A fatal case of Legionnaires' disease originating in Scotland

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Summary

A 21-year-old female died in May 1976 from a pneumonic illness presenting with a right pleural effusion. Histopathology showed florid hyaline membrane disease of the left lung only, and focal pneumonitis in the lower lobe. Further investigations carried out by the Center for Disease Control, Atlanta, Georgia, showed that this patient had Legionnaires' disease infection, the first indigenous case diagnosed in Scotland. Post-mortem examination showed features differing from those in other published cases.

Introduction

Intensive investigation of an outbreak of at least 182 cases of pneumonia with 29 deaths at the American Legion convention in Philadelphia in 1976 revealed that the causative Legionnaires' disease (LD) agent was a Gram-negative organism demonstrable only by special techniques and capable of growth only on special media (Fraser, *et al.*, 1977; McDade *et al.*, 1977; Chandler, Hicklin and Blackmon, 1977). The development of serological tests for infection with this agent by the Center for Disease Control, Atlanta, Georgia, has indicated that Legionnaires' disease is not a new entity, that its distribution is widespread, and that it may occur sporadically as well as in epidemics (McDade *et al.*, 1977).

This first case of indigenous infection in Scotland has already been noted briefly (Lees, Tyrrell and Boyd, 1977), and now that investigations are completed a fuller report is given.

Case report

A 21-year-old female who suffered from grand mal epilepsy injured her right chest during a convulsion. A chest X-ray taken the next day showed no abnormality, but she began to feel breathless, feverish and unwell a few days later and was admitted to a local hospital 9 days after the X-ray. On

admission her temperature was 39.2°C, pulse 150/min, respiration 40/min. She was slightly cyanosed, had tenderness over the 8th and 9th right ribs, and had dullness to percussion and bronchial breathing over the right side of the chest. A chest X-ray now showed a large right pleural effusion with shift of the mediastinum to the left. She was maintained on her regular anti-convulsant treatment of phenobarbitone 60 mg 4 times/day, phenytoin 100 mg 4 times/day, ethosuximide 250 mg daily and folic acid 5 mg daily.

On the day of admission she looked toxic and her temperature was 40.2°C. Her right chest was aspirated, but after removal of 400 ml of fluid, she became distressed and complained of severe chest pain. Papaveretum injection 20 mg, and later dihydrocodeine were given. The fluid was straw-coloured, and contained an excess of neutrophil polymorphs and some red blood corpuscles. The total protein content was 54 g/l (albumin 29 g/l, globulin 25 g/l). Culture for pyogenic organisms was negative, and direct examination and culture for *Mycobacterium tuberculosis* were negative.

Her fever continued the next day, and haematology results were Hb 12.4 g/dl, RBC $4.18 \times 10^{12}/l$, PCV 35.2, MCV $86 \mu^3$, MCH 29.2 pg, MCHC 34.4 g/dl, WBC $11.9 \times 10^9/l$ (neutrophils 73%, lymphocytes 14%, monocytes 13%). Biochemistry results were plasma Na 126 mmol/l, K 3.9 mmol/l, Cl 94 mmol/l, bicarbonate 25 mmol/l, urea 3.5 mmol/l, bilirubin 4 μ mol/l, alkaline phosphatase 78 i.u./l, thymol turbidity 0.5 u., zinc turbidity 5 u., serum mucoid 14.4 μ g/dl, and total serum protein 59 g/l (albumin 30 g/l, globulin 29 g/l).

Culture of another sample of pleural fluid was again negative for pyogenic organisms (and later for *M. tuberculosis*). Treatment was instituted with streptomycin 1 g/day, isoniazid 300 mg/day, penicillin 1.2 Mu./day, erythromycin 1 g/day, and prednisolone 40 mg/day.

The next day her condition was deteriorating and

she was transferred to Ruchill Hospital, Glasgow. She was toxic, drowsy, dyspnoeic and slightly cyanosed, temp. 39°C, pulse 140/min, resp. 40/min, BP 140/70 mmHg. The patient was conscious, co-operative and orientated in time and space, and her reflexes, pupillary reactions and optic fundi were normal. There was no clubbing, lymph node enlargement or oedema. The JVP was not raised. The percussion note was dull over the right mid zone and base, there was bronchial breathing over the right mid zone, and crepitations were present over both lung fields. Repeat investigations were essentially the same as before, but additionally the WBC count was now $14.7 \times 10^9/l$ (neutrophils 80%, lymphocytes 11%, monocytes 9%), ESR 23 mm in the first hour (Westergren), blood pH 7.34, arterial P_{CO_2} 38 mmHg, arterial P_{O_2} 74.2 mmHg, and arterial oxygen saturation 72%.

A chest X-ray showed a right pleural effusion and the development of extensive patchy consolidation in the left lung. Aspiration of 120 ml of slightly blood-tinged straw-coloured fluid was carried out before pain and distress ensued. The fluid had a protein content of 50 g/l and glucose content of 4.8 mmol/l. Blood culture for pyogens was again negative, and virological studies were also negative. Culture of sputum was again negative for pyogenic organisms and also for *M. tuberculosis*; it yielded a few *Candida albicans* only. Treatment with erythromycin was continued but gentamycin 80 mg thrice daily was substituted for streptomycin, and metronidazole 200 mg thrice daily was also given. At 22.30 hours the patient collapsed and became unconscious, but consciousness returned after hydrocortisone and frusemide therapy. Next day, 4 days after admission, however, she suddenly collapsed and died.

Post-mortem findings

The post-mortem was carried out on the same day 7 hr after death. The body was that of a well built, rather obese young adult female. There was no gross abnormality of any body system except the respiratory tract.

The larynx, trachea and major bronchi showed no inflammation, hypersecretion of mucus or frothy pulmonary oedema. The right lung (555 g) was about 20% increased in weight, while the left lung (860 g) was about 100% increased in weight. There was a moderate fibrinous pleurisy over the surface of the right lung and deposits of fibrin connected the lung surface to the chest wall, thereby loculating the 750 ml of clear straw-coloured fluid in the right pleural cavity. Dissection of the partly collapsed right lung showed moderate congestion and minimal oedema affecting all lobes equally. There was no evidence of consolidation. The bronchi were not

thick-walled or prominent and contained no mucus or pus. The left lung (Fig. 1) was voluminous, dark and heavy, and both lobes were purple and equally firm throughout. Dissection showed rather marked severe oedema of both lobes and nowhere was there convincing evidence of consolidation. The left pleural cavity was normal.

FIG. 1. Section of firm left lung. Smooth pleural surface. Dark purple lung. Uniformly firm lung substance. $\times 50\%$.

The heart (300 g) showed no abnormality on inspection or after dissection. The origin of the circumflex branch of the left coronary artery showed a one-cm soft plaque of atheroma but the lumen was patent; the rest of the coronary arterial tree was normal.

Conventional bacteriological cultures of the right pleural fluid taken at post-mortem yielded no growth after 48 hr and 5 days, and culture of material from the lower lobes of the right and left lungs and of post-mortem blood were negative. Virological study of a tracheal swab and the virus antibody titres in a

post-mortem sample of blood were also diagnostically unhelpful.

Histology of the right lung showed only partial collapse in all lobes with rather marked capillary congestion and with haemosiderin-bearing macrophages in most alveoli. A rather marked aseptic fibrinous pleurisy was evident. There was no evidence of infection. On the other hand, histology of the left lung showed very severe pulmonary oedema rich in hyaline membranes (Fig. 2) and the lower lobe showed in addition scanty scattered foci of pneumonitis. In these areas one or 2 alveoli contained a number of neutrophil polymorphs as well as macrophages (heart failure cells) (Fig. 3). There was no evidence of pyogenic organisms or of *C. albicans* in the infected areas on special staining.

FIG. 2. Upper lobe of left lung rich in pale pink oedema fluid. Atria rich in pink hyaline membranes, top left and right and bottom centre. Scanty alveolar macrophages. No capillary congestion. HE, $\times 150$.

The brain (1235 g) appeared normal on inspection but showed rather marked oedema on histology. There were no signs of hypoxic damage. The other major organs showed no histological abnormality.

Further investigation

Two specimens of serum, one taken the day before and one the day after death, were sent to CDC, Atlanta, Georgia, and Dr W. Cherry reported the indirect fluorescence antibody titres to Legionnaires' disease agent to be 512 and 1024 respectively (significant titres higher than 128 in doubling dilution

FIG. 3. Lower lobe of left lung showing one of the most severe areas of 'pneumonitis'. Hyaline membrane lining a lung atrium cut obliquely, and also plugging 2 alveoli. Alveolar hyper-cellularity is due mainly to 'heart-failure' cells, but some alveolar walls are thickened and hypercellular owing mainly to neutrophil polymorphs. Neutrophil polymorphs are also present in atrium and in alveoli. HE, $\times 150$.

tests). He also reported that the LD agent could not be identified by direct immunofluorescence staining of smear preparations made from a formalin-fixed block of tissue from the lower lobe of the left lung, but pointed out that this result did not necessarily exclude the presence of the LD organism elsewhere in the lung. A further block from another area of the same lobe was sent to CDC, and was also reported to be negative for the LD agent. Dr J. A. Blackmon, CDC, reported that the Dieterle staining method (van Orden and Greer, 1977) had also failed to reveal the LD agent.

When information about the Dieterle staining method became available in Glasgow, sections from the lower lobe of the left lung were stained and studied with the oil immersion objective at several sittings. After persistent search, 3 highly suspicious areas have been photographed which appear to show LD organisms (Fig. 4). The problems of the interpretation of Dieterle-stained sections have been referred to (Chandler *et al.*, 1977; Blackmon, Hicklin and Chandler, 1978; Boyd *et al.*, 1978).

Discussion

The development of serological tests for Legionnaires' disease, notably the direct and indirect

FIG. 4. (a) Alveolar septal cell containing carbon deposit but also containing about 2-3 dozen intracytoplasmic coccobacilli in various attitudes, (b) rounded alveolar macrophage lying free in alveolar oedema fluid and bearing six or so coccobacilli, (c) one extracellular bacillary form. Dieterle $\times 1500$.

fluorescence antibody techniques, have shown that the condition is not a new one and is widespread (McDade, *et al.*, 1977). These authors refer to outbreaks in the Washington area and Pontiac (Michigan) while Macrae and Lewis (1977) refer to an outbreak in Nottingham, England, and Lawson *et al.* (1977), Lawson (1978), and Reid, Grist and Nájera (1978) record the disease in Scottish tourists returning to Glasgow after holidays in Spain. The pathology of the deaths among these last cases has been reported (Boyd *et al.*, 1978), and the pathology of the original Legionnaires' disease episode is also on record (Chandler *et al.*, 1977; Blackmon *et al.*, 1978). The infection has also been recorded recently in renal transplant patients (Bock *et al.*, 1978).

Sporadic cases occurring in the U.S.A. (McDade *et al.*, 1977; Keys, 1977; Jones, Beecham and Dennehy, 1978), and elsewhere (Lees *et al.*, 1977; Ashford, Edmonds and Shanson, 1977; Meenhorst *et al.*, 1978) have also been noted. The present case is the first one known to originate in Scotland. The patient had no contact with illness resembling Legionnaires' disease and there were no secondary cases. Nor had she been out of Scotland except for a visit to Ireland 8 years previously.

In the Philadelphia outbreak typically the early symptoms of disease were malaise, muscle aches and headache, followed in a day or so by rapidly rising

pyrexia, unproductive cough and chest pain (pleuritic in 33% of the patients). Physical examination usually revealed rales but no evidence of consolidation. Chest X-rays showed areas of infiltration or consolidation which usually progressed to consolidation of greater extent. Effusions when present were usually minimal and did not require special treatment. The present case appears to be the first reported in which the presentation was a large pleural effusion and is also unusual in having a fatal outcome despite the youth of the patient, since deaths are commoner in the older age groups. In the Philadelphia outbreak erythromycin and tetracyclines appeared to be the most effective antibiotics. Experimental results from infected guinea-pigs lend support to this finding (Fraser *et al.*, 1978). In one sporadic case (Keys, 1977) doxycycline and in another (Meenhorst *et al.*, 1978), a combination of rifampicin and a tetracycline were thought to be beneficial. In the present case, treatment with erythromycin did not prevent a fatal outcome but may have accounted for the paucity of LD organisms found on histological examination, virtually all of which were intracellular.

In the Philadelphia outbreak, hyaline membrane formation in the lungs was a prominent feature *post mortem* in a number of cases (Blackmon *et al.*, 1978). It was appreciated that many factors could be responsible for this finding and one possibility was the prolonged inhalation of high oxygen concentrations (Fraser *et al.*, 1977; Blackmon *et al.*, 1978). Hyaline membrane formations were also a prominent feature in the present case, but only in the left lung. Oxygen therapy was no more intensive than in many routine cases so that it seems probable that in this case at least hyaline membrane formation was an integral feature of the disease.

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