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CASE REPORT

Mandibular Defect Reconstruction Using Tissue Engineering: Case Report and Long-Term Follow-Up

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Abstract
Tissue engineering is a new alternative for the treatment of severe mandibular defects,due to its low morbidity and predictability. Specifically, the use of adipose-derived stemcells (ADSc) combined with ceramic substitute like β-TCP. A male patient comesprivate clinic of Rodrigo Fariña, due to slow-growing and asymptomatic right facialasymmetry. The CT shows a unilocular radiolucent area of 6 cm in its longest axis withdefined borders causing rizalysis of adjacent teeth in the right mandibular body.Histopathological examination after incisional biopsy, it´s diagnoses was plexiformunicystic ameloblastoma. Prior to surgical intervention, abdominal adipose tissue wascollected for culture with osteoinductive media, in this case ascorbic acid anddexamethasone co-cultivated with blocks of β-TCP. One months later, the mandibularsegmental resection with a safety edge is performed where, in the same surgical act,the combination of ADSc and the β-TCP is placed on a titanium mesh at the resectionsite. Six months later, a biopsy is performed that corroborates the bone neoformationwhere it is decided to carry out dental rehabilitation on osseointegrated implants. Thecombination of biomaterials in conjunction with ADSc allows an effective therapy, witha good prognosis for the treatment of severe mandibular defects caused by benignneoplasms.

Keywords Scaffolds · Tissue engineering · Ameloblastoma · Adipose-derived stem cells · β-tricalcium phosphate · Case report

Introduction

The efficient reconstruction of mandibular ablative defects resulting from resection, trauma, or nonunion fractures still requires the implantation of bone grafts, to restore main functions such as speech, mastication, deglutition, and esthetics. Adipose stem cells (ASCs) are among the most studied and currently used, these have osteogenic and chondrogenic potential, and they are highly angiogenic tissues [1, 2]. Added to recent advances in tissue engineering (TE) and the application of osteogenic environments based on Sándor et al. [3], technique is proved suitable for applications in mandibular defects.

In this article, the treatment for a plexiform ameloblastoma in a male young patient is presented using TE principles.

Case Report

An 17-year-old male patient was referred to oral and maxillofacial surgery service, presenting facial asymmetry (Fig. 1a). Clinical records did not exhibit any comorbidities or substance use. Intraoral findings demonstrated an edentulous area delimited by 4.6 and 4.8 presenting fluctuating consistency in some sectors with mild painful symptoms (Fig. 1b).

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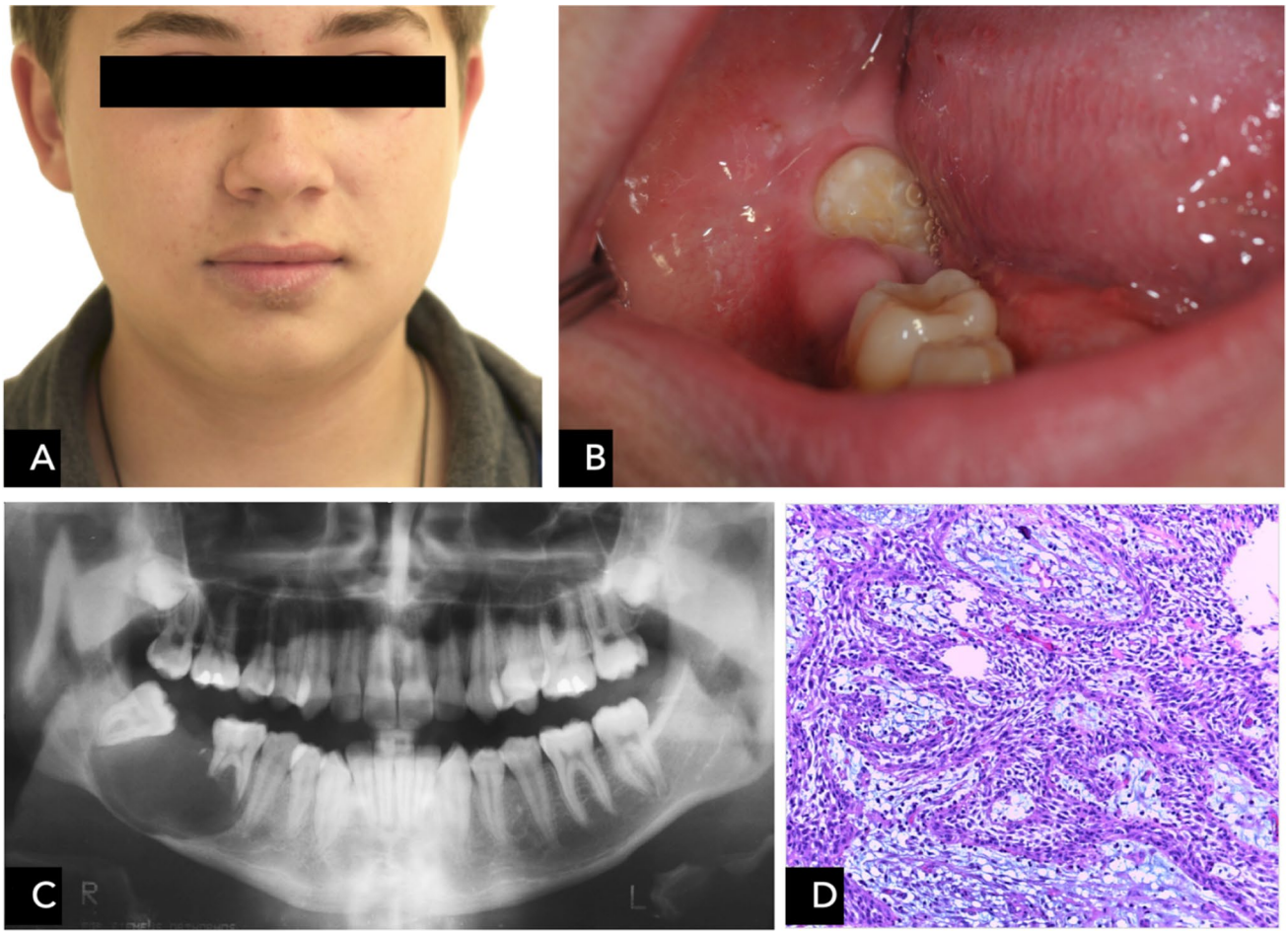

Fig. 1 **a** Frontal image showing slight right facial asymmetry. **b** Intraoral image showing mesioangulated semi-erupted tooth 4.8 with an irregular mesial edentulous area. **c** Panoramic radiography showing a radiolucent area in the right mandibular body with defined limits and edges that generated external root resorption in the roots of tooth 4.6 **d** Histological examination showing long anastomosed cords of odontogenic epithelium surrounded by cells with an ameloblastic appearance

An orthopantomography was requested, revealing an extensive radiolucent area in the right mandibular body, between teeth 4.6 and 4.8 displaced distally, tooth 4.6 with knife-edge external root resorption and mandibular canal displaced caudally. It should be added that there is agenesis of tooth 4.7, possibly caused by an aggressive radiolucent lesion occupying the area thereof (Fig. 1c). Incisional biopsy was performed, confirming the diagnosis of plexiform ameloblastoma (Fig. 1d). Based on Sandor's method [3] for treating severe mandibular defects, TE modality combining ASCs was carried out. Six weeks prior to resection surgery, dental extraction of teeth 4.5–4.6 and 4.8 using the protocol established by Fariña et al. [4], (Fig. 2a–c).

Three weeks prior to the mandibular resection, 200 mL of subcutaneous adipose tissue (AT) was harvested from the anterior abdominal wall for ex vivo tissue culturing (Fig. 3a–c) and future autologous reimplantation. Once cell confluence was achieved, approximately 25 million cells were combined with β-TCP granules (Fig. 4a–c).

A stereolithographic mandibular biomodel was created prior to the resective surgery to assess the defect's location and size. A patient-specific reconstruction plate, titanium mesh, and cutting guides were pre-bent and designed according to the planned safety margins [5].

Under general anesthesia via submandibular approach, a 5-cm-long lesion was exposed, which was resected through a segmental osteotomy, defining safety margins 1 cm distally and medially from the lesion (Fig. 5a–d). The inferior alveolar nerve was preserved using the pull-through technique described by Ishikawa et al. [6, 7], and then end-to-end neurorrhaphy was performed on the trunk of the mental nerve, ensuring preservation of the patient's lower lip sensitivity. (Fig. 5e, f).

The defect was covered by a titanium mesh and the reconstruction plate filled with β-TCP and ASCs (Fig. 6a–c). The

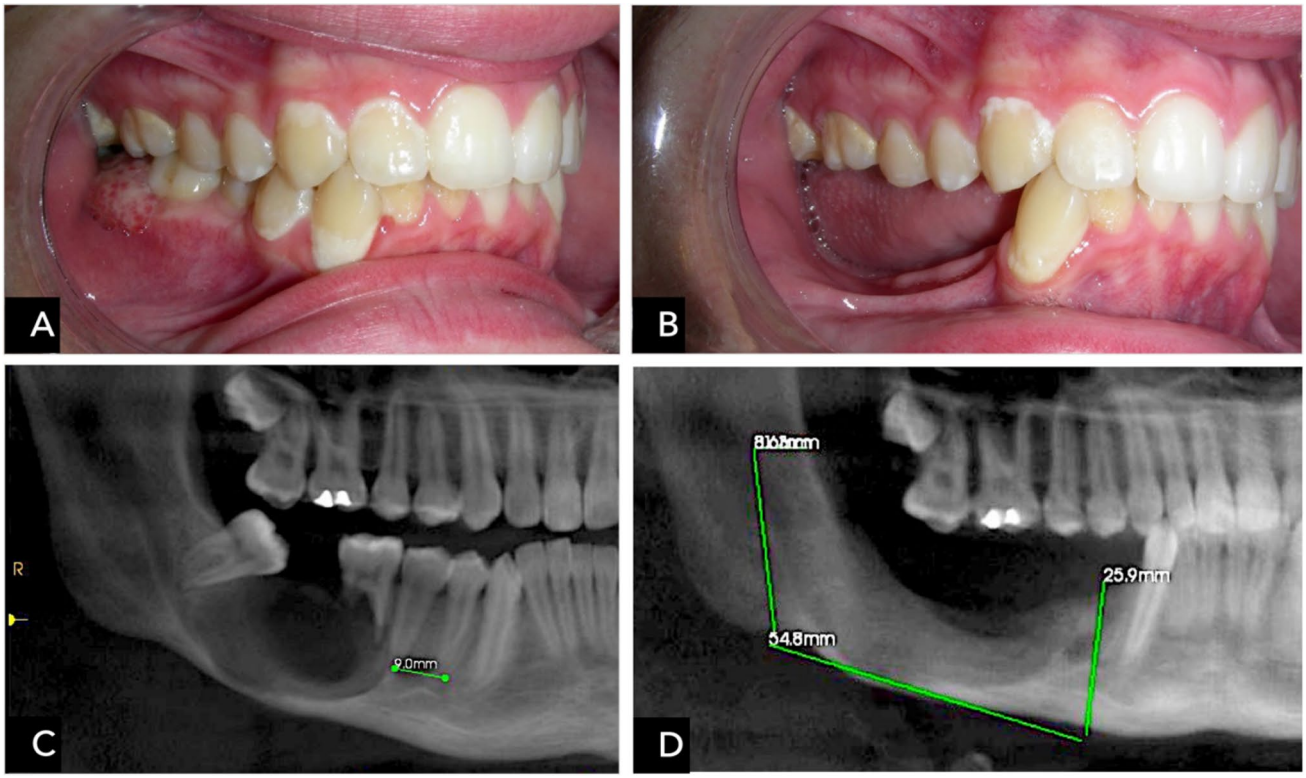

Fig. 2 **a** Intraoral image where the bulging of the vestibular bone is observed**. b** Lateral occlusal view 6 months after teeth extraction, observing complete soft tissue healing. **c** Preoperative orthopantomography prior teeth extraction (**d**). Surgical planning on CBCT contemplating 1-cm-margin resection

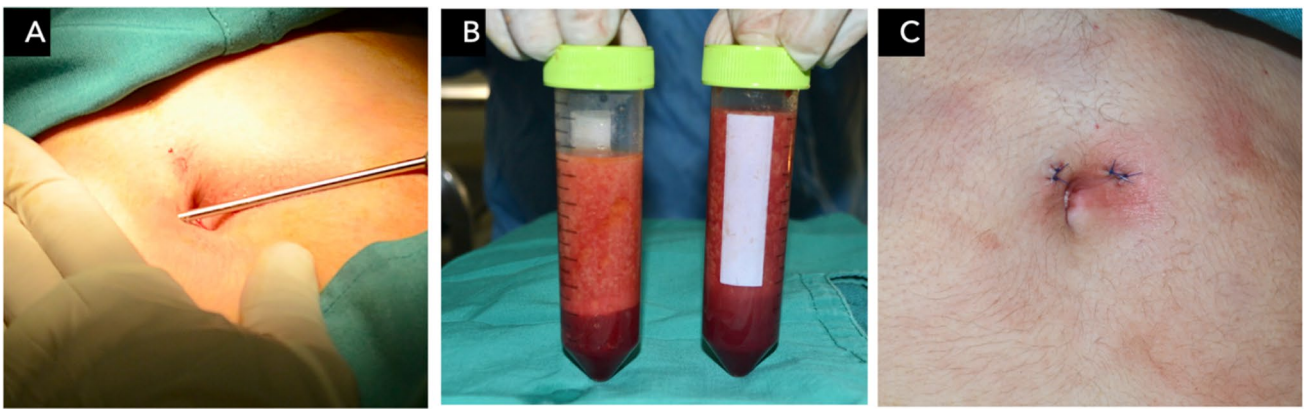

Fig. 3 **a** Periumbilical abdominal liposuction. **b** Collection of adipose tissue. **c** One-week postoperative control observing complete cutaneous closure

postoperative period concluded uneventfully with complete skin closure. Since no donor site was required, the intraoperative time was significantly reduced to 90 min, resulting in lower morbidity and allowing for early hospital discharge.

Twelve months after mandibular reconstruction, facial symmetry and stable occlusion were achieved (Fig. 7a–c), CT scan showed graft stability with a regular radiopaque area in the right mandibular body (Fig. 7d). A SPECT scintigram was requested to evaluate the viability and bone metabolism of the reconstructed site to define the appropriate time for the installation of dental implants (Fig. 8a). With a positive bone metabolism scintigram, the implants were installed, in which a biopsy was performed with a trephine drill of the reconstructed site for deferred histopathological

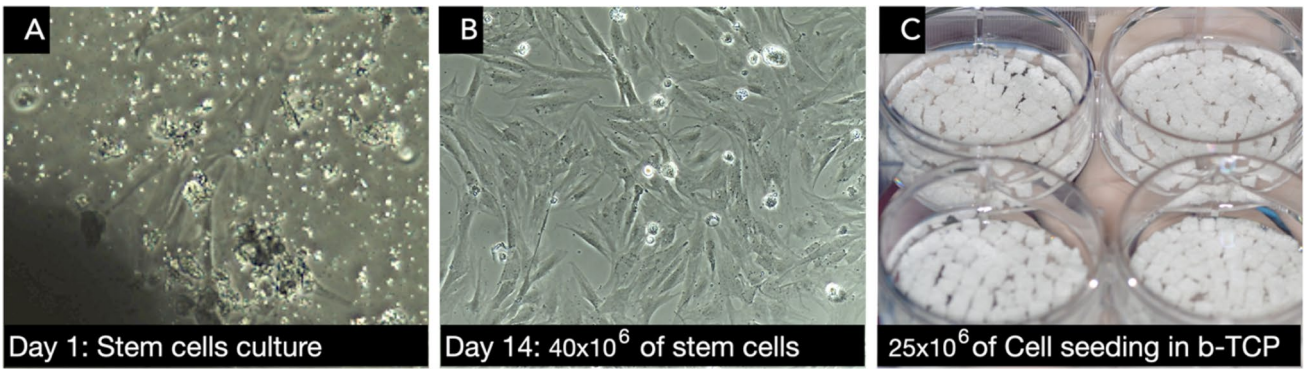

Fig. 4 **a** Day 1: Primary cell culture of adipose stem cells. **b** Day 14: Confluence of 40 million prolonged adipose stem cells. **c** Cell co-culture of adipose stem cells and b-tcp as a cell scaffolding

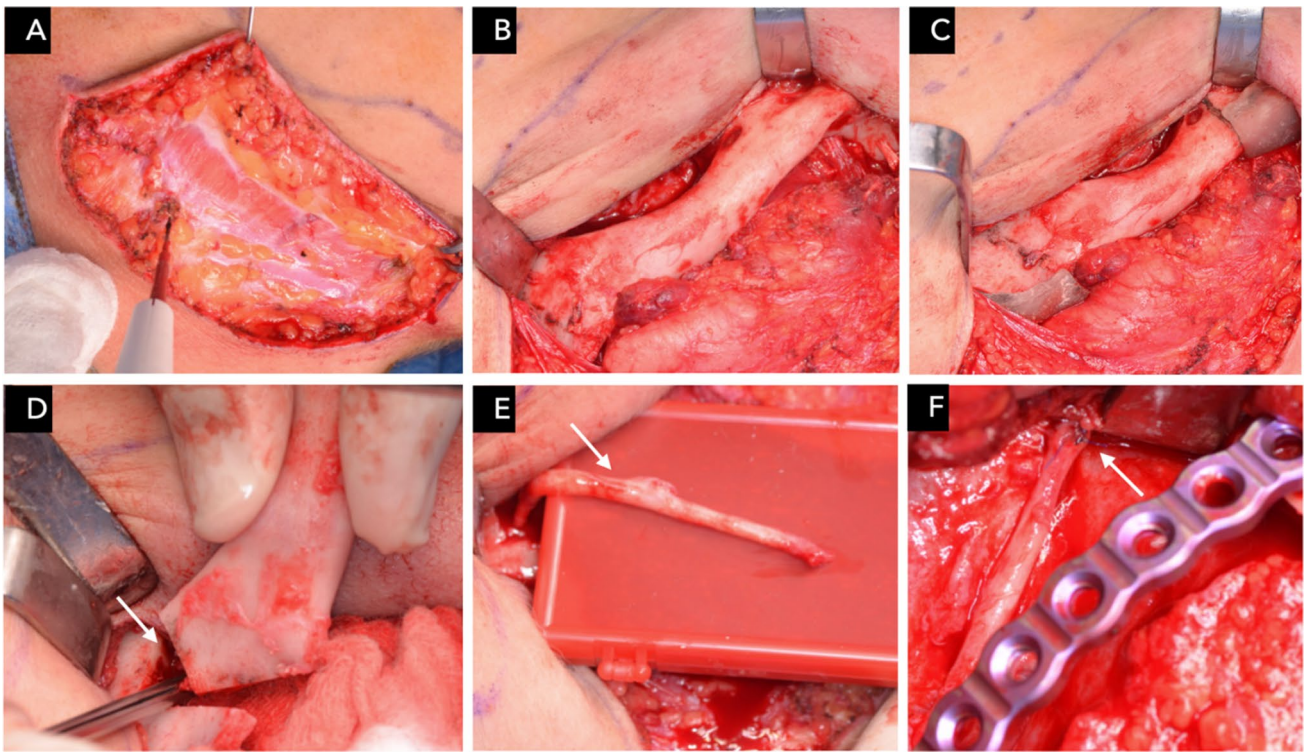

Fig. 5 **a** Submandibular approach. **b** Exposure of affected mandibular site. **c** Placement of surgical cutting guide (Fariña´s Splint) **d** After distal osteotomy, proximal osteotomy is performed where inferior alveolar nerve is preserved through pull-through technique. **e** Exposure of proximal end of inferior alveolar nerve. **f** White arrow depicts terminal-terminal neurorrhaphy between alveolar and mental nerves, with overlying healthy soft tissue

study and to check the type of newly formed bone (Fig. 8b). The histopathological study shows formation of mature and vital lamellar bone tissue at the reconstructed site. (Fig. 8c, d).

Three Zimmer TSV 3.7 × 11.5 mm dental implants were installed. Six months later, definitive dental crowns were installed. To date, after long-term follow-up (9 years), the clinical, functional, and aesthetic results have not presented any problems, the bone stabilized and ossified adequately allowing the installation of dental implants with a long-term follow-up without surgical or prosthetic complications (Fig. 9a–c). The patient's outlook to date is satisfactory; he reports that he can lead a life without problems with eating, self-esteem or complications related to surgery and therapy.

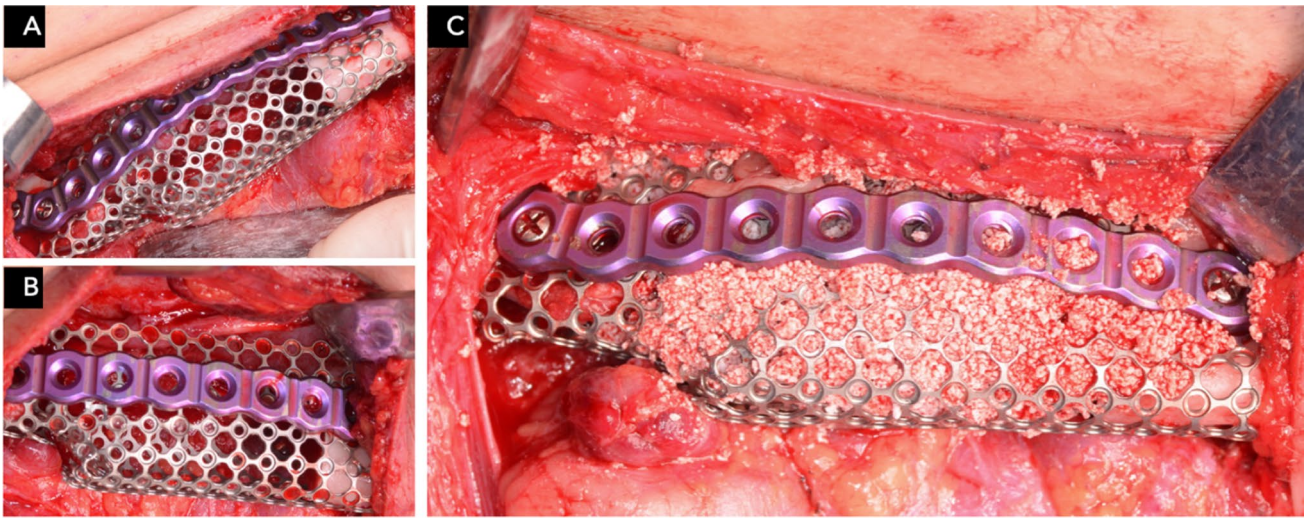

Fig. 6 **a** Intraoperative view of mesh and osteosynthesis plate previously molded from a stereolithographic model. **b** Basket-like receptacle of titanium mesh for further graft. **c** Deposition of β-TCP and ASC granules onto titanium mesh

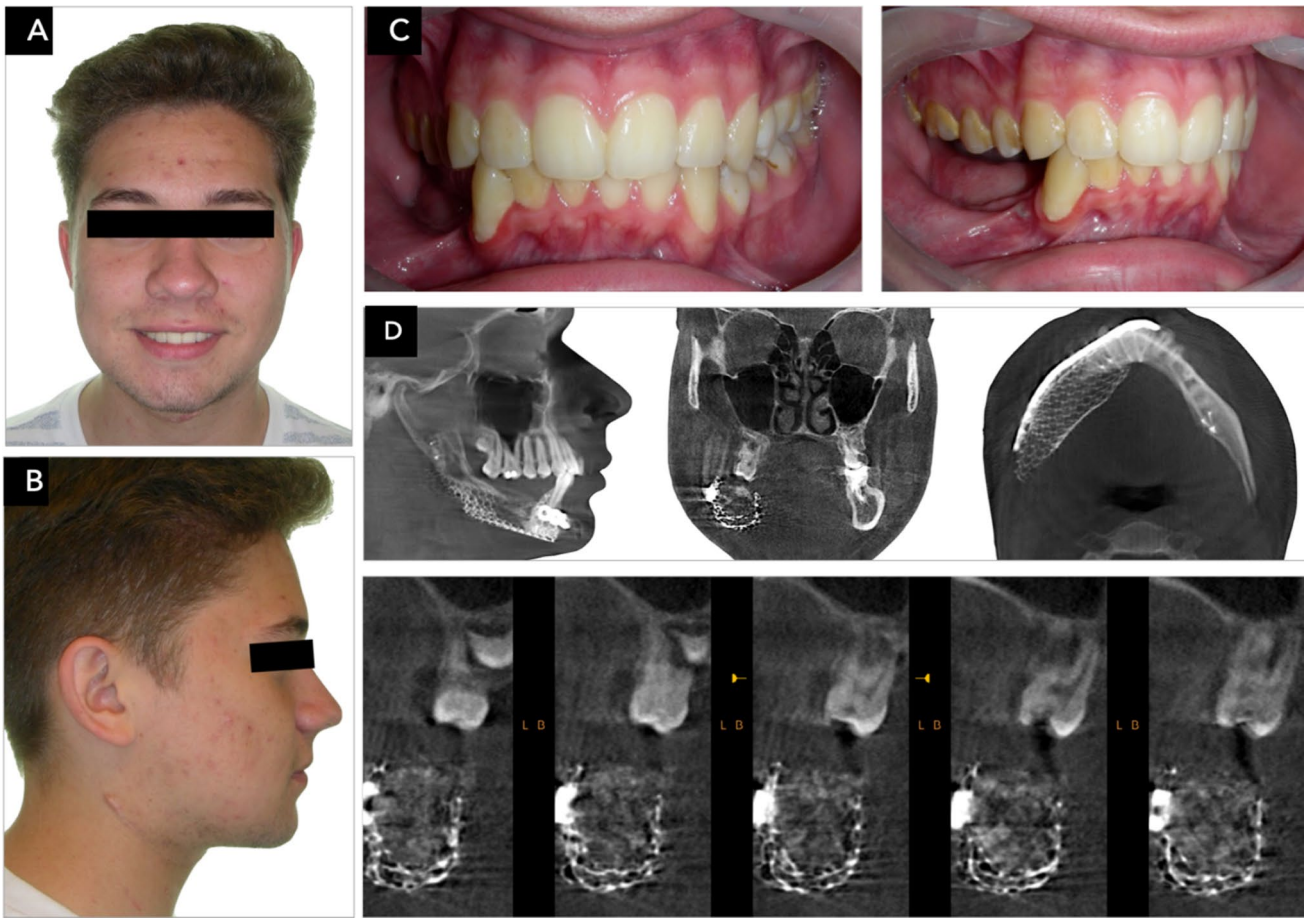

Fig. 7 One-year follow-up after mandibular reconstruction and inferior alveolar nerve preservation. **a**, **b** Facial view and intraoral views **c** exhibit an edentulous area with no additional complications. **d** Postoperative computed tomography exhibits graft integration and evidence of bone neoformation

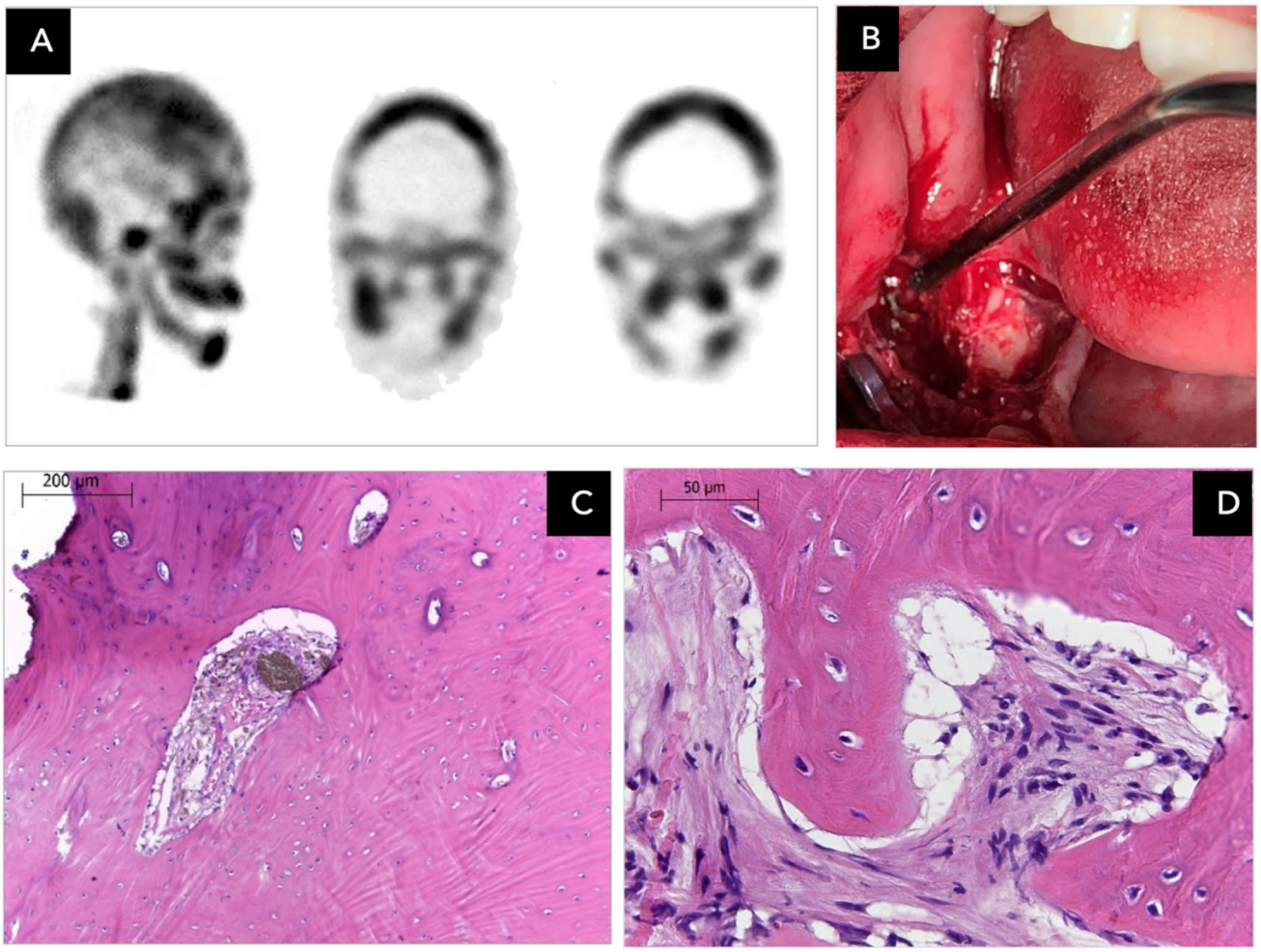

Fig. 8 **a** Bone scintigraphy 18-month postoperative where right mandibular uptake is observed suggestive of active cellular metabolism. **b** Intraoral biopsy of the right mandibular body. **c**, **d** Histological view of bone tissue where mature lamellar bone is observed

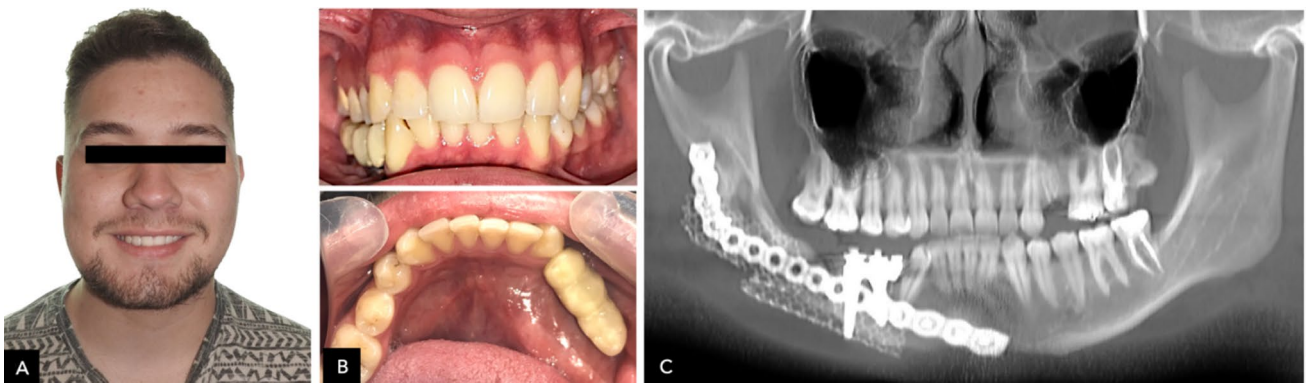

Fig. 9 Five-year postoperative follow-up of the patient. **a** Facial view, **b** intraoral images, with proper occlusion, **c** 5-year post-surgery follow-up cone beam CT with dental implants in bone regenerated with TE. No further complications

Discussion

The most frequent mandibular reconstruction technique is a free fibula flap surgery, and Iliac bone graft with good results; however, morbidity of the donor site can lead to functional consequences afterward, implying challenges from both medical and dental standpoints [1–9]. A comparison between fibula free flap and TE is presented in Table 1. TE stands as an alternative approach, where an ideal scaffold for bone reconstruction should combine desirable biological and structural characteristics to restore complex tridimensional defects [4, 10]. In recent years, β-TCP has been regarded as one of the most appraised bone graft substitutes, due to its modulable porosity facilitating graft vascularization, successfully leading to cell growth, differentiation and tissue regeneration [3, 12].

Regarding ASCs, these are multipotent cells with high potential for osteogenic and chondrogenic differentiation in vitro [9]. This could imply possible benefits for regenerating tissues involved in large defects or those with compromised healing capacity, increasing vitality and oxygen supply of the custom-made scaffolds [1–3]. Therefore, combining the homing capacity of the ASCs and the osteoconductivity of the β-TCP, it can have both agents acting synergistically toward producing a well-ossified construct [12, 13].

Dexamethasone and ascorbic acid acts as a cofactor essential for the normal formation of bone [10]. Different growth factors have been described in TE applied to mandibular defects as platelet rich plasma and fibrin have been successfully used, praising both for their accessibility, and the latter for its physiologic rate of growth factor liberation. Another widely accepted growth factor corresponds to bone morphogenetic proteins (BMPs) exhibiting remarkable results when combined with allografts and xenografts. However, significant costs associated with BMPs must be kept in mind [8].

In recent years, β-TCP has emerged as one of the most attractive bone graft substitutes, its modulable porosity facilitates graft vascularization. Thus, cell growth, differentiation and tissue regeneration are easily achieved [3, 12]. Undoubtedly, the homing capacity of the ASCs and the osteoconductivity of the β-TCP act synergistically toward producing a well-ossified construct [12, 13].

Environmental factors such as oxygen levels, nutrient supply, and growth factors can affect the success of TE complemented with ASCs. In addition, the use of growth factors such as dexamethasone and ascorbic acid as cofactors proves essential for the normal formation of bone [12]. Different growth factors have been described in TE applied to mandibular defects. Platelet-rich plasma and fibrin have been successfully used, praised for their accessibility and

Table 1 Comparison between tissue engineering and fibula free flap in mandibular reconstruction

Therapy	Brief technique description	Advantages	Disadvantages	Morbidity	Cost
Tissue engineering	Creation of functional tissues/organs using cells, scaffolds, and bioactive molecules. Requires adequate soft tissue coverage	Customized tissue constructions: potential to repair cartilage and bone	Complex biological processes, contraindicated when radiotherapy is to be performed	Significantly less donor site morbidity; eliminates need for autologous bone graft harvesting. Use of stem cells from autologous fat, with a very low morbidity	Lower cost compared to fibula flap procedures
Fibula flap	Reconstruct bone and soft tissue in the maxillofacial region using autologous tissue	Reliable source of vascularized bone and soft tissue Can be used when radiotherapy is necessary	High donor site morbidity, including lower limb functional impairment, sensory alterations, and gait disturbances	Significant morbidity associated with bone harvesting; requires secondary surgical site and prolonged operative/anesthetic time	Higher cost due to additional extensive surgical procedures, hospitalization, and postoperative care

physiologic rate of growth factor liberation. Another widely accepted growth factor corresponds to bone morphogenetic proteins (BMPs) exhibiting remarkable results when combined with allografts and xenografts. However, significant costs associated with BMPs must be considered [8]. TE stands as a modality which presents significant advantages. Since it allows the regeneration of extensive areas of damaged tissue. In the maxillofacial territory, successful outcomes have been reported regarding the treatment of both bone and soft tissue defects caused by trauma or ablative surgery.

However, there are also disadvantages, such as requiring more preoperative preparation time since adipose tissue must be obtained, ASCs must be processed and prepared, and the culture must be performed on the bone substitute, compared to other approaches. However, it allows for a surgical intervention with shorter operating times and lower postoperative morbidity.

Specifically, stem cell-based tissue engineering requires specialized equipment and a center for the preparation of cultures, which represents an additional cost, which can be high if other growth factors are added. However, these costs are minimized by a shorter hospital stay and lower surgical morbidity. There is also some uncertainty as it is an emerging therapy that may have a certain degree of risk in malignant pathology or that extensive involves the surrounding soft tissue, due to the growth factors used and the eventual requirement for radiotherapy, which is why it is absolutely contraindicated in this type of pathology. It has been shown through in vitro and animal studies that ASCs can interact with tumor cells and induce tumor proliferation [3, 12, 14]. On the other hand, a risk of disease transmission from the source materials used in tissue engineering has been described, so we prefer to use autologous materials and allografts to avoid this. It should be noted that proper patient selection is crucial for an optimal result, and we consider important factors such as age, nutritional status of the patient and their bone biological response capacity and above all absence of communication to the oral environment to avoid contamination and eventual loss of the injector.

To date, multiple therapies associated with tissue engineering have shown a good evolution and prognosis, weighed the advantages and attenuating the possibility of risks [15]. To conclude, the successful outcome of this clinical case opens the way for future clinical trials using β-TCP-based ASC grafts without the need for biological factors as an alternative for the reconstruction of craniofacial bone defects, presenting a valid alternative method with satisfactory results, presenting lower donor site morbidity, lower healthcare costs involved and compared to other techniques described in ablative craniofacial surgery.

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Declarations

Competing interest The authors report no conflicts of interest.

Ethical Approval An exemption statement was obtained from the ethics board.

Patient Consent Written consent was obtained for treatment and publication.

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