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Diffuse alveolar hemorrhage – point of view by an ICU specialist and by a pediatrician

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Abstract: Although by definition rare diseases are rare, taken all together they represent sufficient part of difficult to diagnose and treat cases. Diffuse alveolar hemorrhage is such rare yet serious medical emergency that often results in acute respiratory failure and death. The lung can be affected by systemic disease in different ways and every organ involvement or specific therapy could lead to life-threatening lung complications. We present two cases of patients with diffuse alveolar hemorrhage one in a pediatric department and the other one in ICU. Both cases despite respiratory symptoms had other organs involved. The specialists need to be aware that multisystem diseases may present initially with respiratory signs and symptoms. The correct diagnosis is crucial for prevention of life-threatening complications and for appropriate emergency treatment.

Keywords: diffuse alveolar hemorrhage, glomerulonephritis, autoimmune disesases

INTRODUCTION

Diffuse alveolar hemorrhage (DAH) is a rare yet serious medical emergency that often results in acute respiratory failure and death. The classical triad of DAH includes hemoptysis, anemia and alveolar infiltrates, seen as diffuse opacities on chest X-ray[1]. The symptoms characteristic like hemoptysis or non-specific as cough and dyspnea can be subtle escalating slowly day by day or be with rapid acute presentation[2]. In a presence of massive hemorrhage there is a risk for respiratory failure resulting[3,4] in mortality increase to 20% .

DAH may be result from lung injury due to coagulation disorders, inhaled toxins, or infections. Many cases demonstrate capillaritis - neutrophilic inflammation of the alveolar interstitium, most of the times associated with systemic autoimmune diseases, either through injury to the capillary basement membrane by specific autoantibody or through deposition of immune complexes[5].

There are two steps to the diagnosis of DAH: identification of DAH and identification of its underlying cause. Both are essential, because the prompt therapy increases the chances for survival. Due to the rarity of the condition the management universally is mainly empiric based on small case series[6].

By showing two different cases we present the point of view of intensive care specialist and pediatrician in attempt to help in providing those specialists with a rational approach to cases with DAH.

Clinical cases: *First case* is a 17-year old girl with hazardous behavior (heavy alcohol, joint and cigarette abuser for more than 4 years with promiscuous behavior) admitted in the clinic with history for hemoptysis up to 30 ml daily and exercise intolerance since 4 months ago. On a chest X-ray alveolar opacities in both lower lobes could be seen (**Fig**. 1).

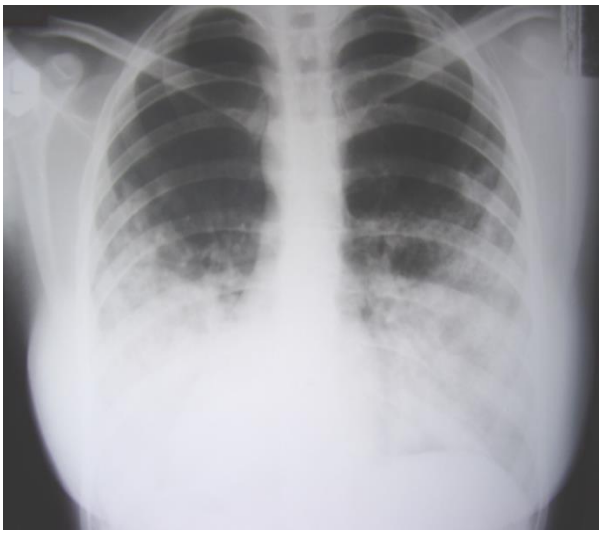


Figure 1: X-ray of the patient at the admission

Inflammatory cases account 80-90% of hemoptysis cases in this age, so possible infection or hemosiderosis (due to characteristic X-ray changes), were considered as leading diagnosis. The girl's past

medical history was not remarkable – recurrent upper airway infections up until the age of 2 with known polyallergy to antibiotics (Biseptol, Doxycyclin, Ampicillin, Chloramphenicol). At admission the patient was with normal body temperature and basic life parameters. The only abnormalities found were pale skin and slight dullness on percussion and diminished breath sounds in the bases of the lungs, no rales or roncchi were heard.

From the initial laboratory results notable was mildly elevated WBC count (12 700 /mm3, with leftward shift) and low borderline haemoglobin level (11,2 g/dl). Blood gas analysis revealed hypoxemia with hypocapnia with $SatO_2$ – 87,5%. Biochemistry - normal (liver and kidney function). Low iron level with high iron binding capacity was seen. Serologic investigation for Mycoplasma pneumoniae, Chlamydia pneumoniae, Aspergilosis, HIV, HBV and HCV were negative, as well as screening for tuberculosis. Sputum sample microbiology culture was negative. The urine analysis was normal. There were no abnormalities in immunoglobulin levels and complement fractions.

While waiting all the test results an antibiotic treatment with Clarythromycin and supportive care was initiated for suspected pneumonia. With repeated analysis we found hemosiderin-laden macrophages on sputum cytology and performed a bronchoscopy with lavage and biopsy confirming alveolar haemorrhages (**Fig.2**)

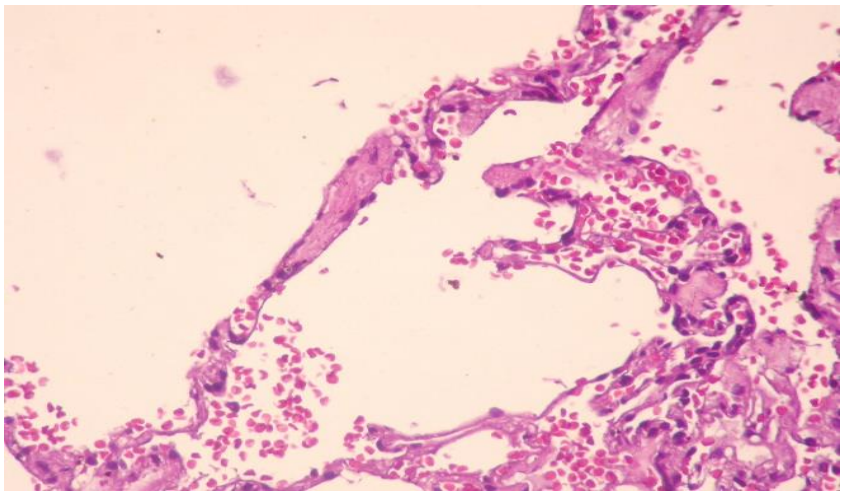


Fig. 2 lung biopsy from the patient

Having been assured there is no immunodeficiency or other serious infection with confirmed presence of DAH and leading diagnosis of pulmonary hemosiderosis we initiated corticosteroid therapy per protocol. On the second day a sudden deterioration occurred with a massive hemoptysis (over 200 ml/day), the girl collapsed there was drop in haemoglobin level (Hb - 7,8g/dl), hematuria (it was the first day of her regular cycle) and worsening in X-ray changes. The patient became oxygen-dependant, required blood transfusion and intensified therapy.

We extended the test with panel for autoimmune disease: ANA – negative, Anti-ds DNA – negative, pANCA – 1:128 (slightly positive), cANCA –negative, CIC – negative, ***Anti-GBM antibodies strongly positive.*** Suspecting Goodpasture's disease we performed kidney biopsy: the basal membranes of the

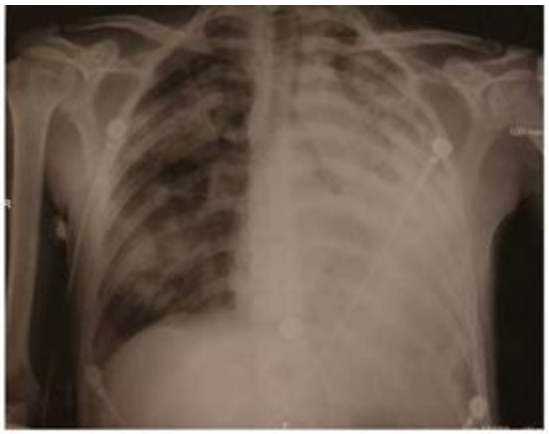
glomerular cappiliaries are thickened; in some tubules erythrocyte and protein cylinders are present; extraglomerular interstitium and vessels are with preserved structure; immunofluorescence testing showed linear deposition of IgG along the glomerular basement membrane.

The treatment was modified with corticosteroids in initial dose 2 mg/kg for 1 month, tapered weekly to 20 mg/d for 8 months and Cyclophosphamide – 2 mg/kg for 3 months. Six months after treatment the girl is in good health, normal renal function and chest radiograph showing fine interstitial changes in the right base of the lungs and she is in a clinic for substance abuse treatment

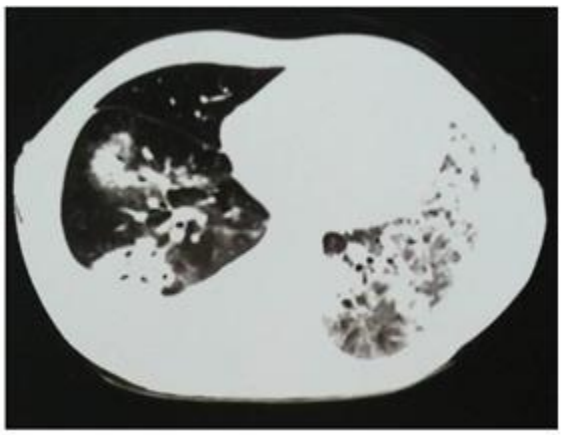
Second case is a 26 year old male admitted in the ICU for severe hemoptysis and acute respiratory and renal failure. From the past history it was noted that the patient was treated for pneumonia a month ago and he had joint swelling and episcleritis 6 months ago treated with different symptomatic medication without significant improvement. Two days after the admission the patient developed neurologic manifestations, which involved general seizures.

From the laboratory results notable was very low haemoglobin level (44 g/dl), markers for inflammation (elevated CRP, elevated WBC and platelets) for renal failure (elevated creatinine, BUN and potassium, proteinuria). Blood gas analysis revealed severe respiratory acidosis. Liver biochemistry - normal. From autoimmune disease screening notable was extremely elevated cANCA - confirming the diagnosis of granulomatosis with polyangiitis (GPA) previously known as Wegner's granulomatosis.

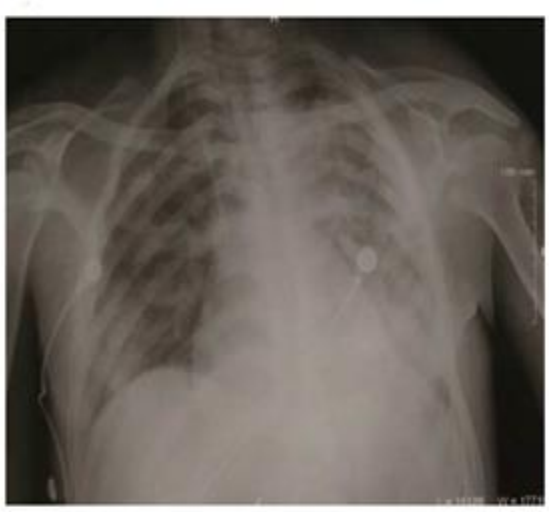
The imaging data of the lungs (**Fig 3**) revealed diffuse nodular inflammatory affection of all the left lung segments, as well as of some of the right subsegments. In the right pleural cavity and the interlobar pleura between the right lower and middle lobes an effusion of 400-500 cc. Bilateral broncho-pulmonary lymphadenomegaly – more severe to the left. Partialy reduced volume of left lung and mediastinal shift. In the follow up there was collapse of all the three right lung lobes and hydropneumothorax of 1000 cc in the right. All mediastinal structures are shifted in the left.



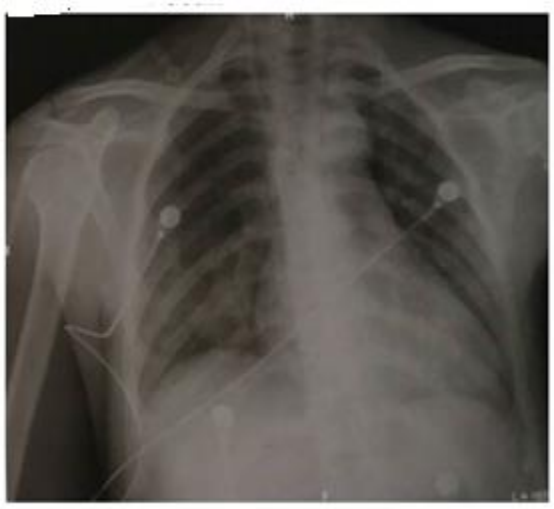
(a). Day 1- X ray



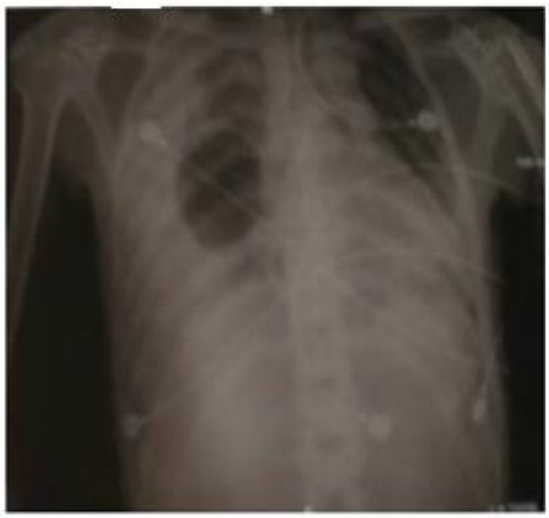
(b). Day 1-CT Scan



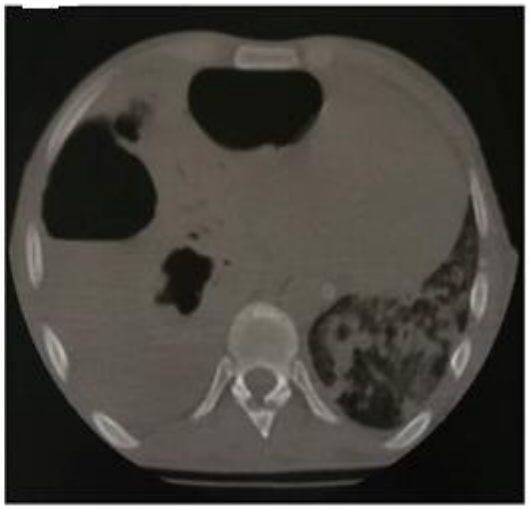
(c). 07- X ray



(d). Day 14- X ray



(e).Day 28- X ray



(f). Day 28-CT Scan

Fig 3(a-e): X ray and CT Scan Imaging studies of the lung in the patient

The head CT initially (**Fig 4A**) showed six different in shape low density zones on the convexity of both brain hemispheres. These observations imply small meningeal implants, which cause massive perifocal vascular edema. The last CT (**Fig 4B**) showed diffuse brain edema more distinguished in the left occipital brain lobe. In the same zone can be vizualized a recent oval haemorrhage, 40 mm x 20 mm x 20 mm in size with capacity of 15-20 cc.

Despite the aggressive polytherapy (antibiotics, antimicotics, H2-blockers, anticoagulants, salt and glucose solutions, bioproducts, parenteral nutrition, diuretics, anticonvulstants, hepatoprotectors, catecholamines, cytostatic and steroid therapy the patient died on the 28th day after admission.

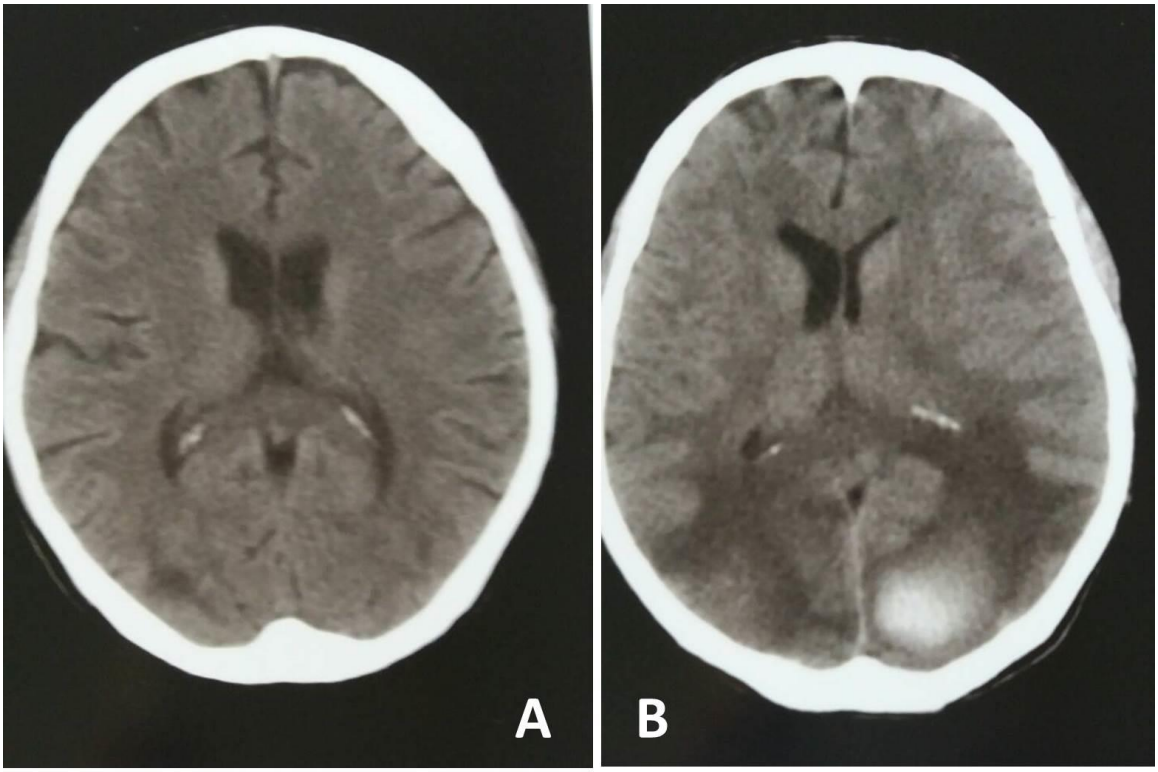


Fig.4: CT of the brain of the patient

DISCUSSION

Unlike the more common forms of pulmonary hemorrhage that result from focal lesions (e.g., necrotizing pneumonia, bronchitis, bronchiectasis, malignancy, pulmonary infarction, arteriovenous malformation), DAH affects the majority of the alveolar capillary surface. DAH represents a medical emergency, and clinicians must have a quick and proper management in order to save the affected person's life. It is defined by the triad of hemoptysis, anemia and diffuse alveolar infiltrates clinically could be presented with the extended range from nonspecific symptoms like slight cough through progressive dyspnea, chest pain to severe hemoptysis [Collard HR, 2004]. These symptoms however don`t have to occur simultaneously and the absence of classic features does not exclude DAH[7]. In up to 33% of cases, hemoptysis is initially absent. In the literature there have been described cases with fulminant course with fatal end (like in our second case) or other ones with slow progression.

In the diagnostic process very careful attention to the medical history and physical examination directed towards possible associated condition (e.g., systemic vasculitis, connective tissue disease, anticoagulant medications, trauma) is essential. Usually the lung examination is nonspecific, sometimes with inspiratory crackles common but not universal. There may also be physical findings suggesting a systemic disease – when other organ is involved.

The combination with renal failure can occur in certain collagen vascular diseases (eg. SLE, rheumatoid arthritis), mycroscopic polyartheritis, idiopathic rapidly progressive glomerulonephrytis, Wegener's granulomathosis, and essential mixed cryoglobulinemia.

The initial studies should include an imaging study of the chest, complete blood count, and examination of the urine sediment. Specific targeted laboratory evaluation often suggests the underlying cause. If we suspect DAH, bronchoscopy should be performed as soon as possible. Sequential bronchoalveolar lavage (BAL) specimens for cell count and differential (looking for an increasing red blood cell count) and for quantitative scoring of the hemosiderin concentration in alveolar macrophages[8] are consistent with the diagnosis. BAL serves to rule out other diagnostic considerations such as infection, acute hypersensitivity pneumonitis, acute eosinophilic pneumonia, and pulmonary alveolar proteinosis. In patients with evidence of DAH and renal involvement, kidney biopsy should be considered to identify the underlying cause and help direct therapy.

After confirming the diagnosis of DAH the second step is identification of its underlying cause. Travis et al in a retrospective review of 34 cases of diffuse alveolar hemorrhage found systemic vasculitis to be the most common cause in 41% (14 cases: 5 definite granulomatosis with polyangiitis (Wegener granulomatosis), 6 probable, and 3 unclassifiable), followed by unclassifiable pulmonary renal syndromes – 14% (5 cases), Goodpasture syndrome 12% (ABMA disease) (4 cases), idiopathic pulmonary hemorrhage (IPH) (4 cases) 12%, connective tissue disease 12% (4 cases: 2 systemic lupus erythematosus, 1 rheumatoid arthritis, 1 juvenile rheumatoid arthritis), and other rare causes 9% (3 cases: 2 idiopathic glomerulonephropathy, 1 immunoglobulin A nephropathy)[9]

The most common causes of DAH include:

1. **Vasculitis**: granulomatosis with polyangiitis (Wegener granulomatosis), microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), isolated pulmonary capillaritis, mixed cryoglobulinemia, behçet syndrome, Henoch-Schönlein purpura, pauci-immune glomerulonephritis, antiphospholipid antibody syndrome
2. **Immunologic:** Goodpasture syndrome (ABMA disease), connective tissue disease associated, immune complex–associated glomerulonephritis, acute pulmonary allograft rejection, celiac disease, immunodeficiency,bone marrow transplantation, behcet syndrome, cryoglobulinemia, Antiphospholipid antibody syndrome
3. **Coagulation Disorders**:
4. **Idiopathic Pulmonary Hemosiderosis:** (a diagnosis of exclusion, the biopsy shows evidence of acute, subacute, and chronic bland diffuse alveolar hemorrhage and no evidence of vasculitis.)
5. **Acute Idiopathic Pulmonary Hemorrhage Of Infancy:** (an illness in a previously healthy infant (< 1 year) with a gestational age of >32 weeks, no history of neonatal medical problems that might cause pulmonary haemorrhage, and whose illness is consistent with the following criteria: (a) Abrupt or sudden onset of overt bleeding or frank evidence of blood in the airway; (b) Severe presentation leading to acute respiratory distress or respiratory failure resulting in hospitalisation in a paediatric intensive care unit with intubation and mechanical ventilation; (c) Diffuse, bilateral pulmonary infiltrates on a chest radiograph or computed tomography of the chest.)

6. **Other Causes** - drugs/toxins (such as trimellitic anhydride, insecticides, and pesticides, anticoagulant, D-penicillamine, nitrofurantoin, amiodarone, propylthiouracil, cocaine, orsirolimus), diffuse alveolar damage, mitral stenosis, pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis , lymphangioleiomyomatosis, tuberous sclerosis, Heiner syndrome, infanticide/child abuse

7. **Diffuse Infiltrative Lung Diseases**

The presence of proteinuria and an abnormal urinary sediment (red blood cells and red blood cell casts) suggests an underlying glomerulonephritis consistent with the diagnosis of systemic vasculitis, Goodpasture syndrome, some connective tissue diseases, or rarely infection. Vasculitis is associated with the presence of antineutrophil cytoplasmic antibodies (ANCAs) directed against either proteinase 3 (cytoplasmic ANCA [c- glomerulonephritis, Churg-Strauss syndrome, and sometimes isolated pulmonary capillaritis[10].

The diagnosis of Goodpasture syndrome is established by the ANCA]) or myeloperoxidase (perinuclear ANCA [p-ANCA])[11]. Elevation of the c-ANCA is seen in Wegener granulomatosis, whereas elevated p-ANCA is a marker for microscopic polyangiitis, pauci-immune presence of serum antiglomerular basement membrane antibodies (ABMA). DAH due to SLE is accompanied by reduced serum complement levels as well as the presence of antinuclear and native anti-DNA (ANA) antibodies in the serum. Characteristic for Henoch-Schönlein purpura is the formation of immunoglobulin A (IgA) immune complexes present in the circulation and also bound to tissue[12].

Here it is an algorithm to follow after establishing the diagnosis of DAH.

If there is obvious reason (or known underlying condition) an etiological treatment should be initiated/continued. In cases without obvious reason beside physical examination, heart echography and complete blood count, coagulation status, creatinine, brain natriuric peptide, urine analysis, ANA, ANCA, ABMA tests should be done. If the test results are sufficient for identifying non-immune cause an etiological therapy should be prescribed. In cases where the tests suggest immune cause we should screen for renal, neurological, dermatological and ear-nose-throat involvement and relevant biopsy should be performed. In cases where the tests are inconclusive it is possible to repeat them and schedule a lung biopsy.

If this diagnostic workup is unremarkable, there are several more differential diagnosis:

1. Antiphospholipid syndrome with vasculitis and / or pulmonary embolism

2. Mixed connective tissue diseases (systemic sclerosis, polymyositis)

3. Thrombotic thrombocytopenic purpura.

4. Infectious diseases involving kidney and lung (e.g Hanta-virus, cytomegalie-virus, Legionella, Mycoplasma, Leptospirosis, tuberculosis, sepsis)

Specific for ICU

A significant number of patients with DAH deteriorate rapidly and present with life threatening respiratory failure requiring admission to ICU. Their management represents a major challenge as

mortality is of the order of 25-50%. In the majority of patients admitted to ICU the diagnosis is already known[13,14]. Diagnosis of DAH in the ICU can be challenging. There is considerable overlap with other common ICU presentations such as sepsis and cardiorespiratory compromise. Even in severely unwell patients haemoptysis is frequently absent despite radiological suggestion of DAH. Distinguishing vasculitis from infection in the ICU setting is essential. Persistently negative microbiological samples, in the context of an inflammatory illness, make the presence of vasculitis more likely.

Therapy for DAH consists of treating both the autoimmune destruction of the alveolar capillary membrane and the underlying condition. For all cases of acute onset the therapeutic objectives should be stabilization and suppression of active disease. Positive end-expiratory pressure during mechanical ventilation may produce a tamponade effect to limit capillary bleeding. Severe hemorrhage or hemorrhage associated with hemodynamic instability may require transfusion of packed red blood cells. Corticosteroids and immunosuppressive agents (cyclophosphamide, mycophenolate mofetil, azathioprine) are the gold standard therapy for underlying conditions. In patients with pulmonary-renal syndrome, therapy should be started as soon as possible to prevent irreversible renal failure.

Plasmapheresis is indicated for DAH associated with Goodpasture syndrome or with other vasculitic processes in which the titers of pathogenetic immunoglobulins and immune complexes are very high. Recombinant-activated human factor VII seems to be a promising new therapy, although further evaluation is needed[15].

Intensive care unit specific management for these patients includes: minimizing the risk of sepsis; careful monitoring for bone marrow suppression and superadded infection; lung protective ventilation, as used in the management of ARDS, with tidal volumes of 6 ml/kg and inspiratory plateau pressures below 30 cmH2O with permissive hypercapnia may reduce lung injury; cardio- and kidney support and protection[5] [16].

SPECIFIC FOR PEDIATRIC

Specific for neonatal age is a pulmonary haemorrhage that could occur in preterm infants secondary to severe pulmonary oedema in association with respiratory distress syndrome and patent ductus arteriosus. Neonatal pulmonary haemorrhage has also been associated with the administration of exogenous surfactant. Other predisposing factors include birth asphyxia, excessive fluid administration, hypoglycaemia, coagulation defects, intercurrent infection, hypothermia and cardiac failure. Treatment includes the use of high levels of positive end-expiratory pressure (PEEP), replacement of blood loss but with overall fluid restriction and correction of coagulation deficiencies. If there is an associated patent ductus arteriosus then this should be closed as soon as possible.

Beside that unique for pediatric patients entities that could present with DAH are acute idiopathic pulmonary hemorrhage (AIPH) of infancy and controversy Heiner syndrome is a unique form of DAH in infants who present acutely with respiratory failure. Early reports linking AIPH to mycotoxins from Stachybotrys chartarum have not been substantiated, and the true cause of AIPH remains unknown. [17][Montana E,1997] Skeptics also doubt the existence of Heiner syndrome[6].

Because these disorders are quite rare in children, there is very little evidence to support the management and treatment options recommended. Treatment options are based to some extent on adult studies[18].

CONCLUSION

Pulmonary hemorrhage though rare, can be potentially fatal and may also lead to long term morbidities. The management depends on the type and severity of bleeding, the age of the patient and also underlying etiology.

Although diffuse alveolar hemorrhage can have various causes the most common causes are autoimmune disorders. Usually symptoms, signs, and chest-x-ray findings are not specific. For confirming DAH a BAL showing persistent hemorrhage with sequential lavage samples is required.

Two way management is needed maintaining the vital functions with minimizing the possible complications and treatment of the underlying cause. The specialists need to be aware that multisystem diseases that may present initially with only non-specific signs and symptoms involving one organ. The correct diagnosis is crucial for prevention of life-threatening complications and for appropriate emergency treatment.

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