

Clinical, Biological and Therapeutic Features of a Patient with Acro Dermato Ungual Lacrimal Tooth Syndrome

Case Report

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Abstract

Background: Acro-Dermato-Ungual-Lacrimal-Tooth syndrome is a rare autosomal dominant disorder resulting from TP63 gene mutation. ADULT syndrome is clinically manifested by ectodermal dysplasia, limb defects, nasolacrimal duct obstruction, absence of orofacial clefting, primary hypodontia and the early loss of permanent teeth. The aim of this report was to study the clinical, histological and therapeutic features of the early loss of permanent teeth of a 22-year-old Tunisian female.

Case Presentation: A 22-year-old female, born to clinically healthy and consanguineous parents, was referred to the removable partial denture department for full mouth rehabilitation. The patient's medical history included a continuous follow up of her chronic dacryocystitis and a hand surgery at the age of 17.

On general examination, the patient was mildly mentally retarded, underweight and photosensitive. She presented a fine hair, hypoplastic mammary glands and bilateral nasolacrimal duct obstruction complicated with corneal abscess. The examination of her digits showed onychodysplasia, fingers camptodactyly and toes syndactyly.

The oral examination showed the presence of a temporary tooth and the early loss of several permanent teeth. The present teeth were peg shaped and mostly decayed. Enamel was poorly formed.

Temporary and decayed permanent teeth were extracted. Polarized light microscopy was then performed to observe half teeth sections stained with hematoxylin-eosin. The other half was observed under scanning electron microscopy.

Results: The patient underwent full mouth rehabilitation with a complete fixed maxillary prosthesis and a combined mandibular prosthesis with extracoronal castable precision attachment.

The histological findings revealed that enamel was hypoplastic, hypocalcified and dystrophic. The acellular extrinsic fiber cementum and vertical periodontal fibers were absent. The cellular intrinsic fiber cementum was present on the root layer and on a great part of the enamel surface.

Conclusion: The premature loss of permanent teeth reported in ADULT syndrome patients can be the consequent result of the absence the periodontal attachment.

Keywords: Ectodermal Dysplasia; ADULT Syndrome; Dental Cementum; Epithelium.

Introduction

Acro-Dermato-Ungual-Lacrimal-Tooth (ADULT) syndrome, also known as Propping Zerres syndrome and pigment anomaly-ectrodactyly-hypodontia (OMIM 103285, ORPHA 978), is a very rare ectodermal dysplasia. This syndrome was first described in 1993 by Propping and Zerres [1-3]. The prevalence is 1 in 1000000 and it is inherited autosomal-dominantly [4]. Heterozygous muta-

tions in P63 gene have been identified as the cause [5]. P63, as a transcription factor, is crucial during embryonic ontogenesis, mostly in the development of limbs and other ectodermal derived tissues [6].

Symptoms include prominent ectodermal signs comprising syndactyly, ectrodactyly and ectodermal abnormalities such as finger and toenails dysplasia, intensive freckling and hypoplastic breasts

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and nipples [7]. The orofacial features, uncommonly studied, are sparse hair, lacrimal duct atresia [8], absence of lip and/or palate cleft, xerostomia, primary hypodontia and loss of permanent teeth because of weak fixation [9].

This paper reports a patient presenting the clinical features of ADULT syndrome and expands the spectrum of histological features of deciduous and permanent teeth.

Materials and Methods

A 22-year-female, born to clinically healthy and consanguineous parents, was referred to the removable partial dentures department of the Dental Clinic of Monastir for full mouth rehabilitation. The patient's medical history included a continuous follow up of her chronic dacryocystitis [Figure 1] since the age of 6 and a hand surgery at the age of 17.

Figure 1. Chronic dacryocystitis secondary to the nasolacrimal duct obstruction.



On general examination, the patient was mildly mentally retarded and underweight. Her hair was fine and since childhood, she has been suffering from photosensitivity. She presented bilateral nasolacrimal duct obstruction complicated with corneal abscess. This defect had been treated surgically by probing the duct obstruction to relieve the chronic dacryocystitis. The examination of her digits showed horizontal grooves along the length of the nails, finger camptodactyly, toe syndactyly and ectrodactyly [Figure 2]. Her mammary glands were hypoplastic and her salivary glands were non palpable.

Figure 2. Limb malformations.



A- Preoperative hand X-ray showing right index camptodactyly. B- Hand X-ray after surgery. C- Postoperative clinodactyly. D- Lobster claw malformation. E- Feet X-ray showing toes syndactyly.

Oral examination showed peg shaped teeth, a poorly formed enamel, an abnormal cusp pattern and a considerable amount of

dental decay [Figure 3].

Minor labial salivary glands biopsies were performed by midline incision of the lower lip under local anesthesia. Five minor salivary glands were harvested because of prominent variation in the degree of the inflammatory involvement of salivary glands and lobes. The biopsy was followed by histological examination after hematoxylin-eosin staining in order to evaluate the degree of lesion (frequency and intensity of ductal lesions fiber) using the CHOMETTE and coll classification.

Figure 3. oral examination



A, B, - Intraoral examination revealing peg shaped teeth (→), poorly formed enamel (), periodontal disease. C- Orthopantomogram examination showing hypodontia, spread dental decay, enamel hypoplasia and spaced teeth.*

Three teeth (1 temporary + 2 permanent) and mucosa were taken under local anesthesia. After extraction, teeth were fixed with para-formaldehyde for 10 days and sectioned in two parts. They were then dehydrated in a graded series of alcohol. Three sections were coated in a thin layer of gold (100 Å of thickness). The other three sections were stained in hematoxylin-eosin. Polarized light microscopy and scanning electron microscopy were then performed.

Results

Full Mouth Rehabilitation

The treatment included the use of set up diagnostic wax-up and the diagnostic occlusal adjustment in order to establish the accurate diagnosis and the treatment planning.

The management has associated fixed prosthesis and precision attachments-retained removable partial prosthesis in order to re-increase the occlusal vertical dimension, restore the morphology of the residual teeth and replace those absent.

After several months of follow-up, the patient has not presented any symptoms and the rehabilitation appeared to be effective in balancing the functional stability and the cosmetic appeal [Figure 4].

Figure 4. Full-mouth rehabilitation

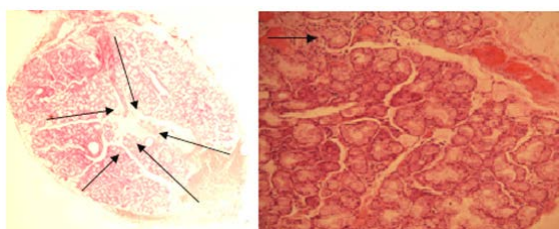


Minor Salivary Glands

Polarized light microscopy (PLM) showed an organized glandular parenchyma made of mucous acini and tubuloacinar separated

into lobules by connective-tissue-septa. A slight inflammatory infiltration of lymphocytes and plasma cells was also noticed [Figure 5].

Figure 5. Light microscopy observation of accessory salivary gland biopsy (Hematoxylin-eosin staining).

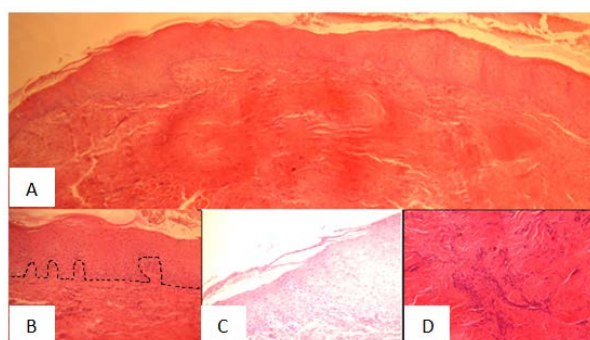


A- organized glandular parenchyma separated into lobules by connective-tissue-septa. (magnification $\times 5$). B- glandular parenchyma made of mucous acini and tubulo-acini. In the top left of the image, a slight inflammatory lymphoplasmacytic infiltration (magnification $\times 20$).

Mucosa

Under PLM, the observed mucosa was made of a squamous parakeratinized epithelium with notable presence of keratin and cell nuclei on the most superficial layers. The epithelium's basal membrane presented some mesenchymal papillae and erased epithelial ridges which gave a flat appearance to the basal membrane. The underlying connective tissue showed a non oriented dense connective tissue, presenting by places a slight inflammatory lymphoplasmacytic infiltration [Figure 6].

Figure 6. Light microscopy observation of oral masticatory mucosa biopsy (Hematoxylin-eosin staining).



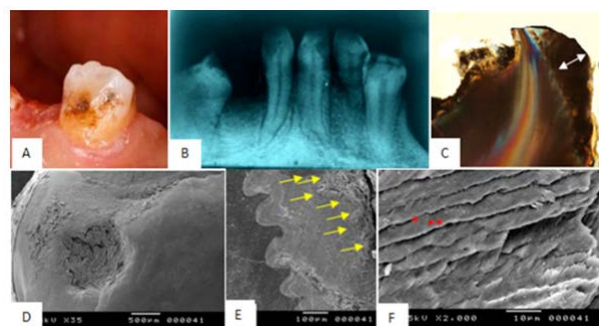
A-Oral masticatory mucosa covered with a squamous keratinized epithelium (magnification $\times 5$). B- The epithelium's basal membrane presenting some mesenchymal papillae and erased epithelial ridges giving a flat appearance to the basal membrane (magnification $\times 20$). C- Squamous parakeratinized epithelium with notable presence of keratin and cell nuclei on the most superficial layers (magnification $\times 20$). D-The underlying connective tissue showing a non-oriented dense connective tissue and presenting by places a slight inflammatory lymphoplasmacytic infiltration (magnification $\times 20$).

Enamel

PLM revealed the presence of dystrophic and globular enamel. The scanning electron microscopy of tooth's (72) distal surface showed not only the absence of perikymata on enamel outlayer but also a cellular cementum layer covering a great part of enamel surface. SEM performed on the impacted lower second molar (47) showed normal rods trajectory in the inner two thirds of the

enamel layer and visualized the rod-interrod relationship [Figure 7].

Figure 7. Enamel examination.

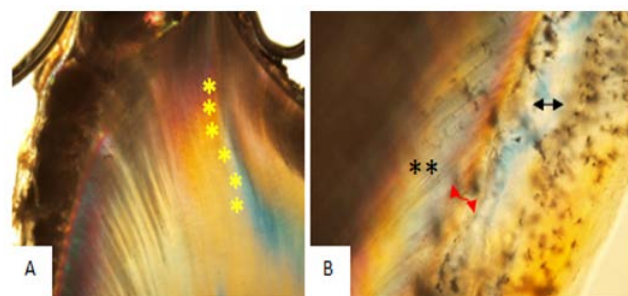


A- Intra oral observation showing poorly formed enamel and absence of physiological wear. B- Periapical X-ray examination showing hypoplastic and hypocalcified enamel. C- Polarized light microscopy on 47 illustrating the thin and irregular thickness of enamel (\leftrightarrow) (magnification $\times 5$). D-SEM of 72's distal surface showing decay on a deciduous tooth (magnification $\times 35$). E- SEM of 47 showing prismatic enamel and cemento-enamel junction (\rightarrow) (magnification $\times 150$). F- Trajectory of enamel rods observed under SEM. When rods (R) were exposed longitudinally, interrod enamel (IR) surrounded each rod (magnification $\times 2000$).

Dentin

Dentinal tubular appearance and the parallel arrangement of tubules in dentine were observed under PLM. These tubules showed an S-shaped curvature in the coronal portion and a more straight curvature in the root portion [Figure 8].

Figure 8. Dentin examination.



A- PLM of 47 showing the parallel arrangement of tubules in the dentine and the S-shaped curvature in coronal portion ($*$) (magnification $\times 5$). B- PLM of 47 showing the straight curvature of tubules in root portion ($**$), the Tomes granular layer (\rightarrow) and the hyaline layer of root dentin (\leftrightarrow) (magnification $\times 5$).

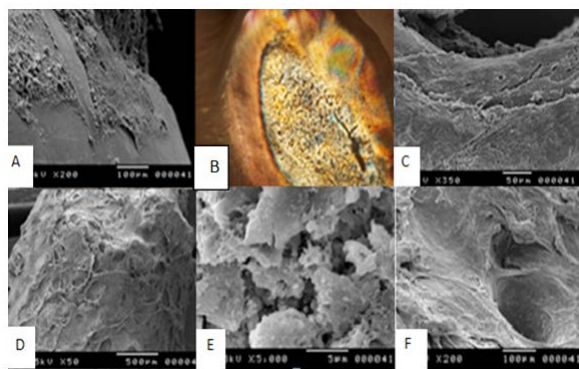
Cementum

PLM revealed the presence of a thick cellular cementum layer on tooth (47). Indeed, a big amount of cellular cementum was present near the crown. It was dense in cementocytes and some empty cementoblasts were found. The enamel outer layer covered with cellular intrinsic fiber cementum (CIFC) was also observed on the SEM.

As for root, the outer layer of the deciduous and permanent teeth was also covered by CIFC. A cellular extrinsic fiber cementum (AEFC) was not noticed. SEM revealed the absence of Sharpey's

fibers projections on the root dentin layer of tooth (47)'s furcation [Figure 9].

Figure 9. Cementum examination.



A- SEM of 72 showing a layer of cellular intrinsic fiber cementum covering enamel outer layer (magnification $\times 200$). B-Polarized light microscopy of 28 showing the interradicular cellular cementum. C- Absence of Sharpey's fibers projections on the root dentin layer of 47's furcation shown by SEM (magnification $\times 350$). D- SEM of 72 showing the absence of a cellular extrinsic fiber cementum on root surface (magnification $\times 50$). E- SEM of 28's root outer layer (magnification $\times 5000$). F- Absence of root resorption of a temporary tooth shown by SEM (magnification $\times 200$).

Discussion

Decay [10-13], xerostomia [4, 8, 14], hypodontia [1, 4, 7-9, 14-19] and premature loss of permanent teeth are commonly reported features in ADULT syndrome. However, these oral features have been largely unexplored within the scientific community.

Mucosa.

Thurfjell [20] described the function of P63 in mucosa development. He reported that knockout mice, in which the P63 gene has been functionally deleted, had shown severe developmental abnormalities of squamous epithelia and die rapidly due to dehydration, Kock [21] stated that P63 has been also observed in the nuclei and epithelial cells of stratified epithelia in human tissues. These data indicate that P63 expression is vital for the development of oral mucosa.

Enamel.

Enamel defects may result from P63 mutation affecting the enamel embryonic development. Indeed, according to Kock's [21] study of P63 expression in human prenatal tooth primordia, there was a marked positive reaction to P63 in both cap stage and bell stage. In the cap stage, a strong positivity was noticed in the inner and outer enamel epithelium, in dental lamina and in the enamel knot [8]. Thesleff [22] reported that P63 mutations affect Wnt and BMP signals regulating the development of enamel knot and affects the dominant function of the enamel knot in the morphogenesis of the tooth crown [23]. Shh signal, which is essential for the epithelium proliferation and the regulation of the reciprocal interaction between the epithelium and the mesenchyme, is also affected by P63 mutations. Thus, the epithelium-derived enamel can be affected by P63 mutations and the deposition of this defective enamel, together with xerostomia, can be the susceptible

reasons of caries [24]. In addition, P63 expression has a close link with the apoptosis of the enamel knot which arrests tooth development at the cap stage [21]. These findings explain, probably, the multiple agenesis of teeth seen in individuals with mutations in P63.

Cementum.

A cellular extrinsic fibers cementum (AEFC) is the tissue covering the cervical portion of the tooth root, important for attachment of the periodontal ligament (PDL) to the root surface [25]. In this study, the AEFC was absent on root surface and furcation. The consequent absence of Sharpey's fibers projections on the root dentin layer revealed induced the absence of periodontal attachment. These results may explain the premature loss of deciduous and permanent teeth.

P63 expressed in the inner and outer enamel epithelium can interfere with the development of the adamantine epithelium and thus with the genesis of the Hertwig's epithelial enamel root sheath [26]. The cellular intrinsic fiber cementum (CIFIC), covering a great part of enamel surface and the whole outer layer of the deciduous and permanent teeth in this study, may have an epithelium origin which concurs with Zeichner findings [27].

Conclusion

To our knowledge, this is the first report discussing the histological and the therapeutic features of the premature loss of permanent teeth described in ADULT syndrome patients.

Immunohistochemistry, osteoimmunology and genetic studies are proposed to clarify the developmental biology of tooth tissues in the case of ADULT syndrome.

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