A CASE OF PRIMARY PULMONARY HAEMORRHAGE AND RENAL DISEASE (GOODPASTURE'S SYNDROME)

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The association of primary pulmonary haemorrhage and glomerular disease in a young adult male, was first described by Goodpasture in 1919.[1] Similar cases are being reported with increasing frequency. Stanton and Tange[2] described 9 cases, all in males, and suggested the name 'Goodpasture's syndrome'. Seven of their cases were in the third decade and 2 in the fifth decade of life. More recently Saltzman *et al.*[3] reviewed 36 cases from the literature and added another 3 cases.

A definite clinical syndrome of haemoptysis and anaemia, followed by glomerular disease, has thus emerged. The lesion, which appears to be confined to the lungs and kidneys, progresses rapidly and the prognosis is grave, most cases terminating within a few months.[4] Young adult males are almost exclusively affected and the aetiology is unknown.

Few of the documented cases have had a lung biopsy during the illness. A further case, in which a lung biopsy was performed, is here recorded.

CASE REPORT

A 29-year-old White male, a welder, was admitted to the Boksburg-Benoni Hospital in January 1964 with a 2-weeks history of cough, productive of a blood-stained sputum, shortness of breath and vague chest pains, which were aggravated by respiration. There was no history of previous ill-health and the family history was not relevant. He smoked 20 cigarettes a day.

On examination, the patient was found to be well built and muscular, weighing 160 lb. He was dyspnoeic, coughed up moderate amounts of bright red blood and exhibited marked pallor. On chest examination some crepitations were heard at the right base. The heart sounds were normal. Pulse rate was 100/min., BP was 140/70 mm.Hg, the temperature 99·4°F. There were no other positive physical findings.

The patient stayed in hospital for 16 days. During this time his temperature remained around 100°F, until the 13th day, when it suddenly returned to normal. He continued to cough up fairly large amounts of blood for about a week.

Blood count showed Hb. of 7·0 G/100 ml.; PCV 23%; MCHC 30%; white cells 11,300 cu.mm. (neutrophils 67%, monocytes 2%, lymphocytes 29%, eosinophils 2%); ESR (Wintrobe) 50 mm in one hour; platelets were plentiful. Total serum protein 6·9 G/100 ml; (albumin 4·5, globulin 2·4). A chemical and microscopic examination of the urine, 2 days after admission, yielded no evidence of renal disease. Bronchoscopy showed generalized bronchial haemorrhage and bronchial washings for malignant cells were negative.

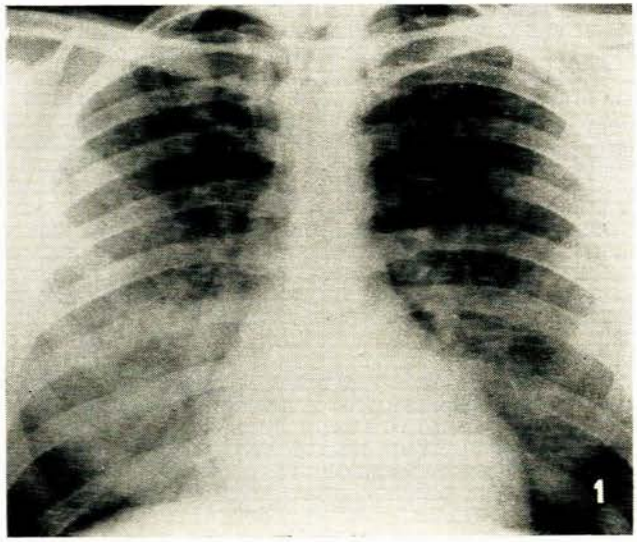

Fig. 1. Chest X-ray showing bilateral diffuse perihilar opacities.

ECG 2 days after admission showed T-wave flattening in V4, V5 and V6. The SGOT, however, was normal.

X-ray examination. There were bilateral perihilar diffuse opacities (Fig. 1). There was no evidence of increased hilar vascularity and the heart shadow was normal in size.

Treatment. The patient was treated symptomatically with blood transfusion and antibiotics. A tentative diagnosis of left ventricular failure with pulmonary oedema was considered and digoxin was given. He was discharged from hospital on

30 January 1964, his condition then being fairly satisfactory. No definite diagnosis had been made at this stage.

Follow-up. He was seen again as an outpatient on 7 and 19 February 1964. He had not experienced any further haemoptysis but was dyspnoeic, complained of dizziness and looked pale. BP was 146/80 mm.Hg. His ECG was now completely normal and a chest X-ray showed some improvement. Blood urea was 33 mg./100 ml; Cl 105 mEq./l; Na 130·4 mEq./l. and K 4·1 mEq./l.

Readmission. A month after discharge from hospital he was readmitted with severe haemoptysis. A few crepitations were heard at the bases of the lungs and a subconjunctival haemorrhage was present in the left eye. His fundi appeared pale but otherwise normal. Hb was 5·4 G/100 ml. The clotting and bleeding time, the direct Coombs' test, the one-stage prothrombin time and platelets were all found to be normal and 'LE' cells were not detected (the red cells showed evidence of mild iron deficiency).

It was during this second admission to hospital that the patient developed a definite and persistent proteinuria and a provisional diagnosis of Goodpasture's syndrome was made.

Urinalysis. On 9 March (9 days after his second admission), the urine report read: Protein + + +, 8-10 polymorphonuclear leucocytes and moderate numbers of red cells per high power microscopic field, together with a moderate number of hyaline and granular casts. The blood urea rose to 70 mg./100 ml. and the urea clearance test was 25% of normal. SG of the urine ranged from 1010-1020.

A lung biopsy by thoracotomy was performed on 10 March 1964.

Microscopic examination. The alveoli contained red blood corpuscles and haemosiderin-laden macrophages. The alveolar walls were thickened in some areas and foci of newly-formed fibrous tissue were observed along some of the alveolar ducts.

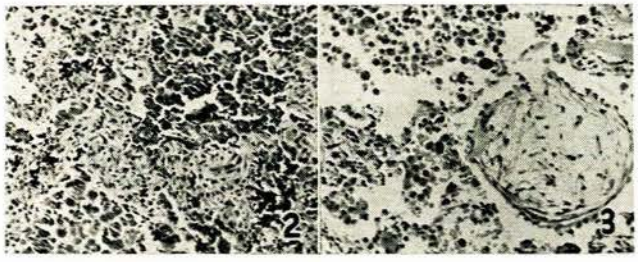

Fig. 2. Lung biopsy showing an area in which there are thickened alveolar walls, alveoli filled with haemosiderin-laden macrophages and evidence of fresh haemorrhage. (Masson's trichrome x 200.)
Fig. 3. Lung biopsy showing a focal area of newly formed fibrous tissue. (H. & E. x 120.)

The reticulin and elastic fibrils in the walls and around the smaller vessels were intact. Oedema fluid though present was not a striking feature. No evidence of an acute alveolitis was found and no significant deposition of iron pigment was seen in the interstitial tissues (Figs. 2 and 3).

A renal biopsy was considered, and also steroid therapy, but the patient felt better after further blood transfusions and decided against any further investigation and treatment. He left hospital on 17 March 1964.

Final admission. He was admitted for the third and final time on 11 May 1964 (4 months after the first admission) with haemoptysis and anaemia. He was oliguric and the urine was loaded with protein.

On examination. BP 120/70 mm.Hg. Hb 4·1 G/100 ml.; blood urea 157 mg./100 ml., rising to 364 mg./100 ml. 2 days later; Na 119·6 mEq./l.; Cl 92 mEq./l. and K 4·9 mEq./l., serum cholesterol 269 mg./100 ml. and total serum protein 5·6 G/100 ml., with an essentially normal electrophoretic pattern. X-ray examination of the chest showed confluent heavy opacities in both lung fields, which were reported as due to pulmonary oedema and alveolar haemorrhage.

On 13 May 1964 he became extremely dyspnoeic and was not relieved by oxygen, intravenous aminophyllin, diuretics or digoxin by injection. He died, apparently from pulmonary oedema complicated by a massive intrapulmonary haemorrhage.

Autopsy findings. The lungs were heavy and firm with a reddish-brown colouration.

Microscopic findings. The pathological changes were essentially the same as those seen in the biopsy, except that oedema was now much more prominent and many alveoli in addition contained fibrin, which had formed hyaline membranes within

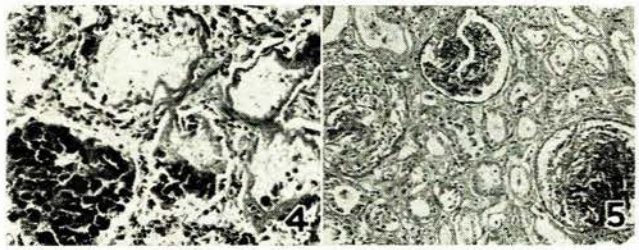

Fig. 4. Postmortem section of lung showing intra-alveolar haemosiderin, oedema and fibrin organized into hyaline membranes. (H. & E. x 200.)
Fig. 5. Shows proliferative changes and hyaline necrosis of glomerular tufts. (Masson's trichrome x 120.)

the alveoli and alveolar ducts (Fig. 4).

The hilar glands contained a moderate amount of haemosiderin.

The kidneys were increased in size and pale. Lobulation was prominent and the capsule stripped easily.

Sections showed a diffuse glomerulonephritis. The glomerular lesions included partial or complete hyalinization of the tuft and a proliferative glomerulitis. Epithelial crescents were present, but not prominent. Some of the tubules contained red cells. Apart from a mild intimal thickening of the medium-sized arteries, no significant arteriolar lesion was seen (Fig. 5).

There was no evidence of either vascular lesions or haemosiderin deposition in the other organs.

DISCUSSION

The above case presented a difficult diagnostic problem particularly on the first admission to hospital when haemoptysis and anaemia were the main features.

The heart was normal clinically and radiologically and cardiac causes, e.g. left ventricular failure, mitral stenosis and myxoma of the left atrium, could all be excluded. The BP was normal and, in fact, remained so throughout his illness. The X-ray findings were compatible with pulmonary oedema, but the hilar regions were devoid of the increased vascular markings usually associated with this condition.

Various bronchial causes were considered. There was no previous history suggestive of bronchiectasis, clubbing was absent and the bases of lungs were radiologically clear. Haemorrhage from a tumour is unlikely to produce diffuse radiological opacities bilaterally. Furthermore, bronchoscopy and examination of bronchial washings were negative. The pyrexia suggested a possible atypical pneumonia, but the severe pulmonary haemorrhage, anaemia and progress of the condition, made this diagnosis unlikely. The X-ray appearances were also unlike that of a tuberculous infection and sputa were negative.

The early phase may be clinically and radiologically indistinguishable from ideopathic pulmonary haemosiderosis. This condition occurs most commonly in childhood. Adult cases have, however, been described[5] but an association with renal disease is rare.[6]

Haemoptysis can occur as a complication of uraemia or left ventricular failure in any form of acute nephritis, so that for the clinical diagnosis of Goodpasture's syndrome it is essential to have a history of haemoptysis with a subsequent development of renal failure. Haemoptysis, preceding an onset of haematuria or proteinuria, however, can occur in some cases of pulmonary allergic granulomatosis,[7] the fully-developed form of Wegener's syndrome,[8] and in polyarteritis nodosa.[9]

It is of interest to note that the serum-K level remained below 5·0 mEq./l. and that the blood pressure stayed within normal limits throughout. This is unusual for progressive glomerular disease.[10]

This case emphasizes that a postmortem diagnosis of Goodpasture's syndrome may be impossible, because terminally the lung changes can be virtually identical with those of 'uraemic pneumonitis', and the kidney picture of a diffuse proliferative glomerulonephritis is not specific for this syndrome. McCaughey and Thomas[11] reviewed 252 autopsied cases with glomerulonephritis and found that 39 were associated with severe pulmonary haemorrhage. In 25 of these cases fresh haemorrhage was the outstanding feature and in 14 haemosiderosis was dominant. The former were characterized by an acute alveolitis with intense focal accumulations of polymorphonuclear leucocytes around the alveolar septa. De Gowin *et al.*[12] reported a case of nephritis with lung haemorrhage in a male aged 59 years, which they considered to be compatible with Goodpasture's syndrome, although in this case haemoptysis occurred after a 7-year history of renal disease. At autopsy the lungs showed focal destruction of alveolar septa, fresh haemorrhage and a necrotizing alveolitis. A fibrinoid arteritis involving the small vessels of the upper gastro-intestinal tract was also found.

The cases of severe pulmonary haemorrhage and acute alveolitis, and those of haemosiderosis without an alveolitis, may represent different histological manifestations of the same disease. We feel, however, that at this stage some distinction should be made between cases like the one reported here, where haemoptysis clearly preceded the onset of renal signs, and intra-alveolar haemosiderosis without an acute alveolitis was the dominant lung finding in both the biopsied and postmortem sections, and those cases where haemorrhage and acute alveolitis are more prominent, particularly when only necropsy tissue is available for study.

In order to make this distinction, lung biopsy, before the development of uraemia, may therefore be necessary. Even then the histology is not diagnostic. The features can be identical with those in the acute phase of idiopathic pulmonary haemosiderosis[13] and may also be mistaken for the pulmonary changes of mitral stenosis. Idiopathic pulmonary haemosiderosis, however, tends to occur in a younger age group and in the later stages of the disease haemosiderin-laden macrophages occur in the interstitial tissues and characteristic siderotic nodules form in the walls of alveolar ducts and respiratory bronchioles.[14]

The kidney lesion is very similar to that which is associated with Henoch-Schönlein purpura. Zollinger and Hegglin[15] consider idiopathic pulmonary haemosiderosis to be a pulmonary form of Henoch-Schönlein purpura, while McCaughey and Thomas[11] suggest that the syndrome of lung haemorrhage with nephritis, and idiopathic pulmonary haemosiderosis, may be related entities. Experimental studies have shown that nephrotoxic antibodies which are specific for glomerular capillary basement membrane, and which are capable of producing experimental glomerulonephritis, also localize in the alveolar wall capillary basement membranes, though not as intensely.[16,17] Lung lesions and nephritis have been produced in dogs by rabbit antiserum to dog lung, suggesting that lung and kidney are antigenically similar.[12]

The possibility therefore exists that Goodpasture's syndrome, idiopathic pulmonary haemosiderosis, Henoch-Schönlein purpura and proliferative glomerulonephritis represent a closely allied group of conditions, where the fundamental lesion is an allergic capillaritis, which may have different target organs and where the more severe cases develop an often fatal glomerulitis. Furthermore, Walker and Joekes[18] suggest that lung purpura with nephritis and polyarteritis nodosa 'may be manifestations of the same underlying disease'.

Treatment and Prognosis

The case described received only symptomatic and supportive therapy, but many of the cases documented were treated with corticosteroids, the value of which is disputed.[4, 19] Only 2 cases which we consider to be identical with this one, have survived. Both cases are symptom-free 6 years after diagnosis.[13, 18]

SUMMARY

The clinical course of a case of pulmonary haemorrhage with nephritis (Goodpasture's syndrome) is fully described. It is emphasized that for the clinical diagnosis of this syndrome the pulmonary symptoms precede the onset of renal disease. The differential diagnosis and the histological findings are discussed. Mention is made of conditions which may be related to this syndrome.

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