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Diffuse alveolar hemorrhage: how relevant is etiology?

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Abstract. *Background:* Diffuse Alveolar Hemorrhage (DAH) is a rare and potentially life-threatening clinical syndrome whose early recognition is essential. *Objectives:* Characterization of patients with DAH and comparison of presentation and evolution of the disease according to etiology. *Methods:* We retrospectively reviewed the clinical records of patients admitted to our hospital over a 7-year period with DAH. Criteria for DAH (1+2): 1 - hemoptysis and/or pulmonary infiltrates and/or anemia (DAH triad); 2 - hemorrhagic bronchoalveolar lavage (BAL) or siderophagic alveolitis. DAH was grouped in immune and nonimmune and the course of disease was compared. *Results:* We included 24 patients admitted with DAH, of which 11 had an immune cause: p-ANCA vasculitis (n=7), Systemic Lupus Erythematosus (n=2), c-ANCA vasculitis (n=1), Rheumatoid Arthritis (n=1) and 13 had a nonimmune cause: heart disease (n=6), amiodarone toxicity (n=2), clotting disorder (n=2), cannabis toxicity (n=1), *S. aureus* infection (n=1) and idiopathic (n=1). Patients with nonimmune DAH were significantly older than those with immune DAH (67.9±18.1 *vs* 56.6±18.8 years, p=0.042). DAH triad was observed in 54% of all patients, hemoptysis in 67%, anemia in 79%, and pulmonary infiltrates in all cases. Patients with immune DAH had more frequently pulmonary-renal syndrome (p<0.001), kidney failure (p=0.048), shock (p=0.049) and needed more frequently admition in ICU (p=0.039) and blood transfusion (p=0.043). Hospital length of stay was superior in immune group (29.5±20.0 *vs* 19.5±14.3 days, p=0.047). In-hospital mortality was exclusive to immune DAH (12.5%). *Conclusions:* Patients with DAH due to immune causes were significantly younger, had more severe presentations of the disease and worst outcomes. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36: 47-52)*

Key words: diffuse, alveolar, hemorrhage

Introduction

Diffuse Alveolar Hemorrhage (DAH) is a rare syndrome resulting from diffuse bleeding into the acinar portions of the lung (1). It is characterized by the association of hemoptysis, new pulmonary infiltrates on chest radiograph and anemia, although its presentation may vary, with about one-third of patients presenting without hemoptysis (2). Other symptoms are usually nonspecific and include cough, dyspnea and fever.

DAH is a potentially life-threatening syndrome and it has an overall poor prognosis, with in-hospital mortality ranging from 20 over 50% (3). Rapid identification of the underlying cause of DAH is essential in order to initiate appropriate treatment and prevent acute respiratory failure and death.

Classic treatment regimens include corticosteroids and immunosuppressive agents (4), but these can be potentially harmful when DAH is due to infection.

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The results of this research were presented at ERS International Congress, Milan, 2017, as a thematic poster.

N. de Prost et al (5) reviewed the etiology and prognosis of a series of 112 patients with DAH, but there is still a lack of studies focused on the causes of DAH and most of the series address primarily on immune causes, with the nonimmune causes being probably underestimated. The prognosis of DAH according to the specific etiology is not well documented either.

In order to help to answer these questions, we reviewed the cases of DAH in a single center over 7 years, we characterized these patients and compared the presentation, evolution and prognosis of the disease according to the specific etiology.

Methods

We performed a retrospective cohort study analysing the medical records of patients admitted between January 2010 and December 2016 for suspected DAH in our center. For patients with several admissions for DAH of the same etiology, only the first admission was considered for analysis, the following being referred to as a relapse.

The definition of DAH was based on two basic criteria. First, the clinical picture and radiological data were compatible, including hemoptysis and/or new pulmonary infiltrates on chest radiograph and/or anemia (DAH triad). Second, the bronchoalveolar lavage (BAL) fluid had to be compatible, being either macroscopically hemorrhagic (and not clearing after several aliquots) or presenting siderophagic alveolitis on the cytological analysis (≥20% of haemosiderin-laden macrophages). Patients with hemorrhage of bronchial origin were excluded.

Variables analysed included demographics, past medical history, clinical and laboratory features, hospital length of stay, need for admission in intensive care unit (ICU), need for invasive or noninvasive mechanical ventilation, hemodialysis, blood transfusion and either in-hospital death and death during a follow-up period of 1 year after discharge.

DAH causes were classified into two groups: immune and nonimmune.

For the immune causes, which included systemic vasculitides and connective tissue diseases, the diagnosis was based on compatible clinical features plus either a serological marker or histological confirmation of immune disease.

For the nonimmune causes, DAH related to heart disease was diagnosed based on compatible clinical and echocardiographic features; infection was based on compatible clinical features and microbiological tests; amiodarone toxicity was established based on compatible exposure and suggestive BAL findings; cannabis toxicity was diagnosed based on compatible exposure and urine analysis; clotting disorders were diagnosed in patients taking anticoagulant drugs and evidence of altered coagulation tests; idiopathic DAH was defined when the search for the possible causes remained negative.

Statistical analysis was performed using IBM SPSS Statistics® v.22. Continuous variables were reported as mean±standard deviation and compared with the T-test when normally distributed or the Mann-Whitney test if not normally distributed. Categorical variables were reported as percentages and compared using the chi-square or the Fisher exact test. P values less than 0.05 were considered significant.

Results

Between January 2010 and December 2016, 24 patients were admitted to our center with the first episode of DAH.

We identified 14 different causes of DAH. An immune cause was diagnosed in 11 patients (small vessel vasculitis in 8 patients, connective tissue disease in 3 patients). A nonimmune cause was diagnosed in 13 patients (heart disease in 6 patients, amiodarone toxicity in 2 patients, clotting disorder secondary to anticoagulant treatment in 2 patients, cannabis toxicity in 1 patient, *S. aureus* infection in 1 patient and idiopathic in 1 patient). The different causes of DAH are specified in table 1.

Patients with nonimmune DAH were significantly older than those with immune DAH (67.9±18.1 *vs* 56.6±18.8 years, p=0.042).

DAH triad was observed in 54% (n=13) of patients. 67% (n=16) presented with hemoptysis, 79% (n=19) with anemia and all patients had new pulmonary infiltrates on chest radiograph at admission. All of these features showed no significant difference between the two groups.

These and other demographic, clinical and laboratory data are specified in table 2.

Table 1. Etiology of DAH

Immune	**n=11**
Small vessel vasculitis	**8**
Microscopic polyangiitis	7
Granulomatosis with polyangiitis	1
Connective tissue disease	**3**
Systemic Lupus Erythematosus	2
Rheumatoid Arthritis	1
Nonimmune	**n=13**
Heart disease	**6**
Mitral stenosis	3
Left ventricle dysfunction	2
Atrial myxoma	1
Toxic-induced	**3**
Amiodarone toxicity	2
Cannabis toxicity	1
Clotting disorder	**2**
***S. aureus* infection**	**1**
Idiopathic	**1**

All patients were submitted to bronchoscopy with BAL. In 83% (n=20) of cases, the BAL fluid was macroscopically bloody and did not clear after several aliquots. In 63% (n=15) of cases, the BAL fluid cytology showed the presence of ≥20% haemosiderin-laden macrophages (siderophages). Patients in the immune group had a significantly larger percentage of neutrophils (36,1±39,0 *vs* 9,0±12,5%, p=0,027). The other variables showed no difference between the two groups and are specified in table 3.

Anti-neutrophil cytoplasmatic antibody (ANCA) tests were positive in 73% (n=8) of patients in the immune group – 7 patients had a p-ANCA pattern with MPO specificity and 1 patient had a c-ANCA pattern with PR3 specificity. ANA tests were positive in 18% (n=2) of patients in the immune group.

Kidney biopsy was performed in 36% (n=4) of patients with immune DAH and histological exami-

Table 2. Demographics, clinical and laboratory data

	All patients (n=24)	Immune DAH (n=11)	Nonimmune DAH (n=13)	P
Age, years	62,7±18,9	56,6±18,8	67,9±18,1	**0,042**
Male gender	15 (62,5)	7 (63,6)	8 (61,5)	1,000
Smoking history	6 (25,0)	4 (36,4)	2 (15,4)	0,357
Alcohol abuse	1 (4,2)	1 (9,1)	0 (0)	0,458
Known cardiac disease	16 (66,7)	6 (54,5)	10 (76,9)	0,390
Known respiratory disease	8 (33,3)	5 (45,5)	3 (23,1)	0,390
DAH triad	9 (37,5)	4 (36,4)	5 (38,5)	1,000
Hemoptysis	16 (66,7)	6 (54,5)	10 (76,9)	0,390
Pulmonary infilitrates	24 (100)	11 (100)	13 (100)	-
Anemia	19 (79,2)	10 (90,9)	9 (69,2)	0,294
Hematuria	8 (33,3)	7 (63,6)	1 (7,7)	**0,008**
Proteinuria	8 (33,3)	8 (72,7)	0 (0)	**<0,001**
Kidney failure	10 (41,7)	7 (63,6)	3 (23,1)	**0,048**
Pulmonary-renal syndrome	7 (29,2)	7 (63,6)	0 (0)	**<0,001**
Thrombocytopenia	4 (16,7)	3 (27,3)	1 (7,7)	0,300

Table 3. Bronchoalveolar lavage analysis

	All patients (n=24)	Immune DAH (n=11)	Nonimmune DAH (n=13)	P
Hemorrhagic	20 (83,3)	10 (90,9)	10 (76,9)	0,596
Total cell count, 10^3 / mL	4,0±3,0	4,7±3,7	3,4±2,2	0,288
Macrophages, %	65,7±31,6	55,3±37,3	74,5±24,0	0,142
Neutrophils, %	21,4±30,6	36,1±39,0	9,0±12,5	**0,027**
Lymphocytes, %	11,3±15,6	6,8±5,2	15,1±20,2	0,177
Eosinophils, %	1,1±1,4	1,3±1,7	0,9±1,1	0,557
Presence of ≥20% siderophages	15 (62,5)	7 (63,6)	8 (61,5)	1,000
% of siderophages (when present)	40,0±32,2	37,7±32,5	42,2±34,9	0,822

Table 4. Hospital course and outcome during follow-up period

	All patients (n=24)	Immune DAH (n=11)	Nonimmune DAH (n=13)	P
Hospital length of stay, days	24,1±17,5	29,5±20,0	19,5±14,3	**0,047**
ICU admission	6 (25,0)	5 (45,5)	1 (7,7)	**0,043**
Shock	3 (12,5)	3 (27,3)	0 (0)	**0,049**
Invasive machanical ventilation	2 (8,3)	2 (18,2)	0 (0)	0,199
Noninvasive mechanical ventilation	2 (8,3)	2 (18,2)	0 (0)	0,199
Hemodialysis	3 (12,5)	2 (18,2)	1 (7,7)	0,576
Blood transfusion	6 (25,0)	5 (45,5)	1 (7,7)	**0,043**
In-hospital mortality	3 (12,5)	3 (27,3)	0 (0)	**0,049**
Relapse of DAH	1 (4,2)	1 (9,1)	0 (0)	0,381
Mortality during follow-up	2 (8,3)	1 (9,1)	1 (7,7)	1,000

nation showed a necrotizing crescentic glomerulonephritis in 3 cases. One biopsy was not representative of kidney tissue, but the diagnosis was still assumed without histological confirmation.

We observed a significantly higher need for admission in ICU for patients in the immune group (45%, n=5 *vs* 8%, n=1; p=0,043), with also a higher incidence of shock (27%, n=3 *vs* 0%; p=0,049) and need for blood transfusion (45%, n=5 *vs* 8%, n=1; p=0,043).

Hospital length of stay was also significantly superior in the immune group (29,5±20,0 *vs* 19,5±14,3 days, p=0,047), as well as in-hospital mortality (27%, n=3 *vs* 0%; p=0,049).

During follow-up, 1 patient in the immune group, which had been diagnosed with Systemic Lupus Erythematosus (SLE), had relapse of DAH requiring a new admission to the hospital 8 months after the initial discharge.

All-cause mortality during follow-up was 21%, including both in-hospital mortality and mortality in discharged patients. 2 patients died during the follow-up period after hospital discharge, 1 of each group. The death in the immune group refers to the patient with SLE in whom DAH relapsed. In this case, DAH was directly responsible for mortality. The patient in the nonimmune group died of congestive heart failure 5 months after the initial discharge. In this case, there was no relapse of DAH.

Data on hospital course and outcome are specified in table 4.

Discussion

The first step in the diagnostic approach of a patient with suspected DAH, especially when presenting with hemoptysis, is to distinguish this syndrome from other causes of bleeding. Several infections, bronchiectasis and neoplasms may result in focal aspiration of blood and this may simulate alveolar bleeding in some cases. This distinction has important implications in terms of diagnostic approach, as well as treatment options and prognosis.

Some series report that about one-third of patients do not present with hemoptysis (6). Our series is consistent with this finding since exactly one-third of all patients did not experience hemoptysis initially. This supports the idea that the absence of this sign should not exclude the diagnosis, which is important since hemoptysis is often considered the classic sign of DAH.

Patients with DAH commonly exhibit anemia, leukocytosis and elevation of inflammatory markers, but these are nonspecific findings. Pulmonary-renal syndromes are frequently associated with specific disease markers, including anti-glomerular basement membrane (anti-GBM) antibody in Goodpasture syndrome and ANCA in granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA). When clinical suspicion exists, elevation of some of these markers may help to make an early diagnosis of the cause of DAH.

Chest radiograph classically shows diffuse bilateral alveolar opacities with basal predominance, but recurrent episodes of hemorrhage may lead to fibrosis, producing a reticular interstitial pattern. Despite this, imaging of the lung can be normal in 20 to 50% of cases in the acute setting (7), so this should not discourage the physician to suspect the diagnosis. In our series, all the patients had new pulmonary infiltrates on chest radiograph at admission, which were bilateral in all cases.

Bronchoscopy with BAL is an essential tool to make a confident diagnosis of DAH but it does not diagnose the underlying etiology of hemorrhage in most cases (8), although it can be helpful in the diagnosis of infectious causes and neoplasms. A hemorrhagic BAL fluid that does not clear after sequential aliquots is consistent with DAH. Alternatively, the Golde score is often used to quantify the macrophagic hemosiderin content, which is usually observed only after the first 48 hours of bleeding. However, it is a slow process and there are some studies that have shown a good correlation between a siderophageal cell percentage ≥20% and a Golde score suggestive of DAH (9). In our series, patients with immune DAH had a significantly larger percentage of neutrophils, a finding that, to our knowledge, is not reported elsewhere in literature. The percentage of macroscopically hemorrhagic BAL fluid and the percentage of siderophages did not appear to be significantly different between immune and nonimmune groups.

Systemic vasculitides have been classically associated with DAH. Quadrelli et al (10) characterized 39 patients with DAH of proven immunological etiology, the most frequent being ANCA-related vasculitides (74%), mainly granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). In their series, these two diseases accounted for a similar number of cases (14 GPA *vs* 13 MPA). In our series, ANCA-related vasculitides were also the predominant etiology of immune-related DAH (73%), but with a higher number of MPA cases against GPA (7 *vs* 1). Connective tissue diseases accounted for the remaining cases, including one case of Rheumatoid Arthritis, which is considered a rare cause of DAH.

There are multiple nonimmune-mediated causes of DAH that are frequently ignored in studies. Heart disease and toxic causes are etiologies that are frequently overlooked. Infectious diseases can cause DAH even in immunocompetent patients, the most frequent being influenza A, dengue, leptospirosis, malaria and *Staphylococcus aureus* (11). In immunocompromised patients, the main infectious diseases that cause DAH are cytomegalovirus (12), adenovirus (13), invasive aspergillosis (14), mycoplasma (15), legionella (16) and strongyloides (17) infections. Our series included a single immunocompetent patient with DAH secondary to *Staphylococcus aureus* infection, which was isolated in the BAL fluid microbiological culture, hence strengthening the role of BAL in these patients. Heart disease accounted for 46% of the nonimmune DAH, and echocardiography has proven to be an essential tool in the evaluation of the main cardiac anomaly. N. de Prost (5) found 85% of cases of DAH secondary to heart failure not related to valvular disease. In fact, mitral stenosis has been considered the classic feature of DAH of cardiac origin (18), but several series include other cardiac anomalies. In our case, mitral stenosis accounted for half the cases of DAH due to heart disease (n=3). The other cases were due to left ventricular dysfunction (n=2) and 1 case of a large left atrial myxoma, which was later surgically removed and led to resolution of the symptoms. Our series included 3 cases of toxic-induced DAH. 2 patients had amiodarone-related pulmonary toxicity. In both cases, they were taking this medication for over 10 years and the BAL fluid cytology showed foamy macrophages. One patient had DAH secondary to cannabis smoking. This is a rare cause of DAH, with only anecdotal cases reported, and should, therefore, be sought in all patients with suspected DAH. In the 3 toxic-related cases, all the other common causes of DAH were excluded. We report only one case of idiopathic DAH. This seems to be a rare condition, but its incidence is difficult to calculate because some of the cases reported in literature could be categorised differently in the present with newer diagnostic tools (19).

N. de Prost et al (6) evaluated factors associated with in-hospital and long-term mortality. In their series, in-hospital mortality was 25%. Shock, elevated plasmatic lactate dehydrogenase level and glomerular filtration rate <60 mL/min were independently associated with in-hospital mortality. In their study, the mortality rate of discharged patients was 16% during the follow-up period. Age >60 years, previous cardiovascular disease and persistent renal failure requiring chronic hemodialysis were associated with long-term mortality. Our series reports an all-cause mortality during follow-up of 21%, including both in-hospital mortality and mortality in discharged patients, which is lower than previously reported. In-hospital mortality was significantly superior in the immune group, which is consistent with the significantly higher need for admission in ICU, blood transfusion and incidence of shock in this group of patients, suggesting a more aggressive disease. Hospital length of stay was also significantly superior in the immune group. This can be explained by the more aggressive

disease and possibly by a slower response to therapy than, for example, patients in which is possible to rapidly remove a causal factor.

In conclusion, although this is a single-center retrospective analysis, DAH appears to be a heterogeneous syndrome in which etiology may confer distinct disease course. In our series, patients with immune DAH had a significantly larger percentage of neutrophils on BAL fluid analysis, a finding that, to our knowledge, is not reported elsewhere in literature. We also report one case of cannabis-induced DAH, which is rarely reported in literature. Patients with immune DAH were significantly younger, had more severe presentations of the disease and worst outcomes. Prospective multi-center studies are needed to clearly understand the best diagnostic and therapeutic approach to each group of patients.

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