Acute pulmonary oedema: rare causes and possible mechanisms

Yung-Hsiang HSU*, Shang Jyh KAO†, Ru-Ping LEE‡§, and Hsing I. CHEN‡*

*Department of Pathology, Tzu Chi University, Hualien, Taiwan, †Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan, ‡Institute of Medical Sciences, Tzu Chi University, 701, section 3, Chung-Yan Road, Hualien 97004, Taiwan, and §Department of Nursing, Tzu Chi University, Hualien, Taiwan

ABSTRACT

Acute pulmonary oedema usually has a fatal outcome. In this clinical report, we present rare cases of pulmonary oedema that were associated with Japanese B encephalitis, lymphangitis in breast carcinoma, fat embolism due to long-bone fracture, and the rupture of cerebral mycotic aneurysms. A total of 18 patients in the four disease categories were collected in two teaching hospitals in Taipei and Hualien. Upon admission, routine and specific examinations were taken and all patients showed clear lungs by chest X-ray; however, signs of acute pulmonary oedema occurred within 7 days. After resuscitation, all patients died of acute pulmonary oedema. In patients with fat embolism, the levels of non-esterified plasma fatty acids, cGMP, 5-hydroxytryptamine (serotonin) and nitrates/nitrites were increased during pulmonary oedema. Immunohistochemical staining revealed virus infection and neuronal death, predominantly in the medial, ventral and caudal medulla in cases of Japanese B encephalitis. The pulmonary oedema due to central sympathetic activation in Japanese B encephalitis may be related to destruction of depressor mechanisms in the medulla. The rupture of mycotic aneurysms is known to cause cerebral compression that results in acute pulmonary oedema. Blockade of lymphatics, capillaries and venules in breast carcinoma with lymphangitis causes the development of rapid lung oedema. The pathogenesis of pulmonary oedema is much more complicated in fat embolism. Mediators such as cGMP, 5-hydroxytryptamine, nitric oxide and presumably other chemical substances may also be involved.

INTRODUCTION

Oedema formation depends on the balance between hydrostatic and oncotic forces in capillaries and their interstitial forces and lymphatic drainage[1,2]. In humans and animals, acute pulmonary oedema can occur owing to cerebral compression [3–5], enterovirus infection in hand, foot and mouth disease [6], endotoxin shock [7,8], air embolism [9,10] and ischaemia–reperfusion [11,12]. In this clinical investigation, we investigated 18 cases of acute pulmonary oedema associated with Japanese B encephalitis, breast carcinoma with lymphangitis, fat embolism and ruptured cerebral mycotic aneurysms. We report rare types of death associated with pulmonary oedema caused by different mechanisms.

MATERIALS AND METHODS

Patient population

Data from all patients were collected over a period of more than 2 years. Patients were evaluated in two
Teaching hospitals. Table 1 shows the basic major laboratory and pathological findings. After obtaining the consent from either patients or their relatives, a total of 18 patients was studied: six with Japanese B encephalitis, two with breast carcinoma and lymphangitis, six with fat embolism and four in which mycotic aneurysms ruptured into cerebral ventricles.

### Examinations

Upon admission, all patients received routine check-ups including measurement of body weight, body height and blood pressure, and analysis of blood, urine and stool samples; chest X-rays were also taken. Free plasma fatty acid, cGMP, 5-hydroxytryptamine (serotonin) and nitrates/nitrites were determined according to methods that were described previously [13–16]. These were measured because pulmonary oedema might be induced by chemical factors [9,17,18]; for example, our recent report [19] and many others [8,11,18] have revealed that nitric oxide (with nitrate and nitrite end-products) is toxic to the lung and may be the mediator that causes severe lung injury after endotoxin shock and ischaemia–reperfusion. We further demonstrated that lung itself is the major site for the production of nitric oxide that causes pulmonary oedema [19]. In the case of fat embolism, the levels of non-esterified fatty acids, cGMP, 5-hydroxytryptamine and nitrates/nitrites were found to be increased [17]; however, it is uncertain if nitric oxide is involved. At post mortem, all organs were examined for gross pathological lesions. Lungs were removed, weighed and inspected. Lung tissues were then sectioned and stained with haematoxylin and eosin. In patients with Japanese B encephalitis, an immunohistochemical stain with mouse anti-Japanese B encephalitis monoclonal antibody was used to localize virus infection in the brain stem [20,21]. Fat in tissues from patients with fat embolisms was stained using methods described by Schemitsch et al. [22].

### RESULTS

Table 1 summarizes the basic data and major clinical findings for patients who died from acute pulmonary oedema due to Japanese B encephalitis, breast carcinoma with lymphangitis, fat embolism and disruption of mycotic aneurysms into cerebral ventricles. X-rays revealed that all patients had clear lungs on admission; however, dyspnoea, cyanosis, generalized weakness and heart arrest occurred within 7 days of hospitalization and all patients subsequently died as a result of an acute episode of pulmonary oedema. Before death, measurements of pulmonary arterial pressure using a Swan–Ganz catheter revealed a high level in all patients, compared with the normal value of 12–17 mmHg [2]. The lung weight in all patients increased remarkably from the normal value (350–400 g), particularly in cases of ruptured cerebral aneurysm and Japanese B encephalitis with viral infection in lower brain-stem.
Rare causes of pulmonary oedema

Figure 1 shows the pathological changes that occurred in the lung of a representative Japanese B encephalitis patient. The normal alveolar structure had disappeared and air spaces were filled with red blood cells and exudates (Figure 1A). Staining of the brain-stem revealed extensive virus infection in neurons and the formation of nodules (Figure 1B).

Immunohischemical staining of the brain-stem in patients with Japanese B encephalitis showed virus infection in neurons and the formation of nodules (Figure 2A). Cross sections (Figure 2B) and longitudinal sections (Figure 2C) revealed positive staining for virus infection, predominantly in the medial, ventral and caudal areas of the medulla oblongata.

Figure 3 shows pathological changes occurring in the lungs from patients with breast carcinoma and lymphangitis (Figure 3A) and from patients with fat embolism (Figure 3B). In two cases of breast carcinoma (one on the left breast, and the other on the right), a marked lymph oedema was found in the arm on the cancer side. Approx. 700 ml of fibrinosanguinous pleural effusion was collected from the lesioned side, with 50–70 ml present on the contralateral side. Multiple metastatic cancer masses were found in the axillary, para-aortic lymph nodes, chest wall, pleura, kidney and liver. In fat embolism caused by fracture of the femur and tibia, progressive decreases in haemoglobin levels and oxygen saturation were observed. Microscopic examination revealed fat droplets, not only in the lungs, but also in other organs. In four cases with ruptured mycotic aneurysm, the episode of acute pulmonary oedema was very sudden and patients died within 2 days; they were admitted with symptoms such as headache, weakness and dizziness. Measurement of blood pressure in these patients revealed hypertension with a mean blood pressure of 146–186 mmHg. Patients were given anti-hypertensive drugs and then received a detailed physical examination; however, they developed vomiting and a rapid loss of consciousness on the following day. A sudden episode of acute pulmonary oedema occurred and mean blood pressure was high, exceeding 210 mmHg. Measurement of intracranial pressure through a puncture into the foraman magna revealed that intracranial pressure was also elevated to more than 170 mmHg and cerebrospinal fluid contained blood. Histological section of the brain revealed massive blood clots in cerebral ventricles (results not shown).

DISCUSSION

Acute oedema occurring in the lung has a high clinical risk because it can affect the pulmonary gas exchange [2,5,23]. Guyton and Hall [2] studied the effect of elevated left atrial pressure and decreased plasma proteins on the development of pulmonary oedema. They found that left atrial pressure greater than 25 mmHg caused fluid accumulation in the lung; the degree of oedema increased with the level of left atrial pressure. Fishman and Pietra [23] used haemoglobin as a tracer; the studies in dogs had similar findings. When the pulmonary arterial pressure was kept at 15 mmHg for 10 min, the electron micrograph showed that haemoglobin was confined in the vascular lumen. Endothelial and epithelial junctions, and the interstitial space appeared normal. Although these substances were significantly elevated in six patients with fat embolism after the onset of signs of pulmonary oedema, chemical changes in other types of pulmonary oedema were not significant.
Figure 2  Immunohistochemical stain showing brain-stem lesions in patients with Japanese B encephalitis

(A) Immunohistochemical staining of the brain-stem with anti-Japanese B encephalitis viral monoclonal antibody in the brain stem (magnification ×400). The virus infection involves both neurons and dendrites. In six cases of Japanese B encephalitis infection, the distribution of positive staining is predominant in the medial and caudal portions of the medulla (horizontal section) (B). The cross-section (C) indicates that lesions are found mainly in the ventral portion of the medulla. In (B) and (C), the scales are divided into 1-mm segments.

At this point, the lung oedema was reversible when the pulmonary arterial pressure was returned to 15 mmHg. As pulmonary arterial pressure was further elevated to 70 mmHg for only 3 min, the tracer leaked into the alveolar space, with disruption of the epithelial junctions. The severity of this lung oedema was irreversible and caused alveolar flooding.

Since 1973, our laboratory has carried out a series of studies in the neural and haemodynamic mechanisms of neurogenic pulmonary oedema caused by either head injury or intracranial hypertension [3,4,24]. We found that cerebral compression caused a rapid increase in systemic arterial pressure and left atrial pressure. Microscope images showed the alveolar space filled with blood cells and the perivascular space was severely distended. High-power microscopy revealed congestion and rupture of vascular wall, with leakage of blood cells into surrounding spaces. Electron microscopic observation showed that endothelial and epithelial junctions were markedly stretched and ruptured. Leaking of blood cells and plasma through the damaged endothelial and epithelial barriers resulted in severe alveolar oedema, similar to the lung pathology of alveolar flooding [3]. In a later study of the mechanism of volume and pressure loading in the pulmonary circulation, we found that cerebral compression or increased intracranial pressure caused imbalance in the right and left cardiac output. The aortic flow rapidly decreased to 45–50% of the normal value, but the pulmonary arterial flow increased at first and then decreased with the aortic flow. In the rat, the cardiac output imbalance caused an approx. 6-ml shift of the blood volume from the systemic circulation to the lung. Finally, left atrial pressure increased to 40–50 mmHg and fulminant pulmonary oedema occurred [4,24]. These studies suggested that over-activation of the medullary sympathetic vasomotor mechanisms was the major cause of these pulmonary changes, because vagotomy, decerebration and adrenalectomy did not affect these pulmonary pathological changes [3,4,24]. In the present report, four patients had long-term hypertension without treatment and acute pulmonary oedema suddenly occurred following intracranial hypertension due to the rupture of cerebral aneurysms. It is interesting that one patient was relatively young, only 42 years old. Accordingly, long-term hypertension, as evidenced by ventricular hypertrophy, can also occur in the relatively young adult. The mechanisms of pulmonary pathological changes may be similar to those in the rat that underwent cerebral compression as described above. In addition, the levels of plasma chemicals were not increased in these patients, suggesting that compression of the brain was the major cause of pulmonary oedema.

Japanese B encephalitis virus is among the most common causes of arthropod-borne human encephalitis. Major epidemics of encephalitis have been recorded in Japan since 1870s, and the virus was discovered in 1934. The prevalence of Japanese B encephalitis has declined in Taiwan because of routine immunization of children [6,25]. We studied six cases in two Taiwanese hospitals over a 2-year period. Clinical manifestations and patho-
logical findings demonstrated that these patients had viral infections in the medulla oblongata (Figure 2) and medullary depressor areas were destroyed [26], which led to extensive activation of the sympathetic system, a mechanism similar to that associated with severe hemorrhagic oedema induced by cerebral compression in the lungs of the rat [3,24]. Since Chang et al. [6] reported fulminant neurogenic pulmonary oedema in patients with enterovirus infection, the pattern of Japanese B encephalitis and enterovirus infections certainly suggests that viral infection involving the lower brain stem is the major cause of acute pulmonary oedema.

In a review article, Bruce et al. [27] reported that 46% of patients with lymphangitis carcinomotosa developed respiratory insufficiency. To our knowledge, breast carcinoma with severe pulmonary hypertension and pulmonary oedema due to multiple obstructions of capillaries, venules and lymphatics (Figure 3) has not been described. Jaundice, pleural effusion, ascites and disseminated intravascular coagulation were present in two cases of breast carcinoma with lymphangitis; however, non-esterified plasma fatty acid, cGMP, 5-hydroxytryptamine and nitrate/nitrite levels were not

Table 2 Non-esterified fatty acid, cGMP, 5-hydroxytryptamine and nitrate/nitrite levels before and after acute pulmonary oedema

<table>
<thead>
<tr>
<th>Condition</th>
<th>Non-esterified fatty acid (mmol/l)</th>
<th>cGMP (pmol/ml)</th>
<th>5-Hydroxytryptamine (ng/ml)</th>
<th>Nitrate/nitrite (pmol/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japanese B encephalitis</td>
<td>Before: 0.46 ± 0.03 (0.38–0.54)</td>
<td>4.04 ± 0.07 (0.38–0.54)</td>
<td>4.50 ± 0.10 (0.35–0.46)</td>
<td>4.92 ± 0.08 (0.35–0.46)</td>
</tr>
<tr>
<td></td>
<td>After: 0.46 ± 0.03 (0.38–0.54)</td>
<td>0.45 ± 0.08 (0.36–0.46)</td>
<td>4.54 ± 0.07 (0.35–0.46)</td>
<td>4.83 ± 0.08 (0.35–0.46)</td>
</tr>
<tr>
<td>Breast carcinoma with lymphangitis</td>
<td>Before: 0.46 ± 0.03 (0.38–0.54)</td>
<td>5.34 ± 0.07 (0.35–0.46)</td>
<td>5.45 ± 0.07 (0.35–0.46)</td>
<td>5.67 ± 0.07 (0.35–0.46)</td>
</tr>
<tr>
<td></td>
<td>After: 0.46 ± 0.03 (0.38–0.54)</td>
<td>0.45 ± 0.08 (0.36–0.46)</td>
<td>4.54 ± 0.07 (0.35–0.46)</td>
<td>4.83 ± 0.08 (0.35–0.46)</td>
</tr>
<tr>
<td>Fat embolism</td>
<td>Before: 0.46 ± 0.03 (0.38–0.54)</td>
<td>4.04 ± 0.07 (0.38–0.54)</td>
<td>4.50 ± 0.10 (0.35–0.46)</td>
<td>4.92 ± 0.08 (0.35–0.46)</td>
</tr>
<tr>
<td></td>
<td>After: 0.46 ± 0.03 (0.38–0.54)</td>
<td>0.45 ± 0.08 (0.36–0.46)</td>
<td>4.54 ± 0.07 (0.35–0.46)</td>
<td>4.83 ± 0.08 (0.35–0.46)</td>
</tr>
<tr>
<td>Rupture of cerebral aneurysm</td>
<td>Before: 0.46 ± 0.03 (0.38–0.54)</td>
<td>5.34 ± 0.07 (0.35–0.46)</td>
<td>5.45 ± 0.07 (0.35–0.46)</td>
<td>5.67 ± 0.07 (0.35–0.46)</td>
</tr>
<tr>
<td></td>
<td>After: 0.46 ± 0.03 (0.38–0.54)</td>
<td>0.45 ± 0.08 (0.36–0.46)</td>
<td>4.54 ± 0.07 (0.35–0.46)</td>
<td>4.83 ± 0.08 (0.35–0.46)</td>
</tr>
</tbody>
</table>
significantly changed, which suggests that mechanical factors play an important role in the development of pulmonary hypertension and oedema.

Fat embolism after a crush injury is a serious clinical problem [17]. Fat staining revealed the presence of fat droplets, not only in lung tissue (Figure 3B), but also in the case of fat embolism after fracture of the femur and tibia (three cases of each). Non-esterified plasma fatty acid, cGMP, 5-hydroxytryptamine and nitrate/nitrite levels were significantly increased in these patients. To our knowledge, this report is the first to suggest the possibility of nitric oxide involvement in the lung injury following fat embolism. The formation of nitric oxide in pulmonary oedema formation associated with human studies are required to clarify the role of nitric oxide, cGMP, 5-hydroxytryptamine and nitrate/nitrite that causes acute pulmonary oedema. More animal or human studies are required to clarify the role of nitric oxide in pulmonary oedema formation associated with fatty acid embolism.

ACKNOWLEDGMENTS

The present study was supported in part by Grants from the National Science Council (NSC 90-2320-B-002 and 90-2320-B-320-004), Outstanding Scholarship Development (1996-2001) and Shin Kong Wu Ho-Su Memorial Hospital Foundations. Authors are grateful to Lucy Y. I. Chen (Department of Psychology, Simon Fraser University) and Dr Aubrey E. Taylor (University of Alabama College of Medicine, Mobile, AL, U.S.A.) for their help in preparation of this manuscript.

REFERENCES