Mucocutaneous Candidiasis as First Manifestation of Autoimmune Polyglandular Syndrome Type I

Pia López-Jornet, MD, DDS C. García-Ballesta, MD, DDS L. Pérez-Lajarín, MD, DDS

ABSTRACT

Autoimmune polyglandular syndrome type 1 exhibits very specific oral manifestations in the form of enamel hypoplasia and oral candidiasis. The authors present the case of a 10-year-old girl with autoimmune polyglandular syndrome characterized by chronic mucocutaneous candidiasis infections, hypoparathyroidism, and enamel hypoplasia. The importance of this entity is stressed, with special attention to the observed oral anomalies. (J Dent Child 2005;72:21-24)

KEYWORDS: CHRONIC CANDIDIASIS, ENDOCRINOPATHY SYNDROME, ENAMEL HYPOPLASIA

Autoimmune polyglandular syndrome type 1, also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED; Online Mendelian Inheritance in Man [OMIM] reference 240300), is an autosomal recessive disease characterized by the triad comprising: (1) chronic mucocutaneous candidiasis; (2) endocrinopathy (normally hypoparathyroidism); and (3) adrenocortical failure. Patients must satisfy at least 2 of these criteria to confirm diagnosis of the syndrome.[1] Other secondary autoimmune alterations can also be included, such as ectodermal dysplasia, keratoconjunctivitis, and gastrointestinal diseases.[2-4]

Type 1 syndrome tends to manifest in childhood, or before the age of 35 years. Gonadal insufficiency appears after puberty in 60% of women, and in about 15% of affected males. Diabetes mellitus is infrequent. This pattern can be associated with HLA A3 and $A_2$8 or with a locus in region q22.3 of chromosome 21.[5] The disease is infrequent, with a reported prevalence of 1:25,000 in Finland and 1:9000 in Iran.[6]

While the disorder's typical manifestations appear in young subjects, the associated alterations may develop in the course of the patient's life.[3,4,7] Dental developmental defects together with recurrent candidal infections characterize the syndrome's oral manifestations. The present study reports the case of a girl with enamel hypoplasia, hypoparathyroidism, and chronic mucocutaneous candidiasis.

Dr. López-Jornet is professor, Department of Oral Medicine, Hospital Morales Meseguer, Clínica Odontológica, Murcia, Spain; Drs. García-Ballesta and Pérez-Lajarín are professors, Pediatric Dentistry, Dental Clinic, University of Murcia, Murcia. Correspond with Dr. López-Jornet at majornet@um.es

CLINICAL CASE

A 10-year-old girl was referred for the study and management of chronic oral candidiasis and enamel hypoplasia. The candidiasis was diagnosed when the child was 1 month old because of episodes of oral pseudomembranous candidiasis and angular stomatitis, which responded to short courses of topical nystatin and miconazole gel. The family history showed maternal panhypopituitarism as a result of postpartum hemorrhagic shock.

The patient history revealed an uneventful neonatal period, with normal growth and development. She suffered asthmatic episodes caused by extrinsic asthma to dust mites, for which she regularly used a beta-adrenergic inhaler. The child had routine immunizations.

PRESENT ILLNESS

The patient presented with generalized stiffness episodes, with contracture of the hand, hypocalcemia (4.5 mg/dl), and hyperphosphatemia (8 mg/dl). Evaluation was carried out with the diagnostic orientation of hypoparathyroidism. The patient, moreover, presented with mucocutaneous candidiasis (angular cheilitis with erythema and fissuring, maceration, and soreness at the corners of the mouth).

SYSTEMIC EXPLORATION

The patient presented in good general condition, with adequate nutrition and development and no skin or nail signs. The head and neck appeared normal, with a symmetrical thorax. The

Complementary Test Resuls	
Ca	6.4 mg/dl (8.5 to 10.2 mg/dl)
P	10.8 mg/dl (2.4 to 4.1 mg/dl)
Mg	1.6 mg/dl (1.8 to 3 mg/dl)
Alkaline phosphatase	667 U/l (44 to 174 U/I)
Urine Ca	2 mg/dl (50 to 150 mg/dl)
Ca/creatinine	0.04 mg/dl (0.6 to 1.2 mg/dl)
Phosphate tubular reabsorption was	97%
PTH	<1 pg/ml (10 to 55 pg/ml)
Hematological	Normal (hemoglobin, total and differential white cell count, platelet count, red cell folate)
Hormones normal	FSH, LH, estradiol, testosterone, ACTH, cortisol, calcitonin, 17-OH-progesterone, S-DHEA, androstenedione, T3, T4, and TSH

abdomen was neither distended nor painful, and no masses or enlarged organs were palpated. The cranial nerve exploration proved normal, with no Trousseau or Chvostek signs. Cutaneous candidiasis was identified, which responded to fluconazole (3 mg/Kg/day for 7 to 10 days).

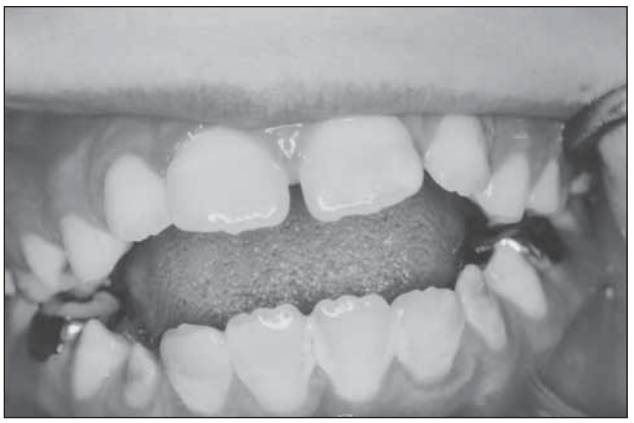

Figure 1. Note the anterior sector enamel hypoplasia.

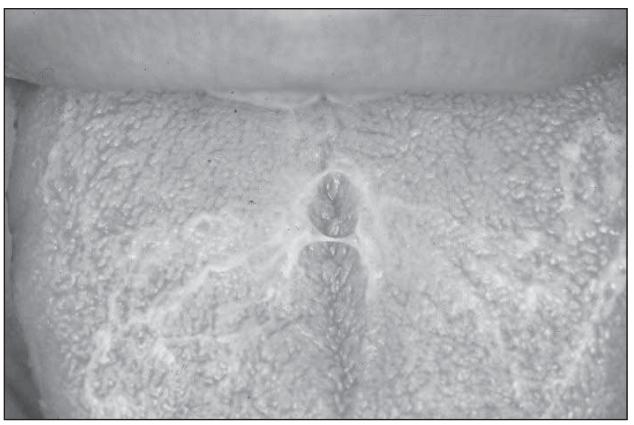

Figure 2. Oral pseudomembranous candidiasis of the tongue.

ORAL EXAMINATION

The dental examination revealed enamel hypoplasia affecting teeth nos. 8, 9, 22, 25, 26, and 27 (Figure 1). No hypoplasia was observed in primary teeth. Malocclusion (anterior open bite) was observed, along with oral candidiasis (Figure 2).

RADIOGRAPHIC FINDINGS

To complete the case study, and to discount possible effects due to alterations in calcium phosphate metabolism, a bone survey was made. (The patient presented with generalized stiffness episodes with contracture of the hand). The plain chest X-rays showed no thymus shadow, and the radiological bone study presented no alterations.

The diagnosis was confirmed with the clinical history, exploration, and complementary tests. There was no evidence of adrenal failure or any other endocrine disorders. Treatment was started in the form of calcium via the oral route (100 mg elemental calcium/Kg/d) and vitamin D3 (20.000 UI/d). Eighteen days after calcium ingestion, tetanic crisis was resolved. Autoimmune polyglandular syndrome type 1 with hypoparathyroidism was diagnosed, associated with chronic candidiasis of the skin, oral mucosa, and enamel hypoplasia. The patient is currently being cared for on a multidisciplinary basis by the Services of Pediatrics, Endocrinology, and Odontology.

Dental treatment consisted of restoration with composite material to avoid caries in zones suffering from enamel demineralization and periodic checkups. The prognosis for this child was considered to be good. The importance of oral hygiene and periodic examinations, however, must continue to be emphasized.

DISCUSSION

The present case is particularly interesting, due to the great variety of clinical problems involved. In autoimmune polyglandular syndrome type 1, it should be pointed out that candidiasis is characteristically the first clinical manifestation to appear (generally before 3 years of age), and usually predates the endocrine alterations.[3] According to Tencer et al,[8] candidiasis is found in 73% to 78% of all patients with this syndrome. Hypoparathyroidism is typically the second disorder to appear. Addison's disease, secondary to autoimmune destruction of the adrenal gland, is usually the third manifestation (oral manifestations frequently include enamel hypoplasia, oral candidiasis, and oral hyperpigmentation). Other autoimmune processes (thyroid disease, diabetes mellitus, vitiligo, autoimmune gastritis) can appear in the course of the patient's life–a fact that explains the need for continuous follow-up of such cases.[9-10]

Hypoparathyroidism is the endocrine disorder most commonly associated with the syndrome and is characterized by reduced parathyroid hormone production, leading to low blood calcium levels, hyperphosphatemia, and occasionally hypomagnesemia. Parathyroid hormone (PTH), which regulates calcium metabolism, acts directly upon calcium uptake by bone and its renal excretion. The hormone also regulates calcium metabolism indirectly, by acting upon vitamin D. The signs and symptoms of hypoparathyroidism are:

(1) weakness; (2) muscle cramps; (3) restlessness; (4) headache; (5) hyperexcitability; and (6) spasms of the hands and feet. Breathing difficulties may also be caused by the appearance of laryngeal spasms.[1,3]

Chronic mucocutaneous candidiasis due to Candida albicans is the first manifestation of the syndrome.[7,11-15] Ahonen et al,[3] in a study of 68 patients with the syndrome, found that all patients develop repeated candidiasis at some time.

Chronic mucocutaneous candidiasis does not constitute a characteristic disorder, and can be associated with immune, autoimmune, or endocrine alterations.[16-18] While many classifications have been proposed, an orientation can be obtained by dividing the disease into 3 clinical categories:

1. Without associated endocrine disease—This category comprises a broad range of clinical presentations. The disease may be either diffuse or localized, and can affect various tissues. The condition can exhibit an autosomal recessive or dominant inheritance pattern, though it mainly occurs sporadically.
2. Associated with endocrine disease—This category is characterized by candidiasis associated with one or more autoimmune endocrine disorders such as hypoparathyroidism, hypoadrenalism, hypothyroidism or diabetes mellitus. In such cases, candidiasis generally precedes the endocrine disorder.[3] The condition can also be associated with other autoimmune alterations, such as vitiligo and idiopathic thrombocytopenic purpura. Candidiasis in such situations exhibits an autosomal recessive pattern with usually benign presentations in children.[2,7]
3. Associated with thymoma—This category appears in the third decade of life associated with tumors of the thymus gland.

An important aspect regarding the clinical presentation of candidiasis associated with endocrinopathy is the absence of a correlation between the severity of the endocrine problem and the severity of candidiasis. In fact, treatment of the underlying endocrine disorder does not improve the fungal infection. The latter responds well, however, to conventional antifungal therapy such as fluconazole (3 mg/Kg/day for 7 to 10 days)–as was the case in this study's patient.[19,20]

For reasons which remain unknown, in this disorder, enamel hypoplasia affects the permanent teeth–not the deciduous dentition. The defects in such cases mainly consist of cracks or lines of variable width and depth.[21-24] The lesions follow the perikymata pattern horizontally around the dental crown, which normally turns yellowish-brown in alternation with well-formed enamel areas (as was seen in this study's patient).

In 1998, Perniola et al[25] conducted a study of enamel hypoplasia in this syndrome. They found the upper and lower canines to be the most affected teeth. Moreover, hypoparathyroidism was not found to be responsible for the observed enamel hypoplasia, though it could contribute to the damage as a result of the alterations in calcium and phosphorus metabolism, with consequent impairment of hard tissue mineralization.

These patients may also present with other autoimmune disorders such as gastrointestinal problems that may manifest as pernicious anemia or atrophic gastritis, among other alterations. This study's patient, however, presented no other associated autoimmune problems.

Finally, emphasis should be placed on the need to conduct long-term follow-up of the affected patients, since new manifestations may develop in the course of the life of the individual. This is particularly important in the dental setting. In patients presenting with chronic mucocutaneous candidiasis, the possible existence of an associated endocrine disorder should be evaluated.

REFERENCES

1. Betterle C, Greggio NA, Volpato M. Autoimmune polyglandular syndrome type I. J Clin Endocrinol Metab 1998;83:1049-1055.
2. Friedman TC, Thomas PM, Fleisher TA, et al. Frequent occurrence of asplenism and cholelithiasis in patients with autoimmune polyglandular disease type I. Am J Med 1991;91:625-630.
3. Ahonen P, Myllarniemi S, Sipila I, Perheentupa J. Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. N Engl J Med 1990;322:1829-1836.
4. Ahonen P. Autoimmune polyendocrinopathy-candidosis-ectodermal dystrophy (APECED): Autosomal recessive inheritance. Clin Genet 1985;7:535-542.
5. Nagamine K, Peterson P, Scott HS, et al. Positional cloning of the APCED gene. Nat Genet 1997;17:393-398.
6. Zlotogora J, Shapiro MS. Polyglandular autoimmune syndrome type 1 among Iranian Jews. J Med Genet 1992; 29:824-826.
7. Perheentupa J. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). Horm Metab Res 1996;28:353-356.
8. Trence DL, Morley JE, Handwerger BS. Polyglandular autoinmune syndromes. Am J Med 1984;77:107-116.
9. O'Sullivan DJ, Cronin C, Buckley D, Mitchell T, Jenkins D, Greally J, O'Brien T. Unusual manifestations of type 1 autoimmune polyendocrinopathy. Ir Med J1997;90: 101-103.
10. Gylling M, Kaariainen E, Vaisanen R, et al. The hypoparathyroidism of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy protective effect of male sex. J Clin Endocrinol Metab 2003;88:4602-4608.
11. Walls AW, Soames JV. Dental manifestations of autoimmune hypoparathyroidism. Oral Surg Oral Med Oral Pathol 1993;75:452-454.
12. Porter SR, Eveson JW, Scully C. Enamel hypoplasia secondary to candidiasis endocrinopathy syndrome: Case report. Pediatr Dent 1995;17:216-219.
13. Porter SR, Haria S, Scully C, Richards A. Chronic candidiasis, enamel hypoplasia, and pigmentary anomalies. Oral Surg Oral Med Oral Pathol 1992;3:312-314.
14. Porter SR, Scully C. Candidiasis endocrinopathy syndrome. Oral Surg Oral Med Oral Pathol 1986;6:573-578.
15. Peterson P, Perheentupa J, Krohn KJE. Detection of candidal antigens in autoimmune polyglandular syndrome type I. Clin Diagn Lab Immunol 1996;3:290-294.
16. Jorizzo JL. Chronic mucocutaneous candidosis: An update. Arch Dermatol 1982;118:963-965.

17. Peterson P, Pitkanen J, Sillanpaa N, Krohn K. Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED): A model disease to study molecular aspects of endocrine autoimmunity. Clin Exp Immunol 2004;3:348-357.
18. Ruan QG, She JX. Autoimmune polyglandular syndrome type1 and the autoimmune regulator Clin Lab Med 2004;1:305-317.
19. Viudes A, Peman J, Canton E, Lopez-Ribot J, Gobernado M. The activity of combinations of systemic antimycotic drugs. Rev Esp Chemio 2001;14:30-39.
20. Cha R, Sobel JD. Fluconazole for the treatment of candidiasis: 15 years experience. Expert Rev Anti Infect Ther. 2004;3:357-366.
21. Morabito A, Defabianis P. Hypoplasia of enamel and systemic pathology. Minerva Stomatol 1988;37:1037-1039.
22. Goepferd SJ, Flaitz CM. Enamel hypoplasia associated with congenital hypoparathyroidism. Pediatr Dent 1981;3:196-200.
23. Lukinmaa PL, Waltimo J, Pirinen S. Microanatomy of the dental enamel in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED): Report of three cases. J Craniofac Genet Dev Biol 1996;3:174-181.
24. Riley DJ. Dental changes in patients with idiopathic hypoparathyroidism: Report of two cases. J Oral Surg 1969;1:44-47.
25. Perniola R, Tamborrino G, Marsigliante S, De Rinaldis C. Assessment of enamel hypoplasia in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). J Oral Pathol Med 1998;27:278-282.