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Editorial

Autoimmunity in Inborn Errors of Immunity: A Diagnostic Challenge Beyond Immunodeficiency

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Inborn errors of immunity (IEI) are a group of inherited immune system disorders that commonly present with recurrent infections; however, other clinical complications, such as autoinflammation, autoimmunity, allergy, and/or malignancy, are also observed in IEI patients (1). In previous years, numerous studies have reported the occurrence of autoimmune disorders in various types of IEI (2). The breakdown of self-tolerance is the primary mechanism underlying the development of autoimmunity in patients with IEI, leading to abnormalities in the frequency and function of multiple cellular subsets, the emergence of autoreactive T and B cells, and the production of inflammatory cytokines (3).

In IEI, the concurrent development of immunodeficiency and autoimmunity is typically a result of genetic defects that lead to defects in immune tolerance or regulatory functions. Mutations in genes such as *CTLA4, LRBA, PIK3CD, STAT3* Gain-of-Function, *FOXP3, FAS, PGM3*, and others disrupt immune regulation and self-tolerance and lead to the development of autoimmunity in IEI (4). Although some autoimmune disorders may exhibit a polygenic inheritance pattern (5). The use of advanced diagnostic tools, including next-generation sequencing (NGS) and flow cytometry, contributes to the identification of IEI with autoimmune phenotypes, although challenges remain in distinguishing primary autoimmunity from immune dysregulation secondary to immunodeficiency.

Autoimmunity can present as the first presenting clinical feature or can arise subsequently as a complication in some IEI patients, most often leading to misdiagnosis of IEI as an idiopathic autoimmune disorder. There are no certain pointers for suspecting IEI patients who develop autoimmunity. Some indicative clinical features are the onset of autoimmunity at a young age, the presence of poly autoimmunity, the association of autoimmunity and infections, and a history of autoimmunity in the family (6). Unusual age of disease onset, i.e., early-onset chronic immune thrombocytopenia and/or late-onset autoimmune neutropenia must be considered as

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a compelling suspect for IEI. When early-onset polyautoimmunity is accompanied by infections or in a patient with a positive family history, physicians should consider the prospect of IEI in the suspected patient and initiate an immunological evaluation. It is a valuable step to prevent complications by early treatment.

Thus, misdiagnosis of IEI patients with autoimmunity causes significant delay in diagnosis, deferring appropriate immunological evaluation and targeted therapy. Patients who receive symptomatic treatment with immunosuppressants without further investigation of an underlying immune defect may experience exacerbated infections and worsened disease outcomes.

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