Parapneumonic pleural effusion – difficulties in making therapeutic decisions

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Abstract: Pneumonia is the second most common cause of pleural effusion. The presence of pleural fluid makes the prognosis in patients with pneumonia worse and causes a higher mortality rate. This is why it is very important to undertake suitable treatment as soon as possible. Most parapneumonic pleural effusions resolve with antibiotic alone, but sometimes more invasive treatment is necessary. Therapeutic decisions are based on different criteria. For many years the determination of biochemical fluid characteristics has been used for this purpose. At present the usefullness of new parameters is being evaluated. Their application in diagnostics was possible thanks to better knowledge of mechanisms that are involved in the development of parapneumonic pleural effusion.

Key words: biochemical criteria, parapneumonic pleural effusion, pleural drainage

INTRODUCTION

Parapneumonic pleural effusion (PPE) is fluid that accompanies pneumonia or other infections of lung parenchyma. Annual incidence of pneumonia ranges from 5 to 11 cases per thousand persons. 20% of them require hospitalisation [1]. Due to its high frequency, pneumonia is the second, after malignancies, most common cause of pleural exudates [2,3]. Pleural fluid occurs in about 30% of patients with bacterial pneumonia [4,5,6]. A higher percentage (even 75%) is observed in these cases in which hospitalisation is required [7,8]. As the occourence of fluid worsens the prognosis in these patients and causes higher morbidity, it is crucial to implement an appropriate treatment as soon as possible.

Most pleural effusions resolve as result of an antibiotic therapy. However, in about 10% of cases more invasive treatment is necessary, one that includes pleural drainage and sometimes thoracoscopy [4,6]. Tardiness of an appropriate treatment is one of the main causes of higher morbidity and more common occurrence of complications such as pleural fluid loculations and pleural thickening. Therefore it is necessary to establish proper criteria, which would enable to make an appropriate therapeutic decision as soon as possible [8]. Some of them were implemented few years ago and they still can be useful in clinical practice. However, because of their low sensitivity and specificity, studies concerning the utility of these new markers are still being conducted.

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Pathogenesis of parapneumonic pleural effusion

Parapneumonic fluid is an exudate. It develops as a result of a direct pleural involvement in the course of an ongoing inflammatory process and of a dysfunction of the mesothelial cell barrier [5, 9]. Exposure of these cells to lipopolisacharyd, trombin, and bacteria leads to changes in permeability of parietal pleura vessels, accumulation of protein-rich fluid in the pleural space and recruitment of inflammatory cells. VEGF, released from mesothelial cells activated by cytokines and bacteria, participates in this process [9]. In the acute phase an influx of neutrophils takes place, which is followed by an inflow of mononuclear phagocytes and T-limphocytes, activated secondary to mesothelial cells. The latter participate in penetration of effector cells into pleural space. Adhesion molecules play a crucial role in this process [5]. Intercellular adhesion molecule – 1 (ICAM-1) is present on mesothelial cell surface. The process of its interaction with integrin CD11/CD18 (lymphocyte function antigen – 1, LFA-1) occours on the surface of phagocytes under the influence of cytokines, such as tumor necrosis factor alfa (TNF-α) or interferon gamma (IFNγ). This faciliates the adhesion of neutrophils and monocytes to mesothelium and their penetration to pleural space [9].

Many cytokines participate in the ongoing inflammatory process. One of them is interleukin-8 (IL-8), belonging to chemokine family [9,10,11,12]. It is secreted by: endothelial cells, epithelial cells, mesothelial cells, neutrophils, T-lymphocytes and mononuclear phagocytes among other different cells.

Only some of them are present in the pleural space. It is not exactly known which of them, except mesothelial cells, may be responsible for the synthesis of IL-8. This cytokine plays an important role in the migration of effector cells, particularly neutrophils, into pleural space. A high concentration of IL-8 was found in parapneumonic pleural effusion, particularly in empyema [10].

Another cytokine participating in local immunological process is TNF-α, which is released mainly by mesothelial cells and pleural macrophages. It stimulates neutrophil chemotaxis, activates inflammatory cells and regulates the acute phase of the inflammatory reaction by an intensification of other cytokine secretions, among them IL-8. Additionally, it influences the proliferation of fibroblasts and mesothelial cells and collagen synthesis [9,12]. Its high concentration has been found in different pleural diseases, amongst others infectious and malignant ones [12].

A significant participation of nitrogen oxide (NO) in induction of the inflammatory process has been shown as a result of an increase in vascular permeability, stimulation of fibroblasts proliferation, releasing of cytokines, among them IL-8 and TNF-α and chemotactic action on monocytes and macrophages [12].

The formation of PPE consists of three overlapping stages [7]:

1) exudative
2) fibropurulent
3) fibrous.

Therefore, parapneumonic exudate is not a designation of a state but of a dynamic process of changes ongoing in the pleural cavity.

In the successive stages an increase in leucocytes, and lactate dehydrogenase (LDH) concentration, as well as a decrease of glucose concentration in pleural fluid and of its pH takes place [6,8]. The metabolic activity of bacteria and inflammatory cells influences these parameters. The time necessary for the transition from the first to the last phase is estimated at 2–3 weeks [8]. In regard to the course of PPE development it was divided into two groups:

1) uncomplicated parapneumonic exudate
2) complicated parapneumonic exudate [7].

The end stage of the ongoing processes is development of empyema. It is defined as an infection of pleural space associated with the formation of thick, purulent pleural fluid [13]. Parallel to the progress of an empyema, fibrosis of pleural space develops. It may lead to formation of fibrothorax. This means that an inelastic fibrin layer is forming on lung surface that in the course of time organizes and causes restrictive ventilation disturbances. The exact mechanisms causing fibrosis in pleural space remain unknown. One of the factors, that may participate in this process is transforming growth factor beta (TGF-β), belonging to cytokines. It stimulates both fibroblasts proliferation and extracellular matrix proliferation. It is also an immunosupresive factor for lymphocytes. Normal mesothelial cells both synthesise and release TGF-β and have receptors for this cytokine, which indicates its autocrine acting in pleural space [13].

The proinflammatory cytokine IL-1β has been shown to stimulate the expression of TGF-β and is thought to be involved in fibrin deposition in pleural effusion, as TGF-β can stimulate the secretion of PAI-1 by human pleural mesothelial cells. These findings indicate that pleural inflammation may induce the local release of TGF-β and proinflammatory cytokines and may subsequently enhance the release of PAI-1. The imbalance of PAI-1 and tPA may lead to the formation and deposition of fibrin in pleural spaces and loculation of pleural effusions.

TGF-β is a protein with five isoforms [13]. In fibrosis TGF-β_1 play the role. An increase of this cytokine concentration has been shown in PPE. The positive correlation of its concentration with LDH concentration, which is an inflammatory marker, was found. Sasse et al. showed that concentration of TGF-β_1 increases with fibrosis development, correlating with fibroblast number [13].

The pleural fluid loculations develop in the fibropurulent phase and they are connected with fibrin deposition [2,14]. This state is a poor prognostic factor that makes pleural drainage more difficult. An increase in procoagulative fluid activity is observed, owing mainly to tissue factor [15]. A decrease regulated by precise interaction of activators and inhibitors in the fibrinolytic system activity is to be observed. High concentration of tissue plasminogen activator (t-PA), urokinase plasminogen activator (u-PA) and their inhibitors (plasminogen activation inhibitor – PAI-1 and PAI-2) in pleural space has been found in patients with pleural effusion [3,15]. However, fibrinolytic processes are less active in these patients, which is mainly due to the higher activity of PAI. Plasma fibrinolytic activity is regulated by inflammation. A relationship between fibrinolytic and inflammatory processes in pleural fluid is also being postulated [15]. Proinflammatory cytokines, such as TNF-α or interleukin 1 beta (IL-1β), that deregulate equilibrium between PAI-1 and PAI-2 in pleural cavity, may play a role here.

Differentiating between uncomplicated and complicated PPE is significant, because it influences the process of therapeutic decision making. Complicated fluid character indicates that the application antibiotic therapy only may be insufficient and the patient may require pleural drainage. A detailed study of both these pathophisiological processes and new factors that participate in pleural fluid accumulation may result in obtaining new markers helpful in differentiating these two types of fluid and effective treatment.

Differentiation of uncomplicated and complicated parapneumonic exudate

Despite the fact that most PPE resolve by antibiotic treatment, it is recommended to carry out thoracocentesis in each case. The material is analyzed by physical (appearance and color), immunobiochemical and microbiological criteria.

Therapeutic decisions are to be made solely on the basis of the fluid appearance. Its purulent character point to empyema and need of pleural drainage [16]. The same management is recommended in case of the positive microbiological test, however, some observations and analyses indicate that about 10% of patients with positive culture react well to antibiotic therapy. Sometimes pleural drainage is also necessary in cases in which there is no purulent fluid. This is the group of the so called complicated PPE. Their identification is a great challenge for clinicians [6].

In clinical practice of diagnosing complicated pleural fluid biochemical criteria are used. According to the American College of Chest Physicians and the British Thoracic Society a pH below 7.2 and a low (below 60 mg/dl) glucose concentration are connected to poor prognosis and must be treated as an indication for a more aggressive therapy [16,17]. Light added high concentration (above 1000 U/l) of LDH [18] to the criteria mentioned above.

The biochemical parameter change depends on the duration and seriousness of the lung infection and host immunological response [7]. In the early state a high protein concentration is observed, which reflects protein's filtration to pleural cavity as result of increased vascular permeability. Increased LDH concentration results from its local release from cells. Under normal conditions glucose concentration reflects its serum concentration, but during the inflammatory process the metabolism of effector cells and bacteria causes an excessive glucose utilization and release of lactic acid and carbon dioxide resulting in pH decrease.

The measurement of the pH of the fluid by estimation of macroscopic fluid appearance was one of first examinations that allowed to differentiation between uncomplicated and complicated character. Acid fluid reaction is an indication of pleural drainage. We must remember that a pH increase takes place in an advanced infection phase and an inappropriate material taking and a delay in analysis making may additionally influence the results of an acid-base equilibrium [7]. That is why it is necessary not only to obtain the fluid in strict an aerobic conditions, but also to conduct its quicker analysis. However, in practice these conditions are not always fulfilled. There are situations, in which pH estimation has a rather a doubtful value during the therapeutic decision making [7]. In the first case pH varies between 7 and 7,2. It is difficult to unambiguously affirm whether antibiotics or antibiotics combined with drainage should be used. Other situations that make the fluid's pH measurement unreliable are earlier mentioned technical difficulties with fluid transport and probe analysis and prior antibiotic application.

Other methods of differentiating the fluid character were glucose and LDH concentration. A metaanalysis has shown that, in comparison to all biochemical markers mentioned above, fluid's pH measurement has the highest discriminative value. It allows to distinguish the group of patients who require pleural drainage compared with glucose and LDH concentration [19] most precisely.

These parameters may also be useful for the diagnosis of cases, in which complications such as loculations or pleural thickening may develop. Himelman and Callen showed lower pH and glucose concentration, higher LDH concentration and larger fluid volume in patients who tended to loculations formation than in patients with free-flowing pleural effusion [20]. Similar results were shown by Chunga et al. [15].

Maskell et al. showed that in the case of pleural fluid loculations pH might differ in different spaces [2]. The main factors that cause pH reduction in pleural fluid are leucocytes and bacteria. They metabolise glucose to lactic acid and carbon dioxide, a gas that easily diffuses and is distributed in pleural space. Carbon dioxide cannot be the cause of the pH differences between locules. For that reason, it is believed that pH differences in locules result from differences in lactic acid and other soluble acid concentration. These results indicate that in the case of loculations we should be extremely cautious during the therapeutic decision-making. If in the first investigation we ascertained a high pH in patient with a high probability of complicated fluid, we should perform other tests. It is also reasonable to make a precise ultrasonographic estimation of pleural cavity, which enables a better visualization of septations and a precise localization of each locule.

New parameters in decision making

The criteria used for differentiating between uncomplicated and complicated parapneumonic exudate are not precise and have insufficient specificity. For that reason studies in search for new markers, which will allow the diagnosis of these fluid types are being conducted.

As earlier mentioned, in pathophysiological processes occurring during the fluid's development different proinflammatory cytokines partake. That is why the usefulness of their concentration measurement while making therapeutic decision is to be estimated. In PPE a high concentration of IL-8 [9,10] has been found. It has been affirmed, that that it is higher in empyema than in uncomlicated exudate. Empyema is a fluid in which specific conditions are to be observed. Its acid reaction and high activity of proteolitic enzymes cause a fast degradation of many proteins. IL-8 seems to be resistant to inactivation and it may maintain its activity for a longer period of time [10]. Studies carried by Utine et al. on children with PPE confirm the utility of IL-8 as a marker for differentiation between uncomplicated and complicated pleural character [12].

TNF-α plays a crucial role in immunological response. There are studies indicating that it may be useful for identification of patients with complicated pleural effusion [6]. Odeh et al. showed its higher concentration in these groups of exudates in comparison to uncomplicated fluid [21]. Furthermore, Porcel et al. regarded TNF-α as a good marker of inflammation in patients with pleural effusion, as he proved its higher diagnostic sensitivity compared with pH and glucose concentration measurement [6]. Combination of the TNF-α and

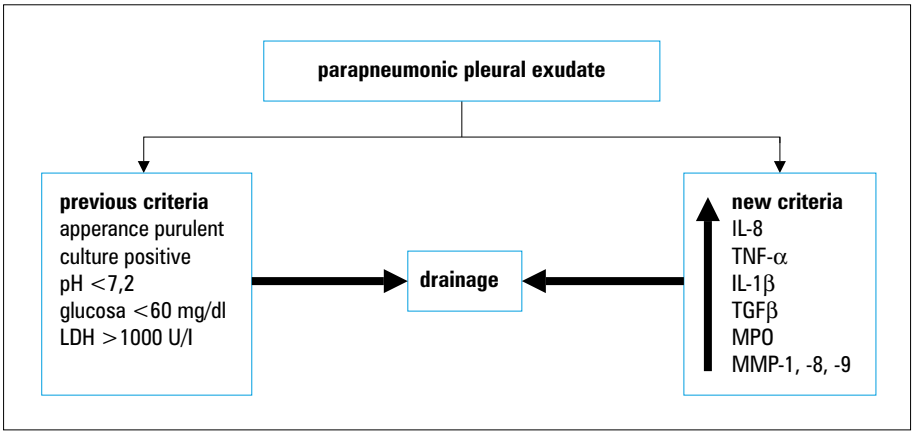

Fig. Previous and new criteria qualificating parapneumonic pleural effusion for drainage. LDH – lactate dehydrogenase, IL-8 – interleukin-8, TGFβ – tumor necrosis factor β, IL-1β – interleukin-1β, TGF-α – transforming growth factor – α, MPO – myeloperoxidase, MMP – metalloproteinase

LDH concentration together made the sensitivity even higher. These data indicate that elevated TNF-α concentration allows to identify the group of patients with non-purulent fluid who require pleural drainage more precisely than traditional biochemical criteria. Utine, already mentioned above, compared the usefulness of the measurement of both of the cytokines in differentiating uncomplicated and complicated parapneumonic exudates, indicating higher sensitivity, specificity and precision of IL-8 in comparison to TNF-α [12].

The cytokine concentration measurements may play a significant role in the process of the identification of patients in which complications such as pleural fluid loculations may develop. As earlier mentioned, the emergence of septetion is associated with fibrin deposition in pleural cavity. In this process both TNF-α and IL-1β, which disturb the equilibrium between the processes of fibrin production and degradation, play an important role. A TGF-β may also be significant, as it stimulates fibrosis [15]. Chung et al. showed differences between regulation of fibrinolytic processes in patients with free-flowing and those with loculated pleural effusion [15]. These differences may be a result of different activity of pro-inflammatory cytokines and TGF-β. A higher concentration of TNF-α, IL-1β, TGF-β1 and PAI-1 in fluid of patients with loculeted pleural effusion than in those with free-flowing has been shown.

While searching for new markers differentiating between uncomplicated and complicated pleural effusions, Alegre et al. estimated how useful myeloperoxidase (MPO) – an proteolytic enzyme released in the acute phase of an inflammatory reaction of azurophil granulations of neutrophils can be in this diagnosis [7]. The role of MPO as the marker of an inflammatory reaction has been used in diagnosis of otitis, chronic sinusitis, chronic bronchitis, and peritonitis of bacterial etiology. In these cases a correlation between its activity and IL-8 concentration gas has been observed. Elevated MPO concentration has been shown in patients with complicated PPE (in comparison to those with uncomplicated PPE) [7]. In addition a correlation between its concentration and the concentration of enzymes traditionally used for differentiating has been found. Estimation of this enzyme may be particularly important in cases, in which it is difficult to make the decision based on classic criteria.

In further studies the usefulness of other proteolitic enzymes (proteases), which degrade extracellular matrix was estimated [14]. One of them are metalloproteinases (MMP), which cause degradation of almost all extracellular matrices. For the time being few subgroups regarding to their structure and substrat specificity were described. There are:

1) collagenases (MMP-1, MMP-8)
2) gelatinases (MMP-2, MMP-9)
3) stromelysins
4) transmembrane metalloproteinases.

Their activity is controlled and modulated by specific tissue inhibitors (TIMP – *tissue metalloproteinase inhibitor*). In course of different disease processes disequilibrium between MMP and their natural inhibitors takes place.

Iglesias showed very high concentrations of MMP-1, MMP-9 and particularly MMP-8 in patients with empyema and complicated PPE [14]. Elevated MMP-1 concentration may be associated with its release by mesothelial cells stimulated by inflammatory mediators. An increase in MMP-8 and MMP-9 is a result of a higher activity of neutrophils. There was a correlation between MMP concentration and other inflammatory markers, especially IL-8 and TNF-α, which are responsible for the activation, chemotaxis and degranulation of neutrophils in pleural space. It indicates that these enzymes play an important role in the development of later complications [14].

CONCLUSIONS

The term parapneumonic pleural exudate is used to describe the dynamic process of changes ongoing in pleural cavity as a result of infection factor action. The physicochemical and immunological proprieties of the fluid accumulating in the pleural space differ in particular stages. The applied management has a big influence on the clinical response. In the early phases of fluid development its resolution is caused

only by a proper antibiotic therapy. In the following stages this management may be insufficient and more invasive methods of treatment are necessary, such as:

1) pleural drainage or
2) toracosurgical procedures.

In the process of decision making measurement of biochemical inflammatory indicators of pleural fluid play a crucial role. For many years indications for pleural drainage were made on their basis. As they are not aimed at precise, studies searching for new markers to differentiate fluid type are under way (fig.). Studies on pathogenesis of fluids and measurement of proinflammatory cytokines and of these released by the surplus of enzymes (participating in its creatin) concentration may constitute new markers to help distinguish patients who require treatment in the form of pleural drainage. Further investigations aimed at estimating its sensitivity and specifity are necessary.

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