Polyautoimmunity and multiple autoimmune syndromes: A neglected clinical challenge

Dear Editor,

Polyautoimmunity – defined as the presence of two or more well-defined autoimmune diseases in a single patient – and multiple autoimmune syndrome (MAS) – characterized by the coexistence of three or more autoimmune conditions – represent an underrecognized yet clinically significant phenomenon. The coexistence of two autoimmune diseases is relatively common, with prevalence rates exceeding 30% in systemic lupus erythematosus (SLE), type 1 diabetes mellitus, Sjögren's syndrome, and systemic sclerosis, and to a lesser extent in vitiligo, multiple sclerosis, rheumatoid arthritis, and myasthenia gravis. It is important to distinguish polyautoimmunity from overlapping syndromes, in which autoimmune features are partially evident but the diagnostic criteria for multiple distinct diseases are not fully met.

Familial autoimmunity – defined as the occurrence of diverse autoimmune diseases within a nuclear family – and Amerindian ancestry have been identified as major factors associated with polyautoimmunity. MAS is a complex clinical entity that presents significant diagnostic and therapeutic challenges, highlighting the need for increased clinical awareness and dedicated research.

The pathogenesis of MAS is multifactorial, involving genetic predisposition, environmental triggers, and dysregulated immune responses. Specific susceptibility genes contribute to MAS development, while environmental factors such as infections, stress, and chemical exposures may precipitate the onset of multiple autoimmune conditions.

MAS Classification MAS can be classified into three types based on common disease combinations [Table 1]. To enhance clarity, the classification is summarized below:

While this classification is based on the patterns observed in clinical cohorts,[1-3] further validation through large-scale studies is warranted.

Patients with MAS often present with overlapping symptoms such as joint pain, fatigue, skin rashes, muscle weakness, and organ-specific manifestations, which complicate diagnosis and management. A comprehensive evaluation – including detailed history, physical examination, autoantibody profiling, imaging, and tissue biopsy – is essential. Notably, up to 25% of patients with one autoimmune disease may go on to develop additional autoimmune conditions.[2]

Recent research highlights the role of the exposome – the cumulative burden of environmental exposures – and gut microbiome dysregulation in the pathogenesis of MAS. For example, increased intestinal permeability ("leaky gut"), marked by elevated levels of zonulin and lipopolysaccharides, has been demonstrated in patients with Hashimoto's thyroiditis and polyautoimmunity, suggesting a link between gut barrier dysfunction and systemic autoimmune activation.[1,4]

Management Challenges and Clinical Insight The management of MAS requires a multidisciplinary approach involving rheumatologists, endocrinologists, dermatologists, and other specialists. Treatment is individualized and often includes a combination of immunosuppressive therapies, biologic agents, and symptomatic care, along with lifelong monitoring to prevent the complications. A notable dilemma arises in patients with both SLE and type 1 diabetes mellitus, where immunosuppressive therapy may improve lupus activity but exacerbate glycemic control. Balancing immunomodulation with metabolic stability remains a clinical challenge.

From my own experience in the Iranian clinical settings, I have encountered several patients with MAS involving combinations such as SLE, autoimmune thyroiditis, and vitiligo. These cases often present with atypical symptom progression and require nuanced diagnostic strategies. The prevalence of MAS in our region may

Table 1: Classification of multiple autoimmune syndrome (MAS) types and their associated autoimmune diseases

Type	Autoimmune diseases included
Type 1	Myasthenia gravis, thymoma, polymyositis, giant cell myocarditis
Type 2	Sjögren's syndrome, rheumatoid arthritis, scleroderma, autoimmune thyroid disease
Type 3	Systemic lupus erythematosus, type 1 diabetes mellitus, Sjögren's syndrome Addison's disease, vitiligo, dermatitis herpetiformis, autoimmune thyroid disease

be underreported due to limited awareness and diagnostic resources, underscoring the need for regional studies and clinician education.

In conclusion, increased clinician awareness of polyautoimmunity and MAS is essential for early detection, risk stratification, and personalized care. Given the rising prevalence of MAS, further research into its pathophysiology and preventive strategies is urgently needed.

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