Case Report

Ectodermal Dysplasia – A Case Report and Comprehensive Literature Review

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ABSTRACT:

Ectodermal dysplasia (ED) is a rare genetic condition characterized by a variety of deformities in ectodermal derivatives. Skin, nails, hair, teeth, and exocrine glands are derived from ectodermal germinal layers during the development of an embryo. ED has been reported in more than 150 variants in the literature. An average of seven cases are reported for every 100,000 live births. anhidrotic (Hypohidrotic) and hydrotic ED are the two types based on the degree of function of sweat glands. A 42-year-old male with characteristic features of ectodermal dysplasia visited our dental department and was treated with complete denture prosthesis described in this case report.

KEYWORDS: Ectodermal dysplasia, Shamroth-window test, Complete denture.

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INTRODUCTION:

Ectodermal dysplasia (ED) disorder is a rare inherited disease characterized by primary developmental defects[1]. One or more diversified ectodermal structures are affected, including hair, sweat glands, teeth, and nails, eyes, ears, and nervous system [1]. It can also affect other endocrine glands of ectodermal origin such as pituitary gland, adrenal gland, and exocrine glands such as meibomian glands, lacrimal glands [1]. The incidence of ED is estimated to be around seven cases per 100,000 [2]. The degree to which sweat glands function determines the type of ED[2]. A classical triad of hypohidrosis, hypotrichosis, and hypodontia is exhibited in the first type of X-linked hypohidrotic disease[3]. The second variant of ED, the hydrotic type, occurs as an autosomal dominant and exhibits a lack of development and involvement of the sweat gland [3]. There is still no clear understanding of how ectodermal dysplasia occurs or the underlying molecular mechanisms behind or associated with these disorders [3]. ED has been linked to loss-of-function variants of the epilepsy-associated repeats, Thrombospondin Type Laminin G Domain And Epilepsy Associated Repeats (TSPEAR) gene[4]. The expression of genes that regulate the signaling pathway notch and play a role in murine tooth and hair development was altered as a result of TSPEAR mutations or down-regulation[5]. The function of this gene in the human hair follicle and tooth morphogenesis is still unknown, so to evaluate its phenotypic association further functional evidence is needed[5]. In this case report, we aim to present concepts on theoretical aspects of our discipline and advise potential solutions for similar cases in the future.

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CASE PRESENTATION:

A 42-year-old male presented to our department with a chief complaint of missing teeth. History revealed he was born from parents of consanguineous marriage. He has no teeth from birth. Extraoral examination revealed sparse hairs on the head and complete loss of hair in both eyebrows, frontal bossing, discrete pigmented papules on the forehead skin, periocular pigmentation due to darkening of the skin around the eyes, saddle nose, depressed nasal bridge, increased intercanthal distance, and coarse thick lips [Figure 1].

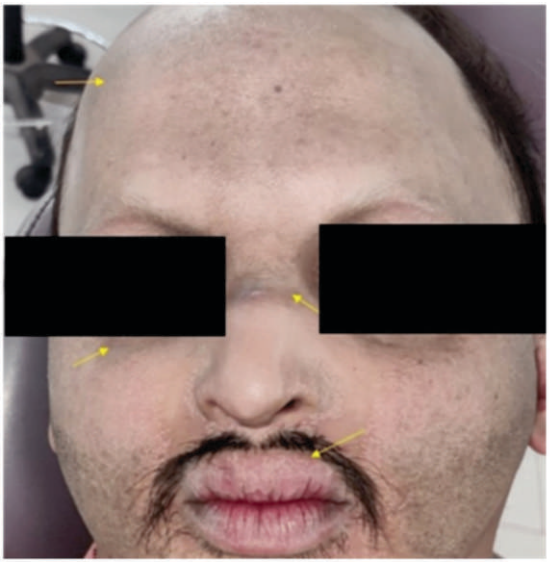

Figure 1: Extraoral clinical examination revealed sparse hair on head, frontal bossing, periocular hyperpigmentation,depressed nasal bridge, coarse thick lips

On further extraoral examination revealed dryness (hypohidrosis) and discrete hyperpigmented papules on forehead skin, sparse hair and severe recession of hairline on head [Figure 2A, B].

On further clinical examination of his lower limbs a flat spoon-shaped nail bed with loss of lustre on his left greater toe of his left leg [Figure 3].

Extraoral examination also revealed convexity of nail plates on all his finger digits and dry pigmented skin on the external surfaces of his hands [Figure 4].

Schamroth's window test performed revealed intact but smaller rhomboid shaped space between finger nail beds, suggestive of moderate clubbing [Figure 5].

Intraoral examination revealed completely edentulous maxillary and mandibular arch, thickened

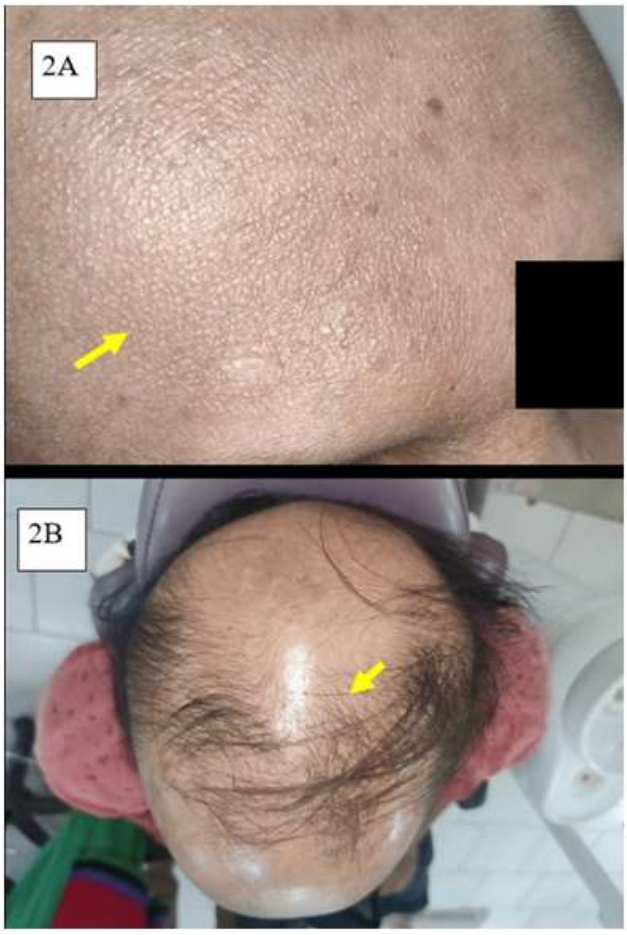

Figure 2: A) Extraoral examination revealed dryness and discrete hyperpigmented papuleson forehead skin, B) sparse hair and severe recession of hair line.

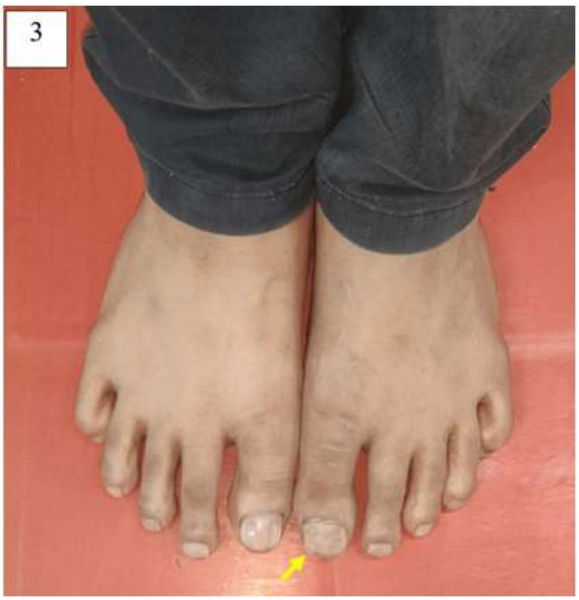

Figure 3: Extraoral examination of his legs revealed a flat spoon shaped nail bed on his left leg.

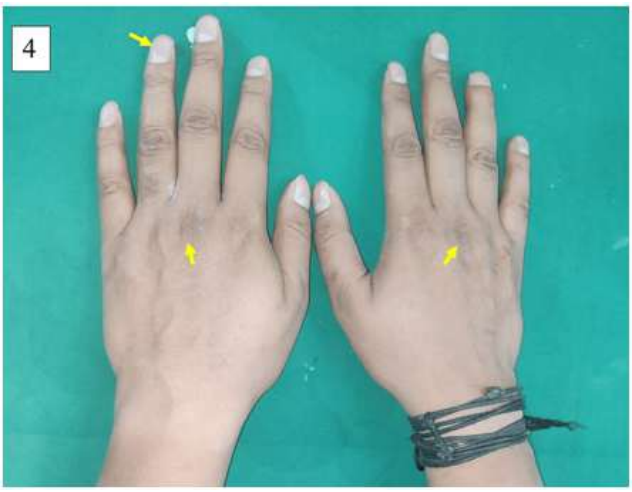

Figure 4: Extraoral examination revealed convexity of nail beds on all his finger digits and increased dryness and pigmentation on the extensor surface of his hands.

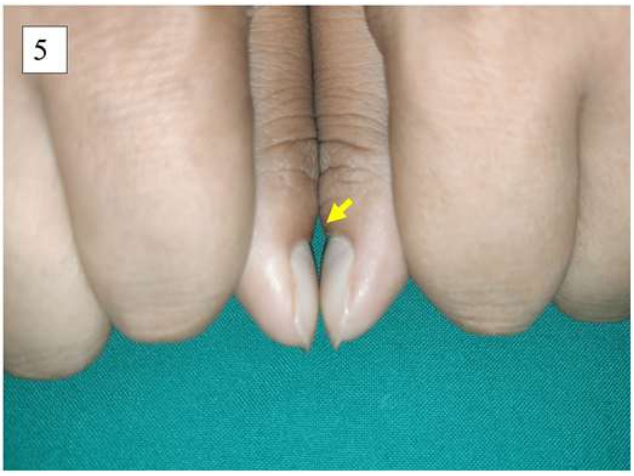

Figure 5: Schamroth window test or schamroth's sign revealed reduced diamond-shaped space between nailbeds suggestive of moderate clubbing of finger digits.

maxillary labial frenum attached near the crest of edentulous maxillary alveolar ridge [Figure 6 A, B].

The removable complete denture prosthesis was fabricated to restore tooth loss and improve masticatory efficiency [Figure 7 A, B].

The differential diagnosis of various syndromes associated with Ectodermal dysplasia is described [Table 1].

DEFINITION:

EDs form a multisystem genetic disorder with dental defects characterized by a diversified heterogeneous developmental defect in one or more structures of ectodermal origin, one of which involves teeth, hairs, nails, or sweat glands. Other organs derived from ectodermal derivatives include structures

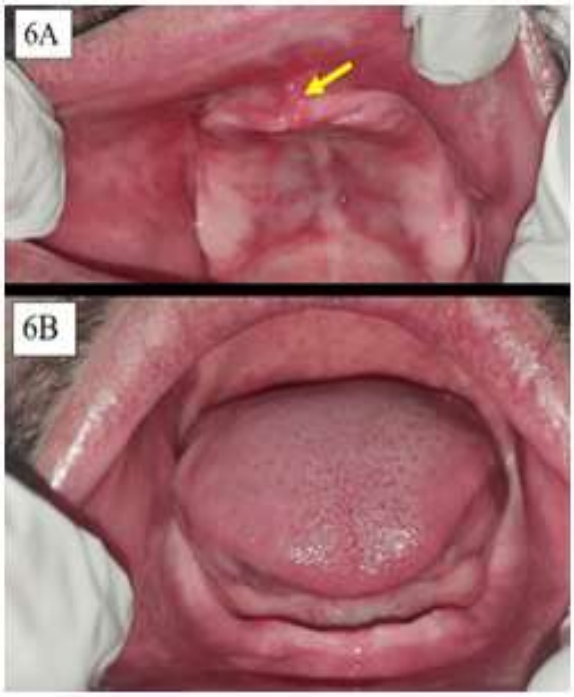

Figure 6: A) Intraoral examination revealed thickened maxillary labial frenum and completely edentulous maxilla B) completely edentulous mandibular arch.

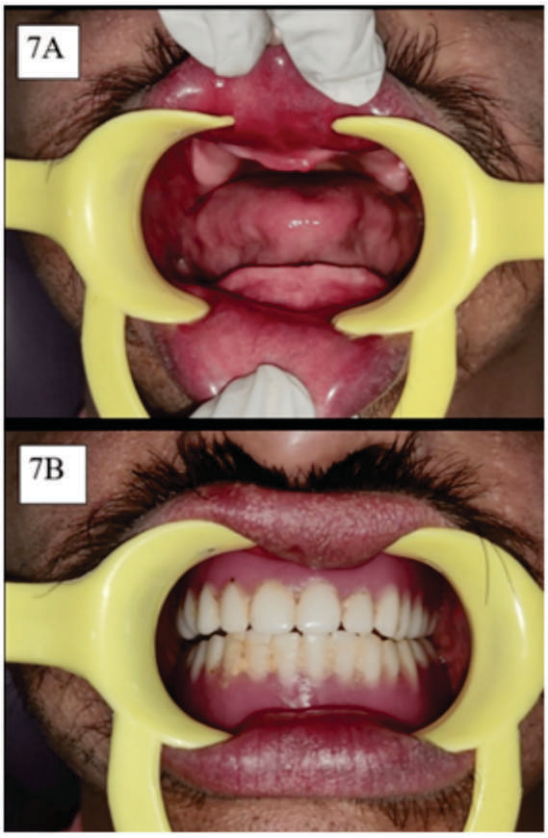

Figure 7: A, B) The completely edentulous maxilla and mandibular arch were rehabilitated with removable complete denture prosthesis.

Table 1: Syndromes associated with Ectodermal dysplasia.

Syndromes with Ectodermal dysplasia	Clinical features
Clouzton syndrome	Dystrophy of Nails, Palmo-plantar Hyperkeratosis, alopecia (Partial or Total), Hypotrichosis.
Christ-Siemens-Touraine syndrome	Hypodontia, hypohidrosis, hypotrichosis, onychodysplasia.
Ectrodactyly-Ectodermaldysplasia-clefting syndrome (EEC)	Ectrodactyly (split hand and foot deformity), Ectodermal dysplasia (defects of the hair, teeth, nails, and sweat glands), and altered nasal phonation due to Cleft lip/palate (EEC), hearing difficulty due to nasolacrimal ductus agenesis.
Ankyloblepharon Ectodermal dysplasia -Clefting (AEC) syndrome or Hay-Wells syndrome	Ankyloblepharon, Ectodermal defects, Cleft lip/palate (AEC)
Rieger syndrome	A Mesoectodermal dysplasia of the cornea and iris, missing teeth, peg laterals, enamel hypoplasia, short dilacerated roots, hyperplastic maxillary labial frenum, malocclusion, microdontia in some cases short stature, abnormal external ears, hypertelorism,mental retardation in some cases, kyphosis, scoliosis, arachnodactyly, polydactyly, imperforate anus, umbilical hernia, myopathy.
Rapp Hodgkin syndrome	Ectodermal dysplasia,hypodontia, cleft lip and palate, scalp dermatitis,hypospadias

of the central nervous system, mammary glands, adrenal, pituitary endocrine glands, meibomian glands, external ear, melanocytes, cornea, conjunctiva, and exocrine glands of lacrimal apparatus[6].

Synonyms:

Ectodermal dysplasia syndrome, Hereditary ectodermal dysplasia.

Epidemiology:

The incidence of ED is about 7 per 10,000 live births. The x-linked mode of inheritance is commonly seen among males as the fathers do not transmit to their sons[7].

Etiology, *Genes:*

Mutations in the Ectodysplasin A (EDA), Ectodysplasin A Receptor (EDAR), or EDAR associated Death Domain protein (EDARADD) gene located on the long arm (q) of the X chromosome between positions 12 and 13, 2q11-q13, 1q43 respectively prevent mutual mesoderm and ectodermal interactions and affect the usual regular development of teeth, hair, sweat glands resulting in clinical manifestations of sparse or loss of hair, hypohidrosis, intolerance to heat, anodontia or oligodontia. Other genes involved in the etiopathogenesis of ectodermal dysplasia include the Gap Junction Protein beta-6 (GJB6) gene mapped to chromosome 13q, which encodes for connexin-30. Mutations of the Polio Virus Receptor related-1 (PVRL -1) gene, which encodes a cell-cell adhesion molecule or herpesvirus receptor have been reported in those cases of cleft lip/ cleft palate ED. Mutations in Muscle Segment Homeobox genes (MSX1) cause autosomal dominant tooth agenesis primarily of second premolars and third molars. Mutations in the Paired Box gene 9 (PAX9) transcription factor result in maxillary and mandibular second molar tooth agenesis and oligodontia. Wingless related integration site (Wnt) signaling regulator Axin-related inhibition protein 2 (AXIN2) gene mutations were causative for oligodontia due to missing incisors and predisposition to colorectal cancer [8].

MODE OF INHERITANCE:

The hypohidrotic type of ED has several forms of heterogeneous patterns of inheritance with variable clinical expressions. The majority are caused by mutations in EDA gene, which are inherited in a X

gender chromosome-linked recessive pattern in which the altered gene is present on the X gender chromosome. In males with only one gender X chromosome, a lone standing mutated gene in each cell is sufficient to cause the condition. Mutated gene results from mutation must be in either copy of the female X- chromosomes to cause the disorder. Females are less affected by gender-linked (X-linked) recessive disorders than males. A remarkable feature of gender-X chromosome-linked inheritance is that males cannot transmit X-linked quality of character to their male siblings. In the gender X-linked recessive form of inheritance, a carrier is a female with a single mutated gene in each germ cell. In about seventy percent of cases, female carriers of hypohidrotic ED experience some clinical features of this disorder These clinical signs and symptoms are usually mild and include oligodontia or hypodontia or abnormal malformed teeth resembling tapered conical or peg-shaped anterior teeth, molars with the smaller mesiodistal diameter with taurodontism (enlarged pulp chambers) sparse, the lowered density of hair or absence of hair and some problems with the function of sweat glands. The partial expression of an abnormal mutated gene shown by affected females includes hypodontia, oligodontia (teeth reduced in number), or may have mild morphological tooth alterations such as tapered or conical pointed incisors, molars with smaller mesiodistal diameter, or taurodontism (elongated pulp chambers). The incomplete clinical presentation in females is explained by the Lyon hypothesis, which states one X-chromosome in females gets inactive early during embryonic development. so only half of the X-chromosome expresses an unaffected gene and the other half expresses a gene, which is mutated and defective. Hypohidrotic variant can also rarely result from EDARADD or EDAR genetic mutations. An autosomal dominant or recessive mode of inheritance is associated with mutations of EDAR gene, and mutations in EDARADD gene have a pattern of autosomal recessive mode of inheritance. Each cell with a single mutated gene cause ED in autosomal dominant inheritance. Both copies of the mutated gene are altered in each cell in autosomal recessive pattern. Most often in autosomal recessive disorder, the affected person parents with ED do not reveal the clinical symptoms and signs of this disorder, even though they are carry a solitary copy of the altered mutated gene [9].

CLASSIFICATION:

Freire-Maia and Pinheiro (1977) classified ED according to clinical features and associated located areas of developmental defects (1-4) such as 1-Hair, 2-nails, 3- the tooth, and 4-sweat glands[9].They divided the ED into two groups namely Group-A if two ectodermal structures such as hair, nails, tooth, or sweat glands are affected, and Group-B, if one ectodermal structure is affected but had other defects of lip, ear, soles, or palms [10].

CLINICAL FEATURES:

ED is a heterogeneous hereditary condition in which two or more embryonic ectoderm tissues develop abnormally at the same time. ED is a syndrome when an ectodermal defect is associated with other anomalies and also isolated in which the defect is isolated only affecting structures derived from ectoderm. The prevalent variants of ED are hypohidrotic and hidrotic [11]. Different types of clinical manifestations of hair vary from fine, and short to complete baldness and sparse or complete loss of eyebrow hairs. According to this present case report, our patient has clinical similarities of ED with hair manifestations that include severe recession of the hairline, scant scalp hairs, hairs on the mustache and beard are not affected, and absent eyebrow lashes[11] Saddle noses, depressed nasal bridges, and thick coarse lips are common manifestations. Delayed eruption of permanent teeth, Complete loss of teeth (anodontia), oligodontia, and peg-shaped or conical teeth are some of the dental manifestations of this disease[11]. Our case exhibits similar extraoral and intraoral clinical manifestations, including a flat depressed sunken nasal bridge and coarse, thick lips, xerostomia due to salivary gland hypoplasia elicited by stick sign (mouth mirror sticks to the buccal or labial mucosa during clinical examination), and partial hypodontia with conical or tapered peg-shaped central incisor teeth[11]. Our patient also had excoriated papules, generalized xerosis, and hypohidrosis all over her forehead, nasolabial fold, and face[12]. Children affected by hypohidrotic ED can die within first three years of life due to failure to survive due to a variety of complications, such as acute fatal lung infections like pneumonia, and hyperthermia, as a result of lack of thermal regulation. Therefore, newborns and young children should be given special attention by the treating physician. A typical life expectancy is three years after birth[12].

DIAGNOSIS:

No diagnostic guidelines or criteria currently exist for hypo hidrotic ED. Hypohidrotic type must be suspected if a patient has (hypotrichosis) sparse hair on the scalp, or body, (hypohidrosis) reduced ability to

Table 2: Diagnostic modalities in Ectodermal dysplasia.

Pilocarpine Microneedles-Sweat induction (PM-SI)		Patches contain 100 microneedles and 600 µm long made of water-soluble materials encapsulating pilocarpine nitrate. These microneedles deliver pilocarpine dosage greater than 0.5 mg/ cm^2 , which is doubler dose when compared to conventional iontophoresis and induce sweating. Sweating is either reduced or absent in Ectodermal dysplasia patients.
Skin biopsy	Invasive	Eccrine sweat glands -absent in hypohydrotic Ectodermaldysplasia.
Radiological imaging		
Orthopantomography	Non-invasive	Gross evaluation of number and shape of teeth. Either complete absence of teeth or hypodontia or oligodontia or conical anterior teeth.
Lateral cephalometric radiographs	Non-invasive	Frontal bossing, depressed mid-face/nasal bridge.
Paranasal sinus view (water's view)	Non-invasive	Opacification of the affected maxillary sinus due to recurrent Chronic maxillary sinusitis that occurs in ectodermal dysplasia patients.
Hand-wrist radiographs	Non-invasive	Decreased tubulation of long bones, osteopenia
Limb radiographs	Non-invasive	To detect decreased tubulation occurring in long bones, fracture lines due to osteopenia, and decreased bone density in ectodermal dysplasia.
DEXA (Dual Energy X-ray Absorptiometry)	Non-invasive	Decreased bone mineral density in the Lumbar spine (L1-4)
CBCT (Cone Beam Computed Tomography)	Non-invasive	For measuring compromised airways (oropharynx) in mid-facial hypoplasia, anteroposterior skeletal abnormalities due to maxillary hypoplasia in Ectodermal dysplasia. Laryngopharynx in Laryngitis, recurrent sore throat in Ectodermal dysplasia patients. It also helps to diagnose fine deviation of inferior turbinates that results in chronic maxillary sinus pathologies in ectodermal dysplasia.

sweat, lower than an actual number of teeth (hypodontia) congenital absence of all teeth (true complete anodontia). If teeth are present, they are usually smaller in size, conical, or pegged in shape, (taurodontism) elongated enlarged pulp chambers in comparison equally to root resembling bull-like is more common in molar teeth[13].

Table 3: Management of clinical manifestations of Ectodermal dysplasia.

clinical Manifestations of Ectodermal dysplasia	Treatment
Hypotrichosis	Wigs, 3% Minoxidil topical solutions for sparse hair.
Hypohidrosis	Cool environment (e.g., use of an air-conditioner, a spray bottle of water, cool-ventilated vests) Frequent sipping of water stored in water bottles during a Hot Climate • Skin care products such as emollients containing lanolin, liquid paraffin for dry skin (xerosis), moisturizing creams for eczema, and antihistamine-containing calamine lotions for rashes associated with eczema and certain outdoor activities (e.g., swimming)
Hypodontia	Mandibular implant- assisted Overdentures, complete Dentures, Telescopic dentures for maxilla, Implant retained overdentures, and All-on-four Implants were considered for prosthetic rehabilitation depending on whether only a few (oligodontia or hypodontia) or complete loss (anodontia) of teeth. other dental treatment procedure modalities include dental implants, bonding of conical teeth, and or dentures, and Orthodontic movement of malaligned teeth. simple restorations at an early age of 1.5 to 2 years to complex fabrication of dentures at older age greater than 16 years of age. Bonding of conical teeth improves aesthetics and increased masticatory efficiency. • Dental implants have proven successful in the anterior mandibular arch only in children aged greater than seven years of age. Children with hydrotic ectodermal dysplasia need to replace dental prostheses every two and a half years as dental prostheses cannot accommodate increased edentulous spaces as jaw growth is not hampered in ectodermal dysplasia. Dental implants in adults can support aesthetics & function like occlusion and mastication.
Hyposalivation	Therapeutics (e.g., Artificial salivary substitutes containing carboxy methyl cellulose) directed at coating dry mucosa and maintaining oral lubrication, and reducing the risk of dental caries
Dysphagia	Direct implantation of feeding tubes Percutaneous Endoscopic Gastrotomy (PEG) tube in stomach or Nasogastric tube - passed through nose into stomach. Modifications in diet. Endoscopic assisted Surgical dilatation of oesophagus with non-biodegradable Esophageal Stents namely Allimax - Esophageal Stent (ES) Fully covered Esophageal Stent (Merit Medical Endotek), Boston Scientific's Polyflex Esophageal Stent, WallFlex -fully or partially covered Esophageal Stent and bio-degradable (Self Expandable) SX- Ella-Danis Esophageal Biodegradable Stent,
Dental caries	Decreased salivation increases the risk of dental caries. Fluoride varnishes and Pit and fissure sealants
Dry eyes	Ophthalmic Lubrication with instillation of eye drops containing carboxy methyl cellulose .
Respiratory manifestations	Recurrent fever from respiratory infections like Pneumonia. External punging with wet cotton towels placed on the forehead and body wash with moist water-soaked cotton towels for children Breathing difficulty due to asthma in Ectodermal dysplasia patients. use of Nebulizers containing salbutamol, a bronchodilator for difficulty in breathing. Referral to allergist or pulmonologist.
Solidified cerumen ear wax	Instill 5-10 drops into the ear canal followed by the use of a cotton plug placed near the entrance of the ear canal. cotton plug moistened with Soliwax@ Ear drops is removed after an hour or a day. The procedure is repeated twice daily for seven days which helps in removing cerumen ear wax. Soliwax@ Ear drops NuLife Pharmaceuticals which contains paradichlorobenzene 2.0 % w/w, Benzocaine 2.7 % w/v, chlorbutol 5.0% w/v, Turpentine oil 15.0% w/v, Butylated HydroxyAnisole (B.H.A) Antioxidants. Referral to (Ear,Nose,Throat) ENT physician

DIAGNOSTIC MODALITIES IN ECTODERMAL DYSPLASIA:

The various diagnostic modalities in ED are categorized as non-invasive, semi-invasive, invasive as per the diagnostic procedures encountered. These are listed [Table 2] [14].

MANAGEMENT:

The treatment of ED depends on the type of affected exocrine or endocrine organ, and rapid timely intervention is crucial for a successful and effective outcome[15]. Exposure to a hot climate should be managed with physical methods of cooling such as drinking cold beverages frequently and wearing cooling vests which aid in ventilating hot air while working out[15]. The cosmetic appearance and function of teeth can be improved with early intervention by dental treatment[15]. Dental implants, bone grafting, and dental prostheses should be performed under the supervision of a Prosthodontist[15]. Topical 3% minoxidil solutions recently have a promising role in increasing the density of sparse hair in ED patients[15]. The therapeutic management of xerosis involves topical emollients such as lanolin, and liquid paraffin. In our case, conservative management of the skin was performed with moisturizing cream[15]. The patient must be created awareness about the importance of dental care and replacement of missing teeth[15]. The various management of clinical manifestations of ectodermal dysplasia are enumerated [Table 3] [16,17].

Future Prenatal Targeted drug therapies, that target neonatal Fc receptors are under Phase II clinical research. The prenatal intraamniotic administration of Fc-EDA, a recombinant Ectodysplasin A1 protein into the amniotic cavity of affected embryos can prevent the disease and not recommended before gestational week 25 due to risk of miscarriages [18,19].

CONCLUSIONS:

The term ED describes a group of disorders affecting the ectodermal derivatives such as dermal appendages of the skin, exocrine salivary glands, hair, and teeth. This developmental disorder may affect many ectodermal organs and imparts a variety of clinical symptoms. In patients with ED, physiological and psychological development is impaired due to the dysfunction of orofacial structures and unattractive appearance. The importance of primary provider education in detecting this illness as early as possible cannot be overstated. Multidisciplinary treatment involving Pediatricians, dermatologists, dentists, and other health care providers is needed as many body organs are affected. The condition and the importance of providing timely routine treatment of these individuals must be explained adequately to parents to prevent adverse treatment outcomes in such individuals. The rehabilitation of missing teeth in our case has resulted in the restoration of lost masticatory function, thereby improving masticatory efficiency.

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Conflicts of interest
There are no conflicts of interest.

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INFORMED CONSENT:

Informed consent was obtained from all individuals, or their guardians included in this study.

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