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Case report

Two cases of extrapulmonary onset granulomatosis with polyangiitis which caused diffuse alveolar haemorrhage

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A B S T R A C T

Granulomatosis with polyangiitis (GPA) is a rare form of vasculitis. Multidisciplinary therapeutic approach and early diagnosis assume vital importance in management of patients with diffuse alveolar haemorrhage caused by GPA, which is a rare complication. The purpose of this study was to present the diagnostic and therapeutic challenges experienced by clinicians in management of two severe cases of GPA with insidious extrapulmonary manifestations which rapidly progressed into acute kidney injury, alveolar haemorrhage and acute respiratory failure.

Introduction

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a form of vasculitis which belongs to the group of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides. It is rare systemic disease which involves small size vessels and is characterised by necrotising granulomatous inflammation [1]. Its clinical picture and prognosis may vary with the affected organ system. At the outset, it may follow a mild course with non-specific constitutional symptoms. However, it may rapidly progress into involvement of vital organs, causing fatal outcomes.

Despite the commonly used criteria, diagnosis of vasculitis remains under debate [2,3]. In diagnosis of GPA, clinicians should suspect vasculitis first and establish the diagnosis based on a combination of clinical assessment, radiologic evidence, serological tests and tissue biopsy, wherever applicable. In the updated definitions of vasculitis, ANCA serology is mentioned as one of the diagnostic criterion for GPA and recognised as a diagnostic value because a positive c-ANCA (cytoplasmic) serology may provide diagnosis of GPA without further requirement for biopsy in some patients [3].

Diffuse alveolar haemorrhage (DAH) is a clinical syndrome which can be fatal if not diagnosed properly and treated in time. DAH, which may be caused by a number of factors, is rare determinant of poor prognosis in patients with GPA and a precursor of early mortality [4,5].

The purpose of this study was to present the diagnostic and therapeutic challenges experienced by clinicians in management of two severe cases of GPA presenting with insidious extrapulmonary findings which rapidly progressed into acute kidney injury (AKI), DAH and severe acute respiratory failure (ARF).

Case reports

Case 1

A 60-year-old male patient presented to the emergency department with complaints of rapid onset nausea and vomiting in addition to fever and malaise over the last month. He carried no previous diagnosis of any disease and was not on continuous pharmacotherapy; however, he had a 10 pack-year history of smoking (an ex-smoker of 25 years). Physical examination revealed that his overall clinical status was moderate and he was conscious and cooperative. His pulse rate was 95/min, his blood pressure was 130/80 mmHg, his respiratory rate was 16/min, his temperature was 38.2 °C and his oxygen saturation (SO_2) level was 98% in room air, as measured by pulse oxymetry. His complete blood count, serum biochemistry, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are demonstrated in Table 1. His urinalysis showed 2 + blood. Electrocardiogram, echocardiogram, abdominal ultrasound and chest x-ray (CXR) showed no evidence of pathology in the patient. He was transferred to Intensive Care Unit (ICU) of the Nephrology Department due to fever of unknown origin and

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Table 1
Evolution of laboratory results of the cases with granulomatosis with polyangiitis.

Laboratory findings	Case 1 (alive)			Case 2 (death)		
	D0	D12	D22	D0	D7	D14
Hemoglobin (g/dl)	12.2	6.1	10.9	9.9	7.3	5.2
Haematocrit (%)	37.2	18.3	32.8	28.3	20.5	15.4
White blood cells ($\times 10^3/\mu l$)	12.5	8.0	9.9	20.	18.3	15.7
Platelets ($\times 10^3/\mu l$)	322.	341.	345.	604.	625.	565.
Serum urea (mg/dl)	172	70	70	106	99	179
Serum creatinine (mg/dl)	6.2	2.15	0.9	3.0	3.8	8.6
Serum potassium (mmol/l)	5.5	3.6	4.9	5.3	4.6	5.7
Serum albumin (g/dl)	2.75	2.4	3.5	1.5	1.5	1.6
C-reactive protein (mg/dl)	12.5	15.9	0.7	18	17	23
Erythrocyte sedimentation rate (mm/h)	46	66	12	52	55	64
SO_2 (%) (with pulse oxymetry or ABG)	98[a]	85[a]	96[a]	93[a]	80[b]	95[b]
PaO_2 (mm Hg)	–	50	65	64	42	100
Bicarbonate (mmol/l)	–	23	28	23	23	15

[a] Breathing room air.
[b] Breathing supplemental oxygen, D: Day, ABG: Arterial blood gases. SO_2: Oxygen saturation, PaO_2: Partial oxygen pressure, $PaCO_2$: Partial carbon dioxide pressure.

diagnosis of AKI. He was put on intravenous (IV) fluid therapy and supportive care, avoiding particularly nephrotoxic drugs. His 24-h urine protein was 20 mg/dl.

The follow-up showed that the patient's renal functions improved markedly and he required no dialysis. No bacterial growth took place in his blood and urine cultures. Despite this good prognosis, he developed minor haemoptysis, severe anaemia and moderate hypoxaemia, as measured by the arterial blood gas analysis (ABG) on the twelfth day of hospitalisation (Table 1). His coagulation parameters were within the normal range. Urine sedimentation examination demonstrated 20–25 red blood cells and 6–8 leukocytes. In addition, CXR showed evidence of recently developing bilateral diffuse alveolar infiltrates (Fig. 1). He was transferred to respiratory ICU with a pre-diagnosis of DAH. Physical examination revealed that he was dyspnoeic, tachypnoeic (28 breaths/min) and tachycardic (118 beats/min) and his SO_2 level was 85%. Diffuse coarse crackles were heard in both sides of the lung in osculation. He was diagnosed with ARF associated with DAH and put on oxygen mask treatment at 10 1/min. However, this treatment was replaced by non-invasive ventilation (NIV) as his clinical status deteriorated. His blood pressure gradually increased and saturation reached 96% in 24 h following initiation of the treatment. Serological tests were requested for the patient on suspicion of vasculitis and it was found that he was strongly c-ANCA positive, antinuclear antibodies (ANA) negative, antiglomerular basal membrane antibodies (anti-GBM) negative and peri-nuclear ANCA (p-ANCA) negative. In addition, enzyme linked immunosorbent assay showed high levels of serum anti-proteinase 3 antibody (anti-PR3) titre. Fiberoptic bronchoscopy (FOB) was considered for definite diagnosis; however it could not be performed due to the respiratory failure the patient suffered. The patient who was clinically diagnosed with GPA was put on the following combined immunosuppressive treatment: IV pulse cyclophosphamide (1 g/once) and methylprednisolone (1 g/day) during the first three days, followed by methylprednisolone (1 mg/kg/day). Plasmaphaeresis was administered simultaneously with the immunosuppressive treatment, every day during the first week.

The follow-up showed that his hypoxia and overall clinical status improved. Therefore, dose of the oxygenation treatment was reduced to 2 l/min and he was put on nasal cannula and intermittent NIV. During hospital stay, he had no recurrent haemoptysis. Serial CXR showed evidence of partial remission of bilateral

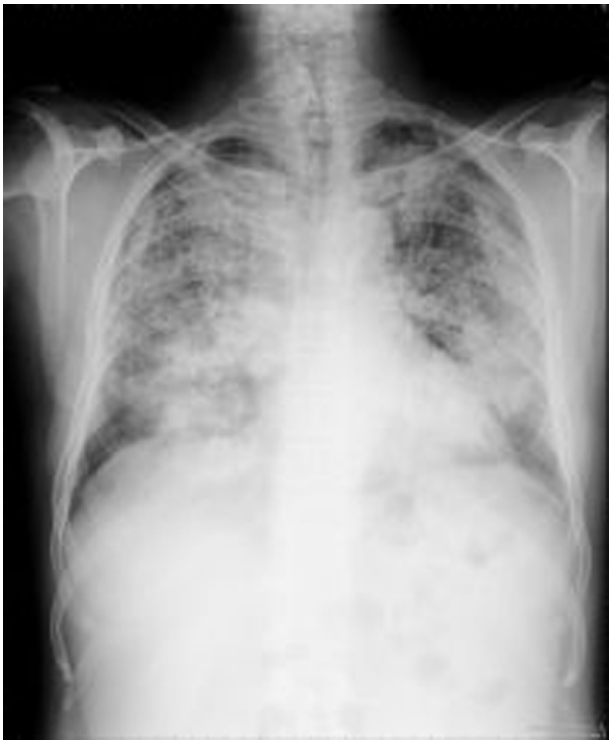

Fig. 1. Chest X-ray of Case 1 showing bilateral diffuse alveolar infiltrates (on the 12th day of hospitalisation).

interstitial alveolar infiltrates. He required significantly lesser amount of oxygen and was transferred to the clinical department and put on intermittent oxygen treatment at 2 l/min. Chest computed tomography (CT) showed bilateral and extensive ground glass opacities, interlobular septal thickening and mosaic perfusion from place to place. On the 22nd day of hospitalisation, his clinical status and laboratory results improved (Table 1) and he was referred to a specialised rheumatology centre. Ear-nose-throat (ENT) examination performed in that centre showed perforation of nasal septum. Biopsy material taken from the patient was in agreement with the diagnosis of GPA. In addition, renal biopsy confirmed that the patient had GPA with renal, pulmonary and upper respiratory tract involvement. He was recommended daily oral methylprednisolone and monthly IV cyclophosphamide treatment. The patient, who is on immunosuppressive treatment, has been followed up for four months now and no complications have occurred in this period of time.

Case 2

A 48-year-old male patient presented to the emergency department with fever, cough, bloody sputum, shortness of breath, chest pain, nausea, vomiting, malaise, loss of appetite and articular pain. He had antibiotic-resistant otitis media in the last three months and respiratory symptoms over the last month. He was referred to our hospital by another healthy facility due to evidence of a mass lesion filling the left upper lobe (Fig. 2(a)) and bilateral multiple nodules in the chest CT, which physicians thought could be malignant. He was not on continuous pharmacotherapy; however he had a 30 pack-year history of smoking. Physical examination revealed that his overall clinical status was poor; he was conscious but not fully cooperative. His pulse rate was 90/min, his blood pressure was 120/70 mmHg, his respiratory rate was 15/min, his body temperature was 37.8 °C and his SO_2 level was 93% in room