HHS Public Access

Author manuscript

Indian J Rheumatol. Author manuscript; available in PMC 2019 December 27.

Published in final edited form as:

Indian J Rheumatol. 2019 March ; 14(1): 9–11. doi:10.4103/0973-3698.254192.

Utility of CD64 Expression on Neutrophils as a Marker to Differentiate Infectious versus Noninfectious Disease Flares in Autoimmune Disorders

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Developing biomarkers that will differentiate etiologies of inflammatory processes has been an ongoing conundrum for experimental biologists and physician scientists. Inflammation is a developmentally conserved process utilized by vertebrates to primarily protect themselves from infectious agents. The same inflammatory process is also a hallmark of autoimmune disorders noted in higher vertebrates. Clinicians often encounter dilemmas when patients with autoimmune disorders present with acute inflammatory states as these inflammatory states could have varying etiologies.[1] Individuals with autoimmune disorders are often treated with immunosuppressive agents, potentially increasing their risks for infections and malignancies. When patients with systemic autoimmune disorders develop fever, myalgias, and arthralgias, clinicians often ponder if the acute inflammatory state is secondary to an underlying infection or exacerbation of the autoimmune disorder. Although history and clinical examination can positively assist in deciphering the etiology of the acute inflammatory state, there exists a paucity of reliable laboratory tests that will help to rule in/out infection over exacerbation. This is a clinically relevant distinction as disease flare may warrant increasing immunosuppression while infection may necessitate decreasing immune suppression and treating with antimicrobial therapy. These factors highlight the need to have biomarkers that will enable clinicians to determine the exact etiology of the acute clinical state with certainty. Existing laboratory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), total leukocyte count, and neutrophilic predominance in differential counts with presence of bands do have reasonable sensitivity to diagnose an infectious etiology, yet all these tests lack specificity.[2] Molecular tests with high specificity may be available for some infectious agents, but when negative, the tests do not necessarily help in determining if the etiology is infectious or not. Molecular studies have comparable specificity to gold standards, but the later have the highest specificity, with the limitations of blood culture being the longer reporting time and effect of antibiotics on blood culture outcomes.

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Thus, current tests with higher specificities and sensitivity can be cumbersome and time consuming. For individuals presenting with clinical symptoms suggestive of an inflammatory process, timely clinical decision-making becomes critical and the wrong choice (such as increasing immunosuppression for a presumed disease flare when the cause is actually infectious) can have detrimental consequences. Therapeutic options employed in treating inflammatory exacerbations of autoimmune disorders are significantly different from treating inflammation secondary to infectious etiology. Thus, studies on optimal biomarkers that can help delineate between inflammation due to infectious and noninfectious etiologies have significant clinical values.

Ajmani *et al.*[3] have undertaken an observational study with an attempt to address the above-mentioned conundrum. The authors have analyzed biomarkers in patients with systemic rheumatic diseases with and without concomitant infections as well as healthy controls. The aim of this study was to develop a biomarker signature that will enable clinicians to delineate infection driven from noninfection-driven inflammation during autoimmune disease flares. Previous studies have analyzed soluble and nonsoluble (cell surface) molecules such as procalcitonin, sTREM, CRP, and ESR as surrogates of inflammation. One attractive candidate in this regard has been utilization of surface expression of CD64 on neutrophils during sepsis[4] and systemic inflammatory response syndrome.[5] The authors make a compelling argument that percentage of neutrophils expressing CD64 on the cell surface can be used as a surrogate to delineate inflammatory processes due to infection versus acute exacerbation in the ongoing autoimmune processes. This small observational study re-enforces data from previous studies regarding the utility of surface expression of CD64 on neutrophils to differentiate infectious from noninfectious disease flares.[6-8] A novelty of the study by Ajmani *et al.* is utilization of surface expression of CD64 on neutrophils to negatively predict acute disease exacerbation state in patients with rheumatic diseases.[3] This study has significant clinical relevance and considerable application. Administering systemic glucocorticoids during acute infections could lead to significant morbidity in patients; conversely, not administering systemic glucocorticoids in patients with acute exacerbation of autoimmune disorders could be detrimental. Hence, developing a panel of biomarkers that can be utilized in the early clinical decision-making process has considerable clinical value. This could influence various clinical outcomes such as number of days of hospitalization, morbidity, and mortality of patients and ultimately drive health-care expenditures.

Although neutrophil CD64 (nCD64) as a biomarker to differentiate between infectious and autoimmune disease flare is garnering considerable support, the basic biology behind the regulation of CD64 expression is poorly understood. We believe CD64 expression on neutrophils can be induced either by pathogen (bacteria or virus)-derived molecular patterns (PAMPs) through toll-like receptor stimulation or host inflammatory mediators such as interferon-γ (IFN-γ) and/or granulocyte-macrophage-colony-stimulating factor (GM-CSF).[9,10] Higher expression of CD64 on neutrophils in patients with dengue virus infection reported by Ajmani *et al.* further supports that PAMPs may regulate expression of CD64. However, no definite studies have been performed to identify the mechanism for the induction of CD64 on neutrophils. Further studies are required to delineate the molecular

pathways that regulate CD64 expression. The functional relevance of inducing CD64 on neutrophils could be explained by the importance of CD64 (FCγR1) in phagocytosis due to its high avidity for IgG.[11] It can be argued that, during infection, macrophages respond to PAMPs and secrete IFN-γ, GM-CSF, and other mediators that lead to induction of CD64 on neutrophils. This will eventually enhance phagocytosis and clearance of microbes to help resolve infections. In this study, some of the patients were on immune-modulating agents, and it is also plausible that immune-modulating agents can confound CD64 expression on neutrophils. Data from the studies by Ajmani *et al.*[3] and Deodhar *et al.*[6] suggest that enhanced CD64 expression on neutrophils can occur in certain autoimmune diseases such as antineutrophil cytoplasmic antibody-associated vasculitis or in conditions often occurring in the context of rheumatologic diseases such as macrophage activation syndrome. As both these clinical conditions are characterized by severe inflammation, it can be argued that the severity of inflammation (quantity and quality) rather than the etiology of inflammatory processes may be the key factor driving the upregulation of CD64 on neutrophils. Nonetheless, these studies highlight the clinical importance of significantly escalated levels of inflammation during infectious process compared to those during flares of autoimmune disease.

Some of the limitations of using CD64 expression as a biomarker on neutrophils include expertise needed in handling neutrophils. Although a biochip has been recently developed that can measure neutrophil CD64 at point of care,[12] the utility of the same in primary care or remote health center is unclear. It is also important to note that neutrophils need to be analyzed within a few hours of isolation due to their short life span. Given these time constraints, utility of this test at community hospitals may be limited, making this a less feasible screening tool at primary health-care centers. The feasibility of CD64 expression on neutrophils as a screening tool can be challenging at community hospitals with limited resources. Most health-care centers will need human expertise and technical infrastructure such as a flow cytometry analyzer to acquire and analyze data. These requirements might limit the wider applicability of the test in the field.

In summary, the study by Ajmani *et al.*[3] validates the significance of neutrophil CD64 expression as a useful biomarker to delineate infectious etiology from disease exacerbation in autoimmune disorders. Thus, this study is an important step in the right direction. The existing studies were small observational cohorts; therefore, further validation needs to be performed in larger prospective studies.

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