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CLINICO-PATHOLOGICAL CONFERENCE: FATAL LUNG DISEASE COMPLICATING NEPHRITIS

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CASE PRESENTATION

Dr Anderton

The case for discussion is that of a man born deaf and dumb in 1923. He had a past history of mild asthma and a left inguinal hernia repair in November 1991. In June 1992 he presented to the Urology department with left loin pain. Urine examination revealed blood. An abdominal ultrasound disclosed a mass in the left kidney measuring 4 cm in diameter and an IVU showed absence of the calyces in part of the left kidney. One month later his blood urea was noted to be 7·2 mmol/l with a serum creatinine of 132 umol/l. An abdominal CT scan was reported to be normal. He had lost 3 kgs in weight and complained of anorexia and abdominal pain. In September 1992 he was admitted as an emergency to the Surgical department when his blood urea was found to be 37 mmol/l, with a serum creatinine of 857 umol/l. It did not appear as if he had pre-renal failure in that he was not shocked. A further ultrasound showed no change in appearance from the first; the kidneys were of normal size and there was no evidence of obstruction. We would have liked to perform a renal biopsy but the patient was a Jehovah's Witness and would have refused transfusion if bleeding complicated the procedure. There were red cells casts in his urine which suggested a diffuse glomerular disease rather than a tumour as had been suspected. In these circumstances we considered a diagnosis of rapidly progressive glomerulonephritis which can be due to a number of causes, the main two of which are an anti-GBM antibody disease (Goodpasture's syndrome) and systemic vasculitis. Subsequently circulating plasma anti-neutrophil cytoplasmic antibody tests indicated that he did have a vasculitis while his anti-GBM antibody test was negative. On the 11th September, before these results were available, he was treated with high dosage steroids and cyclophosphamide. If he had not been a Jehovah's Witness, he would have been given plasmapheresis. Over the next two weeks he improved considerably with a good diuresis and his renal function improved to a blood urea of 22 mmol/l and a serum creatinine of 249 umol/l. He was therefore discharged home and reviewed one month later when he was clinically well.

RADIOLOGICAL FINDINGS

Dr Wild

In June 1992 the IVU showed a normal right kidney. The left kidney outlined reasonably well but there was some calcification which appeared to be outwith the kidney. This was thought to represent calcified lymph nodes which was confirmed later on CT. There was no sign of any collecting system in the left kidney, but there was a normal ureter.

In this situation when the collecting system is not satisfactorily demonstrated the next appropriate investigation is an ultrasound. This appeared to reveal a

mass 4·2 cm × 3 cm situated in the centre of the left kidney. My own interpretation is that the echo levels within this mass are similar to his renal cortical tissue. This suggests the possibility that it is a false impression or pseudo tumour (a so-called Column of Bertin) which is due to an ingrowth of normal cortex and is a well recognised normal variant. In order to decide whether the 'mass' represents a normal cortex or not the next logical investigation would be a DMSA isotope scan which examines functioning tubular tissue. This showed a reduced uptake at the upper pole of the left kidney but this did not correspond in position or size to the suspicious area described in the ultrasound scan, and was interpreted as due to scarring of the upper pole.

I think that the radiographic findings are consistent with a pseudo tumour rather than a real tumour because there is normal functioning renal tubular tissue in the area where the tumour was thought to be on ultrasound. The final investigation was a CT scan both with and without contrast. This showed, patchy uptake of contrast in the left kidney, particularly posteriorly, but no mass lesion. This therefore excluded a tumour, but suggests the presence of a parenchymal or infiltrative disease.

When he was admitted acutely ill the repeat ultrasound showed parenchymal echo levels in the kidney identical to those in the adjacent liver. This indicates a higher echo level than normal from which one would conclude that there was a diffuse abnormality of the renal cortex. All the nephritides and many other infiltrative conditions can cause this appearance. The left kidney on this occasion was thought to be normal.

Chairman

We will now hear from Dr McHardy the subsequent clinical developments.

Dr McHardy

The patient was re-admitted under the care of Dr Anderton five months later, on the 28th November 1992 with breathlessness of a few days duration but was rapidly transferred to the respiratory ward, having rigors and coughing up mucopurulent sputum. Information from his general practitioner indicated that he was a non-smoker but had been treated for asthma for the previous 3 years with occasional courses of prednisolone. His peak flow at its lowest had been 160 1/min. On admission to the respiratory unit he was pyrexial, cyanosed even when breathing oxygen at 3 1/min and tachypnoeic with a diminished percussion note and bronchial breathing at the base of the left lung. Blood gases showed significant hypoxia. The urea was unchanged from the level at first admission. The haemoglobin was low but the white count was elevated. Before discussing the further investigations and outcome in this case I will ask today's discussant Dr C. Swainson for his comments on the case so far.

Dr Swainson

This patient represents one of the most challenging and difficult problems—that is one who develops serious complications while on immunosuppressive therapy. Dr Anderton has presented the case as one of rapidly progressive glomerulonephritis occurring in a patient aged 69 with a history of asthma for some years. Predating his acute admission there was an episode of loin pain which is so far unexplained. One could approach this, and the signs on the CT scan, by

considering conditions which give rise to patchy inflammation in either one or both kidneys. Secondly, he had other vague symptoms, in particular weight loss, anorexia and abdominal pain. On admission to the renal unit he had very poor renal function with a creatinine greater than 800 mmol/l. The presence of red cell casts confirms that this was a nephritic process and this degree of renal failure has to be associated with crescent formation in the kidneys. There are three principal conditions to consider. The one that most people think of first is antiglomerular basement membrane (anti-GBM) disease (Goodpasture's syndrome) which is the association of acute nephritis with pulmonary haemorrhage described first after the great influenza epidemic in 1918. This condition is rare. This patient did not have evidence of pulmonary haemorrhage and the anti-GBM antibody test was negative. The second diagnosis to consider is a vasculitis. Vasculitic syndromes are non-immune complex diseases characterised by inflammation of blood vessels without evidence of the deposition of complement or immunoglobulins. That distinguishes them from the third group of conditions called idiopathic immune complex disease which can affect the kidney and other organs and are not well characterised.

In recent years anti-GBM disease has become unusual. There was an upsurge of 14 cases between 1972 and 1986 in Edinburgh but since that time we have only seen two. This is the pattern of this disease throughout Great Britain. It has been replaced by acute vasculitis. We have seen 36 cases of acute vasculitis presenting with renal failure over the last 6 years. If we look back to our records in the 1960s and 1980s we had no such incidence. The reasons are not clear.

Features which support the diagnosis of vasculitis in this patient are firstly the presentation of rapidly progressive renal disease with red cell casts in the urine; secondly the suggestion of multisystem involvement with systemic features of weight loss, anorexia and abdominal pain which may be related to vasculitis affecting the gut. Finally the patient is said to have a serum positive anti-neutrophil cytoplasmic antibody (ANCA) test. The ANCA tests are now crucial to understanding the diagnosis and management of these diseases. First described in 1985 a positive test is the demonstration in serum of IgG antibodies which react with the cytoplasm of freshly fixed neutrophils. Two distinct patterns are observed. The first, known as c-ANCA, is cytoplasmic granular fluorescence. This type is associated with several forms of vasculitis but in particular with Wegener's granulomatosis—a multisystem disease characterised by involvement of both the kidney and the respiratory tract. The second, known as p-ANCA, shows antibodies aggregated around the nucleus and this may be difficult to distinguish from antinuclear antibody. This type is associated with a wider range of acute diseases in particular microscopic polyarteritis. This is similar to Wegener's disease but picks out the kidney, the liver and the nervous system with less involvement of the respiratory tract. p-ANCA has also been associated with rheumatoid arthritis complicated by vasculitis, Henoch-Schönlein disease and other multisystem inflammatory diseases. Recent studies have shown that c-ANCA antibodies are directed against proteinase 3; over 90 per cent of patients with Wegener's granulomatosis have antibodies to this enzyme during the acute illness. The p-ANCA's antibodies are to other neutrophil proteins, for example, lactoferrin. In polyarteritis nodosa, which affects larger blood vessels and presents with a syndrome of multiple organ infarction both these tests are negative.

This patient showed the expected response to steroids and immunosuppressives. Over 90 per cent of these patients will recover and the disease will be controlled. The prognosis for this condition has changed greatly in the past 30 years. Before steroids were used the 5 year survival was less than 10 per cent and many patients were dead after one year. With the use of steroids in the 1950s and 60s the survival of patients improved considerably although to no better than about 35 per cent survival at 5 years. In the past 10 years with the introduction of cyclophosphamide the one year survival is over 90 per cent and the 5 year surivival is now 80–85 per cent in large series.

Now to turn to the diagnostic dilemma when a treated patient returns with involvement of another major organ. There are three possibilities to consider. The first is that the disease is uncontrolled and the presentation is due to another manifestation. The second is a complication of the therapy has occurred and the third is that the extension is due to a side effect of the drug therapy; thus 'cyclophosphamide lung' can present at any time during the course of treatment. The condition is idiosyncratic and unrelated to the plasma concentration of the drug.

Recurrence of disease within the first 3 months of treatment is nowadays unusual providing it comes under initial control. Relapse is usually associated with other systemic features of the disease and I would have expected a major deterioration of renal function at the same time if that had been the diagnosis. This therefore leaves two other possibilities. The timing of this new development is critical. The infective complications of immuno-suppressive treatment follow a well defined pattern. The complication in this case occurred about 2 months after starting treatment which places it towards the end of the period of bacterial complications but at the peak time when opportunistic infection occurs and before one would expect complications of viral infection. I would like to eliminate bacterial infection as a cause of his breathlessness and having done so I would be strongly considering opportunistic infection with protozoan or fungal organisms.

Dr McHardy
Unfortunately the patient's progress was rapidly downhill following his admission. Within hours of admission we were able, with the help of Dr Burns in the Virology department, to establish that there were indeed pneumocystis fluorescent antibodies in the sputum. No other pathogens were identified. Despite making the diagnosis rapidly we had great difficulty maintaining oxygen saturation above 90 per cent. Even with high concentrations of oxygen he became agitated, confused and communication became impossible. His urea began to rise as did his serum potassium which was treated appropriately. During this period his haemoglobin fell to 7·89 gms but blood transfusion was not an option because of his religious belief. His platelet count began to fall and we thought this was due to the high dose cotrimoxazole and his therapy was therefore changed to pentamidine. He appeared to develop disseminated intravascular coagulation (DIC) and died in respiratory failure a week after admission.

Member of audience
Was ventilation considered at any time?

Dr McHardy
Ventilation was considered but believed to be inappropriate.

Dr Swainson
As I said earlier the timing of this complication made pneumocystis the likeliest diagnosis. Can I just make a point about cyclophosphamide treatment. Monitoring the dose of cyclophosphamide is important in patients of this age. My experience is that most patients can tolerate a dose of 100 mgs for about 2–3 weeks but then the dose needs to be reduced because of a falling white count. It is a drug where the white count continues to fall for 3–4 days after reducing the dose and also takes 1–2 weeks to rise again.

Chairman
Can I ask Dr Thomas to outline the post mortem findings.

Dr Thomas
External examination of the body showed widespread purpuric haemorrhages in the skin of both arms, and legs, appearances consistent with the clinical diagnosis of DIC. The most striking findings were in the lung both of which were markedly heavier than normal—right (1,350 gm), left (1,440 gm). On section both showed diffuse consolidation throughout all lobes. Small pulmonary emboli were also noted but there was no pulmonary infarction. The heart showed small vegetations on both the mitral and the aortic valves consistent with non-bacterial thrombotic endocarditis. The kidneys were of normal size weighing right, 130 gm, and left, 115 gm.

Histological examination showed diffuse alveolar damage (shock lung) in the lungs (Fig 1) along with extensive pneumocystis pneumonia confirmed by immunocytochemistry (Figs 2 and 3). Examination of the kidneys showed no evidence of active glomerulonephritis but there were moderate numbers of glomeruli showing global sclerosis while others showed segmental sclerosis (Fig 4). Approximately 30 per cent of the glomeruli appeared abnormal while the remainder appeared histologically normal presumably reflecting the good response to treatment. Histology also confirmed the impression that the lesions on the cardiac valves were of non-bacterial thrombotic type.

Member of audience
Do you think that there was a delay in making the diagnosis in this man who presented with haematuria?

Dr Swainson
No, not at all. The great problem with these patients in the early stages of their disease is that they have non-specific symptoms and signs which can reasonably be interpreted with several different diagnoses. It is only when many conditions have been excluded that the diagnosis becomes clear. You can sometimes retrospectively identify a pattern of illness for anything up to a year prior to the patient becoming acutely ill.

Dr Burns
I would just like to summarise how we can diagnose pneumocystis before a patient reaches the pathologist. Firstly the clinician must think of the possibility of such a diagnosis. The best material for microbiological purposes is an induced sputum or a bronchial lavage specimen. (The induced sputum specimen is

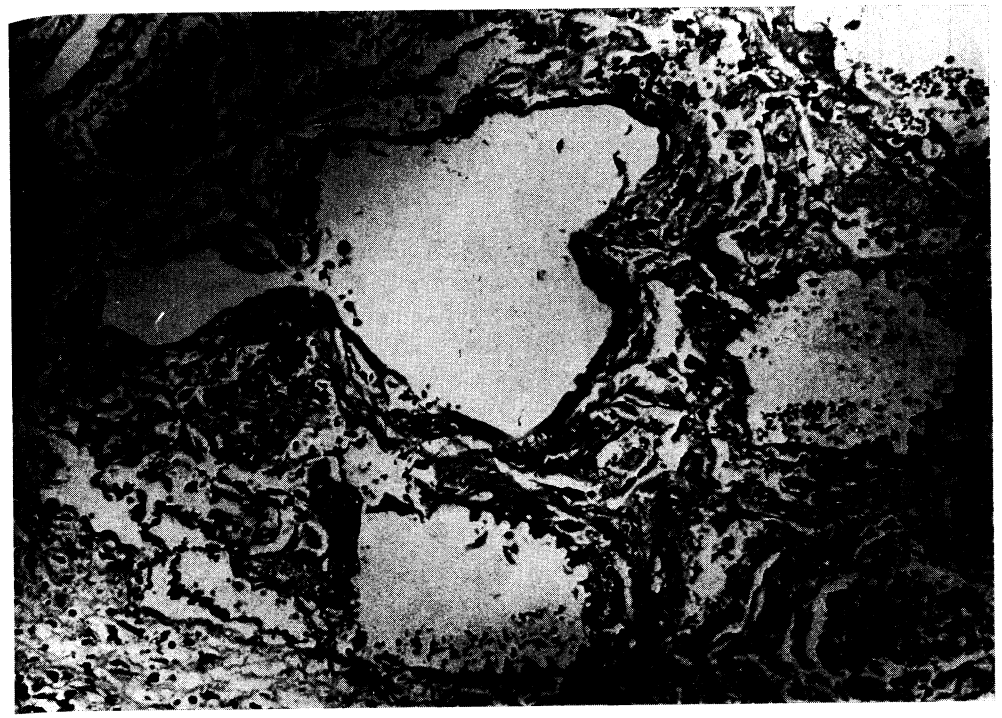

FIGURE 1
Section of shock lung showing hyaline membrane formation.

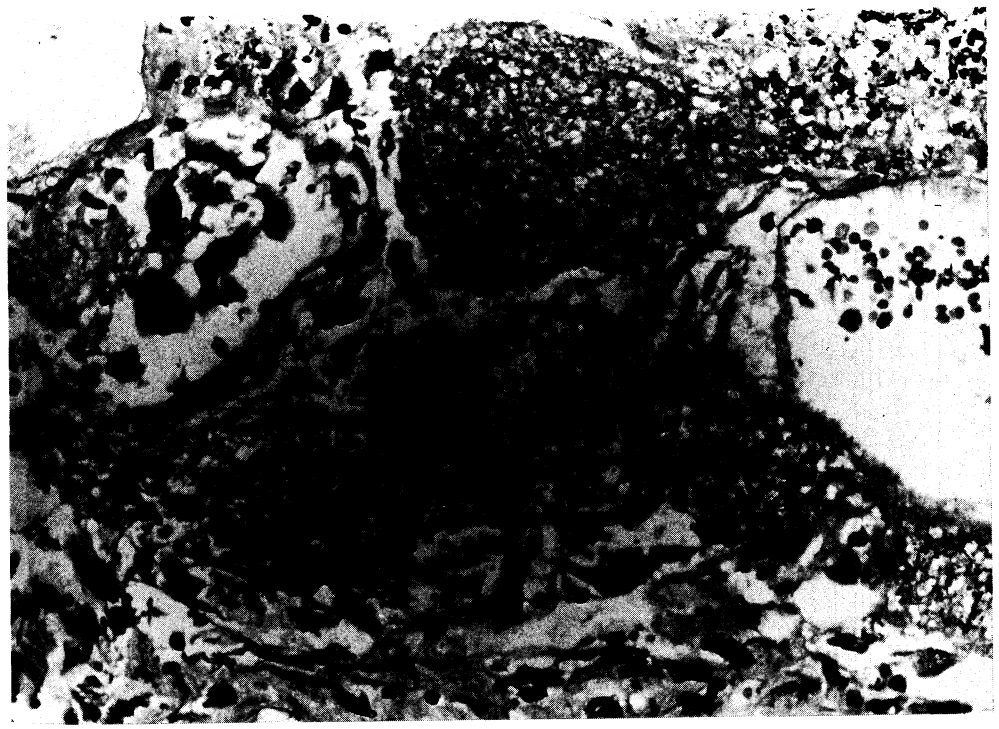

FIGURE 2
Section of lung showing intra-alveolar exudate associated with pneuomocystis carinii infection.

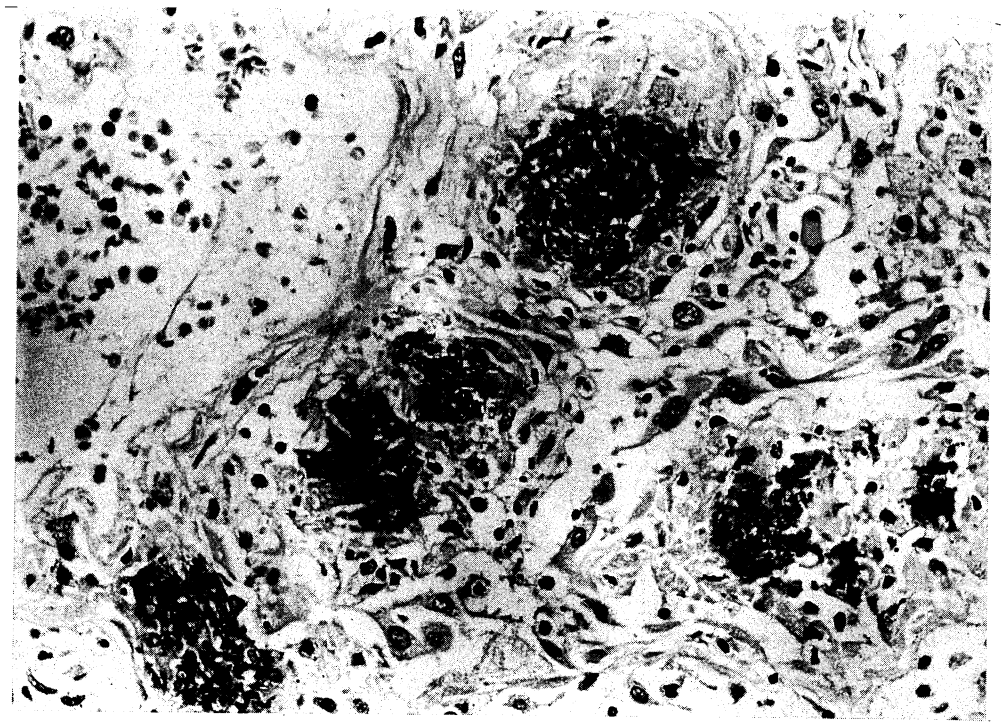

FIGURE 3

The same section as in Figure 2 but stained with immunoperoxidase to show the pneumocystis colonies.

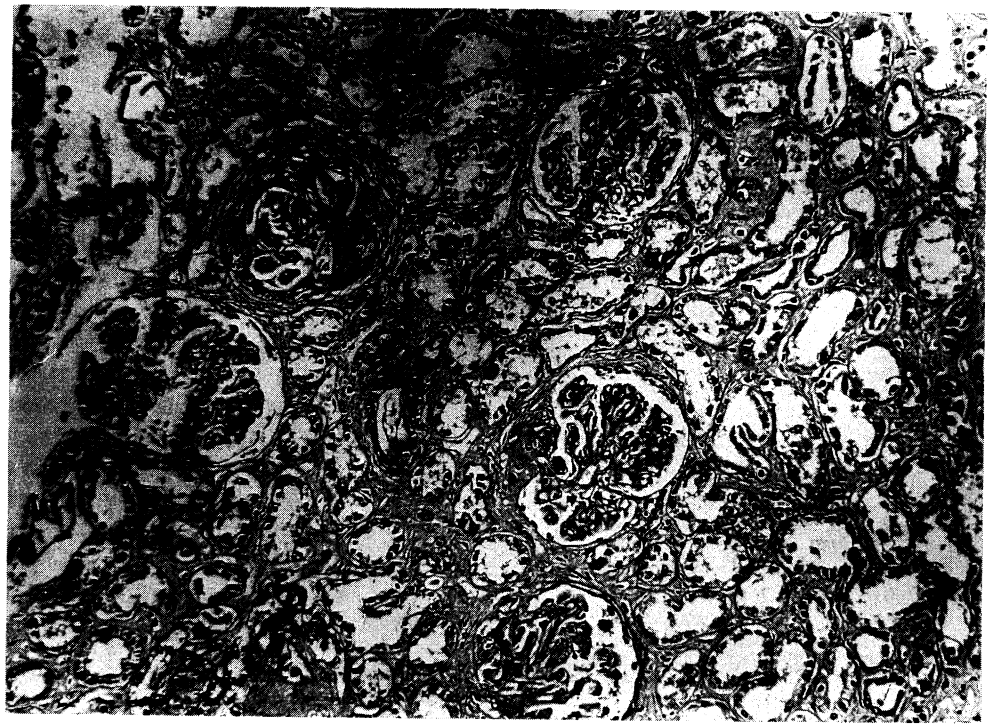

FIGURE 4

Section of kidney showing the residual changes of crescentic glomerulonephritis after treatment.

produced by giving the patient nebulised hypertonic saline.) Dr Thomas has demonstrated immunological identification of the organisms in histological sections and we use the same technique on the lavage specimens. In the laboratory we concentrate the sample, and produce a slide preparation and stain it with a monoclonal antibody directed against both cysts and trophozoites.

Dr Anderton

His initial urea and creatinine when seen by the Urologists was 7 mmol/l and 132 umol/l respectively. These are not normal. The upper limit of normal for urea is 5 mmol/l. The creatinine of 132 umol/l falls within the normal range for this laboratory but that range includes healthy young adults and takes no account of age. Most people as they age lose muscle mass and probably his creatinine should have been less than 100. In retrospect therefore, at presentation he had evidence of significant renal failure which indicates that his glomerulonephritis was probably well established when he first presented to the urologists. Success in overcoming the primary disease unhappily resulted in death from a complication of the treatment.

Dr Swainson

Summarising the lessons to be learned from this case,

a. 'Normal' plasma creatinine needs to be carefully interpreted in relation to age and muscle mass.
b. Diagnosis of systemic vasculitis requires a high index of suspicion. The initial presentation may be to a variety of specialists.
c. Prompt immunosuppressive therapy is successful but careful monitoring is required.
d. The complications of treatment, especially infection and drug reation, is the most common contribution to mortality in these diseases.
e. Breathlessness and a non-productive cough in an immunosuppressed patient is more likely to be due to an opportunist infection than heart failure or bacterial infection.

FINAL AUTOPSY DIAGNOSIS

1. Kidney. Rapidly progressive glomerulonephritis (ANCA positive).
2. Lung. Pneumocystis pneumonia complicating immunosuppressive therapy.

CONTRIBUTORS

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