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Modern Understanding of the Role of Immune Factors in the Development of Megaloblastic Anemia: Literature Review

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Annotation: Megaloblastic anemia is a hematological disorder characterized by impaired DNA synthesis in erythroid precursor cells, leading to the formation of abnormally large but functionally deficient red blood cells. One of the primary causes of this condition is a deficiency of vitamin B12 and folic acid, which may result from malabsorption in the gastrointestinal tract, inadequate dietary intake, or genetically determined pathologies. In recent years, research has increasingly focused on the immune mechanisms underlying megaloblastic anemia, particularly autoimmune processes that cause chronic gastric damage. Autoimmune atrophic gastritis is a key mechanism leading to the gradual destruction of the gastric mucosa and a decrease in intrinsic factor secretion, which is necessary for vitamin B12 absorption. This deficiency results in megaloblastic anemia. Studies confirm that the pathogenesis is primarily associated with autoantibody formation against gastric parietal cells and intrinsic factor. This review summarizes current knowledge regarding the role of immune factors in the development of megaloblastic anemia and discusses possible diagnostic and therapeutic approaches.

Keywords: Megaloblastic anemia, vitamin B12 deficiency, autoimmune gastritis, atrophic gastritis, parietal cell antibodies, intrinsic factor antibodies.

Introduction

Megaloblastic anemia is a hematological disorder in which DNA synthesis in erythroid cells is impaired, leading to the formation of large, immature red blood cells with reduced functional capacity. A primary cause of this condition is vitamin B12 deficiency, which can be due to various factors, including malabsorption in the gastrointestinal tract, insufficient dietary intake, or genetic disorders [1, 2, 3].

Recently, researchers have focused on the immune aspects of megaloblastic anemia, particularly autoimmune processes that lead to chronic gastric injury [4]. Autoimmune atrophic gastritis is a significant mechanism contributing to the gradual destruction of the gastric mucosa and the reduction of intrinsic factor secretion. This intrinsic factor is necessary for vitamin B12 absorption in the small intestine [5, 6]. When this process is disrupted, cobalamin deficiency develops, eventually resulting in megaloblastic anemia [7].

Methods

This review is based on a comprehensive analysis of existing literature related to the role of immune factors in the pathogenesis of megaloblastic anemia. The sources included studies from PubMed, Google Scholar, and other sourses, focusing on autoimmune gastritis, the role of autoantibodies, and genetic predispositions contributing to the disease. Data were analyzed concerning clinical manifestations, laboratory diagnostics, and therapeutic approaches.

Findings and Discussion

Autoimmune Mechanisms in Megaloblastic Anemia

Autoimmune processes play a crucial role in megaloblastic anemia development, primarily through the production of autoantibodies targeting parietal cells and intrinsic factor [8]. These autoantibodies can: block hydrochloric acid production, destroy gastric mucosal cells responsible for intrinsic factor secretion, lead to irreversible impairments in vitamin B12 absorption [9].

Over time, autoimmune gastritis progresses into pernicious anemia, the final stage of this pathological process [6]. Clinical studies indicate that parietal cell destruction is associated with a significant decrease in pepsinogen I levels and an increase in gastrin levels, which may serve as early diagnostic markers [3]. Moreover, iron deficiency anemia often precedes megaloblastic anemia in patients with autoimmune gastritis due to impaired gastric acid production and decreased iron absorption [9].

Role of Autoantibodies in Pathogenesis

Autoantibodies are key players in megaloblastic anemia pathogenesis. Parietal cell antibodies are detected in 80-90% of autoimmune gastritis cases, leading to the destruction of acid-secreting gastric cells [11]. Intrinsic factor antibodies prevent vitamin B12 from binding and being absorbed in the small intestine, which directly contributes to cobalamin deficiency [8]. These antibodies are frequently found in patients with pernicious anemia, making them important diagnostic criteria [3].

Genetic and Infectious Factors

Beyond autoimmunity, genetic predisposition also plays a role. Studies indicate that HLA-DRB103 and HLA-DRB104 alleles are associated with an increased risk of developing autoimmune gastritis and pernicious anemia [10]. Additionally, Helicobacter pylori infection is considered a possible trigger for autoimmune responses, leading to parietal cell damage and eventual destruction [12].

Clinical Progression

Early stages of autoimmune gastritis are marked by elevated gastrin levels, decreased pepsinogen I levels, iron deficiency, often preceding vitamin B12 deficiency [9]. As the disease progresses, full-blown megaloblastic anemia develops, leading to classic symptoms of vitamin B12 deficiency, such as persistent fatigue and pallor due to impaired red blood cell production, as well as neurological dysfunction, including ataxia, paresthesia, and cognitive impairment, which result from demyelination of nerve fibers in the central and peripheral nervous systems [13].

Comorbidities

Pernicious anemia often coexists with other autoimmune diseases due to shared immune system dysfunction, including autoimmune thyroiditis (39.9%), type 1 diabetes, vitiligo, celiac disease, primary biliary cholangitis, and rheumatoid arthritis. In addition, thyroid disease may lead to a B vitamin deficiency due to increased consumption in hyperthyroidism. Potentially, autoimmune atrophic gastritis can also disrupt vitamin absorption, making the deficiency and its symptoms worse [11, 14].

Treatment Approaches

The cornerstone of megaloblastic anemia therapy is parenteral vitamin B12 administration, as its absorption is impaired in autoimmune gastritis patients [10]. In severe cases, immunosuppressive therapy may be required [6].

Recent research is focused on targeted immunomodulatory therapies, which selectively suppress autoimmune mechanisms destroying gastric parietal cells [4].

Conclusion

Immune factors play a pivotal role in megaloblastic anemia pathogenesis, particularly in pernicious anemia. Autoantibodies against parietal cells and intrinsic factor disrupt vitamin B12 absorption, leading to deficiency and subsequent hematological abnormalities.

Current research continues to explore autoimmune mechanisms, with the potential for developing novel diagnostic and therapeutic approaches for autoimmune gastritis and pernicious anemia.

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