Classification of pedicle ossification after maxillofacial reconstruction with bony free flap: an observational study

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Abstract:

Introduction: Maxillofacial reconstruction with bony free flap is a classical technique. However, pedicle ossification after such reconstruction is a misunderstood complication that is rarely reported in the literature. It is usually manifested as trismus, neck pain, and hard swelling, but it is predominantly asymptomatic and, thus, mainly incidentally discovered at a later stage. The aim of our study is to propose a classification for pedicle ossification based on both radiological features and vascular calcification progression. We also describe a case of metachronous ossification after two fibula free flap procedures.

Material & Methods: Our observational study includes all patients from our unit who underwent maxillofacial reconstruction with bony free flap from 2003 to 2018. We collected all cases of pedicle ossifications identified during the follow-up and described the radiological status of each one to categorise them in different groups and propose a classification scheme for the same.

Results: Radiological and histological analysis showed a progressive three-step evolution of pedicle ossification, starting from the media, progressing into the lumen, and then reaching completion in the extravascular region. The final stage was observed in all symptomatic patients.

Conclusion: Pedicle ossification is a progressive process that passes through three successive histological stages that may be associated with factors such as smooth

muscle cell phenotype modification[1]. This complication may lead to more severe clinical symptoms and may require surgery for removal of the calcification.

Keywords: maxillofacial reconstruction; bony free flap; pedicle calcification; vascular calcification

Introduction:

Several conditions, such as cancer, infections, and osteonecrosis, affect the integrity of the maxilla and mandible and cause maxillofacial defects. The most frequently used method to correct large defects is reconstruction with vascularized bony free flap (BFF). Fibula free flap (FFF) is a type of BFF that is widely used because of the length of the harvestable bone; the relative ease of shaping; the possibility of performing composite flap with skin, fascia, and muscle tissue; and its accuracy is improved by the actual progress in digital navigation [2]. Another common BFF is the scapula free flap (SFF), which is mostly used for maxillary reconstruction because of its natural conformation.

Some recent studies show that ossifications might occur along the vascular pedicle of the BFF after reconstruction of the jaw mainly because of the osteogenic properties of its vascularized periosteum [3,4]. Other factors, such as vascular flow, mechanical tension, radiotherapy, local or systemic growth factors, inflammatory and osteoprogenitor mediators [5–7], pain, and hard swelling [8], have also been implicated. Unfortunately, ossifications are typically diagnosed only during radiologic follow-up[9] or remain undiagnosed [5], knowing that incidence is relatively rare[10]. To avoid recurrence, some authors suggest that periosteum excision be performed in addition to vascular calcified pedicle excision [11].

The aims of this retrospective study were to identify all pedicle ossifications associated with BFF procedures performed during 2003–2008 at our Department of Oral and Maxillofacial Surgery, and to propose a radiologic classification for pedicle ossifications. We also describe the natural evolution of these bony lesions and the first case of two consecutive pedicle ossifications after two successive FFF

procedures. Finally, we discuss the pathophysiological aspects of this entity based on the proposed classification.

Material and methods:

In this retrospective study that was conducted from 2003 to 2018, we included all patients who underwent maxillary or mandibular reconstruction with BFF, including SFF and FFF. Patients were included if they had had at least one head and neck computed tomography (CT) scan in their follow-up material. The main aim was to collect cases of pedicle ossifications and describe the radiological status of each one in order to categorise them into different groups. Radiological evaluation was performed by two different practitioners. Tests for measurement error included intra-rater reliability in determination of calcification type, which resulted in an R2 value of 1. Other clinical data have been collected such as age at the time of free flap surgery; sex; type of BFF; location of resection; radiotherapy after surgery; onset between the reconstruction and radiological emergence; and clinical symptoms such as trismus, hard swelling, and pain, which are most frequently described in the literature.

All procedures performed in the study were in accordance with the ethical standards of the Helsinki Declaration. No IRB evaluation was required due to the retrospective nature of the study. All data were anonymized and the “Commission Nationale de l’Informatique et des Libertés de France” declaration was provided in accordance with French law.

Results:

Patient characteristics:

From a total of 345 free flap reconstructions performed between 2003 and 2018, 274 BFFs were included in this study; 71 free flaps were excluded because they had no bony component. 257 were mandibular reconstruction and 17 maxillary reconstruction. Among the 274 patients who underwent BFF surgery, 35 pedicle ossifications were described in a group of 34 patients (12.4% of the cases reviewed). One patient, who underwent two successive FFFs, showed ossification of each pedicle.

Table 1 shows the main characteristics of the 34 patients (28 men and 6 women) who presented with pedicle ossification. The mean age at the time of BFF reconstruction was 53.6 years, and the median age was 53 years. The resection location was the mandible in 31 cases (88.6%) and the maxilla in 4 cases (11.4%). Hence, pedicle ossification occurred in 12% (31/257) of mandibular reconstruction versus 23.5% (4/17) of maxillary reconstruction. The most common primary disease was squamous cell carcinoma, with 27 (77.1%) patients showing osseous invasion. We also noted two cases of adenoid cystic carcinoma (5.9%), two cases of dental tumours (ameloblastoma and odontogenic carcinoma), one case of mucoepidermoid carcinoma of the accessory salivary gland, one case of Ewing sarcoma, and one facial ballistic wound. Radiotherapy after BFF reconstruction was performed in 19 (54%) cases. All patients had undergone at least one CT scan during their follow-up. The delay between the day of reconstruction and the first visualization of a pedicle ossification ranged from 70 to 570 days (median: 202 days). Clinical signs were noticed in 5 (14.7%) patients with pedicle ossification. Four (11.7%) patients presented with a hard swelling on the cervical or cheek area, and one of them

additionally presented with trismus. Further, one patient experienced pain in the neck.

Radiological classification:

Data from the initial CT scan and the follow-up scans were analysed to understand the process of ossification, which was found to have a linear development process. We ranked the detected pedicular ossifications into three main stages (Table 2): first stage, medial and intimal calcification; second stage, intra-luminal extension; and third stage, extra-vascular extension. The first stage was further stratified based on radiological analysis into the discontinued (Stage Ia) and continued medial calcification (Stage Ib) substages. Indeed, the process affected only some parts of the pedicle (Ia) or the full length of the pedicle (Ib) (Figure 1). With regard to stage II, intra-luminal calcification continues in the absence of any extravascular extension. With regard to stage III cases, extravascular ossification could present in several forms, of which the main one is a wide growth with a base on the junction between the pedicle and the bony flap (Figure 2). However, atypical excrescence could also lead to fusion with osteo-cartilaginous entities, such as the maxillary or hyoid bone, in case of jaw reconstruction.

Table 3 presents the classification of the patients according to ossification stage: the majority of the patients had stage II (14 cases, 40%) or stage III ossifications (16 cases, 46%). The data also indicate that all the patients who presented with clinical symptoms had stage III disease.

Description of a case of two consecutive pedicle ossifications:

Of the 34 patients with confirmed pedicle ossifications, one presented with two pedicle ossifications. The patient had bone infiltration of the posterior mandible (stage: pT4 N2a M0) and was followed up at our department for oral cancer. One year after the first FFF, the control CT scan indicated stage 1a pedicle ossification. A second FFF was performed 4 years later because of osteoradionecrosis of the remaining jaw. The new CT scan showed a second ossification along the second FFF pedicle (stage Ia); additionally, the first ossification had evolved from stage Ia to stage III. The first pedicle ossification had extended to the proximal part of the pedicle, next to the fibula flap. It measured 3.5 (length) × 3 cm (height) (Figure 3). Anatomopathological analysis revealed a mature bone without a vascular pedicle between the proximal and distal part of the sample. Some vascular elements were found next to the ossification structure, but there were no signs of calcification (Figure 4).

Discussion:

The present study shows that ossification of the vascular pedicle in BFF is not a rare side effect of this BFF reconstruction, given that it occurred in 35 cases in our study population. Moreover, 5 of these 35 patients (that is, 14.7%) were symptomatic, and they represented 1.8% of the total population. This is higher than the incidence of 4% reported in other studies such as those of Baserga *et al.* [6] or Autelitano *et al.*[12] This difference could be explained by a systematic CT-based and longer duration post-operative follow-up in the present study, as it allowed for the detection of late pedicle ossification. Nevertheless, only a few patients in this population were symptomatic, and this indicates that this complication is typically underestimated.

The mechanism underlying pedicle ossification could be attributed to several factors that may act in synergy. The periosteum may play a major role in pedicle ossification, based on its osteogenic properties [3] which are stimulated by several signalling factors, such as bone morphogenetic protein (BMP), which may be activated by surgery, and its proximity with the pedicle. BMP is an osteoinductive molecule that regulates periosteal activity [4] and is released in large amounts in response to bone injury or fracture to stimulate bone regeneration [13]. Accordingly, several research teams [12] have suggested that the portion of the empty periosteum along the proximal part of the pedicle should be excised to avoid ossification risk. In this context, several studies [11,14] also described a modified surgical technique that did not increase the risk of flap failure. However, based on the rate of symptomatic patients and the risk of pedicle injury jeopardizing the success of flap reconstruction, we recommend that pedicle dissection be performed as per the standard method[14]. This point of view is also shared by Wood and Al [15], mentioning the “low likelihood that patients will become symptomatic secondary to pedicle ossification”.

The periosteum is not the only factor associated with ossification. A mechanical theory has also been proposed to explain pedicle calcification [5]. That is, local tension on the flap's bundle in the neck and flap stress may enhance molecular signalling of BMP [4] and lead to ossification. Furthermore, the location of the reconstruction plays a role, ossification of the vascular pedicle occurred in 12% of mandibular reconstructions (31/257) and in 23,5% of maxillary reconstructions (4/17). Hence, maxillary reconstruction seems to be associated with a higher risk of pedicle calcification than mandibular reconstruction. Another potential risk factor for pedicle calcification is radiotherapy. However, this is debatable, as no significant differences in calcification onset were found between radiotherapy and non-radiotherapy populations [5]. Hormonal factors, such as oestrogen deficiency and short-term corticoid therapy, may further augment periosteal osteogenesis and the calcification process [6]. However, no significant results have been reported in this regard.

Here, we propose a new theory based on our results and radiological observations. Recently, it was reported that vascular calcification is an active process regulated by several signalling pathways [1,16] and seems to be initiated from within the media [17]. The major factors associated with medial calcification are smooth muscle cell (SMC) proliferation [17]. Specifically, in a recent study [1], the authors suggested that interaction between several factors, such as hormonal regulation, lack of calcification inhibitors, and oxidative and mechanical stress, could stimulate SMCs contained in the vascular media to differentiate into osteoblast-like SMCs and lead to vascular calcification. Indeed, SMCs can alter their phenotype in response to local cues because of their phenotypic plasticity. Thus, under conditions that are conducive for calcification, SMCs undergo differentiation into osteoblast-like SMCs,

express bone-related proteins, and initiate the calcification process. In the case of application of BFF for maxillofacial reconstruction, the vascular pedicle is exposed to different local and circulating factors that are known to initiate medial calcification, including oxidative and mechanical stress, high local levels of calcium and phosphate from the bone split and calciprotein particles, and a high level of apoptosis. The process of vascular calcification and SMC modification is depicted in Figure 5. Once the process is started, histological modifications occur, and ossification of the pedicle is initiated with granular calcifications in the media. These calcifications increase in size and become confluent and cover the entire circumference of the media, and this is considered as stage I. All these calcifications eventually lead to bone formation [17]. After invasion, the calcification passes from the media to the intima and invades the lumen, leading to occlusion in several parts of the pedicle; this is described as stage II. Owing to the capacity of soft tissue invasion, the process can pass through the adventitia and to the external environment, leading to extravascular ossification as stage III. This last stage is probably potentialized by the proximity of the periosteum and its osteogenic capacities. Moreover, another previous study has indicated BMP expression in arteriosclerotic lesions [18], further implicating the role of the periosteum in extra-vascular calcification.

Based on these pathophysiological pathways, we can hypothesize the progression of ossification based on radiological findings. The ossification seems to be initiated from the media, without other extensions, and may be discontinued or continued along the pedicle. The second step is the extension to the entire vessel wall mainly through the intima, and within the lumen. Hence, the pedicle, in its proximal or distal part, may have an ossified endovascular lumen. Because of the onset of ossification, lack of vascularisation should not influence osteointegration or

flap vitality, as the BFF is already independent of the vasculature. Extravascular ossification is the final step and is commonly detected next to the bony insertion of the pedicle, in the flap's proximal part. It may extend to other adjacent facial bones or tissue. We showed that all patients who presented with symptoms had stage III disease. On the other hand, extra-vascular ossification seems to be the main cause of limited mouth opening, pain, and hard swelling, and is probably due to soft and hard tissue relationship-related conflict. The case of our patient with two successive pedicle calcifications perfectly illustrated the radiological and histological calcification process. Based on the data, it can be assumed that the ossification substituted all the original pedicle cells and also the soft tissue around it. This is consistent with the molecular process of SMC phenotype modification into osteoblast-like cells. With regard to the present study, we need to mention the probability of individual factors, for example, epigenetic and genetic factors, as well as vascular conditions prevalent before the harvest for the surgery [19]. Indeed, a patient's cardiovascular pattern may already indicate arteriosclerosis and, therefore, initiation of the process of medial calcification. Furthermore, medial calcification could be catalysed by surgery and additional circulating and local factors. Thus, young patients without cardiovascular risk might have a lower risk of pedicle ossification.

Another classification of heterotopic ossification of the vascular pedicle has been proposed [20]. It differentiates only extravascular locations as four patterns are described: transition zone from fibula graft and vascular pedicle, only on the pedicle, only on periosseous tissue, and both vascular bundle and periosseus tissue.

In practice and according to other studies [5,6,21], only symptomatic calcified pedicles must be removed. Removal of a calcified pedicle has no consequence on the flap's vascularization and vitality, provided that a sufficient period of time has

passed between the reconstruction and removal. During this period, the flap develops an independent vascular network.

To conclude, BFF reconstruction is a common surgery performed in maxillofacial units to correct jaw defects. According to our report, pedicle ossification is not a rare complication, given that it had an incidence rate of 12.4% in our study sample. However, most patients are asymptomatic, and ossification is usually found on CT performed during the follow-up. Several factors have been deemed responsible, such as the osteogenic capacity of the periosteum, mechanical and oxidative stress, radiotherapy, and hormonal factors. In particular, SMC phenotype modification appears to play a major role in this condition. The findings of radiological analysis corroborate this mechanism, and allows us to establish a classification with three main stages. The third stage comprised extra-vascular ossification, and was the only case where the patient was symptomatic. In addition, the case of two pedicle ossifications after two successive BFFs with radiological progression is a good example to explain the process, which still remains incompletely understood.

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Figure and table legends:

Table 1: Description of the population presenting with pedicle ossification after bony free flap reconstruction (BFF: Bone free flap; SCC: squamous cell carcinoma; ACC: adenoid cystic carcinoma)

Table 2: Radiological classification according to vascular calcification features and progression

Table 3: Number and percentage of patients in each radiological stage (All the symptomatic patients are in stage III)

Figure 1: Case of stage I pedicle ossification

A 64-year-old man who underwent jaw reconstruction with FFF for SCC of the mandible. He was classified under pedicle ossification stage I with medial and intimal calcification without intra and extra-luminal extension. The calcification seems to be extended all along the vessel.

Figure 2: Case of stage III pedicle ossification

A 40-year-old woman who was followed up for an adenoid cystic carcinoma underwent maxillary resection with FFF reconstruction. The patient presented with trismus and hard swelling on the left side. CT scan showed stage III pedicle ossification with a large extravascular extension leading to fusion and consolidation between the FFF and mandible.

Figure 3: Stage III ossification sample, magnification 2x

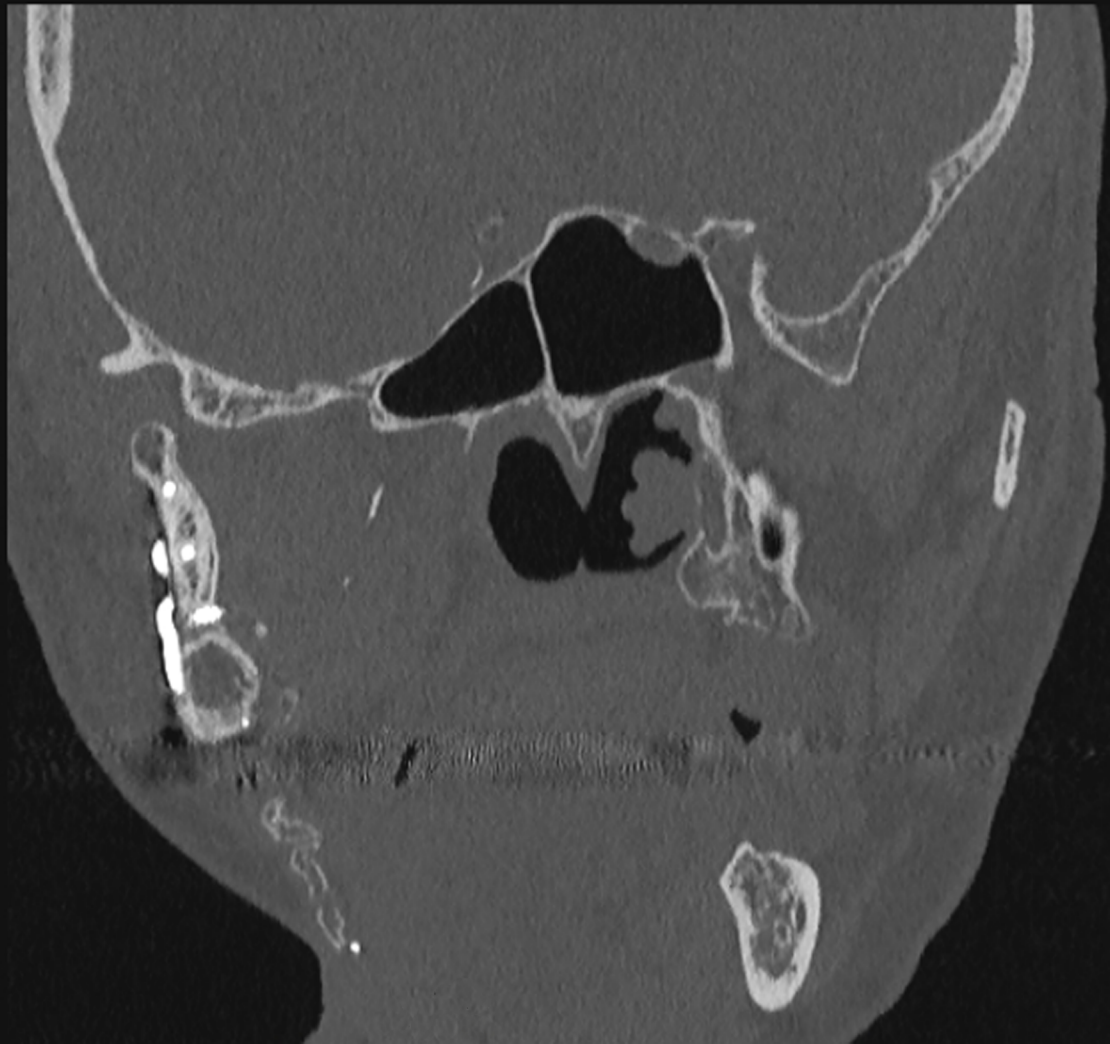
Resected ossification sample showing pedicular extension (white arrow) and extravascular ossification (circle)

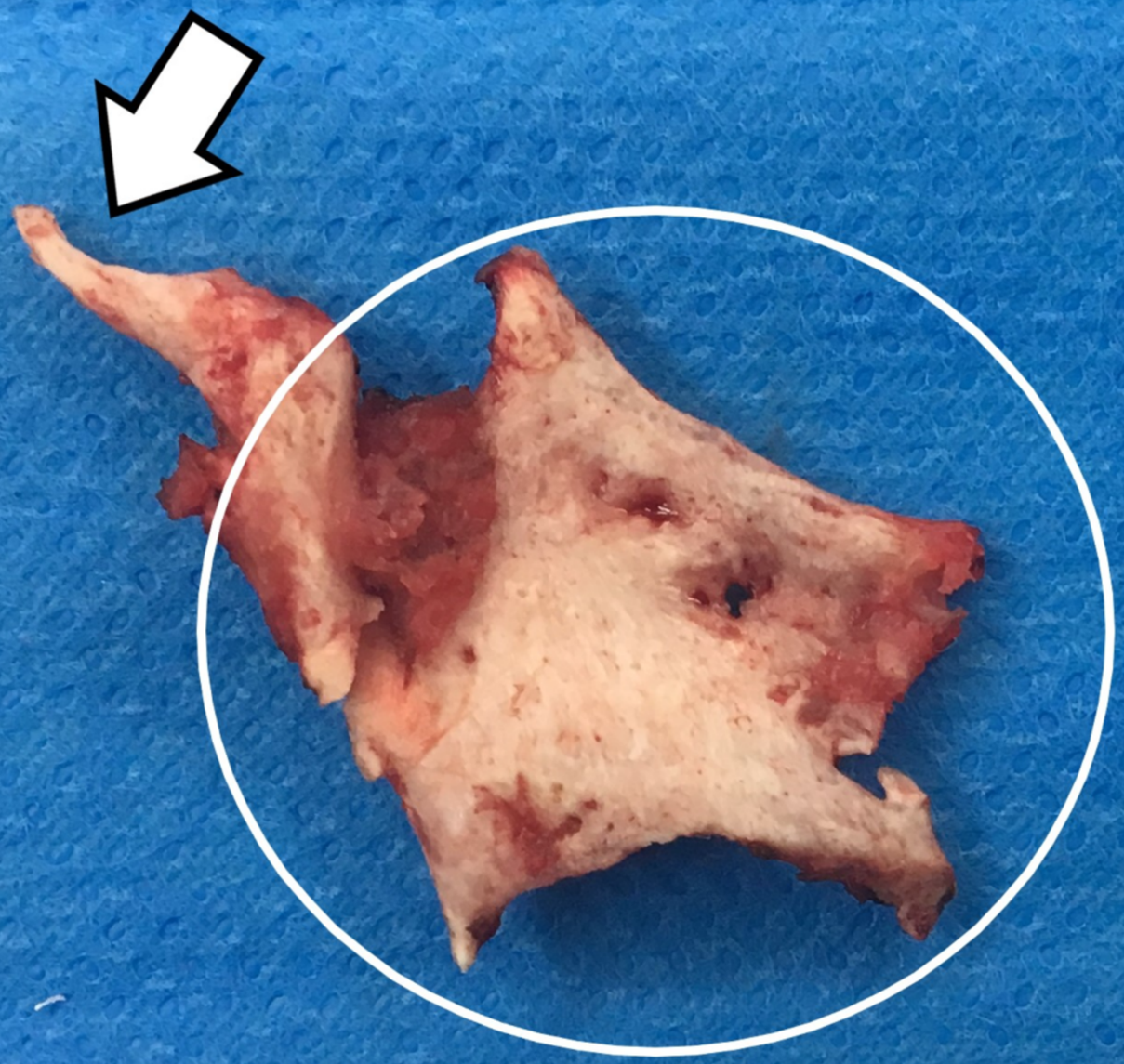
Figure 4: Histological analysis of a stage III ossification sample

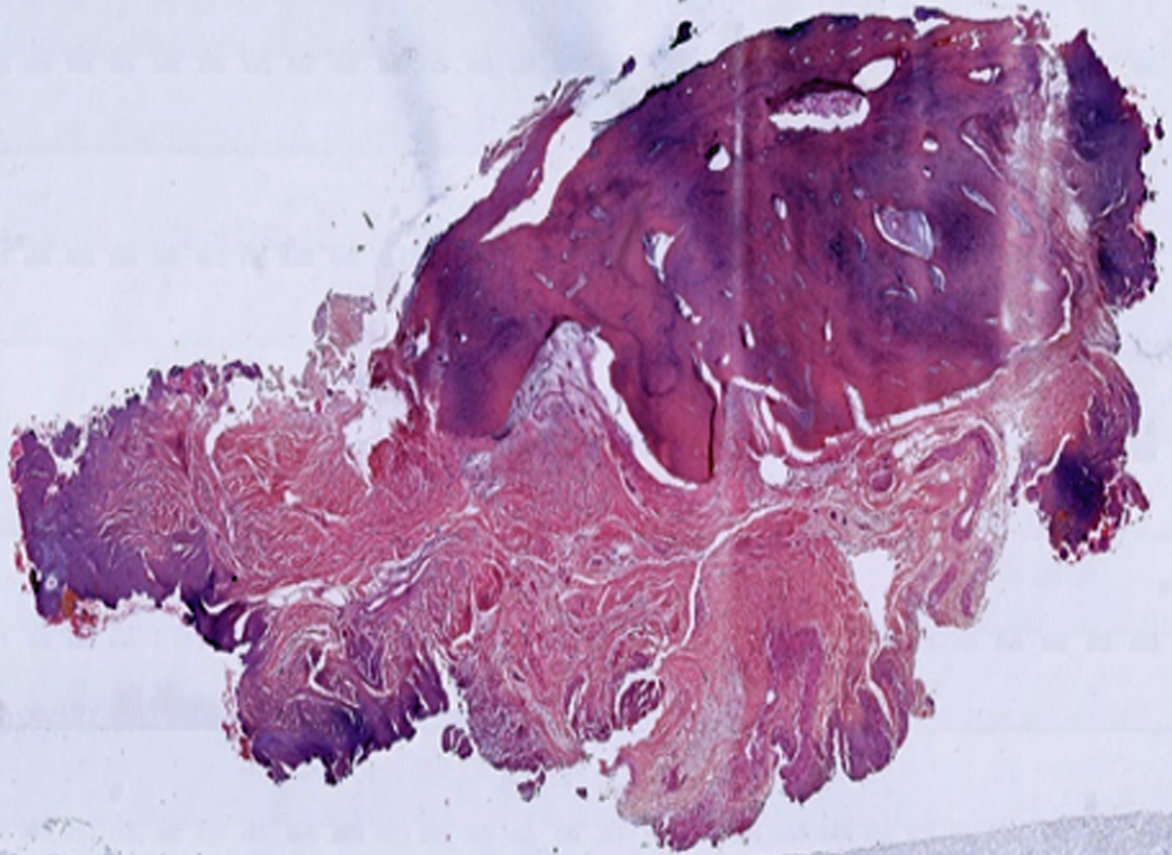
Histological analysis showing different foci of the mature bone lacking vascular cells as a result of complete ossification of the pedicle.

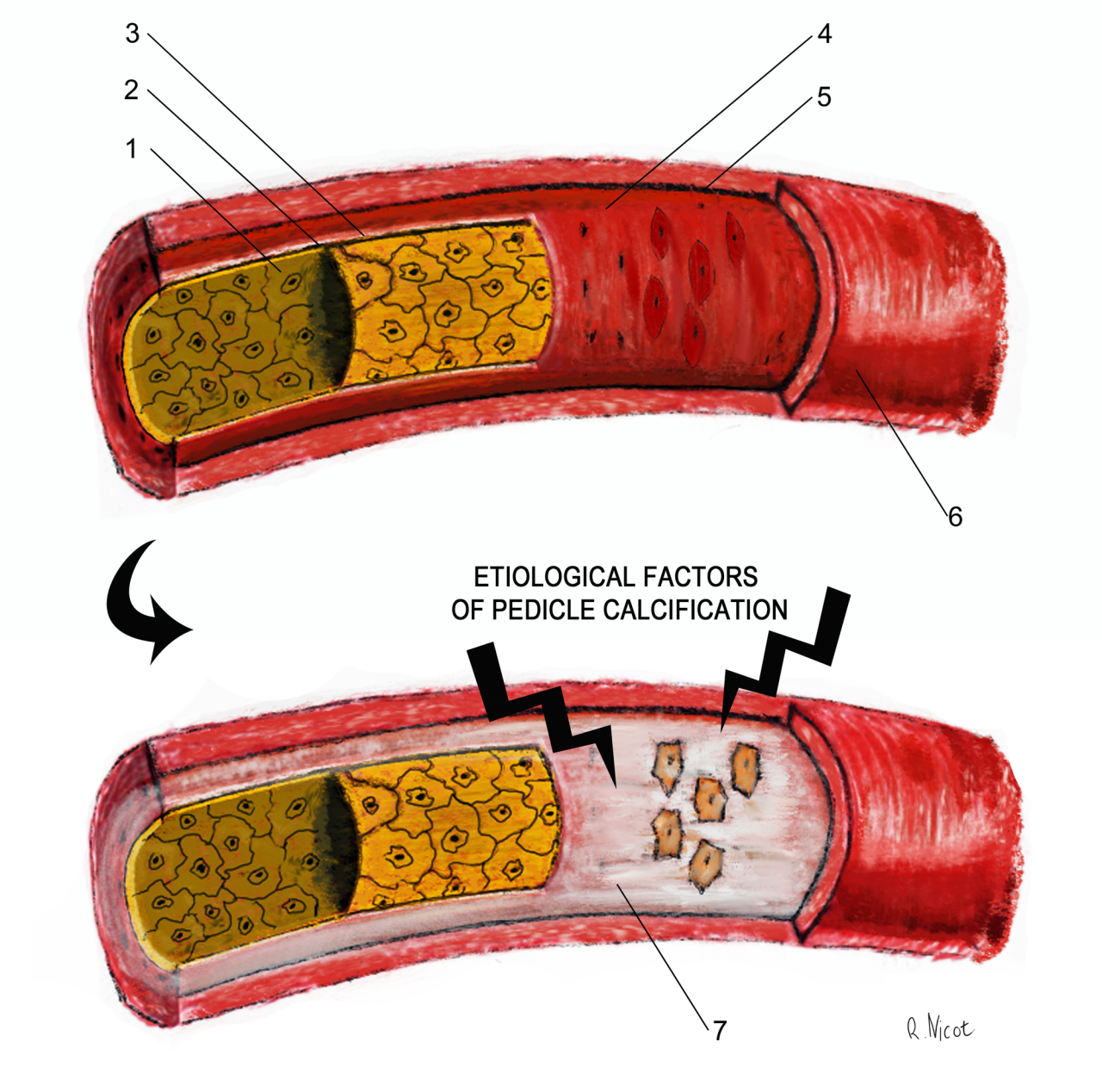
Figure 5: Schematic presentation of SMC phenotype modification

Several factors and pathways, such as oxidative stress, local factors, and mechanical tension, lead to SMC differentiation into an osteoblast-like phenotype. Ossification starts in the media and intima (stage I), and progresses into the lumen (stage II) and then the area outside of the pedicle (stage III). The radiological classification is based on this process. Landmarks: 1: endothelium; 2: intima; 3: internal elastic lamina; 4: media; 5: external elastic lamina; 6: adventitia; 7: vascular calcification





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ETIOLOGICAL FACTORS
OF PEDICLE CALCIFICATION
7
R. Nicot

Total Patients	34
Total pedicle ossifications	35
BFF type	
Fibula	34 (97,1)
Scapula	1 (3,9)
Sex	
Female	6 (17,65)
Male	28 (82,35)
Age at BFF, median	53
Primary disease	
SCC	27 (77,1)
ACC	2 (5,9)
Others	6 (17)
Radiotherapy following BFF	
Yes	19 (54,3)
No	16 (45,7)
Reconstruction location	
Mandibular	31 (88,6)
Maxillary	4 (11,4)
Delay BFF/calcification (days)	
Median	202
<150	10 (28,6)
150-250	12 (34,3)
>250	13 (37,1)
Clinical signs	
Asymptomatic	29 (85,3)
Symptomatic	5 (14,7)

Table 2:

Radiological stage:	**Vascular ossification:**
I	non-endoluminal / non-extraluminal
a:	discontinued
b:	continued
II	endoluminal / non-extraluminal
III	extra-luminal

Table 3:

Stage	Number of patients	Percentage of patients	Symptomatic patients
I	5	14%	0
Ia	2	6%	0
Ib	3	9%	0
II	14	40%	0
III	16	46%	5