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ORIGINAL ARTICLE

Study on the clinicopathological correlation in the secondary acute respiratory distress syndrome

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KEYWORDS
Respiratory failure;
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Necropsy;
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Abstract
Objective: This study has aimed to study the clinicopathological correlation of patients with secondary acute respiratory distress syndrome (ARDS), specifically having extrapulmonary causes.
Setting: A 22 beds intensive care unit.
Design: An observational study of case series.
Patients: Seventeen patients whose death was caused by acute respiratory distress syndrome were included.
Intervention: A systematic histopathological study was made of all the pulmonary lobes of patients who died in our ICU with the clinical diagnosis of secondary ARDS, who had undergone an autopsy between 1999 and 2009. The Kappa analysis was used to analyze the grade of correlation between the clinical and the pathological diagnosis.
Results: The autopsy confirmed to cases of false positive in 17 patients with ARDS (11%). The kappa value was 0.77, so that the concordance analysis was considered to be satisfactory.
Conclusions: The clinical criteria for ARDS correlate well with acute alveolar damage (AAD) in the autopsy study in patients with secondary ARDS, although some false positive cases can be observed.

PALABRAS CLAVE
Insuficiencia respiratoria;
Síndrome de distrés respiratorio agudo;

Estudio sobre la correlación clínico-patológica en el síndrome de distrés respiratorio agudo secundario

Resumen
Objetivo: El objetivo principal del estudio es analizar la correlación clinicopatológica en el diagnóstico de síndrome de distrés respiratorio agudo (SDRA) de origen extrapulmonar.

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Daño alveolar difuso;
Análisis de kappa;
Necropsia;
Estudio clinicopatológico;
Lesión pulmonar aguda

Diseño: Se trata de un estudio observacional de una serie de casos.
Ámbito: UCI de 22 camas de un hospital universitario con 450 camas.
Pacientes: Diecisiete pacientes fallecidos a causa de un SDRA secundario.
Intervención: Análisis histopatológico sistemático de todos los lóbulos pulmonares de pacientes que fallecieron en nuestra UCI con el diagnóstico clínico de SDRA secundario y en los que se realizó necropsia entre los años 1999 y 2009. A fin de analizar el grado de correlación entre el diagnóstico clínico y el patológico se aplicó el análisis de kappa.
Resultados: En 17 pacientes con SDRA secundario la necropsia permitió confirmar 2 casos falsos positivos (11%). El valor kappa fue de 0,77, por lo que el análisis de concordancia fue considerado como satisfactorio.
Conclusiones: Los criterios clínicos para el diagnóstico de SDRA se correlacionan bien con la presencia de daño alveolar agudo en el estudio patológico necrópsico en pacientes con SDRA secundario, aunque pueden detectarse algunos casos falsos positivos.

Acute respiratory distress syndrome (ARDS) is a clinical condition that was first described in 1967,[1] and the diagnosis is established on the basis of clinical, radiological and blood gas criteria. A distinction is made between ARDS of intrapulmonary origin (primary ARDS) and ARDS of extrapulmonary origin (secondary ARDS) - the latter more probably being related to systemic inflammatory response syndrome and to what Roger Bone called immune dissonance phenomenon,[2] with prognostic and clinical features that differentiate it from primary ARDS. Although there is no direct histopathological correspondence, ARDS is correlated to specific pathological findings that conform what is known as diffuse alveolar damage.

The 1994 Consensus Conference[3] established the diagnostic criteria of the syndrome, including oximetric, radiological, ventilatory and hemodynamic parameters. The Conference for the first time allowed universal protocolization of the diagnosis of ARDS, though few studies have examined the diagnostic precision and chronological histopathological correlation of the syndrome.

It is known that the histological findings of acute alveolar damage are temporary, and can be conveniently divided into three inter-related and overlapping evolutive phases that are correlated to the clinical course of the disease.[4] These phases are characterized by the presence of: 1) edema (first 48 h); 2) hyaline membranes and exudation (day 3-7); and 3) fibrosis, alveolar hyperplasia and interstitial infiltrates (day >7).[5] These histological alterations are related to variations in mechanical ventilation[6] and have physiopathological bases that have not yet been well clarified.[7] The ventilatory strategy in ARDS has also recently been revised; in this sense, the use of small volumes, early prone decubitus and high positive end expiratory pressure (PEEP) have been shown to be of great benefit.[8-11]

Recently, Esteban et al.,[12] in a clinicopathological study, had the opportunity to assess the validity of the clinical criteria on a histological basis, confirming superior validity of the clinical criteria in extrapulmonary ARDS. Nevertheless, controversy over the distinction between primary and secondary ARDS continues.[13]

The objectives of this study are the following: 1) to corroborate the clinical diagnostic validity of the Consensus Conference criteria, studying the clinical sequence of ARDS with the end histology of acute alveolar damage in secondary ARDS; and 2) to assess the chronological clinicopathological correlation from the moment of clinical diagnosis of extrapulmonary ARDS to the performance of necropsy in a series of secondary ARDS patients who died in the Intensive Care Unit (ICU)(comparing this time with the chronology based on the histopathological findings).

Material and method

The study was carried out in a polyvalent, 22-bed ICU. Over a 10-year period (1 January 1999 to 12 December 2009), we included those patients with a clinical diagnosis of secondary ARDS in which a necropsy study was available, following the obtainment of consent from the relatives. The clinical diagnostic criterion applied was that of the 1994 Consensus Conference. At the same time, we reviewed all the necropsy pathology studies of those who had died in the ICU during this 10-year period with a diagnosis of ARDS.

The following variables were prospectively collected in the context of a case series study: patient age and sex, reason for admission to the ICU, the Murray lung injury scale,[14] the clinical duration of ARDS, the duration of mechanical ventilation, microbiological findings in the case of sepsis, histopathological findings, and duration of ARDS as established from the histological study. The clinical diagnosis was established on a consensus basis among at least three physicians in the Department, in all cases including the physician in charge of the patient. The diagnosis could be established both upon patient admission (ARDS being the reason for admission or one of the main reasons for admission) and during the stay in the ICU (evolutive complication).

Other potential causes of these lesions were discarded (cardiogenic lung edema, nitric oxide or oxygen toxicity, etc.).

The necropsy studies were made following a protocol. To our knowledge, the literature offers no reference to the appropriate methodology in studies of this kind; the approach suggested by the pathologists was therefore used in this study. The 5 main lung lobes were analyzed, particularly the pulmonary zones of each lobe in which more alterations were macroscopically manifest. Samples of these zones were subjected to histopathological evaluation on an independent basis by two pathologists. In

those cases where the chronology criteria of the two pathologists did not coincide, a consensus based agreement was reached.

The following criteria were established for chronological - histological assessment: 1) acute phase (first 48 hours), determined by the predominance of interstitial edema and alveolar edema; 2) subacute phase (day 3-7), characterized by the predominant presence of hyaline membranes and fibrin deposits; and 3) proliferative phase (day >7), determined by the presence of abundant fibroblasts within the interstice, fibrosis and type II cell hyperplasia. Lastly, based on the predominance of these lesions in the 5 lung lobes, the pathologists reported their evolutive estimate in days. This evaluation in turn was compared with the time elapsed from the clinical diagnosis of SARS to the death of the patient. The clinico-histological correlation was analyzed by intergroup concordance analysis, assessed by the kappa index[15] (non-pondered value). In this context, the association was considered satisfactory, according to the criteria of Landis and Koch,[16] if the kappa index was found to be >0.60, and excellent if ≥0.8. Likewise, and using the methodology of Esteban et al., we evaluated the sensitivity and the specificity of the clinical criteria, independently of also assessing the concordance index. In this way a dual statistical approach was used to explore the validity of the clinical diagnosis in this concrete form of ARDS.

Results

The study included a total of 17 patients clinically diagnosed with secondary ARDS who died and were subjected to necropsy study after obtaining consent from the relatives. There were 14 males and 3 females, with a mean age of 41±20 years. The systematic pulmonary examination confirmed the presence of hyaline membranes in some of the 5 lung lobes, in 15 of the patients. In the course of these 10 years a total of 85 non-legally mandatory necropsy studies were made of patients who died in the ICU (representing 5% of those who died during that period of time).

Tables 1-3 report the clinical characteristics and histopathological findings of the patients included in the study. The histological study confirmed the clinical diagnosis of secondary ARDS in 15 subjects (88%). Two patients showed no histopathological evidence of ARDS (2 false-positive cases). One of them presented lung infarction and the other was found to have bilateral pneumonia. In the review of the necropsies during this period (n=85), one patient was found to present lung edema and hyaline membranes as signs of acute alveolar damage that had not been previously suspected from the clinical viewpoint (1 false-negative case). Based on these data, the sensitivity of the clinical diagnosis was 94%, with a specificity of 97%. The concordance (validity) index between the clinical and histopathological diagnosis was 0.88 (table 2).

Among the 14 patients with clinically suspected and confirmed ARDS (true-positive cases), two showed a clinical duration or course of <48 hours, 8 had a clinical course of 3-7 days, and 4 presented a course of >7 days.

The histological study showed that two patients predominantly suffered diffuse lung edema with the isolated presence of hyaline membranes; 8 showed mainly hyaline membranes; and 4 showed signs of fibrosis.

Table 3 shows the chronological correlation between the clinical diagnosis and the histological findings. The kappa value was 0.77 - the lower and upper limits (with 95% confidence interval) being 0.48 and 1, respectively, with a standard error of 0.15.

No relationship of any kind was observed between the principal diagnosis or microbiology and the presence of acute alveolar damage.

Discussion

The incidence of ARDS among hospitalized patients is increasing, and the syndrome is known to be associated to important mortality (often over 50%). This explains the interest in establishing an early diagnosis and in adequately guiding treatment, particularly in the form of protective ventilation.

Although to date the histopathological studies of ARDS have not been able to establish a clear correlation between the open biopsy pathology findings and the degree of pulmonary functional impairment, our *postmortem* histopathological findings are clearly correlated to the clinical diagnosis, in coincidence with the study published by Esteban et al.,[12] though in addition they are also correlated to the evolutive chronology of the syndrome.

The findings in the early phase of distress (first 48 hours) are characterized by interstitial and alveolar edema. At histological study, the type I alveolar cells appear edematous and denuded; hyaline membrane genesis is in preparation at this point, secondary to the destruction of these type I pneumocytes. The accumulation of fibrin and its polymerization, together with type I pneumocyte destruction, contribute to generation of the second (hyaline membrane) phase between days 3 and 7. This second phase often shows concomitant cell infiltration within the intraalveolar space. Posteriorly, in the proliferative phase (after the second week), fibroblast proliferation is observed in the interstitial space, with the accumulation of collagen, fibrosis and type II cell hyperplasia - these cells being responsible for the formation of new type I pneumocytes.

The development of respiratory failure with bilateral lung infiltrates in patients admitted due to extrapulmonary disease often poses diagnostic problems. Such problems are even more accentuated if the patients are in serious condition and are subjected to ventilation. In this context, the list of possible etiologies is relatively extensive.

The diagnosis furthermore can be complicated by the fact that the development of ARDS as a consequence of pneumonia is not uncommon, and inversely, pulmonary overinfection can be observed in ARDS patients.

Different criteria have been used by a series of authors and centers in diagnosing ARDS, and a patient diagnosed with pneumonia in one center or by a given clinician can easily be diagnosed with ARDS in another center. In fact, patients with respiratory failure have often been grouped under the term ARDS without distinguishing among pneumonia, pulmonary embolism and atelectasis. Such

Table 1 Histopathological results and clinical and pathological chronology of the patients included in the study

URL	MRL	LRL	ULL	LLL	T. ARDS (d)	Chron.-P	Concordance	Difference (d)
HM. Alv. hyperpl. Interst. infl.	HM. Alv. hyperpl. Interst. infl.	HM. Alv. hyperpl. Infl inters. PMN	HM. Alv. hyperpl. PMN	Edema. HM. PMN	8	1 week	Yes-C	+1
HM. Interst. infl. PMN	HM. Interst. infl. Fibrosis. PMN	HM. Interst. infl. Fibrosis. PMN	Edema. HM. Interst. infl. PMN	HM. Interst. infl. Fibrosis	8	1 week	Yes-C	+1
Alv. hyperpl. Fibrosis. PMN	Alv. Hyperpl. Fibrosis. PMN	HM. Alv. hyperpl. Fibrosis. PMN	Edema. HM. Alv. hyperpl. PMN	Iv. Hyperpl. AFibrosis. PMN	16	>1 week	Yes-C	+8
Edema. HM. Fibrosis. PMN	Edema. HM. Fibrosis. PMN	Edema. HM. Fibrosis. PMN	Edema. HM. fibrosis.	Edema	3	1 week	No	−4
Edema	Edema. Alv. hyperpl.	Edema. Alv. hyperpl.	Edema. HM. Alv. hyperpl.	Edema. Alv. hyperpl.	3	3-7 days	Yes-C	−1
Edema. HM. Alv. hyperpl. PMN	Edema. HM. Alv. hyperpl. PMN	Edema. HM. Alv. hyperpl. PMN	Edema. HM. Alv. hyperpl. PMN	Edema. HM. Alv. hyperpl. PMN	4	3 days	Yes-C	+1
HM. Alv. hyperpl.	Edema. HM. PMN	Edema. HM. Interst. infl. PMN	HM. Interst. infl. PMN	Interst. infl. PMN	6	3 days	Yes-C	+3
*Pulmonary infarction	*	*	*	*		Negative	No	
	Edema. Interst. infl. PMN	Edema. Interst. infl. PMN	Interst. infl. PMN. HM. PMN	Edema	1	1	Yes-C	+0
Edema. PMN	HM. PMN	HM. PMN		HM. PMN	3	3-7 days	Yes-C	−1
*PMN	PMN	*		*	3	Negative	No	
HM. PMN	HM. PMN	Edema. HM. PMN	Edema. HM. Alv. hyperpl. PMN	Edema. HM. Alv. hyperpl. PMN	3	3 days	Yes-C	+0
Alv. hyperpl. Interst. infl. Fibrosis. PMN	Alv. hyperpl. Fibrosis	Edema. HM. Alv. hyperpl. PMN	Edema. HM. Alv. hyperpl. PMN	Edema. HM. Interst. infl. PMN	14	>1 week	Yes-C	+6
Edema	Edema	Edema	Edema	Edema. Interst. infl. PMN	1	1 day	Yes-C	0
Edema. HM. Alv. hyperpl. PMN	Edema. HM. Alv. hyperpl. PMN			Edema. HM. Alv. hyperpl. PMN	3	3 days	Yes-C	0
Alv. hyperpl. PMN	PMN	Alv. hyperpl. PMN	Edema. Alv. hyperpl. PMN	Edema. Alv. hyperpl. PMN	5	3 days	Yes-C	+2
Edema. HM. PMN	Edema. HM. PMN	Edema. HM. PMN	Edema. HM. PMN	Edema. HM. PMN	12	3 days	Yes-C	+9
					Mean (SD) 5.5 (4.5)	Mean (SD) 1.7 (3.5)		

Alv. hyperpl.: alveolar cell hyperplasia; ARDS: acute respiratory distress syndrome; C: concordance between the clinical and pathological duration of ARDS; Chron.-P: estimated duration of distress on the basis of the histopathological findings; Difference: difference between the clinical and pathological duration of ARDS; HM: hyaline membranes; Interst. infl.: interstitial inflammation; LLL: lower left lobe; LRL: lower right lobe; MRL: middle right lobe; PMN: polymorphonuclear cells; SD: standard deviation; T. ARDS: clinical duration (course) of distress; ULL: upper left lobe; URL: upper right lobe; Yes-C: Existence of concordance.

*Absence of pathological findings. No: absence of concordance.

Table 2 Concordance tests. Results of the ARDS diagnostic concordance study

	Presence of acute alveolar damage	Absence of acute alveolar damage
Clinical diagnosis of ARDS	15	2
No clinical diagnosis of ARDS	1	67

Kappa index: 0.88.
Sensitivity=94%; Specificity=97%.

confusion persisted up until the 1994 Consensus Conference,[3] which now represents a reference and point of inflexion for all professionals, since it makes use of common criteria and language in application to ARDS. The main difficulty is that according to the Consensus Conference, the diagnosis is based on two principal criteria: radiological (conditioned by observer skill and subjective clinical criterion) and blood gases (in which PEEP is not contemplated or used); as a result, a patient could easily shift from a PaO_2/FiO_2 ratio of ≤ 200 to >200 by simply modifying the ventilatory pattern. This explains the ongoing existence of criticism of the mentioned Consensus Conference, though the latter is universally recognized as a step forward. In the same way as other Consensus Conferences, studies are needed to support the criteria used, including prospective studies to establish new criteria aimed at improving the precision of the diagnostic criteria of ARDS. In this context, studies that attempt to correlate the histopathological findings in ARDS to the clinical picture and to the degree of alveolar damage are limited.

The reason for selecting secondary ARDS was largely based on the difficulties of distinguishing among the primary syndrome, bilateral pneumonia and ARDS generated by mechanical ventilation. In fact, at present the lung damage caused by mechanical ventilation can be regarded as a source of ARDS and multiorgan dysfunction.[14] In this sense, we found it reasonable to initially assess whether the clinical criteria for diagnosing ARDS are valid in secondary ARDS (at a distance), since the physiopathological mechanisms of the primary syndrome are not necessarily analogous to those of the secondary syndrome.

In this study we feel that we have been able to confirm that the currently applied ARDS diagnostic criteria are reliable and valid in secondary ARDS and make it possible to establish development of the syndrome in the initial phase with considerable reliability. The satisfactory concordance index in the upper range indicates not only that there is good concordance in the diagnosis of ARDS but also that the timing of the clinical diagnosis is opportune.

Another aspect worth mentioning, and which has not been addressed in our study, is the proportion of patients with histopathological findings compatible with ARDS and who do not meet clinical criteria of the syndrome - such examples representing false-negative cases. In our series we recorded one such case.

However, given the limited number of patients involved, we consider it necessary to expand upon the series, including patients with both primary and secondary ARDS, and assessing whether the clinicopathological correlation is equally strong in both.

Table 3 Concordance tests. Results of the clinico-histopathological evolutive concordance study

Clinical evolution	Histopathological evolution		
	Edema	Hyaline membrane	Fibrosis
<48 h	2	0	0
3-7 days	0	7	1
>7 days	0	1	4

Kappa index: 0.77.

Conflict of interest

The authors declare no conflict of interest.

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