Zygomatic Implant Survival in 9 Ectodermal Dysplasia Patients with 3.5 to 7-year Follow Up

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ABSTRACT

Objective: Ectodermal dysplasia syndrome is a complex group of genetic disorders identified by the abnormal development of the ectodermal structures. The aim of this retrospective clinical case series report was to evaluate the outcomes of the ectodermal dysplasia syndrome patients that underwent zygomatic implant surgery.

Materials and Methods: A total of 9 ectodermal dysplasia syndrome patients aged between 21 to 56 years (mean age 36.8) with severely atrophic maxilla were included in this study. All the patients were treated with a total of 19 zygomatic implants. The mean follow-up of the patients was 55 months (with a range of 44 to 84 months). The implant survival rate was evaluated as a primary outcome. The intra and postoperative complications were evaluated as additional criteria for success.

Results: The overall implant survival rate was 100 % without any complications. Final or provisional prosthesis were delivered on the same day of surgery, which resulted in an improvement of the quality of life of the patients.

Conclusion: According to the results of this study, zygomatic surgery can be considered as a viable and safe alternative to conventional treatment modalities for oral rehabilitation of ectodermal dysplasia syndrome patients.

INTRODUCTION

Ectodermal dysplasia (ED) was first defined by Charles Darwin in 1860s (Balshi & Wolfinger, 2002). ED is a syndrome of a complex group of hereditary or congenital malformations identified by the abnormal development of the ectodermal structures (Itin & Fistarol, 2004, Lypka et al., 2008). The transmission of the ED can be either autosomal dominant or recessive. The characteristics of the condition include abnormal development of the skin, sweat glands, sebaceous glands, hair, nails, and teeth (Itin, 2013, Itin & Fistarol, 2004, Lypka et al., 2008). Additionally, ED syndrome can affect other organs, which develop from ectoderm such as, nervous system, tooth enamel, mammary glands. In general, ED can occur in isolation or in association with other more complex clinical manifestations involving the mesodermal and endodermal structures (Itin, 2013, Carvallo, et al., 2013).

Dental dystrophies of the ED contain complete anodontia, hypodontia and oligodontia (Deshpande& Kumar, 2010). The clinical oral manifestations of ED patients include maxillary hypoplasia, mandibular protrusion, and developmental defects of the alveolar ridges (Bani et al., 2010, Wang et al., 2019).

Oral rehabilitation in ED patients represents a major surgical challenge (Deshpande et al., 2010). This difficulty is primarily due to anatomical problems, such as the shape and density of the edentulous jaw bones and secondly due to the poor quality of the oral soft tissue with limited attached gingiva. These factors are usually considered as unfavorable for the prognostic of healing in cases of bone grafts and dental implants. Ectodermal dysplasia has a negative impact on the oral health-related quality of life of patients (Hanisch et al., 2019). According to a systematic review by Wang et al in 2016 dental implants with or without bone augmentation are commonly used methods

for oral rehabilitation of ED syndrome (Wang et al., 2016, Deshpande & Kumar, 2010). The insertion of conventional dental implants in patients with ectodermal dysplasia syndrome were reported in literature with high survival rates by several authors (Chrcanovic, 2018)

Zygomatic implants (ZI) were introduced by Branemark as a successful and promising alternative for oral rehabilitation of the patients with extremely atrophic maxillary bone (Malo 2008, Branemark 1998). The advantages of the technique include reduced number of surgeries, reduced time, decreased need for additional bone grafting, and less expenses when compared to conventional implant procedures (Chana 2019, Aparicio 2006, Aparicio 2014). Dental rehabilitation of ED patients with zygomatic implant fixations and maxillary prosthesis were reported in literature, although with very limited numbers (Peñarrocha-Diago et al., 2004, Balshi et al., 2002). Wang et al in a radiographic study evaluated the anatomical features of ED patients and reported that the development of zygomatic thickness and length in ED patients with oligodontia can be limited and can represent some difficulties for zygomatic implant insertions (Wang et al., 2019).

The oral rehabilitation of ED patients is quite challenging with conventional implants and prosthesis in terms of function and esthetics. One of the major limitations is the severe maxillary hypoplasia and success might decrease critically due to insufficient retention and stability of the prosthesis. Integration of zygomatic implant surgery with implant-supported prosthetic rehabilitation can significantly optimize the quality of life of the ED patients. The aim of this retrospective clinical case series report was to evaluate the outcomes of ectodermal dysplasia syndrome patients that underwent oral rehabilitation with zygomatic implant surgery.

MATERIALS AND METHODS

This retrospective study consisted of 9 ectodermal dysplasia syndrome patients with severely atrophic maxilla that were treated with zygomatic implants at the Department of Dentistry and Maxillofacial Surgery, University of Milan, (section of Galeazzi Hospital, Italy) between March 2013 and March 2016 (out of 76 ED patients that received oral rehabilition in the same section). A signed informed consent agreement form was obtained from all the patients and the study protocol was in compliance with the principles laid down in the Declaration of Helsinki on medical protocol. This study was approved by institutional scientific review board of Galeazzi Hospital (Milan, Italy; authorization no. 2552377-L2058. "Implant rehabilitation of the partially or totally edentulous patient: evaluation of techniques and materials to improve predictability and maintenance"). The data of the patients were identified from the medical records as ectodermal dysplasia syndrome patients with severely atrophic maxilla that were treated with the use of implants inserted into the zygomatic bone.

Inclusion criterion was ectodermal dysplasia syndrome patients with severely atrophic maxilla and failure of previous bone grafting procedures that were treated with zygomatic implants. No additional exclusion criterion was set. The surgical, prosthetic and the follow-up protocol were described in detail in a previous article by the same team (Goker et al. 2020).

Presurgical protocol included clinical examinations with preoperative cone beam computed tomography (CBCT) scans and panoramic radiographs. A professional oral hygiene session was given to each patient one week before the surgical operations.

All the patients were prescribed with pre- and post-operative antibiotics (Augmentin at a dosage of 1-g tablet every 8 hours for a total of 6 days or Azithromycin 500 mg for 3 days in cases of allergy to penicillin).

All surgeries were carried out by the same surgeon (Fr.G.) under general and with local anesthesia (4% articaine with 1:100,000 adrenalin). “Extra- sinus approach” was utilized in all patients for insertion of zygomatic implants (Noris Medical Ltd., Israel or Medentis Medical ICX GmbH, Germany). In brief; the operation started with a palatal incision in the maxillary crest with vertical posterior releasing incisions and the muco-periosteal flap reflections. After flap reflection, all the bone surgeries and the implant site preparations were performed using drills and burs according to the instructions from the manufacturer. Finally, the ZIs were carefully inserted at a low speed (max 40 rpm), with a torque of 40 to 80 Ncm. The last 360 turn is done manually with an extraoral screwdriver. The surgical sites were covered with resorbable membrane or with Bichat fat pad and the wounds were repositioned and sutured using continuous resorbable sutures (Vicryl, Ethicon FS-2, Johnson & Johnson, USA).

Final or provisional prosthesis were delivered on the same day of surgery, which resulted in an improvement of the quality of life of the patients. The patients were recalled for clinical follow-up after 10 days, 1 month and every 3 months for the first year, and then twice a year. The occlusion was examined carefully at the delivery of the final prostheses and at each follow-up. In the first year following ZI insertions, follow up criteria for the patients with Toronto bridge prosthesis included additional interventions. Every six months, Toronto bridge prosthesis were unscrewed to check the status of the surrounding tissues.

Implant survival rate was the primary outcome. Intra-operative and post-operative complications were evaluated as additional criteria for survival. Implant survival rate was evaluatedaccording to the following clinical and radiological criteria:

- absence of clinically detectable implant mobility;
- no evidence of peri-implant radiolucency;
- no spontaneous ZI failure;
- absence of pain, and infections.

The representative pre-operative intraoral and panoramic x-ray views of one of the ED patients can be seen in Figure 1 and Figure 2. The representative intraoral and panoramic x-ray views of the same patient with zygomatic implants inserted can be seen in Figure 3 and Figure 4. Figure 5 and Figure 6 are intraoral views at 18 months follow up. Figure 7 shows the panoramic x-ray image from 26 months after insertion of implants, which was taken at the last follow up appointment.

This article was written following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (http://www.strobe -statement.org, von Elm, et al., 2008).

Statistical analysis

Given the small sample size, descriptive statistics was done using mean values and range for quantitative variables. The effect of the different variables (gender, age, antagonist dentition, reason for ZI, Number of zygomatic and conventional implants, loading mode, prosthesis type, and ZI location) on implant survival was not evaluated, because no failures occurred in this study. Statistical analysis was performed using GraphPad Prism 5.03 (GraphPad Software, Inc., La Jolla, CA, USA).

RESULTS

A total of 9 ectodermal dysplasia syndrome patients aged between 21 to 56 years (mean age 36.8) with severely atrophic maxilla were included in this study. In the population, one of the patients had diabetes and no other patient had any additional chronic or other health condition.

All the included patients were Class VI -V Cawood and Howell. The quality of bone of all patients was D1 and D2, which can be assumed to be mainly due to the total absence of the teeth.

Eight patients had severe oligodontia (with six or more teeth missing:

1- Maxilla (2 incisors+2 canine+2 molar) Mandible(none)

2- Maxilla (none) Mandible (4 incisors+2 canine+4 premolar+1 molar)

3- Maxilla (3 incisors) Mandible (none)

4-Maxilla (3 incisors) Mandible (none)

5- Maxilla (4 incisors+2 canine) Mandible (none)

6-Maxilla (3 incisors) Mandible (none)

7-no teeth in maxilla and mandible

8-Maxilla (4 incisors) Mandible (2 canine+2 molar)

9-Maxilla (4 incisors+1 premolar) Mandible (2 molar)

All the patients had severely atrophic maxilla (6 patients with atrophic maxilla, 3 patients with atrophic maxilla and failures of previous bone grafting procedures (2)/ implants (1). Three of the patients had additional orthognathic surgery (Le Fort 1 osteotomy) and only one patient had orthodontic treatment with braces before zygomatic implant surgery. All the other patients had oral rehabilitation with zygomatic implant surgical management without any additional treatment modalities. Two of the patients had failures from previous grafts. One of these was failures was due to a dehiscence in iliac flap. One patient had a failure of previous conventional

implants (two implants were lost due to peri-implantitis) and insertion of zygomatic implants was considered.

All the patients were treated with a total of 19 zygomatic implants. The mean follow-up of the patients was 55 months (with a range of 44 to 84 months).

Primary stability was achieved in all implants with minimum insertion torque of 40 Ncm. Five of the patients received immediate loading of the prothesis while four of the prothesis were done in a delayed approach. The decision for loading protocol based on the request of each patient mostly due to economic reasons, independent of the primary stability of the ZI.

The overall implant survival rate in this study was 100% without any complications and without any dropouts. Eight of the patients had acrylic resin Toronto bridge prosthesis and one patient had metal-acrylic resin prostheses. Details on antagonist dentition can be listed as follows; one patient with acrylic resin Toronto bridge prosthesis, one patient with fixed metal-acrylic resin prosthesis on natural teeth, one patient with removable prosthesis, two patients with natural teeth, three patients with implants with fixed metal-acrylic resin prosthesis, and one patient with natural teeth plus implants with fixed metal-acrylic resin prosthesis.

Additional data of the study group concerning age, gender of the patients, number of zygomatic and conventional implants, ZI location are listed in Table 1. Type of prosthesis, loading protocol and antagonist dentition are listed in Table 2.

DISCUSSION

The reconstruction of oral function in ectodermal dysplasia syndrome patients is a challenging situation for the oral and maxillofacial surgeon (Deshpande & Kumar

2010b). Oral rehabilitation of ED patients with dental implants is a common treatment modality, as reported by various authors (Wang et al., 2016, Lypka et al., 2008, Chrcanovic, 2018). However, ED patients usually have reduced residual alveolar bone with "knife- edge" morphology, making implant reconstruction a challenge (Deshpande & Kumar 2010b). ED patients usually need additional interventions including bone grafting and/or sinus augmentation procedures (Worsaac et al., 2007, Guckes et al., 1991). Additionally, limitations in soft tissues can compromise the aesthetic results and can present a higher risk for possible biologic complications (Salinas et al., 2005).

Oral rehabilitation can afford ED patients, the opportunity to have normal phonation, mastication, swallowing, and aesthetics in means of facial support (Grecchi et al., 2010 a,b). The typical old-age appearance of the face can be decreased by increasing the vertical dimension of the lower face. Consequently, the temporomandibular joint functions can be improved (Grecchi et al., 2010 a,b).

In ED patients sufficient bone may be available only at the mid- symphysial area in the mandible, where one implant could provide stability for a mandibular denture (Kearns et al., 1999). The maxilla is relatively more retruded than the mandible. Additionally, the nasal alar width and mouth width are usually significantly smaller than normal patients (Sforza et al., 2003, Dellavia et al., 2010). Total or partial removable prosthesis or overdentures is often the first treatment choice in most cases (Garagiola et al., 2007). However, prosthetic solutions using dental implants should be considered (Grecchi et al., 2010 a,b, Kearns et al., 1999). Dental implants with/without bone grafts can be valuable devices with no difference compared with unaffected patients (Grecchi et al., 2010a).

Zygomatic implant (ZI) surgery can be considered as a treatment option for ED syndrome patients and was tested by researchers with positive results (Peñarrocha-Diago et al., 2004, Balshi et al., 2002). However, data concerning the outcome of this approach in such patients is currently very limited. According to the successful results obtained from this study, the oral rehabilitation of ED patients can be a valuable treatment option.

ZI is considered as a successful alternative for rehabilitation of patients with severe maxillary atrophy, however ZI insertion is a major surgery and can represent some risks (Aparicio et al., 2014, D'Agostino et al., 2016, Yates et al., 2014, Candel-Marti et al., 2012, Chrcanovic et al., 2016, Chrcanovic & Abreu, 2013, Brånemark et al., 2004, Goker et al., 2020). The possible complications of ZI surgery include sinusitis, soft tissue infections, paresthesia, and oroantral fistula, penetration of the orbital cavity during the drilling protocol, and failure of the implants (Malo et al., 2015, Filho et al., 2016, Nobre, et al., 2014).

According to an anatomical analysis of zygomatic bone by Wang et al in 2019, zygomatic thickness and length in EC patients is usually limited and insufficient. This can represent some limitations, especially for quad (4 ZIs) zygomatic implantations (Wang et al., 2019) . However, where the anatomy is appropriate, the quad zygomatic protocols can be used. In the present study, the insertion of quad (four) ZIs was possible just in one patient. Seven patients received bilateral 2 zygomatic implants (in the molar region), while one patient received unilateral 1 ZI.

The incidence of EDs is approximately 7 in 10,000 (Bani et al., 2010) physiological and esthetic considerations in such patients are compromised due to the condition (Carvalho et al., 2013). The clinical manifestations of ED cause considerable social

problems in individuals affected by the condition (Carvalho et al., 2013). Patients with ectodermal dysplasia rate their quality of life worse than is usually prevalent in the normal population (Hanisch et al., 2019). Currently, long-term data outcome reports based on clinical evidence for conventional implant and bone augmentation procedures and or zygomatic implant interventions in ED patients are very limited.

In the present study, the decision for loading protocol for prosthetic over-structure was discussed by each patient. The primary stability of the ZI was present in all the cases and the choice mostly was based on economic reasons.

CONCLUSIONS

This retrospective clinical case series evaluated the outcomes of the ectodermal dysplasia syndrome patients that underwent zygomatic implant surgery with at least 3 years follow up. Limited outcomes per se were reported. High success rate reported is mostly dependent on the experience of the single surgeon that performed all ZI surgeries. The limitations of the present study include a single center retrospective report with no control groups. Future studies should focus on case-control studies with longer follow up periods and larger groups.

According to the results of this study, zygomatic surgery can be considered as a viable and safe alternative to conventional treatment modalities for oral rehabilitation of ectodermal dysplasia syndrome patients. However, clinicians must be aware that zygomatic implant insertion is a challenging procedure and is not risk free. Highly experienced surgeon with prior special training is crucial for safe procedures and successful outcomes.

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Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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Author Contributions

F.G., E.G., M.D.F., E.G.M. and Fr.G., conceived and designed the analysis. Databases were searched and data was collected by F.G., E.G., and Fr.G. Maxillofacial surgical interventions and zygomatic implant insertions were performed by Fr.G. All the authors contributed on analysis and interpretation of data for the work. F.G. drafted the work and wrote the manuscript with input from all authors. M.D.F., F.G., E.G., E.G.M. and Fr.G. revised the work critically for intellectual content. Integrity of the work was appropriately investigated and resolved by all authors. All authors contributed and approved equally to the final version of the manuscript.

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FIGURE LEGENDS

FIGURE 1: The initial intraoral image of an ectodermal dysplasia patient.

FIGURE 2: The initial panoramic x-ray image of the patient.

FIGURE 3: The post-prosthetic intraoral image of the patient.

FIGURE 4: The panoramic x-ray image of the same ectodermal dysplasia patient 18 months after implant insertion surgery. Note: The conventional implants in the lower jaw of this patient were inserted using the technique of bypass of the inferior alveolar nerve. In this case, the position of the nerve was superficial, situated rather buccally in the mandibular bone and insertion of the implant was possible without damaging the nerve.

FIGURE 5: The intra-oral view of the patient 18 months after implant surgery. Front view.

FIGURE 6: The intra-oral view of the patient 18 months after implant surgery. Occlusal view.

FIGURE 7: The panoramic x-ray image of the patient 26 months after implant surgery.

Table 1: Patient demographics and data regarding the implant success

Patient	Age	Gender	N. ZI	N. CI	ZI location	Total follow up	ZI Survival %	Complications
1	51	F	2	4	16, 26	52	100	None
2	47	F	2	4	16, 26	60	100	None
3	21	F	2	4	16, 26	55	100	None
4	56	F	2	4	16, 26	46	100	None
5	25	M	2	2	16, 26	65	100	None
6	52	M	4	2	16, 26, 13,23	44	100	None
7	27	M	2	2	16, 26	84	100	None
8	23	M	2	3	16, 26	77	100	None
9	29	F	1	4	26	51	100	None

ZI: Zygomatic implant, CI: Conventional implants, N: Number

Table 2: Data regarding the prosthetic treatment

Patient	Loading	Prosthetis type	Antagonist dentition	Prosthesis Survival %	Complications
1	Immediate	toronto (resin)	Implant supported fixed prosthesis	100	None
2	Immediate	toronto (resin)	Natural teeth	100	None
3	Immediate	toronto (resin)	Natural teeth	100	None
4	Immediate	fixed (resin)	Implant-supported fixed prosthesis	100	None
5	Delayed	toronto (resin)	Toronto resin	100	None
6	Delayed	toronto (resin)	Implant-supported fixed prosthesis	100	None
7	Delayed	toronto (resin)	Removable prosthesis	100	None
8	Delayed	toronto (resin)	Implant-supported fixed prosthesis and natural teeth	100	None
9	Delayed	toronto (resin)	Natural teeth-supported fixed prosthesis	100	None

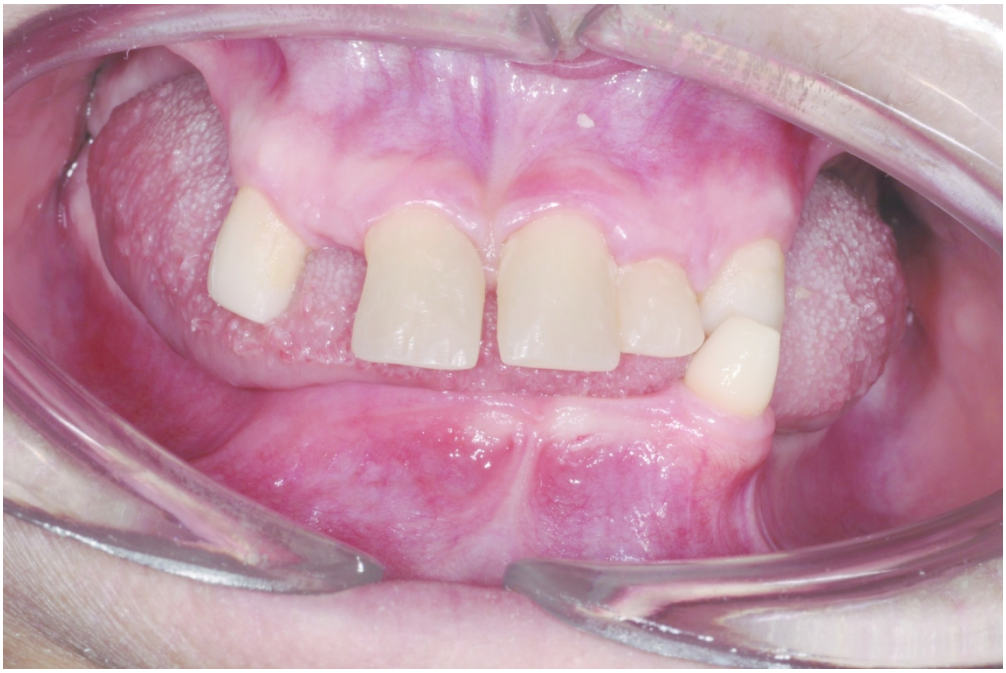

FIGURE 1 The initial intraoral image of an ectodermal dysplasia patient.

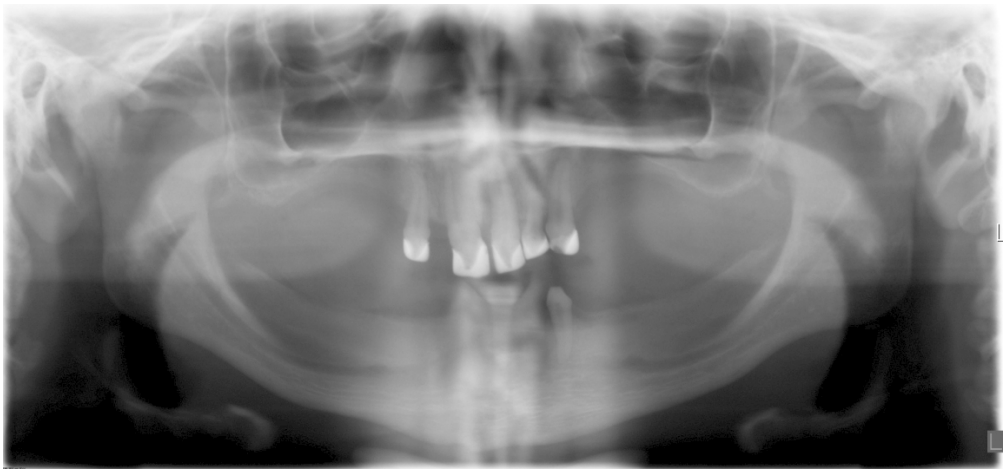

FIGURE 2 The initial panoramic x-ray image of the patient

97x45mm (300 x 300 DPI)

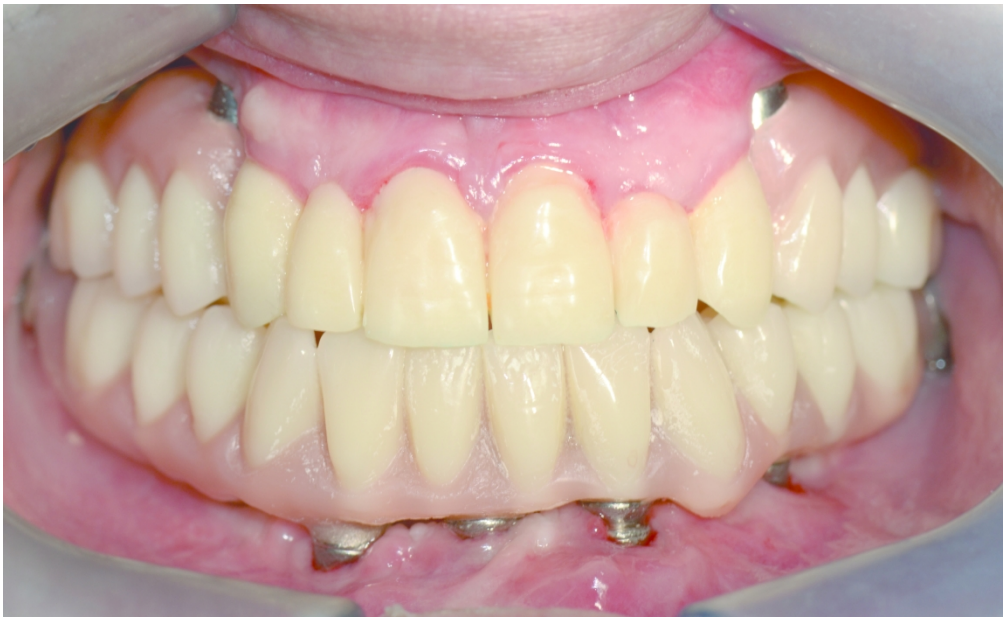

FIGURE 3 The post-prosthetic intraoral image of the patient.

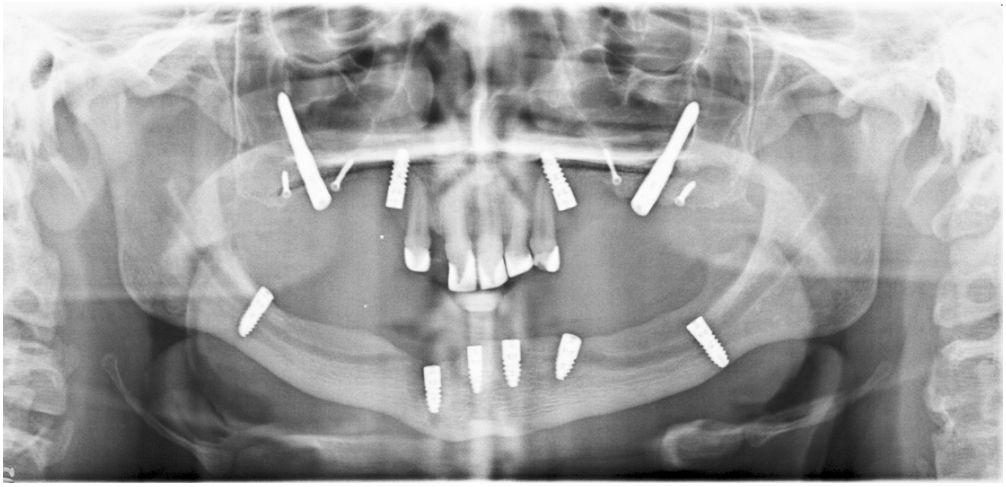

FIGURE 4 The panoramic x-ray image of the same ectodermal dysplasia patient 18 months after implant insertion surgery. Note: The conventional implants in the lower jaw of this patient were inserted using the technique of bypass of the inferior alveolar nerve. In this case, the position of the nerve was superficial, situated rather buccally in the mandibular bone and insertion of the implant was possible without damaging the nerve.

94x45mm (300 x 300 DPI)

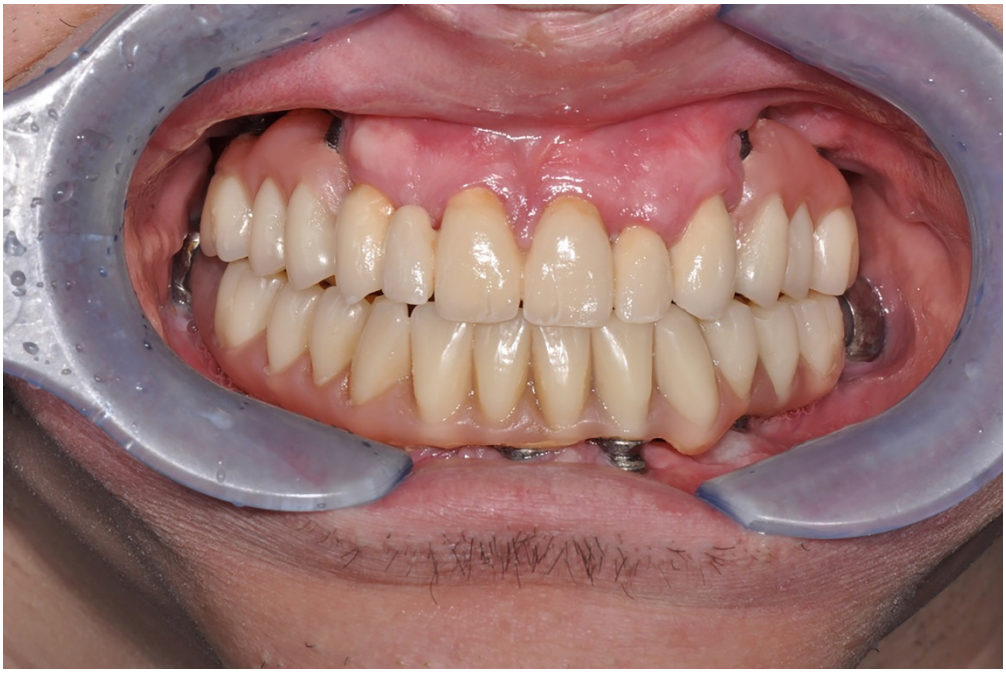

FIGURE 5:- The intra-oral view of the patient 18 months after implant surgery. Front view.

383x255mm (300 x 300 DPI)

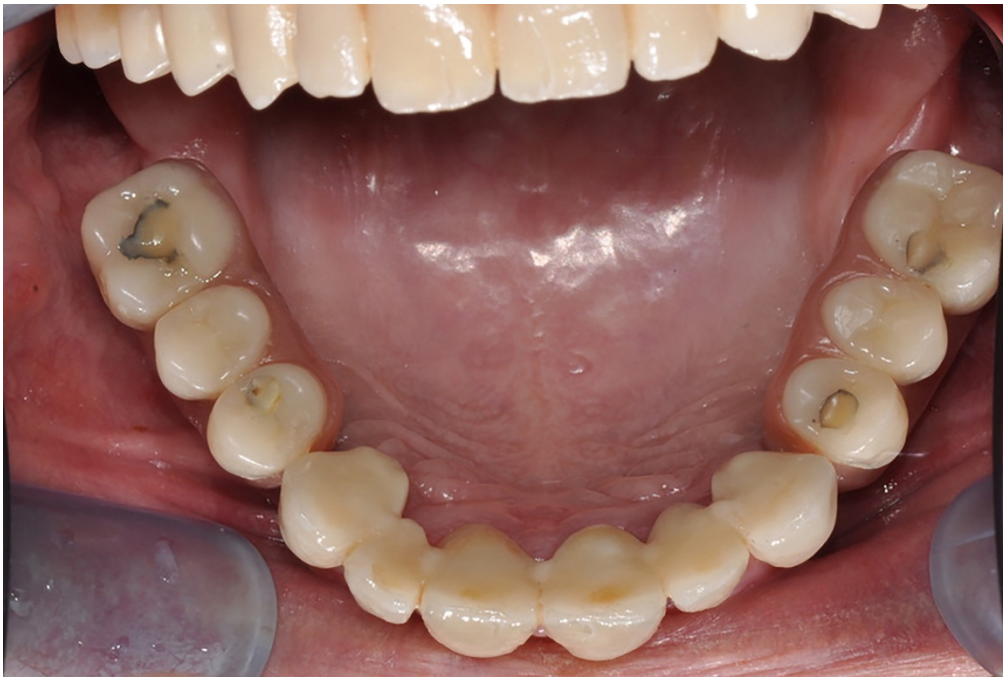

FIGURE 6: The intra-oral view of the patient 18 months after implant surgery. Occlusal view.

272x183mm (300 x 300 DPI)

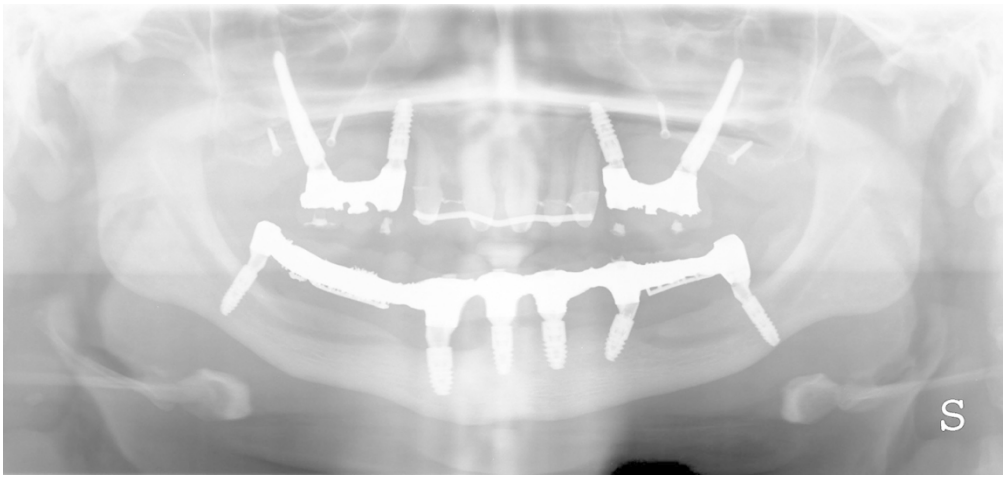

FIGURE 7: The panoramic x-ray image of the patient 26 months after implant surgery.

119x56mm (300 x 300 DPI)

STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study Design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	NA
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	NA
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	5
		Case-control study—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	NA
Study Size	10	Explain how the study size was arrived at	5
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	NA
		Case-control study—If applicable, explain how matching of cases and controls was addressed	NA
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5,8
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	NA
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5,8
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key Results	18	Summarise key results with reference to study objectives	8-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.