Foreign Body Giant Cell–Related Encapsulation of a Synthetic Material Three Years After Augmentation

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Bone substitute materials of different origin and chemical compositions are frequently used in augmentation procedures to enlarge the local bone amount. However, relatively little data exist on the long-term tissue reactions. The presented case reports for the first time histological and histomorphometrical analyses of a nanocrystalline hydroxyapatite–based bone substitute material implanted in the human sinus cavity after an integration period of 3 years. The extracted biopsy was analyzed histologically and histomorphometrically with focus on the tissue reactions, vascularization, new bone formation, and the induction of a foreign body reaction. A comparably high rate of connective tissue (48.25%) surrounding the remaining bone substitute granules (42.13%) was observed. Accordingly, the amount of bone tissue (9.62%) built the smallest fraction within the biopsy. Further, tartrate-resistant acid phosphatase–positive and –negative multinucleated giant cells (4.35 and 3.93 cells/mm², respectively) were detected on the material-tissue interfaces. The implantation bed showed a mild vascularization of 10.03 vessels/mm² and 0.78%. The present case report shows that after 3 years, a comparable small amount of bone tissue was observable. Thus, the foreign body response to the bone substitute seems to be folded without further degradation or regeneration.

Key Words: nanobone, multinucleated giant cells, foreign body reaction, osteoclasts

INTRODUCTION

The different chemical and physical material characteristics of synthetic bone substitute materials have a major influence on the cellular tissue reaction and its severity, including the induction of multinucleated giant cells and the extent of implantation bed vascularization.¹,²

In previous in vivo and clinical trials, the cellular and tissue reactions to the nanocrystalline hydroxyapatite (HA)–based bone substitute material Nanobone (NB; Artos, Roctock, Germany) has been investigated. In vivo already at early time points, the biomaterial showed relatively high levels of vascularization and tartrate-resistant acid phosphatase (TRAP)–positive and –negative multinucleated giant cells together with macrophages and lymphocytes.³,⁴

In a clinical trial 3 and 6 months after sinus augmentation, biopsies from the augmentation bed were harvested simulaneously with implant placement and investigated histologically and histomorphometrically. It was shown that already 3 months after augmentation, a comparable amount of newly formed bone (3-month group: 24.89% ± 10.22%; 6-month group: 31.29% ± 2.29%) could be achieved. Further, no significant difference could be seen in the number of multinucleated giant cells present in the augmentation bed.⁵,⁶

In further clinical studies, split-mouth sinus augmentation trials were performed to compare the tissue reactions to the synthetic bone substitute NB and the bovine-based bone substitute Bio-Oss (BO; Geistlich Biomaterials, Wolhusen, Switzerland) in patients with head and neck cancer⁷ and in a healthy patient collective.⁸ It was shown that NB underwent a higher vascularization and induced significantly more TRAP-positive multinucleated giant cells, while BO induced mainly mononuclear cells. However, no significant difference was observed in the extent of new bone formation.⁷,⁸

This findings show that the initial tissue reaction up to 6 months after augmentation is well researched and documented. However, in particular, the tissue’s long-term reaction and the ability of a bone substitute material to form a sufficient and stable implantation bed over years are of striking importance. For the first time, the case report presents here a histological and histomorphometrical analysis from a sinus biopsy harvested 3 years after augmentation with the bone substitute material NB.
Presented Case

For the presented case, an unilateral sinus augmentation with the synthetic bone substitute material NB (Artoss) was performed 3 years ago according to previously published methods. Because of personal and financial reasons, the patient refused implantation 6 months after augmentation. Three years after augmentation, the patient presented again in the same private dental practice, and a titanium dental implant (CAMLOG Screw Line, CAMLOG Biotechnologies, Basel, Switzerland) was inserted simultaneously with extraction of a bone biopsy.

Simultaneously with the insertion of the implant, a bone biopsy was obtained, histologically processed, and stained to investigate the bone-biomaterial interaction and tissue reaction according to previously published methods.

The processed slides were histologically and histomorphometrically analyzed according to previously described methods to assess the long-term tissue-biomaterial interaction within the implantation bed and the peri-implant tissue. Using the NIS-Elements software (Nikon, Tokyo, Japan), the total implant area; amount of newly formed bone, connective tissue, and remaining bone substitute material; number and area (in \( \text{mm}^2 \)) of vessels; total number of vessels (in vessels/mm\(^2\)); and the percentage of vessel area were calculated. Further, the amounts of material-associated multinucleated giant cells and their subforms (TRAP-negative and TRAP-positive multinucleated giant cells) were counted and calculated related to the implant bed area (cell number/mm\(^2\)).

Histological analysis revealed the presence of NB granules, mainly encapsulated in connective tissue (Figures 1a and 2).
Within the crestal parts of the biopsy material, granules integrated in newly built bone tissue could be detected (Figure 1), while in the apical parts of the biopsy, almost no bone tissue was present (Figure 2). Within the intergranular connective tissue throughout the biopsy, vessels could be detected (Figures 1c and 2d). In the crestal part, low numbers of multinucleated giant cells and a comparably high amount of mononuclear cells were found adjacent to the material surface (Figure 1b). In contrast, the material granules in the apical parts of the biopsy were covered by collagen fibers arranged circularly (Figure 2a through c). Within these collagen-rich areas, only low amounts of mononuclear cells and no multinucleated giant cells were found (Figure 2).

The histomorphometrical analysis showed a mild vascularization with a vessel density of 10.03 vessels per mm², a percentage vascularization of 0.78% (Figure 3a), and 4.35 TRAP-positive and 3.93 TRAP-negative multinucleated giant cells per mm² (Figure 3b). Distribution of the different tissue fractions within the sinus biopsy showed 9.62% of bone tissue, 42.13% of remaining bone substitute material, and 48.25% of connective tissue (Figure 3c).

**DISCUSSION**

In the presented case report, a biopsy harvested 3 years after sinus augmentation with the synthetic bone substitute NB was investigated. To the best of our knowledge and literature research, this is the first report of 3-year histological results regarding this specific bone substitute material.

Histological analysis of the sinus biopsy showed mainly fibrous encapsulation of the granules, while only a low amount of newly built bone tissue was found. Histomorphometric analysis revealed a relatively low vascularization rate and the
presence of relatively few biomaterial-associated TRAP-positive and -negative multinucleated giant cells limited to the crestal implant region.

Altogether, the presented data show that only in the crestal part of the implant region did a regular bone substitute material-mediated regeneration process take place, while no histological signs of an ongoing foreign body response and a material-mediated bone regeneration were found in the major area of the biopsy. An explanation for this finding could be the nonloading situation of the implanted region. It might be possible that a potential bone formation, which has been shown to have reached also the apical parts of the biopsy, underwent a regression resulting in an encapsulation of the remaining bone substitute granules over time. When comparing the tissue fractions within the here-analyzed biopsy with the corresponding values after 3 and 6 months, it becomes obvious that the extent of the bone tissue is comparably reduced while the other parameters are more or less equal. The

FIGURE 3. Results of the histomorphometrical analyses. (a) Implant bed vascularization including vessel density (vessels/mm²) and percentage vascularization. (b) Total numbers of material-induced multinucleated giant cells and their tartrate-resistant acid phosphatase-positive and -negative subforms per mm². (c) Tissue distribution within the implant area including the percentage area of bone tissue, remaining bone substitute, and connective tissue.
encapsulation of the granules throughout the study reflects a terminal aspect of a potential foreign body giant cell reaction, which might have been frustratingly involved in material degradation. This assumption also becomes substantiated by the comparably higher amount of the TRAP-positive multinucleated giant cells in the material's implantation bed after 6 and 6 months, respectively.\(^5\)

Furthermore, it is known from previous investigations that in the initial phase after augmentation, multinucleated giant cells on the surface of the biomaterial granules seem to expand their effort in degrading the synthetic biomaterial, without really reducing the ratio of the biomaterial. These findings are in accordance with the previously described characterization of multinucleated giant cells, which seem to act more as foreign body giant cells than as osteoclastic cells without the ability of degrading synthetic, HA-based bone substitute materials.\(^9\)

Based on the presented data, it is conceivable that a foreign body response that initially involves multinucleated giant cells can also be terminated at a later stage of the integration period of a bone substitute material ending up in the encapsulation of the granules without any further regenerative material characteristics. The question arises as to which material characteristics have influence on the formation of multinucleated giant cells and the degradability of a bone substitute material.

**ABBREVIATIONS**

BO: Bio-Oss  
HA: hydroxyapatite  
NB: Nanobone  
TRAP: tartrate-resistant acid phosphatase

**REFERENCES**


