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Children with life-threatening pulmonary haemorrhage

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Introduction

Pulmonary haemorrhage is rare in children. Its incidence is unclear as paediatric data is incomplete. However, it is a potentially life-threatening condition even on first manifestation and can occur at any age. We present here a few such patients whom we have managed.

Patient 1

A 17-year-old girl with epilepsy was admitted for breakthrough seizures and pneumonia. She also had multiple medical problems including Down syndrome, mental retardation, primary hypothyroidism, Lennox-Gastaut syndrome with intractable epilepsy, swallowing dysfunction requiring gastrostomy feeding, obstructive sleep apnoea and alpha thalassaemia trait.

On admission, vital signs were stable and SpO_2 was 98% in room air. Chest X-ray showed bilateral lower zone haziness but there was no cough or dyspnoea and chest auscultation was clear. CT brain was unremarkable. She progressively became dyspnoeic and developed chest crepitations over both lung bases. Cefotaxime and azithromycin were started. She developed cyanosis, haemoptysis and shock about 4 hours after admission, with an estimated 600 ml blood loss based on oropharyngeal aspirate volume. Blood tests showed mild anaemia (Hb 10.3 g/dL) with normal white cells, platelets, coagulation profile, renal and liver function while arterial blood gases showed type II respiratory failure (pH 7.34, pCO_2 6.2 kPa, pO_2 8.8 kPa, base excess -2). She was resuscitated with 100% oxygen, intravenous fluid boluses, endotracheal intubation (Figure 1), and transferred to a paediatric intensive care unit for further management.

After stabilisation with mechanical ventilation, intravenous tranexamic acid and blood transfusion, emergency bronchoscopy was performed. It showed diffuse blood stained secretions but could not identify any specific bleeding sites. CT thorax (contrast) revealed patchy consolidations over bilateral upper and lower lobes (Figure 2) but no bronchial artery abnormalities.

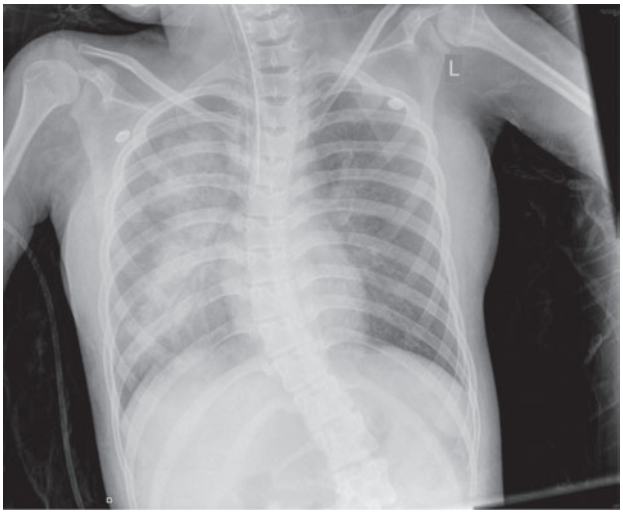

Figure 1. Chest X-ray post-intubation.

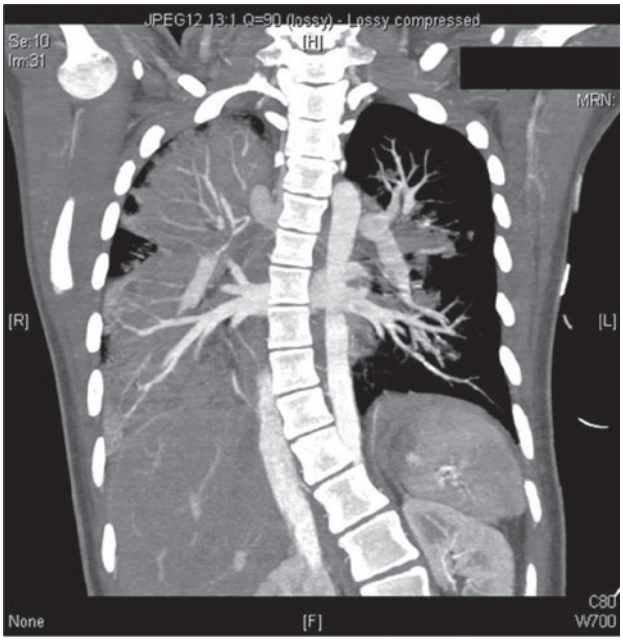

Figure 2. 3D-CT thorax (contrast) in PICU.

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ENT assessment and repeat bronchoscopic examination 2 days later could not locate specific bleeders either. Tracheal aspirate culture, Mantoux test and initial immune screen (antinuclear factor, rheumatoid factor, anti-ds DNA and anti-glomerular basement membrane (GBM) antibodies, immunoglobulin pattern) were all normal. Her haemoptysis stopped and she was extubated on day 4. Her pneumonia also responded well to antibiotics and she was discharged home one week later.

However she was re-admitted 2 months later for recurrent haemoptysis. There was bilateral lower zone haziness on chest X-ray and CT thorax showed diffuse ground glass opacities in both lung fields (Figure 3).

Complete blood counts showed no anaemia (Hb 12.2 g/dL), no thrombocytopenia, normal white cell counts with no eosinophilia. Clotting profile, erythrocyte sedimentation rate, C-reactive protein, renal and liver function, urinalysis were normal. There were haemosiderin-laden macrophages noted in sputum but sputum culture (including tuberculosis, fungus and actinomyces) and cytology were negative. Anti-ds DNA and anti-GBM antibodies, rheumatoid factor, cryoglobulin remained negative and complements were normal. However, antinuclear factor was raised (titre 1:1280, atypical speckled pattern) and antineutrophil cytoplasmic antibodies (ANCA) were positive (anti-proteinase 3=48.8 RU/ml, anti-myeloperoxidase=39.4 RU/ml, normal reference both <20 RU/ml), compatible with ANCA-associated vasculitis (AAV). ENT reassessment showed normal nasal septum and mucosa, clear oropharynx and vocal cords.

She developed pulmonary haemorrhage with respiratory distress again and was unfit for lung biopsy. She was treated with intravenous methylprednisolone followed by oral corticosteroid. Her haemoptysis subsided within a week and she was subsequently commenced on immunosuppressive therapy consisting of oral corticosteroid and methotrexate.[23] ANCA antibody titres decreased gradually and were normalised 4 months later (anti-proteinase 3=18.7 RU/ml, anti-myeloperoxidase= 18.3 RU/ml) while repeat CT thorax also noted interval improvement despite some residual ground glass opacities. At one year follow up, she remained in remission with no further haemoptysis while on maintenance dose of methotrexate and low-dose prednisolone.

Figure 3. CT thorax on readmission.

Patient 2

A 16-year-old boy was admitted at about midnight for fever and haemoptysis. He enjoyed good past health and there was no contact history of known tuberculosis. He developed bouts of vigorous cough abruptly 3 days before admission and had been treated by his private doctor with clarithromycin but with little response. The cough became productive and blood clots were noticed mixed with sputum. There was no dyspnoea, night sweating, malaise, weight loss and other sites of bleeding. He developed fever on the day of admission.

Physical examination noted fever of 39.3°C but vital signs were stable. He had mild tachypnoea (breath rate 22/min) and chest crepitations were heard over left lung base but oxygen saturation remained normal (SpO_2 97%) in room air. There was no finger clubbing, skin rash, supraclavicular or cervical lymphadenopathy. A BCG scar was noted over his left arm. Cardiac, abdominal, neurological, ear, throat and nose examinations were unremarkable.

Blood tests showed normal complete blood counts (WBC $6.8x10^9$/L, Hb 13.9 g/dL, platelet $237x10^9$/L), clotting profile, renal and liver function. Chest X-ray revealed patchy reticulonodular opacities over left upper zone (Figure 4). Sputum was sent for culture, including acid fast bacilli, and Mantoux test planned in the next morning.

He remained stable but suddenly deteriorated 6 hours later, with acute respiratory distress, central cyanosis and massive haemoptysis of about 100 ml fresh blood. Oxygen saturation dropped to 74% and he developed tachycardia (heart rate 142/min) although blood pressure was maintained (157/78 mmHg). Arterial blood

gases showed type II respiratory failure (pH 7.26, pCO_2 7.09 kPa, pO_2 3.33 kPa, base excess -4) and repeat chest X-ray showed bilateral diffuse pulmonary infiltrates (Figure 5).

He was resuscitated with 100% oxygen, endotracheal intubation, intravenous fluid boluses and admitted to intensive care unit (ICU) where he was mechanically ventilated via a double-lumen endotracheal tube (Figure 6).

Emergency bronchoscopy showed blood clots in major airways. Despite clot removal and adrenaline injection, active oozing persisted from left upper lobe bronchus. Urgent left bronchial artery angiogram revealed normal-sized left bronchial artery with no hypertrophy or arteriovenous shunting but a few small pseudoaneurysms were identified. Bleeding was stopped after left bronchial artery embolisation using 300-500 micron contour particles. He was extubated and transferred to paediatric general ward 2 days later. Tracheal aspirate revealed Mycobacterium tuberculosis and he was started on isoniazid, rifampicin, ethambutol and pyrazinamide before discharge on day 7. A total 9-month course of anti-tuberculosis drugs was completed. Recovery was uneventful and there was no recurrence after follow up for 2 years post-treatment.

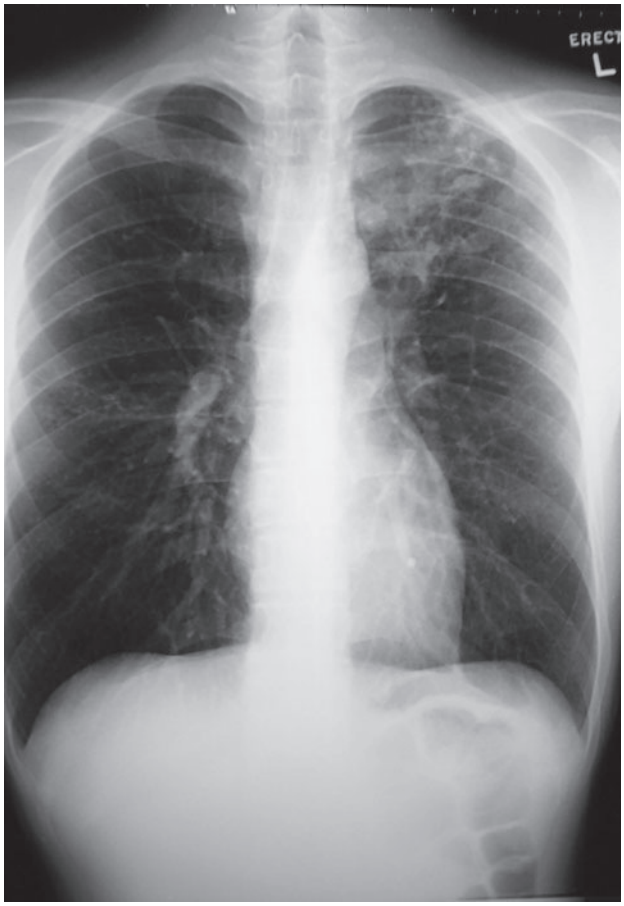

Figure 4. Chest X-ray on admission.

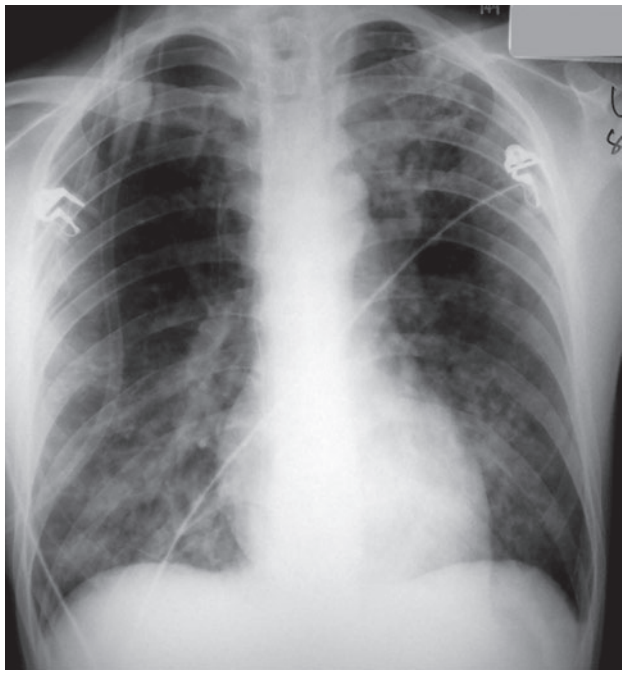

Figure 5. Chest X-ray at deterioration.

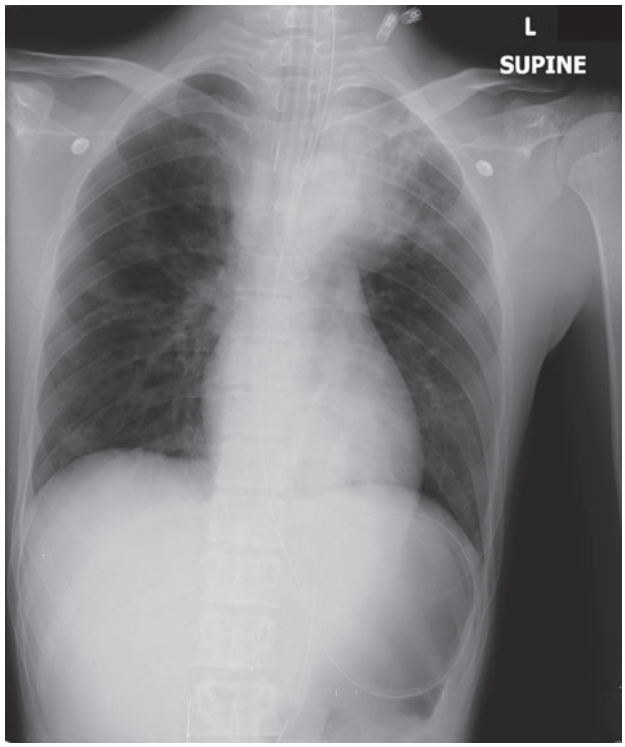

Figure 6. Chest X-ray in ICU.

Patient 3

A 6-year-old girl was admitted for fresh haemoptysis for 3 days following on and off dry cough for 1 month not responding to a course of augmentin. She enjoyed good past health and there was no contact history with known tuberculosis. She had no known food or drug allergy.

Physical examination showed pallor, tachycardia but no fever, rash, petechiae, purpura, ecchymoses or any joint abnormalities. She was not in respiratory distress and chest, cardiac, abdominal and neurological examinations were normal. Her blood pressure was 109/75 mmHg, pulse rate 127/min, respiratory rate 28/min, SpO_2 100% in room air. She passed pinkish urine but there was no dysuria, urinary frequency, frothy urine or loin pain. Chest X-ray showed bilateral pulmonary infiltrates with alveolar-filling opacities (Figure 7).

Blood investigations revealed normal white cell and differential counts, microcytic hypochromic anaemia (Hb 5.5 g/dL, MCV 58.9 fL), thrombocytosis ($613x10^9$/L), no evidence of haemolysis on peripheral blood smear, normal coagulation profile, negative direct antiglobulin test, raised blood urea (35.3 mmol/L) and creatinine (605 umol/L) levels, hyperkalaemia (6.2 mmol/L) with no blood acidaemia, normoglycaemia, elevated C-reactive protein (24.4 mg/L). Electrocardiogram showed sinus tachycardia with tall T-waves. Urinalysis revealed numerous red cells, 2+ white cells, 2+ proteinuria, negative nitrite.

Hyperkalaemia was controlled by resonium and sodium bicarbonate (potassium reduced to 5.8 mmol/L) but haemoptysis continued and renal function kept deteriorating. She was transferred to a tertiary renal centre where haemodialysis was initiated to stabilise her conditions. Immune work-up showed normal complement levels but presence of anti-GBM antibody of 74 (normal <20) RU/ml and anti-myeloperoxidase antibody >200 (normal <20) RU/ml. Goodpasture's syndrome was diagnosed and she was treated with intravenous metylprednisolone, cyclophosphamide and plasmapheresis. Haemoptysis was stopped. Subsequent renal biopsy confirmed Goodpasture's syndrome with cresentic glomerulonephritis. Anti-GBM antibody was cleared up after 11 sessions of plasmapheresis but she was left with chronic renal failure.

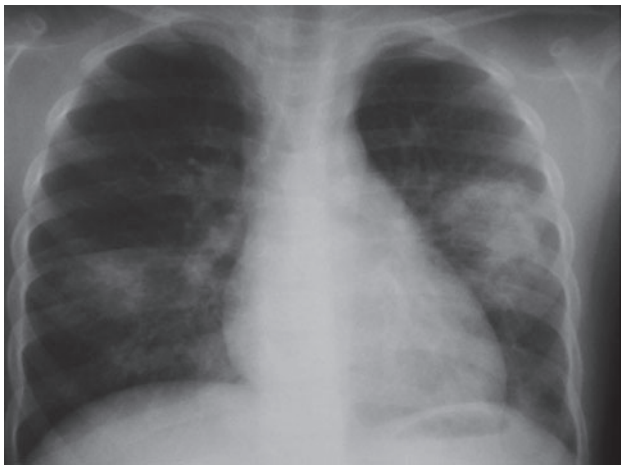

Figure 7. Chest X-ray on admission.

Discussion

Pulmonary haemorrhage refers to extravasation of blood into airways and / or lung parenchyma. Clinical presentation can vary from silent bleeding with respiratory distress and anaemia to massive fatal haemoptysis. The patients we described belonged to the latter category and all illustrated well the acute life-threatening nature on their first presentation which required immediate emergency interventions.

Definition

The definition of massive pulmonary haemorrhage has not been completely agreed upon. In adults, although it is usually defined as >600 ml of expectorated blood in 24 hours, the amount described in the literature varies from 100 to 1000 ml per 24 hours.[1-7] Consensus in the paediatric population is also lacking. Esterly and Oppenheimer have characterised massive pulmonary haemorrhage in newborn as the involvement of at least two pulmonary lobes by confluent foci of extravasated erythrocytes.[8] In a paediatric series, blood loss >400 ml/day was considered as massive haemorrhage.[9] Some authors defined blood loss of 10% of a patient's circulating blood volume into the lungs causing a significant alteration in cardiorespiratory function, regardless of age, as massive bleeding.[10] Others believe in defining it according to body size index or weight of the paediatric patient.[11] Quantification of expectorated blood may be inaccurate and often difficult in children. Using this as defining criteria for massive pulmonary haemorrhage is arbitrary and not practically helpful. From a clinical point of view, haemoptysis that jeopardizes respiratory function and/or causing haemodynamic instability should be treated as a medical emergency.[12] It has been advocated in recent years to

use the term "life-threatening" instead of "massive", which necessitates identification of a specific volume of blood.[13]

Aetiology

Aetiologies for pulmonary haemorrhage in children may be focal or diffuse, idiopathic or associated with an underlying disease (Table 1).[11-12,14] Focal pulmonary haemorrhage is commonly responsible for more profuse bleeding and carries a higher mortality. It is usually associated with congenital anomalies or localised acquired disease and typically affects preschool children but may also occur in infancy. Diffuse pulmonary haemorrhage is usually associated with less total blood loss and can occur from either immune or non-immune mechanisms. It involves bleeding from small pulmonary vessels (capillaries, venules and arterioles) into lung alveoli and can be divided into diseases with and without pulmonary capillaritis.

Diagnosis

Because of the wide range of potential aetiologies, rapid determination of the cause of life-threatening pulmonary haemorrhage is often challenging. Diagnostic approach is directed by clinical history and presentation, but investigations often have to proceed with therapeutic interventions. Initial investigation panel typically includes complete blood count, coagulation profile, renal function tests, autoimmune markers, urinalysis, sputum for culture, acid-fast bacteria and cytology, and Mantoux test. Chest X-ray may reveal an infective cause such as pneumonia or tuberculosis but usually it is insufficient to identify the source of bleeding. CT thorax is a more useful tool in localising the bleeding and planning for embolisation or cardiothoracic surgery. It is important to discuss early with the angiographer or cardiothoracic surgeon about the exact imaging requirement, i.e. plain or contrast, conventional or high-resolution CT. Bronchoscopy may help to determine the exact location of the haemorrhage and broncho-alveolar lavage fluid can be sent for microbiological culture and cytology. Occasionally, a foreign body may be discovered and removed during the procedure. Echocardiography may reveal cardiac causes of pulmonary haemorrhage as well as evaluating pulmonary hypertension. Open lung biopsy may be needed to diagnose vasculitis, Goodpasture's syndrome or other immune-mediated diseases.

Management

General measures

The first priorities in treatment of life-threatening haemoptysis are to maintain the airway, optimise oxygenation and stabilise the haemodynamic

Table 1. Aetiologies of pulmonary haemorrhage

Focal pulmonary haemorrhage
Acute lower respiratory tract infection
Necrotizing pneumonia
Tuberculosis
Lung abscess
Fungal infection – invasive aspergillosis, stacybotryotoxicosis
Parasitic infection – hydatid cyst
Chronic bronchitis
Bronchiectasis (especially cystic fibrosis)
Trauma – foreign body aspiration, lung contusion
Congenital anomalies – lung cyst, sequestration, pulmonary arteriovenous malformation
Neoplasm – angiomas, adenomas
Diffuse pulmonary haemorrhage
Without pulmonary capillaritis
Idiopathic pulmonary haemosiderosis
Pulmonary hypertension
Cardiac diseases associated with congestion
Coagulation disorders, including post – bone marrow transplantation
With pulmonary capillaritis
Goodpasture's syndrome
Systemic lupus erythematosus
Polyarteritis nodosa
Henoch-Schonlein purpura
ANCA-associated vasculitis – Wegener's granulomatosis, microscopic angiitis, Churg-Strauss syndrome

status. General care measures include oxygen supplementation, systemic haemostasis therapy and putting the patient in Trendelenburg position as tolerated (to assist clots to propagate superiorly and exit the airway) or decubitus position (if one is sure of the site of bleeding).

Endotracheal intubation is indicated when there is severe respiratory distress, haemodynamic instability, ongoing haemoptysis, large bleeding volume or poor gas exchange. A large bore single lumen endotracheal tube is recommended until the bleeding is localised, as it is easier to insert, less likely blocked and less difficult for subsequent bronchoscopic examination. In localised persistent bleeding, airway control may be achieved by insertion of a double-lumen endotracheal tube to isolate and ventilate the lungs separately, or by endobronchial tamponade with, for instance, a Fogarty cathether. Our second patient first received a single-lumen endotracheal tube and later, when the bleeding source had been identified, a double-lumen tube was introduced to prevent further soiling of his unaffected side.

Following airway control, mechanical ventilation with positive end-expiratory pressure helps to reverse hypoxaemia and provide a measure of tamponade to the site of haemorrhage. Bronchoscopy can then be introduced for diagnostic purposes as aforementioned and therapeutic interventions to control the bleeding, e.g. iced saline, epinephrine and balloon tamponade. Some would prefer rigid bronchoscopy to flexible as the former provides better scope for suctioning and ventilation of patient.

Specific therapy

Specific treatment depends on the cause and anatomical localisation of haemorrhage. Focal pathologies, congenital anomalies, traumatic causes and foreign bodies require surgical interventions. Treatment of the underlying infection, tuberculosis in our second patient for example, provide definitive cure.

Bleeding from bronchial or other small systemic arteries is treated preferably by selective embolisation, as was performed in our second patient. Success rate reported for immediate control of haemorrhage ranged between 75% and 97%.[12,14-16] Bronchial arteriography for a thorough understanding of bronchial artery anatomy is required before embolisation to avoid potential complications, including transverse myelitis, bowel necrosis, aortic subintimal dissection, bronchial necrosis.

In cases of diffuse pulmonary haemorrhage, most would treat with large doses of corticosteroid until the bleeding is under control, followed by addition of therapeutic regimes of cytotoxic drugs. Plasmapheresis is particularly useful for the group of immune-mediated pulmonary-renal syndromes.

Prognosis

Adequate early management of the cardiorespiratory system is essential to the outcome of life-threatening pulmonary haemorrhage. Aggressive measures to delineate the cause of haemoptysis and prompt therapy are warranted to prevent recurrent bleeding. Long term prognosis depends on the underlying disease.

ANCA-associated vasculitis (AAV)

AAV constitutes a subgroup of disorders affecting small- to medium-sized vessels and includes Wegener granulomatosis, microscopic polyangiitis and Churg-Struass syndrome.[17-20] Immunosuppressive therapies for AAV[21-23] have greatly advanced patient survival but have turned them into chronic, relapsing disorders. There are few reports describing outcome in children[24] but data in an adult collaborative study noted >90% of treated patients achieving remission at 1 year.[25]

Tuberculosis

Outside the western world, tuberculosis remains a major cause of life-threatening haemoptysis both in children[14] and adults,[1,15,16] although bleeding during active pulmonary tuberculosis, as in our second patient, is much less common than those with previous history of pulmonary tuberculosis with or without bronchiectasis.[16] Prognosis is good provided that the initial acute management was prompt and full antituberculosis chemotherapy completed.

Goodpasture's syndrome

Goodpasture's syndrome is one of the pulmonary-renal vasculitic disorders, characterised by diffuse pulmonary haemorrhage and glomerulonephritis. It is associated with autoantibodies to the glomerular and alveolar basement membrane. Treatment is based on plasmapheresis, corticosteroids and cytotoxic drugs[26] but infections are frequent contributors to death. Prognosis depends on the degree of renal impairment. Renal transplantation can be used in patients with end-stage renal failure.[27]

Conclusion

Three patients with life-threatening pulmonary haemorrhage of different aetiologies were presented. Prompt airway management, early provision of PICU care and a systematic diagnostic and management approach have contributed to their survival and successful management of the underlying diseases. There is a need for more paediatric studies on long term outcome and development of evidence based treatment regimes.

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