Primary diffuse alveolar septal amyloidosis

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Poh, S. C., Tjia, T. S., and Seah, H. C. (1975). *Thorax*, 30, 186–191. Primary diffuse alveolar septal amyloidosis. The case is reported of a 61-year-old man with primary diffuse alveolar septal pulmonary amyloidosis. Amyloid infiltration of the heart and other organs was also observed. The clinical findings and laboratory investigations reveal features characteristic of defective gas transfer with pulmonary oedema due to left ventricular failure from myocardial involvement.

Of the various forms of primary amyloidosis involving the respiratory system, diffuse alveolar septal amyloidosis is by far the most uncommon. In this paper we report a case of this unusual form of primary amyloidosis of the lung.

CASE REPORT

A 61-year-old Chinese man first presented in December 1973 complaining of progressive breathlessness on exertion and slight swelling of the legs of three months' duration. Except for a history of psoriasis for the previous year there was no other history of note. He had smoked about 10 cigarettes daily for the past 30 years and worked as an assistant in a coffee stall until his admission.

On examination he was slightly dyspnoeic and had signs of congestive cardiac failure. The heart was clinically normal and the systemic blood pressure was 110/80 mmHg. The reflexes were normal and there was no clubbing nor cyanosis. Some psoriatic skin lesions were present on the upper limbs and body. He improved with treatment for the cardiac failure and then remained fairly well except for two episodes of abdominal pain over the left loin and right iliac fossa which lasted about four days on each occasion in February and March 1974 and for which no cause could be found clinically. He continued to be slightly breathless at rest and lethargic, and crepitations were heard occasionally over the left lower lobe. Investigations failed to reveal the cause of his dyspnoea. He refused a lung biopsy. He suddenly became more ill on 9 July 1974 and died the following day. Only a 'limited' necropsy was permitted.

INVESTIGATIONS The following investigations were normal: haemoglobin, total white and differential count, platelet count, routine urinalysis, blood urea, serum electrolytes, pyruvic acid, and glutamic oxalic transaminase. His erythrocyte sedimentation rate was 54 mm per hour. Blood tests for lupus erythematosus cells, rheumatoid arthritis, and antinuclear factor antibodies were negative. Serum electrophoresis showed a total protein of 6.5 g per 100 ml with albumin 3.4, α_1 globulin 0.6, α_2 globulin 0.9, β globulin 0.4, and γ globulin 1.2 g per 100 ml. Estimation of serum immunoglobulins revealed a low IgA of 96 mg per 100 ml and normal levels of IgG and IgM at 1,040 mg per 100 ml and 74 mg per 100 ml respectively.

His chest radiograph on admission showed slight cardiomegaly and pulmonary oedema (Fig. 1). These abnormalities subsided with treatment (Fig. 2), but diffuse reticulonodular opacities persisted, especially over the middle and lower zones.

An electrocardiogram showed sinus rhythm with low voltages in lead I and nonspecific ST-T wave changes in leads V1 to V3. Cardiac catheterization and angiocardigraphy performed on 27 March 1974 were reported as follows: 'The pulmonary artery pressure is mildly elevated to a mean of 25 mmHg and the pulmonary capillary wedge pressure is raised to 18 mmHg. There are no shunts detected and there is no gradient across the right ventricular outflow tract. The pulmonary vasculature is normal and the left atrium is normal in size and configuration'.

Pulmonary function studies performed on 16 March 1974 showed normal lung volumes and flow rates. The fractional uptake of carbon monoxide and the transfer factor were markedly

FIG. 1. *Chest radiograph on admission showing slight cardiomegaly and pulmonary oedema.*

FIG. 2. *Chest radiograph taken on 21 March 1974 showing clearing of the oedema and diffuse reticulonodular opacities in middle and lower zones bilaterally.*

reduced. Blood gas analysis revealed chronic hypocapnoea and mild hypoxaemia. The findings were in keeping with a defect in gas transfer (Table).

TABLE
PULMONARY FUNCTION TESTS

Measurement	Predicted	Observed
Vital capacity (l.)	2.80	2.71
Functional residual capacity (l.)	2.66	2.60
Residual volume (l.)	1.98	1.54
Total lung capacity (l.)	4.55	4.25
Mixing efficiency (%)	49	47
FEV _{0.75} × 40 (l/min)	86	80
Maximum mid-expiratory flow rate (l/sec)	2.8	2.9
Transfer factor CO (ml/min/mmHg)	11.2	5.3
Fractional uptake CO (%)	45	23
Blood gas		
pH	7.40	7.43
Standard HCO ₃ (mEq/l)	24	19
Paco ₂ (mmHg)	40	23
Pao ₂ (mmHg)	78	69

NECROPSY FINDINGS The necropsy was limited to an examination of the thoracic and abdominal organs. Each pleural cavity contained about 300 ml of straw-coloured fluid. The lungs were bulky and revealed a uniform rubber sponge-like appearance on their cut surfaces (Fig. 3). The trachea and bronchi were normal. The pulmonary arteries were slightly dilated and showed some atherosclerotic changes, while the pulmonary veins showed a diffuse thickening of their walls.

The aorta was moderately atheromatous. The heart was slightly enlarged and weighed 420 g. The pericardium and aortic and pulmonary valves were normal in appearance. Both the mitral and tricuspid valves, however, showed a generalized thickening of the cusps although still retaining their normal shape. The coronary arteries were patent. The atria were dilated and the endocardium thickened. The right and left ventricles were hypertrophied with a wall thickness of 6 mm and 16 mm respectively. The myocardium appeared brownish.

The liver showed chronic venous congestion. The left kidney revealed an area of infarction at the lower pole. Other abdominal organs appeared normal.

Microscopically the lung architecture was relatively well preserved. There was diffuse thickening of the alveolar walls due to deposition of an amorphous eosinophilic substance in all the sections (Fig. 4). Heavy deposits in the walls of the blood vessels were also noted. Many of the arteries showed hypertrophic changes in their walls. The amorphous substance was weakly periodic acid-

FIG. 3. Cut section after formalin fixation showing diffuse rubber-sponge appearance.

Schiff positive, stained well with crystal violet and Congo red stains, and fluoresced brightly with thioflavin T, thus confirming the presence of amyloid (Fig. 5). The bronchial mucosa was not thickened and amyloid deposits were limited to the walls of the blood vessels within the mucosa.

Sections from various parts of the heart, including the tricuspid and mitral valves, showed the presence of a varying amount of amyloid within the muscle fibres, interstitium, endocardium, and in the walls of the coronary vessels. Similar deposits were found within the walls of the aorta, venae cavae, and oesophagus.

The abdominal organs were not available for microscopic examination.

DISCUSSION

Primary amyloidosis involving the respiratory system has been classified into three groups: (1) amyloidosis of the tracheobronchial membrane; (2) nodular parenchymatous amyloidosis;

FIG. 4. Amyloid deposits in alveolar walls. Haematoxylin and eosin $\times 150$.

FIG. 5. Alveolar walls and pulmonary capillaries fluoresce brightly. Some of the histiocytes within the alveoli also give a dim fluorescence. Thioflavin T, ultraviolet fluorescence $\times 100$.

and (3) diffuse parenchymatous alveolar septal amyloidosis (Bachmann, 1967). While reports of moderate focal deposition of amyloid in the alveolar walls and pulmonary vessels are not uncommon in primary amyloidosis (Dahlin, 1949; Symmers, 1956a), the diffuse alveolar septal form has rarely been documented.

A search through the world literature reveals only 15 such cases (Larsen, 1930; Burumcekci, 1938; Sappington, Davie, and Horneff, 1942; Dirkse, 1946; Bachman, 1967; Gonzalez-Cueto *et al.*, 1970; Rajan and Kikkawa, 1970) Ferris (1936) mentions two cases of Lubarsch (1929) as bearing 'a fairly close resemblance' to his own case. Almost all the patients presented with dyspnoea and fatigue, although the patient of Michelson and Lynch (1935) had no untoward respiratory symptoms in spite of radiological changes. Lung function tests showing a restrictive ventilatory defect were reported in only three cases (Blasi, Vitali Mazza, and Berti, 1963; Candiani, Di Jasi, and Pasetti, 1965; Zundel and Prior, 1971) but in another case (Crosbie *et al.*, 1972) multiple myeloma was associated with amyloid infiltration of the alveolar vessels and impairment of gas transfer.

As in the majority of cases previously reported, extrapulmonary disease was present in this patient. In retrospect, it is likely that the episodes of abdominal pain were due to infarction of the left kidney and amyloid involvement of the gastrointestinal tract. The low IgA is probably due to decreased synthesis and to gastrointestinal and renal losses (Barth *et al.*, 1968).

The patient had the clinical, physiological, and pathological features of the syndrome associated with impairment of gas transfer. This is in agreement with the findings of Zundel and Prior (1971) but is at variance with the conclusions of Gonzalez-Cueto *et al.* (1970), who failed to find 'any good evidence of such functional derangement' although no pulmonary function tests were performed on their patient.

Symmers (1956a), in his review of primary amyloidosis, states 'when there is widespread amyloidosis of the lungs, there is likely to be morbid anatomical evidence suggestive of hypertension in the pulmonary circulation such as pulmonary atherosclerosis and arteriolosclerosis, and hypertrophy of the right ventricle'. The findings in our patient at both cardiac catheterization and necropsy fully support these conclusions.

The pulmonary radiological findings of increased prominence of the bronchovascular markings and diffuse reticulonodular opacities, while

not pathognomonic, are suggestive of the disease (Wang and Robbins, 1956). A feature which may give a clue to the diagnosis is the presence of pulmonary oedema as well. The catheterization studies indicated that the pulmonary oedema was due to failure of the left ventricle. This, as shown histologically, was the result of amyloid involvement of the myocardium. It has been stated that pulmonary amyloidosis usually manifests itself clinically in people over 50 years of age (Lunzenauer, 1952) and that most cases of generalized amyloidosis are fatal within one to three years of the first symptom (Symmers, 1956b). We would suggest that a middle-aged patient presenting with progressive dyspnoea, no gross clinical abnormality of the heart, and a chest radiograph with diffuse bilateral reticulonodular opacities and pulmonary oedema is likely to have diffuse alveolar septal amyloidosis with amyloid involvement of the heart.

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