymorphs. The platelet count was 370,000 per cu. mm. and the partial thromboplastin time 105 secs. The bleeding and clotting times were normal. The erythrocyte sedimentation rate was 62 mm. per hour. The sputum smear for acid fast bacilli was negative and the throat swab grew B. pyocyaneus. Urinalysis was normal. The serum electrolytes were normal and the blood urea which was initially raised fell to 50 mg. per 100 ml. Her E.C.G. did not reveal any evidence of myocarditis. Blood cultures were sterile and the Widal and Weil-Felix tests were negative. L.E. cells were not found and the blood for antinuclear antibodies and R.A. factor were both negative. Her serum proteins and immunoglobulin levels were normal. Complement fixation tests on her serum against Influenza A & B viruses, adenovirus, Mycoplasma pneumoniae, Coxiella burneti, respiratory syncytial virus and psittacosis antigens were negative. The chest X-ray initially showed diffuse mottled opacities over both lung fields (Fig. 1).

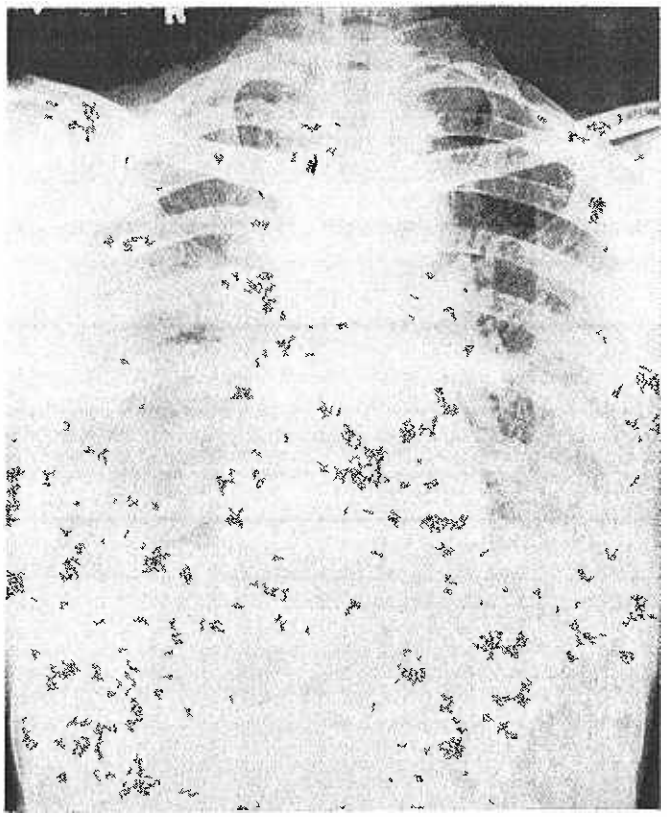

Fig. 1. Chest radiograph taken on 6th October 1970 shows diffuse mottling over both lung fields.

Necropsy

The body was that of a thin Chinese female adult. The relevant findings were in the heart and lungs. The heart was slightly enlarged showing right ventricular hypertrophy. Otherwise the myocardium, the valves and the coronary arteries were normal. Both lungs were aerated with soft spongy feeling. There were multiple bullous out-pouching with cystic areas on the periphery throughout all lobes of lungs giving rise to the so-called hobnail appearance. The lungs were fixed in 10% neutral formalin and subsequently large lung sections were prepared by the Gough-Wentworth technique. On the large lung sections (Figs. 3(*a*) and 3(*b*)), both lungs revealed a honey-comb appearance with tiny cystic areas varying in diameter from 1 mm. to 4 mm. In the periphery were loculated areas of these cystic spaces separated by thin fibrous bands. Near the hilar region were thick fibrous bands obliterating all spaces. The pleura was thickened. Small

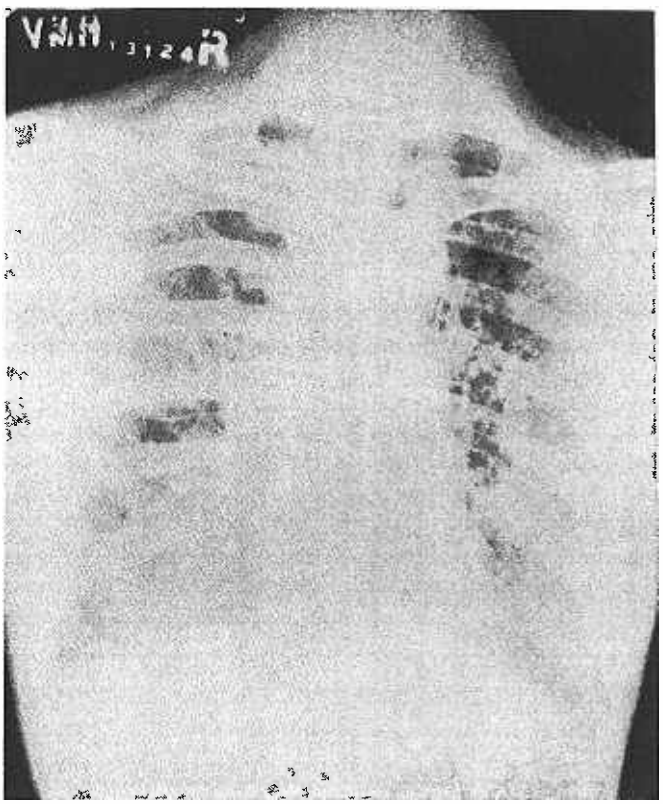

Fig. 2. Chest radiograph taken on 26th October 1970. There is some slight clearing of the diffuse opacities with cystic appearances over both apical and basal regions.

dilated bronchi were seen approaching to within 2 mm. of the pleural surface as shown in the left upper lobe.

Microscopic examination revealed that the alveolar walls were greatly thickened with collagenous tissue obliterating most of the capillary spaces. In the less damaged areas were greatly dilated and distended capillaries, some with aneurysmal dilatation (Figs. 4 and 5). In other areas, there was great proliferation of histiocytic cells totally obliterating the alveolar spaces, though there is absence of cellular reaction. The bronchial epithelium showed hyperplasia (Fig. 6). The dense areas at the hilar region seen macroscopically showed obliteration of alveolar spaces by collagenous tissue (Fig. 7).

DISCUSSION

The syndrome of diffuse interstitial fibrosis of the lungs has been arbitrarily delineated into three separate clinical patterns, acute, sub-acute and chronic by Furstenberg, 1960. Those whose symptoms and signs are acute and the duration of the illness is 6 months or less are considered acute. This variety as originally described by Hamman and Rich is relatively rare as compared to the chronic and sub-acute types; only twenty one cases have been reported since 1944. The patient described here had an acute febrile onset of her illness with a rapid downhill ocurse resulting in death from respiratory failure 36 days later. There was no industrial or occupational histroy of note and she was not on any drugs prior to the illness. The limited search for viral or other infective agents has proved negative.

The response to steroids has been described as "often favourable" (Crofton and Douglas, 1969), and "success is more likely to be achieved by the early administration of steroids in adequate amounts" (Livingstone *et al*, 1964). However, out of the six reported cases in whom steroids were given (Callahan *et al*, 1952; Chernoff and Hast-

Fig. 3(*a*).

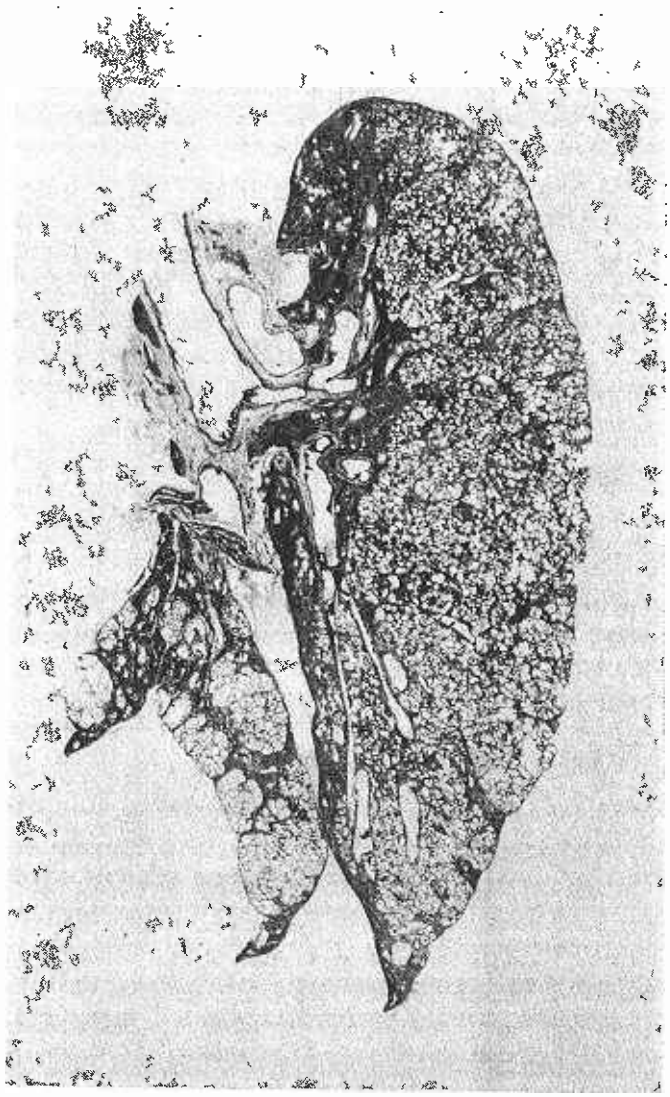

Fig. 3(*b*).

Figs. 3(*a*) and 3(*b*). Large lung sections prepared by the Gough-Wentworth Technique. Both lungs show a diffuse honey comb appearance with cystic spaces varying from 1 mm. to 4 mm. Near hilar region are dense fibrotic areas.

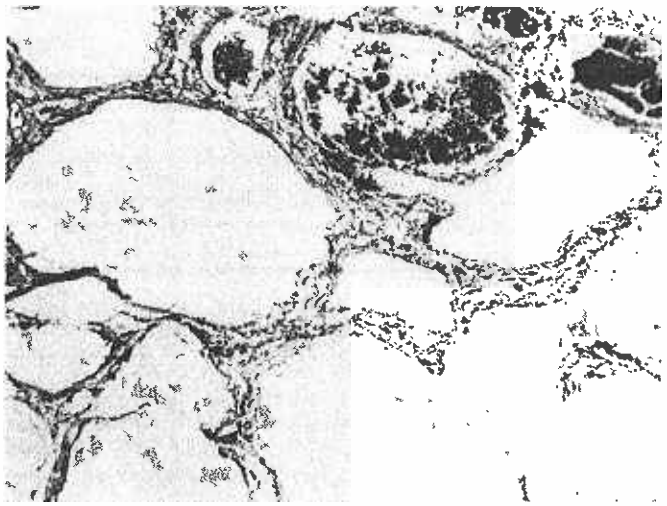

Fig. 4. Thickened alveolar septae with greatly dilated capillaries (H. and E. × 45).

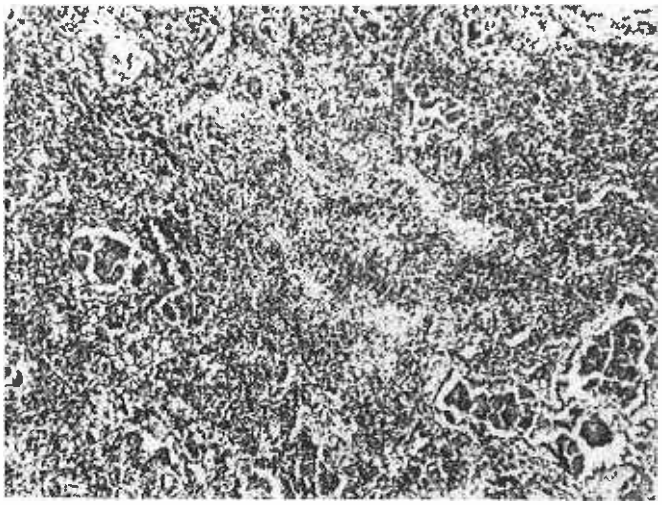

Fig. 6. Extreme proliferation of histiocytic cells obliterating the alveolar spaces and hyperplasia of the bronchial epithelium (H. and E. × 75).

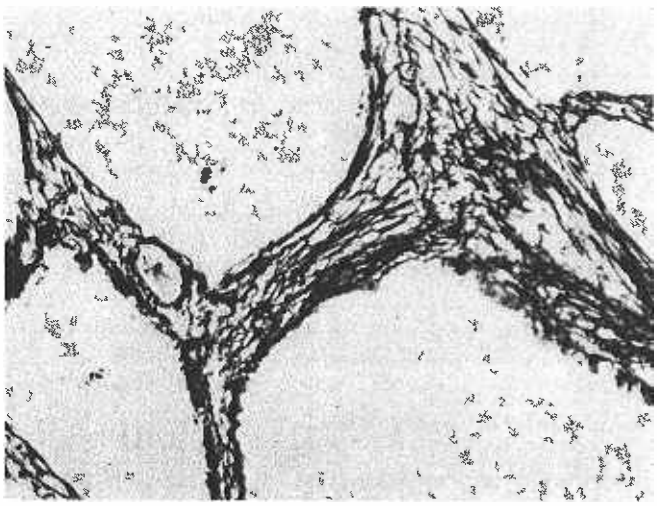

Fig. 5. Alveolar septae greatly thickened by reticulin fibres with obliteration of most of the capillaries, except one dilated capillary (Silver Reticulin Stain × 150).

Fig. 7. Obliteration of alveolar spaces by collagenous fibres in the denser areas at the hilum (Verhoeff Elastic and van Gieson Stain × 75).

croft, 1956; Livingstone *et al*, 1964; Read and Holland, 1959; Scadding and Hinson, 1967) only three responded favourably. One of these was thought to be drug induced (Read and Holland, 1959), whilst no details are available on the other two (Scadding and Hinson, 1967). Our patient received initially 60 mg. Prednisolone daily; there was only a temporary improvement as judged clinically and from the blood gas studies.

The chest radiographs reflect the course of the pathological process. The initial bronchopneumonic like shadows gradually cleared and gave rise to a more reticulated pattern with cystic appearances over the apical and basal lung regions (Fig. 2).

Pathologically, the main change is the interstitial fibrosis which is progressive and interferes with gaseous diffusion and vascular perfusion ending in cor pulmonale (Spencer, 1968). Various stages of the disease have been described. It is believed that initially, there is an intra-alveolar exudate of fibrinous oedema fluid, red blood cells and desquamated histiocytic cells often accompanied by hyaline membrane formation. Then there is great proliferation of histiocytic cells with deposit of reticulin fibrous leading to interstitial mural thickening. The reticulin matures into collagen and a stage of diffuse interstitial fibrosis develops. There may be hyperplasia and metaplasia of the alveolar and bronchiolar epithelium. Part of the alveolar capillary bed is obliterated, but the less damaged portions would show distension and dilatation of the capillaries and in places aneurysmally dilated. Broncho-pulmonary arterial precapillary anastomoses may be established.

The course of the disease varies from several days to several months. Our patient ran a rapid downhill course of 36 days. The aetiological factor is still in dispute; in our patient, no aetiological or associated factors were demonstrated.

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