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REVIEW ARTICLE

Toxic granulations: a key marker in sepsis

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ABSTRACT

Currently, sepsis is considered a potentially life-threatening organ dysfunction that represents an alarming challenge in medical practice, especially in the management of critically ill patients. In this regard, toxic granulations in neutrophils have emerged as an ideal marker to aid in its diagnosis. Therefore, the aim of the study was to analyze the importance of toxic granulations in the diagnosis of sepsis, their prognostic marker potential, and their incorporation into daily clinical practice. A literature review was conducted on studies published between 2019 and 2024 that assessed the relationship between toxic granulations and sepsis. Toxic granulations were associated with a severe inflammatory response, such as sepsis, but have also been observed in other severe infections and some hematological disorders, limiting their utility as a sole marker. In conclusion, toxic granulations are an essential diagnostic, prognostic, and follow-up tool in sepsis, although further research is needed to standardize their use in clinical practice.

Granulaciones tóxicas: un marcador clave en sepsis

Palabras clave:
sepsis; gránulos citoplasmáticos; biomarcadores; granulaciones tóxicas; sepsis (Fuente: DeCS - BIREME).

RESUMEN

Actualmente, la sepsis es considerada una disfunción orgánica potencialmente mortal que representa un desafío alarmante en la práctica médica, de manera especial en el manejo de pacientes en estado crítico. En este sentido, las granulaciones tóxicas en neutrófilos han surgido como un marcador ideal para facilitar su diagnóstico. Por ello, el objetivo del estudio fue analizar la importancia de las granulaciones tóxicas en el diagnóstico de la sepsis, su capacidad como marcador pronóstico y la incorporación en la práctica clínica diaria. Se realizó una revisión bibliográfica de estudios publicados entre 2019 y 2024 que evaluaron la relación de las granulaciones tóxicas con la sepsis. Las granulaciones tóxicas se relacionaron con una respuesta inflamatoria severa, tal como la sepsis, pero también se han observado en otras infecciones graves y algunos trastornos hematológicos, limitando su capacidad como único marcador. En conclusión, las granulaciones tóxicas constituyen una herramienta diagnóstica, pronóstica y de seguimiento esencial en la sepsis, a pesar de que se necesita más investigación para estandarizar su uso en la práctica clínica.

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INTRODUCTION

Sepsis is defined as a potentially life-threatening organ dysfunction caused by a dysregulated host response to infection [1–3]. Thus, it poses an alarming challenge in medical practice, especially in the care and management of critically ill patients. Although significant progress has been made in the discovery of new diagnostic tools and in the understanding of sepsis pathophysiology [4], early diagnosis of this condition remains difficult due to the nonspecific clinical characteristics presented by patients, in addition to the inherent limitations of current diagnostic methods [2]. A gold standard for diagnosis is still lacking, and commonly used cultures require a considerable amount of time [1]. Therefore, morphological changes in leukocytes represent an appealing, simple, and cost-effective method to differentiate sepsis [5]. For this reason, toxic granulations—cytoplasmic alterations characteristically observed in neutrophils during severe inflammatory processes [6]—have emerged as a valuable diagnostic marker for sepsis [7].

Toxic granulations in neutrophils are prominent cytoplasmic inclusions, essentially composed of primary or azurophilic granules [6], which become visible under the microscope during severe inflammatory processes [8], such as sepsis. They are distinguished by their dark blue to black color observed in the cytoplasm of mature neutrophils and are indicative of intense neutrophil activation in severe bacterial infections [9–12]. Their origin is believed to be due to the accumulation of acidic mucosubstances in the azurophilic granules [13], representing an active immune response to infection. They can be visualized through stains such as Wright, Giemsa, and Leishman [9,13,14], and serve as an important marker of cellular stress and immune response, indicating the body's capacity to respond effectively to pathogens.

This review article aimed to analyze the importance of toxic granulations in the diagnosis of sepsis, their potential as a prognostic marker, and their incorporation into daily clinical practice. Through a critical synthesis of available information, it seeks to highlight their potential as an appealing, simple, and cost-effective diagnostic tool, in contrast to other more complex and expensive markers. This analysis also intends to fill gaps in our current understanding of this marker and to propose new potential lines of research in the field of clinical laboratory and medicine.

The importance of this article lies in the fact that this topic has been little explored in the scientific literature despite its clinical relevance. Its originality stems from reassessing a traditional laboratory finding from the perspective of current needs in the management of sepsis. Therefore, it not only aims to broaden the understanding of toxic granulations but also to contribute to the creation of faster and less complex diagnostic strategies that could improve the management of sepsis.

METHODS

This article was based on a literature review to critically analyze the available scientific literature on toxic granulations and their role in the diagnosis of sepsis. A search was conducted in recognized academic databases (PubMed, Scopus, and Google Scholar) using keywords such as "neutrophil toxicity," "neutrophil toxic granules," "toxic granules in neutrophils," "sepsis," and their possible combinations. The search focused on articles published between 2019 and 2024 (excluding those used to define certain terms), in both English and Spanish, to obtain recent and relevant sources. Only original and recent studies addressing the clinical, diagnostic, and prognostic features of toxic granulation in patients with sepsis were selected (see Figure 1).

A systematic approach was used to select and analyze the information. Initially, the retrieved articles were reviewed by title and abstract to identify their relevance according to the study objectives. Subsequently, a full-text review was conducted, using a data extraction table constructed in Microsoft Excel, in which the articles were categorized by title, year of publication, publication database, key findings, and relevant conclusions. This process enabled the compilation of important information and facilitated a reflective analysis contributing to the current knowledge on toxic granulations in the context of sepsis.

It is worth noting that, in addition to the studies included in the bibliographic review flowchart, complementary bibliographic sources were used to enrich the information presented in this work.

RESULTS

In this article, 17 recent studies were analyzed to examine the relationship between toxic granulations and their significance as a diagnostic marker in sepsis.

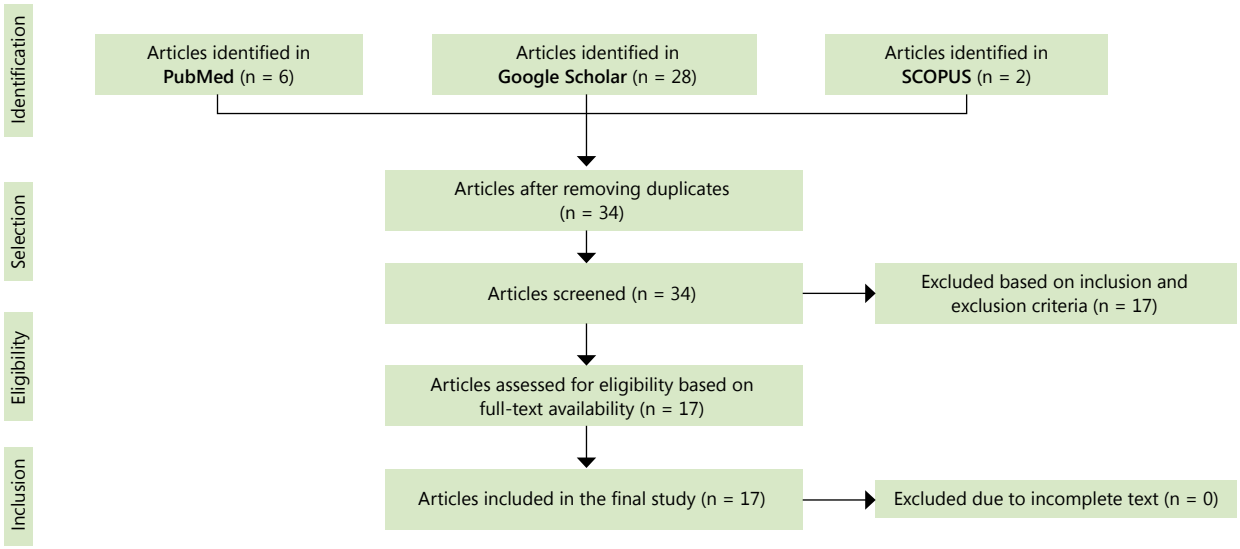

Figure 1. Literature review flowchart

Initially, 36 articles were identified through database searches; however, after applying the inclusion and exclusion criteria, the final selection comprised 7 observational studies (cross-sectional, retrospective, and prospective studies) and 10 literature reviews.

Among the included studies, 12 were published in English, while the remaining 5 were in Spanish. These studies were conducted in various countries, with China standing out with two highly relevant studies on sepsis and toxic granulations, as well as India, with three studies—two directly related to the main topic of analysis and the third less directly related but providing valuable insights into sepsis. The rest of the studies were conducted in other countries, including the United States, South Korea, the United Kingdom, Egypt, France, Germany, Canada, Mexico, Colombia, Paraguay, and Ecuador. Although not all of them are directly related to the primary subject of this research, these studies significantly contribute to defining key concepts that help form a comprehensive understanding of the topic.

Below are the most relevant findings regarding toxic granulations according to the reviewed bibliographic sources.

Toxic granulations: description and clinical relevance

The precise mechanism of formation of toxic granulations in neutrophils is not yet well defined. Recent studies indicate that these granulations mainly consist of enzymes found in the primary granules of neutrophils, suggesting that their genesis may be attributed to these structures [6,15,16].

Toxic granulations are rare findings in peripheral blood smears and can be observed within the cytoplasm of both mature neutrophils and their immature forms, typically in the context of inflammatory processes such as sepsis [6,9]. They are primarily composed of primary or azurophilic granules, which appear dark blue or black in color [9]. Their formation is associated with the accumulation of acidic mucosubstances in the azurophilic granules [17,13], which reflects the intense activation of neutrophils in response to a severe infection.

Neutrophils possess various types of granules that are activated and mobilized in response to

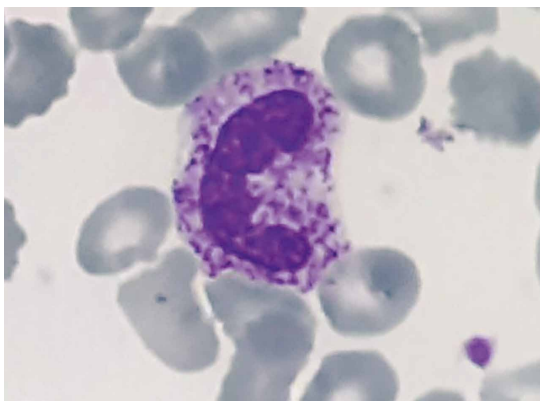

Figure 2. Microphotograph at 1000x magnification showing the presence of band neutrophils with toxic granulation, stained with modified May-Grünwald-Giemsa for emergency use

inflammatory stimuli such as cytokines and pro-inflammatory mediators [16]. Among these, the primary or azurophilic granules are of particular importance, as they contain antimicrobial proteins such as myeloperoxidase (MPO), elastase, and α-defensins, which are essential for the toxic and bactericidal activities of activated neutrophils [6,15,18].

These granules are mobilized during sepsis toward the cell surface or phagosomes for rapid release of their toxic contents. This mechanism, regulated by proteins such as Rab27 and Slp1, leads to the development of visible toxic granulations in neutrophils [6]—a morphological change characteristic of the intense immune response observed in severe infections. Such changes can be detected by hematology analyzers or laboratory procedures such as peripheral blood smears, thereby enhancing the diagnosis of sepsis.

In the existing scientific literature, this finding has been described using various terms, including "toxic granulation in neutrophils" [2], "toxic granules" [5], "granules in the cytoplasm of neutrophils" [19], or "toxic granules in neutrophils" [9]. Although there is no consensus on the nomenclature, several publications describe them as the presence of large, dark granules in segmented neutrophils [2,5,9]. These terms reflect the toxicity of their content against pathogens and indicate an altered immune response. During a severe inflammatory response, other cytoplasmic changes such as Döhle bodies [20] and vacuoles [21] may also be observed, which can be mistaken for toxic granulations and must be accurately differentiated.

The reviewed studies did not specifically mention the original discovery or initial description of toxic granulations in neutrophils, nor when this finding was first identified. However, it is known that these cellular inclusions have been observed in cases of severe infections and specific disorders such as sepsis [9], COVID-19 [22–24], hematologic neoplasms [25,26], congenital tuberculosis [27], drug toxicity [8], and other acute infectious conditions. Additionally, no data are currently available regarding mortality in sepsis patients presenting with toxic granulations.

DISCUSSION

Sepsis is one of the leading causes of mortality worldwide and represents a major challenge in clinical practice, due to its heterogeneous nature and rapid progression. It affects all age groups, from newborns to the elderly, with an estimated 50 million cases globally each year [28], and has a mortality rate of 25% to 30%, posing a serious threat to public health [2,29]. For this reason, early diagnosis and management of sepsis are essential to reducing these figures [30].

Currently, developing an early and effective diagnostic method that allows timely intervention in sepsis remains a challenge for researchers. This is mainly due to the wide variety of clinical signs and symptoms with which the disease may present, most of which are nonspecific [31]. As such, it becomes even more difficult to detect sepsis in its early stages, which delays early treatment and increases the risk of adverse outcomes. Therefore, accurately identifying and establishing a diagnosis of sepsis in a rapid, reliable, and cost-effective manner has become an urgent need in clinical laboratories and medicine [2].

Today, various diagnostic methods are used in the context of sepsis, such as blood cultures, C-reactive protein (CRP), procalcitonin (PCT), and interleukin-6 (IL-6) [2,19]. However, none of these have demonstrated high sensitivity and specificity in detecting sepsis, as the presence of these biomarkers has been observed in various inflammatory and infectious conditions [2], limiting their ability to accurately differentiate between severe systemic infections like sepsis and other inflammatory processes, as well as to predict clinical outcomes [31]. Therefore, further studies are needed to identify more specific biomarkers that allow early and accurate diagnosis.

The identification of toxic granulations in neutrophils has become a significant finding in the diagnosis of sepsis. These inclusions, resulting from a severe inflammatory response, clearly indicate neutrophil activation in the presence of serious infections [2]. Several studies have shown that their presence is associated with a higher bacterial load and increased infection severity, making them a valuable marker for the early identification of sepsis [6,9].

Accordingly, Sharman et al. found that the presence of toxic granules (55.8% vs. 12.5%; $p < 0.001$) was significantly higher in the sepsis group compared to the non-sepsis group, concluding that this morphological change may be a useful finding in the early management of septic patients, particularly in rural settings with limited resources [5]. However, researchers such as Chander et al. [9] found that although none of the individual parameters—such as total leukocyte count, absolute neutrophil count, or

toxic granulations—are diagnostic of sepsis on their own, all are complementary in predicting a sepsis diagnosis. Thus, although further research is required to standardize its use, toxic granulation is increasingly being recognized as an important clinical support tool.

In this sense, toxic granulations are not only used for the diagnosis of sepsis but may also serve as prognostic indicators for patients. Their presence has been associated with greater severity of infection, as a significant positive correlation exists between neutrophil count and the amount of toxic granulation, which is reflected in a darker cytoplasmic coloration compared to lower neutrophil levels [2]. This suggests that the amount—and possibly the type—of toxic granulations may correlate with prognosis, helping predict the risk of complications and mortality, which is critical for clinical decision-making. Despite their usefulness, their prognostic value must be interpreted with caution, as other clinical factors also play a role in patient outcomes [6]. In fact, to date, no specific mortality rate has been established for sepsis patients presenting with toxic granulations in neutrophils, underscoring the complexity of using this marker in isolation to determine prognosis.

A marker's ability to monitor and track patients during treatment is one of the essential features of an effective biomarker. This is particularly crucial in high-severity conditions such as sepsis, where early identification and therapeutic monitoring can mean the difference between life and death. Thus, toxic granulations in neutrophils should not only be sensitive and specific for diagnosis but also useful in evaluating disease progression and treatment response. An example of this was demonstrated in the study conducted by Feng et al. [19], which observed that granules in the cytoplasm of neutrophils—indicators of immune cell cytotoxicity—were thick and dense prior to treatment. However, these granules significantly decreased following therapeutic intervention in different septic patients. This finding reinforces the potential of toxic granulations as a dynamic marker that can guide both the diagnosis and continuous monitoring of sepsis, thereby contributing to more precise and effective clinical decision-making throughout the disease course.

Overall, the integration of toxic granulations into daily clinical practice as a marker for the diagnosis and management of sepsis remains a challenge. Although their detection in peripheral blood smears may be relatively simple, their practical implementation depends on various factors such as resource availability, time and labor constraints, staff expertise, and the clinical variability of sepsis [2,9]. Nevertheless, their growing recognition as a diagnostic and prognostic marker promises to enhance early identification of sepsis, thus contributing to more effective treatment and reduced mortality. However, broader consensus is still needed for their integration into clinical protocols.

It is also important to emphasize that toxic granulations in neutrophils are relatively rare, and despite being a relevant finding in identifying severe infections and systemic inflammation, little information is currently available on various aspects of this finding. Although their association with conditions such as sepsis, severe bacterial infections, and some hematological disorders has been reported, their diagnosis can be difficult due to the lack of uniform nomenclature and confusion with other cellular changes. The origin, exact frequency, and relationship with various clinical conditions of toxic granulation remain poorly understood, as studies and reports are scarce.

Conclusions

Early detection and timely management of sepsis remain fundamental pillars of medical care, as they are critical to reducing the high mortality rates associated with this condition. In this context, toxic granulations represent a valuable diagnostic, prognostic, and monitoring tool—particularly in settings with limited technological and economic resources. Although their identification in peripheral blood smears is accessible and relatively straightforward, their application faces challenges due to a lack of standardization, inter-observer variability, and the need for trained laboratory personnel.

It is important to emphasize that toxic granulations are not specific to sepsis, as they may also appear in other pathological conditions. Therefore, complementary laboratory tests are necessary to ensure diagnostic accuracy. While preliminary studies support their clinical utility, further research involving larger and more diverse populations is essential to validate their effectiveness and develop standardized guidelines for their incorporation into clinical protocols. Achieving consensus on their implementation will help optimize their use and improve outcomes in the diagnosis and management of sepsis.

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Authorship contribution

AIPM: Conceptual study design, article identification and selection, critical analysis of the studies, drafting, reviewing, and final editing of the manuscript, including figures.

MJRP: Analysis of selected articles and contribution to the writing of the introduction and discussion sections.

EAVR: Analysis of selected articles and contribution to the writing of the results and discussion sections.

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The authors declare no conflicts of interest.