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 polyangiitis [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.
Material and methods

After we reviewed 40 autopsy cases between January 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,
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. 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 hemorrhage 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 hemorrhage 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 recognize 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 hemorrhage, they should consider the possibility of MPA [14, 15]. Clinicians should bear in mind that alveolar hemorrhage may appear in chronic and asymptomatic fashion [16].

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

The authors declare no conflict of interest.

References

1. Wilke L, Prince-Fiocco M, Fiocco GP. Microscopic polyangiitis. A large single-center series. J Clin Rheumatol 2014; 20: 179-182.
2. Pesci A, Manganelli P. Respiratory system involvement in antineutrophil cytoplasmic-associated systemic vasculitis. Drugs 2007; 8: 26-42.
3. Martinez-Martinez MU, Herrera-van Oostdam DA, Abud-Mendoza C. Diffuse alveolar hemorrhage in autoimmune diseases. Curr Rheumatol Rep 2017; 19: 27.
4. Lara AR, Schwarz MI. Diffuse alveolar hemorrhage. Chest 2010; 137: 1164-1171.
5. Cardinal-Fernandez P, Lorente JA, Ballen-Barragan A, et al. Acute respiratory distress syndrome and diffuse alveolar damage new insights on a complex relationship. Ann Am Thorac Soc 2017; 14: 844-850.
6. Isono M, Araki H, Haitani T, et al. Diffuse alveolar hemorrhage in lupus nephritis complicated by microscopic polyangiitis. Clin Exp Nephrol 2011; 15: 294-298.
7. Yoshida M. Strategy of infection control in immunosuppressive therapy for ANCA-associated vasculitis. Ann Vasc Dis 2013; 6: 9-15.
8. Takizawa Y, Inokuma S, Tanaka Y, et al. Clinical characteristics of cytomegalovirus infection in rheumatic diseases: multicentre survey in a large patient population. Rheumatology (Oxford) 2008; 47: 1373-1378.
9. Meyer MF, Hellmich B, Kotterba S, et al. Cyto megalovirus infection in systemic necrotizing vasculitis: causative agent or opportunistic infection? Rheumatol Int 2000; 20: 35-38.
10. Kimoto Y, Oroyji K, Uchino A, et al. Perititis clinically diagnosed as aspergillosis during the course of microscopic polyangiitis. Intern Med 2014; 53: 2821-2824.
11. Miyoshi I, Daibata M, Taguchi H, et al. Viral pneumonia: coinfection of cytomegalovirus and herpes simplex virus. Intern Med 2005; 44: 518-519.
12. Engelmann I, Hesse N, Fegbeutel C, et al. Incidence and impact of herpes simplex and cytomegalovirus detection in the respiratory tract after lung transplantation. Transpl Infect Dis 2011; 13: 259-265.
13. Nagarakanti S, Bishburg E, Bapat A. Adenovirus, herpes simplex virus and cytomegalovirus infection in a lung transplant recipient. IDCases 2018; 11: 91-93.
14. Ward ND, Cosner DE, Lamb CA, et al. To differential diagnosis should be microscopic polyangiitis in ANCA-positive patient with diffuse pulmonary hemorrhage and hemosiderosis. Case Reports in Pathology 2014; 2014: 286030.
15. Lababidi MH, Odighwe C, Okolo C, et al. Microscopic polyangiitis causing diffuse alveolar hemorrhage and rapidly progressive glomerulonephritis. Proc (Bayl Univ Med Cent) 2015; 28: 469-471.
16. Tashiro H, Takahashi K, Sadamatsu H, et al. Chronic and asymptomatic diffuse alveolar haemorrhage with microscopic polyangiitis: A case report and review of the literature. Case Reports in Rheumatology 2016; 2016: 165126.

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