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Anemia of Chronic Disease: Mechanisms, Diagnostic Challenges, and Emerging Therapeutic Strategies

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ABSTRACT

Anemia of chronic disease (ACD), also referred to as anemia of inflammation, is a prevalent form of anemia associated with chronic infections, autoimmune disorders, cancers, and other long-standing inflammatory conditions. Unlike iron deficiency anemia, ACD is characterized by adequate or elevated iron stores with impaired iron mobilization, reduced erythropoiesis, and shortened red blood cell lifespan. A key feature of ACD is the inflammatory upregulation of hepcidin, a liver-derived peptide hormone that inhibits iron absorption and release by targeting the iron exporter ferroportin. This hepcidin-mediated iron sequestration limits iron availability for red blood cell production, contributing to anemia despite sufficient total body iron. Diagnosing ACD can be challenging due to overlapping laboratory features with other anemia types, especially iron deficiency anemia. However, the use of novel biomarkers such as hepcidin, soluble transferrin receptor, and reticulocyte hemoglobin content can improve diagnostic precision. Therapeutic strategies are evolving to include cytokine inhibitors, hepcidin antagonists, hypoxia-inducible factor stabilizers, and selected use of intravenous iron or erythropoiesis-stimulating agents. A deeper understanding of ACD's pathophysiology and the development of targeted treatments hold promise for more accurate diagnosis and effective management, particularly in patients with complex or comorbid conditions.

Keywords: Anemia of chronic disease, hepcidin, inflammation, iron metabolism, therapeutic targets

INTRODUCTION

Anemia of chronic disease (ACD), also referred to as anemia of inflammation, is a non-nutritional, normocytic or mildly microcytic anemia that arises in the context of chronic infections, autoimmune disorders, malignancies, and other long-term inflammatory conditions [1]. It is the second most prevalent form of anemia after iron deficiency anemia and is often underdiagnosed due to its subtle onset and overlapping clinical features [1]. ACD results from a combination of iron-restricted erythropoiesis, reduced red blood cell production, and diminished erythropoietin response [2]. While the anemia is typically mild to moderate in severity, it can significantly impair quality of life and exacerbate the underlying disease. The chronic inflammatory state that drives ACD disrupts normal iron metabolism and erythropoiesis through complex interactions between immune and hematopoietic systems [3]. As our understanding of inflammatory and iron regulatory pathways deepens, new diagnostic and therapeutic opportunities are emerging to address this complex condition.

2. Pathophysiological Mechanisms

2.1 Cytokine-Mediated Iron Sequestration

Pro-inflammatory cytokines, particularly interleukin-6 (IL-6), play a central role in the pathogenesis of ACD. IL-6 stimulates the hepatic synthesis of hepcidin, a peptide hormone that negatively regulates iron efflux by binding to ferroportin, the only known cellular iron exporter [4]. Hepcidin binding causes ferroportin internalization and degradation, thereby trapping iron within macrophages and enterocytes and limiting its availability for erythropoiesis [5]. This sequestration mechanism reduces serum iron levels despite adequate or increased total body iron stores, leading to functional iron deficiency. In this state, iron is inaccessible to developing erythrocytes, which disrupts hemoglobin synthesis and impairs red cell production [6]. Furthermore, chronic inflammation promotes ferritin expression, increasing iron storage while simultaneously suppressing its mobilization [7].

2.2 Suppressed Erythropoiesis

Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and IL-1β inhibit the proliferation and differentiation of erythroid progenitor cells [8]. These cytokines exert their effects by altering transcriptional pathways within hematopoietic stem cells and reducing the availability of essential growth factors required for erythroid maturation [9]. Additionally, the bone marrow environment in chronic disease becomes less conducive to erythropoiesis due to oxidative stress, increased apoptosis, and reduced responsiveness to erythropoietin (EPO) [10]. Increased levels of reactive oxygen species (ROS) further impair hematopoietic cell viability and disrupt the balance between red cell production and destruction [11]. As a result, the output of mature erythrocytes is diminished, exacerbating the anemia.

2.3 Reduced Erythropoietin Activity

In chronic inflammation, EPO production by the kidneys is blunted despite the presence of anemia [12]. The normal physiological response to hypoxia is thus impaired, and EPO levels often remain inappropriately low relative to the degree of anemia [13]. Moreover, cytokines such as TNF-α and IL-1β may impair the sensitivity of erythroid precursors to EPO by downregulating EPO receptor expression or interfering with downstream signaling pathways [14]. This dual effect limits the erythropoietic response to anemia and contributes to its persistence. In some patients, the administration of recombinant EPO is required to overcome this resistance, but responses may still be suboptimal due to the inflammatory milieu [15]. Together, these mechanisms illustrate how chronic inflammation orchestrates a multifaceted disruption of red blood cell production and iron metabolism, culminating in the development and maintenance of anemia of chronic disease.

3. Diagnostic Challenges

3.1 Overlap with Iron Deficiency Anemia

Differentiating anemia of chronic disease (ACD) from iron deficiency anemia (IDA) presents a significant clinical challenge due to overlapping laboratory findings. Both conditions are characterized by low serum iron and decreased transferrin saturation, which can obscure accurate diagnosis [16]. However, a key distinguishing feature lies in the behavior of serum ferritin [16]. In IDA, ferritin levels are typically reduced, reflecting depleted iron stores [17]. In contrast, ACD is marked by normal or elevated ferritin concentrations, owing to the inflammatory blockade of iron release and the sequestration of iron within macrophages [18]. This elevation is not indicative of iron sufficiency but rather reflects ferritin's role as an acute-phase reactant in inflammatory states. Recognizing this distinction is critical in avoiding unnecessary or inappropriate iron supplementation, which may be ineffective or even harmful in ACD.

3.2 Role of Hepcidin and Newer Biomarkers

The identification and measurement of hepcidin, a liver-derived peptide hormone, have significantly enhanced the understanding and diagnostic capabilities in ACD. Hepcidin serves as a central regulator of iron homeostasis, and its production is markedly increased in chronic inflammatory conditions [19]. Elevated hepcidin levels inhibit intestinal iron absorption and promote iron sequestration in macrophages by downregulating ferroportin, the primary cellular iron exporter [20]. Thus, a high hepcidin level supports a diagnosis of ACD, whereas low hepcidin suggests true iron deficiency. To improve diagnostic accuracy, additional biomarkers have emerged [21]. Soluble transferrin receptor (sTfR) levels are typically elevated in iron deficiency but remain normal or only mildly increased in ACD, offering a useful comparative marker [22]. Reticulocyte hemoglobin content (CHr) provides insight into recent iron availability for erythropoiesis, while inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can support the presence of underlying inflammation [23]. The use of these combined parameters enables a more nuanced approach to distinguishing ACD from IDA, especially in complex clinical settings.

3.3 Integration of Clinical Context

An accurate diagnosis of ACD necessitates the integration of laboratory data with the patient's clinical history and the presence of an underlying chronic disease such as rheumatoid arthritis, chronic kidney disease, malignancy, or chronic infection [24]. It is crucial to evaluate for potential coexisting conditions that may contribute to anemia, including nutritional deficiencies such as vitamin B12 or folate deficiency, especially in elderly or malnourished individuals [25]. Moreover, bone marrow disorders or hematologic malignancies must be considered in patients with atypical presentations or refractory anemia [26]. A comprehensive diagnostic approach ensures appropriate management and avoids the pitfalls of treating a presumed iron deficiency in the presence of inflammatory blockade.

4. Emerging Therapeutic Strategies

4.1 Anti-Inflammatory and Cytokine-Targeted Therapies

Given the central role of inflammation in the pathogenesis of ACD, targeting pro-inflammatory cytokines offers a promising therapeutic avenue. Interleukin-6 (IL-6), a key mediator in hepcidin induction, has been the focus of

several clinical trials [27]. Tocilizumab, an IL-6 receptor antagonist, has demonstrated effectiveness in improving anemia among patients with inflammatory diseases such as rheumatoid arthritis [28]. By dampening the inflammatory cascade, these agents reduce hepcidin levels, thereby enhancing iron availability and improving erythropoiesis.

4.2 Hepcidin Modulators and Ferroportin Stabilizers

Therapeutic strategies aimed at modulating the hepcidin-ferroportin axis are under active investigation. Approaches include the use of monoclonal antibodies against hepcidin, small interfering RNA (siRNA) molecules that suppress hepcidin gene expression, and synthetic hepcidin antagonists [29]. These agents are designed to counteract the effects of elevated hepcidin, restore iron homeostasis, and facilitate adequate red blood cell production.

4.3 Hypoxia-Inducible Factor (HIF) Stabilizers

HIF prolyl hydroxylase inhibitors, such as roxadustat, represent a novel class of drugs that stimulate endogenous erythropoietin (EPO) production and promote iron metabolism by reducing hepcidin levels [30]. Originally developed for anemia in chronic kidney disease, these agents have shown potential in broader inflammatory conditions. Their dual action on erythropoiesis and iron availability makes them attractive candidates for ACD therapy.

4.4 Iron Therapy and Erythropoiesis-Stimulating Agents (ESAs)

Iron supplementation, particularly intravenous iron, may be considered in patients with mixed ACD and iron deficiency or in selected cases where hepcidin levels are not excessively elevated [4]. Erythropoiesis-stimulating agents can enhance red blood cell production, especially in cases refractory to other interventions. However, their use is tempered by concerns about thromboembolic events, high cost, and limited efficacy in the presence of ongoing inflammation.

5.0 Future Directions

The management of anemia of chronic disease (ACD) is evolving alongside advances in molecular biology, diagnostics, and targeted therapies. Future research is likely to focus on refining diagnostic tools to enable earlier and more accurate differentiation of ACD from other anemia types, especially iron deficiency anemia. The integration of hepcidin assays into routine clinical practice, along with point-of-care testing for biomarkers like soluble transferrin receptor and reticulocyte hemoglobin content, may enhance diagnostic precision and guide individualized treatment strategies.

Therapeutically, a major area of future exploration lies in the development of agents that selectively modulate iron metabolism and inflammatory pathways without compromising host immunity. Novel hepcidin antagonists, ferroportin stabilizers, and small interfering RNA (siRNA) therapies targeting key regulators of iron homeostasis are under investigation and may offer safer, more effective alternatives to conventional treatments. The expanding role of hypoxia-inducible factor (HIF) stabilizers, initially approved for anemia in chronic kidney disease, could be extended to broader ACD indications pending further safety and efficacy data.

Moreover, personalized medicine approaches that consider a patient's inflammatory profile, comorbidities, and genetic predispositions could optimize therapeutic outcomes. Integration of artificial intelligence and machine learning into clinical decision-making may also enhance risk stratification and treatment planning. Ultimately, interdisciplinary collaboration among hematologists, immunologists, and primary care providers will be essential to translating these innovations into real-world clinical benefits. As understanding deepens, the goal is not only to treat anemia more effectively but also to improve the quality of life and outcomes for patients with chronic inflammatory conditions.

CONCLUSION

Anemia of chronic disease represents a multifactorial condition resulting from complex interactions between immune activation, iron dysregulation, and impaired erythropoiesis. Advances in understanding its molecular basis have paved the way for more accurate diagnostics and targeted therapies. Future strategies will likely focus on personalized approaches that integrate inflammation control, iron homeostasis restoration, and stimulation of effective erythropoiesis. Continued research and clinical innovation are essential for improving outcomes in patients with ACD.

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