Original paper

# Various patterns of acute alveolar haemorrhage in patients with microscopic polyangiitis: a clinicopathological study of four cases

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It is well known that acute alveolar haemorrhage (AAH) is attributed to capillaritis in most cases with microscopic polyangiitis (MPA). In this article, we explore the cause of alveolar haemorrhage in MPA patients. In the present study, we extracted four autopsy cases of MPA with AAH. Patient's sex and age, cause of alveolar haemorrhage, therapy, follow-up duration, and cause of death were investigated. As a result, alveolar haemorrhage was caused by diffuse alveolar damage (DAD) due to candidiasis or influenza virus infection, haemorrhagic infarct due to aspergillosis, capillaritis due to MPA, vasculitis due to cytomegalovirus (CMV), and herpes simplex virus (HSV) infection. All patients received corticosteroid therapy, and one patient additionally underwent administration of cyclophosphamide. The duration of follow-up ranged from one to 26 months with a mean of eight months. All patients died of respiratory failure. In summary, clinicians and pathologists should recognise some causes of alveolar haemorrhage in MPA patients, which include DAD, haemorrhagic infarct, virus-associated vasculitis, or MPA-associated capillaritis.

**Key words:** alveolar haemorrhage, microscopic polyangiitis.

## Introduction

Microscopic polyangiitis is a rare systemic vasculitis associated with antineutrophil cytoplasmic antibody and characterised by necrotising small vessel involvement with few or no immune complex deposits [1]. It is well known that acute alveolar haemorrhage (AAH) is attributed to capillaritis in most cases with microscopic polyangitiis [2]. Pulmonary capillaritis or diffuse alveolar haemorrhage (DAH) has been seen in about 10% to 30% of cases [1, 3]. There are theories that some immunosuppressive drugs can induce DAH [3]. DAH is often a dismal clinical syndrome causing respiratory failure. DAH is caused by papillary capillaritis, bland pulmonary haemorrhage, or diffuse alveolar damage (DAD) [4]. Diffuse alveolar damage is considered the morphological hallmark for the acute phase of acute respiratory distress syndrome (ARDS) and is characterised by an acute phase with oedema, hyaline membrane, and inflammation, followed by an organising phase with alveolar septal fibrosis and type II pneumocyte hyperplasia [5]. Most studies performed using open lung biopsy or autopsies have found that only approximately one-half of patients with ARDS have DAD, whereas the other half were found have heterogenous disorders including pneumonia [5]. The aetiology of DAH includes pulmonary capillaritis, bland pulmonary haemorrhage, and DAD [4]. However, we recently found various patterns of DAH in MPA. In this article, we report four cases of MPA with DAH and discuss the cause of DAH.

**Table I.** Summary of four cases with microscopic polyangitis (MPA) with alveolar hemorrhage

| Age | Sex | Cause of alveolar hemorrhage | Therapy | Follow-up (months) | Cause of death | UIP | Glomerulo-nephritis | Other lesions |
|---|---|---|---|---|---|---|---|---|
| 80 | F | DAD due to candidiasis | SAID | 1 | respiratory failure | + | cresentic | pancreatic fat necrosis, uterine leiomyomas, neurofibromatosis |
| 83 | F | hemorrhagic infarct due to aspergillosis | SAID, CPA | 2 | respiratory failure | + | cresentic | shock kidney, implanted cardia pacemaker |
| 73 | F | DAD due to influenza | SAID | 26 | respiratory failure | + | IgA nephropathy | pulmonary hypertension, neurofibroma |
| 88 | M | capillaritis due to MPA, CMV and HSV | SAID | 3 | respiratory failure | + | cresentic | pulmonary hypertension, cardiac infarct |

*F – female; M – male; DAD – diffuse alveolar damage; CMV – cytomegalovirus; HSV – herpes virus; SAID – steroidal anti-inflammatory drug; CAP – cyclophosphamide.*

## Material and methods

After we reviewed 40 autopsy cases between January in 2014 and March 2018, we selected four cases of MPA with AAH. Patient's sex and age, cause of alveolar haemorrhage, therapy, follow-up duration, and cause of death were examined. All surgically resected organs were fixed in formalin and embedded in paraffin. Thick sections were cut into 4-mm slices and stained with haematoxylin and eosin. For the detection of mycosis, periodic acid-Aschiff and Grocott stains were performed. Antibodies against aspergillus (polyclonal, 1 : 200, Biocare Medical, CA, USA), cytomegalovirus (CCH2, 1 : 200, DAKO, Glostrup, Denmark), and herpes simplex virus (polyclonal, 1 : 40, Biogenex, CA, USA) were employed in the present study. For the immunohistochemistry, BenchMark Ultra (Ventana Medical Systems, Inc., Tucson, AZ, USA) was employed as an autostainer. Tissue specimens of nasal cavity, lung, and oesophagus with aspergillus, cytomegalovirus, and herpes simplex virus infection were used as positive controls, respectively. Written, informed consent was obtained from all bereaved of patients.

## Results

The clinicopathological data were summarised in Table I. The sex ratio of male versus female was 1 : 3. The age of patients ranged from 73 to 88 years with a mean age of 81 years. Representative chest X-ray is shown in Fig. 1. Macroscopically, haemorrhage was observed in pulmonary parenchyma (Fig. 2). Microscopically, haemorrhage was identified in the alveolar spaces (Fig. 3A). The cause of alveolar haemorrhage included diffuse alveolar damage (DAD) (Fig. 3B) due to candidiasis or influenza virus infection,

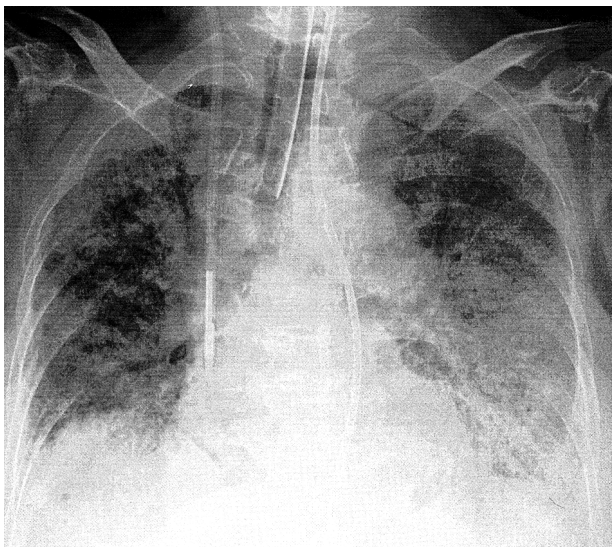

**Fig. 1.** Chest X-ray findings. Infiltrative shadow is seen in bilateral lungs

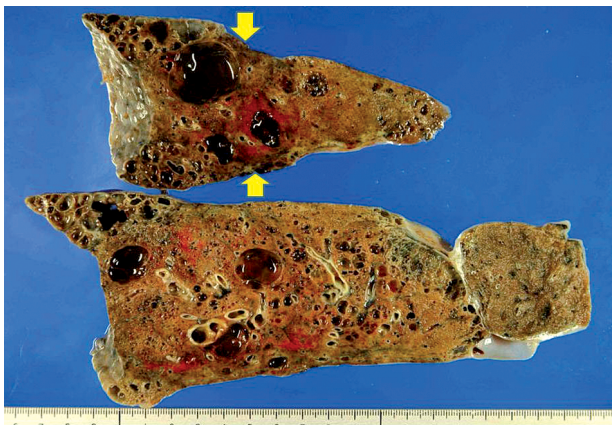

**Fig. 2.** Macroscopic findings of acute alveolar haemorrhage. On the cut surface of the lung, haemorrhage is prominent (arrows)

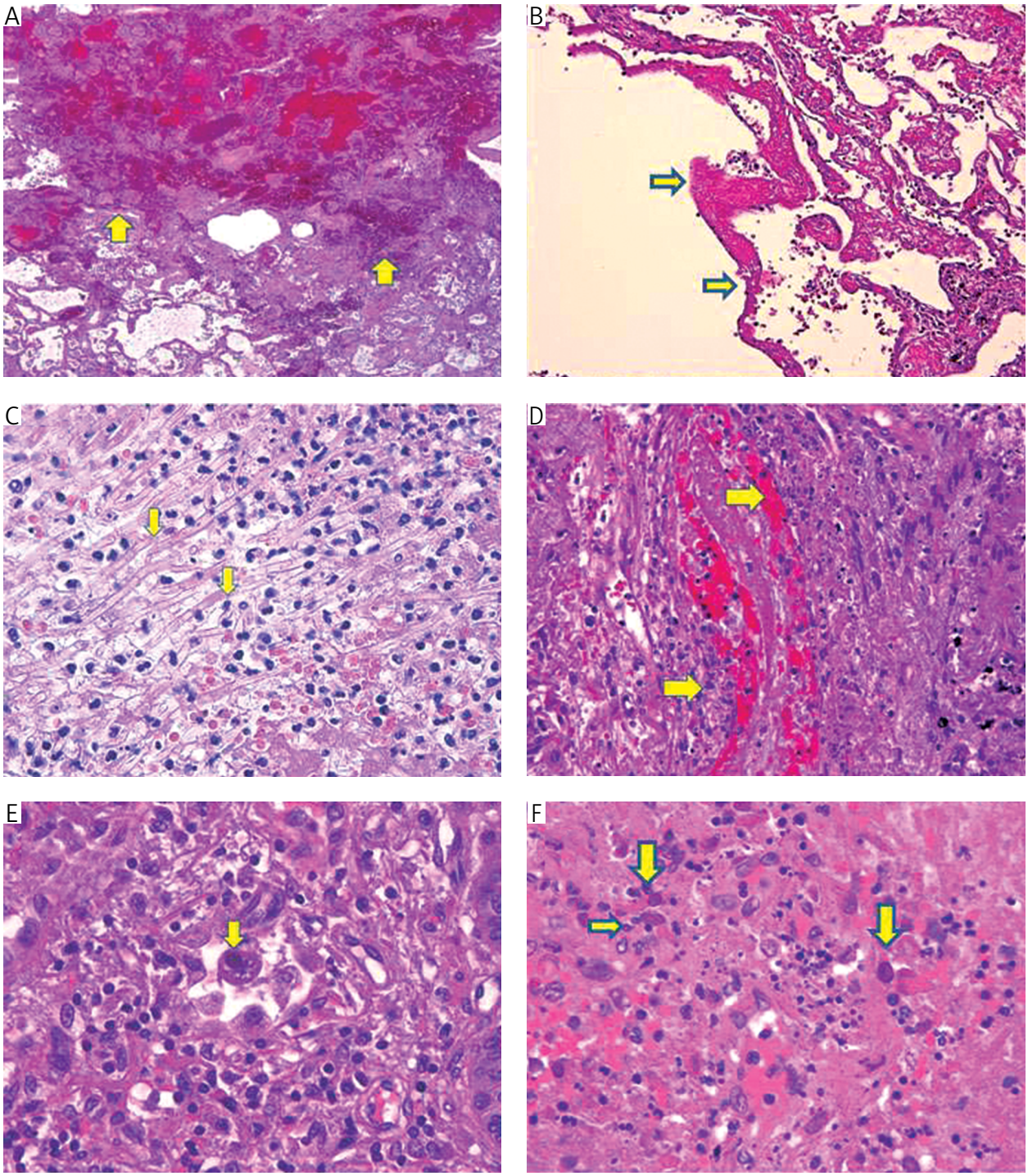


**Fig. 3A-F.** Microscopic findings. A) Alveolar haemorrhage (arrows). B) Diffuse alveolar damage. Hyaline membranes are observed along alveolar ducts (arrows). C) Haemorrhagic infarct due to aspergillosis showing Y-shaped branching (arrows). D) Capillaritis due to microscopic polyangiitis. Inflammation on vascular wall is seen (arrows). E) Vasculitis due to cytomegalovirus (CMV) infection. Eosinophilic inclusion in the nucleus can be seen (arrow). F) Vasculitis due to herpes simplex (HSV) infection. Ground glass nucleus is observed (arrow)

haemorrhagic infarct (Fig. 3C) due to aspergillosis, capillaritis due to MPA (Fig. 3D), and vasculitis due to cytomegalovirus (CMV) (Fig. 3E) and herpes simplex virus (HSV) (Fig. 3F) infection. All patients received corticosteroid therapy. Additionally, one patient underwent administration of cyclophosphamide. The duration of follow-up ranged from one to 26 months with a mean of eight months. All patients died of respiratory failure. All patients demonstrated usual interstitial pneumonia. Among four patients, three patients had ANCA-related glomerulonephritis and pulmonary hypertension. Two patients were diagnosed with neurofibroma.

## Discussion

It is difficult for clinicians to identify the cause of alveolar haemorrhage in patients with MPA. Pulmonary capillaritis is often observed in systemic lupus erythematosus but is also seen in MPA [6]. Patients with MPA tend to suffer from various infectious diseases such as miosis, pneumocystis jirovecii, or cytomegalovirus [6, 7, 8, 9]. In general, clinicians should consider capillaritis due to MPA if the disease state of MPA is active. On the other hand, physicians need to consider the effect of infectious disease if immunosuppression exists to some extent in hosts because of SAID or immunosuppressive agents. In the present study, we found a variety of patterns of alveolar haemorrhage in MPA, such as DAD due to candidiasis or influenza virus infection, haemorrhagic infarct MPA-induced capillaritis, and CMV- or HSV-induced vasculitis. It is very important for clinicians to recognise these possibilities because the therapeutic modality is quietly different among these causes. These pathological conditions result in respiratory failure and subsequent fatal outcome.

To the best of our knowledge, there is no report on pulmonary haemorrhagic infarct in MPA. Thus, this is the first report on pulmonary haemorrhagic infarct due to aspergillosis in an MPA patient. Previously, a case of pleuritis due to aspergillosis was reported in a patient with MPA. This phenomenon was caused by prior spontaneous pneumothorax [10].

Additionally, there are a few reports on coinfection of CMV and HSV in the lung. Among them, two patients received lung transplantation and one patient was an immunocompromised host [11, 12, 13]. To our knowledge, this is the first report on coinfection of CMV and HSV in an MPA patient.

In contrast, whenever clinicians encounter alveolar haemorrhage, they should consider the possibility of MPA [14, 15]. Clinicians should bear in mind that alveolar haemorrhage may appear in chronic and asymptomatic fashion [16].

In conclusion, clinicians and pathologists should recognise some causes of alveolar haemorrhage in MPA patients, which include DAD, haemorrhagic infarct, virus-associated vasculitis, or MPA-associated capillaritis.

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*The authors declare no conflict of interest.*

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