The Pathogenesis of Pulmonary Edema in Acute Pancreatitis

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Acute pulmonary edema appeared 3 or more days after the onset of acute pancreatitis in 7 patients, an approximate incidence of 8%. The severity of pancreatitis in these patients was characterized by massive requirements for intravenous colloid and by marked hypocalcemia. In addition, at least 5 of the 7 patients had very high serum levels of triglycerides at the time of hospital admission. Hemodynamic studies during pulmonary edema showed normal central venous pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and pulmonary vascular resistance. Cardiac index was appropriately elevated. Respiratory treatment, consisting of endotracheal intubation and controlled ventilation with PEEP, was successful in allowing reversal of the pulmonary injury and recovery of respiratory function within 1-2 weeks in all cases. Two patients died later from pancreatic abscesses. The findings indicate that a distinct form of pulmonary injury may occur in acute pancreatitis, characterized by loss of integrity of the alveolar-capillary membrane, leading to pulmonary edema. The mechanism of injury is not known but may be caused by circulating free fatty acids, phospholipase A, or vasoactive substances. The pulmonary membrane lesion appears to heal during the period of intensive respiratory support.

RESPIRATORY INSUFFICIENCY develops in up to 30% of patients with acute pancreatitis, due in varying degrees to pleural effusions, atelectasis, pneumonitis, diaphragmatic elevation, pain-induced splinting of the abdominal wall, and iatrogenic fluid over-load.[8,17,18,25,27,29] In addition to these factors and in part obscured by them, we believe that there is a distinct form of pulmonary injury in pancreatitis characterized by acute pulmonary edema. This report documents that the entity, "pancreatitis lung," is the result of an alveolar-capillary leak syndrome.

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Clinical Materials and Methods

Each year approximately 135 patients with acute pancreatitis are admitted to the Massachusetts General Hospital. Of 60 unselected patients studied prospectively during one 9-month period, 5 developed pulmonary edema, an incidence of 8%. Observations made during 8 separate attacks of pancreatitis and pulmonary edema in 7 patients (including the 5 patients noted above) are the basis of this report.

Acute pancreatitis was diagnosed using standard clinical criteria and an elevated serum amylase. The primary identifiable etiologic factors were alcohol abuse (3), Type IV hyperlipoproteinemia (2), gastrectomy (1), and idiopathic (1). The diagnosis of pulmonary edema was made radiologically in patients with respiratory distress. Clinical management of pancreatitis consisted of nasogastric suction, antibiotics, and infusion of sufficient intravenous fluids, including colloids, to support blood pressure and urine output. Anticholinergic drugs were not used.

Evaluation of cardiac and pulmonary function included the following parameters: serial chest radiographs, arterial blood gas analyses, central venous pressure (CVP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR), and cardiac index (CI). Pulmonary artery and pulmonary capillary wedge pressures were measured with the use of a flow-directed balloon-tipped (Swan-Ganz) catheter. Cardiac output was determined by the

TABLE 1. *Admission Data*

Pt.	Age, Sex	Amylase (5-25 Russell u)	Calcium (8.5-10.5 mg%)	Triglycerides (40-150 mg%)	Pa_{O_2} (F_IO_2 = .21)	Chest Radiograph
1	45, M	143	7.5	1,450	79	clear lungs, normal heart
2	67, F	336	8.1	——	95	clear lungs, left ventricle enlarged
3A*	41, M	152	6.5	242	—	interstitial edema, normal heart
3B	41, M	141	7.1	1,960	76	clear lungs, normal heart
4	49, F	56	5.9	10,000	91	clear lungs, normal heart
5	62, M	68	6.5	——	—	clear lungs, normal heart
6	47, F	148	5.5	537	95	clear lungs, normal heart
7	38, M	42	9.3	435	70	clear lungs, normal heart

Normal values are given in parentheses
*transferred to MGH on 9th day of illness

dye-dilution method using indocyanine green. Pulmonary vascular resistance was calculated from the mean pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output.

Results

Initial status (Table 1)

At the time of hospital admission no patient was in respiratory distress, despite severe abdominal pain, nor was there evidence of pre-existing pulmonary disease. In each case, a radiograph of the chest showed clear lung fields, no pleural effusions, and normal heart size (with one exception). In all 6 cases in which it was measured on the day of admission, the Pa_{O_2} of arterial blood was greater than 70 torr while the patient was breathing room air. Serum lipids were markedly elevated to the point of visible lactescence in the 6 instances in which observations were recorded. This contrasts strikingly with an overall incidence of 11% for hyperlipidemia in all cases of acute pancreatitis seen during the study period. Serum calcium was below normal in 7 of 8 cases, and was less than 7.0 mg% in 4 of those.

Clinical course

In every case large amounts of 5% albumin in saline were administered intravenously to support blood pressure and urine output at acceptable levels (Table 2). The total colloid volume given in the first 24 hours after admission averaged more than 3400 ml. Generally the need for such fluid therapy was much reduced in the second 24 hours (average, 600 ml of colloid); yet respiratory distress appeared 48-96 hours after admission. Chest radiographs now showed interstitial fluffy infiltrates in a distribution characteristic of pulmonary edema, but heart size did not increase (Fig. 1). Small pleural effusions were present in one-third of the patients, but in none was there a large pleural effusion or major elevation of the diaphragm. Serial Pa_{O_2} measurements indicated progressive hypoxemia (Table 2). All patients required endotracheal intubation and controlled ventilation for respiratory sup-

TABLE 2. *Onset of Pulmonary Edema*

Pt.	1st 24 hrs	24 hrs before intubation	Pulmonary edema, day of intubation	Pa_{O_2} (F_IO_2 = 1.0) after intubation and PEEP
1	6000	6000	2	53
2	2000	500	3	94
3A*	——	——	8	—
3B	3000	500	3	51
4	1500	500	3	260
5	2000	700	3	80
6	5000	800	3	62
7	4750	500	4	132

*transferred to MGH on 9th day of illness.

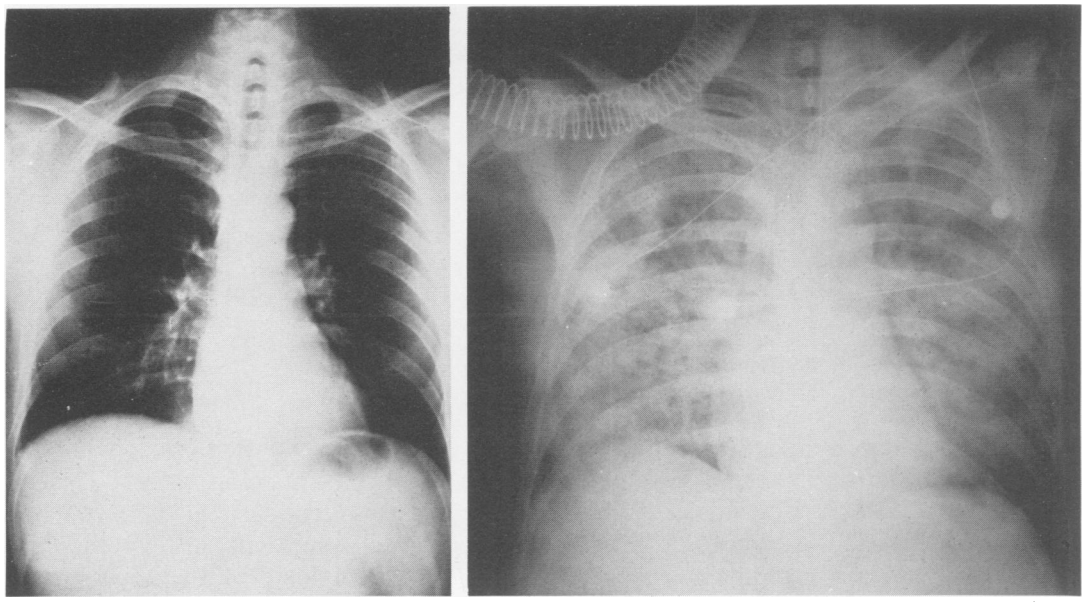

FIG. 1. Radiographs of the chest (patient 3) on admission (left) and on the 3rd hospital day (right), after endotracheal intubation for acute pulmonary edema.

port. Positive end-expiratory pressure (PEEP) was applied in most instances. Examination of the sputum did not yield evidence of infection at the time of intubation.

Special studies

Table 3 contains the pertinent measurements of cardiovascular function. All patients were normotensive at this time. The CVP, PAP, PCWP, and PVR were normal throughout, despite moderate to severe pulmonary edema. CI in each case was high, a normal physiologic response to stress and fever.

In one case sufficient pulmonary edema fluid was present to measure its protein content: the total protein concentration in the edema fluid was 5.4 gms per 100 ml while the serum protein was 5.6 gms per 100 ml.

Outcome

Continuous positive pressure ventilation was necessary for an average of 7 days (range, 3-14 days). PEEP was used routinely to increase functional residual capacity and to allow reduction of the inspired oxygen concentration required for adequate arterial oxygenation. Without PEEP arterial P_{O_2} invariably decreased. No specific attempt was made to extract pulmonary water by the combination of raising serum protein concentration and diuresis.[31]

Five of the 7 patients survived these 8 episodes of pancreatitis and pulmonary edema. Both deaths (patients 2 and 6) were directly due to the development of pancreatic abscesses and occurred on the 37th and 40th hospital day. All 5 survivors, including patient 3 who survived two such attacks of pancreatitis and pulmonary edema, had clinically normal pulmonary function upon discharge.

Discussion

The recognition that respiratory distress is a common feature in acute pancreatitis has led to a number of recent reports emphasizing the roles of pneumonitis, atelectasis, and congestive heart failure.[7,15,27] It is clear from these reports, furthermore, that respiratory distress may become the predominant therapeutic problem of acute pancreatitis and may prove to be lethal.[8,10,25,27] While pleural effusions, restriction of chest and diaphragmatic movement, and infection certainly contribute to respiratory failure in this disease, some patients (8% in our experience) develop unequivocal acute pulmonary edema, a phenomenon which has received little attention.[7,10,15,18] Pulmonary edema appeared several days after the onset of pancreatitis and was of sufficient severity to necessitate endotracheal intubation and positive-pressure ventilation.

The major pathogenetic mechanisms of pulmonary edema are: 1) increased hydrostatic forces (congestive heart failure), in which left atrial hypertension leads to passive increase in the pulmonary vascular pressures with *transudation* of fluid into the pulmonary interstitium. When the rate of transudation exceeds the resorptive capacity of the pulmonary lymphatics, alveolar flooding (pulmonary edema) occurs. 2) Disruption of the alveolar-capillary membrane with secondary *exudation* of protein-rich plasma into the pulmonary interstitium in the presence of normal or decreased hydrostatic forces.[28,32] In the patients we have studied, the evidence strongly suggests the latter set of circumstances. The normal CVP, PCWP, and heart size, despite the fact that these values were obtained during positive-pressure ventilation with PEEP, exclude heart failure, whether due to fluid overloading as a conse-

TABLE 3. *Hemodynamics During Pulmonary Edema*

Pt.	CVP (2-10 cm H_2O)	PAP (15-28/5-15 torr)	PCWP (4-10 torr)	PVR (<2 resistance u)	CI (3-4 L/min/M^2)
1	5	——	—	—	5.8
2	10	15/5	10	—	—
3A	6	——	—	—	—
3B	3	30/11	11	1.0	6.0
4	8	30/10	5	—	—
5	4	25/15	7	1.6	4.1
6	11	——	—	—	5.8
7	10	——	—	—	—

Normal values are given in parentheses

quence of intravenous therapy or to underlying heart disease. The appropriately elevated CI is inconsistent with inadequate myocardial performance, which theoretically could be related to a circulating myocardial depressant factor (MDF) found in experimental pancreatitis.[21,22] Additionally, the elevated protein concentration of the pulmonary edema fluid in one of our patients, almost equal to the serum protein concentration, indicates an exudate, different from the transudate typical of cardiogenic pulmonary edema wherein the protein content is about 40% of the serum protein level.[16] Finally, the normal PAP excludes pulmonary hypertension, which has been reported in acute pancreatitis[13] and which has been postulated to give rise to pulmonary edema via leak from pulmonary arterioles.[36]

The specific agent of the alveolar-capillary membrane injury is unknown, although liberated pancreatic enzymes,[2,9] vasoactive substances,[12,24,30,33] platelet microemboli,[3] and endotoxins[32] are candidates. A particularly attractive hypothesis holds that phospholipase A, a lecithinase released in acute pancreatitis,[37] destroys phospholipid components of the pulmonary membranes, including surfactant. This chain of events has been reproduced in dogs,[23] but its existence in man is speculative.

The relationship between hyperlipidemia and pancreatitis is complex and probably not uniform.[4-6,11] In some cases hyperlipidemia pre-exists and predisposes to pancreatitis; in others it appears only during the acute attack and may be either a consequence of pancreatitis or may be a simultaneous product of a shared process which causes both the pancreatitis and the hyperlipidemia. The extraordinary incidence of hypertriglyceridemia in our patients with pulmonary edema suggests more than a chance association. One possibility is that the elevated triglycerides are metabolized to large quantities of free fatty acids, which in experimental models can damage the alveolar-capillary membrane and produce pulmonary edema.[1] Unfortunately we have no measurements of plasma free fatty acids.

The serum lipids also seem to be the single best index for risk of developing pulmonary edema. At least 5 of the 7 patients (during 6 of 8 episodes) had markedly elevated triglycerides, an observed incidence far exceeding the 11% incidence of hyperlipidemia in our pancreatitis patients or even the 15-39% incidence in other series.[4,6,11] Large requirements for intravenous colloid infusions (possibly indicating widespread increased vascular permeability) and marked depression of serum calcium concentration were also characteristic of these patients but may simply reflect the severity of their pancreatitis.[18,26,27,35] In contrast, clinical respiratory status, x-ray examination of the chest, and arterial blood gas measurements at the time of hospital admission were of no use in predicting pulmonary edema.

The cornerstone of treatment for this form of pulmonary injury is endotracheal intubation with controlled ventilation in order to keep alveoli and small airways open. PEEP in our experience was regularly effective in improving oxygenation and in thereby facilitating the reduction of inspired oxygen concentrations below toxic levels. We made no attempt "to extract pulmonary water" with salt-poor albumin infusions and diuresis,[31] as has been advocated for respiratory failure in pancreatitis.[15,18,27] If damage to the alveolar-capillary membrane has rendered it excessively permeable to protein, infusion of concentrated albumin could not osmotically draw edema fluid from the lung and might theoretically add to the protein exudate.

The membrane injury in acute pancreatitis appears to be reversible: no patient died from respiratory failure, and the 5 ultimate survivors of 6 episodes had no apparent residual lung damage. The aim of treatment therefore is intensive respiratory support and prevention of pulmonary infection during the time necessary for pancreatitis to subside and for the membrane to heal. Steroids have been suggested to promote healing of the damaged lung[14] but their efficacy in this setting is unproven.

Patients who develop pulmonary edema have virulent pancreatitis in other respects as well. Although respiratory failure may become the predominant and longest-lasting feature of the attack, massive volume require-

ments, profound cardiovascular collapse, renal failure, disseminated intravascular coagulation,[19] and profound hypocalcemia occur and demand treatment as well. However, contrary to previous tentative conclusions,[20,27,35] respiratory failure, because of its ready response to supportive treatment, should not be used as a criterion for surgical intervention, peritoneal lavage, or peritoneal dialysis. Pancreatitis of this severity carries a high risk of a consequent pancreatic abscess,[34,35] which occurred twice in this series and was the direct cause of both deaths.

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Discussion

Dr. John Ranson (New York, New York): Dr. Warshaw's presentation describes fascinating new observations on the pulmonary manifestations of pancreatitis.

We recently analyzed our experience at Bellevue Hospital with respiratory complications in 116 patients with acute pancreatitis. We found that some degree of respiratory impairment was detectable by arterial blood gas measurements in 69% of patients during the initial 48 hours illness. This early arterial hypoxemia was not related to the severity of disease nor to any of the laboratory or clinical features that we studied at that time.

Clinically apparent respiratory complications, which included the type of patient presented by Dr. Warshaw, could be related to the presence of severe or continuing pancreatic inflammation. As shown on this slide, they were thus related to early hypocalcemia and fluid