CASE REPORT

Suspicions of titanium allergic reaction influencing the prosthetic solution in a rare case of implant “flowering”

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Abstract
The aim of this paper is to eliminate suspicions of a titanium (Ti) allergy in a rare case of “flowered” implant in a 43-year-old female patient with metal allergies and no history of bruxism, using a histological and immunohistochemical (IHC) analysis to determine the phenotype of cells that participated in the immune response; also, to assess the prognosis of a future implant treatment and to highlight the psychological impact of osseointegrated implant failure caused by fracture, and the influence that the necessity to use extensive surgical procedures for reimplantation can have on the treatment solution chosen by the patient. The results of our IHC analysis did not indicate a clear response for a potential Ti allergy; still, due to psychological reasons, the patient rejected the replantation and considered the use of other restorative option, a three-unit bridge, as being the most appropriate for her. Considering her opinion and attitude, the fixed prosthetic denture assured the therapeutic success.

Keywords: titanium allergy, implant fracture, implant removal, prosthetic solution.

Introduction
There is a daily exposure of patients to titanium (Ti) since it is used in a lot of products, such as tooth-paste, pharmaceuticals, plastics, cosmetics, jewelry, food, paints and medicine, including dental surgery; still, the evidence of its possible toxic effects is scarce, due to the lack of specific diagnostic tests. Dental implants are made of pure Ti and its alloys and it has a favorable bio-response due to the restricted ion release, stability of the alloys and restricted bio-effects of the ions [1]. Still, some authors recommend to avoid using fluorides in the presence of Ti dental implants due to the release of the Ti ions [2]. Although Ti has an excellent biocompatibility, the surface of implants made of pure Ti and its alloys release Ti ions that sometimes reach remote tissues (lungs, lymph nodes) [1, 3]. Some authors found that trace elements in Ti alloys can be responsible for an allergic reaction in an already sensitized patient [4]. Other authors reported a case of allergic contact stomatitis due to the Ti-nitride coating on dental implant abutments; it was completely resolved once the implants were replaced with commercially pure titanium (CpTi) abutments [5]. Du Preez et al. describe a clinically relevant hypersensitivity reaction to Ti dental implants in a case of a 49-year-old female, which experienced a chronic inflammatory response, as well as foreign body giant cell reaction, to the insertion of six Ti-4Al-6V mandibular implants [3].

Implant-related allergic reactions are typically associated with immediate type I or most frequently type IV delayed-type hypersensitivity; studies in literature show that they may be hold responsible for some cases of implant failures [6]. Some authors suggest an allergy evaluation for Ti in patients having antecedents of allergy to other metals and point that corrosion of Ti may appear in the proximity of other metals such as amalgam, gold alloy, or chromium–cobalt alloys, and also in cases of lower pH phenomenon in a peri-implantitis region, or implant facing extreme mechanical forces. Inflammatory reactions in the surrounding tissues can be caused by Ti ions or microparticles of Ti released in the area of periodontal tissue adjacent to the implant [6, 7].

Dental implants are nowadays considered an optimal solution for the rehabilitation of missing single teeth in partially edentulous patients, having high success rates due to good results in function, esthetic and comfort. The success rate is estimated by Pjetursson et al. at 94.5% [8], and by Jung et al. at 97.6% for the first mandibular molar and at 92.9% for the second mandibular molar [9]. In a study made in 2017, by de Almeida et al., including 35 implants placed in 19 patients (six men and 13 women), there are no differences in success rates depending on the implant position [10]. Implant treatment is considered a first option in single edentulous spaces mostly because it conserves the adjacent teeth [11–14].
Complications and failures, such as loss of osseointegration, peri-implantitis, fracture of the implant or of the components, wrong implant positions [15, 16], occur either in early stages, due to surgical factors during placement, or in later ones, in the prosthetic phase of the treatment, usually implying biomechanical factors [17]. Over time, the clinical crown-to-implant ratio increases with marginal bone loss; therefore, the implant will suffer a greater biomechanical load.

Implant fracture is rare, and not always fully understood; data in the literature are scarce. Implant fracture in female patients is even rarer; in a meta-analysis performed by Pommer et al. (2014), the value was 30.5% of all cases included [18]. Regarding the age of our patient, same study mentions 20.6% fractures in patients between 40 and 49 years old [18]. Causes of implant fracture can range from manufacturing to iatrogenic or patient-related factors. However, this is a serious complication and, since the number of placed implants increased dramatically, it is expected that the number of failures also grow. The optimal solution in implant fracture cases is to remove the fractured implant with as little bone damage as possible and to insert another one in the same place, immediately or in a later stage, followed by another prosthetic restoration.

The explantation techniques offer a variety of choices, from the use of thin burs or the trephine drills at low speed under saline solutions cooling, electrosurgery techniques, laser techniques or removal torque procedures. If the origin of the implant is known, the high reverse torque unscrewing technique is most commonly used; specially designed instruments or kits are needed, that contain the screw that is used to engage the implant and the high torque dynamometric ratchet used to unswind the implant. For implants of unknown origin, as in our case, the choice at hand is to use a trephine drill. This drill must have a diameter and a length suited to the size of the implant that has to be removed. The trephine drill technique is simple to use, but unpredictable; it is very important to follow the implant axis, to avoid the distortion of the drill and the implant and also to avoid removing a larger than necessary quantity of bone. A common side effect of this technique is that the amount of bone removed with the implant is unpredictable. Also, the wound could be contaminated with metal particles [19].

In oral rehabilitation process, one of the most important goals is obtaining patient satisfaction [20]. The psychological consequences of implant removal are an important factor to be considered in the implant-prosthetic therapy. Such cases can be difficult to manage, as patients are disappointed of the low result of a treatment advertised in mass media as state of the art and thus creating high expectations. Besides the patient’s frustration in obtaining the expected satisfactory function and esthetics, replantation involves additional surgical and non-surgical procedures and, most frequently, higher costs and as a consequence requires greater motivation. Additional suspicions of Ti allergy are making this entire procedure worthless for our patient so she requested a test to verify this issue.

The aim of the histological and immunohistochemical (IHC) analysis in this rare case of “flowered” implant was to determine the phenotype of cells that participated in the immune response, in order to identify a possible Ti allergy and to assess the prognosis of a future implant treatment. This case highlights the psychological impact of osseointegrated implant failure caused by fracture, and the influence that the suspicion of Ti allergy and the necessity to use extensive surgical procedures for reimplantation can have on the treatment solution chosen by the patient.

Case presentation

A 43-year-old female patient, with no history of bruxism and a history of metal allergies, came to our Office complaining of a “loose crown” on an implant located in a mandibular single edentulous space (tooth number 36). The implant was inserted in another Clinic, approximately one and a half years before, and a crown was made for it in a later stage. After wearing this crown for a few months, the patient went back to the above-mentioned Clinic because the crown had a movement and she could not chew on the left part; she did not know that the implant was “flowered” and that it could not properly hold an abutment. The crown suffered repeated cementations; then, a healing abutment was placed and she came to our Office for a second opinion the next day after it was loosened again, presenting an area of gingival hyperplasia surrounding the transmucosal portion of the implant. Due to the hyperplastic gingivitis associated with an angular cheilitis and having a history of allergies to metals and jewelry, she wanted to be sure that she was not allergic to Ti before she could decide what treatment option is best for her in the future. Considering that poor hygiene was not a possible cause for hyperplasia in her case, other factors, such as lack of attached gingival tissues caused by the permanent movement of the crown or of the healing cap, and also a possible Ti allergy have been considered.

At the clinical examination, we noticed the horizontal movement of the crown, but no movement in the vertical plane. On the periapical and panoramic radiographs, the neck of the implant appeared to be fractured distally (Figure 1a and b). We informed the patient that the only viable solution in this case is to remove the implant, since the incomplete fixture will be unable to hold any abutment anymore. Because the implant was placed only a short time ago and she felt that she did not practically had the chance to use it, she did not accept our plan and she wanted to go back to the first Clinic for a conservative prosthetic solution; a second crown was made there for a short time ago and she felt that she still could not chew on the left side and disappointed because of the failure of this second prosthetic treatment, she came back to our Clinic and asked again for a conservative solution; our opinion to remove the implant was then sustained by the cone-beam computed tomography (CBCT) examination (Figure 2a and b). The patient was shown the three-dimensional (3D) models and cross-sectional views of the area, highlighting the missing distal part of the implant. At that moment, she accepted the loss of the initial treatment and signed the informed consent for removing...
the implant. The healing abutment was lifted; it was almost completely unscrewed. The aspect of mucosa showed redness and swelling (Figure 3a) and she wanted to know if the failure of the implant can be caused by a potential Ti allergy, which could influence the future treatment solutions.

**Figure 1** – (a–c) Panoramic and retro-alveolar radiography at presentation offering a detailed image of the bone resorption and the fractured implant; the second healing abutment in place.

**Figure 2** – (a and b) The CBCT images: 3D models and cross-sectional views of the area, highlighting the missing distal part of the implant. CBCT: Cone-beam computed tomography; 3D: Three dimensional.

**Figure 3** – (a) The aspect of mucosa after the healing abutment was lifted; (b) Epithelial aspect of an abundant chronic infiltrate in the gingival chorion (HE staining, ×200); (c) Vascular congestion (GStricrome staining, ×200).

**Materials and methods of the histological and IHC study**

We took an injured sample of gingival mucosa in the immediate surrounding area of the fractured implant. The dimensions of the sample were 1.8 mm in thickness and 4 mm in height. It was immediately fixed in 10% formalin solution and accordingly embedded in paraffin, using the standard protocol of histopathology. The sample of gingival mucosa was examined from the histological and IHC point of view at the Research Center for Microscopic Morphology and Immunology, University
and were left in the thermostat at 37°C for 24 hours. In slides that had the surface covered with poly-L-lysine Eosin (HE) and Goldner–Szekely (GS) trichrome. For could be associated with allergenic potential of Ti. Local inflammatory markers (CD3 and CD68), findings that logical and IHC analysis highlighted the presence of small number of B-lymphocytes (Figure 4c). Our histo-

periodontium, the microscopic image showed a relatively granular (Figure 4b). At the level of superficial injured phagocytosis process, their cytoplasm was vacuolar and (Figure 4a). Macrophages were numerous; due to the immunoreaction of cellular type was quick and intense (Figure 4a). Macrophages were numerous; due to the phagocytosis process, their cytoplasm was vacuolar and granular (Figure 4b). At the level of superficial injured periodontium, the microscopic image showed a relatively small number of B-lymphocytes (Figure 4c). Our histo-

logical and IHC analysis highlighted the presence of inflammatory markers (CD3 and CD68), findings that could be associated with allergenic potential of Ti. Local presence of abundant T-lymphocytes and macrophages could indicate sensitivity to Ti, but the presence of the B-lymphocytes, although in a small quantity, could also show a strong defense response against local bacterial aggression as a consequence of the local trauma.

The patient was explained that, considering the amount of vertical bone loss in the area both before and after the subsequent explantation, placing another implant in the same site would involve guided bone regeneration and/or bone grafting procedures, depending on the severity of bone atrophy. We also informed her that, while useful in improving the periodontal condition of the second premolar and molar, these extensive surgical procedures, considered simultaneously or prior to implant placement, involved supplementary costs, a longer period of time (four to eight months) until the subsequent prosthetic treatment can be effective and also risks such as bone graft failure, lack of osseointegration, marginal bone loss, peri-implantitis, etc. Because she was still disappointed, frustrated and fearful, considering also the results of the histological and IHC study which can be correlated with the allergenic potential of the Ti, the patient did not want to place another implant immediately, preferring to have the explantation procedure first, then to wait for the healing and reevaluate afterwards, at a later stage, the opportunity of replacing the lost implant with a new one at the same site.

Since the fixture was split, there was no possibility of firmly fitting the guiding cylinder. Also, for the same reason, since the implant was completely immobile and perfectly osseointegrated, it could not be removed using reverse torque techniques. A trephine drill remover used to explant failing implants of unknown origin was chosen accordingly to the diameter and length of the implant. After flapping (Figure 5a), the fracture of the neck became evident in the distal area. The drill was positioned around the outside diameter of the implant and slowly lowered down more than half way, trying to cause as little bone damage as possible. The trephine drill was positioned over the implant and into the bone using a low speed 50–80 rpm of drilling with a light pressure and a running saline cooling. The outside rings on the drill helped us to control the exact depth. The implant was still firm after the trephine drill had been lifted, so the drilling depth was insufficient. We used an elevator placed into the gap and lightly twisted it to brake the bony connections in order to remove the implant (Figure 5, b and c).

A retro-alveolar radiography was indicated after the procedure to be sure that all the pieces were removed and that no damage was done to the adjacent teeth; the healing was good, without any complications (Figure 6, a and b). After four months, we discussed again with the patient the treatment options; she wanted to be sure that, after the healing, the bone augmentation is still needed. Our opinion was that it was impossible to obtain an adequate quantity of bone otherwise, and a second CBCT examination sustained it (Figure 7, a and b), revealing the amount of vertical bone loss and the status of the adjacent teeth.

Results of the histological and IHC study

The samples were histologically examined and showed the existence of a chronic infiltrate in the gingival chorion and also areas of necrosis and vascular congestion (Figure 3, b and c). In the IHC study, we remarked the presence of a great number of CD3+ T-lymphocytes in the injured gingival mucosa; we concluded that the immunoreaction of cellular type was quick and intense (Figure 4a). Macrophages were numerous; due to the phagocytosis process, their cytoplasm was vacuolar and granular (Figure 4b). At the level of superficial injured periodontium, the microscopic image showed a relatively small number of B-lymphocytes (Immunostaining with anti-CD20 antibody, ×200). Our histo-

logical and IHC analysis highlighted the presence of inflammatory markers (CD3 and CD68), findings that could be associated with allergenic potential of Ti. Local presence of abundant T-lymphocytes and macrophages could indicate sensitivity to Ti, but the presence of the B-lymphocytes, although in a small quantity, could also show a strong defense response against local bacterial aggression as a consequence of the local trauma.

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![Figure 4](image-url)
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Figure 5 – (a) Intraoperative view of the fracture area after the reflection of mucoperiosteal flap; (b) Close-up view of the trephine drill, the implant and the amount of bone that was removed; (c) Intraoperative view of the cortical bone after the removal of the implant.

Figure 6 – (a) Retro-alveolar radiography showing no damage was done to the adjacent teeth; (b) Occlusal view of the area.

Figure 7 – (a and b) The second CBCT images, 3D models and cross-sectional views of the area, highlighting the amount of bone loss. CBCT: Cone-beam computed tomography; 3D: Three dimensional.

For psychological reasons, the solution to replace the fractured implant with another one in this situation was not acceptable for the patient. She felt unable to undergo another uncomfortable procedure, considered by her as being stressful, painful, time-consuming and adding a great deal of expense to an already expensive procedure; in this situation, she absolutely did not want to replace the explanted implant with a new one at the same site, and opted for a three-unit bridge (Figure 8, a and b), considering even the preparation of the intact teeth as a
more acceptable alternative. We made a metal–ceramic bridge on the abutment teeth 35 and 37, taking care to keep intact their pulp, trying to ensure as much as possible their longevity. This treatment was more suitable for her because it was faster, less stressful and it offered more predictability and lower additional costs.

Figure 8 – (a) Occlusal view of the fixed prosthetic restoration; (b) Final view of the restoration.

Discussions

In most cases, the implant failure has been reported as being most probably caused by a fabrication error or by overloading; still, studies show that Ti can determine hypersensitivity in some patients and also can have a role in implant failure [21]. Ti is used successfully as material for dental implants due to its high resistance to corrosion and very good biocompatibility [22]. There are a number of case reports in the literature showing that in rare circumstances Ti dental implants can induce an allergic reaction. Although Ti allergy has a low prevalence rate [23], people with antecedents of allergies to metals or jewelry present a higher risk of having a hypersensitivity reaction to a dental metal implant [24].

Studies regarding Ti and its alloys as allergens are scarce in literature, but efforts are made to develop methods for early diagnosis of Ti allergy. Patch tests, memory lymphocyte immunostimulation assay (MELISA) test, blood tests, in vitro lymphocyte transformation test (LTT) were used with various results and interpretation. LTT test results, showing proliferation of lymphocytes, are shown by some authors as being false positive. Type I, III and IV allergies are the most commonly associated with orofacial regions. Local presence of abundant T-lymphocytes and macrophages and the absence of B-lymphocytes show sensitivity to Ti, indicating type IV, with the characteristic features related to allergy starting from a few days to several years of contact with allergens. A clinical study made on 1500 dental implant patients showed that Ti allergy can be detected, in dental implant patients, provoking type IV or type I reactions, with a low prevalence of 0.6% [25].

In a study trying to histologically evaluate host response to Ti dental implant placement in a human oral model [26], the authors analyzed tissue reactions by coded histometric analysis at four defined areas at increasing distance from the oral epithelium. Tissue sensitivity reactions to Ti implants were not disclosed and the experimental biopsies contained most likely metal particles. In another study made on five human subjects [27], to conduct a comparative IHC evaluation of vascular endothelial growth factor (VEGF) and nitric oxide synthase (NOS) expression, inflammatory infiltrate, proliferative activity expression and microvessel density (MVD) in peri-implant soft tissues of Ti and zirconium oxide healing caps, the authors performed gingival biopsies (1.7 mm thickness and 3 mm height) after six months, around the healing caps which were immediately fixed in 10% neutral buffered formalin and accordingly embedded in paraffin. Three-μm sections were subsequently obtained with a microtome and stained with HE. For Ti, the inflammatory infiltrate was mostly present and mainly consisted of lymphocytes, plasma cells and histiocytes. No differences occurred in the number of B-lymphocytes (CD20+) and T-lymphocytes (CD3+).

Lalor et al. (1991) found large quantities of Ti particles in samples of tissues obtained from five patients who underwent revision operations for failed hip replacement; sensitization to Ti was suggested by monoclonal antibody labeling that showed the absence of B-lymphocytes and abundant macrophages and T-lymphocytes [28]. Beside the macrophage reaction to the Ti debris, they also reported a very large T-lymphocyte response, implying type IV sensitivity (cell-mediated immunity, contact sensitization). Still, all five patients patch tested with dilute Ti salt solutions had negative results [28]. Same results were obtained by Goutam et al. [22]. In contrast, Flatebø et al. [26] treated with Ti dental implants 13 patients without previous implantation. In biopsies obtained six months after the treatment, but not in the initial ones, dense particles, most likely metals were observed, but no tissue sensitivity reactions to the Ti implants were detected.

Comparing to these studies, our IHC analysis highlighted the presence of inflammatory markers (CD3 and CD68), findings that could be associated with allergenic potential of Ti. In our case, the presence of abundant T-lymphocytes and macrophages and a relatively small number of B-lymphocytes could indicate also a strong defense response against local bacterial aggression, which
could be the consequence of the local trauma, such as the fractured margin of the implant that irritated the gingival chorion. In this case of implant fracture in a young female patient, with no history of bruxism, it might be speculated that the cause is biomechanical, linked to the absence of the bone around the neck of the implant and biomechanical overload. The masticatory forces in the posterior mandibular area are high; in the absence of a good quality bone, that can be an added factor conducing to fracture. The crown-to-implant ratio was from the beginning higher than 1, and the patient was also wearing a loosening crown, although for a short while. Still, the fact that the implant maintained its osseointegration under those loading conditions can suggest that the cause can also be design and/or material related.

In an overview article about failure of the abutment connections, Shenava mentions that abutment screw loosening has occurred with many designs used for single tooth implant restorations and also that the amount of torque applied and the way it is applied, manually or mechanically, is an important factor in treatment’s failure or success [29]. Since the patient came to us when the implant was already fractured, we cannot know for sure if the first mechanical complication that appeared in this case was screw loosening or the fracture of the implant’s neck, which is the rarest of all, and although it is impossible to understand if that was an immediate fracture after application of the load, or most probably a time-dependent one, caused by corrosion, fatigue or combination, as it is sustained by Shemtov-Yona & Rittel [30]. In the same experiment, Shemtov-Yona & Rittel examined the surface of 100 dental implants retrieved due to biological complications and having absolutely no sign of mechanical damage and found that 62% of them were flawed or cracked to a definite extent, showing then signs of the metal fatigue. No information of the time spans the implants were used for was included [30].

In literature, fracture of the implant is reported as a relatively rare complication; studies estimate it at 1.6% [18]; only 56% were preceded by screw loosening. Gibney considers it as being a common cause of late failure and suggests as cause the occlusal overload [31], recommending careful treatment planning in order to reduce its incidence. Implant fracture can have multiple causes, such as implant production, design and material, too much insertion torque applied in dense mandibular bone, absence of bone around the upper treads, implant inclination, bad fit of the abutment on the implant platform, long-term metal fatigue, wearing an unstable crown for a long time, occlusal trauma, or parafunctions as bruxism. It is an important complication because it involves the complete loss not only of the treatment (implant and crown), but also of the surrounding bone [17, 32, 33], and because of the possible psychological consequences for the patient.

Studies in literature consider that the fracture of an osseointegrated implant is in most cases a problem of biomechanics [17]. Some authors consider as fracture causes the abnormal occlusal forces in direction and intensity, using a too short or too narrow implant or an implant having an incorrect position [34]. Suzuki et al. show that the localization and the possibility of fracture depend on the relationship between the loading angle and the embedded depth of implant. The capability of the implant to tolerate a greater inclination of the force increases when the embedded depth of implant is greater. Implant fracture was observed at inclination over $10^5$, for a 5 mm depth, while at 10 mm depth appeared over $15^5$ loading [35]. Engel et al. report that more than 77% of implant fracture cases are found in patients with bruxism [36]. Another study shows that in many cases the fracture of the implant is preceded by problems occurred at the fixture level or at the crown (loosening or fracture of the screw or crown) [33, 37]. According to another author, implant fracture is found in only 0.2% of cases from 4045 implants in five years of function and it is associated with a bone loss that can be radiologically observed in the fracture area [38]. Shemtov-Yona & Rittel consider that the mechanical failures as fracture are rare in implants, yet problematic, and caused by metal fatigue, related to the implant design and its surface and service condition [30]. Morgan et al. investigated the cause of mechanical failure of the fixture component of an osseo-integrated implant, comparing five clinical specimens that had fractured to new ones fractured in laboratory, and concluded that, for a specific design, fracture of the fixture occurred by fatigue under physiological loads, associated with marginal bone loss around the fixture [39].

There are a few available procedures in these cases, depending on factors related to each clinical situation. The explantation of a fractured implant has to be made with as little as possible bone damage using a trephine drill or a piezoelectrical device [40, 41], or by the high reverse torque unscrewing technique, with kits containing specially designed instruments, such as the screw that is used to engage the implant and the high torque dynamometric ratchet used to unwind the implant. The trephine drill technique is simple to use, but unpredictable; it is very important to follow the implant axis, to avoid the distortion of the drill and the implant and also to avoid removing a larger than necessary quantity of bone. Dvorak et al. consider that the piezoelectrical technique is more conservative than the trephine drilling one [41]. If the clinical situation permits, in the same intervention another implant of a larger diameter can be inserted [40]; another option is to wait and reevaluate the situation after the healing process. In cases with extreme bone loss, major surgical procedures as guided bone regeneration and bone grafting are necessary to reconstruct bone volume.

In a study conducted by Mardinger et al. (2008), it is shown that eliminating a failed implant as soon as it is diagnosed as lost improves the chance for reimplantation [42]. The same study concluded that the chances of a patient having a clinical situation with minor bone loss undergoing reimplantation was 20 times greater than a patient with severe bone loss; patients refused reimplantation for reasons varying from costs (27%), fear of additional pain (17.7%) and fear of a second failure (16.2%) [42]. Using a fixed partial denture as alternative treatment solution in implant failure cases with extensive marginal bone loss offers to the patient a tailored and more comfortable plan. Data in the literature sustain that, for the implant-supported reconstructions compared with tooth-supported fixed partial dentures, the incidence of technical complications is significantly higher [43].
Conclusions

Cohort studies and clinical cases reported hypersensitivity to Ti used in dental implants or other medical appliances. Further studies are necessary to investigate separately early and late implant loss and to develop new diagnostic tools in order to obtain a better risk assessment in implantology. Although implant fracture is rare, the consequences of osseointegrated implant failure are both biological and psychological and can affect the patient’s quality of life. Surgical procedures for the explantation of an osseointegrated implant are discouraging and hard to accept for the patient, considering not only the bone loss and the lower chewing efficiency but also the trauma. In this case, for placing another implant on the same site, further costs and additional procedures should follow, since extensive guided bone regeneration or bone grafting had to be considered simultaneously or prior to implant replacement. The results of our IHC analysis did not indicate a clear response for a potential Ti allergy; still, due to psychological reasons, the patient rejected the replantation and considered the use of other restorative option, a three-unit bridge, as being the most appropriate for her. Considering her opinion and attitude, the fixed prosthetic denture assured the therapeutic success.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors’ contribution

Authors #1 (OCA) & #3 (MB) have equal contributions to this paper.

References

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Received: December 16, 2018
Accepted: June 4, 2019