

ACUTE INFLAMMATION BIOMARKERS IN PLEURAL EFFUSIONS

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The diagnosis of pleural effusions is a difficult challenge because the catalog of the diseases they cause is as big as it is diverse and in most cases of pleural effusions data are not pathognomonic. The more frequent dilemma in diagnosis of exudative pleural effusions is the differentiating of malignant pleural effusions from inflammatory non malignant one. A dilemma not less challenging is to differentiate if the pleural effusions with inflammatory origin are infectious or not.

In etiologic diagnosis of pleural effusions of inflammatory origin one important step is to find out if the inflammation is acute, sub acute or chronic. This will help not only in diagnostic but also in treatment approach.

In former dilemma settling, the biomarkers have an important and indispensable role. The number of biomarkers of inflammation with infectious origin is as large as diverse. This diversity bewilders us in deciding of choosing the type biomarker and the quantity. The smartest approach in selecting the biomarkers would be picking out the one which would give us at once as much information as possible. Is any biomarker which shows us that the pleural effusion is of inflammation origin or not, that inflammation is acute, sub acute or chronic that can almost exclude malignant origin of effusion?

It would be wisely questioned what is the difference between acute and chronic inflammation. It is known that acute inflammation normally begins immediately and lasts for hours or several days. Patients who are presented with exudative pleural effusion have a history of the diseases, in many cases, over a week or month. The diagnosis of parapneumonic effusion or empyema is decided in most of the cases without the need of using new

biomarkers. The combination of past history, the presence of polymorphonuclear preponderance, the reduced levels of glucose and pH, the high levels of lactate dehydrogenase (LDH) in pleural effusion and leukocytosis and increased presence in the blood of the bends form of white blood cell, are fully enough to accurately diagnose the presence of an acute inflammation of infectious origin. Thus, the more difficult diagnosis would be the distinction between sub acute and chronic inflammation. The presence of lymphocytes excludes the acute nature of inflammation and is characteristic of sub acute and chronic inflammation. The presence of neutrophils over 50% is a sufficient data in diagnosis of pleural effusions due to acute inflammation. Therefore the use of biomarkers of acute inflammation is essential not only in differentiating the activity of inflammation, sub acute or chronic, but also in excluding the non inflammatory etiology of pleural effusion.

Inflammation is the root of many diseases like respiratory, cardiovascular, immunologic, diabetic, arthritis, neurologic, cancer and etc. The inflammation is triggered by many stimuli like Infections (bacterial, viral, parasitic) and microbial toxins, trauma (blunt and penetrating), physical and chemical agents (thermal injury, e.g., burns or frostbite; irradiation; some environmental chemicals), tissue necrosis (from any cause), foreign bodies (splinters, dirt, sutures), immune reactions (hypersensitivity or autoimmunity). Considering the big number of causes of acute inflammation it is not reasonable to spend so much energy with new biomarkers of acute inflammation. There are traditional biomarkers

and data of acute inflammation like values of glucose, pH and lactate dehydrogenase and the presence or not of neutrophils in pleural effusions [1]. We would like to point out that in etiologic diagnosis of pleural effusion, as the result of acute inflammation; it is more difficult to find out the cause of infection than to differentiate if it is of infectious or not infectious origin.

The first step in diagnosing pleural effusion is to find out if it is with inflammatory origin or not. After that it is important to differentiate if the inflammation is acute or chronic. The more frequent causes of acute inflammation in pleural effusion are parapneumonic effusions, pulmonary infarction, post cardiac injury syndrome (PCIS), lupus pleuritis, acute pancreatitis, subdiaphragmatic abscesses, liver, hepatic and splenic abscesses, splenic infarction.

Pleural fluid analysis together with the clinical presentation should enable a definitive or confident presumptive diagnosis in close to 95% of patients [2]. The predominant cell population is determined by the type of pleural injury and the timing of thoracentesis in relation to the acute pleural injury. The acute response to any pleural injury, whether infectious, immunologic, or malignant, is the attraction of neutrophils to the pleural space, initiated by the chemotaxin interleukin-8 [3,4].

Within 72 hours following the cessation of acute pleural injury, mononuclear cells enter the pleural space from the peripheral blood and become the predominant cells [5].

This macrophage predominance is subsequently replaced by lymphocytes in effusions that persist for more than 2 weeks. Therefore, a neutrophil-predominant exudate is the rule when the patient presents shortly after the onset of symptoms, i.e., acute bacterial pneumonia, acute pulmonary embolism with infarction, and acute pancreatitis. In contrast, with the insidious onset of disease, as with malignancy and tuberculosis, a lymphocyte-predominant exudate is found [2].

The efficacy of biomarkers to acute inflammation due to infectious diseases lies in their capability to provide early detection, establish highly specific diagnosis, determine accurate prognosis, direct molecular-based therapy and monitor disease progression.

They are increasingly important in both therapeutic and diagnostic processes, with high potential to guide preventive interventions [6].

According to Infectious Disease Biomarker Database (IDBD) there are currently, 611 biomarkers for 66 infectious diseases and 70 pathogens [7]. The database contains approximately 8–9 biomarkers per pathogen, comprising proteins, nucleic acids, carbohydrates and small molecules. Each biomarker contains a number of categories of information [7]. Therefore, in diagnosing pleural effusions due to infectious pathogens we can measure the pathogen specific biomarkers in blood. However, the most difficult and frequent dilemma in diagnosis of pleural effusion is to differentiate the subacute inflammation from chronic one, whether or not it is triggered by an infection. According to [8,9] elevated pleural fluid levels of CRP, soluble triggering receptor expressed on myeloid cells (sTREM-1), and lipopolysaccharide-binding protein (LBP), identify patients with infectious effusions, particularly those with CPPE, but none of the new biomarkers achieved better performance characteristics than pH, glucose or lactate dehydrogenase in labeling CPPE [8,9].

C-reactive protein (CRP) is considered to be the biomarker of choice to detect an inflammatory state, whether or not it is triggered by an infection. Thus, it is very important to know which are the differences of its values in inflammatory states of infectious and non infectious origin and especially between subacute and chronic infections. Porcel and al [9] and Alvin Tung and al [10] showed that a pleural fluid CRP level $>80 \text{ mg}\cdot\text{L}^{-1}$ argues for the presence of a parapneumonic (PPE) (LR+7.4), whereas CRP levels $<20 \text{ mg}\cdot\text{L}^{-1}$ are a strong indicator against an infectious pleural effusion, whether of bacterial or mycobacterial nature. In our practice of more than 200 cases with pleural effusions the CRP has been less than 20mg/L in 16 cases of 58 with tuberculous effusion. These results show us that the values of CRP in pleural effusion can help to know if the inflammatory state is sub acute or chronic. Therefore the CRP values in pleural effusions less than 20 are characteristic for chronic inflammation and do not exclude the diagnosis of tuberculosis or other chronic infection. These findings are the same as in the study of Castaño Vidriales IJL et al [11] where they found out that two exudates with tuberculosis origin had a C-reactive protein value lower than 10 mg/L.

A number of studies highlight the use of CRP as a diagnostic aid in tuberculous pleuritis; low

pleural CRP levels ($<30 \text{ mg}\cdot\text{L}^{-1}$) make this diagnosis unlikely while being more indicative of a malignancy in patients with exudates [9,10,12,13,14].

Our experience with more than 200 cases with pleural effusions provide support for the use of CRP as a diagnostic aid in differential diagnosis between tuberculous and malignant effusions not for its value $<30 \text{ mg/L}$ but for values $>30 \text{ mg/L}$, value which almost exclude the malignancy as the cause of pleural effusions. The same result is presented in the study of Garcia-Pachon E et al [15], where a level above 45 mg/l virtually rules out this possibility.

We would like to point out the overuse of CRP in daily practice especially in patients with acute presentation of the disease where the utility of using CRP values in blood or fluid is smaller than in patients with subacute or chronic diseases. The reason is simple, in front of acute inflammation whatever would be the cause, infectious or not, the CRP values will be high. I do not think that CRP is superior to pH, glucose, in the diagnosis of complicated parapneumonic effusions. Do we really need in patients with

neutrophilic pleural effusions, acute symptoms and findings of pH, glucose, LDH, the new acute inflammation biomarkers to make the diagnosis of acute inflammation or to decide our approach? Considering the results of many studies [1,8,9,10] and our daily practice we do not need new biomarkers of acute inflammation in diagnostic step of acute pleural effusions. The biomarkers of acute inflammation like CRP help in diagnosis of pleural effusion almost excluding malignancy (CRP $>30 \text{ mg/L}$) and narrowing diagnostic options of lymphocytic exudative effusions.

The pleural fluid CRP $>$ than 20 mg/l virtually exclude transudative nature of pleural effusion [16,17].

Considering these results, the measuring of CRP in pleural effusion has to be a routine examination of pleural effusions because it gives broad information to following dilemma: inflammatory origin or non inflammatory one, subacute or chronic inflammation, the possibility of malignant origin or not.

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