OPEN

PRS GLOBAL OPEN

CASE REPORT
Reconstructive

A Case of Fibula Regeneration after Below-the-knee Amputation in an Adult

Michiko Fukuba, MD, PhD*
Kyoko Dogo, MD, PhD*
Koji Saito, MD‡
Tsuyoshi Ishida, MD, PhD§
Hisayo Yamaoka, MD, PhD*
Masayuki Okochi, MD, PhD*
Naoshi Ogata, MD, PhD†
Yuzo Komuro, MD, PhD*

Summary: We report the case of an adult with fibula regeneration after below-the-knee amputation. Fibula regeneration conventionally occurs at the donor site of children after autogenous fibula transplantation when the periosteum is preserved. However, the patient was an adult, and the regenerated fibula was 7-cm long and grew directly from the stump. A 47-year-old man was referred to the plastic surgery department owing to stump pain. He had an open comminuted fracture of the right fibula and tibia due to a traffic accident when he was 44 years old and underwent below-the-knee amputation and negative pressure wound therapy for skin defects. The patient recovered and was able to walk using a prosthetic limb. Upon radiography, the fibula was found to have regenerated 7 cm directly from the stump. Pathological examination revealed that the regenerated fibula contained normal bone tissue and neurovascular bundles in the cortex. The periosteum, mechanical stimuli with limb proteases, and negative pressure wound therapy were suspected to have accelerated bone regeneration. He had no inhibitory factors for bone regeneration, including diabetes mellitus, peripheral arterial disease, or active smoking status. After the resection of the regenerated fibula, the patient was ambulatory without further bone regeneration or pain. This case report suggests that bone regeneration may occur even in adults. The surgeon should not leave any part of the periosteum behind in patients undergoing amputation. In adult amputees complaining of stump pain, the possibility of bone regeneration may be considered. *(Plast Reconstr Surg Glob Open 2023; 11:e4968; doi: 10.1097/GOX.0000000000004968; Published online 10 May 2023.)*

Fibula regeneration at the donor site after autogenous fibula transplantation has been previously reported.[1] In these cases, the periosteum was preserved and the fibulae regenerated, with the caveat being that the patients were children. We herein report the case of a 47-year-old male patient who underwent below-the-knee (B-K) amputation and was observed to have a regenerated fibula that grew directly from the fibular stump. The regenerated fibula was 7-cm long.

*From the *Department of Plastic, Oral and Maxillofacial Surgery, Teikyo University, School of Medicine, Tokyo, Japan; ‡Department of Pathology, Teikyo University Hospital, Tokyo, Japan; §Department of Diagnostic Pathology, National Hospital Organization Saitama Hospital, Saitama, Japan; and †Department of Rehabilitation Medicine, Teikyo University, School of Medicine, Tokyo, Japan.*

Received for publication January 16, 2023; accepted March 7, 2023.

A summary of this case report was presented at the 14th Annual Meeting of Japan Society for Surgical Wound Care, July 14 and 15, 2022, Kobe, Japan.

DOI: 10.1097/GOX.0000000000004968

CASE REPORT

A 47-year-old man who had undergone B-K amputation was referred to the plastic surgery department because of complaints of pain, dark red stump skin, and occasional stump ulceration (Fig. 1). He had right fibula and tibia open comminuted fractures owing to a traffic accident when he was 44 years of age. The patient underwent B-K amputation, debridement twice, and NPWT for 13 days on his stump. The stump healed, and he was ambulatory with a prosthesis (Fig. 2).

As observed by radiographs taken at the plastic surgery department 2 years and 7 months after amputation, the fibula and tibia had regenerated by 7 cm and 1 cm along the stump, respectively (Fig. 3). The length of the leg stump did not increase during bone regeneration. The regenerated fibula was thought to have caused the pain, and surgical resection of the regenerated fibula and excess skin was performed under general anesthesia 2 years and 9 months after amputation. The regenerated tibia was not removed because it did not cause any pain. The regenerated fibula

Disclosure statements are at the end of this article, following the correspondence information.

Fig. 1. Lateral view of the lower limb before regenerated fibula resection. The left side is the anterior. The skin of the stump is shown in deep red.

Fig. 2. Fifty-one days after B-K amputation. Bone regeneration was not clearly observed.

was similar to a normal fibula regarding thickness and hardness. Pathological examination revealed that the regenerated fibula comprised normal bone tissue, including cortical and cancellous bone with fatty bone marrow. In the cortex, bundles of arteries, veins, and nerve fascicles, similar to the normal feeding vasculature and nerve, had grown (Fig. 4). Approximately 3 years and 9 months after the resection of the regenerated fibula, the patient was ambulatory and did not have any bone regeneration or pain.

DISCUSSION

Fibula regeneration has been reported to occur at the donor site after autogenous fibula transplantation when the periosteum is preserved. However, this usually occurs in children. Bettin et al reported that the only predictor of fibular regeneration was younger age (cutoff: 15 years) at the time of transplant.[1] In addition, the regenerated fibulae reportedly filled the bone harvesting section. However, in this case, the regenerated fibula extended directly from the stump. Bone overgrowth of the residual limb after an amputation is rare in adults; hence, reported cases are few.[2]

We had thought that the major contributing factor to fibula regeneration in this case was the periosteum, which may have remained in the wound. Pathological examination revealed that the regenerated fibula had bundles of arteries, veins, and nerves, and the periosteum was observed circumferentially. In general, newly regenerated nerves tend to form a tangle of bundles called a traumatic neuroma. However, the nerves in the regenerated fibula had intact microfascicles, suggesting that they formed normally and that the periosteum, which contained nerves, remained partly intact. This also suggests that the new periosteum and nutrient neurovascular bundles of the regenerated fibula may have arisen from original preexisting tissue. Duchamp de Lageneste et al showed that "periosteal cells and their periosteum niche are two key components that act locally to allow callus formation and bone bridging for fracture consolidation."[3] Additionally, musculoperiosteal flaps were reported to contribute to the formation of large amounts of bone.[4] Although the periosteum contributes to fibula regeneration, such occurrences are only observed in children.

Another possible factor of fibula regeneration is the mechanical stimuli for the stump. Mechanical stimuli are essential for bone growth and regulation.

Fig. 3. Two years and seven months after amputation. The fibula and tibia regenerated by 7 cm and 1 cm from each stump, respectively.

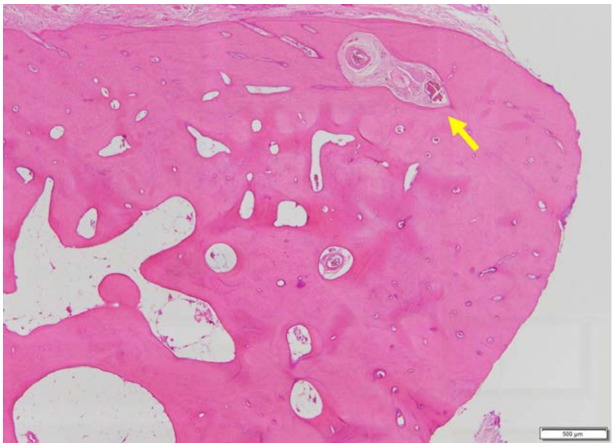

Fig. 4. Histopathological cross-sectional view of the resected fibula. The regenerated fibula comprised morphologically normal-looking bone tissue (including the periosteum), and cortical and cancellous bone with fatty bone marrow. In the cortex, a bundle of arteries, veins, and nerve fascicles, similar to the normal feeding vasculature and nerve, was observed (yellow arrow). In the serial section, neurovascular structures were seen to penetrate the cortical-like bone tissue from outside of the bone and reach the medullary cavity-like bone tissue.

Watanabe-Takano et al reported that physiological loading induces the expression of osteocrin, a periosteal-osteoblast-derived secretory peptide, in the periosteal osteoblasts of long bones, promoting bone growth by enhancing C-type natriuretic peptide signaling.[5] A limb prosthesis could constantly stimulate the periosteum, consequently enhancing osteogenesis. NPWT has also been reported to enhance bone regeneration. Zhang et al reported that "NPWT promoted bone regeneration in vivo" and that "negative pressure treatment induced osteoblast differentiation in vitro."[6] The patient received post-amputation NPWT for 13 days. Therefore, NPWT may be effective in bone regeneration.

The patient's background was suitable for bone regeneration. He was relatively young and had no peripheral arterial disease. Therefore, blood flow in the stump was thought to have been sufficient. Sufficient blood flow is essential for bony callus formation.[7] Moreover, the patient did not have diabetes mellitus, which is a known risk factor for delayed fracture healing. Finally, the patient was not a smoker, which is a habit known to increase the risk of nonunion and delayed union of fractures.[8]

Heterotopic ossification (HO) is the formation of mature lamellar bone in the soft tissue. HO occurs after extremity trauma and is associated with inflammation[9]; both the characteristics were observed in this case. However, we believed that the present case was not of HO, but bone regeneration, primarily because the generated fibula grew directly from the stump. Moreover, this growth was not heterotopic but orthotopic. Furthermore, the generated bone had a clearly defined border, whereas HO tends to acquire a chaotic form. It may be clinically crucial to differentiate between HO and bone regeneration because noninvasive treatment options are available for HO, such as nonsteroidal antiinflammatory drugs, diphosphonate, and local radiation therapy.[10]

CONCLUSIONS

This case report suggests that bone regeneration can occur even in adults. The periosteum is believed to be the main factor involved in bone regeneration. To prevent bone regeneration, surgeons should not leave any part of the periosteum behind during limb amputation. Although bone regeneration is rare, it should be considered if adult amputees complain of stump pain. However, it remains unclear whether this phenomenon is based on individual-specific traits or can occur in any amputee. Therefore, similar cases should be gathered and investigated.

Michiko Fukuba, MD, PhD
Department of Plastic, Oral and Maxillofacial Surgery
Teikyo University School of Medicine
2-11-1 Kaga Itabashi-ku, Tokyo, 173-8606, Japan
E-mail: michikofukuba@med.teikyo-u.ac.jp

DISCLOSURE

The authors have no financial interests to decleare in relation to the content of this article.

ACKNOWLEDGMENT

The authors thank the staff of the Department of Orthopedic Surgery, Teikyo University Hospital, for insightful discussion related to this case study.

REFERENCES

1. Bettin D, Böhm H, Clatworthy M, et al. Regeneration of the donor side after autogenous fibula transplantation in 53 patients: evaluation by dual x-ray absorptiometry. *Acta Orthop Scand*. 2003;74:332–336.
2. Dudek NL, DeHaan MN, Marks MB. Bone overgrowth in the adult traumatic amputee. *Am J Phys Med Rehabil*. 2003;82:897–900.
3. Duchamp de Lageneste O, Julien A, Abou-Khalil R, et al. Periosteum contains skeletal stem cells with high bone regenerative potential controlled by periostin. *Nat Commun*. 2018;9:773.
4. Takato T, Harii K, Nakatsuka T, et al. Vascularized periosteal grafts: an experimental study using two different forms of tibial periosteum in rabbits. *Plast Reconstr Surg*. 1986;78:489–497.
5. Watanabe-Takano H, Ochi H, Chiba A, et al. Mechanical load regulates bone growth via periosteal Osteocrin. *Cell Rep*. 2021;36:109380.
6. Zhang S, Xie Y, Yan F, et al. Negative pressure wound therapy improves bone regeneration by promoting osteogenic differentiation via the AMPK-ULK1-autophagy axis. *Autophagy*. 2022;18:2229–2245.
7. Gueorguiev-Rüegg B, Stoddart M. Biology and biomechanics in bone healing. In: Buckley RE, Moran CG, Apivatthakakul T, eds. *AO Principles of Fracture Management*. 3rd ed. New York: Thieme Medical Publishers; 2018;1:9–26.
8. Lee JJ, Patel R, Biermann JS, et al. The musculoskeletal effects of cigarette smoking. *J Bone Joint Surg Am*. 2013;95:850–859.
9. Kraft CT, Agarwal S, Ranganathan K, et al. Trauma-induced heterotopic bone formation and the role of the immune system: a review. *J Trauma Acute Care Surg*. 2016;80:156–165.
10. Shehab D, Elgazzar AH, Collier BD. Heterotopic ossification. *J Nucl Med*. 2002;43:346–353.