Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy

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ABSTRACT

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy is a rare autoimmune disorder. The clinical spectrum of symptoms is diverse; the diagnosis relying on the presence of at least two out of the three main conditions defining the syndrome: chronic mucocutaneous candidiasis, hypoparathyroidism, and Addison's disease.
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Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), also called autoimmune polyendocrine syndrome type I (APS-1), is a rare organ-specific autosomal recessive disease (OMIM 240300).[1–3] Although APECED may occur worldwide, it remains most common in Iranian Jews (1:9,000),[4] Sardinians (1:14,500),[5–12] Finns (1:25,000),[13] Slovenians (1:43,000),[14] Norwegians (1:80,000),[15] Polish (1:1,29,000),[16] and Japanese (1:10,000,000).[17] Multiple organ failures in APECED are caused by a progressive loss of tolerance against self-antigens resulting in an immunological attack and secondary destruction of the adrenals, parathyroid glands, β cells of islet of Langerhans,[18] stomach, and small intestine.[13] Many of the auto-antigens have been identified and characterized.[9,12,19]

DIAGNOSIS

The diagnosis of APECED requires the presence of at least two of the following three classical conditions (diagnostic dyad): chronic mucocutaneous candidiasis (CMC), hypoparathyroidism, or Addison's disease (adrenocortical failure).[20] Other endocrine or nonendocrine manifestations of APECED may include thyroid autoimmune disease (autoimmune thyroiditis, Grave's disease), gastrointestinal manifestations (chronic active hepatitis, malabsorption, asplenia, juvenile onset pernicious anemia), dermatological conditions (alopecia areata, vitiligo), primary hypogonadism, kidney disease, and oral or esophageal cancer. The intestinal dysfunction has been attributed to bacterial overgrowth, pancreatic insufficiency, lymphectesia, candidal infection, and cholecystokinin deficiency. Humoral immunodeficiency may also be seen in rare cases.[21] All of the previously mentioned pathological characteristics are secondary to an autoimmune phenomenon.[21]

Besides these aforementioned conditions, features of ectodermal dystrophy, such as enamel hypoplasia, punctuate nail dystrophy, atrophy, and calcification of tympanic membrane, and disorders of sweat glands, may also be observed.[22] This condition exhibits a wide variation in its clinical picture,[4,23] and less common disease manifestations may also dominate the picture for many years. The early diagnosis of APECED can help prevent potentially life-threatening conditions, such as Addison's disease.

IMMUNOLOGICAL STUDIES

The innate, humoral, and adaptive arms of the immune system help provide protection against *Candida albicans*.[24] Protection is provided against systemic infections by neutrophils as well as the T helper cell 2 (Th2) immune response. In cases involving the mucous membranes, protection largely depends on cell-mediated immunity by the generation and activation of a dominant, antigen-specific Th1-cell response.[25,26] Patients with CMC are noted to display an impaired or low proliferation response against Candida antigens.[27] Despite this idea, Arulanantham et al[28] reported that one patient in their study demonstrated an increased T-cell response, whereas two other patients developed an adequate response. To

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understand this paradox, Brannstrom et al[29] examined the role that the autoimmune regulator (AIRE) gene plays in the defense against *C. albicans*. They investigated the proliferative response in AIRE-deficient mice and APS-1 patients challenged with a Candida cell wall extract; or more specifically, T-cell activation and the ability of antigen presenting cells to internalize and become activated against Candida antigens. T-cells from AIRE-deficient mice and from APS-1 patients both demonstrated an increased proliferation against Candida antigens, yet did not offer the expected protection from mucocutaneous candidiasis. However, it was noted that the exaggerated T-cell mediated response caused destruction of multiple endocrine organs in APECED/APS-1. It was eventually observed that there was an altered and delayed receptor mediated internalization of zymosan (yeast cell wall derivate) in AIRE-deficient antigen presentation. Therefore, it was concluded that T-cells from AIRE-deficient individuals have a competent proliferative response against *C. albicans*. However, monocytes from APS-1 patients exhibit defective internalization and intracellular signaling after exposure to Candida antigens. This defect likely alters the effectiveness in clearing muco-cutaneous candidiasis. Recently, autoantibodies against Th17-related cytokines interleukin-22 (IL-22), IL-17A, and IL-17F were discovered in the sera of APS-1 patients, suggesting a probable role of the Th17 immune response in the pathogenesis of this disease.[30,31]

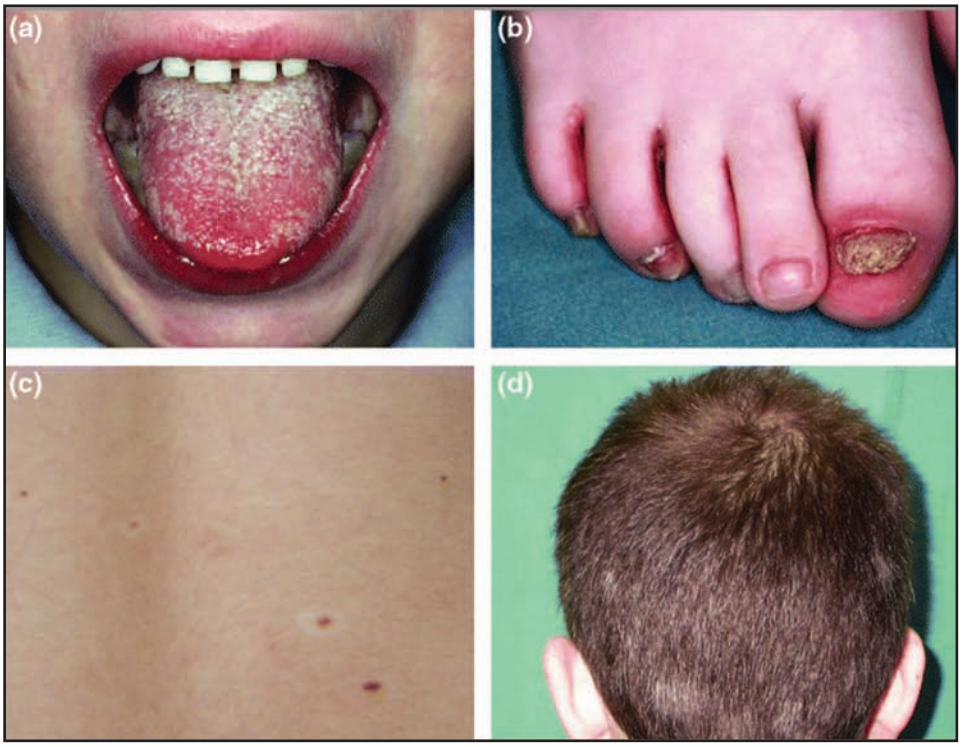

Figure 1. Dermatological manifestations of autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy syndrome. (a) Oral candidiasis (Patient 5); (b) candidal onychomycosis and paronychia (Patient 5); (c) halo nevi (Patient 14); (d) poliosis (Patient 14). Reproduced with permission from John Wiley and Sons.[33]

DERMATOLOGICAL FEATURES

The main skin manifestations of APECED include CMC, nail dystrophy, alopecia areata (AA), vitiligo, and Addison-related hyperpigmentation (Figure 1). Less common manifestations include recurrent urticarial vasculitis, scleroderma, Sjogren's syndrome, lichen planus, and oral squamous cell carcinoma. Candidiasis is usually the first manifestation of the disease and may occur before the age of five years.[32]

Collins et al[33] examined the dermatological manifestations of APECED in an Irish case series with focus on the timing of their appearance, association with disease severity, and genotype-phenotype correlation. In their series of 18 patients, all showed evidence of CMC, but its course and severity widely varied, including presentations of angular cheilitis, oral (leukoplakia) and esophageal candidiasis, esophageal web, and stricture. A large percentage (72%) showed candidal paronychia and/or onychomycosis. The age of onset ranged from infancy to 18 years with fingernails being more commonly affected than toes and the thumb being the most commonly affected finger. The majority of patients failed treatment with systemic antifungals. Patchy AA was observed in 33 percent of the patients either as a single episode or a recurrence. All the patients with AA also suffered from concomitant hypoparathyroidism. The investigators otherwise failed to find a correlation between the genotype and dermatological phenotype.

ENDOCRINOLOGICAL FEATURES

Hypoparathyroidism may appear before 10 years of age, while adrenal insufficiency can present before 15 years of age.[34] Hypoparathyroidism and Addison's disease (adrenal insufficiency) are two of the autoimmune conditions that patients with APECED are predisposed to developing. At least one study demonstrated that 54 of 68, or 79 percent, of patients had hypoparathyroidism.[13] Clinical symptoms of hypoparathyroidism are caused by hypocalcemia due to inadequate parathyroid hormone secretion. The presenting symptoms include tetany, seizures, altered mental status, congestive heart failure, stridor, twitching spasms, muscle cramping, parasthesias, and numbness. The acute phase of hypoparathyroidism can be life threatening. The reason for the development of the autoimmunity has been attributed to a loss of tolerance resulting from mutation in the AIRE gene. AIRE normally expresses a diverse number peripheral

self-antigens in the thymic medullary epithelial cells, thereby facilitating negative selection of T cells that recognize these peripheral antigens strongly.[35,36] Animal models of this autoimmune disorder have suggested that genes within the major histocompatibility complex, particularly the immune-response genes (similar to the HLA-DQ and HLA-DR alleles in humans) are responsible for the alteration in autoimmunity.

Adrenal insufficiency can be difficult to diagnose due to its gradual and vague symptoms unless the physician's suspicion is high. The classic symptoms include chronic fatigue, muscle weakness, loss of appetite, weight loss, nausea, vomiting, diarrhea, hyperpigmentation of the skin, and low blood pressure. Children may develop hypoglycemia while females may suffer from primary or secondary amenorrhea. Careful observation and knowledge of APECED can help detect early symptoms of an adrenal crisis—a situation that should be avoided and is preventable if the diagnosis is made early. Adrenal crisis typically presents with vomiting, diarrhea, dehydration, low blood pressure, and loss of consciousness.

GENETIC FEATURES

The underlying genetic defect most often associated with APECED is a mutation in the AIRE gene, which is located on chromosome 21q22.3. AIRE is mainly expressed in a subset of the medullary thymic epithelial cells (mTEC) and in dendritic cells in the spleen and lymph nodes.[37,38] Various gene defects, such as point mutations, insertions, and deletions, spread over the entire coding region of the AIRE gene have been identified and demonstrated to be responsible for the clinical presentations of APECED.[39–44] More than 50 different mutations have been identified to date and are known to affect different aspects of intracellular targeting and transcription regulation functions.[21,40,45]

The most prevalent mutation, R257X, found in the Finnish population, was present in 89 percent of the Finnish chromosomes examined.[40] The most common mutation in British,[46] Irish,[47] North American,[42,48] and Norwegian patients is 1094–1106del13 (or 967–979del13 bp).[40] The Y85C mutation is typical among Iranian Jews. In Sardinia, the AIRE gene mutation known as R139X causes a nonsense mutation on exon 3, resulting from a C to T transition. Associations between certain alleles of the human leukocyte antigen (HLA) class I (HLA A, B, Cw) and Class II (DR, DQ, DP) and autoimmune manifestations of APECED have also been suspected. Halonen et al[49] studied the AIRE and HLA class II genotypes in a series of 104 patients with APECED.[49] They demonstrated that direct associations between the APECED phenotype and the AIRE mutation may exist for the R257X mutation and the high frequency of mucocutaneous candidiasis. Addison's disease was associated with HLA-DRB1*03, alopecia with HLA-DRB1*04-DQB1*0302, whereas type I diabetes showed a negative correlation with HLADRB1*15-DQB1*0602. They concluded that mutation of AIRE *per se* has little influence on the APECED phenotype, whereas HLA class II is a significant determinant.

MANAGEMENT

Currently, the management of APECED/APS-1 involves the treatment of its individual conditions. Knowledge and a high index of suspicion of this rare syndrome can lead to its early detection and prevention of most of the complications. It must be remembered that in case of simultaneous hypothyroidism and Addison's disease, glucocorticoid replacement should be performed prior to thyroid hormone replacement to avoid an adrenal crisis. The development of Type 1A diabetes should be expected and closely monitored. The challenge is to detect the syndrome in a timely fashion and to anticipate its other manifestations. For example, in a patient with known Type 2 autoimmune polyendocrine syndrome, but no features of Addison's disease, regular screening for antibodies against 21-hydroxylase (a feature of Addison's) may prompt early intervention and hydrocortisone replacement to prevent the characteristic crises. Hypocalcemia associated with hypoparathyrodism should be approached depending on its severity.[50] In the acute situation, intravenous calcium gluconate should be used along with 5% dextrose or 0.9% sodium chloride given over five minutes.[50] In chronic hypoparathyroidism, oral calcium supplements 1,000 to 1,500mg per day along with calcitrol 2µg per day should be used to bring the calcium level within the low normal range.[50] Supplementing too much calcium should be avoided to decrease the risk of inducing nephrolithiasis.[50]

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