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Review Article

Diffuse Alveolar Hemorrhage in Patients With Systemic Lupus Erythematosus. Clinical Manifestations, Treatment, and Prognosis☆

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ABSTRACT

Diffuse alveolar hemorrhage (DAH) in patients with systemic lupus erythematosus is a rare but potentially fatal condition. Although the pathogenesis of this condition is unknown, high disease activity is the main characteristic; moreover, histopathology in some studies showed alveolar immune complex deposits and capillaritis. Clinical features of DAH include dyspnea, a drop in hemoglobin, and diffuse radiographic alveolar images, with or without hemoptysis. Factors associated with mortality include mechanical ventilation, renal failure, and infections. Bacterial infections have been reported frequently in patients with DAH, and also invasive fungal infections including aspergillosis. DAH treatment is based on high dose methylprednisolone; other accepted therapies include cyclophosphamide (controversial), plasmapheresis, immunoglobulin and rituximab.

Hemorragia alveolar difusa en pacientes con lupus eritematoso sistémico. Manifestaciones clínicas, tratamiento y pronóstico

Palabras clave:
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Hemorragia alveolar difusa
Infecciones

RESUMEN

La hemorragia alveolar difusa (HAD) es una manifestación rara pero potencialmente fatal en pacientes con lupus eritematoso sistémico (LES). La patogenia de esta manifestación es desconocida, aunque los pacientes se presentan con datos clínicos de actividad del LES en el momento de la hemorragia; estudios de histopatología han implicado depósitos de complejos inmunes e infiltrado celular (capilaritis). El cuadro clínico clásico de la enfermedad consiste en disnea, descenso en la hemoglobina e imágenes radiográficas alveolares difusas habitualmente, con o sin la presencia de hemoptisis. Se han identificado diversos factores asociados a mortalidad, entre los que se encuentran la ventilación mecánica, falla renal e infecciones; estas últimas se han descrito como frecuentes en diversas series, aunque principalmente son bacterianas, también pueden observarse infecciones fúngicas invasivas como aspergilosis. El tratamiento de la HAD se ha basado en pulsos de metilprednisolona; pueden ser útiles también, ciclofosfamida (uso controversial), plasmaféresis, inmunoglobulina y rituximab.

Introduction

It's been over 100 years since Osler's description of a patient with erythema, and assumed pulmonary hemorrhage, who presented with systemic lupus erythematosus (SLE).[1] DAH, today, remains one of the most devastating complications in patients with SLE; having a high mortality[2] and representing a diagnostic and therapeutic challenge for the rheumatologist.

The frequency of the disease varies depending on the series consulted, from 0.63 to 5.4%[4] cohorts of lupus and from 0.5[5] to 9%[2] of hospital admissions to 5.7% of the internments to intensive care[6] and 12.3% of autopsies.[7] As in SLE, the frequency is higher in women and, although most of the case series reported that pulmonary hemorrhage occurs early, the mean or median progression of SLE at the time of DAH goes from 6 months[8] to 14.1 years[4] (Table 1).

The knowledge we have of this deadly association is based on reports and case series; Table 1 shows the main series; most are from Asia and Latin America, particularly Mexico.

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Table 1
Selected Series' Demographic Characteristics.

Authors, year of publication	Country	No. episodes	Frequency	Females	Age	Evolution SLE	Decrease in hemoglobin
Araujo et al., 2012[9]	Brazil	28 JSLE: 13 ASLE: 15	1.6%[a]	JSLE: 77% ASLE: 87%	JSLE 15.3[d] ASLE: 28.7[d]	JSLE 2.6 a[d] ASLE: 5.6 a[d]	JSLE: 2.9 g/dL[d] ASLE: 5.5 g/dL[d]
Martínez-Martínez and Abud-Mendoza, 2011[2]	Mexico	29	9%[b]	75.9%	25.1[d]	1.5 a[d]	3.4 g/dL[d]
Kwok et al., 2011[10]	South Korea	21	1.4%[b]	90.5%	29.7[d]	5.4 a[d]	2.1 g/dL[d]
Shen et al., 2010[11]	China	29	1.4%[b]	86.2%	31[e]	42 m[e]	32 g/L[e]
Rojas-Serrano et al., 2008[3]	Mexico	14	0.6%[a]	92.8%	22.4[d]	–	–
Cañas et al., 2007[6]	Colombia	7	5.7%[c]	71.4%	24.3[d]	15.7 m[d]	–
Badsha et al., 2004[12]	Singapore	22	1.5%	91%	31.6[d]	0.96[e]	3.2 g/dL[d]
Chang et al., 2002[5]	Taiwan	8	0.5%[b]	100%	32.5[e]	36 m[e]	3.0 g/dL[e]
Lee et al., 2001[13]	Korea	9	–	100%	26[e]	2m[e]	1.9 g/dL[e]
Santos-Ocampo et al., 2000[14]	EE. UU.	1	1%[b]	81.8%	31.1[d]	4.5 a[d]	-
Lee et al., 2000[8]	Korea	6	–	83.3%	28[d]	6 m[d]	2.1 g/dL[d]
Liu et al., 1998[15]	Taiwan	13	4.3%[b]	92.3%	26[d]	23 m[d]	2.4 g/dL[d]
Zamora et al., 1997[16]	USA	19	3.7%[b]	68.4%	27[e]	31 m[e]	7.1% Ht[d]
Koh et al., 1997[17]	Singapore	10	–	80%	25[e]	21.5 m[d]	–
Barile et al., 1997[4]	Mexico	34	5.4%[b]	94.1%	34.5[d]	14.1 a[d]	–
Schwab et al., 1993[18]	USA	8	–	75%	37.9[d]	2.3 a[d]	–
Abud-Mendoza et al., 1985[19]	Mexico	12	1.6%[b]	100%	25[d]	24 m	–
Mintz et al. July 1978	Mexico	7	–	100%	30	3.2 a	–

In the series of Lee et al.,[8] the data was extracted from 6 patients with lupus and in 10 patients with DAH due to different causes.
y, years; Ht, hematocrit; SLE, systemic lupus erythematosus; ASLE, adult-onset SLE; JSLE, Juvenile-onset SLE; m, months; –, not reported.
[a] Cohort.
[b] Hospital admissions.
[c] UCI internment.
[d] Mean.
[e] Medium.

Pathogenesis and Risk Factors

Active disease is part of the DAH associated with SLE; as shown in Fig. 1, the mean or median of disease activity is high (greater than or equal to 12), indicating that the activity of SLE can be a trigger, or at least associated with DAH (Fig. 1).

Additionally, the different series highlight the importance of disease activity of SLE by exposing the high frequency of nephritis, arthritis and neuropsychiatric disorders associated; for example, lupus nephritis is reported by the majority of studies in more than 70% of patients and in whom, very often, the histopathology was compatible with proliferative types (Table 2).

Immune complexes have been described in patients with DAH associated with SLE. Hughson et al.,[20] made a compilation of the literature of 20 cases of DAH in SLE patients, 15 of which showed the so-called soft bleeding, the remaining 5 DAH had capillaritis;

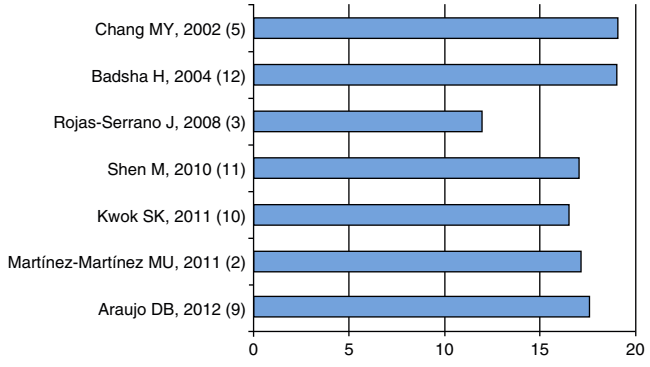

Fig. 1. Mean 2,10,11,3 or median 5,9,12 of disease activity as measured by the various scales (SLEDAI 2K2 {3 or SLEDAI)}.[3,5,9–12] The first author, year and reference, in parenthesis, are shown. Data extracted from each article.

additional Immune complexes were identified in the alveolar wall in 11/15 cases of patients with soft hemorrhage and 3/5 cases of capillaritis. In the same study, the authors describe the similarity between the vascular pathology observed in the soft hemorrhage with renal microangiopathy in lupus nephritis.[20]

Although the above may indicate the involvement of immune complexes as an expression of disease activity in its pathogenesis, Haupt et al.,[21] study of 120 autopsies of patients with SLE, in the pursuit of alternative explanations, reported 29 patients with DAH and in only 2/29 (6.9%) there was no other factor to explain the DAH; in 5/29 (17.2%) there was evidence of aspiration as an associated factor and in 7/29 (24.1%), congestive heart failure, 9/29 (31%) presented infection and 6/29 (20.7%) renal insufficiency. We consider that, in addition to the activity of the disease, there may be other factors or conditions that favor DAH, as aforementioned.

Infections are common in SLE associated with DAH and they deserve a special section within this review.

It is reported that DAH is more common in winter[2]; although the cause of this fact is unknown, however, there are symptoms exacerbated by cold conditions, including epistaxis and hemoptysis,[22,23] to mention an association of cold and respiratory tract bleeding.

Little is known about the type of immune response that triggers DAH in patients with SLE. In a model of DAH pristane-induced SLE in susceptible mice, the involvement of the innate immune response has been shown; severity or recovery from the insult (DAH) is dependent on adaptive immunity with significant participation of B[24] cells. In this mouse model of SLE and pulmonary hemorrhage, hemorrhage is preceded by infiltration of macrophages and neutrophils[24]; although, on the other hand, immune deposits have not been demonstrated in this model.[25]

Risk factors for the development of DAH in SLE patients have been poorly described by the different series. Liu et al. report that 4 of 13 patients developed DAH the third day after treatment initiation[15] plus 3 patients received cyclophosphamide in the