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Brief original

Diffuse alveolar hemorrhage: Causes and outcomes in a referral center

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ABSTRACT

Objective: To identify the most common causes of diffuse alveolar hemorrhage (DAH) and the evolution of cases during hospitalization.
Patients and methods: A review of cases diagnosed with DAH; the diagnoses were classified according to existing criteria and the progression of the cases was determined.
Results: We identified 17 cases of DAH, with the leading cause being ANCA associated vasculitis (41% of cases), followed by cases secondary to drugs (18%). In 35% of the cases, there was a failure in identifying an etiology. Six patients died (35%), the only factor associated with mortality was male gender 5/6 vs 3/11, *P*=.05.
Conclusions: The most frequent cause of alveolar hemorrhage was ANCA associated vasculitis. The mortality in DAH is about 35%, males seem to have a worse prognosis.

Hemorragia alveolar difusa: causas y desenlaces en un instituto de tercer nivel

Palabras clave:
Hemorragia alveolar difusa
Vasculitis asociadas a anticuerpos anticitoplasma de neutrófilos
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Anticuerpos anticitoplasma de neutrófilos
Poliangeítis microscópica

RESUMEN

Objetivo: Identificar las causas más frecuentes de hemorragia alveolar difusa (HAD) y conocer la evolución de los casos durante su hospitalización.
Pacientes y método: Revisión de expedientes con diagnóstico de HAD. Se clasificaron los diagnósticos de acuerdo con los criterios vigentes y se determinó la evolución.
Resultados: Se identificaron 17 casos de HAD, la principal causa fueron las vasculitis asociadas a ANCA (el 41% de los casos) seguida de las secundarias a drogas (el 18% de los casos). En un 35% no se logró identificar una etiología. Seis pacientes fallecieron (35%), el único factor asociado a mortalidad fue el sexo masculino (5/6 vs.- 3/11; p = 0,05).
Conclusiones: La causa más frecuente de hemorragia alveolar son las vasculitis asociadas a ANCA, la mortalidad de la HAD es del 35% y los hombres parecen tener peor pronóstico.

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Introduction

Diffuse alveolar hemorrhage (DAH) is an emergency that requires early and aggressive treatment. The term DAH refers to different forms of hemorrhage that originate in the lung microcirculation (alveolar capillaries, arterioles and venules) and that may affect multiple areas of the lung parenchyma.[1]

The first description of DAH is attributed to Virchow in the XIX century, who reported what seems to be a case of idiopathic lung hemosyderosis.[1]

The physiopathology of DAH due to alveolar microcirculation damage, and the cause might be lung-specific (as in diffuse alveolar damage or an infection) or generalized (as in systemic vasculitis). In the latter case, the presence of alveolar capillaritis, described in other systemic autoimmune disease such as systemic lupus erythematosus,[2,3] has been described. There is little information on the causes of DAH, which comes from case reports or series. One of these studies described Wegener's granulomatosis as the most common cause (32% of cases) followed by Goodpasture's syndrome, idiopathic lung hemosyderosis and other systemic autoimmune diseases.[2]

The most common symptoms in DAH are hemoptysis, dyspnea and acute or subacute onset coughing.[7] Physical examination is generally non-specific. In cases secondary to a systemic disease there might be symptoms related with the underlying disease.[1] Laboratory testing shows a fall in hemoglobina and hematocrite along with azoemia and changes in urinary sediment in kidney-lung syndromes. Because the Instituto Nacional de Enfermedades Respiratorias is a referral center, we decided to identify the most common causes of DAH and know the progression of cases during hospitalization.

Patients and methods

We reviewed patient files for the period of 2001-2006 and considered patients complying with the following as true DAH cases:

1) Clinical manifestations: dyspnea, cough (with or without bloody discharge) and fever for the week prior to hospitalization.
2) Diffuse alveolar lung infiltrates in radiographic studies.
3) Anemia (hemoglobin under 13 g in men and 11 g in women).
4) Exclusion of other diagnosis which would explain the lung findings and/or the demonstration of hemosyderin-laden macrophages in the bronchial lavage and/or lung biopsy, compatible with DAH.

Laboratory variables were registered (complete blood count, blood chemistry, urinalysis, anti neutrophil cytoplasm antibodies, anti-PR3, anti-MPO, antinuclear antibodies, anti-double stranded DNA antibodies and complement levels [C3 and C4]). Chest x ray and high resolution computed tomography (HRCAT) were registered, as was the etiologic diagnosis for DAH. In those cases in which the diagnosis was small caliber vessel vasculitis, it was only taken as true if it had positive anti neutrophil cytoplasm (ANCA) antibodies along with positive anti-PR3 or MPO. In the case of systemic lupus erythematosus, the patient was classified according to the ACR criteria.[4] The other cases were discussed among the authors and a consensus on diagnosis was reached, or the conclusion that identifying a cause for DAH was not possible was given.

Statistical analysis

Statistical analysis was performed using Fisher's exact test for categorical variables and Wilcoxon's summed rank test for numerical values. A two tailed p value of $P<.05$ was considered significant.

Table 1
General and clinical characteristics of the population

Variable	Frequency n=17, n (%)
Women	9 (53)
Age, years*	45.17 (16-66)
Active smoking	3 (18)
Clinical manifestations	
Dyspnea	12 (71)
Cough	14 (82)
Hemoptisis	14 (82)
Laboratory	
Hemoglobin, g/dl*	9.9 (5.7-15.7)
Leukocytes*	11.210 (6.200-20.000)
Platelets,* thousands	307 (156-485)
Creatinine,* mg/dl	1.18 (0.54-4.3)
Erythrocyturia +++	10 (59)
Causes of alveolar hemorrhage	
ANCA associated vasculitis	7 (41)
Drugs or medication	3 (18)
Systemic lupus erythematosus	1 (6)
Undetermined	6 (35)
Normal echocardiogram	5 (29)

ANCA indicates anti neutrophil cytoplasm antibodies.
*Median (minimum-maximum value).

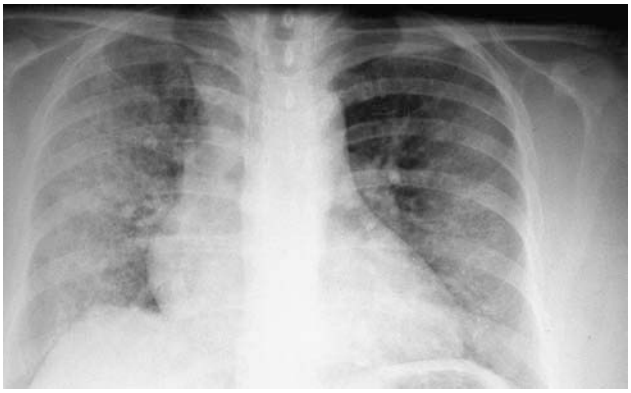

Figure. Chest x ray with disseminated heterogeneous bilateral opacities in a patient with the diagnosis of diffuse alveolar hemorrhage.

Results

Seventeen cases were identified (Table 1). In 16 this was the first episode of DAH and only one had a history of a prior episode which had been treated at another hospital. Nine were women (53%) with a median age of 45.17 years. The most common cause of DAH was ANCA associated vasculitis with 7 cases, 5 of which were Wegener's granulomatosis and 2 microscopic polyangiitis. The second most common cause was secondary to drug use in three cases, two due to cocaine and one after the use of propylthiouracil, which developed a secondary ANCA positive vasculitis, and this patient was the one with a history of DAH also related to this drug.

Cultures for mycobacteria and pyogenous bacteria were taken in 15 patients (88%), negative in all of them. Chest x ray and HRCAT were requested in 100% finding, in the prior bilateral alveolar opacities in all of the studies and, in the latter, areas of consolidation alternating with ground glass images and normal parenchyma (Figure). No biopsies were carried out in any patients.

Eleven patients survived and were discharged due to improvement, six died (35%), of which 5 were men (83%), with a $P=.05$ when

Table 1
Comparison between the dead and surviving patients with diffuse alveolar hemorrhage

Variable	Dead n=6	Surviving n=11	*P*
Male gender	5 (83%)	3 (27%)	.05
Anemia[a]	6 (100%)	6 (54%)	.10
Azoemia[b]	4 (66%)	4 (36%)	.33
Hemoglobinuria	4 (66%)	7 (63%)	1
Entry into the ICU	1 (16%)	5 (45%)	.33
>10 days in ICU	1 (16%)	4 (36%)	.60
Mechanical ventilation	1 (16%)	3 (27%)	.580
Methilprednisolone pulses	6 (100%)	5 (45%)	.62
Prednisone	1 (16%)	9 (81%)	.035
Antibiotic	5 (83%)	9 (81%)	1
Cyclophosphamide	3 (50%)	3 (27%)	.60
Rheumatoid factor >20	1 (16%)	1 (9%)	1
Bronchoscopy	1 (16%)	5 (45%)	.33
Hemoptisis	5 (83%)	9 (81%)	1
Dyspnea	4 (66%)	8 (72%)	1
Cough	5 (83%)	9 (81%)	1
Hemoglobin, gm/dl[c]	9.5 (5.7-11.6)	10.3 (6.4-15.7)	0.36
Age, years[c]	42 (16-62)	46.9 (21-66)	0.42
Leukocytes[c]	12.7 (7.5-18.6)	11.32 (6.2-19.8)	.51
Platelets[c]	288.5 (166.392)	351 (156.703)	.54
Creatinine[c]	2.26 (0.62-3.9)	1.54 (0.54-4.3)	.36
Days in ICU[c]	3 (0-3)	6 (0-16)	.28

ICU indicates intensive care unit.
[a]Defined as Hb<10 gm/dl.
[b]Defined as creatinine over 1,2 mg/dl.
[c]Median (minimum-maximum value).

compared to the survivors (Table 2). Survivors mostly received support treatment with prednisone (81 vs 16%; *P*=.035), with no differences in the rest of the variables analyzed (Table 2).

Discussion

In this study we found that the main cause of alveolar hemorrhage in our environment is ANCA associated vasculitis, and of them, Wegener's granulomatosis is the most common, something that coincides with reports from other series which report ANCA associated small caliber vessel vasculitis as the main cause of DAH.[5-7,9-12] This finding confirms the need for an exhaustive evaluation of patients to rule out ANCA associated vasculitis when faced with a case of DAH.

The second most common cause of DAH were those associated to drugs, in two cases with cocaine and one with propylthiouracil. This series is the first that, to our knowledge, informs that the use of drugs is a frequent cause of DAH. In the case of cocaine it reinforces the need to interrogate on prior drug use; on the other hand, it is well described that propylthiouracil may provoke secondary vasculitis and positive ANCA. The progression of these patients was towards improvement and disappearance of the antibodies once the offending drug was suspended. Some would argue that, in our series, this case should also be catalogued as an ANCA associated vasculitis; however, because the association between the use of anti-thyroid drugs and secondary vasculitis is well described and ceases after drug suspension, we decided to include it with the drug related cases. We had 35% of hemorrhages in which the cause was undetermined and, in this respect, we should comment that some of the patients came to the emergency room in very poor condition and died in their first hours after hospitalization, making it impossible to completely study the patients. Patients who did undergo a bronchoscopy were only subjected to lavage, because transbronchial biopsy's sensitivity and specificity are well documented and none of the patients was subjected to an open biopsy. Regarding the HRCAT, we corroborated the imaging findings of ground glass alveolar infiltrates and normal parenchyma in 100% of patients.

Of the 6 patients that were hospitalized in the ICU, one died (17%), and this percentage is less than that of the study by Semple et al, where a mortality of 50% is reported for patients treated in an intensive care unit.[8] The nature of this difference cannot be explained due to the type of the study. The only variable that seems to be associated to mortality is male gender. The other variable that was statistically significant was treatment with oral prednisone; however, this could be a result of a survival bias, because we consider that the result only reflects that patients who survived were able to take prednisone orally or had less severe disease when hospitalized. It is important to comment that there are no differences regarding survival for patients using pulse methylprednisolone.

The limitations of the study are those of a retrospective study and due to the small number of patients. Another limitation is that patients at our institution with DAH were not evaluated in a systematic manner and not all variables could be identified in all cases, with attending physicians deciding tests based on their own criteria. However, due to the rarity of DAH, this study provides useful information to clinicians evaluating this group of patients.

In conclusion, the most frequent cause of DAH in our environment were ANCA associated vascultiis, with mortality around 35% and male gender having a seemingly worse prognosis in this condition.

Disclosures

The authors have no disclosures to make.

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