CASE REPORT

A Rare Case of Autoimmune Polyendocrinopathy-candidiasis-ectodermal Dystrophy Syndrome: Dental Perspective on Diagnosis and Management

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Abstract

Aim: To report a unique case of Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a young boy and discuss the oral health impact and management of the disease.

Background: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a rare autoimmune disorder with various clinical manifestations. Biallelic mutations in the autoimmune regulator (AIRE) gene lead to impairment of central immune tolerance and a targeted attack on various endocrine and non-endocrine organs. Patients classically suffer from a triad of disorders, including chronic mucocutaneous candidiasis (CMC), hypoparathyroidism, and adrenocortical failure (Addison's disease).

Results: In recent times, it has been observed that oral manifestations of the disorder, such as enamel hypoplasia, appear early and frequently. Affected individuals require a comprehensive preventive and minimally invasive approach for oral health along with follow-up throughout their lifespan to manage potentially life-threatening disease manifestations.

Conclusion: Prompt recognition by a pediatric dentist can facilitate an earlier diagnosis and allow for screening, preventive and therapeutic services.

Clinical Significance: To deliver oral health care in an effective and comprehensive manner, clinicians should be able to recognize, diagnose and manage the signs and symptoms of the disease.

Keywords: Autoimmune polyendocrinopathy, Candidiasis, Ectodermal dystrophy.

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Introduction

Autoimmune polyendocrine syndromes (APS) are a group of disorders that involve at least two endocrine gland insufficiencies mediated by autoimmune mechanisms.[1] APECED, also known as juvenile autoimmune polyendocrinopathy or Whitaker's syndrome, is APS Type 1 as per the Neufeld and Blizzard Classification of 1980.[2] A rare monogenic autoimmune disease, APECED is associated with mutations in the AIRE gene which code for the AIRE transcription factor.[3] Mutations in AIRE lead to impairment of central immune tolerance and a negative selection of autoreactive T cells.[4] The prevalence ranges between ~1:100,000–1:200,000 people internationally, with females being affected twice as often as males. Increased prevalence has also been noted in children born to consanguineous marriages due to the autosomal recessive inheritance pattern.[5]

Among the various manifestations of the disorder, a classical "triad" is formed by CMC, hypoparathyroidism, and adrenocortical failure (Addison's disease). Development of any two of the above ("diagnostic dyad") may be adequate to formulate a clinical diagnosis.[6] However, in the scenario where a relative is affected, the development of only one manifestation is required for the diagnosis.[2] Enamel and developmental defects are one of the hallmark features of APECED, with studies reporting up to 75% of the sample as affected.[7] Studies have highlighted the crucial role of a pediatric dentist in identification as the early symptoms of this disorder appear first in the oral cavity and at a young age.[8] The following review of literature and case report explores the oral health impact of APECED and the dental management of a young boy with the disorder.

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General Manifestations, Diagnosis, and Management

The wide variety of manifestations seen in patients of APECED is due to the targeted attack of the autoimmune system on the hormone-producing glands (Table 1). The development of autoimmunity is due to the loss of the AIRE gene, which facilitates

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Table 1: Clinical manifestations of APECED[6,8]

Clinical manifestations
Intraoral
CMC (oral)*
Enamel hypoplasia
Aphthous ulcers
Sjogren like syndrome
Oral SCC
Other dental developmental defects (hypodontia, microdontia, shortened roots, malformed roots, enlarged pulp chambers, pulp calcifications, and delayed tooth eruption)
Increased dental caries
Poor periodontal health
Enamel erosion
Reduced salivary flow
Extraoral
CMC (nails, esophagus, scalp, vaginal candidiasis, penile candidiasis)*
Urticarial eruption (non-pruritic, self-limiting)
AlopeciaVitiligo
RetinitisKeratoconjunctivitisHypoparathyroidism*Adrenal insufficiency (Addison's disease) *
Intestinal malabsorption
Autoimmune pneumonitis
Autoimmune hepatitis
Growth hormone deficiency
Autoimmune gastritis
Gastric carcinoma
Pernicious anemia
Iron deficiency
Type 1 diabetes
Exocrine pancreatic insufficiency
Nephrocalcinosis
Tubulointerstitial nephritis

*Components of the classical triad of APECED

the escape of auto-reactive T cells into the periphery. The frequency of APS1 is highest among communities with genetic homogeneity which includes Finns, Sardinians, and Iranian Jews, where specific founder mutations have been described.[9] A recent study describing the features of 45 Indian patients of APECED in comparison to other ethnic groups found the female/male ratio to be 25/20, the median age of referral at 16.23 years (range, 6 months–48 years), and early disease onset with a median age of 7.23 years (range birth–34 years), based on the appearance of the first component of the triad and severe phenotype.[10]

One of the earliest reports of the disorder dates back to 1969, which mentions the presence of idiopathic hypoparathyroidism, chronic candidiasis, and dental hypoplasia in a 16-year-old boy.[11] Oral candidiasis is often the earliest manifestation of the disease, commonly seen in children aged 3–5 years, followed by chronic hypoparathyroidism. Primary adrenal insufficiency (autoimmune Addison's disease) manifests in the second decade of life and completes the classical triad for the disorder.[12] Diagnosis involves the development of the classical triad, which has been expanded now to include non-triad adjunct manifestations of non-endocrine APECED rash, enamel hypoplasia, and intestinal malabsorption. The proposal of the expanded criteria has been useful in reaching the diagnosis about 4 years earlier as compared to the development of a diagnostic dyad among the classic triad manifestations, which decreased the time to clinical diagnosis by half.[6] The development of a classical diagnostic dyad raises suspicion for APECED, which then leads to the sequencing of the AIRE gene and testing for the presence of antibodies against type-I interferons (IFNs), predominantly directed to IFN-ω and majority of the 13 subtypes of IFN-α.[13] Genetic testing has revealed many mutations, with studies claiming p.C322fsX372 as the most common mutation seen in Indian cohorts.[9]

Hypoparathyroidism is the first endocrine anomaly detected in such cases, and it is seen in 79-96% of individuals, with females being more commonly affected. Diagnosis is based on biochemical measurements, and patients present with numbness around the mouth, hands, or feet, seizures, low blood pressure, and coarse or brittle hair.[14,15] Periodic measurement of calcium and intact parathyroid hormone levels should be conducted to prevent unsuspected acute hypocalcemic seizures and/or tetany.[16] Addison's disease or adrenal insufficiency usually presents by the age of 12 years, and patients present with fatigue, weight loss, hypotension, abdominal pain, and increased pigmentation of the oral mucosa and skin. Hyperpigmentation of the mucosa and skin is generally observed prior to other manifestations.[12] Other autoimmune disorders reported in the literature include autoimmune hepatitis, alopecia, keratoconjunctivitis, and rheumatologic, bony, muscular, renal, and hematologic impairments.[15] A more detailed list is given in Table 1.

Management revolves around the monitoring of hormone levels and replacement therapy. The aim of replacement therapy involves the prevention of crises and, in the case of hypoparathyroidism, the prevention of the development of nephrocalcinosis, nephrolithiasis, and renal failure resulting from excessive replacement.[17] Recently, the advent of recombinant PTH has helped achieve homeostasis in patients with poorly controlled hypoparathyroidism.[18] Replacement with glucocorticoids and mineralocorticoids is required to manage adrenal insufficiency, with dose adjustment to tide over periods of stress exacerbated by surgery, infection, or illness. Replacement therapy is also required for the proper growth and development of patients suffering from hypogonadism.[19]

Oral Manifestations and Management

Oral candidiasis seen in early childhood in patients of APECED, together with enamel hypoplasia, forms the major oral characteristics of the disease.[14] Candidiasis preferentially affects the oral mucosa with a mild form of intermittent angular cheilitis and may eventually spread to the nails and rarely genitals.[14] A Finnish study found oral *Candida* in 75% of the patients investigated. The authors identified *Candida albicans* as the causative agent in 63% of the APECED patients.[20] In the Indian scenario, a study by Fierabacci et al. found that in 64.7% of patients of the cohort, CMC was the first disease manifestation, isolated or in association with other symptoms, with a mean age of onset as 5.22 years.[10] Furthermore, various studies have linked chronic oral candidiasis in patients of APECED with a higher likelihood of developing oral squamous cell carcinoma (SCC) in later life, which highlights the importance of early detection and timely review by a dentist. Rautemaa et al. pointed out the possibility that in immunocompromised patients, long-standing oral candidosis formed part of the etiology of SCC. They attributed this fact to T cell defects which disabled inflammatory responses and allowed high numbers of *Candida* to colonize the mucosa. The age of diagnoses for oral SCC was 29–44 years, lower compared to general cases, with six patients of their cohort developing SCC before the age of 44 years.[21] Management of CMC included

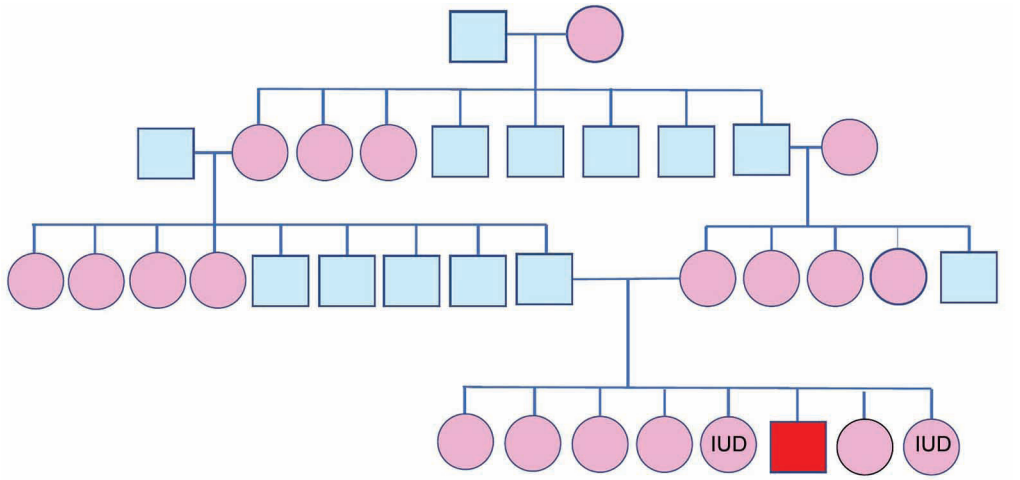


Fig. 1: Pedigree analysis for the patient. Blue square, male; pink square, female; red, index case; IUD, intrauterine death

the use of systemic and topical antifungal therapy along with the maintenance of strict oral hygiene.[22] Studies have reported that alternatives to azoles, such as chlorhexidine, should also be considered as options for *Candida* treatment.[23]

Literature also reports the prevalence of non-triad manifestations in 80% of the affected individuals, including enamel hypoplasia.[8] A study by McGovern et al. reported that lesions appeared mostly in the form of grooves or rows of pits distributed horizontally around the circumference of the crown with varying width and depth.[24] Lukinmaa et al. in 1996 studied enamel microanatomy by light microscopy and scanning electron microscopy in patients of APECED. The authors concluded that the incremental pattern in the abnormal enamel was obscure, and the prisms were either barely detectable or accentuated and disoriented.[25] Perniola et al. studied the enamel defects of four patients of APECED and observed that lesions followed the pattern of the perikymata and ran horizontally around the circumference of the crown. Further investigation of microanatomy revealed several alterations in the enamel, while dentine was either normal or minimally altered. Enamel defects are most commonly seen in permanent dentition, with primary teeth rarely affected.[26] Both hypoplastic and hypomineralized lesions have been reported; however, there is no final consensus on the etiology. Associations between hypoparathyroidism and enamel hypoplasia have been proposed, along with theories of an autoimmune attack on the enamel during development.[14] Table 2 highlights the literature available detailing the dental manifestations seen in patients of APECED.

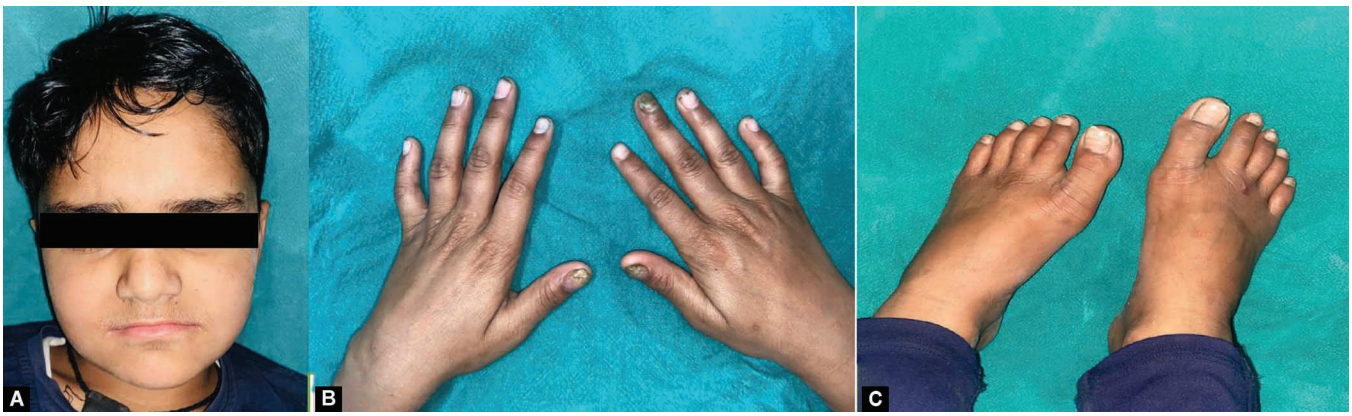
In view of the burden of systemic manifestations, oral healthcare can often take a backseat. However, the importance of dental pathologies must be stressed with a focus on specialized care. Enamel hypoplasia can lead to a heightened risk of dental caries and erosion from acids in foods, beverages, and medications. Therefore, a strict preventive regimen should be employed to prevent and intercept any developing carious lesions during the course of the disease. Excellent oral hygiene, remineralizing agents such as casein phosphopeptide amorphous calcium phosphate (CPP-ACP) or silver diamine fluoride (SDF), along with routine topical fluoride application, can help reduce the caries burden for such patients.[8] Patients of APECED also present with oral conditions such as xerostomia, aphthous ulcers, aphthous stomatitis, and atrophic glossitis.[20] Furthermore, the risk of adrenal crisis during the dental procedure must be considered. For patients with adrenal insufficiency, steroid cover during invasive dental procedures is a prerequisite.[27] Collaboration and proper communication with the physicians and endocrinology team are required to prevent such an attack which may manifest as nausea, vomiting, abdominal pain, hypotension, and tachycardia.[28]

Case Report

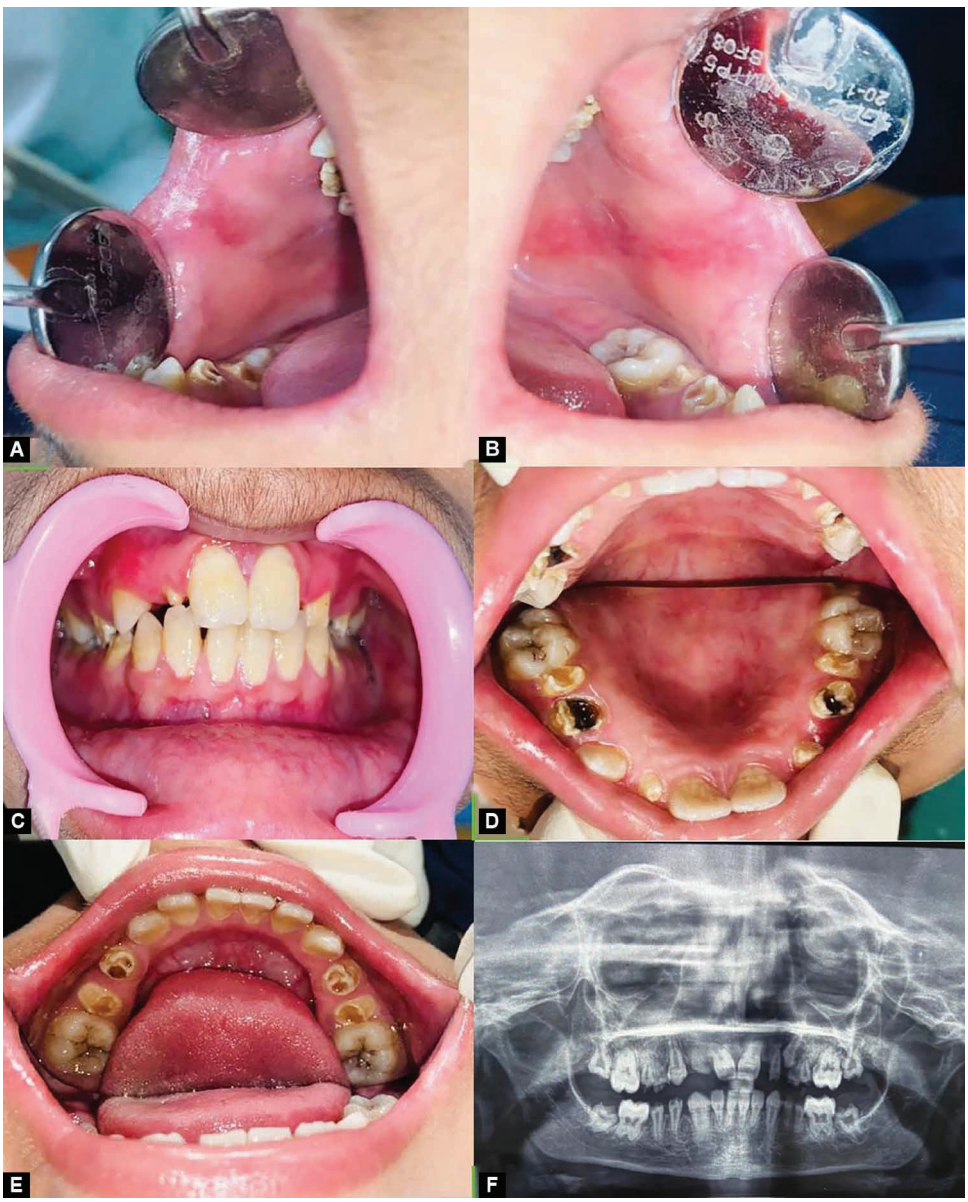
A 12-year-old boy reported to the Department of Pedodontics and Preventive Dentistry with concerns regarding the irregular shape and decaying of teeth. The patient had previously been diagnosed with APECED (type 1 anti-IFN antibodies positive) syndrome 5 years back. The child was born to a consanguineous marriage of the 3rd degree. Pedigree analysis revealed six siblings and a history of two intrauterine deaths. While five siblings presented with normal development and growth, the youngest sibling, aged 8 years, was found to have symptoms similar to the index case (Fig. 1). The patient had achieved milestones appropriate for his age; however, he had stopped attending school due to visual disturbances. The child was active, and no mental abnormality was detected. Growth analysis at the time of presentation revealed short stature with a height below the 3rd centile, normal weight, and a body mass index (BMI) of 17.2 kg/m^2 using the BMI Quick Screening Tool by Khadilkar et al.[29]

The patient's medical history included the onset of seizures at the age of 3.5 years, which could not be explained by the treating doctor at that time. Seizures were associated with tongue biting, urinary incontinence, and loss of consciousness, which lasted for 5 minutes. At the age of 7 years, the nature of seizures changed with stiffness of hands and feet, proceeded by a tingling sensation that was suggestive of tetany. This was also followed by deviation of the mouth to the right side.

Similarly, around the age of 4 years, the child also presented with recurrent bilateral oral lesions and lesions on the nail, which began with the right thumb. The lesions were black in color and associated with pain and increased fragility. The patient also reported recurrent lesions over the penile region associated with papular eruptions, which worsened during the summers. The diagnosis of candidiasis was confirmed with potassium hydroxide smears. The patient's mother also reported the absence of major secondary sexual characteristics, such as the growth of pubic and



Figs 2A to C: (A) Extra oral view. (B) Bilateral subungual onycholysis on hands (C) Bilateral subungual onycholysis on feet with prominent transverse ridges over the great toe



Figs 3A to F: (A and B) Bilateral oral candidiasis; (C) Intraoral buccal view (top left); (D) Occlusal Maxillary arch view; (E) Occlusal mandibular arch view (F) Orthopantomogram

Table 2: Literature detailing the different oral manifestations and their finer aspects in patients of APECED

S. no	*Author*	*Sample size*	*Age group*	*Methodology*	*Main dental findings*
1	Graham et al. (2022)[14]	1	12 years	Case description, clinical examination, and management	• Generalized enamel hypoplasia with reduced enamel thickness. • Retained and unerupted teeth. • High caries riskManagement with preventive, esthetic, and orthodontic procedures. Steroid cover provided for exodontia.
2	Brenchley et al. (2021)[8]	1	15 years	Case description and clinical examination	• Irregular clinical crown size with pointy cusp tips and narrow shape. • Pitted enamel hypoplasia, white cusp tips, and thin and opalescent enamel are seen at various locations. • Generalized spacing, missing permanent first molars, taurodontism of second molars.
3	Bruserud et al. (2018)[33]	10 APS-1 17- controls	10–64 years	Whole unstimulated saliva was examined by high throughput sequencing of the hypervariable region V1-V2 of 16S rRNA	• Findings showed an altered oral microbiota, a higher proportion of firmicutes, and a reduction of bacteroidetes. • On a genus level, Streptococcus and Gemella were increased in APS-1. • Altered microbiota may lead to altering immunity in APS-1 patients and contribute towards manifestations such as cancer or CMC.
4	Mcmanus et al. (2011)[23]	16	2–39 years	• Lesions clinically diagnosed oral candidiasis recorded and classified. • Oral rinses and nitrogen-gassed oral swabs were procured from lesions. • Culture, nucleic acid isolation, and gene expression were analyzed.	• Clinical signs suggestive of oral candidiasis were not supported by microbiological evidence of candidiasis in 32% of patients. • Suggestive of bacterial or viral etiology for lesions resembling candidiasis. • Monospecies colonization of the oral cavities of these APECED patients was seen with *Candida albicans*.
5	McGovern et al. (2008)[24]	16	2–39 years	• Assessment of oral health through periodontal examination, recording DMFT/S, dmft/s, dft, dfs. • Assessment of enamel defects through modified developmental defects of enamel and time of development of enamel defects. • Assessment of erosion and fluorosis.	• Patients had poorer oral health, higher periodontal needs, and increased dental caries compared to controls. • Higher prevalence of enamel defects; hypoplastic in nature; pits and grooves. • 70% of teeth have less than one-third of the total tooth surface affected. Defects were chronological in a pattern. • Strong association of defects between the development of enamel defects and the onset of hypoparathyroidism.
6	Pavlic et al. (2008)[34]	3	8–10 years	Assessment of naturally exfoliated teeth and teeth indicated from exodontia under a scanning electron microscope	• Hypoplastic pits and hypomaturated patches in the deciduous teeth with underlying changes in the prismatic ultrastructure. • Coarse prisms with empty prism head suggestive of impaired mineralization. • Whirl-like formations in the enamel of the permanent molars. • The likelihood that enamel hypoplasia is due to an autoimmune attack on ameloblasts instead of as a result of hypoparathyroidism.

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S. no	*Author*	*Sample size*	*Age group*	*Methodology*	*Main dental findings*
7	Rautemaa et al. (2007)[20]	92	2.8–60.5 years	• Medical history. • Clinical check-up for oral mucosal lesions.	• Six out of 92 patients were diagnosed with oral or esophageal SCC before the age of 44 years. • Candida mucositis was pseudomembranous with pain and erosion on oral/esophageal mucosa. • Additional extrinsic risk factors like smoking and high consumption of alcohol may further increase the risk for oral cancer.
8	Perniola et al. (1998)[26]	4	9–20 years	• Quantitative assessment of defect in each tooth using the hypoplastic area method. • Assessment of the degree of damage to each tooth. • Determination of chronology of the enamel hypoplasia.	• A defect is mainly represented by grooves or rows of pits of variable width and depth; a large portion of the crown may be hypoplastic. • Pitted hypoplasia is most frequently seen on posterior teeth, especially the premolars. • Canines were the most severely affected among maxillary and mandibular teeth, but all tooth types were involved. • Hypoparathyroidism is not an etiological factor, although it may contribute to the damage.
9	Ahonen et al. (1990)[27]	68	10 months–20 years	• Clinical examination of patients with the longest follow-up of 31 years. • 56 patients had a dental examination, and the chronological age at the development of enamel defects was determined.	• 77% of the patients had enamel hypoplasia. • Deciduous teeth were not affected. • The occurrence of enamel hypoplasia was not related to hypoparathyroidism.

DMFT/S, Decay-Missing-Filled Teeth/surfaces (for Permanent Teeth); dmft/s, Decaymissing-filled teeth/surfaces (for primary teeth)

axillary hair, growth spurt, and enlargement of the testis. The patient was eventually diagnosed with hypocalcemia secondary to hypoparathyroidism, CMC, along with bilateral cataract and medullary nephrocalcinosis.

Dental history included an early loss of deciduous teeth and a delay in the eruption of permanent successors. The patient also complained of bleeding of gums during brushing.

Clinical Examination

Extraoral examination of the patient revealed medium-built, immature facies with dry and coarse skin with no palpable lymphadenopathy. Bilateral subungual onycholysis was observed over the nails of the hands and toes. The nails appeared discolored and thickened with separation from the nail bed. Transverse ridges were also observed over the great toe (Figs 2A to C). The patient had dense cataracts and pallor of the eyes, with the left eye visibly more affected than the right.

Intraoral examination revealed depapillation of the tongue and an erythematous lesion present on the buccal mucosa bilaterally, extending posteriorly from the angle of the mouth, suggestive of angular stomatitis and oral candidiasis (Figs 3A and B). The patient complained of slight burning on eating spicy food but no difficulty or pain during swallowing. The gingiva was generally inflamed, enlarged, and tender to palpation. The patient presented with adult dentition, and on examination, the maxillary lateral incisors were observed to be malformed (Fig. 3C). Microdontia was seen affecting the maxillary lateral incisors, all premolars, and the maxillary second molars. Further examination revealed generalized enamel hypoplasia with pitting and yellowish-brown discoloration affecting a large portion of the crown structure of the maxillary and mandibular premolars. The left maxillary canine was unerupted. Generalized spacing was noted, which could be attributed to the smaller, narrower size of the affected teeth (Figs 3D and E).

Carious lesions were present on the maxillary first premolars and affecting the pits and fissures of the maxillary and mandibular first molars. Radiographic findings revealed short, blunted, conical roots, impacted left maxillary canine, and taurodontism of the maxillary and mandibular molars (Fig. 3F). Overall, oral hygiene was judged as sub-optimal with plaque retention on multiple surfaces.

Treatment

In this case, the treatment was carried out keeping in mind the patient's signs and symptoms and his underlying systemic condition to create a specifically tailored treatment plan. At the time of presentation, the patient was undergoing treatment for generalized tonic-clonic seizures and mucocutaneous candidiasis with antiepileptic and antifungal drugs, respectively. The last attack of seizure was recorded within the previous month. Hence patient was classified as American Society of Anesthesiologists 3 as per guidelines, and modifications were made accordingly.[30]

Informed consent and pediatric assent were obtained at each stage during diagnostic records and treatment planning. The prognosis and future treatment modalities were explained to the parents. The medical clearance for chairside dental palliative care was given by the Department of Endocrinology and Pediatrics

of our hospital. All chairside treatment was provided in the presence of a physician from our hospital.

A preventive regimen was adopted for the patient, and at the first visit, dietary counseling, oral hygiene instructions, and brushing demonstrations were provided to the child and parent. Specific attention was given to medications and nutritional supplements being taken and their cariogenic and erosive potential. In the second visit, CPP-ACP based varnish (GC Tooth Mousse, G C Dental, India) was applied using a paint-on technique to all teeth. In the same visit, 38% SDF (FAgamin Tedequim SRL, Argentina) was applied to the maxillary premolars, followed by glass ionomer cement (FX ULTRA, SHOFU) using the silver-modified atraumatic restorative Technique. In the third visit, resin fissure sealants (Helioseal, Ivoclar Vivadent) were placed on the maxillary and mandibular molars. As the patient was photophobic, all the treatments were carried out with dimmed lighting and with the use of protective eyewear, such as FL-41 tinted glasses.

The patient continues to report to our outpatient settings for his routine follow-ups as required to date, where the application of remineralizing varnish is done every three months. The aim is to maintain a higher standard of oral health and to evaluate the oral health status for early detection of further developing oral abnormalities.

Discussion

The present case depicts a classic case of APECED and its myriad manifestations. As discussed in the above-mentioned case report, generalized enamel hypoplasia was observed with interspaced areas of normal enamel. Perniola et al., in their study, found that enamel hypoplasia resulted in the acquisition of yellow-brown discoloration and alternate zones of well-formed enamel.[26] Enamel hypoplasia has also been linked to various other systemic and local disturbances such as vitamin deficiency, maternal deficiency, low birth weight, or environmental factors such as trauma to the teeth during development. While the etiology in patients of APECED is obscure, it has been considered that hypoparathyroidism might intensify the damage.[26] Other features in our case which are generally consistent with the diagnosis of hypoparathyroidism included spacing of dentition, delayed eruption, malformed, short blunted conical roots, along with taurdontism, which has been previously reported in patients of APECED.[8] As mentioned by Mcgovern et al., poorer oral health is seen in these patients as compared to controls. Due to increased prevalence of enamel defects and the associated problems of increased plaque accumulation, oral health maintenance is a task, and the patients present with higher periodontal needs.[24] Therefore, for the current patient, a specially tailored treatment plan was instituted that focused on preventive management. SDF combines the antibacterial effects of silver and the remineralizing effects of fluoride with the advantage of psychological management of children as it avoids the need for drilling and anesthesia.[31] CPP- ACP, which is a naturally derived protein-based remineralizing, has been proposed for simultaneously enhancing remineralization and reducing the occurrence of white spot lesions and dental caries.[32] As the patient was undergoing treatment for generalized tonic-clonic seizures, the dental treatment was done following medical clearance in the presence of a physician with the preparation of seizure management in accordance with guidelines.[30] More extensive management for the case was deferred till a time the seizures were under better control. Since no invasive surgical procedure was undertaken, the dose of steroids for the patient was unchanged.

Due to its multifaceted nature, the management of APECED requires a multidisciplinary team approach with the active participation of dental professionals. Collaboration and interface with the medical and endocrinology team are important to provide comprehensive oral and medical care to the patient. As two of the earlier manifestations are oral in origin, a large role can be played by dental professionals in the early diagnosis of the disorder.[8] While enamel hypoplasia is a common occurrence with various etiological factors, in combination with mucocutaneous candidiasis, a potential for diagnosis of APECED exists. Furthermore, dental professionals may be involved in treatment and follow-up, with emphasis on new manifestations and screening for oral SCC. Patients should be counseled for regular oral screening, detriments of smoking, and alcohol, which are additional risk factors for carcinogenesis, self-examination, documentation and acknowledgment of any new symptoms, and the importance of regular follow-up. Although a rare disorder, awareness and understanding of the disease can facilitate a timely diagnosis and largely help improve the quality of life for patients of APECED.

Conclusion

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a rare disorder with a variety of manifestations that leads to high morbidity and mortality. Early diagnoses and detection can collectively improve the clinical outcomes and psychosocial status of affected patients. The role of a pediatric dentist is stressed due to the early presentation of oral manifestations in these patients. To deliver oral health care in an effective and comprehensive manner, clinicians should be able to recognize, diagnose and manage the signs and symptoms of the disease.

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