CASE REPORT

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Diffuse alveolar haemorrhage – case report and literature review

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Abstract

Diffuse alveolar haemorrhage (DAH) is a pulmonary disease where bleeding into alveoli via damaged basement membrane causes respiratory failure. Clinical manifestations are: anaemia, haemoptysis, dyspnea, fever and hypoxic respiratory failure. The origin can be immune-mediated or non-immune-mediated. Auto-immune causes of DAH are considered more serious prognostically. Vasculitis is the most common cause. To decrease mortality DAH needs to be recognized early and requires prompt treatment. Despite major mortality, treatment options are only empirical. One of them is treatment with steroids combined with rituximab/cyclophosphamide. In the most severe cases, plasma exchange therapy, mechanical ventilation or veno-venous extracorporal membrane oxygenation (vv-ECMO) are used. Diffuse alveolar bleeding should be differentiated from coagulophaty, cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), allergic alveolitis, and acute respiratory distress syndrome (ARDS).

Key words

diffuse alveolar haemorrhage, hypoxic respiratory failure, vv-ECMO

INTRODUCTION

Diffuse alveolar haemorrhage (DAH) is a life-threatening pulmonary disease where bleeding into alveoli via damaged basement membrane causes respiratory failure [1–3]. To decrease mortality it needs to be recognized early and requires prompt treatment [4,5]. Clinical manifestations of this condition are: anaemia, haemoptysis, dyspnea, fever and hypoxic respiratory failure [3,4,6]. Symptoms rapidly develop within hours or days [3]. This condition has various origins. It can be immune-mediated or non-immune-mediated. Immune causes are 30–40% of all cases [7,8]. Many systemic diseases can cause DAH, but the pathogenesis is unclear. Vasculitis is the most common cause (more often anti-neutrophil cytoplasmic antibody-vasculitis [ANCA-vasculitis]) with others, such as: systemic lupus erythematosus (SLE), inflammatory myopathies, Henoch-Schönlein purpura, Anti-GBM antibody syndrome, also being frequent [3, 4, 9, 10]. Among the factors causing non-immune DAH are: *Pseudomonas aeruginosa, Aspergillus spp., Cytomegalovirus* infections, haematopoietic stem cell transplantation, mitral stenosis, pulmonary hypertension or other cardiovascular diseases [10].

Despite major mortality, treatment options are only empirical. One of them is treatment with steroids combined with rituximab/cyclophosphamide. In the most severe cases, plasma exchange therapy, mechanical ventilation or veno-venous extracorporeal membrane oxygenation (vv-ECMO) are used [8]. An important aspect of treatment is maintaining the proper level of haemostasis. Platelet transfusions, vitamin K supplementation, cryoprecipitates, fresh frozen plasma (FFP) and tranexamic acid (TXA) have been used for this purpose [10].

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CASE REPORT

The case is presented of a 36-year-old female with severe respiratory failure, secondary to alveolar bleeding. The patient was not under treatment for any chronic diseases and did not take any medications or stimulants. The patient came to the District Hospital with a fever of 39 degrees Celsius, cough and haemoptysis. Symptoms appeared two days before the start of hospitalization. A test for influenza and RSV infection was performed, but was negative. After being admitted to hospital, the patient's condition deteriorated, and soon required mechanical ventilation. Blood was taken for laboratory tests and anaemia was confirmed (haemoglobin level 7 mg/dl) and a positive ANCA result. The patient was transferred to the Intensive Care Unit to be treated with vv-ECMO (blood flow (BF) -3,5 l/min, sweep gas – 6 l/min) (Tab. 1). Her condition was serious. The projectional radiography image of the chest on admission (Fig. 1) showed blotchy, inflammatory parenchymal densities in both lung fields, which became more and more fused as the disease progressed. She was

Table 1. vv-ECMO parameters

Days of treatment	Blood flow [l/min]	Sweep gas [l/min]
1–2	3.5	6
3	3.5	7
4	Changed from 3.5 to 3	5 to 3
5	3	6
6	3	0

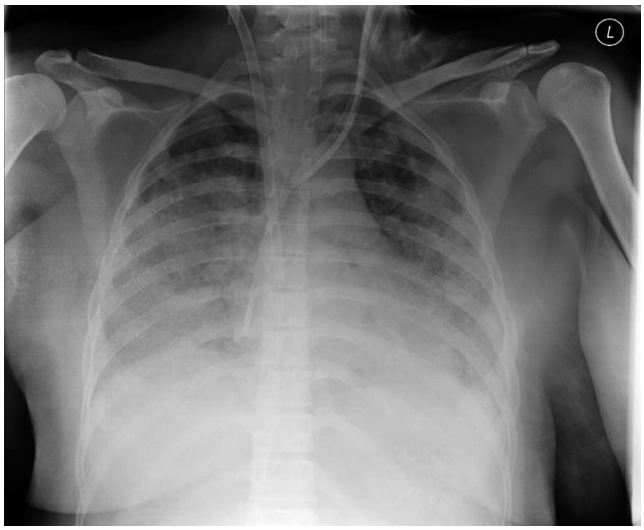

Figure 1. Chest X-ray on admission

mechanically ventilated, anaemic, and bloody mucus was aspirated from the bronchial tree. The patient woman was undergoing ultra-lung-protective ventilation (duo positive airway pressure [DUOPAP] mode 15/30 flow – 15/min, tidal volume [TV] – 250 ml, fraction of inspired oxygen [FiO_2] -0,4) (Tab. 2) with adequate analgosedation with fentanyl, midazolam and propofol and rocuronium bromide-induced muscle relaxation, that was discontinued on the next day. Circulatory system required supply of catecholamines.

On admission day, plasmapheresis was performed to remove the autoantibodies. It was continued every 2 days, with a total of 6 therapies. Each exchange comprised 1–1.5 times the total plasma volume and was replaced with FFP. Moreover, to control anti-inflammatory activity, treatment with steroids was initiated. Rituximab was given for persistent symptoms of acute respiratory failure and lack of reaction for hydrocortisone pulse. On the 6th day of hospitalization, a positive weaning trial took place. Patient was decannulated successfully and vv-ECMO therapy was completed. On the next day rocuronium bromide was introduced to the treatment due to elevated airway pressure. The patient's condition continued to be serious. Lung auscultation revealed symmetrical vesicular sound and numerous crackles. Generalized oedema was noticed. Saturation had begun to gradually decrease (Tab. 3). To improve ventilation parameters she was placed in a prone position. To switch from pressure regulated volume controlled synchronized intermittent mandatory ventilation (SIMV-PRVC) mode to continuous positive airway pressure (CPAP) with pressure support of every breath, the midazolam dose was reduced and fentanyl was substituted by remifentanil.

On the 10th day, the patient developed a fever and inflammatory parameters began to rise (Fig. 2). Blood and urine samples were taken to perform culture. Empirical antibiotic therapy with linezolid and meropenem was administered. Heart rate started to increase (Tab. 3). Tracheostomy was performed and for deeper sedation dexmedetomidine was administered. Patient's condition deteriorated. Pulmonary compliance and ventilation parameters started to worsen drastically (Tab. 3). Due to low saturation content of oxygen in the respiratory mixture was raised (FiO_2 50 -> 60) (Tab. 2). During lungs auscultation abnormal sounds were heard – crackling and rhonchi.

Table 3. Circulatory parameters of the patient

Day of treatment	BP [mmHg]	HR [beats/per minute]	SpO_2 [%]	Temperature [°C]
1	110/50	70	100	37.1
2	120/ 60	50–60	98–100	37.3
3	120/ 60	50–60	99–100	36.7
4	127/70	51–55	98–100	36.4
5	130/70	55–75	98–100, 96–99	36.6
6	120/55	63	97–100, 94–97	36.8
7	105/65 120/70	68–80		36.6
8			98	36.6
9	120/70, 130/90	60–70	97, 98–100	36.6
10				36.6
11	120/60, 140/80	100–140	88	37.8
12			87–94	38.9
13	120/70		87–94	38.4
14	130/80	130–140	80–88, 80–91	38.4, 39.1
15	110/50	70	66–80, 60–65	39,4

Table 2. Ventilation mode during treatment

Days of treatment	Ventilation mode	Other parameters
1	DuoLevel 50% FiO_2	TV – 250ml, f – 15/min
2	DuoLevel 50% FiO_2, propofol added to anesthesia	P1/P2 10/26cm H_2O, TV – 220–240ml, f – 15/min, Cstat 15
3	DuoLevel 40% FiO_2	P1/P2 10/26cm H_20, TV – 240–340ml, f – 25/min, Cstat 15
4	DuoLevel 60% FiO_2	P1/P2 13/28cm H_20, TV – 180–200ml, f – 13/min, Cstat 15
5	DuoLevel 60% FiO_2	P1/P2 13/28 cmH_20, TV – 180–200 ml, f –13/min, Cstat 15
6-7	DuoLevel 30% FiO_2, after switching off ECMO PRVC-SIMV 60% O_2,	P1/P2 10/26cm H_20, TV – 200 ml, f – 25/min; PEEP 8cmH20, TV – 400ml f – 24/min
8	PRVC-SIMV 60% O_2	TV – 370ml, PEEP – 7, ΔP – 27, f – 27/min, Cstat 14
9	PRVC-SIMV 60% O_2	PEEP – 8, TV – 330 ml, f – 30/min
10	PRVC-SIMV 35% O_2	PEEP – 5, TV – 480 ml, f – 25/min
11	PRVC-SIMV 40% O_2	PEEP – 5, TV – 480 ml, f – 25/min
12–13	PRVC-SIMV 60-80% O_2	TV – 420ml, f 25/min, Cstat 12
14	PRVC-SIMV 80-100% O_2	Cstat 10
15	PRVC-SIMV 100% O_2	Cstat 7

Table 4. Laboratory parameters of the patient

Day of treatment	Hemoglobin [g/dl] N: 12.0-16.0	Platelet count [K/uL] N: 130-400	Fibrinogen (g/L) N:2.0-3.9	D-Dimer [ng/ml] N: <500	Procalcitonin [ng/ml]	CRP [mg/l] N: <5
1	8.9	188	3.3	6889	0.42	74,4
2	8.4	161	2.3	4438	0.45	27,3
3	9.9	136	2.3	17648	0.40	56,3
4	9.8	118	3.2	16675	0.24	71,5
5	10.7	114	3.8	32615	0.20	40,3
6	10.3	111	3.1	27327	0.13	34,8
7	10.6	127	3.3	32652	0.13	55,1
8	10.1	122	3.4	3709	0.10	43,7
9	9.8	143	3.9	2279	0.10	46,9
10	10.6	204	4.8	5919	0.09	132,8
11	8.5	186	5.5	4704	0.15	179,9
12	9.8	206	6.3	3262	0.16	176,1
13	9.6	231	5.0		0.15	192,8
14	9.7	236	5.8		0.13	250,7
15	*	*	5.2	3499	0.20	*

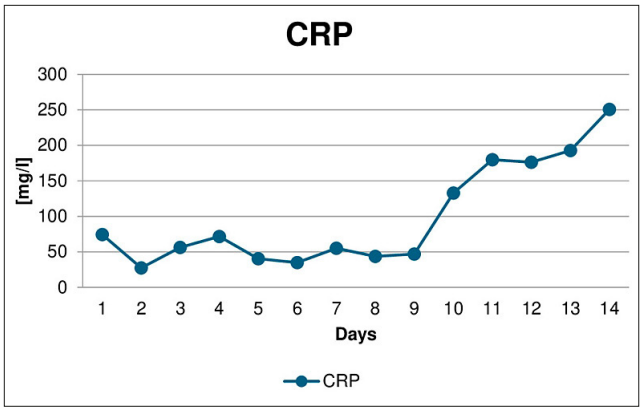

Figure 2. Inflammatory marker

Bronchofiberoscopy was performed and bronchoalveolar lavage (BAL) obtained for culture. Cyclophosphamide was added to treatment and mesnum as a protector. The patient died after 14 days of hospitalization.

DISCUSSION

Diagnosis of DAH should be suspected when a patient presents hypoxaemia, is anaemic, has haemoptysis and features of alveolar infiltrates on chest radiographs [3]. It manifests itself on chest scans by diffuse bilateral alveolar opacities with basal predominance. As a consequence of haemorrhage, the image may present as fibrosis, creating a reticular interstitial pattern [11]. In this case, the patient had all syndromes including bloody, mucous secretion from the trachea. Due to the non-specific clinical and radiological picture, diffuse alveolar bleeding should be differentiated with coagulopathy, cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), allergic alveolitis, and acute respiratory distress syndrome (ARDS) [10].

To identify DAH, invasive diagnostic procedures like bronchoscopy should also be performed [5]. Aliquot of bronchoalveolar lavage (BAL) that features ≥20% haemosiderophages confirms alveolar haemorrhage, and is also associated with severity [5,10]. After diagnosis, the next step is origin conformation [12] which determines treatment strategy [3]. In this case, infectious etiologies were considered and excluded, due to negative samples from nasopharyngeal swab and urine sample. Mortality is established at 25–50% [4]. Auto-immune causes of DAH are considered more serious prognostically compared to non-immune origins [8]. Appropriate and rapid treatment contributes to patients' survival [3]. To identify the cause of DAH, various examinations and thorough medical history should be performed. White blood cell, red blood cell and platelet counts should be investigated and their abnormal count indicates autoimmune etiology. In the presented case, the patient had lowered platelets and red blood cell count, which may suggest autoimmune causes. (Tab. 4) Autoantibody panels for antinuclear antibodies (ANA), ANCA, rheumatoid factor (RF), antiphospholipid antibodies (APL), antibodies, anti-glomerular basement membrane (GBM), lupus anticoagulant, anti-cardiolipin (CL) antibodies, anti-β-2 glycoprotein1 (β2GP),) also should be performed [10, 12]. In some cases even an open lung or surgical biopsy might be needed to identify the origin [9]. Performance of transbronchial lung biopsy to establish the cause is recommended among patients with an unclear etiology of DAH. This should not be a crucial criterion in the diagnosis, because the affected area is often inhomogenous [13, 14]. BAL aliquots should be sent for culture to determine if DAH has infectious etiology [6,9]. Infectious disease can be the origin even when the patient is immunocompetent. Within them, the most common are *influenza A* virus, dengue, leptospirosis, malaria and *Staphylococcus aureus*. The main infectious factors that cause DAH in immunocompromised people are as follows: *Human Cytomegalovirus*, *Adenovirus*, invasive aspergillosis, *Mycoplasma spp.*, *Legionella spp.* and *Strongyloides spp.* infections [11]. Bronchofiberoscopy was performed in the presented case, but unfortunately, at the time of the patient's death, the results had not been received from the laboratory. To exclude heart failure echocardiogram should be performed to rule out pulmonary oedema and

valvular pathologies [14]. Besides treatment of the origin supportive therapy consisting of mechanical ventilation and oxygen perfusion and BAL are also needed [12, 15]. Because the main pathophysiology of DAH is the inflammatory process, corticosteroids and immunosuppressive therapies are the standard treatment [5, 6].

CONCLUSIONS

Diffuse alveolar haemorrhage is a life-threatening disease, where respiratory failure is caused by bleeding into alveoli via damaged basement membrane. It is a complex and diagnostically challenging condition with a difficult to predict outcome, which may vary from case-to-case. Many factors influence the course of the disease, which makes it difficult to find the cause and understand the exact mechanism. Therefore, more thorough clinical research is needed to improve our knowledge and expand treatment options.

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