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EDITORIAL

Lung Injury in Acute Pancreatitis

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Introduction

Most knowledge has been accumulated on the mechanisms involved in the development of distant organ injuries during the course of severe acute pancreatitis. Among the various distant organ dysfunctions, both the development of acute lung injury and acute respiratory distress syndrome represent serious complications. In the following paragraphs the pathophysiological mechanisms capable of determining lung injury during the course of acute pancreatitis will be reviewed.

Pancreatic Enzymes and Lung Damage

Elevated concentrations of pancreatic enzymes might be associated with the development of lung injury, even if additional information is needed. In particular, the relationship between phospholipase A_2 and clinical lung injury during acute pancreatitis has been studied. In the pancreas, phospholipase A_2 induces cell necrosis by converting the lecithin of cellular membranes into the more toxic compound lysolecithin [1]. Thus, phospholipase A_2 may play a role in acute pulmonary injury by damaging pulmonary surfactant since surfactant contains phospholipids which are substrates for phospholipase A_2 [2]. In subjects with severe acute pancreatitis, an elevated serum concentration of phospholipase A_2 was correlated with pulmonary complications [3]; furthermore, the serum concentrations of phospholipase A_2, are positively correlated to the lung injury score [4] and elevated phospholipase A_2 concentrations may have a predictive value for the development of pulmonary complications.

Key words Acute Lung Injury; Blood Platelets; Cytokines; Leukocytes; Lymphocytes; Oxidants; Pancreatitis, Acute Necrotizing; Respiratory Distress Syndrome, Adult

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Leukocytes and Lung Damage

It has been found that the presence of a high number of leukocytes and the presence of lung alterations may identify those patients with severe acute pancreatitis [5]; in fact, using a cut-off value of 13,000/mm^3, 45% of patients with severe pancreatitis and 17% of those with mild acute pancreatitis had a peripheral leukocyte count greater than 13,000/mm^3. Pleural or pulmonary alterations observed on chest X-ray were found in 66% of patients with severe pancreatitis and in 2% of those with mild acute pancreatitis. A peripheral leukocyte count greater than 13,000/mm^3 and/or pleural or pulmonary alterations present on chest X-ray were found in 78% of the patients with severe pancreatitis and in 19% of those with mild pancreatitis. Pulmonary leukocyte infiltration measured by technetium-99m-labelled leucocytes demonstrates that leucocytes in the lungs are increased in animals with both moderate pancreatitis and severe pancreatitis induced by the intraductal infusion of glycodeoxycholic acid while moderate alterations were noted in animals with mild pancreatitis induced by intra-arterial infusion of cerulein [6]. In rats with experimental necrotizing pancreatitis induced by the intraductal administration of sodium taurocholate [7], significant pulmonary edema, hyperemia and inflammatory infiltrates, predominantly composed of polymorphonuclear leucocytes in the alveoli, were noted 12 h after the induction of pancreatitis, accompanied by an increase in the levels of the arachidonic acid metabolites. Transport of carbon dioxide through the alveolar barrier was significantly compromised due to increased interstitial edema and type I pneumocyte dysfunction or the existence of arteriovenous shunting in the lungs as well as in other tissues [8]. The activated alveolar macrophages were characterized by an increase in the generation of nitric oxide, tumor necrosis factor (TNF-alfa) and macrophage inhibitor protein 2. Most importantly, the instillation of supernatants from activated alveolar macrophages harvested from pancreatitis animals caused neutrophil sequestration in normal animals [9], implying that the activation of lung

tissue macrophages plays an important role in the chemotaxis of leucocytes and tissue injury.

Lymphocytes and Lung Damage

The CD40 receptor is a 50 kDa protein expressed on the membranes of B lymphocytes, monocytes, dendritic cells and biliary epithelial cells. In a model of antigen-induced airway inflammation, CD40 ligand-deficient mice were protected [10] while the disruption of CD40-CD40 ligand interaction prevented the pulmonary lesions induced by the high fraction of inspired oxygen [11]. In the cerulein model of pancreatitis, mice deficient for the CD40 ligand had a marked decrease in the severity of both pancreatic and lung damage [12]. Interestingly, both CD40 and the CD40 ligand were expressed at the acinar cell surface, suggesting that therapeutic interventions designed to prevent CD40 ligation may have clinical value in reducing the severity of pancreatitis and the associated acute lung injury.

Platelets and Lung Damage

The platelet activating factor is a low-molecular-weight phospholipid acting via specific cell surface receptors which have been identified on numerous cells and tissues including platelets, leukocytes and endothelial cells [13]. This bioactive phospholipid increases vascular permeability, attracts leukocytes, and primes and triggers their secretory responses [13]. The role of platelet activating factor on lung injury induced by hydrochloric acid has been investigated using mice over-expressing or lacking the platelet activating factor receptor [14]. It was found that control mice died rapidly after developing inflammation, pulmonary edema, and impaired oxygenation. The response was amplified in animals which over-expressed the platelet activating factor receptor. Conversely, animals lacking a platelet activating factor receptor did not die during the experiment and had much better oxygenation and little edema. These findings demonstrate the importance of the platelet activating factor receptor in the pathogenesis of acute lung injury and constitute a smoking gun which implicates platelet activating factor or platelet activating factor-like compounds in this process.

Chemokines and Lung Damage

The destruction of the pancreatic parenchyma during acute pancreatitis quickly induces an inflammatory reaction at the site of injury. Following an experimental insult, there is rapid expression of TNF-alfa, interleukin-1 (IL-1), and other chemokines such as interleukin-6 (IL-6) and interleukin-8 by pancreatic acinar cells and/or transmigrated leukocytes [15, 16]. In the severe forms of acute pancreatitis, there is also a low production of anti-inflammatory cytokines such as interleukin-10 which is capable of blocking the action of the pro-inflammatory cytokines [17]. The production of elevated quantities of pro-inflammatory cytokines in severe acute pancreatitis determines the typical systemic effects of severe acute pancreatitis such as acute respiratory distress syndrome.

Neuropeptides and Lung Damage

Neuropeptide substance P which is released from the nerve endings and binds to the neurokinin-1 receptors can mediate abnormal vascular permeability during acute inflammation. Neurokinin-1 receptor and substance P are both expressed in the pancreas, at least in an experimental model of pancreatitis [18]. Deletion of the neurokinin-1 receptor gene reduces both pancreatitis and pancreatitis-associated lung injury as compared to control mice, and the increase in lung microvascular permeability associated with acute pancreatitis is strongly attenuated in the absence of the neurokinin-1 receptor [19]. These results emphasize the role of substance P acting on endothelial cells via neurokinin-1 receptors, increasing pulmonary vascular permeability and promoting edema formation in the surrounding tissues. This hypothesis is supported by the finding that the concentration of substance P was twofold higher in the pulmonary edema fluid of patients with acute respiratory distress syndrome than in the edema fluid of control patients with congestive heart failure [20].

Complement factors and Lung Damage

C5a, which acts via the C5a receptor, is an anaphylatoxin and a chemoattractant which exerts a proinflammatory effect by increasing blood flow and by promoting vascular permeability. In genetically modified mice which lack the C5 or C5a receptor, the severity of pancreatitis and lung injury was surprisingly greater than the injury observed in wild-type mice [21].

Oxidants and Lung Damage

The levels of malondialdehyde, a marker of lipid peroxidation, in the lungs were elevated during the early phase after induction of acute pancreatitis and returned to control levels at 8 and 12 h [22]. Oxidative modification of lung proteins by lipid peroxidation was only detected in dying pancreatitis animals. It seems that oxidative stress is involved in the initiation and further development of acute pancreatitis-associated lung injury, followed by a rapid repair process during which the number of type II pneumocytes increased and migrated closer and/or through the alveolar type I epithelial cells [23]. Without successful compensation of tissue recovery, oxidative damage may be one of the factors responsible for the development of pulmonary dysfunction. It is possible that xanthine oxidase released from the compromised pancreas may be a source of reactive oxygen species [24] or that the over-activation of local resident cytolytic macrophages may be responsible for the production and release of oxygen-free radicals and other inflammatory mediators [25]. The main resource of free radical generation and release is considered to be activated neutrophils since depletion of neutrophils using antineutrophil antibodies abolishes the generation of superoxide anions and

prevents neutrophil-dependent acute pancreatitis-associated lung injury [26].

Epidemiology of Lung Injury

The incidence of pulmonary complications in acute pancreatitis ranges from 15 to 55%, and their severity vary from mild hypoxemia without clinical or radiologic abnormalities [27] to acute respiratory distress syndrome. About 10% of patients may have alveolar edema on chest radiograph [28] and progressive hypoxemia develops in about one third of patients within hours or within 2 to 3 days. Interiano *et al*. [29] found that 18% of patients with acute pancreatitis had diffuse pulmonary infiltrates consistent with lung injury and 10% died from acute respiratory distress syndrome; survivors recovered with normal pulmonary function. In a study comprising 539 patients, we have recently found that abnormal chest radiographic findings were present in 20% of the patients: 6% had pulmonary infiltrates and 14% had pleural effusions [30]. The mortality rate significantly correlated with the presence of pulmonary infiltrates and effusions; radiologic abnormalities were associated with a 15-fold increase in the mortality rate. Most effusions were on the left side, although some were bilateral and the pleural fluid contained an elevated amylase concentration of up to 30 times that of the simultaneous serum value and remained elevated even after the serum concentrations had returned to a normal level. Large pleural effusions were also associated with subdiaphragmatic collections of fluid probably due to the immobility of the diaphragm induced by local inflammation. [31] A reduced PaO_2 on hospital admission has long been regarded as a prognostic factor for the severity of acute pancreatitis. Although all patients with an abnormal index were hypoxemic, the PaO_2 values did not reflect the extent of increased lung vascular permeability [32]; thus, pulmonary infiltrates and pulmonary edema in patients with acute pancreatitis can be attributed to an increase in pulmonary vascular permeability. Local and systemic infections can contribute to the worsening or the persistence of pre-existing acute respiratory distress syndrome. The delay between hospital admission and pulmonary complications was investigated by Berry *et al*. [33] who found that radiologic abnormalities were present in 15% of patients with acute pancreatitis on admission and an additional 71% of patients developed new chest abnormalities after five days. Gong and Tang [34] reported that the mean onset of acute respiratory distress syndrome was 3.2 days; in particular, 33% developed acute respiratory distress syndrome within the first 24 hours, 25% in following 2 days and the remaining 42% after this time.

Assessment of Lung Damage in Clinical Practice

Patients with acute pancreatitis should be monitored for the development of acute respiratory distress syndrome; however, only those patients who meet the following criteria should be considered as having this complication [35]: those with identifiable associated condition (acute pancreatitis in our case), those with a disease having an acute onset, those having pulmonary artery wedge pressure less than, or equal to, 18 mmHg or absence of clinical evidence of left atrial hypertension, those with bilateral infiltrates on chest radiography or at computed tomography scan, those with acute lung injury having the PaO_2/FiO_2 ratio (partial pressure of arterial oxygen/ percentage of inspired oxygen) less than or equal to 300, and finally those with acute respiratory distress syndrome and PaO_2/FiO_2 ratio less than, or equal to, 200.

Conclusions

From a practical point of view, when we care for a patient with acute pancreatitis, we need: to establish the severity of the attack within the first 24 hours using well-established single or multiple criteria such as interleukin 6 determination or APACHE II score [36]; to confirm the presence of the severity of the acute pancreatitis using imaging techniques; finally, to put the patient in an intensive care unit, in the case of severe acute pancreatitis to carefully monitor his clinical condition in order to detect the presence of systemic complications, mainly those of the lungs, as soon as possible [37].

Conflict of interest The authors have no potential conflicts of interest

References

1 Schmid H, Creutzfeld W. The possible role of phospholipase A in the pathogenesis of acute pancreatitis. Scand J Gastroenterol 1969; 4:39-48. [PMID 4899633]

2 Vadas P. Elevated plasma phospholipase A2 levels: correlation with the hemodynamic and pulmonary changes in Gram negative septic shock. J Lab Clin Med 1984; 104:873-881. [PMID 6548766]

3 Nevalainen TJ, Hietaranta AJ, Gronroos JM. Phospholipase A2 in acute pancreatitis: new biochemical and pathological aspects. Hepatogastroenterology 1999;46:2731-2735. [PMID 10576338]

4 Gronroos JM, Nevalainen TJ. Increased concentrations of synovial-type phospholipase A2 in serum and pulmonary and renal complications in acute pancreatitis. Digestion 1992; 52:232-236. [PMID 1459357]

5 Pezzilli R, Billi P, Barakat B, Broccoli P, Morselli Labate A. The use of the peripheral leukocyte count and chest X-rays in early assessment of the severity of acute pancreatitis in comparison with the Ranson score system. Panminerva Med 1999;41:39-42. [PMID 10230256]

6 Werner J, Dragotakes SC, Fernandez-del Castillo C, Rivera JA, Ou J, Rattner DW, Fischman AJ, Warshaw AL. Technetium-99m-labeled white blood cells: a new method to define the local and systemic role of leukocytes in acute pancreatitis. Ann Surg 1998; 227:86-94. [PMID 9445115]

7 Closa D, Bardají M, Hotter G, Prats N, Gelpí E, Fernández-Cruz L, Roselló-Catafau J. Hepatic involvement in pancreatitis-induced lung damage. Am J Physiol 1996;270:G6-13. [PMID 8772495]

8 Wang XD, Andersson R, Kruse P, Ihse I. Carbon dioxide transport in rats with acute pancreatitis. Int J Pancreatol 1996;19:103-112. [PMID 8723552]

9 Closa D, Sabater L, Fernandez-Cruz L, Prats N, Gelpì E, Rosello-Catafau J. Activation of alveolar macrophages in lung injury

associated with experimental acute pancreatitis is mediated by the liver. Ann Surg 1999;229:230-236. [PMID 10024105]

10 Lei XF, Ohkawara Y, Stämpfli MR, Mastruzzo C, Marr RA, Snider D, Xing Z, Jordana M. Disruption of antigen-induced inflammatory responses in CD40 ligand knockout mice. J Clin Invest 1998; 101:1342-1353. [PMID 9502776]

11 Adawi A, Zhang Y, Baggs R, Finkelstein J, Phipps RP. Disruption of the CD40-CD40 ligand system prevents an oxygen-induced respiratory distress syndrome. Am J Pathol 1998; 152:651-657. [PMID 9502405]

12 Frossard JL, Kwak B, Chanson M, Morel P, Hadengue A, Mach F. CD40 ligand deficient mice are protected against cerulein-induced acute pancreatitis and pancreatitis-associated lung injury. Gastroenterology 2001; 121:184-194. [PMID 11438507]

13 Prescott SM, McIntyre TM, Zimmerman GA. Platelet-activating factor: a phospholipid mediator of inflammation. In Gallin JI, Snyderman R (eds). Inflammation: Basic Principles and Clinical Correlates. Philadelphia, Pa, Lippincott Williams & Wilkins: 1999:387-389.

14 Nagase T, Ishii S, Kume K, Uozumi N, Izumi T, Ouchi Y, Shimizu T. Platelet-activating factor mediates acid-induced lung injury in genetically engineered mice. J Clin Invest 1999; 104:1071-1076. [PMID 10525045]

15 Norman J. The role of cytokines in the pathogenesis of acute pancreatitis. Am J Surg. 1998;175:76-83. [PMID 9445247]

16 Pezzilli R, Billi P, Miniero R, Fiocchi M, Cappelletti O, Morselli-Labate AM, Barakat B, Sprovieri G, Miglioli M. Serum interleukin-6, interleukin-8, and beta 2-microglobulin in early assessment of severity of acute pancreatitis. Comparison with serum C-reactive protein. Dig Dis Sci 1995;40:2341-2348. [PMID 7587812]

17 Pezzilli R, Billi P, Miniero R, Barakat B. Serum interleukin-10 in human acute pancreatitis. Dig Dis Sci 1997;42:1469-1472. [PMID 9246048]

18 Grady EF, Yoshimi SK, Maa J, Valeroso D, Vartanian RK, Rahim S, Kim EH, Gerard C, Gerard N, Bunnett NW, Kirkwood KS. Substance P mediates inflammatory edema in acute pancreatitis via activation of the neurokinin-1 receptor in rats and mice. Br J Pharmacol 2000; 130:505-512. [PMID 10821777]

19 Maa J, Grady EF, Yoshimi SK, Drasin TE, Kim EH, Hutter MM, Bunnett NW, Kirkwood KS. Substance P is a determinant of lethality in diet-induced hemorrhagic pancreatitis in mice. Surgery 2000;128:232-239. [PMID 10922997]

20 Espiritu RF, Pittet JF, Matthay MA, Goetzl EJ. Neuropeptides in pulmonary edema fluid of adult respiratory distress syndrome. Inflammation 1992; 16:509-517. [PMID 1428125]

21 Bhatia M, Saluja AK, Singh VP, Frossard JL, Lee HS, Bhagat L, Gerard C, Steer ML. Complement factor C5a exerts an anti-inflammatory effect in acute pancreatitis and associated lung injury. Am J Physiol 2001; 280:974-978. [PMID 11292607]

22 Gilgenast O, Brandt-Nedelev B,Wiswedel I, Lippert H, Halangk W, Reinheckel T. Differential oxidative injury in extrapancreatic tissue during experimental pancreatitis. Dig Dis Sci 2001;46:932-937. [PMID 11330437]

23 Wang XD, Börjesson A, Sun ZW, Wallèn R, Deng XM, Zhang HY, Hallberg E, Andersson R. The association of type II pneumocytes and endothelial permeability with the pulmonary custocyte system in experimental acute pancreatitis. Eur J Clin Invest 1998;28:778-785. [PMID 9767378]

24 Folch E, Gelpi E, Rosselo-Catafau J, Closa D. Free radicals generated by xanthine oxidase mediate pancreatitis-associated organ failure. Dig Dis Sci 1998;43:2405-2410. [PMID 9824126]

25 Andersson R, Deng XM, Wang XD. The role of macrophage overactivation in the development of acute pancreatic injury in rats. Br J Surg 1997;84:775-80. [PMID 9189083]

26 Murakami H, Nakao A, Kishimoto W, Nakano M, Takagi H. Detection of O2-generation and neutrophil accumulation in rat lung after acute necrotizing pancreatitis. Surgery 1995;118:547-554. [PMID 7652692]

27 Polyzogopoulou E, Bikas C, Danikas D, Koutras A, Kalfarentzos F, Gogos CA. Baseline hypoxemia as a prognostic marker for pulmonary complications and outcome in patients with acute pancreatitis. Dig Dis Sci 2004;49:150-154. [PMID 14992450]

28 Malik AB. Pulmonary edema after pancreatitis: role of humoral factors. Circ Shock 1983;10:71-80. [PMID 6339103]

29 Interiano B, Stuard ID, Hyde RW. Acute respiratory distress syndrome in pancreatitis. Ann Intern Med 1972;77:923-926. [PMID 4566284]

30 Talamini G, Uomo G, Pezzilli R, Rabitti PG, Billi P, Bassi C, Cavallini G, Pederzoli P. Serum creatinine and chest radiographs in the early assessment of acute pancreatitis. Am J Surg 1999;177:7-14. [PMID 10037300]

31 Wilkinson MJ, Robson DK, Basran G. Pleural complications of acute pancreatitis: an autopsy study. Respir Med 1989;83:259-260. [PMID 2595047]

32 Groeneveld AB, Raijmakers PGHM. The 67gallium-transferrin pulmonary leak index in patients at risk for the acute respiratory distress syndrome. Crit Care Med 1998;26:685-691. [PMID 9559605]

33 Berry AR, Taylor TV, Davies GC. Pulmonary function and fibrinogen metabolism in acute pancreatitis. Br J Surg 1981;68:870-873. [PMID 7317769]

34 Gong ZY, Tang YQ. Onset time of complications in patients with severe acute pancreatitis receiving nonoperative therapy. Hepatobiliary Pancreat Dis Int 2002;1:143-145. [PMID 14607645]

35 Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med 2000;342:1334-1349. [PMID 10793167]

36 Pezzilli R, Mancini F. Assessment of severity of acute pancreatitis: a comparison between old and most recent modalities used to evaluate this perennial problem. World J Gastroenterol 1999;5:283-285. [PMID 11819448]

37 Pezzilli R, Uomo G, Zerbi A, Gabbrielli A, Frulloni L, De Rai P, Delle Fave G, Di Carlo V; Italian Association for the Study of the Pancreas Study Group. Diagnosis and treatment of acute pancreatitis: the position statement of the Italian Association for the study of the pancreas. Dig Liver Dis 2008;40:803-808. [PMID 18387862]