JOURNAL OF FORENSIC SCIENCES

J Forensic Sci, September 2010, Vol. 55, No. 5
doi: 10.1111/j.1556-4029.2010.01413.x
Available online at: interscience.wiley.com

CASE REPORT

PATHOLOGY AND BIOLOGY

Francesco Ventura,[1] *M.D., Ph.D.; Alessandro Bonsignore,*[1] *M.D.; Raffaella Gentile,*[2] *M.D.; and Francesco De Stefano,*[1] *M.D.*

Two Fatal Cases of Hidden Pneumonia in Young People*

ABSTRACT: Acute respiratory distress syndrome (ARDS) is a severe lung disease characterized by inflammation of the lung parenchyma leading to impaired gas exchange. This condition is often lethal, usually requiring mechanical ventilation and admission to an intensive care unit. We present two fatal cases of hidden pneumonia in young people and discuss the pathophysiological mechanism of ARDS with reference to the histological pattern. A complete forensic approach by means of autopsy and histological, immunohistochemical, and microbiological, examination was carried out. In both cases the cause of death was cardio-respiratory failure following an acute bilateral pneumonia with diffuse alveolar damage and ARDS associated with sepsis and disseminated intravascular coagulation. Our cases suggest on one side the importance of an early diagnosis to avoid unexpected death while on the other that the diagnosis of ARDS has to be confirmed on the basis of a careful postmortem examination and a complete microscopy and microbiological study.

KEYWORDS: forensic science, forensic pathology, hidden pneumonia, adult respiratory distress syndrome, diffuse alveolar damage, sudden death, young people

Acute respiratory distress syndrome (ARDS) is a severe lung disease characterized by inflammation of the lung parenchyma leading to impaired gas exchange with concomitant systemic release of inflammatory mediators by local epithelial and endothelial cells, causing inflammation, hypoxemia resulting often in multiple organ failure (MOF), and disseminate intravascular coagulation (DIC) (1). This condition is often lethal, usually requiring mechanical ventilation and admission to an intensive care unit (2).

Physiopathologically when the endothelium of lung capillaries and the alveolar epithelium are damaged, plasma and blood flood the interstitial and intra-alveolar spaces. Such a change implies decreased lung compliance, pulmonary hypertension, reduced functional capacity, compromised ventilation/perfusion ratio, and hypoxemia (3).

Acute respiratory distress syndrome can occur within 24–48 h of an injury or attack of acute illness. In such a case the patient usually presents with shortness of breath and tachypnea, usually associated with hypoxemia, petechiae in the axillae, and neurologic abnormalities such as mental confusion (4).

Typical histological presentation involves diffuse alveolar damage (DAD) and hyaline membrane formation in alveolar walls (5). Hyaline membranes, especially, as a result of the acute inflammatory processes in the alveolar compartment (6) is the histological hallmark of ARDS.

[1]Department of Legal and Forensic Medicine, University of Genova, Via de Toni 12, 16132 Genova, Italy.
[2]Department of Clinical Pathology, San Martino Hospital, Piazza R. Benzi 10, 16132 Genova, Italy.
*Presented at the 61st Annual Meeting of the American Academy of Forensic Sciences, February 16–21, 2009 in Denver, CO.

Received 30 Mar. 2009; and in revised form 10 July 2009; accepted 12 July 2009.

If the underlying disease or injurious factor is not removed, the amount of inflammatory mediators released by the lungs in ARDS may result in a systemic inflammatory response syndrome (or sepsis if there is lung infection) (7). The evolution toward shock and/or MOF follows the same pathophysiological path of sepsis (8).

It is estimated that ARDS is caused by septic shock—characterized by leukocytosis or leukopenia, fever, hypotension, and the identification of a potential source of systemic infection with positive blood cultures for pathogenous agents—in more than 30% of cases (9).

Pneumonia is thought to be the most common lung disease leading to ARDS as it determines a direct lung injury in the immunocompetent host (10).

In cases of severe ARDS the survival rate is 50% with appropriate and early treatment, but if the ARDS-induced severe hypoxemia is not recognized and treated or if the disease reaches medical attention only in the terminal phase then cardio-respiratory arrest occurs in more than 90% of patients (11).

We present two fatal cases of hidden pneumonia in young people who died within a few hours. The clinical presentation, the radiological and laboratory findings in one case, and the postmortem examination with histological, immunohistochemical, and microbiological exams in both cases, led us to conclude for an acute cardio-respiratory failure secondary to bilateral pneumonia with DAD and consequently ARDS associated with sepsis and DIC. The features of the disease are discussed with reference to the histological and immunohistochemical evaluation.

Case 1

A 29-year-old man was found dead at home by his girlfriend who was sleeping with him. The night before he went out with

his friends and came back home late. His friends reported that nothing "strange" happened during the evening he spent with them. The day after, in the afternoon, when he should wake up his girlfriend saw the presence of foam around his mouth and nose and when she tried to wake him up he did not respond. So she called the emergency services who could do nothing but declare him dead.

He took psychodrugs and was known to be a drug addict and a heavy drinker. Family history was reported negative for sudden death. Death scene investigation was unremarkable.

Autopsy Findings

A complete postmortem examination was performed 4 days after death. External examination did not show any visible sign of injury. The internal examination revealed polyvisceral stasis, diffuse microthrombosis, cerebral and pulmonary edema. Free citrine liquid was found on both sides of the pleural cavities. A marked lung congestion and the release of foamy material were bilaterally observed. "Hydrostatic docimasia" for large and small fragments was bilaterally positive in all fields. Also known as "the flotation test," or "the lung test," this old test is still in use to check if there are areas of increased density within the adult lung parenchyma. In these cases lung specimens, being not inflated with air, do not float. Such is the case of pneumonia (12).

Histological Studies and Findings

The microscopic histological study, performed using formalin-fixed paraffin-embedded tissue sectioned at 4 μm and stained with hematoxylin-eosin (H&E), revealed the typical findings of DAD: alveolar septa mildly thickened by edema and capillary congestion, alveolar edema, hyaline membranes lining the denuded alveolar walls, hyperplastic type II pneumocytes, alveolar infiltrates of polymorphonuclear neutrophilic leukocytes, pigmented macrophages, monocytes and plasma cells (Fig. 1*A*), fibrin thrombi in small arteries. In some fields, numerous endoalveolar erythrocytes were also observed. Bronchial walls presented epithelial denudation, inside the lumen there were infiltrates of leukocytes, mostly neutrophils, and a moderate quote of eosinophilic amorphous material.

All these findings were suggestive for a typical DAD in the early exudative phase, confirmed by the positive results to immunohistochemical dye for surfactant apoprotein (PE-10) that outlines hyperplastic type II pneumocytes (13). Fungal infections were not found on slides by Grocott staining. Gram staining did not give evidence for bacterial colonies. The examination of other histological samples was unremarkable.

The lung samples were also examined under a confocal laser scanning microscope (14), and a three-dimensional reconstruction was performed (Fig. 2).

Microbiological Studies and Findings

Additional microbiological tests (15) to identify possible pathogenous agents were carried out through isolation of nucleic acids from formalin-fixed paraffin-embedded tissue sections. To control the course of extraction and check for PCR inhibitors, a fragment of the *Homo sapiens* beta-globin gene was amplified. The purified DNA sample was negative for all bacterial cultures. The positive result for beta-globin demonstrated that the DNA extraction procedure was efficient in extracting amplifiable DNA from the sample.

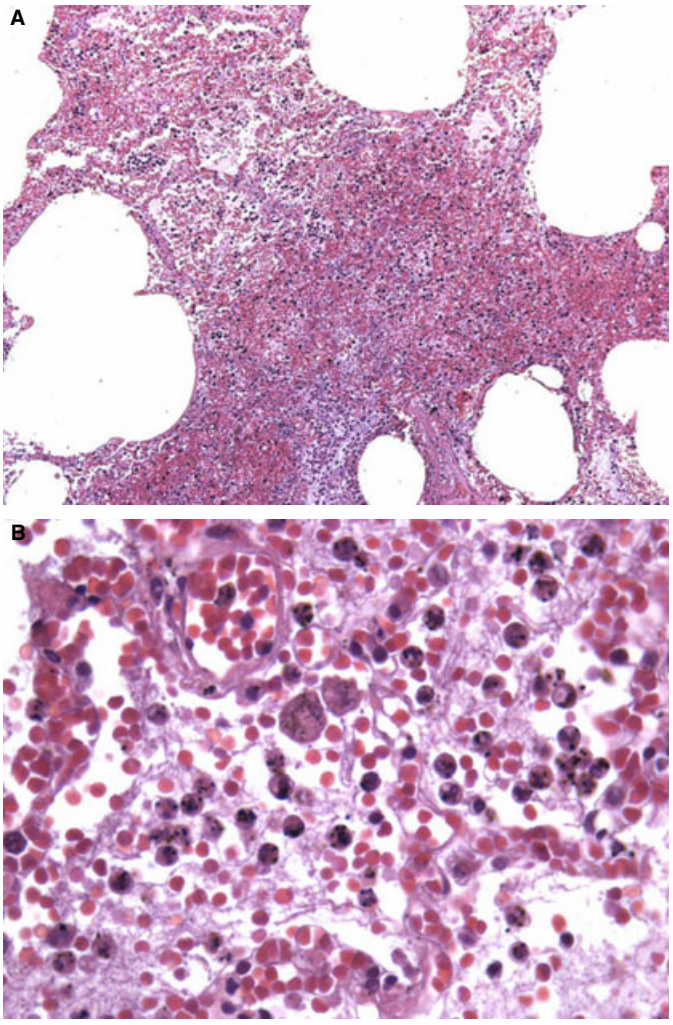

FIG. 1—*Alveolar infiltrates of polymorphonuclear neutrophilic leukocytes, pigmented macrophages, monocytes and plasma cells, and hyaline membranes (Hematoxylin and eosin). Case 1 (A) and case 2 (B).*

Toxicology was negative for drugs and alcohol. Thus, viral infection was a diagnosis of exclusion, according with recent literature which reports a prevalence of viral etiologies in community-acquired pneumonia up to 9% (16) and an extremely high incidence of lung injury and ARDS arising from coronavirus and avian influenza virus infection (17,18).

Case 2

A 31-year-old previously healthy man presented to the hospital with a 12-h history of sore throat, fever, and cough. The clinical prodromes were followed by the acute onset of increasing shortness of breath quickly progressing in acute respiratory failure with hemoptysis. Chest X-ray demonstrated bilateral diffuse airspace opacification; the high-resolution CT (HRCT) confirmed the presence of bilateral, symmetric diffuse ground-glass attenuation associated with liquid in pleural cavities. The patient was admitted to the intensive care unit with severe leukopenia, but he got worse and after few hours died. Two postmortem blood cultures were positive for group A beta-hemolytic Streptococcus which is well known for causing invasive disease leading to death even though diagnosis is not always made in life, as in this case (19). No other pathogenous agents were present.

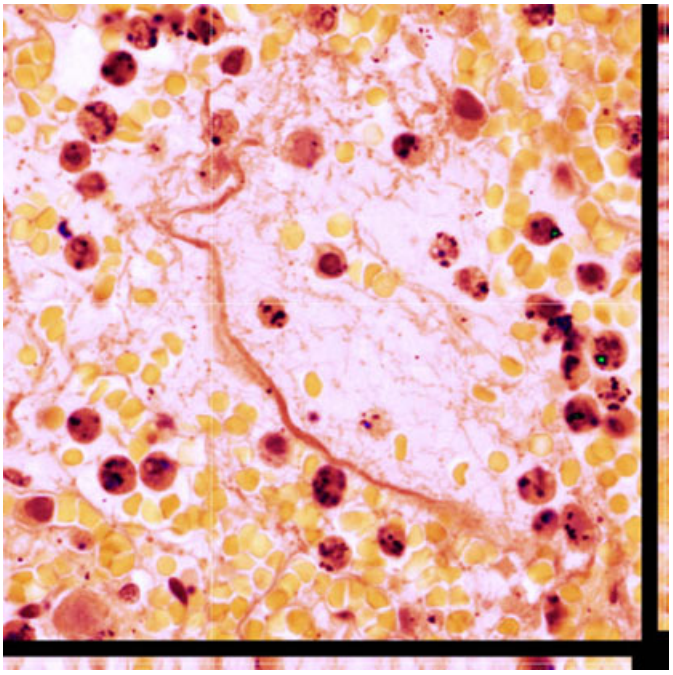

FIG. 2—*Three-dimensional reconstruction of hyaline membranes examined under a confocal laser scanning microscope.*

Autopsy Findings

An autopsy was performed within 48 h after death. External examination was irrelevant. Internal examination revealed an increased consistency and weight of the lungs (1070 g the left and 1100 g the right respectively) with positive hydrostatic docimasia in all fields and intense congestion which was ascribed to a bilateral pneumonia. The examination of other organs was unremarkable except for intense polyvisceral stasis.

Histological Studies and Findings

The histological examination of lung specimens (one sample per lobe and more samples in increased thickening pulmonary areas as common practice), performed by using the same method described earlier for the previous case, showed alveolar septa that mildly thickened by edema and capillary congestion, alveolar edema, hyaline membranes coating alveolar septal surfaces, flattened pneumocytes, alveolar infiltrates of polymorphonuclear neutrophilic leukocytes, pigmented macrophages, monocytes and plasma cells, fibrin thrombi in small arteries (Fig. 1*B*). All these findings suggested a typical DAD, confirmed by positive results to immunohistochemical dye for surfactant apoprotein (PE-10) (data not shown) (13).

In the kidneys was found a thrombotic microangiopathy compatible with DIC. The lung samples were examined under a confocal laser scanning microscope, and a three-dimensional reconstruction was performed (14).

Results and Discussion

The silent (case 1) and the paucisymptomatic (case 2) presentations, and the histological and immunohistochemical findings led us to the diagnosis of ARDS supporting the conclusion that both were affected by a quite rare type of pulmonitis definable as hidden pneumonia.

Acute respiratory distress syndrome is a pathological entity arising from multiple pulmonary or extrapulmonary causes (20). Generally, patients with ARDS report a short prodromal illness characterized by few symptoms like fever and cough, followed by the acute onset of progressive shortness of breath which rapidly evolves to respiratory failure (21). Chest radiographs typically show bilateral diffuse airspaces opacifications (22). Chest HRTC scans are significative for bilateral ground-glass attenuation (23). The histological features of ARDS, investigated from open lung biopsies or autopsies, are those of DAD, a nonspecific pattern of acute lung injury (24).

Acute respiratory distress syndrome has a poor prognosis, with reported mortality rates still appearing to be higher than 50% (25).

The first case concerns a 29-year-old man found lifeless at home by his girlfriend. At autopsy polyvisceral stasis, diffuse microthrombosis, free citrine liquid on both sides of the pleural cavities, a marked lung congestion, and the release of foamy material were found. Hydrostatic docimasia for large and small fragments was bilaterally positive in all fields. The histological evaluation of lungs samples stained with H&E, also examined under a confocal laser scanning microscope, gave evidence of a pattern of DAD. The presence of hyperplastic type II pneumocytes and hyaline membranes was confirmed by the positive reaction of the immunohistochemical dye for surfactant apoprotein (PE-10). Additional tests were carried out to identify possible pathogenous agents through microbiological studies but all the cultures showed no bacterial growth. Toxicology was negative for drugs and alcohol.

The second case involves a 31-year-old previously healthy man who presented, after a 12-h history of sore throat, fever, and cough, an acute onset of increasing shortness of breath rapidly progressing in acute respiratory failure with hemoptysis. Chest X-ray and HRCT showed the typical pattern of ARDS, with bilateral, symmetric, diffuse ground-glass attenuation. Despite admittance to the intensive care unit, the patient died after few hours. Two blood cultures were positive for group A beta-hemolytic Streptococcus. The macroscopical and histological patterns were similar to that of case 1.

In both cases the cause of death was attributed to an acute cardio-respiratory failure secondary to acute bilateral pneumonia and consequently ARDS, sepsis, and DIC.

These cases demonstrate how ARDS can rapidly lead to death in young patients that can generally be successfully treated in case of pneumonia.

In the first case the postmortem diagnosis of ARDS and sepsis with DIC (26) was made exclusively on the basis of a careful postmortem examination and a complete histological study.

Therefore, the authors underline that forensic pathological procedures should be applied in all cases of sudden death using systematic practical investigations to find the cause of death, more so in fatal cases involving young people. Just in this way it is possible to perform an adequate differential diagnosis when sudden cardiac death is more likely to be expected because of the young age of the patient.

The second case, which has attracted the medicolegal interest because of medical liability profiles that were assumed as fault for doctors, suggests that clinicians should be suspicious of all community-acquired pneumonia (27), especially in young people, because rigorous diagnosis as well as early and appropriate therapy is mandatory to avoid unexpected death (28).

Particularly, from a forensic point of view, in such cases the authors suggest the importance of taking postmortem bacterial and viral cultures.

Last, the forensic community should not forget the role played by ARDS as a potential cause of sudden and unexpected death in previously healthy young people.

Acknowledgments

The authors thank Prof. Vittorio Fineschi for his help in histological and immunohistochemical studies. They also thank Margherita Neri, M.D. and Irene Riezzo, M.D. for their excellent technical assistance in confocal microscopy. Finally the authors thank Claudio Giacomazzi, M.D. for his help in microbiological studies.

References

1. Hardaway RM, Vasquez Y. A shock toxin that produces disseminated intravascular coagulation and multiple organ failure. Am J Med Sci 2001;322(4):222–8.
2. Malhotra A. Low-tidal-volume ventilation in the acute respiratory distress syndrome. N Engl J Med 2007;357(11):1113–20.
3. Bernard G, Artigas A, Brigham K, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149(3):818–24.
4. Irwin RS, Rippe JM. Irwin and Rippe's intensive care medicine, 5th edn. Baltimore, MD: Lippincott Williams & Wilkins, 2003.
5. Cotran RS, Kumar V, Fausto N, Robbins SL, Abbas AK Robbins and Cotran pathologic basis of disease. St. Louis, MO: Elsevier Saunders, 2005;715.
6. Peres e Serra A, Parra ER, Eher E, Capelozzi VL. Nonhomogeneous immunostaining of hyaline membranes in different manifestations of diffuse alveolar damage. Clinics 2006;61(6):497–502.
7. Ware L, Matthay M. The acute respiratory distress syndrome. N Engl J Med 2000;342(18):1334–49.
8. Abraham E, Singer M. Mechanisms of sepsis-induced organ dysfunction. Crit Care Med 2007;35(10):2408–16.
9. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003;31(4):1250–6.
10. Sloane PJ, Gee MH, Gottlieb JE, Albertine KH, Peters SP, Burns JR, et al. A multicenter registry of patients with acute respiratory distress syndrome. Physiology and outcome. Am Rev Respir Dis 1992;146(2):419–26.
11. Amato M, Barbas C, Medeiros D, Magaldi R, Schettino G, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998;338(6):347–54.
12. Chapman HC. Docimasia pulmonum hydrostatica. In: Chapman HC, editor. A manual of medical jurisprudence, insanity and toxicology, 3rd edn. Philadelphia, New York, London: Saunders & Company, 1903;192–4.
13. Turillazzi E, Di Donato S, Neri M, Riezzo I, Fineschi V. An immunohistochemical study in a fatal case of acute interstitial pneumonitis (Hamman-Rich syndrome) in a 15-year-old boy presenting as sudden death. Forensic Sci Int 2007;173(1):73–7.
14. Turillazzi E, Karch SB, Neri M, Pomara C, Riezzo I, Fineschi V. Confocal laser scanning microscopy. Using new technology to answer old questions in forensic investigations. Int J Legal Med 2008;122(2):173–7.
15. Ridgway EJ. The microbiology of the autopsy. In: Burton JL, Rutty GN, editors. The hospital autopsy, 2nd edn. London: Arnold, 2001;134–46.
16. de Roux A, Marcos MA, Garcia E, Mensa J, Ewig S, Lode H, et al. Viral community-acquired pneumonia in nonimmunocompromised adults. Chest 2004;125(4):1343–51.
17. Beigel JH, Farrar J, Han AM, Hayden FG, Hyer R, de Jong MD, et al. Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5. Avian influenza A (H5N1) infection in humans. N Engl J Med 2005;353(13):1374–85.
18. Bauer TT, Ewig S, Rodloff AC, Müller EE. Acute respiratory distress syndrome and pneumonia: a comprehensive review of clinical data. Clin Infect Dis 2006;43(6):748–56.
19. Batalis NI, Caplan MJ, Schandl CA. Acute deaths in nonpregnant adults due to invasive streptococcal infections. Am J Forensic Med Pathol 2007;28(1):63–8.
20. Pelosi P, Caironi P, Gattinoni L. Pulmonary and extrapulmonary forms of acute respiratory distress syndrome. Semin Respir Crit Care Med 2001;22(3):259–68.
21. Esteban A, Fernández-Segoviano P, Frutos-Vivar F, Aramburu JA, Nájera L, Ferguson ND, et al. Comparison of clinical criteria for the acute respiratory distress syndrome with autopsy findings. Ann Intern Med 2004;141(6):440–5.
22. Kobayashi H, Itoh T, Sasaki Y, Konishi J. Diagnostic imaging of idiopathic adult respiratory distress syndrome (ARDS)/diffuse alveolar damage (DAD). Hystopathologic correlation with radiological imaging. Clin Imaging 1996;20:1–7.
23. Goodman LR, Fumagalli R, Tagliabue P, Tagliabue M, Ferrario M, Gattinoni L, et al. Adult respiratory distress syndrome due to pulmonary and extrapulmonary causes: CT, clinical, and functional correlations. Radiology 1999;213(2):545–52.
24. Tomashefski JF Jr. Pulmonary pathology of acute respiratory distress syndrome. Clin Chest Med 2000;21(3):435–66.
25. Brun-Buisson C, Minelli C, Bertolini G, Brazzi L, Pimentel J, Lewandowski K, et al. Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. Intensive Care Med 2004;30(1):51–61.
26. Tsokos M. Post-mortem diagnosis of sepsis. Forensic Sci Int 2007;165:155–64.
27. Mandell LA, Bartlett JG, Dowell SF, File TM Jr, Musher DM, Whitney C, et al. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 2003;37(11):1405–33.
28. Estenssoro E, Dubin A, Laffaire E, Canales H, Sáenz G, Moseinco M, et al. Incidence, clinical course, and outcome in 217 patients with acute respiratory distress syndrome. Crit Care Med 2002;30(11):2450–6.

Additional information and reprint requests:
Francesco Ventura, M.D., Ph.D.
Department of Legal and Forensic Medicine
University of Genova
Via de Toni 12
16132 Genova
Italy
E-mail: francesco.ventura@unige.it