ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

What can thymic alterations tell us about autoimmunity?

O que as alterações tímicas nos contam sobre a autoimunidade?

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Dear Editor,

The article "Updating and expanding the universe of: 'A new class of diseases - autoinflammatory disorders'"[1] provides an overview of how advances in immunogenetics have reshaped the conceptual boundaries between autoimmune and autoinflammatory diseases, emphasizing the central role of innate immune dysregulation in a growing number of clinical syndromes. Building on this perspective, we propose that recurrent structural and functional thymic alterations may represent a common substrate underlying autoimmune diseases.

Myasthenia gravis (MG) is the autoimmune disease with the largest number of studies describing thymic alterations at both structural and functional levels. As early as 1917, thymic lesions were already recognized in patients with MG, and thymectomy was proposed as a therapeutic option[2]. Thymic hyperplasia is frequently observed in these patients[3]. In such cases, the organ becomes enlarged and infiltrated by B cells forming ectopic germinal centers (Figure 1). This differs from true thymic hyperplasia, which preserves normal architecture despite enlargement. In contrast, follicular lymphoid thymic hyperplasia (classically associated with MG) reflects a disruption of thymic architecture, which may compromise central tolerance and thereby influence peripheral immune homeostasis. Additionally, plasma cell infiltration, local autoantibody production, proinflammatory cytokine overexpression, and functional impairment of thymic regulatory T cells (Tregs)[5] have been reported, suggesting that multiple thymic abnormalities may cooperate in the initiation and maintenance of the autoimmune response in MG.

Importantly, these thymic alterations are not exclusive to MG but recur across autoimmune diseases. Similar structural changes have been described in systemic lupus erythematosus[6]. In addition to hyperplasia and thymic enlargement, reduced thymic export of naïve T cells has been reported in rheumatoid arthritis, Sjögren's syndrome, and multiple sclerosis[7-9]. Type 1 diabetes remains an exception, with few human studies available; most of the data comes from the Non-Obese Diabetic (NOD) mouse model, allowing for a more detailed cellular and molecular characterization of thymic dysfunction[10]. Across these diseases, the observed differences likely reflect variations in research focus and tissue availability rather than true disease-specific patterns.

Research into thymic alterations in autoimmune diseases holds a therapeutic potential. By better understanding how structural and functional changes in the thymus contribute to the breakdown of central tolerance, it may become possible to develop earlier diagnostic tools, identify predictive biomarkers, and design more targeted immunomodulatory therapies. The main therapeutic strategies include corticosteroids and conventional immunosuppressants, which have proven effective for most patients[11]. Even today, thymectomy remains a therapeutic option for selected cases of MG with hyperplasia, even in the absence of thymoma[12].

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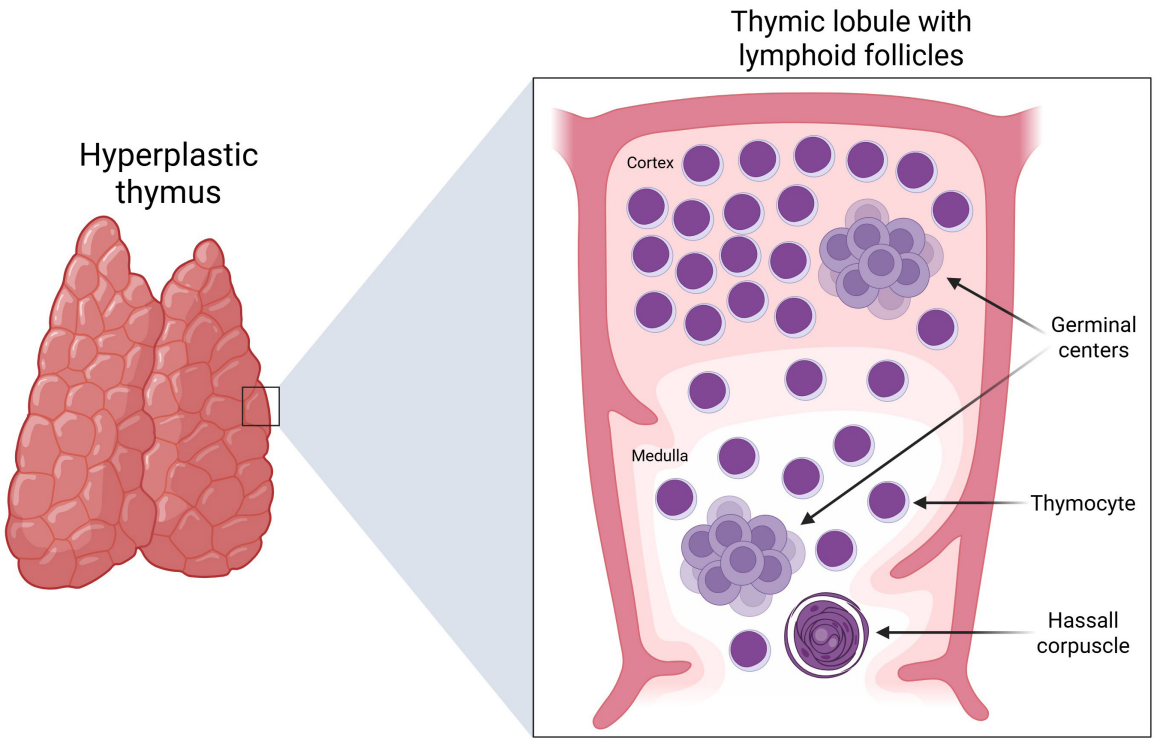

Figure 1
Main alterations observed in the thymus during autoimmune diseases. Hyperplasia or enlargement of thymic tissue is a common feature of several autoimmune disorders. Lymphoid follicles are present in the thymic parenchyma, associated with B cell proliferation and antibody secretion. The number of Hassall's corpuscles is also increased. Created with BioRender.com[4].

Considering the genetic investigations of Autoimmune Regulator (AIRE) transcription factor and its polymorphisms[13], as well as the evaluation of intracellular pathways in medullary thymic epithelial cells (mTECs) in animal models[14] and their association with autoimmune diseases, it is necessary to conduct integrative studies that combine immunology, histopathology, and clinical data from human subjects. Additionally, thymectomy in adults has been associated with an increased risk of developing autoimmune diseases and cancer later in life[15], raising concerns about its long-term use as a therapeutic intervention. Furthermore, pregnant women with autoimmune conditions have shown a reduced fetal thymus-thoracic ratio[16], highlighting how the thymus may be affected early in the course of these disorders. Together, these findings position the thymus as both a central regulator and an early indicator of immune dysregulation.

In conclusion, the thymus plays a pivotal role in maintaining immune tolerance, and its structural and functional alterations are closely associated with a wide range of autoimmune diseases. Advancing this field will require high-resolution imaging, single-cell profiling, and functional assays to better characterize thymic architecture and cell populations at different stages of autoimmunity. However, the limited access to thymic tissue in adult patients remains a significant challenge, hindering direct observation and validation of research findings. Overcoming these obstacles will be crucial for translating thymic research into improved diagnostic and therapeutic strategies in autoimmune diseases.

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