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Acquired Autoimmune Polyglandular Syndrome, Thymoma, and an AIRE Defect

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To the Editor

Paraneoplastic autoimmunity frequently accompanies thymoma. Because thymic tumors can support thymocyte development, aberrant T-cell generation has been suggested as a cause.¹

The autoimmune polyglandular syndrome type 1 (APS1), a monogenic syndrome of pleomorphic autoimmunity characterized by the clinical triad of hypoparathyroidism, hypoadrenalism, and candidiasis, arises from defects in the *AIRE* (auto-immune regulator) gene,² which mediates the expression of tissue-specific self-antigens by medullary thymic epithelial cells. In the absence of the AIRE protein, many tissue-specific self-antigens are not expressed in the thymus, and multiorgan autoimmunity develops because of faulty negative selection of autoreactive T cells.^{3,4} (Negative selection is a process resulting in the death of T cells with receptors highly specific for self-peptides, which can lead to autoimmune disease if left unchecked.) We now report a case of acquired APS1 coincident with thymoma.

A 64-year-old woman presented with cough, nausea, weakness, and confusion. Routine testing prompted admission for hypocalcemia; primary hypoparathyroidism was diagnosed. The patient's serum calcium level was 7.8 mg per deciliter (2 mmol per liter), the albumin level was 4.7 mg per deciliter, and the intact parathyroid hormone (PTH) level was 9 pg per milliliter.

Ten months later, mild hyponatremia and hyperkalemia with relative hypotension developed, suggesting hypoaldosteronism, which was confirmed by the elevated plasma renin activity (26.8 ng per milliliter per hour [7 ng per liter per second] and low aldosterone level (2.8 ng per deciliter [78 pmol per liter]). The cosyntropin stimulation testing indicated an adequate adrenal response (basal cortisol level, 11.8 μ g per deciliter [326 nmol per liter]; and post-stimulation cortisol level, 18.7 μ g per deciliter [516 nmol per liter]) with a normal basal adrenocorticotropin level (24 pg per milliliter [5 pmol per liter]). However, the level of 21-hydroxylase antibodies was markedly elevated, at 126.2 U per milliliter (normal range, 0.0 to 1.0), indicating underlying adrenal autoimmunity. (Fig. 1A in the Supplementary Appendix, available with the full text of this letter at NEJM.org, notes normal ranges of all laboratory tests.)

Nine months later, the patient returned with respiratory symptoms. Chest imaging indicated a large mediastinal mass suspicious for thymoma; radical thymectomy was performed with resection of a stage IV thymoma, but there was no improvement in her endocrine or metabolic derangements.

To verify parathyroid autoimmunity, we tested for NALP5 (NLR family, pyrin domain containing 5 protein) autoantibodies, a marker for auto-immune hypoparathyroidism in patients with APS1.⁵ Our patient's NALP5 autoantibody level was similar to that of patients who have APS1 and parathyroid disease (Fig. 1A). Thus, the clinical presentation met diagnostic criteria for APS1, despite the absence of candidiasis.² Sequencing of the patient's *AIRE* locus revealed no coding mutations (Fig. 1B in the Supplementary Appendix). Given her clinical APS1 disease without an inherited *AIRE* mutation, we hypothesized that the thymoma supported thymocyte development with defective negative selection due to lack of *AIRE* expression.

Pathological analysis revealed a predominantly cortical, organoid type B1 thymoma containing thymocytes in normal ratios (Fig. 1C and 1D in the Supplementary Appendix). The tumor exhibited several functional markers of normal thymic epithelium, including major histocompatibility complex class II molecules, claudin 4, and cyto-keratins 5 and 8 (Fig. 1B, and Fig. 1E in the Supplementary Appendix). *AIRE* was undetectable in the tumor tissue, though all sections had positive staining for cytokeratin 5, a marker of medullary thymic epithelial cells (Fig. 1B). The lack of coding mutations in *AIRE* (Fig. 1B in the Supplementary Appendix) suggested instead a developmental block of *AIRE* expression. As a measure of *AIRE* function, we examined the thymic expression of insulin, one of many tissue-specific self-antigens whose transcription is promoted by *AIRE*.^{3,4} Although cytokeratin 5 was abundant in the thymoma, insulin was undetectable (Fig. 1C), suggesting a defect in the expression of *AIRE*-dependent tissue-specific self-antigens.

The ability of a thymic neoplasm lacking normal mechanisms of negative selection to promote autoimmunity suggests a requirement for ongoing negative selection throughout adulthood. Loss of *AIRE* expression in the patient's thymic tumor provides a potential mechanistic link for the well-recognized association of autoimmunity with thymoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Evidence for the Autoimmune Polyglandular Syndrome Type 1 (APS1) and Loss of AIRE Expression in a Thymoma

Panel A shows the levels of autoantibodies against NALP5 (NLR family, pyrin domain containing 5 protein), detected by means of radioligand binding assay in normal controls, patients with APS1, and our patient. The NALP5 index is based on counts per minute (cpm) and calculated as follows: $[(\text{cpm of sample} - \text{cpm of negative standard}) \div (\text{cpm of positive standard} - \text{cpm of negative standard})] \times 100$. The horizontal bars indicate the means. Panel B shows matched sections from a normal thymus (control) and the patient's thymoma. Staining with 3,3'-diaminobenzidine (brown) was used to show cytokeratin 5, the marker of medullary thymic epithelial cells, and the autoimmune regulator protein (AIRE). Hematoxylin counterstaining (blue) was used to show morphologic characteristics. A dense cellular cortex surrounding the medulla, which shows little staining, is evident in the normal thymus. Cells positive for cytokeratin 5 are visible throughout our patient's thymoma. AIRE-positive cells (arrows) were found in the medulla of the normal thymus. There was no staining for AIRE in sections of the thymoma, including areas with cells positive for cytokeratin 5. Scale bars represent 100 μm . Panel C shows the relative expression of cytokeratin 5 and insulin (each normalized to the expression of actin) in our patient's thymoma, a control thymus, and a control pancreas assayed by means of quantitative real-time polymerase-chain-reaction testing. Insulin expression was nondetectable (ND) in the thymoma. The data are the mean of two or more independent experiments. The T bars indicate standard deviations.