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Review Article

Diagnostic paradoxes of sepsis

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Abstract

Sepsis is currently one of the most important problems of medicine, and the treatment of this category of patients presents great difficulties and is characterized by high mortality. Acute Pneumonia (AP) has been the leading cause of septic conditions for many years, the proportion of which has recently begun to exceed half of all cases. The modern concept of AP considers the causative agent of the disease as the main cause of its occurrence and development, but for many years the search for reliable differential diagnostic criteria depending on the etiology has not been found. The peculiarities of the localization of AP, unlike other inflammatory diseases, force us to pay attention to the fundamental differences in the parameters of blood flow in the two circulatory circles. The inevitability of the onset of the inflammatory process with a vascular reaction forces us to understand the mechanisms of AP development on the basis of already studied, confirmed, and classical materials of medical science. New ideas about the pathogenesis of the disease make it possible to understand its leading importance in the observed pattern of AP and to recognize the obvious over diagnosis of sepsis in this category of patients. Understanding the need for such a step can significantly reduce the number of patients with sepsis, and a pathogenetic approach to medical care will really improve treatment outcomes.

Abbreviations

AP: Acute Pneumonia; SS: Sepsis; CAP: Community-Acquired Pneumonia; WHO: World Health Organization

Introduction

In recent years, Sepsis (SS) has become one of the most serious global health problems, and the negative dynamics of its statistics are of deep concern to specialists who are intensively looking for an effective solution to these problems. A few years ago, the World Health Organization (WHO) reported 30 million cases of SS worldwide per year, of which 6 million were fatal [1]. To date, according to WHO, the number of patients with SS has increased to 49 million per year, and the number of deaths to 11 million [2]. In the United States, the total number of SS diseases has remained stable in recent years, amounting to 1.7 million cases per year, but the number of deaths over the past 6 years has increased from 270 thousand [3] to 350 thousand [4]. The average length of stay of patients with SS in hospitals remains twice as high as with any other lethal exodus [5,6]. The hospital mortality rate, which reached 20% a few years ago [5,6], has increased to 40% in recent years in Europe and North America, that is, in the most advanced healthcare systems [7]. At the same time, in the United States, SS is the main diagnosis of hospital mortality [8].

SS is one of the extreme situations in practical medicine, but it does not belong to the category of suddenly emerging independent nosologies. Septic complications occur against the background of a variety of inflammatory processes and are a secondary pathology in the chain of mechanisms of development of these diseases. In this regard, regardless of our views on this problem and learning preferences, the nature and characteristics of the underlying disease should reflect their specific clinical picture and the observed changes in different categories of patients, right? In recent years, after the introduction of universal diagnostic schemes for SS [9-11], statistics of previous diseases have practically ceased to be given in analytical works on this topic. This is due to the

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fact that this characteristic has undeservedly ceased to be given importance, and SS has increasingly been interpreted as a separate autonomous syndrome. And yet, if desired, in the publications of recent years, you can find data on the frequency of development of SS as a result of various inflammatory processes.

Thus, many studies claim that community-acquired pneumonia, or CAP is the most common cause of SS [12-16]. Some authors note that CAP precedes the development of SS in 50% of cases [17]. Such information forces us to pay close attention to acute nonspecific inflammation of the lung tissue since ineffective treatment of such patients turns out to be the most common cause of SS. The current situation with this problem is perceived by many specialists even more gloomily due to the loss in recent years of their previous positions in the traditional treatment of inflammatory processes. For many years, antibiotics have been the usual basis for the treatment of such diseases, which began to lose not only their effectiveness due to the growth of resistant bacterial strains [18] but also their purpose as a result of an increase in viral forms of inflammation in recent years.

On the one hand, it is known that viruses are more prone to damage lung tissue than other structures of the body, therefore, an increase in the activity of viral infections was accompanied primarily by an increase in the number of viral pneumonia. On the other hand, changes such as a decrease in the effectiveness of antibiotics, and the appearance and growth of resistant strains of microorganisms were predicted and even proved by the founders of antibacterial therapy [19,20]. These side effects have developed and multiplied throughout the use of these drugs. Finally, the diversity and variability of the etiology of pneumonia, which became more apparent against the background of the use of antibiotics, led to the introduction of a new terminology for this disease. It was expected that the separation of pneumonia according to the conditions of their occurrence should reflect the difference in their etiology, which optimizes the choice of antibiotics and improves treatment results. However, over time, the ineffectiveness of this initiative became apparent [21], but the application of the new terminology continues since it is based on the dominant ideas about the leading role of the pathogen. If we do not take into account the declarative nature of the terms generally accepted today, then we are talking about a single nosology, which is known as Acute Pneumonia (AP), which is more appropriate in this context.

The growth of viral forms of AP did not affect the principles of diagnosis and treatment. For example, the previous theoretical and practical foundations for the diagnosis and assessment of the severity of a patient's condition were automatically transferred to viral diseases, including the definition of septic complications [22-24]. It is significant that in recent years there have been reports of an increase in the amount of SS in patients with AP. So, F.Zhou, et al. [25] noted the development of SS during hospitalization in 40.1% of cases among patients with influenza pneumonia and in 39.6% with non-influenza viral pneumonia. C. Cilloniz, et al. [26] reported 61% of cases of SS development among patients with viral pneumonia without concomitant bacterial infection. According to the latest data provided by S.K. Lin, et al. [27], lung infection as the primary diagnosis led to the development of SS in 65% of cases, and if the situation is accompanied by oliguria, this figure increases to 82%.

These figures of septic complications cannot fail to impress with their rapid growth and draw attention to their direct connection with only one localization of inflammatory processes. However, the most striking thing, from my point of view, is that we do not have any convincing evidence of the alleged fact that viral sepsis actually occurs in such observations. Due to the lack of evidence of the viral nature of such a complication, it is necessary to add the identity of the pattern of bacterial and viral SS [28-30], in which, even during the period of predominance of bacterial forms of inflammation, attention was drawn to the absence or insignificant percentage of bacteremia among patients with AP, unlike other localizations [31-33]. Modern simplified stereotypes of the diagnosis of SS, which do not require microbiological confirmation of the diagnosis, are one of the reasons for the overdiagnosis of this complication. But, another, more important reason for false diagnoses of SS is the localization of the process in patients with AP.

In the latter case, we are talking about two different localizations of acute nonspecific inflammatory processes, among which all nosologies affect tissues in the area of a large circle of blood circulation, while only AP occurs in the pulmonary vascular basin. The criteria for the diagnosis of SS were proposed more than 30 years ago [34] and received further justification and dissemination [11]. As is known, shortness of breath and tachycardia are noted already at the very beginning of AP, which, according to these basic criteria, which are usually joined by signs such as fever and leukocytosis, gives reason in most such observations to consider the condition of patients as septic and requires the initiation of intensive general therapy. With peripheral localization of inflammation, shortness of breath and tachycardia are not characteristic of the early clinical picture and their appearance really reflects a new stage of deterioration in the development of the disease. However, the main premise of the existing misconceptions about the diagnosis of SS in patients with AP is associated with the wrong choice of the leading causes of the disease.

For many years, the main factor to which modern medicine has directed all research and therapeutic efforts has been and remains the causative agent of the inflammatory process. The lack of expected success and the periodic change of the main pathogens forced a change in the direction of research and a review of the choice of etiotropic drugs. Unfortunately, the inefficiency of such work did not lead to a natural expansion and change of views on the essence of the problem. To date, not only medical practice but also medical science continue to adhere to the etiotropic concept of AP, leaving without due attention to the basic and unique mechanisms of pathogenesis.

Diagnosis of SS using a point system in patients with AP usually refers to severe patients. It is very positive that modern

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medicine attaches additional importance to such tests as pulse rate, diuresis, blood pressure, and other measurable indicators [35,36], as well as constant monitoring of the hemodynamics of patients who have reached a critical condition [37]. However, in most patients with AP referred to the hospital, earlier clinical signs of changes in peripheral blood circulation may be noted, such as changes in skin color and temperature, the appearance of skin spots, changes in venous pattern, and others. Currently, if a doctor pays attention to such signs during the examination of a patient with AP, he will regard them as the first symptoms of septic complications. Even the suspicion of sepsis, which has not yet been confirmed by the rating scale, is now the basis for starting infusion therapy in accordance with existing general therapeutic standards, without taking into account the peculiarities of the pathogenesis of the disease.

These signs are based on shifts in the general circulatory system, which today are attributed to the pathological action of the pathogen, completely forgetting and ignoring the unique features of the vessels of the small circle. Assessing today the shifts in systemic circulation in patients with AP, which in this process are secondary to disorders of pulmonary blood flow, the modern concept of the disease considers these changes as a result of the action of an infectious factor. The regulatory role of pulmonary vessels in the general blood flow has been completely forgotten and ignored, which is completely inexplicable both from a scientific point of view and from the point of view of analytical logic.

Specialists in the field of pulmonary diseases cannot but know the well-known fact that blood pressure in the vessels of the small circle of blood circulation is normally about 15 mmHg, which is about 8 times lower than in the periphery [38-41]. At the same time, it was found that an increase in pressure in the pulmonary artery by only 5 mmHg contributes to the development of interstitial pulmonary edema, and an increase in this indicator by 10 mmHg causes severe pulmonary edema [41]. We cannot determine and control this indicator, but our body can spontaneously respond to such pressure fluctuations, automatically eliminating dangerous situations. In such cases, we owe the actual saving of life to the protective and adaptive mechanisms that nature has provided us with.

The circumstances that inevitably accompany the inflammatory process of the lung tissue lead to an increase in blood pressure in the pulmonary vessels. The inevitability of such a mechanism is due to the classic onset of inflammation with a vascular reaction, which is accompanied by a slowdown in blood flow, increased permeability of the vascular wall, and edema of the surrounding tissues. Lung tissue, devoid of pain receptors, contains a large number of baroreceptors in its vessels [42], therefore, one of the most effective and rapid adaptation mechanisms is the so-called discharge reflex, described almost a century ago [43]. The reflex nature of such a reaction to an increase in pressure in the pulmonary vessels in patients with AP was proved by us using cervical vagosympathetic blockade on the lesion side, when after a few minutes, along with an improvement in the well-being of patients, respiration and pulmonary blood flow was restored [44]. If the observed functional disorders were mainly due to humoral factors, as many experts present them today, then the usual vegetative blockade would not be able to give such a rapid and demonstrative effect.

The so-called discharge reflex consists of a reflex decrease in the tone of the vessels of the large circulatory circle, a delay in part of the circulating blood at the periphery, and a decrease in venous return, which ultimately reduces the volumetric blood flow in the pulmonary vessels, reducing the intensity of increasing pulmonary edema [43]. Changes in peripheral blood circulation in such a situation have a pulmonogenic rather than septic origin and are characteristic only for patients with AP [44]. In the most aggressive and severe cases, such a reaction fully corresponds to a pulmonogenic shock [44]. However, at present, the concept of this disease, based on the leading role of the pathogen, despite numerous facts refuting such an isolated view of the essence of the problem, continues to consider the shock reaction as septic, which continues to serve as the basis for the application of general therapeutic standards. This approach to the formulation and justification of the diagnosis involves, instead of unloading the vessels of the small circle, infusion therapy with an increase in blood flow to the problem area. Is it any wonder then that the condition of patients with AP after hospitalization continues to deteriorate [45,46] until the development of shock, which did not exist at the time of admission [47,48]?

In addition to the above materials, in recent years additional evidence has emerged of reflex disorders of blood flow in the small circulatory basin in patients with AP. Thus, a number of clinicians drew attention to the discrepancy in the severity of functional disorders in patients with relatively small areas of acute inflammation of the lung tissue. The analysis of computed tomograms in such cases allowed us to establish a decrease in blood flow in pulmonary vessels up to 2 mm in diameter, which the authors regarded as generalized spasm and thrombosis of this part of the vascular network [49,50]. At the same time, it was noted that a decrease in blood flow in the small vessels of the lungs was accompanied by severe gas exchange disorders and high oxygen demand [50]. These data confirm our previous indirect assumptions about reflex vasospasm of the small circle. At the same time, pulmonary vascular thrombosis can only be considered presumably in the area of inflammatory infiltration, since widespread thrombosis of this site in the general bloodstream is unlikely to be compatible with life.

Conclusion

Thus, the above materials and facts indicate that modern principles of diagnosis of SS in patients with AP continue to persistently focus on the priority of the pathogen, ignoring the unique features of the pathogenesis of this disease. The generally accepted assessment of typical manifestations of AP as signs of SS as a result of the action of a virulent pathogen is the reason for the exaggerated diagnosis of this complication already in the early stages of the disease and the appointment of unjustified treatment methods. A radical revision of the concept of AP is a necessary first step in solving not only the problem of pneumonia. Changing professional ideas about

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the nature of AP and the return of the important role of the pathogenesis of the disease, taking into account the classical provisions of medical science, will significantly reduce the undoubtedly overestimated diagnosis of septic complications in this category of patients, whose share among patients with SS is growing at an unprecedented pace and which today already accounts for more than half of septic complications. The adjusted pathogenesis of the disease will make it possible to substantiate the specific pathogenetic methods of first aid for AP that are missing today, which, finally, will make it possible to achieve the long-awaited improvement in results.

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