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A Significant Discrepancy Between Endocrinological, Clinical, and Immunological Phenotype in Autoimmune Polyglandular Syndrome Type 3

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1. Abstract

Autoimmune polyglandular syndrome (APS) type 3 is characterized by autoimmune thyroid disease associated with other organ-specific autoimmune disorders, excluding adrenal insufficiency. We report a 53-year-old woman with APS type 3 who demonstrated a marked discrepancy between extensive immunological abnormalities and relatively mild clinical and endocrinological manifestations. Despite strong positivity for multiple autoantibodies, including anti-thyroid, anti-GAD, anti-IA-2, anti-SSA/Ro, anti-SSB/La, and rheumatoid factor, the patient remained euthyroid, largely insulin-independent, and asymptomatic for rheumatoid arthritis. This case highlights the dissociation between serological autoimmunity and clinical disease expression in APS type 3.

2. Keywords: Autoimmune polyglandular syndrome, Hashimoto thyroiditis, Sjögren's syndrome, type 1 diabetes, autoantibodies

3. Introduction

Autoimmune polyglandular syndromes (APS) are a heterogeneous group of disorders characterized by immune-mediated dysfunction of multiple endocrine organs. APS type 3 is defined by the presence of autoimmune thyroid disease in combination with other organ-specific autoimmune diseases, excluding autoimmune adrenalitis.

APS type 3 is frequently associated with additional autoimmune conditions such as type 1 diabetes mellitus, Sjögren's syndrome, and rheumatoid arthritis. However, the presence of circulating autoantibodies does not always correlate with clinical disease expression. The variability between immunological findings and clinical phenotype remains an important aspect of APS.

We describe a patient with APS type 3 who exhibited extensive autoantibody positivity but minimal clinical and endocrinological disease expression.

4. Case Report

A 53-year-old woman was referred to our hospital for evaluation of hyperglycemia. Her past medical history included autoimmune thyroiditis diagnosed 25 years earlier, based on thyroid enlargement and positivity for anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies. Despite these findings, thyroid function tests remained normal, and no thyroxine replacement therapy was required.

Four years prior to presentation, she was diagnosed with Sjögren's syndrome due to xerophthalmia and xerostomia, supported by positivity for anti-SSA/Ro and anti-SSB/La antibodies. She was treated symptomatically with cevimeline hydrochloride hydrate with good response.

5. Discussion

APS type 3 is defined by autoimmune thyroid disease associated with other organ-specific autoimmune conditions, without adrenal involvement. It commonly overlaps with type 1 diabetes mellitus, Sjögren's syndrome, and rheumatoid arthritis.

This case is notable for a pronounced mismatch between immunological activity and clinical expression. The patient exhibited strong seropositivity for multiple autoimmune markers, yet had minimal organ dysfunction.

5.1. Endocrinological-Clinical Discrepancy

Despite long-standing high titers of thyroid autoantibodies, the patient remained euthyroid over a 25-year period without hormone replacement. Similarly, although anti-GAD and anti-IA-2 antibodies were markedly elevated, endogenous insulin secretion remained preserved, and insulin requirements were minimal.

This suggests that autoantibody positivity alone is insufficient to produce overt endocrine failure, and additional genetic, environmental, or immunological modifiers likely influence disease progression.

5.2. Rheumatologic Discordance

Although rheumatoid factor was markedly elevated, the absence of anti-CCP antibodies, normal CRP, and lack of clinical arthritis indicated no active rheumatoid arthritis. This further supports dissociation between serology and clinical disease.

5.3. Clinical Implications

This case emphasizes several important points:

- Autoantibody positivity does not necessarily predict clinical disease

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- APS may remain clinically silent despite extensive immunological activation
- Long-term follow-up is essential in seropositive patients
- Clinical phenotype may lag significantly behind immunological markers

Understanding this dissociation is important for avoiding overdiagnosis and overtreatment based solely on serological findings.

6. Conclusion

We report a rare case of APS type 3 with a striking discrepancy between immunological profile and clinical/endocrinological phenotype. Despite extensive autoantibody positivity involving thyroid, pancreatic, salivary gland, and rheumatologic markers, the patient remained largely asymptomatic with preserved endocrine function. This case highlights the complex relationship between autoimmunity and clinical disease expression, emphasizing the importance of clinical assessment in addition to serological testing.

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