

Mycoplasma pneumonia with fulminant evolution into diffuse interstitial fibrosis

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ABSTRACT A fatal case of interstitial pneumonia caused by *Mycoplasma pneumoniae* with fulminant evolution into diffuse interstitial fibrosis is reported. Treatment with tetracycline and corticosteroids failed to arrest the progress of the disease. Fatal *Mycoplasma pneumoniae* infections have been reported previously and some degree of pulmonary fibrosis has been described in a few cases but as far as could be ascertained there are no other well-documented cases of diffuse interstitial fibrosis with proved *Mycoplasma pneumoniae* infection.

Mycoplasma pneumoniae is a well-documented and recognised cause of pneumonia, although in most cases infection remains subclinical or limited to upper respiratory tract involvement.¹⁻⁴ Clinical and radiographic features are inconstant and do not allow for differentiation from pneumonias caused by other micro-organisms.^{5,6} *Mycoplasma pneumoniae* usually has a rather benign, self-limiting course. However, besides important extrapulmonary complications such as haemolytic anaemia,^{7,8} myopericarditis,⁸⁻¹⁰ and neurological manifestations,^{3,4} severe and even fatal respiratory disease from *Mycoplasma pneumoniae* has been reported. The pulmonary complications include unilateral and bilateral massive pneumonia,^{3,11,12} large unilateral and bilateral pleural effusions,^{3,11,13} lung abscess,^{3,12} Swyer-James syndrome,¹⁴ and extensive interstitial pneumonia with severe hypoxaemia.¹⁵⁻¹⁷ Although exceptional, persistence of respiratory symptoms after *Mycoplasma pneumoniae* infection has been reported,^{1,8} and on a few occasions some degree of fibrosis has been demonstrated at necropsy¹⁷⁻¹⁹ but this condition has not yet been well documented.

Case report

Sixteen days postpartum, a previously healthy 31-year-old woman complained of rhinitis and general malaise followed the next day by chills, fatigue, and non-productive cough. On the third night she woke up with mild dyspnoea which

became more pronounced during the morning. She also complained of vertigo and anorexia, and vomited once. The next morning she became severely dyspnoeic and was admitted to a local hospital. Arterial blood gas analysis revealed a carbon dioxide tension (P_{CO_2}) of 35 mmHg and an oxygen tension (P_{O_2}) of 75 mmHg while breathing 4 litres of oxygen per minute. The chest radiograph showed patchy lobular shadows involving both lower zones (fig 1). The patient was transferred to the intensive care unit of the University Hospital, with tachypnoea (36 to 40/min), a temperature of 37.5°C, and slightly diminished breath

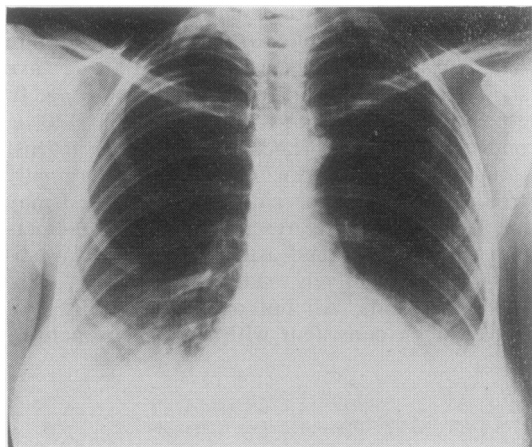


Fig 1 Chest radiograph (PA) on admission to hospital shows patchy lobular infiltration involving both lower zones.

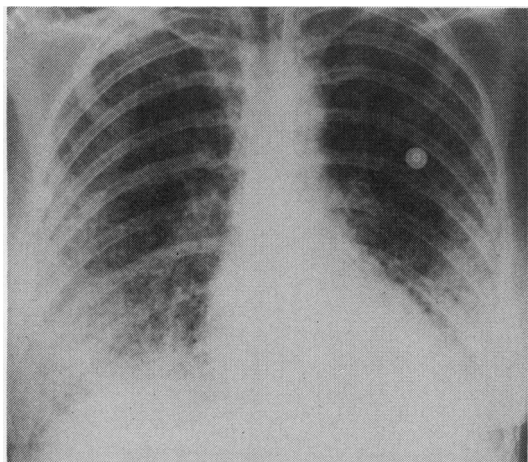


Fig 2 Chest radiograph (PA) on the fifteenth day in hospital shows diffuse mottling of both lungs.

sounds at the right base. Arterial blood gases on ambient air revealed a PCO_2 of 38 mmHg and a PO_2 of 66 mmHg. The erythrocyte sedimentation rate was 100 mm/h, white cell counts $6800/mm^3$ with 70% neutrophils. Treatment was started with doxycycline intravenously, 200 mg daily, and one dose of 25 mg prednisolone.

The next day the patient seemed to improve; chest radiograph was unchanged. During the next two days, she had only mild dyspnoea but her temperature rose to $39^\circ C$ and radiographs showed slightly increased infiltration of both bases.

A technetium perfusion lung scan showed an area of diminished perfusion in the left paracardiac area, and on the fourth day in hospital, in addition to doxycycline, heparin was started in a dose of 37 500 units/day by continuous infusion. On the fifth day the patient's condition deteriorated quickly, with extreme dyspnoea and severe respiratory distress. Arterial blood gas analysis breathing 10 litres/min with an oxygen mask, showed pH 7.58, PCO_2 29.5 mmHg, and PO_2 34.5 mmHg. The patient became apnoeic and was immediately intubated and ventilated. Doxycycline and heparin were continued, and in addition the patient received high doses of betamethasone. For two days there was a progressive improvement with satisfactory blood gas values on PEEP 10 cm H_2O and 50% inspired oxygen initially, reducing to 25% later on. The chest radiograph showed progressive changes, with some early reticular infiltrates in the upper zones. The white cell was between $15\,000$ and $20\,000/mm^3$. On the tenth day in hospital the situation deteriorated again

progressively. The patient went into gradually increasing alveolo-capillary block. Successive chest films showed increasing interstitial infiltrates all over the lungs with massive, patchy, confluent shadows in the lower parts and more reticular shadows in the upper parts with a picture suggesting advanced interstitial pneumonitis (fig 2).

Sputa were purulent, but frequent cultures for aerobic and anaerobic bacteria, mycobacteria, and fungi were all negative. The patient died on the seventeenth day in hospital. At that time the blood gas values ranged around 90 mmHg PCO_2 and 60 mmHg PO_2 despite ventilation. In one week, from the fourth to the tenth hospital day, the titre of complement fixing antibody for *Mycoplasma pneumoniae* rose from less than 1/4 to 1/128. No cold agglutinin titre could be demonstrated. Further studies on paired sera were negative for *Coxsackie* 1-6, *Varicella*, influenza A-B, para-influenza 1-3, adenovirus, psittacosis, ornithosis, and respiratory syncytial virus.

NECROPSY

The left lung weighed 800 g and the right lung 1100 g. They both had a similar external aspect with moderate reticular anthracosis and a purple-grey to reddish appearance. The surface was nodular with fibrous pleura thickening. The lung felt firm and the cut surface was reddish-grey and white, intersected by round microcysts and white nodules. No purulent material could be expressed.

On microscopy similar changes were found in all the lobes. The sections made of formalin-fixed and paraffin-embedded lung tissue were stained with haematoxylin-eosin, PAS, Masson's trichrome, and reticulin. They showed a diffuse interstitial fibrosis (fig 3). The bronchioles were grouped in nodules, dilated and covered with a metaplastic stratified, flattened or squamous epithelium. Some showed cystic dilatation and contained mucus, occasional giant cells, histocytes, polymorph leucocytes, and monocytes.

Severe fibrosis was seen in the thickened inter-alveolar septa and around the bronchioles. The fibrous tissue consisted of young fusiform fibroblasts which formed collagen. Inside the fibrous tissue it was possible to distinguish small haemorrhages, oedema fluid, and the alveolar capillaries which were increased in size and number and surrounded by a cellular infiltrate. Within the fibrotic interstitial tissue the presence of monocytes and histocytes was observed. The alveolar walls were covered by cuboidal cells with abundant, foamy cytoplasm with round vesicular

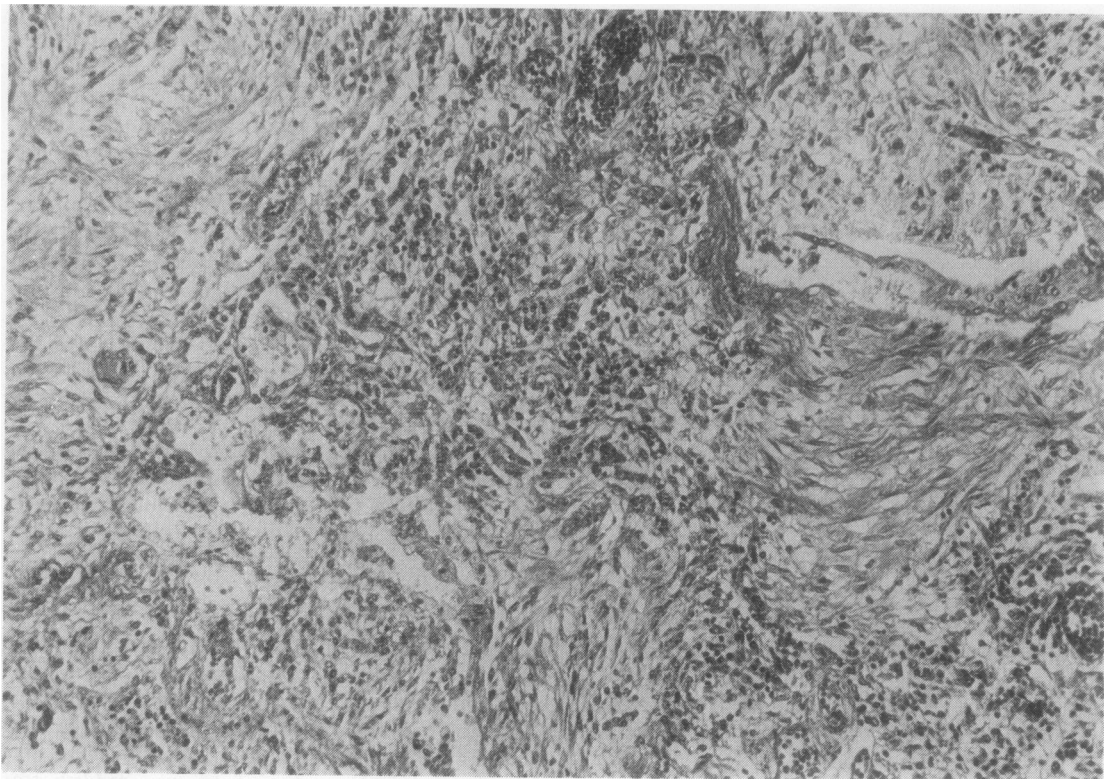


Fig 3 Severe interstitial fibrosis with fibroblast proliferation and monocellular infiltrate. Masson's trichrome stain, original magnification $\times 140$.

nuclei. Some had desquamated into the lumen. The alveoli were filled with a homogenous exudate, haemosiderin laden macrophages, polymorph leucocytes, erythrocytes, and giant cells (fig 4). Fibrin was seen only occasionally. The pleura was thickened by bundles of collagen fibres.

Discussion

Mycoplasma pneumoniae has been mentioned as a possible cause of interstitial fibrosis²⁰⁻²² but only in a few cases has some degree of fibrosis been reported.¹⁷⁻¹⁹ There are no well-documented cases in which evolution of a *Mycoplasma pneumoniae* pneumonia into diffuse interstitial fibrosis has been described. The mechanisms leading to the pathological changes in diffuse interstitial fibrosis are well known but not specific. The alterations can be the result either of direct interstitial involvement or, as in this case, of a primary intra-alveolar process.^{20 23-27} The pneumocytes are desquamated into the alveolar lumen. This is followed by exudation and incorporation of the exu-

date into the alveolar walls. Afterwards, fibroblast proliferation starts between the sixth and ninth day and gives rise to more organised and mature fibrous tissue. The alveolar lining epithelium is changed into type 2 pneumocytes and the bronchiolar lining epithelium grows into the respiratory bronchiole which causes squamous metaplasia.

Numerous different agents are known to cause diffuse interstitial fibrosis. It may follow radiation therapy, oxygen toxicity, anti-neoplastic drugs, paraquat poisoning, inhalation of organic or mineral dust and toxic fumes. It is also seen as a terminal phase of sarcoidosis, collagen diseases, miscellaneous occupational diseases and other interstitial pneumonias. Infectious diseases have also been implicated including bacterial, viral, fungal and parasitic infections. In our case, there was a significant rise in *M pneumoniae* complement fixation titre from 1/4 to 1/128 and most of the other possible aetiological agents could easily be excluded.

Oxygen toxicity may have been a factor in our

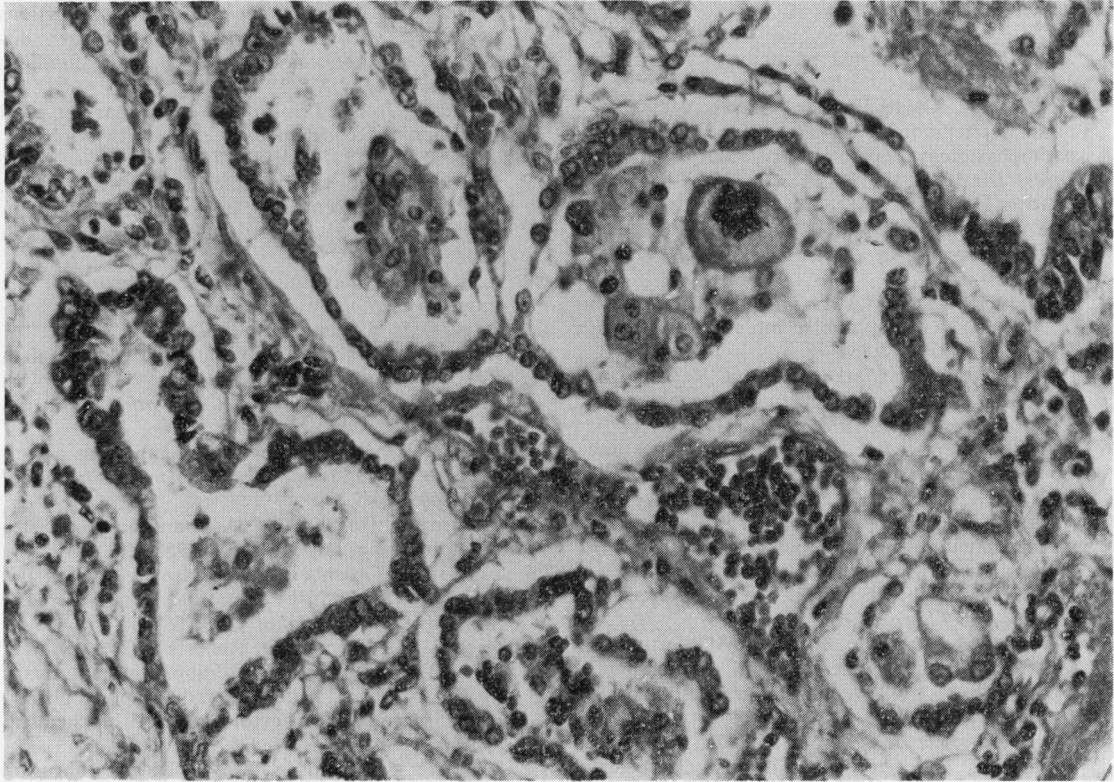


Fig 4 Alveoli covered by cuboidal pneumocytes. The alveolar lumen is filled with macrophages, polymorph leucocytes, erythrocytes, and giant cells. Masson's trichrome stain, original magnification $\times 360$.

case, though this seems very unlikely. Indeed, our patient had been ventilated for less than 24 hours with a gas mixture containing high oxygen concentrations (maximal concentration of 66% oxygen) and at that time there was already diffuse radiological involvement of both lungs. The pathological findings in this patient could only have been provoked by prolonged administration of high oxygen concentrations.²⁸⁻³⁰

Although not well documented previously, the association of pulmonary fibrosis with *Mycoplasma pneumoniae* infection is not surprising, and intermediate stages such as desquamatic interstitial pneumonia have indeed been described before.^{17-19 31}

Some authors suggest that cell-mediated immune mechanisms could be involved in severe cases of mycoplasma pneumoniae.^{8 15} It is, however, not necessary to postulate an immunological mechanism to explain the pathological changes observed in our patient, by analogy with oxygen and paraquat poisoning which can result in the same

histological picture without an immunological reaction. Intensive steroid therapy was not able to influence the course but administration was started only on the eighth day of illness. The lack of response to adequate therapy with high doses of tetracycline in this case is an interesting but not unique feature: resistance of *Mycoplasma pneumoniae* infections to tetracycline has been reported previously, and it is known that medication is effective mainly when administered early in the course of the disease.^{1 2 7 32}

High doses of corticosteroids should probably be considered in those cases of severe *Mycoplasma pneumoniae* pneumonia that do not improve after the fifth day from clinical onset. If started early enough steroid therapy could possibly influence fibroblast proliferation and prevent evolution into chronic or even fatal pulmonary fibrosis.

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