

## Alveolar haemorrhage as a presenting feature of myeloma

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*Alveolar haemorrhage as a presenting feature of myeloma. E. Russi, B. Odermatt, H.I. Joller-Jemelka, M.A. Spycher.*

**ABSTRACT:** An immunoglobulin A (IgA)-paraprotein secreting myeloma was found to be the underlying disease in a patient who presented with alveolar haemorrhage. The diffuse pulmonary bleeding stopped after initiation of treatment consisting of corticosteroids and melphalan. A paraprotein mediated lesion of the alveolar capillary membrane was suspected but could not be demonstrated.

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Alveolar haemorrhage (AH) is a feature of several immune and idiopathic disorders. Immune alveolar haemorrhage is usually due to anti-basement membrane antibody disease, or to one of the vasculitides. It also occurs in rapidly progressive glomerulonephritis, or following exposure to certain drugs or chemicals [1, 2]. A similar pattern of diffuse alveolar bleeding is observed in idiopathic pulmonary haemosiderosis, a diagnosis made in the absence of extrapulmonary features, together with lung biopsy specimens showing no vasculitis and no deposition of immunoglobulins or complement [1].

To our knowledge this is the first reported case of myeloma complicated by AH.

### Case report

The patient was a 47 yr old, previously healthy man, who stopped smoking in 1990 after 20 pack-years. He had suffered from increasing shortness of breath since March 1991, and recurrent haemoptysis for a few months. He had no bone pain. On admission in August 1991 his complexion was pale, he had no fever and his breathing rate was 20 breaths·min<sup>-1</sup>. Blood pressure was 130/75 mmHg, heart rate was regular and breath sounds were normal. Lymph nodes were not enlarged, and the liver and spleen were not palpable. The neurological examination was unremarkable.

The haemoglobin was 65 g·l<sup>-1</sup> and leucocytes were 7.97×10<sup>9</sup>·l<sup>-1</sup> with a normal distribution. The platelet count was 353×10<sup>9</sup>·l<sup>-1</sup>. Coagulation was normal. Sedimentation rate was 120 mm·h<sup>-1</sup>. The C-reactive protein was not elevated. Serum iron was 3.7 µmol·l<sup>-1</sup> (normal >17.9 µmol·l<sup>-1</sup>), ferritin was 95 ng·ml<sup>-1</sup> (normal 15-200 ng·ml<sup>-1</sup>). Electrolytes, calcium,

liver enzymes and alkaline phosphatase were all in the normal range. Serum creatinine was 99 µmol·l<sup>-1</sup> and creatinine clearance 87 ml·min<sup>-1</sup>. Several urine analyses revealed no albumin, microhaematuria or cylinders. Total serum protein was 81 g·l<sup>-1</sup> with 47% albumin, 4% alpha<sub>1</sub>-globulins, 9% alpha<sub>2</sub>-globulins, 10% beta-globulins, 30% gamma-globulins including an M-gradient. The immunoglobulins consisted of 23 g·l<sup>-1</sup> immunoglobulin A (IgA), 5.4 g·l<sup>-1</sup> immunoglobulin G (IgG) and 0.4 g·l<sup>-1</sup> immunoglobulin M (IgM). Immunoelectrophoresis revealed an IgA paraprotein type kappa (kappa/lambda quotient 8.5; IgA subclass 1). In the concentrated urine a paraprotein type Bence-Jones kappa was detectable. Bone marrow aspiration revealed a normal myelo- and megakaryopoiesis, 25% abnormal plasma cells, no sideroblasts and no interstitial iron. Roentgenograms of the skull, the cervical, thoracic and lumbar spine, and the pelvis did not show osteolytic lesions. Antinuclear antibodies, anti-deoxyribonucleic acid (DNA), anti-ribonucleoprotein (RNP), anti-neutrophil-cytoplasm-antibodies (ANCA) and antiglomerular basement antibodies were negative and no circulating immune complexes were detectable. The electrocardiogram (ECG) was normal and the echocardiogram showed a normal left ventricular function and no suspicion of amyloid deposition. The chest roentgenogram revealed diffuse bilateral acinar infiltrates. A high resolution computed tomogram (CT) of the lung confirmed these findings and showed no additional abnormalities (fig. 1).

Pulmonary function tests showed vital capacity (VC) 3.5 l (predicted 3.76 l) total lung capacity (TLC), 5.2 l (predicted 5.93 l), forced expiratory volume in one second (FEV<sub>1</sub>), 2.96 l (predicted 2.91 l).



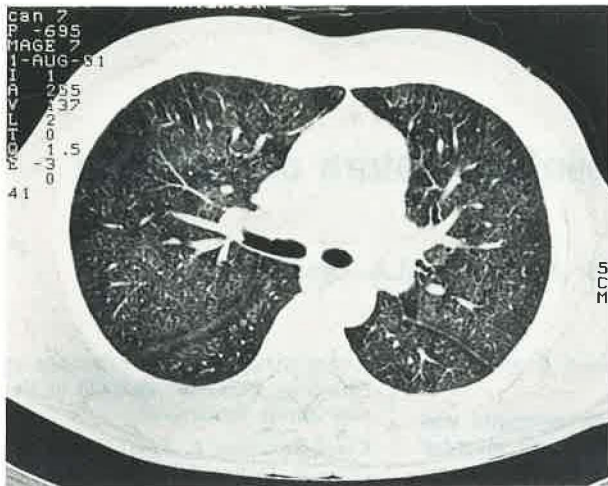


Fig. 1. — High resolution computed tomogram (CT) (2mm slice) of the lung showing an acinar filling pattern.

Carbon monoxide diffusion capacity was  $8.4 \text{ mmol}\cdot\text{min}^{-1}\cdot\text{kPa}^{-1}\cdot\text{l}^{-1}$  (99% of predicted) and the transfer coefficient (Krogh factor)  $2.1 \text{ mmol}\cdot\text{min}^{-1}\cdot\text{kPa}^{-1}\cdot\text{l}^{-1}$  (150% of predicted). Bronchoalveolar lavage was performed from the medial segment of the middle lobe by fiberoptic bronchoscopy. Four 50 ml aliquots of 0.9% NaCl were instilled and 100 ml of bloody fluid was aspirated, which contained 55% macrophages, 14% lymphocytes, 29% neutrophils, 1% basophils and 1% eosinophils. The alveolar macrophages were loaded with haemosiderin. No mycobacteria, other bacteria, or pneumocysts were found. Open lung biopsy was performed, with biopsies taken from the middle lobe and the right upper lobe.

Light microscopy showed alveoli filled with red blood cells and alveolar macrophages containing large amounts of iron. There was no evidence of vasculitis and no deposits of amyloid were detectable.

ANCA, enzyme immunoassay and immunofluorescence of IgG and IgA class were repeatedly negative in serum and bronchoalveolar lavage fluid. Anti-glomerular basement membrane-antibodies of IgG and of IgA class, measured by enzyme-linked immunosorbent assay (ELISA) and using indirect immunofluorescence on frozen sections of normal lung tissue, were not detectable. Direct immunofluorescence on frozen sections of the patient's lung biopsy did not reveal any deposits of immunoglobulins (heavy and light chains) or complement components. Due to the presence of the paraprotein, a diffuse staining of tissue structures could be observed with fluoresceinated antibodies against the light chain kappa and the heavy chain alpha.

Electron microscopy confirmed the histological findings. The alveoli were stuffed with erythrocytes and macrophages, the latter containing ingested red blood cell fragments in various stages of degradation. Alveolar septa were slender and they were lined by pneumocytes of inconspicuous ultrastructure.

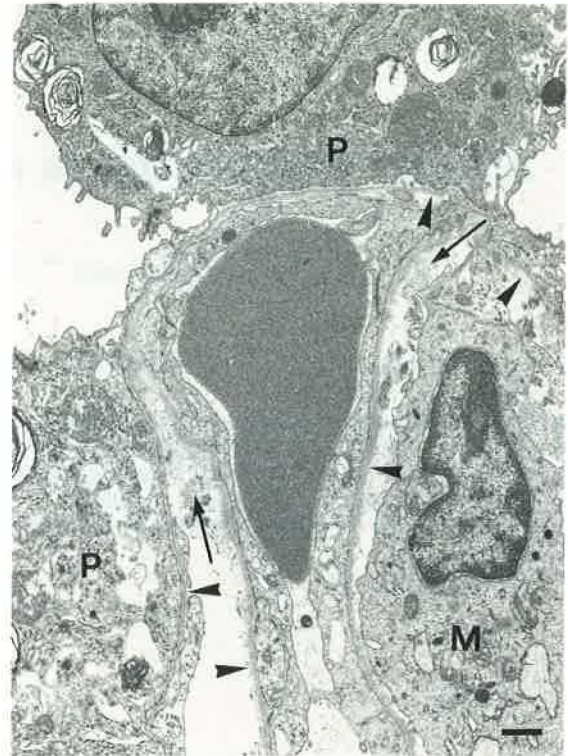


Fig. 2. — Part of an alveolar septum lined by pneumocytes of inconspicuous ultrastructure (P). The blood capillary shows an uninterrupted endothelial lining. Basement membranes are thin (arrow heads), and within the somewhat oedematous interstitial space a macrophage (M) and fine collagen filaments are seen (arrows). (Bar=1  $\mu\text{m}$ ).

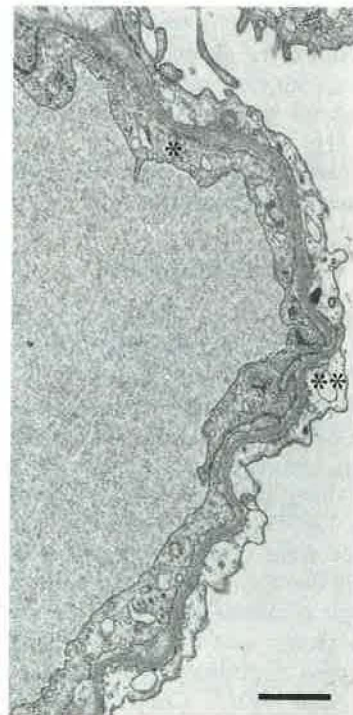


Fig. 3. — Part of a blood capillary. Note flattened endothelial (\*) and epithelial (\*\*) cells and narrow basement membrane. (Bar=1  $\mu\text{m}$ ).



Blood capillaries revealed a flattened uninterrupted endothelial cell lining and extravasation of blood cells could not be detected. Subendothelial and subepithelial basement laminae were normal. Interstitial spaces were somewhat dilated and contained scant collagen fibrils but no amyloid-suspect fibrillary material and no inflammatory cells (figs. 2 and 3).

The patient received methylprednisolone, 30 mg·kg<sup>-1</sup> for 3 days and 3 l of plasma were exchanged by plasmapheresis. As soon as the diagnosis of myeloma was established, chemotherapy, consisting of 100 mg prednisone and 15 mg melphalan orally in a daily dose for 5 days every 4 weeks, was initiated. Alveolar haemorrhage stopped under this treatment, the pulmonary infiltrates cleared and the patients haemoglobin remained stable above 120·g·l<sup>-1</sup>. He is presently without symptoms.

### Discussion

Our patient presented with the three most consistent features of AH: haemoptysis, pulmonary infiltrates and anaemia. Iron deficiency, bloody alveolar lavage fluid which contained abundant haemosiderin in macrophages and an increase of the diffusion coefficient for carbon monoxide confirmed long-lasting and unremitting alveolar bleeding.

Renal function was normal and the pulmonary manifestation of AH was not found to be related to well-known causes of alveolar haemorrhage, such as anti-glomerular basement membrane-antibody also known as Good Pasture's syndrome, hypersensitivity vasculitis, Wegeners granulomatosis, systemic lupus erythematosus, idiopathic rapidly progressive glomerulonephritis, Henoch-Schönlein purpura and cryoglobulinaemia [1, 2]. No evidence for IgA nephropathy or fibrillary glomerulonephritis (immunotactoid glomerulopathy) was found. In both types of kidney disease, a single case of associated alveolar haemorrhage has been reported [3, 4]. Idiopathic pulmonary haemosiderosis is defined as AH that occurs without glomerulonephritis or other extrapulmonary disease and cannot be ascribed to one of the immune disorders mentioned above. It is a diagnosis of exclusion, primarily affecting children, and is an uncommon cause of AH in adults [1].

Further work-up established the diagnosis of an IgA subclass 1 myeloma, secreting kappa light chains. Renal biopsy was not performed, since renal function was normal and there was no evidence of increased glomerular permeability.

Thoracic skeletal abnormalities are the most common finding on chest roentgenograms in patients with myeloma. The ribs, either singly or in combination, are the typically involved thoracic structures. Localised or diffuse pulmonary infiltrates are most often due to infections and were present in 10% of 958 patients with this disease. In four patients, diffuse infiltrates were thought to be caused by a plasma cell infiltrate but conclusively demonstrated in only one [5].

Recently, plasmacytosis has been demonstrated in bronchoalveolar lavage in a patient with a plasma cell dyscrasia [6]. Diffuse lung involvement rarely occurs in myeloma, except in aggressive or terminal phases of the disease or in plasma cell leukaemia [7]. There was no evidence for pulmonary infection or plasma cell infiltration of the lung in our patient.

The deposition of monoclonal immunoglobulin in the kidney and other organs is one of the well-known complications of B-cell dyscrasias. The fibrillar (amyloidotic) and nonfibrillar forms of monoclonal immunoglobulin deposition occur either in overt myeloma or in the course of less neoplastically aggressive plasmacytic dyscrasias [8]. The three forms of monoclonal immunoglobulin deposition diseases that can be distinguished by their immunohistological and ultrastructural features are the light-chain amyloid disease, the light-chain deposition disease and light-and-heavy-chain deposition disease. The dominant feature in these cases is significant renal disease.

Slightly over 90% of the patients suffer from renal insufficiency. Similar percentages of patients have substantial nephropathic proteinuria in addition to the excretion of monoclonal immunoglobulins, and microscopic haematuria occurs in at least 20% of the reported cases.

Pulmonary involvement has been documented primarily as nodular deposits in the lung parenchyma [9] but, to our knowledge, no case of alveolar bleeding has been reported. We could not find any evidence for immunoglobulin deposition disease in our patient.

HUI *et al.* [10] described lower respiratory tract involvement in 48 patients with amyloidosis and found diffuse infiltrates in six. The cellular infiltrates consisted of plasma cells, lymphocytes and giant cells. Plasma cells were usually polyclonal, but in two cases they were predominantly light-chain cells. We found no amyloid deposition in the lung of our patient.

In summary, no light-chain amyloid, light-chain deposits or antibasement membrane antibodies could be found by appropriate technique in our patient. Although lung tissue samples were obtained from two different parts of the lung by open biopsy, it cannot be excluded that because of uneven distribution of the underlying process we might have missed an important morphological aspect. Nevertheless, we believe that this unusual clinical presentation of AH and the cessation of alveolar bleeding after treatment of the myeloma both suggest a pathophysiological link between these two conditions, and speculate that the circulating paraprotein is somehow interfering with the integrity of the alveolocapillary membrane.

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