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Pulmonary histopathologic abnormalities and predictor variables in autopsies of burned pediatric patients

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ABSTRACT

Pulmonary abnormalities occur in 30–80% of fatalities after burn. The objective of our study is to investigate lung pathology in autopsy tissues of pediatric burn patients.

Methods: Three scientists with pathology training in pediatric burn care reviewed masked autopsy slides of burned children who died after admission to a burn center from 2002 to 2012 ($n = 43$). Autopsy lung tissue was assigned scores for histologic abnormalities in 9 categories, including alveolar and interstitial fibrosis, hyaline membranes, and type II epithelial cell proliferation. Scores were then tested for correlation with age, TBSA burn, number of days between burn and death, time between burn and admission, and the presence of inhalation injury using analyses with linear models.

Results: Type II epithelial cell proliferation was significantly more common in cases with a longer time between burn and admission ($p < 0.02$). Interstitial fibrosis was significantly more severe in cases with longer survival after burn ($p < 0.01$). The scores for protein were significantly higher in cases with longer survival after burn ($p < 0.03$). Enlarged air spaces were significantly more prominent in cases with longer survival after burn ($p < 0.01$), and in cases with the presence of inhalation injury ($p < 0.01$).

Conclusions: Histological findings associated with diffuse alveolar damage (DAD), which is the pathological correlate of the acute respiratory distress syndrome (ARDS), were seen in approximately 42% of autopsies studied. Protein-rich alveolar edema, which is the abnormality that leads to ARDS, may occur from multiple causes, including inhalation injury.

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Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; DAD, diffuse alveolar damage; IRB, Institutional Review Board; mm Hg, Millimeters of Mercury; PaO_2:FiO_2, partial pressure of oxygen to fraction inspired of oxygen ratio; SHC-G, Shriners Hospitals for Children-Galveston; TBSA, total body surface area burn; UTMB, University of Texas Medical Branch.

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1. Introduction

Pulmonary pathologic abnormalities occur in 30–80% of deaths from burn [1]. Pulmonary disease exists in several forms, including acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). ARDS is caused by protein-rich pulmonary edema, which reflects disruption of the lung endothelium and epithelium and impairs carbon dioxide release [2]. The clinical definition of ARDS includes acute onset, bilateral lung infiltrates by radiography, and a partial pressure of oxygen to fraction inspired of oxygen ratio (PaO_2:FiO_2) of less than 200 mmHg [3]. In current terminology, patients with PaO_2:FiO_2 of 200–300 mm Hg are diagnosed as having mild ARDS.

Diffuse alveolar damage (DAD) is the histopathologic correlate of ARDS [4]. The acute phase (days 1–6) is characterized by interstitial and alveolar edema, the presence of macrophages, neutrophils and red blood cells in alveoli, endothelial and epithelial cell injury, and hyaline membranes in the alveoli. Following the acute phase, the subacute phase (days 7–14) is identified by proliferation of type II epithelial cells and fibroblasts and collagen deposition. The chronic phase (>day 14) is recognized by resolution of the acute neutrophilic infiltrate, with increased mononuclear cells and alveolar macrophages, more fibrosis, and alveolar epithelial repair [4].

By evaluating multiple histopathologic abnormalities that have been associated with ARDS, we have quantitatively assessed the components of DAD in pediatric nonsurvivors of burns. In the present study, we determined the relationship between the histopathologic abnormalities of DAD and patient characteristics, including age, total body surface area (TBSA) burn, number of days between burn and death, and number of days between burn and admission, in a series of autopsies spanning a 10-year period at one institution.

2. Materials and methods

2.1. *Patient demographics and injury characteristics*

Nonsurviving patients 0–18 years of age who were admitted to the Shriners Hospitals for Children-Galveston (SHC-G) between 2002 and 2012 were included in the study. Slides that were available for the cases autopsied from 2002 to 2012 were reviewed, and cases in which all slides were affected by infection were excluded. Most of the patients had flame burns, but patients with scald burns, injury in explosions or extensive loss of skin due to toxic epidermal necrolysis were also included. The Institutional Review Board (IRB) of the University of Texas Medical Branch (UTMB) granted an exemption for this study. Over 99% of patients who died allowed samples of lung tissue to be taken for diagnosis and research at the time of autopsy. Postmortem examinations included gross and microscopic examination of all organs, written descriptions of the gross and microscopic findings and preparation of macro photographs, and micrographs. In addition to the findings described in this study, the presence or absence of pneumonia or other evidence of invasive infection of internal organs, aspiration of gastric contents, vascular thrombi, bone marrow emboli, pneumothorax, and pleural effusions were noted. Cultures for bacteria and fungi were taken when internal infection was suspected. Histologic samples of lung tissue were taken from visible lesions and relatively unaffected areas. In most cases one lung was sampled in fresh condition and the other was inflated with 10% formalin and fixed overnight prior to sampling for histology. Determination of the cause of death based on autopsy findings correlated well with the clinical diagnoses, but patients with a clinical diagnosis of sepsis often had pneumonia as the only evidence of infection of internal organs, so that pneumonia was considered the immediate cause of death. Subject age, gender, ethnicity, percent of TBSA burned, and percent third degree TBSA burned were recorded at the time of admission. Age-appropriate diagrams were used to determine burn size [5]. Patients were treated according to our previously described standard of care [6].

2.2. *Scoring*

Three scientists with pathology training, one of them a board-certified pediatric pathologist, viewed masked autopsy slides from the lungs of burned children. The histopathologic features related to ARDS/DAD that were scored include: edema, fibrosis, hemorrhage, interstitial fibrosis, hyaline membranes, organized hyaline membranes, protein, type II epithelial cells, and enlarged air spaces. Fibrosis was scored as a percentage from 0 to 100%, which represented the area of the slide that was covered by fibrotic tissue. All other features were scored from 0 to 4, with 4 representing the most severe expression of each abnormality in the entire group. Alveolar fibrosis was scored (0–4) based on the presence of fibroblast-like cell and collagen in alveolar spaces. Scores were assigned for protein when amorphous granular material was seen within alveoli. Regions affected by infection (pneumonia) were excluded from scoring on each slide. All sections were analyzed by each of the three scientists, and the final score for each abnormality per case represented the mean of the three scores. Scoring of histologic findings in this way has been employed by many pathologists and has been used in our research using a large animal model of smoke inhalation injury [7,8]. The specific scale used in this study was developed based on the findings in the autopsies to be studied.

2.3. *Statistical Analysis*

The nine response variables that represented histopathologic abnormalities included edema, fibrosis, hemorrhage, interstitial fibrosis, hyaline and organized hyaline membranes, protein, type II epithelial cells, and enlarged air spaces. The four predictor variables included number of days from burn to death, age, percent TBSA burned, and presence of inhalation injury. These four variables were selected because they were expected to show strong correlation with the features of DAD. The Wilcoxon Rank Sum Test with continuity correction was used to analyze edema, fibrosis, and hemorrhage, while the zero-inflated Poisson model was used to analyze interstitial fibrosis, hyaline membranes, organized hyaline membranes, protein, and enlarged air spaces. Logistic regression was used to model the relation of non-zero scores (as opposed to zero