Clinicopathological Conference

Pulmonary haemorrhage and nephritis

Clinical notes

A 64-year-old woman was admitted to hospital because of haemoptysis. She had been well until the previous day, when she had developed loin pain. This was followed by recurrent haemoptysis, and when she was examined the following morning she was confused and had a blood pressure of 100/60 mmHg. She had had no serious previous illnesses, smoked 10 cigarettes per day and had a mild chronic cough.

The temperature was 38,7°C, the pulse rate 110/min and irregular, and the blood pressure 140/80 mmHg. The patient was well nourished and confused but co-operative. Her breathing was rapid and she was coughing frequently and producing small quantities of fresh blood. There was central cyanosis but no clubbing, jaundice, lymphadenopathy or oedema. The trachea was central, the chest was dull to percussion anteriorly and there were bronchial sounds over the left upper lobe, with a friction rub in this area and extensive bilateral coarse crackles. The venous pressure was normal. Heart sounds were inaudible. On examination of the abdomen there was slight tenderness in the right upper quadrant, but no masses were felt and there was no loin tenderness. Rectal examination revealed occult blood but was otherwise negative. There was no neck stiffness and no focal neurological deficit. Examination of the urine revealed a trace of protein and 3+ haematuria, but no casts or white cells were seen.

The haemoglobin concentration was 13,8 g/dl, the white cell count 3,6 x 10^9/l with 66% neutrophils and the ESR 58 mm/1st h. Serum biochemical values were as follows: sodium 141 mmol/l, potassium 2,9 mmol/l, chloride 107 mmol/l, bicarbonate 24,0 mmol/l, urea 16,8 mmol/l, creatinine 125 μmol/l, total protein 47 g/l, albumin 28 g/l, calcium 1,87 mmol/l, inorganic phosphate 0,71 mmol/l, cholesterol 3,1 mmol/l, urate 0,32 mmol/l, total bilirubin 11 μmol/l, conjugated bilirubin 10 μmol/l, γ-glutamyltransferase 27 U/l; alkaline phosphatase 67 U/l, SGOT 21 U/l and lactic dehydrogenase 329 U/l.

An ECG showed a normal rhythm at a rate of 120/min with frequent atrial ectopic beats. The PR interval was normal. There were Q waves in the inferior leads, and R-wave progression was poor.

A catheter urine specimen showed scanty red cells, occasional pus cells and granular casts but no significant bacteriuria. Microscopic examination of the sputum was negative for acid-fast bacilli, and culture yielded mixed salivary organisms only. Blood cultures were sterile.

The pH on room air was 7,46, the partial arterial oxygen pressure (P_{O_2}) 7,07 kPa, the partial arterial carbon dioxide pressure (P_{CO_2}) 4,0 kPa, base excess -1,3 mmol/l, and standard bicarbonate 23,0 mmol/l. The heart appeared normal on the chest radiograph but there was opacification of the lingula, the anterior segment of the left upper lobe and the left perihilar region. The blood VDRL test was negative.

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Treatment was commenced with penicillin and cefamandole and the patient was given continuous positive airway pressure ventilation (CPAP). The temperature returned to normal on the 3rd day but the pulse rate remained 110/min and she was tachypnoeic (30/min). Persistent hypoxia necessitated a change from CPAP to positive end-expiratory pressure ventilation (PEEP) with 45% oxygen. Repeat chest radiographs showed opacifications throughout the right upper lobe and at the left base. Cefamandole was replaced by gentamicin. A chest radiograph on the 4th day showed some clearing of the right lung, but she was again pyrexial (38-39°C). The white cell count was 23 x 10^9/l with 88% neutrophils and the haemoglobin concentration 7,1 g/dl. The P_{O_2} was 8,4 kPa and the P_{CO_2} 6,0 kPa on 28% oxygen.

Sputum culture yielded a heavy growth of mixed salivary organisms, including *Klebsiella* species sensitive to co-trimoxazole, gentamicin, chloramphenicol and cefamandole. The indirect fluorescent antibody test for legionnaires' disease was negative. There were a few red cells in the urine but there was no significant bacteriuria. There was 3,0% binding of immune complexes in the serum (normal 0-7%) and 2 μg DNA were bound per millilitre of serum (normal 0 - 5 μg). Blood cultures were again sterile.

On the 8th hospital day the blood urea level was 3,7 mmol/l and the creatinine level 73 μmol/l; these values rose to 5,3 mmol/l and 91 μmol/l respectively on the 10th day. Erythromycin was added to the regimen.

Bronchoscopy was performed. Blood was noted to be issuing from the left upper lobe, but no intrabronchial lesion was seen. The bleeding time was 2 minutes, the prothrombin index 81% and the partial thromboplastin time 26,5 seconds (control 40,5 seconds); the fibrinogen level was 670 mg/dl (normal 200-400 mg/dl) and that of fibrin degradation products 40 μg/ml (normal <40 μg/ml). A fresh urine specimen was found to contain large numbers of red cells, red cell casts and hyaline casts, and there was 1+ proteinuria. Renal biopsy was performed.

Prednisone and cyclophosphamide were added to the regimen and plasmapheresis was commenced. During the next 3 weeks eight plasma exchanges were performed. The patient's pulmonary signs improved and renal function remained stable. The slight haematuria persisted and an occasional red cell cast was seen in the urine. On the 23rd day the urine contained 4+ glucose and the blood sugar level was 22,7 mmol/l. The blood sugar value returned to normal on dietary management alone.

Staphylococcus aureus sensitive to fusidic acid and clindamycin only was cultured from the shunt wound. A blood transfusion was given and the shunt removed. Treatment with fusidic acid was commenced. The patient developed rapid atrial fibrillation and became very confused. The chest was clear except for occasional wheezes on expiration. The heart rate was controlled by digitalization, although fibrillation persisted. She became jaundiced. The total bilirubin level was 73 μmol/l, the conjugated bilirubin level 48 μmol/l, the alkaline phosphatase level 87 U/l and the SGOT level 51 U/l.

One week later the values were as follows: total bilirubin 89 μmol/l, conjugated bilirubin 85 μmol/l, alkaline phosphatase 79 U/l, and SGPT 45 U/l. The blood urea level rose to 10 mmol/l, while serum sodium, potassium, calcium, phosphorus and creatinine values remained normal. Although apyrexial the patient

remained lethargic and confused, and she died on the 38th day in hospital.

Differential diagnosis

This patient presented with an acute respiratory illness with haemoptysis, cyanosis, signs of left upper lobe consolidation and bilateral coarse crackles. There was nothing (if one discounts a mild smoker's cough) to suggest underlying lung disease, and the first chest radiograph confirmed left upper lobe consolidation and showed patchy changes in the right lung as well. The widespread crackles, severe hypoxia and cyanosis indicated lesions other than isolated upper lobe consolidation, and these changes could well have been due to aspirated blood.

Of the many causes of haemoptysis only a few are pertinent. Confluent tuberculous lesions may present as bronchopneumonia, but such extensive consolidation is not usual. Haemorrhagic infarction from pulmonary emboli and aspiration of blood could have accounted for some of the clinical findings, but the radiological appearances were not typical and the diagnosis was improbable. Simple pneumonia was also unlikely. While it would have accounted for the pyrexia, the haemoptysis was too severe, the sputum never became purulent and the white cell count was normal. Bronchial carcinoma was a possibility, but with a lesion this size clubbing or constitutional symptoms might have been expected. However, on the basis of the chest radiograph alone, altered by haemorrhage, it was not possible to exclude this diagnosis.

Less commonly, haemoptysis may be due to conditions such as Goodpasture's syndrome (GPS), idiopathic pulmonary haemosiderosis or polyarteritis nodosa. In this case haematuria and mild renal failure were discovered early, but casts were not seen. The discovery of occult blood on rectal examination is not surprising after copious pulmonary haemorrhage. There was no clinical evidence of cardiac or chronic pulmonary disease. The ECG showed some nonspecific changes, but there was no evidence of recent myocardial infarction. The serum albumin content was low, and while this may have indicated greater urinary protein loss than reported there were no initial clues to the nature and extent of renal involvement.

At this stage the patient therefore appeared to have either pulmonary infection, a neoplasm or an embolism with incidental renal disease, or one of the conditions causing pulmonary haemorrhage and haematuria.

The second phase of her illness was dominated by persistently severe lung disease despite treatment with antibiotics. Although the fever declined initially, it soon recurred. The P_{O_2} rose slightly, but serial radiographs showed extensive though evanescent opacities in the right lung, typical of haemorrhage (Fig. 1), the lesion in the left upper lobe remaining unchanged. Her renal function improved, probably in response to correction of the hypovolaemia, but the haematuria persisted and occasional granular casts were seen in the urine.

Because of the probability that a single disease was affecting both lungs and kidneys renal biopsy was performed. There were several possible diagnoses. In systemic lupus erythematosus (SLE) there may be a necrotizing pulmonary vasculitis with haemorrhage and glomerulonephritis, but there was no other clinical evidence for this diagnosis and the anti-DNA antibody titre was not raised. The patient did not have granulomas or ulcers in the upper respiratory tract suggestive of Wegener's granulomatosis, which is usually more common in the 4th and 5th decades than in the 7th; chest films usually show scattered fixed shadows representing granulomas, although shadows of haemorrhage may be superimposed.

GPS most often affects young males between the ages of 16 and 35 years, but this patient's presentation is otherwise typical. Pulmonary haemorrhage usually precedes glomerulonephritis,

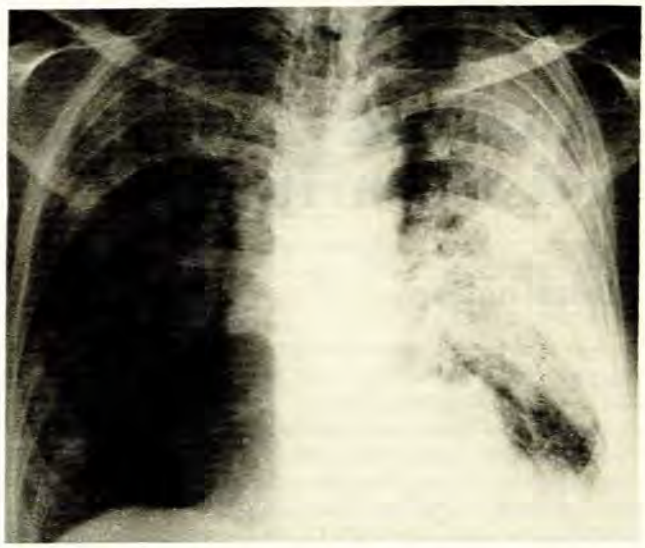

Fig. 1. Chest radiograph showing consolidation of the left upper lobe and perihilar region with patchy shadowing in the right lung.

but haematuria is common and red cell casts are usually present in the urine. Proteinuria is mild to moderate. Anaemia is the rule and hypertension uncommon.

Polyarteritis nodosa does not often cause pulmonary haemorrhage, but this diagnosis must be considered, along with varieties of hypersensitivity angiitis, Henoch-Schönlein purpura and mixed cryoglobulinaemia. An extensive list would include legionnaires' disease, excluded in this case by a negative fluorescent antibody test before renal biopsy. We may assume that the biopsy revealed the presence of anti-glomerular basement membrane (GBM) antibodies, because she was then treated for GPS with plasmapheresis, prednisone and cyclophosphamide. Although this raised her blood sugar level the response was good.

Infection at the shunt wound complicated this patient's illness, and appears to have initiated its terminal phase. The organism was the resistant strain of *Staph. aureus*, known at this hospital as a serious wound contaminant of low virulence. The shunt was removed. We are not told whether blood cultures were carried out or how the patient was treated, but she deteriorated rapidly, became comatose and died. There were no focal neurological signs at any stage, which strongly favours diffuse cerebral dysfunction, and in spite of the low virulence of the organism septicaemia from shunt infection in an immunosuppressed patient is the probable diagnosis. The jaundice which developed during this phase was not accompanied by marked elevation of the liver enzymes, a point supporting septicaemia and a reactive hepatitis and, in this context, making hepatic encephalopathy unlikely.

GPS is also known as lung purpura with nephritis, pulmonary haemorrhage and glomerulonephritis, haemorrhagic pneumonia and nephritis, haemorrhagic pulmonary renal syndrome, and pulmonary haemosiderosis and glomerulonephritis. It is, as has been mentioned, predominantly a disease of young males but can occur at almost any age.[1-4]

In 1919 Ernest Goodpasture[1] described an 18-year-old man who died of an influenzal illness characterized by haemoptysis, alveolar haemorrhage and proliferative glomerulonephritis. The anti-GBM antibody which is the hallmark of the disease was first isolated in 1967.[2]

Because of the number of conditions in which each of these findings may occur the diagnosis of GPS is restricted to those patients who have the triad of proliferative glomerulonephritis of the crescentic type, lung haemorrhage and anti-GBM antibodies.[5] To make the diagnosis of GPS one must therefore be able

to demonstrate the basement membrane antibody. This can be done in three ways.

In a renal biopsy specimen the antibody will show as linear ribbon-like immunofluorescence along the basement membrane of the glomerulus. The anti-GBM antibody is usually IgG, but occasionally is IgA or IgM. C3 is also often demonstrated as an irregular linear immunofluorescence along the basement membrane. The anti-GBM antibody can also be demonstrated in a variety of other conditions including diabetic nephropathy, SLE, necrotizing vasculitis, chronic post-streptococcal glomerulonephritis and focal glomerular sclerosis. Before a diagnosis of GPS is arrived at proliferative glomerulonephritis, preferably of the crescentic type, must therefore be present in addition to the anti-GBM antibody.[5,6] These renal features, proliferative glomerulonephritis and anti-GBM antibody can also be found in the absence of lung haemorrhage, in rapidly progressive idiopathic crescentic glomerulonephritis.

The anti-GBM antibody can also be demonstrated in the serum,[6] in which it is found in more than 90% of cases early in the disease but never in normal controls. The antibody titre does not correlate with the severity of the disease. The antibody cross-reacts with non-GBM antigens of Bowman's capsule, renal tubules and pulmonary alveoli. Usually the antibody is cleared from the serum within 6 months of the onset of symptoms, despite the persistence of disease.

If these two methods fail to demonstrate the antibody it can be eluted from renal or lung tissue. A fair amount of tissue is required and it is not a routine or easy procedure, but fortunately it is rarely necessary.[6]

How does the disease begin? There is often a preceding respiratory tract infection. An association with influenza A and with vaccination against influenza is documented, but no causal relationship has been proved. The fact that occasionally the disease occurs in clusters also suggests that the causation is infectious. There is a strong association with HLA DRw2, and the disease has also been described in families. Hydrocarbon exposure has been implicated as the initiating factor in some cases, but again the evidence is scanty. It is currently believed that some event — infection perhaps — alters pulmonary basement membrane proteins so that they act as neo-antigens, i.e. become foreign to the host and elicit an antibody reaction. Alternatively, the basement membrane is so damaged that proteins previously sequestered from the immune system are now exposed and elicit the antibody response.

A spectrum of clinical presentation is now recognized. This possibly extends from those cases of idiopathic pulmonary haemosiderosis in which anti-GBM antibodies are found in the blood and in the kidney but there is no renal disease to cases of rapidly progressive glomerulonephritis without pulmonary haemorrhage. Within the spectrum one finds patients with mild pulmonary haemorrhage and glomerulonephritis but few abnormalities in the urinary sediment, others with massive pulmonary haemorrhage and little overt renal disease, and others with fulminant crescentic glomerulonephritis and only slight pulmonary involvement.

On examination of a biopsy specimen the kidney may be found to be normal, for glomerulonephritis may only develop later. There may be focal and sequential proliferative changes or extensive crescent formation, and there may also be tubulointerstitial disease. The lungs show intra-alveolar haemorrhages with disruption of the alveolar walls and haemosiderin-laden macrophages.

If the patient is not treated the course is one of progression to renal failure, often within a year of presentation. Sometimes earlier death may result from exsanguinating or suffocating pulmonary haemorrhage. Occasionally spontaneous remission takes place, and in a few cases there will be remission of the pulmonary haemorrhage despite progression of the renal disease.

Today the treatment of choice is plasmapheresis to remove the circulating antibodies, combined with immunosuppression. The results are often dramatic, but not all patients respond.

Clinical discussion

Professor S.R. Benatar: Initially we considered bronchial carcinoma or infection as the probable cause of the first haemoptysis, overlooking the significance of the few red cells in the urine. As Dr Sherman has stressed, there may be little or no evidence of renal involvement early in GPS.

Pulmonary haemorrhage may certainly clear rapidly radiologically, but one should be cautious about deductions from apparent evanescence of shadows, which may merely reflect differences in penetration.

Professor G.R. Keeton: The natural history of GPS is variable and unpredictable. In rare cases renal function may be stable for 20 years and then deteriorate rapidly. Some evidence suggests that intermittent infection may be responsible for abrupt deterioration, possibly through an immune complex nephritis being grafted on to the syndrome. The urine must be examined frequently in all suspected cases of nephritis — red cells and casts may be present one day and not the next.

Dr M. Sherman: A renal biopsy specimen may also be normal early on, and abnormal only months later.

Professor W.P.U. Jackson: Why was the serum albumin level so low? It was probably a true low reading because the calcium level was also low. Was this the nephrotic syndrome? The white cell count varied from low to 23 x 10^9/l. Which is typical of GPS?

Dr Sherman: Neither.

Professor Keeton: The low protein level was probably an acute-phase response, with a shift of albumin which perhaps becomes bound in the reticulo-endothelial system. The acute-phase reaction may be considerable, and in this case the lowering of protein is much greater than can be ascribed to renal loss. This was not a nephrotic syndrome.

Professor Jackson: Was such drastic treatment required?

Professor Benatar: The course is unpredictable and this patient experienced serious pulmonary problems and hypoxia. I think it was quite reasonable to perform plasmapheresis early. I doubt if any patient with GPS as seriously ill as this one would improve without treatment. Usually renal function does not improve.

Professor Keeton: No, not if the patient is in oliguric renal failure, but if not oliguric he or she may improve. Hypoxic and dyspnoeic patients may improve without therapy, although the reports may have described patients not as ill as this woman.

Pathological discussion

In this case the diagnosis hinges upon the renal biopsy specimen. Immunofluorescence studies revealed an intense linear diffuse staining of glomeruli for IgG (Fig. 2) with negative staining for C3, other immunoglobulins and fibrin. There was no antitubular basement membrane staining. These findings suggest a diagnosis of anti-GBM antibody nephritis. The absence of complement staining does not exclude the diagnosis because this may be negative in 25% of cases.[7,8] The findings on light microscopy were unimpressive (Fig. 3). Apart from an occasional obsolescent glomerulus compatible with the patient's age, most glomeruli revealed no more than possible mild mesangial proliferation. There were no segmental lesions or lesions of tubules, interstitium and vessels, but these appearances are still compatible with anti-GBM antibody nephritis, the light microscopic appearance of which can vary from complete normality in the early stages through focal segmental nephritis (in spite of diffuse immuno-

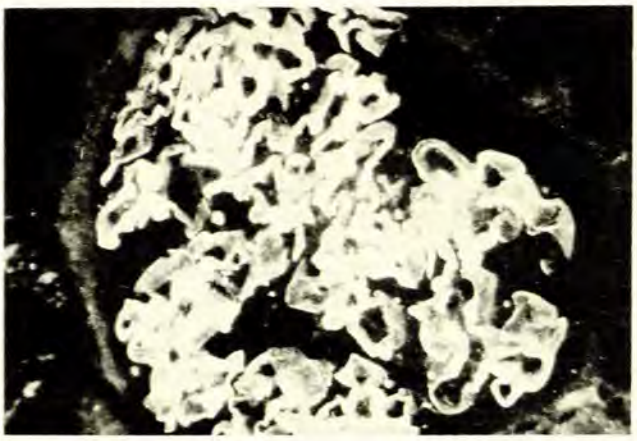

Fig. 2. Linear IgG shown by direct immunofluorescence studies of a glomerular biopsy specimen (x 400).

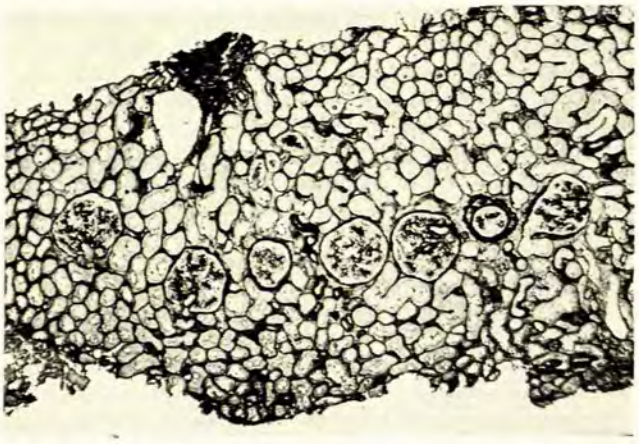

Fig. 3. Renal biopsy specimen showing a slight increase in glomerular mesangial matrix (methenamine silver x 60).

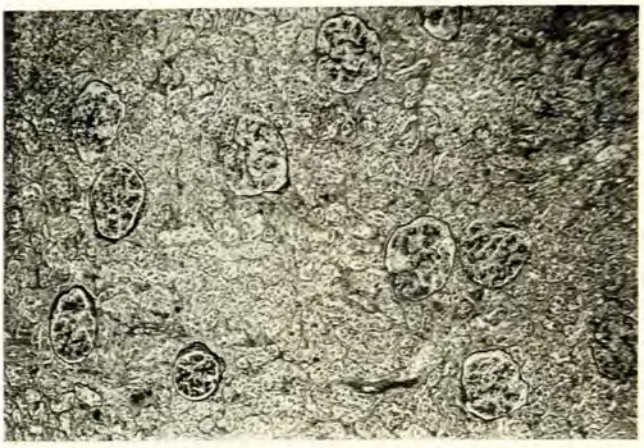

Fig. 4. Slight increase in mesangial matrix in a kidney autopsy specimen (periodic acid-Schiff x 60).

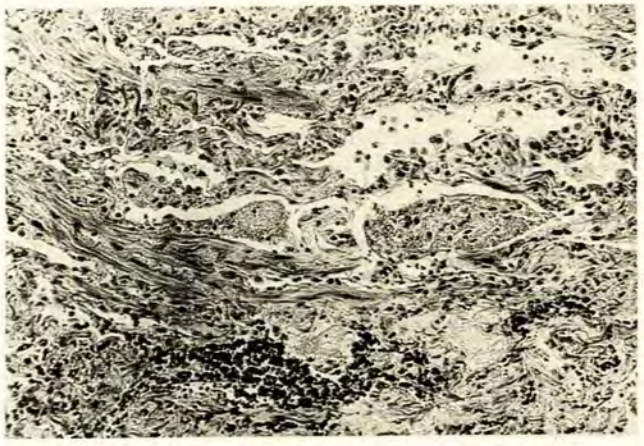

Fig. 5. Haemorrhage, alveolar wall fibrosis and oedema with 'reactive' pneumocytes in a lung biopsy specimen (H and E x 150).

fluorescence) to the classic diffuse crescentic nephritis.[7,9-11] The presence of mesangial proliferation is not considered characteristic, and a distinction is made between segmental lesions occurring on a basis of diffuse mesangial proliferation as in Henoch-Schönlein nephritis and the segmental lesions of anti-GBM nephritis which do not do so.[9] Electron microscopy revealed a nonspecific irregularity and increased thickness of the lamina rara interna and variable increased density of the lamina densa. The density of lamina rara staining on electron microscopy does not correlate with the intensity of immunofluorescence, either in the kidney or in the lung.[12] The presence of pseudolinear immunofluorescence (see Table II) due to numerous subepithelial deposits was excluded by the electron microscopic appearance. Subepithelial deposits may occur in anti-GBM nephritis if immune complex disease is superimposed upon it.[7]

At autopsy, except for a haematoma at the site of renal biopsy and a slight increase in granularity commensurate with the age of the patient, the kidneys appeared normal macroscopically. Light microscopy (Fig. 4) revealed no more than a small number of totally sclerotic glomeruli (again attributable to 'normal' obsolescence) and no segmental lesions in numerous sections. Apart from age-related intimal thickening there were no significant vascular changes, and no diagnostic features of diabetic glomerulosclerosis were noted. The direct immunofluorescence study was entirely negative.

A transbronchial biopsy performed before the renal biopsy revealed fresh haemorrhage, small numbers of siderophages suggesting a diagnosis of GPS, and striking alveolar wall thickening (Fig. 5). Although some of the latter was due to fibrosis, there was also oedema associated with marked cytoplasmic swelling and nuclear pyknosis of pneumocytes. Occasional neutrophils were present but there was no evidence of necrosis, a negative feature remarked upon by others.[9,10] Unfortunately, since the diagnosis of GPS was not entertained at this stage, tissue was not submitted for immunofluorescence studies. The changes in immunofluorescence and under the electron microscope of anti-GBM antibody disease are similar in the lung and kidney,[8,12] although lung immunofluorescence studies are more often negative and may be more difficult to interpret.[12-14] A distinction based on electron microscopy[15] has been made between pulmonary haemorrhage in anti-GBM antibody disease and idiopathic pulmonary haemorrhage/haemosiderosis, with the claim that the site of damage is the endothelial cell in the former and the pneumocyte in the latter. Lung biopsy in this case clearly revealed pneumocyte damage. Separation of these conditions is only possible with a direct immunofluorescence study, upon which classification of lung haemorrhage should depend to a large extent.[16,17]

At autopsy the left lung had a generalized congested appearance with consolidation of the upper lobe and upper parts of the lower lobe by haemorrhage. Microscopy of the upper lobe (Fig. 6) confirmed the presence of fresh haemorrhage as well as numerous siderophages, associated with alveolar septal and intra-alveolar fibrosis, but there was no evidence of necrosis or pulmonary embolism. There was minimal vascular intimal thickening confined to the haemorrhagic fibrotic areas but no

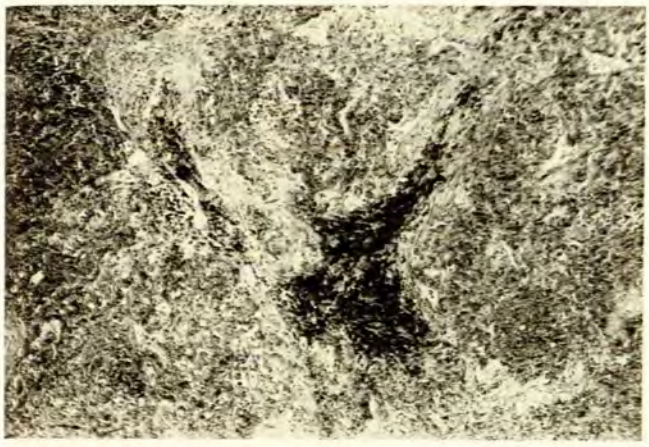

Fig. 6. Siderophages and fibrosis on a background of recent haemorrhage in a lung autopsy specimen (Perls' stain for iron x 60).

vasculitis, which excluded the possibility of polyarteritis nodosa and Henoch-Schönlein purpura, in which there may also be an association between lung haemorrhage and renal disease. Vasculitis is not a hallmark of GPS although in a recent study 2 of 18 patients were found to have vasculitis in the kidney but not in other organs.[18] A section of the right lung appeared normal apart from mild centrilobular emphysema in the upper lobe; however, microscopy revealed patches of fibrosis associated with siderophages suggesting previous haemorrhage. Direct immunofluorescence studies of both lungs were negative, as were indirect immunofluorescent tests for antibodies on a serum sample taken after the patient's death.

Other autopsy findings were as follows. The heart had a 'sigmoid' interventricular septum associated with subaortic endocardial thickening, probably resulting from friction with the anterior mitral valve leaflet (microscopy excluded hypertrophic obstructive cardiomyopathy). This is an asymptomatic anatomical variant. The left coronary vasculature appeared dominant, and 75% atherosclerotic stenosis of the left circumflex artery could have accounted for some of the changes on the ECG. The postero-inferior myocardium showed no morphological evidence of ischaemic disease.

There were mild fatty changes in the liver but no necrosis or bile plugging. These changes, associated with conjugated hyperbilirubinaemia and a normal alkaline phosphatase level, appear to implicate shock or sepsis as the immediate cause of death.[19] The possibility of sepsis was supported by the presence of a diffluent spleen and confirmed by the fact that blood cultures before the patient's death were positive for *Staph. aureus*. Fresh pulmonary haemorrhage may have been an aggravating factor. The lack of circulating antibodies post mortem is a further illustration that episodes of pulmonary haemorrhage do not parallel antibody levels. Other findings are listed in Table I.

The final assessment of this case depends on an explanation of the renal changes (or lack of them). Was the linear immunofluorescent staining of the renal biopsy specimen a technical error or spurious finding (Table II)? One technical pitfall in the performance of direct renal immunofluorescence studies is the autofluorescence which may occur in diabetics or in elderly subjects without diabetes, i.e. prior to the addition of fluorescein-conjugated anti-immunoglobulin.[20] This was excluded in this case by the use of saline controls. Of all renal biopsies 10% may show weak linear immunofluorescence with IgG, the so-called 'linear accentuation'[20] due to the presence of IgG which is not directed against basement membrane. However, the intensity of staining does not equal that seen in this case. It is difficult to exclude a minor degree of glomerulosclerosis entirely; however, such intense immunofluorescence associated with poorly developed nonspecific light microscopic changes would be unusual.[21] There is one unsupported reference[8] to 'severe hypertension' as a cause of spurious linear immunofluorescence — hypothyroidism and SLE are excluded in this case. The knowledge that spurious linear immunofluorescence occurs in perfused donor kidneys is important in trying to assess recurrent GPS after transplantation.[22] Finally, 25% of kidneys from patients without renal disease studied at autopsy may show spurious linear immunofluorescence, thus hindering postmortem assessment.[22]

TABLE I. INCIDENTAL AUTOPSY FINDINGS

Left calf veins	Thrombosis at shunt site
Thyroid	Several 'adenomatous' nodules
Bone marrow	Erythroid hyperplasia
Uterus	Small fibroleiomyoma
Brain (including choroid plexus)	Unremarkable

TABLE II. CAUSES OF SPURIOUS LINEAR RENAL IMMUNOFLUORESCENCE

- Autofluorescence
- 'Linear accentuation'
- Pseudolinear immunofluorescence (intense granularity)
- Diabetic glomerulosclerosis
- SLE
- Hypothyroidism
- 'Severe hypertension'
- Transplantation
- Autopsy

Because the results of immunofluorescence studies can be spurious, detection of circulating anti-GBM antibodies or elution studies are necessary before a diagnosis of GPS is accepted.[22] However, the latter are usually impractical in the clinical situation, and the means to carry out the former were not available at the time of presentation of this case. In addition, because circulating antibodies are transient and patients with negative serum antibodies both with severe[23] and mild[21] renal disease have been reported, this method of diagnosis is not totally reliable. The transience of serum antibodies as well as the effects of plasmapheresis could explain the negative immunological tests at autopsy.

In the final analysis, an association of spurious linear renal immunofluorescence and pulmonary haemorrhage would seem too fortuitous to exclude a diagnosis of GPS. There may have been few renal findings because the patient was seen before renal involvement became severe and the treatment she received prevented further progression. The dramatic results of plasmapheresis in this regard are now well known.[24-26] Nephritis with 60-70% crescent formation has been suggested as the 'watershed' between salvageable and non-salvageable cases.[24] Proliferative lesions, including crescents, may regress,[27] so it is possible that a focal nephritis at the time of renal biopsy had regressed by the time the patient came to autopsy. However, healed necrotic segmental lesions should manifest as segmental fibrosis, of which there was no evidence at autopsy, and this case therefore probably represents the idiopathic pulmonary haemorrhage end of the GPS or anti-GBM antibody disease spectrum. There is adequate documentation of similar cases in the literature.[10,15,21,22,28,29] They may represent a 'subset' in which the renal lesion does not progress.[21] Since at present there are no predictive indicators of the outcome of minor renal disease at the time of presentation these cases pose a dilemma with regard to treatment, considering the possible side-effects of the latter and

the fact that, if significant renal impairment is to be avoided in the more typical 'progressive' case, treatment should be started early.

REFERENCES

1. Goodpasture EW. The significance of certain pulmonary lesions in relation to the etiology of influenza. *Am J Med Sci* 1919; **158**: 863-870.
2. Lerner RA, Glassock RJ, Dixon FJ. The role of antiglomerular basement membrane antibody in the pathogenesis of human glomerulonephritis. *J Exp Med* 1967; **126**: 989-1004.
3. Stanton MC, Tange JD. Goodpasture's syndrome (pulmonary haemorrhage associated with glomerulonephritis). *Australas Ann Med* 1958; **7**: 132-144.
4. Benoit FL, Ruloa DB, Theil GB, Doulon PD, Watten RH. Goodpasture's syndrome: a clinicopathologic entity. *Am J Med* 1964; **37**: 424-444.
5. Glassock RJ, Cohen AH. Secondary glomerular diseases. In: Brenner BM, Rector FC, eds. *The Kidney*. Philadelphia: WB Saunders, 1981: 1493-1570.
6. Wilson CB, Dixon FJ. The renal response to immunological injury. In: Brenner BM, Rector FC, eds. *The Kidney*. Philadelphia: WB Saunders, 1981: 1237-1350.
7. Spargo BH, Anthony E, Seymour AE, Ordonez NG. *Renal Biopsy Pathology with Diagnostic and Therapeutic Implication*. New York: John Wiley, 1980.
8. Albini B, Breutjens JZ, Andres GA. *Immunopathology of the Kidney*. London: Edward Arnold, 1974.
9. Dunnill MS. *Pathological Basis of Renal Disease*. London: WB Saunders, 1976.
10. Heptinstall RH. *Pathology of the Kidney*, vol. 2. Boston: Little, Brown 1974.
11. Jenis EH, Lowenthal DT. *Kidney Biopsy Interpretation*. Philadelphia: FA Davis, 1977.
12. Abboud RT, Chase WH, Ballon HS, Grzybowski S, Magil A. Goodpasture's syndrome; diagnosis by transbronchial lung biopsy. *Ann Intern Med* 1978; **89**: 635-638.
13. Hogen PG, Donald KJ, McEvoy JDS. Immunofluorescence studies of lung biopsy tissue. *Am Rev Respir Dis* 1978; **118**: 537-545.
14. Beachler CF, Enquist RW, Kellog Hunt K, Ward GW, Knieser MR. Immunofluorescence of transbronchial biopsies in Goodpasture's syndrome. *Am Rev Respir Dis* 1980; **121**: 869-872.
15. Donald KJ, Edwards RL, McEvoy JD. Alveolar capillary basement-membrane lesions in Goodpasture's syndrome and idiopathic pulmonary hemosiderosis. *Am J Med* 1975; **59**: 642-649.
16. Thomas HM 3rd, Irwin RS. Editorial: Classification of diffuse intrapulmonary hemorrhage. *Chest* 1975; **68**: 483-484.
17. Turner-Warwick M. *Immunopathology of the Lung*. London: Edward Arnold, 1978.
18. Ming-Jiang Wu, Rajaram R, Shelp WD, Beirne GJ, Buckholder PM. Vasculitis in Goodpasture's syndrome. *Arch Pathol Lab Med* 1980; **104**: 300-302.
19. Desmet VJ. Cholestasis, extrahepatic obstruction and secondary biliary cirrhosis. In: Mac Sween RN, Anthony PP, Scheuer PJ, eds. *Pathology of the Liver*. Edinburgh: Churchill Livingstone, 1979: 272-305.
20. Meadows R. *Renal Histopathology: a Light, Electron and Immunofluorescent Microscopy Study of Renal Disease*. 2nd ed. Oxford: Oxford University Press, 1978.
21. Zimmerman SE, Varanasi UR, Hoff B. Goodpasture's syndrome with normal renal function. *Am J Med* 1979; **66**: 163-171.
22. Wilson CB, Dixon FJ. Diagnosis of immunopathologic renal disease. *Kidney Int* 1974; **5**: 389-401.
23. Beirne GJ, Wagnild JP, Zimmerman SW, Macken PD, Buckholder PM. Idiopathic crescentic glomerulonephritis. *Medicine* 1977; **56**: 349-381.
24. Leading article. Plasmapheresis and severe glomerulonephritis. *Br Med J* 1979; **1**: 434-435.
25. Begrem H, Jervell J, Brodwall EK, Flatmark A, Mellbye O. Goodpasture's syndrome: a report of seven patients including long-term follow-up of three who received a kidney transplant. *Am J Med* 1980; **68** 54-58.
26. Dahlberg PJ, Kurtz SB, Donadio JV *et al*. Recurrent Goodpasture's syndrome. *Mayo Clin Proc* 1978; **53**: 533-537.
27. Rosenblatt SG, Knight W, Bannayan GA, Wilson CB, Stein JH. Treatment of Goodpasture's syndrome with plasmapheresis. *Am J Med* 1979; **66**: 689-696.
28. Saraf P, Bergen HW, Thung SN. Goodpasture's syndrome with no overt renal disease. *Mt Sinai J Med (NY)* 1978; **45**: 451-454.
29. Kincaid-Smith P. *The Kidney; A Clinico-Pathological Study*. Oxford: Blackwell, 1975.
30. Fitzcharles MA, Benatar SR. Goodpasture's syndrome: case report of a survivor. *S Afr Med J* 1978; **53**: 63-66.