Fatal pulmonary haemorrhage following adenovirus infection

R A Abeysekera[1], S A M Kularatne[2], E Noordeen[3], N V I Ratnatunga[4], J M R P Bandara[1]

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Introduction

Adenoviruses (AdVs) are non-enveloped, double-stranded DNA viruses that vary in size from 70 to 100 nm. AdV infections commonly affect infants and children aged around 5 months to 6 years [1]. They are common pathogens of respiratory and gastrointestinal tracts, urethral canal and eyes characterised by self-limiting infection although fatal infections can occur in the immuno-compromised and occasionally in healthy children and adults [2].

Human AdVs belong to the genus *Mastadenovirus*, which include 51 serotypes. AdV serotypes 4 and 7 have caused outbreaks of febrile respiratory illness in young adults in a basic military training setting [no references given]. AdVs infections commonly give rise to a self limiting upper respiratory tract infection but there have been several cases of severe pneumonia with pulmonary haemorrhages reported in the literature. However, there are no reports available on cases with AdV associated pneumonia with pulmonary haemorrhage in Sri Lanka. We report a case of severe AdV pneumonia with diffuse pulmonary haemorrhages which lead to the death of a young boy.

Case report

A 14-year old boy with a known history of mild mitral valve prolapse (MVP) and mild mitral regurgitation (MR) came to the hospital with a history of fever for 5 days duration. With the onset of fever he has had coryza but had been fit enough to attend school. Since the 5th day morning (day of admission) he had felt shortness of breath and had developed a cough with intermittent mild haemoptysis. There were no other bleeding manifestations. He had no chest pain, diarrhoea, dysuria, joint pains, myalgia and no history suggestive of a connective tissue disorder such as oral ulcers, skin rashes or hair loss. There had been no exposure to leptospirosis in the recent past.

On admission he was severely dyspnoeic, ill, drowsy with a Glasgow coma scale (GCS) of 13/15, febrile and pale but not icteric. There were no conjunctival haemorrhages, myalgia or any other obvious bleeding. He was breathing at a rate of 48 breaths per minute with bilateral diffuse coarse crepitations and a pulse oxymeter saturation of 65% in room air. Blood pressure was 130/ 80 mmHg and pulse rate was and 110 beats per minute. Abdominal examination was clinically normal.

He was intubated and admitted to the intensive care unit for ventilation. Upon intubation blood started coming continuously from the endotracheal tube. Saturation only improved only up to 82% with 100% oxygen. Intravenous broad spectrum antibiotics (levofloxacin, clarythromycin) and antiviral treatment with oseltamivir was initiated and blood transfusion started. Fresh frozen plasma (FFP), intravenous vitamin K, tranexemic acid and platelets were given.

Initial investigations showed Hb 8g/dl, total white cell count of 13×10^6 /µl with 88% neutrophils, 12% lympohcytes and a platelet count of 310×10^6/µl. ESR was 50 mm/1st hour and CRP 179 mg/dl. Coagulation profile was normal. Serum electrolytes showed Na of 148 mmol/l and K 4.8 mmol/l and urea was 9 mg/dl. Urine analysis was normal. Chest x-ray showed bilateral diffuse opacities which were consistent with diffuse pulmonary haemorrhages. Abdominal ultrasonography was normal. Despite treatment the bleeding did not stop and three hours after admission the patient had a cardiac arrest.

The post mortem examination showed diffuse bilateral pulmonary haemorrhages. Other organs were normal. There was no evidence of a pulmonary AV malformation or any other lesion which could have caused bleeding. Blood, urine and tracheal cultures had no growth. Nasal and tracheal swabs for influenza A virus subtype H1N1 was negative. Leptospiral antibodies and anti nuclear antibody were also negative. Histology of lungs showed diffuse pulmonary haemorrhages with characteristic smudge cells (Figure 1). Kidneys showed interstitial nephritis, but the rest of the organs were normal and no histological features of vasculitis were found. Immunofluorescence staining of the tracheal aspirate for AdV antigen showed apple green fluorescence, confirming the diagnosis of severe AdV pneumonia with diffuse pulmonary haemorrhages.

[1]*Teaching Hospital, Peradeniya and Departments of* [2]*Medicine,* [3]*Microbiology and* [4]*Pathology, Faculty of Medicine, University of Peradeniya, Sri Lanka.*

Correspondence: RAA, *e-mail: <rajithaasa5@hotmail.com>.* *Received 15 November 2012 and revised version accepted 15 December 2012. Competing interests: none declared.*

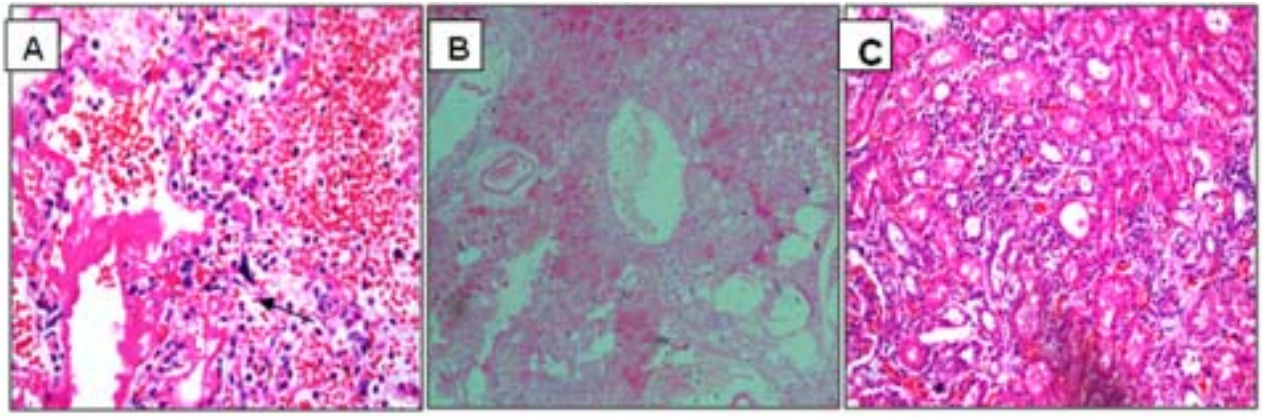

Figure 1. **Histopathological appearance of lungs and kidney.**

A. Lung – The alveolar spaces are filled with blood, neutrophils and fibrin. A smudge cell characteristic of adenoviral infection is seen in the centre. Hyaline membranes are also noted (H & E × 400).

B. Lung – A bronchiole is seen in the centre. The bronchiolar mucosa is completely necrosed. Extensive haemorrhage is seen in the surrounding lung tissue (H & E × 40).

C. Kidney – Interstitial nephritis shows lymphocytes, eosinophils and neutrophils (H & E × 200).

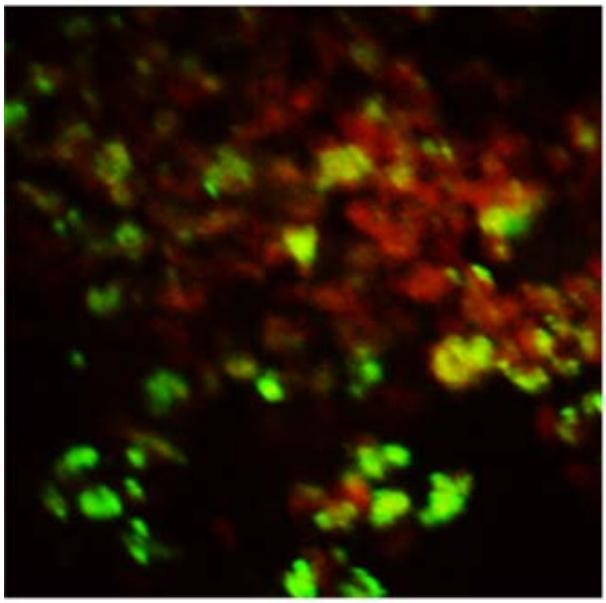

Figure 2. **AdV antigen in the tracheal aspirate of the subject.**

Detection of adenovirus antigens in the tracheal washings of the patient by immuno-fluorescence assay. Apple green fluorescence indication the presence of adenovirus antigen as detected by the monoclonal antibodies directed against adenovirus antigens.

Discussion

There are only a few reported cases of severe AdV pneumonia causing diffuse pulmonary haemorrhages [2,3,4,5]. This boy who had only a small, non significant cardiac abnormality prior to the illness did not recover despite treatment due to the severity of the infection. All other possible causes which could have given rise to a similar clinical picture were ruled out with appropriate investigations and AdV antigen was detected on immuno-fluorescence assay followed by fluorescence microscopy.

The clinical pathogenicity differs among different AdV serotypes. Fifty one serotypes of human AdVs are classified into six subgenera (subgenera A to F) on the basis of erythrocyte coagulation characteristics, oncogenicity and DNA sequence [1]. Respiratory illness is mainly caused by AdVs serotype 3, 4, 7, 14, 21, and to a less extent by serotypes 1, 2, 5 and 6 [6]. Paediatric pneumonia is mainly caused by AdVs serotypes 1, 2, 3 and 7, whereas serotypes 4 and 7 are mainly responsible for adult pneumonia. Due to the limited viral characterisation facilities the exact serotype of AdV could not be identified in this boy but immunofluorescence reliably identified the AdV antigen.

Currently only symptom based treatment and supportive therapy are available for AdV infections and clinically useful antiviral therapy is not yet available. Ribavirin and cidofovir have activity *in vitro* against certain AdVs but definitive efficacy has not been shown in trials. Hence, hand hygiene and respiratory prevention are the key to avoid severe AdV infections.

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Acquired pure red cell aplasia due to anti-erythropoietin antibodies in a patient with end stage chronic kidney disease

H M S Senanayake[1], K Thirumavalavan[1], M N Gunasekara[2], V Ratnamalala[2]

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Introduction

Anaemia is a common problem in end stage kidney disease. Recombinant human erythropoietin (rHuEPO) is commonly used in management of such patients to maintain optimal hemoglobin levels and to minimise transfusion requirements. Acquired pure red cell aplasia (PRCA) is a rare complication of erythropoietin therapy due to development of anti-erythropoietin antibodies (anti-EPOabs). We report a patient with end stage kidney disease who developed pure red cell aplasia following rHuEPO treatment.

Case report

A 57-year old man with end stage kidney disease due to diabetic nephropathy, presented with fatigue and exertional breathlessness worsening over six weeks duration. He was on subcutaneous injections of rHuEPO (EPIAO® – Shenyang sunshine pharmaceutical co. China,) 4000 units biweekly over one year for anaemia associated with chronic renal failure. He had never been transfused with red cells. On examination he was pale and his hemoglobin level was 3.9 g/dl. His white cell and platelet counts were normal. Blood film showed normochromic normocytic red cells. The hemoglobin level was maintained around 10 g/dl with above rHuEPO dose until two months back when it dropped rapidly. Figure 1 shows variation of the hemoglobin level with time.

The reticulocyte count was very low (2760/ mm^3) and serum ferritin was elevated (571.4 ng/ml). Bone marrow aspiration biopsy showed markedly suppressed erythropoiesis with absent normoblasts and proerythroblasts (Figure 2). Granulocytic and megakaryocytic elements were normal. Anti-erythropoietin antibodies (56.6% – normal up to 4.7% binding) were detected by radioimmunoprecipitation (RIPA) assay. A diagnosis of acquired pure red cell aplasia due to anti-EPOabs was made. Recombinant erythropoietin therapy was discontinued. Patient was given packed red cell transfusions and started on immunosuppressive therapy with prednisolone 1 mg/ kg/ daily. After six weeks of steroid therapy the reticulocyte count rose to 5400/ mm^3. Currently he is on regular follow up with top up blood transfusions and is undergoing preliminary investigations for kidney transplantation.

[1]*Medical Unit and* [2]*Department of Hematology, North-Colombo Teaching Hospital, Ragama, Sri Lanka.*

Correspondence: HMSS, *e-mail: <hemal_@live.com>.* *Received 9 August and revised version accepted 17 November 2012. Competing interests: none declared.*