Can inflammatory mediators affect fibrinolysis in the pleural space?

COMMENT

ABSTRACT

The pleural space in patients with empyema and complicated parapneumonic effusions is a stage for intensive activity representing mobilization of various host responses. Release of inflammatory mediators accompanied by influx of leucocytes as well as alternations of the fibrinolytic cascade are some of the characteristic events occurring in the pleural space during infection. The possible relationship between these two systems is the subject of the article by Alemán and co-workers in this issue of *Clinical Science*, and is discussed in this comment.

The pleura consists of a single layer of mesothelial cells that covers the surface of the lungs, including the interlobar fissures, and lines the entire thoracic cage, including the thoracic surface of the diaphragm [1,2]. The portion covering the lungs is called the visceral pleura, whereas the portion covering the surface of the chest wall, diaphragm and mediastinum is called the parietal pleura. The visceral pleura receives its blood mostly from the pulmonary circulation and has no sensory nerves. The parietal pleura, on the other hand, is supplied with blood from the systemic circulation and contains sensory nerves. The parietal layer is also thicker than the visceral layer and is supported by a dense network of elastic and collagen fibres [1,2].

The pleural space is lubricated by a small amount of fluid remaining at a constant level under normal conditions due to a pressure gradient between the visceral and parietal blood capillaries [1,2]. Protein and particles are absorbed by lymphatics, or tissues and venous capillaries. When the normal physiological balance is disturbed, excess fluid accumulates within the pleural space that is referred to as a pleural effusion. Loss of equilibrium between hydrostatic forces and oncotic pressures results in formation of transudates. Exudates, in turn, are formed because of increased capillary permeability and/or blocking of lymphatics [1,2]. Development of inflammation within the pleural space due to, for example, bacterial infection brings about release of proinflammatory cytokines and influx of inflammatory cells [3]. In addition, impaired fibrinolysis is characteristic of the inflammatory response in the pleural space [3,4]. However, the relationship between proinflammatory cytokines and components of the fibrinolytic cascade is not well defined [5,6]. Alemán and co-workers [7], in this issue of *Clinical Science*, attempt to fill this gap. The authors analysed 100 patients presenting with pleural effusions that included 25 empyema or complicated parapneumonic effusions, 22 tuberculous effusions, 28 malignant effusions and 25 transudates. Both inflammatory mediators [tumour necrosis factor-α (TNF-α), interleukin-8 (IL-8) and neutrophil elastase] and the fibrinolytic system parameters [tissue-type plasminogen activator (t-PA), urokinase plasminogen activator (u-PA), plasminogen activator inhibitor type 1 (PAI 1) and plasminogen activator inhibitor type 2 (PAI 2)] were measured in plasma and pleural fluid.

Proinflammatory cytokines are produced by leucocytes that are recruited to the pleural space as well as resident mesothelial cells. The local inflammatory response is accompanied by a systemic response with increased levels of circulating cytokines [3,8]. TNF-α has been detected in plasma and pleural fluid of patients with tuberculous pleuritis, malignant effusions, parapneumonic pleurisy and transudates [6,9–11]. Furthermore, the levels of this cytokine are higher in tuberculous effusions than in other pleural effusions [6,9–12]. IL-8 is also present in inflammatory and malignant pleural effusions as well as in transudates [13–15]. The concentrations of IL-8 [13–15] and neutrophil elastase are significantly more elevated in pleural fluids from patients with empyema [15,16]. In addition, pleural IL-8 levels correlate with neutrophil count or concentrations of elastase [14,15]. Accordingly,

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Alemán and co-workers [7] report higher levels of inflammatory mediators in empyema and complicated parapneumonic effusions than in malignant effusions, and higher concentrations of IL-8 and neutrophil elastase in the same effusions when compared with tuberculous effusions. Furthermore, the highest amount of TNF-α was detected in tuberculous pleural fluid.

It is well recognized that the fibrinolytic system does not function properly in the pleural space in patients with different forms of pleural effusions. Abnormal fibrinolysis occurs when the balance between activators and inhibitors is disturbed. Increased production of PAIs is partially responsible for fibrin deposition within the pleural space of patients with parapneumonic effusions [3,4]. Overexpression of mainly plasminogen activators, on the other hand, leads to excessive fibrinolysis that is observed in patients with malignant effusions [4,6]. In agreement with the previous observations, Alemán and co-workers [7] found significantly higher concentrations of fibrinolytic markers in pleural fluid than in plasma in exudates, but not in transudates. Plasminogen activity and the levels of PAIs were significantly lower in malignant pleural fluid. The concentrations of PAI 2 in empyema and complicated parapneumonic effusions exceeded the ones detected in tuberculous effusions. Finally, patients with tuberculous or malignant effusions had more t-PA than other patients.

Previous studies indicate that proinflammatory cytokines may have a direct effect on the balance between plasminogen activators and inhibitors in the pleural space [5,6]. TNF-α, for example, stimulates human pleural mesothelial cells to release PAI 1 and PAI 2 [5]. Moreover, levels of TNF-α correlate positively with PAI 1 and PAI 1/t-PA, and negatively with t-PA in tuberculous effusions. In malignant pleural fluid, in turn, there is a positive correlation between TNF-α and PAI 1 [6]. Similarly, Alemán and co-workers [7] observed a significant association between TNF-α and PAIs as well as between IL-8 or neutrophil elastase and PAIs overall in the exudative pleural effusions (empyema, complicated parapneumonic and tuberculous). However, when empyema and parapneumonic effusions were analysed separately, no significant correlations were found. Moreover, t-PA and both IL-8 and neutrophil elastase were negatively correlated in every pleural effusion (empyema, complicated parapneumonic and tuberculous). On the other hand, no significant associations between inflammatory and fibrinolytic markers were detected in malignant and transudative pleural effusions.

In summary, it appears that TNF-α, IL-8 and neutrophil elastase may modulate fibrinolytic activity in the pleural space. All of these mediators have been shown to either enhance or reduce activity of the key components of the fibrinolytic cascade in vitro or in animal studies [5,6,17–19]. Therefore the possibility that inflammatory mediators regulate the fibrinolytic system in the pleural space in disease warrants further exploration and may lead to development of new treatment regimens for pleural effusions. Moreover, Alemán and co-workers [7] convey a very important, clinically relevant, message that the association between inflammatory mediators and components of the fibrinolytic cascade in addition to absolute concentrations of these parameters may serve as a novel diagnostic tool, aiding in selecting appropriate treatment modalities for patients presenting with pleural effusions of different aetiology.

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(ON BEHALF OF THE EDITORIAL OFFICE)

REFERENCES


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