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.

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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 a 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 (SO2) 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
nosuppressive treatment: IV pulse cyclophosphamide (1 g/once) diagnosed with GPA was put on the following combined immunosuppressive treatment, every day during the first three days, followed by methylprednisolone (1 mg/kg/day). Plasmapheresis 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 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 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). Plasmapheresis was administered simultaneously with the immunosuppressive treatment, every day during the first week.

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| 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 (>10^3/µl) | 12.5 | 8.0 | 9.9 | 20. | 18.3 | 15.7 |
| Platelets (>10^3/µl) | 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 |
| SO2 (%) (with pulse oxymetry or ABG) | 98a | 85b | 96c | 93a | 80b | 95c |
| PaO2 (mm Hg) | – | 50 | 65 | 64 | 42 | 100 |
| Bicarbonate (mmol/l) | – | 23 | 28 | 23 | 15 | 15 |

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

Fig. 1. Chest X-ray of Case 1 showing bilateral diffuse alveolar infiltrates (on the 12th day of hospitalisation).
air. He had aphthous lesions in the mouth. In addition, he had coarse respiratory crackles. Routine laboratory findings are demonstrated in Table 1. His coagulation parameters were within the normal range. His urinalysis showed 100/μl of leukocytes, 75 mg/dl of protein, 250 mg/l of blood. Electrocardiogram, echocardiogram and abdominal ultrasound gave normal results. He was transferred to respiratory ICU with a pre-diagnosis of AKI, ARF, sepsis, chronic otitis media and suspected malignancy and put on supportive care with oxygenation at 5 l/min, combined IV antibiotics (meropenem and vancomisin) at renal dose, bronchodilatator and IV fluid. His 24-h urine protein was 510 mg/dl. CT scan of bilateral temporal and paranasal sinuses showed evidence of chronic sinusitis and cholesteroloma in the right side.

On the second day of hospitalisation, consultation was requested from an ENT specialist who considered surgery indicated for the patient due to paralysis of peripheral facial nerves and loss of hearing, and the patient underwent radical mastoidectomy. On the fifth day of hospitalisation, purpuric rashes in both legs and trunk were biopsied by a dermatologist (Fig. 2(b)).

On the seventh day of hospitalisation, FOB showed blood clots in the trachea and main bronchi, and bronchoalveolar lavage (BAL) revealed hemosiderin-filled macrophages. Urine sedimentation examination showed erythrocyte cylinders. Diagnosis of DAH was established based on the above mentioned findings and vasculitis markers were requested to be checked. Nephrologists recommended renal biopsy for the patient. However, his relatives did not consent to the procedure. As to his serological tests, he was c-ANCA positive, anti-PR3 positive, p-ANCA negative, anti-GBM negative and ANA negative. Rheumatoid factor (RF) was found to be 250 IU/ml (high) in the patient. His skin biopsy report indicated necrotising leukocytoclastic vasculitis. He was diagnosed with GPA based on positive c-ANCA serology, upper respiratory tract, pulmonary and renal involvement and results of skin biopsy and administered combined immunosuppressive treatment on the 10th day of hospitalisation (IV pulse cyclophosphamide and high dose pulse methylprednisolone). Two days later, he had to be treated with dialysis as his clinical status and laboratory results deteriorated and he had acute metabolic acidosis, as shown by ABG analysis. In addition, he was confused, tachypnoeic (38 breaths/min), tachycardic (110 beats/min) and desaturated (SO2 75%). He was put on invasive mechanical ventilation via endotracheal intubation. Non-contrast chest CT showed recent evidence of bilateral nodules as well as consolidation and multiple cavitary lesions with thick walls particularly in the upper lobe of the left side, of which the largest one was 5.5 cm. It was found that the solid mass lesion detected in the previous CT had turned into a cavitating lesion (Fig. 2(c)). On the 14th day of hospitalisation and the second day of intubation, the patient had cardiopulmonary arrest and could not be saved despite cardiopulmonary resuscitation attempts.

Discussion

Early diagnosis of GPA is not an easy task for clinicians. GPA should be considered in the differential diagnosis of patients with simultaneous or consecutive multiple organ involvement. Severity of presenting symptoms and findings in patients with GPA may vary considerably from asymptomatic (one third of patients) to acute and fulminant alveolar haemorrhage with respiratory failure. Typical early symptoms are fever, loss of weight and malaise; however the disease is usually accompanied by upper and lower

Fig. 2. a.) Mediastinal window of the chest computed tomography of Case 2 showing solid lesion filling the left apex. (b.) Purpuric lesions on the leg of Case 2 (vasculitic skin involvement). (c.) Lung window of the chest computed tomography performed the day before Case 2 died.
respiratory tract problems [6]. Upper airway involvement in the form of sinusitis, otitis media, cholestomatia and loss of hearing may occur in patients a few months before the manifestation of pulmonary and renal problems [7]. In this study, Case 1 presented with constitutional symptoms, followed by severe nasal and pulmonary involvement. Case 2, on the other hand, had prolonged ear-nose-throat symptoms, followed by pulmonary, renal and skin involvement. At the outset, insidious nature of the disease and local presentation may delay the diagnosis, which was exactly the case in our patients. Diffuse alveolar haemorrhage should be considered a medical emergency. Although it occurs only in 5–10% of patients with GPA, it usually acts as a precursor of severe vasculitis. In addition, mortality remains high in these patients due to ARF associated with DAH. Clinicians should suspect DAH in the event of haemoptysis, a sudden drop in haemoglobin levels and recently developing infiltrates in CXR. It should also be kept in mind that haemoptysis may be absent at presentation in up to 33% of patients with DAH. In these patients, the commonest indications for FOB are to assess the airway and perform BAL as findins of BAL form the basis for a definite diagnosis of DAH [4]. In this study, Case 1 had no respiratory symptoms on admission. Later on, he had minor haemoptysis and sudden onset anaemia and recently developing infiltrates in CXR. Based on these findings, he was diagnosed with DAH. Case 2, on the other hand, was referred to our hospital by another health facility due to respiratory symptoms he was complaining about over the last month and suspected malignancy in CT. On admission, he had minor haemoptysis and mild hypoxaemia. His clinical status deteriorated in the hospital and he died despite the use of invasive mechanical ventilation. FOB could not be performed in Case 1 because of the severe ARF he suffered. In Case 2, cytology of BAL confirmed the diagnosis of DAH.

Renal involvement is common in patients with GPA. It may occur either at the outset or during the course of the disease. It can present as asymptomatic haematuria or AKI with haematuria and cellular casts. Proteinuria varies in degree and is usually sub-nephrotic. Serum creatinine test should be run in all patients for determination of a potential kidney injury [8]. In this study, Case 1 had a high serum creatinine level and microscopic haematuria on admission. He had no significant proteinuria in the 24-h urine protein test. AKI that the patient was suffering improved spontaneously without requirement for dialysis. Case 2, on the other hand, had a high serum creatinine level, abnormal urinalysis results and subnephrotic range proteinuria. Renal failure deteriorated in this patient despite the multidisciplinary therapeutic approach that was adopted. It was reported in the literature and also shown by the present study that c-ANCA and anti-PR3 positivity was most consistent with GPA (90% of patients) [3]. In addition to ANCA testing, other laboratory analyses (such as ANA, anti-GBM, cryoglobulins, hepatitis serology, HIV screening, liver function tests and blood cultures) should also be performed in patients with GPA to assess the potential involvement of other organs and exclude other processes in differential diagnosis. Common haematologic abnormalities in GPA include anaemia, leucocytosis, thrombocytosis and markedly elevated levels of ESR and CRP. Rheumatoid factor is positive in 50–60% of patients [6]. In-hospital risk of mortality is quite high among the elderly with serum albumin levels <2.0 g/dl [9]. As demonstrated in Table 1, on admission Case 1 had high levels of leukocytes, urea, creatinine, potassium, CRP and ESR and a low level of albumin in serum. His clinical status markedly improved following the proper treatment. Case 2, on the other hand, had high levels of leukocytes, thrombocytes, urea, creatinine, potassium, CRP and ESR and low levels of haemoglobin and albumin in serum. He had a positive RF test. In addition, he had exitus despite his relative young age. We believe that low serum levels of albumin may have been a marker of mortality in this patient.

Chest X-ray and CT should be performed in all patients who have pulmonary symptoms and are suspected of having GPA. A vast majority of patients with GPA have abnormalities in CXR. Radiographic findings usually include at least one of the following: cavitory nodules, diffuse hazy opacities, lobar or segmental atelectasis, pleural opacities and rarely hilar adenopathy. Chest CT is helpful in exposing the lesions which cannot be seen in CXR and identifying cavitation which was not suspected previously. Nodules may range in size from a few millimetres to 10 cm [10]. In this study, Case 1 had normal CXR findings on admission but developed bilateral diffuse opacities in the post-haemoptysis period. Case 2, on the other hand, had a mass lesion and multiple nodules which looked suspicious on admission. Follow-up CT showed that some of the nodules became cavitary in time.

Given the potential toxicity of the treatment, it is ideal to confirm the diagnosis of GPA by means of tissue biopsy even in patients with a compatible clinical presentation and positive ANCA serology. Biopsy site should be chosen based on the accessibility of specific sites of the disease and tolerability of the planned procedure by the patient. Skin biopsy generally shows non-specific leukocytoclastic vasculitis. Although it is relatively non-invasive, nasal biopsy is limited by the high rate of false negativity. Kidney biopsy typically shows segmental necrotizing glomerulonephritis, usually with crescents. The main indication for lung biopsy is to assess single or multiple pulmonary nodules, especially when extrapulmonary disease is not present or not accessible to biopsy [11]. In this study, Case 1 was diagnosed based on clinical, radiological and serological findings and administered an aggressive treatment. The diagnosis was confirmed by nasal renal biopsy that was performed in the health facility where he was being followed-up. In Case 2, on the other hand, definite diagnosis was established by skin biopsy.

In patients with GPA, conventional induction therapy usually consists of high dose glucocorticoids and cyclophosphamide [5]. When administered shortly after the induction therapy, combined immunosuppressive therapy ensures remission in up to 90% of patients within 6 months [12]. Plasmapheresis reduces the amount of circulating ANCA in the body. Given the high mortality rates (up to 50%), patients with ARF associated with DAH should soon be administered immunosuppressive therapy simultaneously with plasmapheresis [13]. In this study, Case 1 was successfully administrated a combination of plasmapheresis and immunosuppressive therapy. However, plasmapheresis could not be performed in Case 2 as he was hemodynamically unstable.

Patients with GPA who develop respiratory failure, severe haemoptysis, sepsis, acute renal failure and gastrointestinal bleeding must be followed up in the intensive care unit. Pulmonary manifestations (severe haemoptysis and respiratory failure) have a particular association with survival in these patients [14]. In this study, both of the cases developed severe respiratory failure. However, Case 1 showed marked improvement following NIV and did not require oxygenation after he was discharged from the hospital whereas Case 2 showed no improvement possibly due to such negative factors as history of heavy smoking, sepsis and metabolic acidosis.

In conclusion, clinical presentation and course may vary greatly in GPA and clinical suspicion is the most important factor for its diagnosis. DAH may lead to vital outcomes in patients with GPA due to high risk of mortality caused by ARF associated with DAH, which is a rare complication. Biopsy may not be applicable in patients with DAH; however BAL — a minimally invasive procedure — should be performed for definite diagnosis, and proper treatment should soon be administered in these patients who are in need of intensive care. Lastly, clinicians must be aware of the diagnostic challenges of
GPA and adopt a multidisciplinary approach in management of patients with GPA.

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