SECTION EDITOR: WALTER W. TUNNESSEN, JR, MD

Picture of the Month

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A 10-YEAR-OLD boy with a history of a hypocalcemic seizure at age 2 years had a 3-month history of fatigue, nausea, and weight loss. He has received calcitriol and calcium supplementation since his seizure. Depigmented patches around both eyes were noted on physical examination (**Figure 1**). Dental enamel hypoplasia (**Figure 2**), nail pitting (**Figure 3**), and generalized hyperpigmentation of the skin were also found.

From the Developmental Endocrinology Branch, National Institute of Child Health and Human Development, Bethesda, Md.

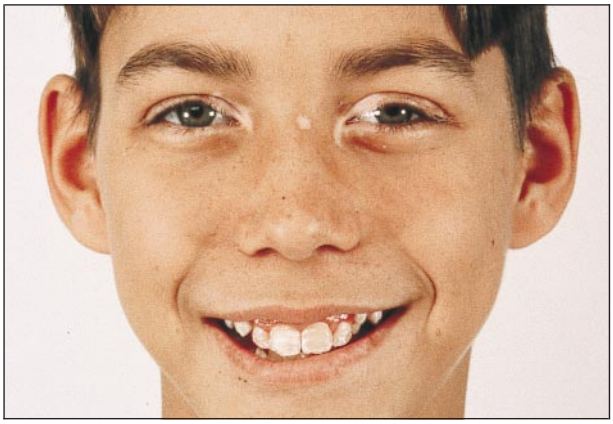

Figure 1.

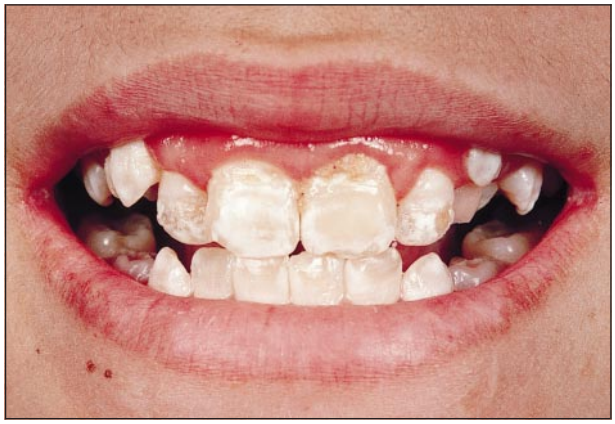

Figure 2.

Figure 3.

Denouement and Discussion

Autoimmune Polyglandular Syndrome Type 1

Figure 1. *Patches of vitiligo are present in the inner canthal areas bilaterally. Generalized hyperpigmentation of the skin makes these areas more prominent.*

Figure 2. *The mottled appearance of the teeth reflects enamel hypoplasia.*

Figure 3. *The nails show signs of dystrophy, vertical ridging, and pitting.*

Autoimmune polyglandular syndrome type 1 (APS-1), also known as polyendocrinopathy-candidiasis-ectodermal dystrophy, is an autosomal recessive disorder characterized by the triad of chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency.[1] A patient must have 2 of 3 major disease components for diagnosis. Other associated disorders include autoimmune endocrinopathies, immune-mediated gastrointestinal diseases, ectodermal dysplasia, keratoconjunctivitis, autoimmune skin disorders, asplenia, and cholelithiasis.

The syndrome's first manifestation typically occurs in childhood with the 3 major disease components seen by age 20 years, while associated disorders continue to appear throughout life.[1,2] In most cases, candidiasis appears first, usually by age 3 years. Mucocutaneous candidiasis is the clinical expression of a selective T lymphocyte dysfunction affecting the nails, skin, esophagus, or vagina. B-cell response of serum antibodies to candidal antigens is normal and prevents systemic candidiasis development.[3] Mucocutaneous candidiasis is typically mild and responds well to topical antifungal treatment or systemic drugs such as fluconazole.

ENDOCRINOPATHIES

Hypoparathyroidism, the most common autoimmune endocrinopathy associated with this syndrome, is usually the second disease to appear.[2] Hypoparathyroidism results in hypocalcemia, hyperphosphatemia, and occasionally, hypomagnesemia, and has symptoms of neuromuscular irritability such as cramping and tetany of the extremities. Hypocalcemic tetany or seizures may be seen by the neonatal period. Addison disease, secondary to the autoimmune destruction of the adrenal gland, is usually the third disease to appear (mean age of onset, 13 years).[1] Adrenal cortex autoantibodies may be detected before Addison disease onset. Symptoms and signs of adrenal insufficiency include weakness, fatigue, anorexia, weight loss, hyperpigmentation, and hypotension.

Other autoimmune disorders may appear. Gonadal failure is more common in females and is associated with lymphocytic infiltration of developing ovarian follicles.[1] Clinical presentation ranges from delayed adolescent puberty to premature adult menopause. When other autoimmune endocrine diseases develop, such as insulin-dependent diabetes mellitus or Hashimoto thyroiditis, associated autoantibodies are typically present. Antibodies may be present without clinical manifestations of the corresponding disease.[1]

OTHER ASSOCIATED AUTOIMMUNE DISORDERS

Gastrointestinal disease may manifest as pernicious anemia, atrophic gastritis, cholelithiasis, malabsorption, or chronic active hepatitis, a major cause of mortality in this disease that may be present without obvious signs of liver disease.[2] Autoimmune destruction of the spleen may occur and can be screened by looking for characteristic erythrocyte abnormalities on peripheral blood smears associated with asplenia: marked variation in size and shape of erythrocytes, Howell-Jolly bodies, and Heinz bodies.[4] Asplenia results in increased susceptibility to bacterial infections, particularly those with capsules such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Patients with asplenia younger than 20 years are particularly susceptible to overwhelming sepsis.

Approximately 75% of individuals with APS-1 have ectodermal dystrophy.[2] Clinical manifestations include pitting of the nails and dental enamel hypoplasia. These changes may occur independently of hypoparathyroidism or candidal infections. Keratopathy (corneal opacities and conjunctival injection) and calcified plaques of the tympanic membrane may also occur. Manifestations of autoimmune disorders of the skin, such as alopecia areata and vitiligo, may appear.

Autoimmune polyglandular syndrome type 1 is a rare disorder, but it is more common in certain populations, with a disease prevalence of 1:25 000 in Finland and 1:9000 in Iranian Jews.[5,6] It is the only known autoimmune disease inherited in a Mendelian fashion. The gene responsible for the syndrome was recently identified on chromosome 21.[7] This recent discovery should provide insight into the pathogenesis of APS-1 as well as autoimmune diseases in general. The clinical spectrum of APS-1 is broad. All patients need lifelong follow-up for the detection of new disease components, some of which may be life-threatening.

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