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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 injury. 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 2002–2012 (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 ($p<0.01$).

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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.

Keywords

Diffuse alveolar damage; Adult Respiratory Distress Syndrome; predictor variables; Pediatric patients; survivability; histology; scoring

INTRODUCTION

Pulmonary pathologic abnormalities occur in 30–80% of deaths from burn injury (Herndon, Barrow et al. 1988). 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 (Ashbaugh, Bigelow et al. 1967). 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 ($\text{PaO}_2:\text{FiO}_2$) of less than 200 mmHg (Bernard, Artigas et al. 1994). In current terminology, patients with $\text{PaO}_2:\text{FiO}_2$ of 200–300 mm Hg are diagnosed as having mild ARDS.

Diffuse alveolar damage (DAD) is the histopathologic correlate of ARDS (Bachofen and Weibel 1977). 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 (Bachofen and Weibel 1977).

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 ten-year period at one institution.

MATERIALS AND METHODS

Patient Demographics and Injury Characteristics

Non-surviving patients 0 to 18 years of age who were admitted to the Shriners Hospitals for Children-Galveston (SHC-G) between 2002 to 2012 were included in the study. Slides that were available for the cases autopsied from 2002 to 2012 were reviewed, and cases with 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 of third-degree TBSA burned were recorded at the time of admission. Age-appropriate diagrams were used to determine burn size (Mlcak and Buffalo 2007). Patients were treated according to our previously described standard of care (Herndon, Rodriguez et al. 2012).

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 0–100%, which represented the area of the slide that was covered by fibrotic tissue. All other features were scored from 0–4, 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 ((Budwit-Novotny, McCarty et al. 1986; Murakami, McGuire et al. 2003)). The specific scale used in this study was developed based on the findings in the autopsies to be studied.

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 of 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 scores) of type II epithelial cells to third degree TBSA burn and days between burn and admission. The days between burn and admission were log-transformed to better approximate a normal distribution. All tests assumed a 95% level of confidence, and analyses were performed with R Statistical Software (R Core Team, 2012, Version 2.15.3).

RESULTS

Semi-quantitative scores included percentage of fibrosis and scores from 0 to 4 for interstitial fibrosis, alveolar fibrosis, edema, hemorrhage, hyaline membranes, organized hyaline membranes, protein, enlarged air spaces, and type II epithelial cells. The mean outcome scores were compared and the scores for all cases were assessed for correlation with four possible predictor variables: number of days from burn to death, age, TBSA burned, and inhalation injury. Table 1 shows the demographic information from the 43 subjects, and Table 2 shows the primary clinical causes of death for each subject.

Examples of scoring for five of the measured outcomes based on histological analysis are included in Figures 1–5. Figure 1 shows (A) 0%, (B) 10%, (C) 25%, and (D) 55% fibrosis. Figure 1B is from a patient whose lungs display septal thickening compared to Figure 1A. The greatest percentage of fibrosis that was seen in all 43 patients is seen in Figure 1D, in which most of the surface area of the section was occupied by fibrous tissue. Figure 2A shows a score of 0 for interstitial fibrosis, while Figure 2B shows a score of 1, Figure 2C shows a score of 3, and Figure 2D shows a score of 4. A score of 0 for type II epithelial cells is shown in Figure 3A, while 3B shows a score of 1, 3C shows a score of 2, and 3D shows a score of 3. Figure 3A displays an intact and flat epithelium, while Figure 3D shows a thickened and cuboidal-shaped epithelium indicating proliferation of type II cells. Figure 4A shows a score of 0 for enlarged air air spaces, while 4B indicates a score of 1, 4C indicates a score of 3, and 4D indicates a score of 4. The abnormality scored under the heading “protein” has not been described in the classical histopathological descriptions of DAD. It represents aggregates of amphophilic dense material in alveolar spaces that does not resemble hyaline membranes and is not adjacent to alveolar septa. Figure 5A shows a score of 0 for protein, while 5B indicates a score of 1, 5C indicates a score of 2, and 5D indicates a score of 4.

Type II epithelial cell proliferation was associated with time between burn and admission

The logistic regression relating non-zero scores for Type II cells to third degree TBSA burned and days from burn to admission (Table 3) found a significant increase in the odds of a patient having a non-zero score with increasing percent of third degree TBSA burn ($p=0.047$) and a significant increase in the odds with increasing days between burn and admission ($p=0.020$, Figure 6). The model indicated that each 1% reduction in percent of third degree TBSA burn corresponded to a 5.5% decrease in the odds of a non-zero score,

with a 95% confidence interval spanning 0.1% to 11.2%. The odds of a non-zero type II cell score increased by 254% for every doubling of time between burn and admission.

The severity of interstitial fibrosis increased with longer survival after burn

The logistic regression relating interstitial fibrosis scores to days from burn to death, age, percent of total TBSA burn, and presence of inhalation injury (Table 3) found a significant increase in the odds of a patient having a higher score for interstitial fibrosis with increasing days from burn to death ($p=0.010$, Figure 7). Interstitial fibrosis score increased by 39% for every doubling of time between burn and death.

Protein scores significantly increased in cases with longer survival after burn

The logistic regression relating protein scores to days from burn to death, age, percent of total TBSA burn, and presence of inhalation injury (Table 3) found a significant increase in the odds of a patient having a higher score for protein with increasing days from burn to death ($p=0.028$, Figure 8). The protein score increased by 45% for every doubling of time between burn and death.

Enlarged air spaces were significantly associated with longer survival after burn and with the presence of inhalation injury

Table 3 shows a significant increase in the odds of a patient having a higher score for enlarged air spaces with increasing days from burn to death ($p=0.012$, Figure 9) and with the presence of inhalation injury ($p=0.011$). The score for enlarged air spaces increased by 66% for every doubling of time between burn and death, and it increased by 450% for those with inhalation injury.

DISCUSSION

We explored possible relationships between the histopathologic abnormalities of diffuse alveolar damage (DAD) and demographic variables including age, percent of total body surface area (TBSA) burned, number of days between burn and death, and number of days between burn and admission. We found that type II epithelial cell proliferation was significantly more frequent in autopsy cases with more days between burn and admission. Additionally, we established that in fatal cases with longer post burn survival, histological scores for interstitial fibrosis, protein, type II epithelial cell proliferation and enlarged air spaces were significantly increased.

Pharmacological therapies such as inhaled nitric oxide and other vasodilators, antioxidants, fluid and hemodynamic management, surfactant therapy, glucocorticoids and other anti-inflammatory agents have been evaluated in Phase II and III clinical trials for the treatment of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (Matthay and Zemans 2011). However, these treatments have not been shown to be significantly effective (Cepkova and Matthay 2006). ARDS was an uncommon diagnosis as the primary cause of death in pediatric burned patients at the Shriners Hospital for Children-Galveston from 2002–2012. However, DAD was found in 18 of the 43 patients (42%), even though ARDS was considered the clinical cause of death in only 3 of 43 patients (7%, Table 2). In

comparing the clinical and pathologic diagnoses of the most important causes of death in these patients, it was remarkable that many of the patients who carried a clinical diagnosis of burn wound sepsis were found to have pneumonia as the only evidence of infection in the internal organs at autopsy. Thus the pathologic diagnosis of immediate cause of death was often pneumonia in the presence of burn wound sepsis. In this study the lesions of pneumonia were avoided in the analysis of lesions related to diffuse alveolar damage (DAD), because the tissue surrounding foci of pneumonia often showed edema, hemorrhage and hyaline membranes that were interpreted as effects of infection rather than DAD.

A recent ten-year review from the National Burn Repository documents that the mortality rate was greater for those patients with inhalation injury than those without (27.3% vs 4.5%) (Latenser, Miller et al. 2007). Mlcak, *et al.*, investigated pulmonary dysfunction in 17 patients with $67 \pm 32\%$ TBSA 8 years post-injury (Mlcak, Desai et al. 1998). Thirteen of the 17 children had been diagnosed by bronchoscopy with inhalation injury on admission. Nine of the 17 patients had evidence of obstructive and restrictive lung disease (Mlcak, Desai et al. 1998). A characteristic of restrictive lung dysfunction is increased collagen deposition in the lung, which contributes to fibrosis (Selman, Thannickal et al. 2004). Approximately 54% of the subjects in our 10-year study had inhalation injury (Table 1). However, the presence of inhalation injury was correlated only with enlarged air spaces ($p=0.011$). Since inhalation of toxic smoke is known to be a cause of ARDS, it was surprising that more associations were not found. A possible explanation for the lack of an association between inhalation injury and other evaluated histopathologic abnormalities such as fibrosis might be our small sample size and our semi-quantitative method of analysis. The lack of association between a clinical diagnosis of smoke inhalation injury and autopsy findings of diffuse alveolar damage leads us to suspect that other conditions that have been associated with ARDS, based on clinical and epidemiological findings and/or animal experimentation, might have been present in our cases in numbers sufficient to conceal a relationship to smoke inhalation injury. DAD is not only related to inhalation injury, as ventilatory parameters including duration, extent of hyperoxia and pressures are known to cause lung injury, in addition to sepsis. Thus, the histological parameters associated with inhalation injury in autopsy tissues are nonspecific.

The majority of the literature addressing ARDS encompasses non-burned patients over the age of 60 years. Our 10-year study addresses a pediatric burned population; the average age of our subjects was 7 years, with a range of 5 years (Table 1). It is possible that the pulmonary changes identified by histology in burned children may be different from those of older adults with various injuries. Within the age range of our subjects, the following measured outcomes did not significantly correlate with age: TBSA burn, number of days between burn and death, the incidence of inhalation injury, percentage fibrosis, alveolar fibrosis, edema, hemorrhage, hyaline membranes, and organized hyaline membranes. Future studies will analyze the autopsy reports from adult subjects at the Blocker Burn Unit, the adult burn unit of the University of Texas Medical Branch, which operates in partnership with the Shriners Hospitals for Children in Galveston.

Additionally, the following measured outcomes did not significantly correlate with TBSA burn: age, number of days between burn and death, the incidence of inhalation injury,

percentage fibrosis, interstitial fibrosis, alveolar fibrosis, edema, hemorrhage, hyaline membranes, organized hyaline membranes, protein, enlarged air spaces, and type II epithelial cells. It is possible that the lack of a significant association between TBSA burn and histopathological abnormalities in this study may be due to the high incidence of sepsis, which was the clinical cause of death in 47% of our subjects. Sepsis occurred in patients with burns of varying sizes. Our current results correspond with our previous study of 5,260 pediatric burned patients at the SHC where sepsis was determined to be the leading cause of death (Williams, Herndon et al. 2009). Sepsis represents a factor other than TBSA that is a strong predictor of death. Since sepsis is a recognized cause of ARDS, it may have been the trigger stimulating the pathologic processes recognized as features of DAD at autopsy. We have observed that ARDS, which was once one of the major clinical diagnoses in patients who died after burns, has been an unusual diagnosis during the last decade. The findings of this study suggest that the pathologic processes that lead to ARDS still occur in patients being treated for burns, but that infection is becoming a more frequent cause of death.

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ABBREVIATIONS

ALI	Acute Lung Injury
ARDS	Acute Respiratory Distress Syndrome
DAD	Diffuse Alveolar Damage
IRB	Institutional Review Board
Hg	Millimeters of Mercury
PaO₂:FiO₂	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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(A)

(B)

(C)

(D)

Figure 1.

These micrographs of H&E-stained sections taken at autopsy illustrate the criteria used to assign an estimate for the percentage of the section occupied by fibrosis. Percentage of fibrosis: (A) 0%, (B) 10%, (C) 25%, and (D) 55%. All figures were taken using a 10x objective.

(A)

(B)

(C)

(D)

Figure 2.

Micrographs illustrating the assignment of scores for interstitial fibrosis: (A) score of 0, (B) score of 1, (C) score of 3, and (D) score of 4. All figures were taken using a 10x objective.

Figure 3. Micrographs illustrating the assignment of scores for type II epithelial cells: (A) score of 0, (B) score of 1, (C) score of 2, and (D) score of 3. All figures were taken using a 20x objective.

Figure 4.

Micrographs illustrating the assignment of scores for enlarged air spaces: (A) score of 0, (B) score of 1, (C) score of 3, and (D) score of 4. All figures were taken using a 4x objective.

Figure 5. Micrographs illustrating the assignment of scores for protein aggregates: (A) score of 0, (B) score of 1, (C) score of 2, and (D) score of 4. All figures were taken using a 20x objective.

Figure 6.

This graph shows the model calculated using logistic regression to relate the presence of a non-zero score for Type II cells to the number of days from burn to admission. The data points used to derive the regression curve are also shown.

Figure 7.

This graph shows the model calculated using logistic regression to relate the histologic score for interstitial fibrosis to the number of days between burn and death.

Figure 8.

This graph shows the model calculated using logistic regression to relate the histologic score for “protein” to the number of days between burn and death.

Table 1

Characteristics	Values (n=43)
Age (Years)	7 ± 5
Gender (M:F)	19:24
Ethnicity (Hispanic, %)	31 (72%)
Total TBSA Burn (%) [Median]	60 ± 26 [63]
Third Degree TBSA Burn (%) [Median]	50 ± 31 [58]
Inhalation Injury	23 (54%)
Burn to Admit (Days) [Median]	5 ± 8 [2]
Burn to Deceased (Days) [Median]	29 ± 42 [12.5]

Table 2

Clinical Causes of Death	Number of Patients (n=43)
Cardiovascular	
Cardiac/Cardiopulmonary Arrest	3 (7%)
Neurological	
Brain Death	4 (9%)
Cerebral Edema	3 (7%)
Respiratory	
Asphyxia	1 (2%)
ARDS	3 (7%)
Pneumonia	2 (5%)
Other (Airway Complications)	1 (2%)
Gastrointestinal	
Intestinal Perforation	1 (2%)
Intestinal Necrosis	1 (2%)
Infectious/Hematological	
Sepsis/Septic Shock	20 (47%)
Disseminated Intravascular Coagulation	1 (2%)
Renal	
Renal Failure	2 (5%)
Electrolyte Imbalance	1 (2%)

Table 3

Significance at $p < 0.05$				
	Factor	CI	CI	p -Value
Interstitial Fibrosis				
Days Burn to Death (Log)	1.39	1.08	1.79	0.010
Age (Log)	0.79	0.51	1.22	0.284
Total TBSA Burn (Log)	0.99	0.97	1.00	0.149
Inhalation Injury	1.32	0.54	3.22	0.541
Protein				
Days Burn to Death (Log)	1.65	1.05	2.60	0.031
Age (Log)	0.91	0.57	1.46	0.689
Total TBSA Burn (Log)	1.00	0.98	1.02	0.986
Inhalation Injury	1.33	0.48	3.65	0.582
Enlarged Air Spaces				
Days Burn to Death (Log)	1.66	1.12	2.45	0.012
Age (Log)	0.70	0.37	1.31	0.263
Total TBSA Burn (Log)	0.99	0.97	1.02	0.638
Inhalation Injury	5.52	1.48	20.54	0.011
	Odds Ratio	CI	CI	p-Value
Type II Epithelial Cell Proliferation				
Third Degree TBSA Burn	0.95	0.90	1.00	0.047
Burn to Admit (Log)	2.54	1.16	5.57	0.020