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Case report

Repair of segmental ulnar bone defect in juvenile caused by osteomyelitis with induced membrane combined with tissue-engineered bone: A case report with 4-year follow-up

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ABSTRACT

Introduction and importance: We used induced membrane combined with tissue-engineered bone (TEB) to repair the 14-cm juvenile ulnar defect formed after osteomyelitis debridement. The TEB was completely transformed into autologous bone after 4-year follow-up.
Case presentation: A 13-year-old male was hospitalized because of right ulna chronic osteomyelitis. After focal debridement, the total length of ular defect was 14 cm. Anti-infective bone cement was filled in the bone defect area. β-Tricalcium phosphate (β-TCP) was used as TEB scaffold. Autologous iliac bone marrow stromal cells (BMSCs) were cultured in vitro and were planted on β-TCP scaffold to form TEB 3 weeks later. 47 months after implantation of TEB, the repaired ulna had continuous and smooth bone cortex, completely ossification of TEB, completely recanalization of medullary cavity. The upper limb function DASH score was 35.
Clinical discussion: Masquelet put forward the concept of "induced membrane" and applied this technique on bone defects treatment formed after debridement of osteomyelitis. β-Tricalcium phosphate (β-TCP) is artificial bone materials commonly used in clinical. In this case, the seed cells used were autologous BMSCs and the culture medium was autologous serum. Cytokines promoting cell growth and differentiation were not used.
Conclusion: The results of this case showed that TEB combined with induced membrane could repair ulna segmental bone defects as long as 14 cm in adolescents. This technique gives one alternative method to repair juvenile bone defects caused by osteomyelities of trauma. More clinical cases are needed to verify the effectiveness of this technique in the next.

1. Introduction and importance

Segmental bone defect of ulna can cause limitation of forearm rotation, flexion and extension, deformity of the forearm, and seriously affect the function of affected upper limb. At present, the repair methods of segmental bone defects include vascularized autologous bone transplantation [1], allogeneic bone transplantation, Ilizarov bone transportation [2] and personalized 3D printed prosthesis technology [3]. Because teenagers are still in the stage of growth and development, the treatment of segmental bone defect of ulnar needs to maintain the growth and development of ulna while reconstructing ulnar scaffold. Therefore, the repair of adolescent ulna defect caused by various reasons is still a medical problem. We encountered a young patient with chronic osteomyelitis of right ulna. After focal debridement, a segmental bone defect of the ulna with a length of about 14 cm was formed. We used the induced membrane combined with tissue-engineered bone to repair the ulnar bone. The patient was followed up for 4 years. The tissue-engineered bone was completely transformed into autologous bone

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tissue, and the ulna defect was completely repaired. This case was reported in line with the SCARE 2020 criteria [4].

2. Case presentation

The patient was a 13-year-old male middle school student at the time of initial onset. The right forearm swelled with pain without obvious cause in August 2017. He was sent to the local county hospital by his parents. The county hospital gave the patient forearm puncture, pus drainage, intravenous antibiotic and other treatment, but the effect was not satisfied. Skin sinus formed in the right forearm two months late without further treatment. In December 2017, the patient was sent to Xijing Hospital, Air Force Military Medical University, by his parents and hospitalized in the Department of Orthopedics with the diagnosis of "right ulnar osteomyelitis (Figs. 1–2). Focal debridement of the right ulnar osteomyelitis, vacuum sealing drainage (VSD) and external fixator fixation was performed. The result of bacterial culture was *Staphylococcus aureus*. Sensitive antibiotics were given intravenously. After focal debridement, the length of complete ulna bone defect was about 7 cm, and the total length of complete defect plus partial defect was about 14 cm (Fig. 3). 1 week after the above operation, the defect area of ulna was filled with anti-infective bone cement. The patient had been ill for 4 months when he went to our hospital. Due to chronic inflammatory stimulation, there were complications including elbow stiffness, right forearm dysfunction and right wrist back extension disorder. The patient had good health in the past, no bad habits such as smoking and drinking, no family history of mental diseases and genetic diseases.

The patient was rehospitalized in May 2018. The following was the contents of admission physical examination. The right ulna was fixed with single-arm external fixator across both ends of the defect area, the external fixator pins were not loose, and there was no redness and swelling around the pin-tract. The skin temperature was normal without tenderness and percussion pain. The right forearm was varus slightly. The lengths of bilateral forearms were basically the same. The right elbow lost the function of flexion, extension and rotation. The range of motion of the right wrist was 0-15^{o} for back extension and 0–90° for flexion. There was no obvious abnormality in the activity of the right finger. The pulse of the right radial artery was normal. X-ray film showed bone defect in the right ulna, the epiphyseal line of the distal and proximal ulna was clear, and the articular surface of the elbow joint was rough.

Both the patient's parents and himself hoped to recover the function of the right forearm as much as possible and live independently in adulthood. There was no report of repairing such a long bone defect in adolescents. The patient was still in the development stage, autologous iliac bone transplantation would limit the development of iliac bone itself. Because the stumps on both sides of the ulna were close to the epiphyseal line, there had no condition for bone transportation using Ilizarov technique. 3D printed prosthesis could not meet the needs of continuous limb growth. With the consent of patient and his family, we formulated the technical route of "induced membrane combined with tissue-engineered bone (TEB) to repair segmental bone defect of ulna".

The data of the defect area of the patient's right ulna was obtained using mirror principle according to the 3-dimensional CT data of the normal side ulna. We designed, constructed and prepared an individualized tissue-engineered artificial bone scaffold matched with the defect

Figs. 1–2. Anteroposterior and lateral X-ray of ulnar osteomyelitis. The focus of ulnar osteomyelitis showed bone resorption.

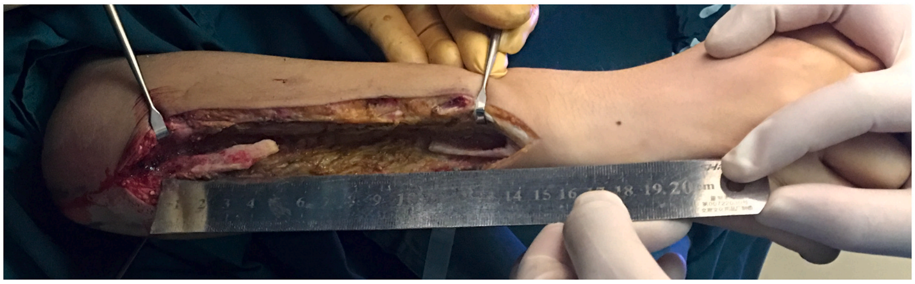


Fig. 3. Bone defect was formed after debridement of ulnar osteomyelitis. The total length of complete bone defect was about 7 cm, and the total length of complete bone defect and partial bone defect is about 14 cm.

area of ulna, which can adhere to autologous osteoblasts cultured in vitro. The scaffold material of TEB was β-tricalcium phosphate (β-TCP, Shanghai Bio-lu Biomaterials Co., Ltd), a kind of porous biomaterial for clinical application. β-TCP particles were filled into a 1:1 mold for ulna defect and then formed and sintered at 1100 °C. Prepared β-TCP tissue-engineered bone scaffold has the porosity of 52 % and pore diameter of (450 ± 50) μ m. It was cylindrical in shape, 140 mm in length, 20 mm in proximal diameter, 15 mm in distal diameter, and the designed "medullary cavity" was 3 mm in diameter (Fig. 4). Tissue engineered artificial bone scaffolds were sterilized by irradiation at a dose of 25 kGy. Autologous iliac bone marrow stromal cells (BMSCs) were cultured in vitro, and the transformation of autologous BMSCs into osteoblasts was induced with the patient's own serum as the culture medium. After having been cultured in vitro for 3 weeks, a sufficient number of autologous BMSCs were obtained and planted on β-TCP scaffold material to form TEB, the cell density was 5×10^6 cells/ml. Implantation of TEB into the induced membrane in ulna bone defect was proceeded in May 2018. The surgical incision was along the original incision of the right ulna to expose the defect area of the ulna. The induced membrane formed on the surface of bone cement was protected and incised, bone cement was taken out, the medullary cavity of the distal and proximal stump of ulna were reopened. Then, TEB was implanted into the patient's right ulna bone defect site, the induced membrane was carefully sutured. Due to its brittleness, a fissure formed at the middle part of TEB during implantation. The stability of TEB was not affected after implantation. Single-arm external fixator provided external stability for TEB (Figs. 5–6). Cefazolin sodium was given intravenously for 48 h to prevent infection (2.0 g, twice a day). The above operations were performed by Professor Guolin Meng and his team. Professor Meng, MD and PhD, has 20 years of clinical experience in orthopedics. The repair progress of TEB was detected through X-ray film, CT image, limb length detection and upper limb function DASH (Disabilities of the Arm, Shoulder and Hand, DASH) score [5].

3. Results

The patient was followed-up regularly. He could cooperate with the rehabilitation exercise requirements of the doctor and had good compliance with reexamination. Erythrocyte sedimentation rate (ESR), hypersensitive C-reactive protein (CRP), and blood routine tests were returned to normal. The wound healed well and the sutures were removed 12 days after operation. 4 months after operation, the X-ray film showed that there was callus formation between the two ends of TEB and autologous ulna, the interface was partially healed (Figs. 7–8). 7 months after operation, TEB and ulna healed gradually, TEB ossified gradually. The fissure at the middle part of TEB formed during implantation began to heal. Because the external fixator was loose, it was removed at the end of 8 months after operation (Figs. 9–10). 37 months after operation, X-ray film showed that the TEB transferred to autologous bone and healed with his own ulna, the medullary cavity of ulna could be seen (Figs. 11–12). 47 months after operation, X-ray films showed continuous bone cortex, complete recanalization of medullary cavity, complete ossification of TEB. The right elbow fused completely. No residual TEB scaffold material could be seen on the X-ray film (Figs. 13–14). The length of ulna increased from 23.5 cm before operation to 26.1 cm by the end of 47 months follow-up. Functional exercise of the affected arm was started 4 weeks after operation under the guidance of a rehabilitation therapist. 47 months after operation, the DASH score of the affected arm was 35. The patient is now 17 years old. He can use the affected limb to complete daily activities such as writing, playing basketball and carrying certain weight items. At present, he is engaged in some manual labor on the construction site.

4. Clinical discussion

Segmental bone defect of ulna can cause limitation of forearm rotation, flexion and extension, it also could cause forearm deformity. At present, the repair methods of segmental bone defects include vascularized autologous bone transplantation, allogeneic bone transplantation, Ilizarov bone transportation and personalized 3D printed prosthesis. Because children and adolescents are still in the stage of growth and development, the repair of large bone defects is different from that of adults.

Free vascularized fibula transplantation can provide abundant blood supply, reduce the probability of infection, facilitate healing and could repair segmental bone defects. After 1 year follow-up, the time of complete bone healing between vascularized fibula and ulna was 4–6 months, the excellent and good rate of forearm rotation was 72.7 % [1]. However, this technology requires skilled microsurgical technology, with large trauma, long operation time, the risk of instability, pain and

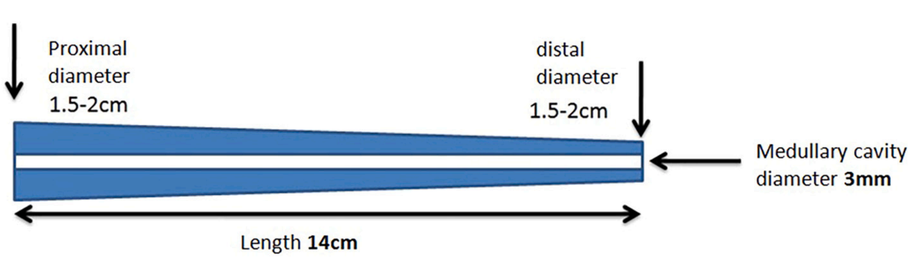
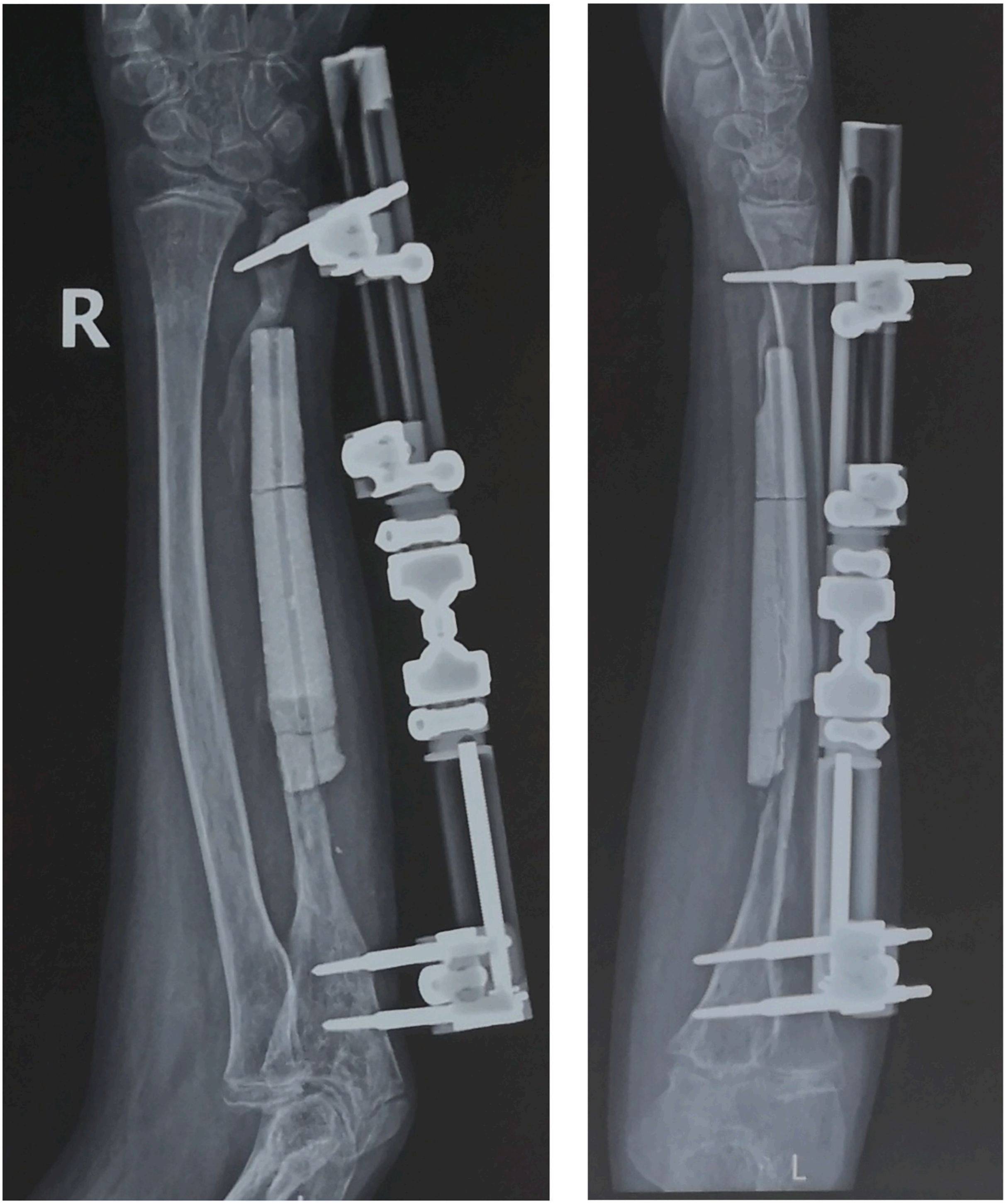


Fig. 4. The diagram of the designed tissue engineered bone scaffold for ulna defect.

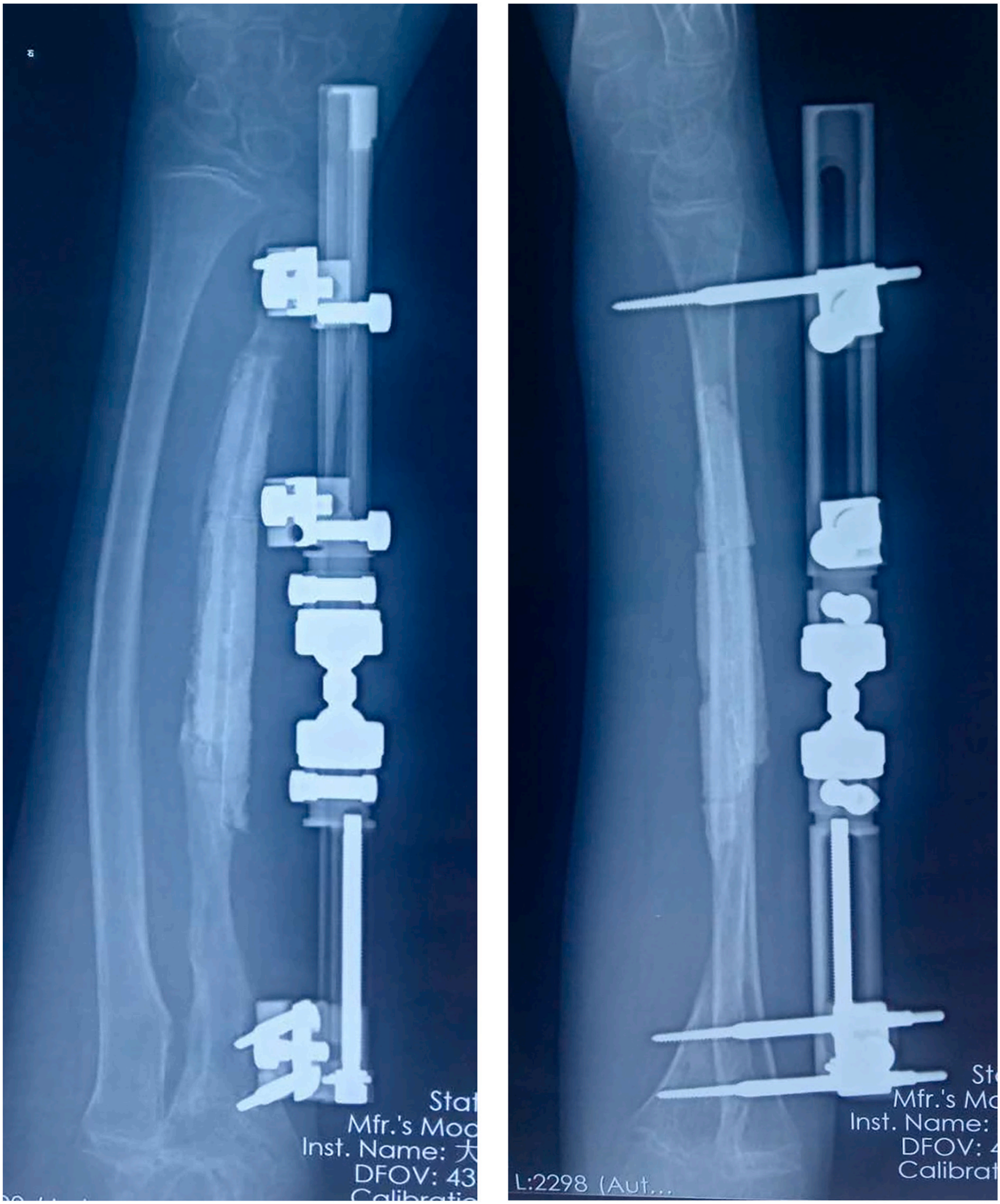


Figs. 5–6. Anteroposterior and lateral X-ray films after the tissue-engineered bone was implanted into ulnar bone defect. A fissure formed at the middle part of TEB during operation could be seen.

deformity of ankle joint on the fibular donor extremity [6].

The bone transportation technique invented by Ilizarov is widely used in clinical practice. Excessive tissue peeling could be avoided. Important blood vessels, tendons, ligaments and nerves could be protected. However, there are still some problems, such as long treatment cycle, inconvenient postoperative care, skin-cutting by external fixator pins, pin-tract infection, poor alignment of fracture ends and incarceration of soft tissue. Multiple operations may be required in the later stage [7]. In this case, the two ends of segmental bone defect of ulna were close to epiphyseal line. There had no condition of bone transportation.

3D printed technology is a hot-spot in orthopedics in recent years. Guo [8] applied the 3D printed titanium alloy prosthesis of scapula and clavicle to repair the defects of scapula and clavicle after tumor resection, which achieved good clinical results. Cheng et al. used individualized 3D printed titanium alloy prosthesis to repair traumatic defects of distal fibula and lateral malleolus, satisfactory results were also achieved [3]. Although 3D printed titanium alloy prosthesis has incomparable advantages over traditional treatment methods, it still has limitation as that it cannot meet the needs of continuous bone growth for



Figs. 7–8. 4 months after operation, the X-ray film showed that there was callus formation between the two ends of TEB and autologous ulna, the interface was partially healed.

children and adolescent patients who are still in the period of bone development.

Masquelet proposed the concept of "induced membrane" and applied the induced membrane technique to the treatment of bone defects formed after debridement of osteomyelitis [9]. After bone cement occupation, "induced membrane" formed on the surface of bone cement could isolate the invasion of surrounding soft tissue to bone graft, and could provide some cytoactive factors such as bone morphogenetic protein(BMP). 35 cases of long bone defects were treated by induced membrane technique, the length of bone defect was from 4 cm to 25 cm. The bone defect healed well after 10 months [10]. Induced membrane is now widely used in the treatment of large bone defects, especially in the treatment of bone defects caused by osteomyelitis. However, the amount of autologous bone required in Masquelet technique is large. Autologous bone needs to be taken from multiple parts of the whole body. Taking large amount of autologous bone could cause iatrogenic trauma in the donor sites. There is still a risk of complications such as bone nonunion and stress fracture in the bone graft area. In this case, it is very difficult

Figs. 9–10. 7 months after operation, TEB and ulna healed gradually, TEB ossified gradually. The fissure at the middle part of TEB began to heal.

Figs. 11–12. 37 months after operation, the TEB transferred to autologous bone and healed with his own ulna.

to take a large amount of autologous cancellous bone to repair the bone defect because it is still in the development stage.

At present, tissue-engineering technique has been proposed as an alternative to traditional technology in bone defect reconstruction [11,12]. Bone defect treatment is developing from traditional autologous and allogeneic bone transplantation to biomaterial based tissue engineering. The combination of living cells with osteogenic potential into biomaterials to construct TEB undoubtedly provides a new idea for the repair of bone defects. β-TCP is one kind of artificial bone materials commonly used in clinical. The complete degradation time of β-TCP in vivo is about 7 months. Chen et al. [13] used TEB to repair large bone defects of goat load-bearing bone. After long-term observation, the

Figs. 13–14. 47 months after operation, the repaired ulna had continuous and smooth bone cortex, completely recanalization of medullary cavity and completely ossification of TEB.

results showed that no inflammatory cells were found in the scaffold at different time-phases. No residual material particles were found in the experimental group. It confirmed that β-TCP has good biocompatibility. The degradation time of β-TCP is close to that of osteogenesis, so it is a more suitable scaffold material for bone tissue engineering [14,15]. In the treatment of this patient, TEB was implanted into the "induced membrane" formed after bone cement occupation. The induced membrane isolated the invasion of surrounding soft tissue to TEB, it also provided some cytokines benefit for the procedure of TEB repairing ulnar bone defect. The applied seed cells were autologous BMSCs, the culture medium was autologous serum. No additional cytokines promoting cell growth and differentiation was used. There was no immune rejection, no need to use anti-rejection drugs, and the safety is good. The X-ray film 7 months after operation showed obvious osteogenic repairment and good revascularization process. 37 months after operation, the morphology of new bone was close to normal, with normal cortical bone structure and recanalization of medullary cavity. After 4 years follow-up, it was observed that the upper limb on the affected side grew in the same proportion with the normal side. The elbow joint of the affected side was stiff, but it had nothing to do with TEB and induced membrane. The ulnar bone defect had been completely repaired. The TEB was completely ossified finally and has the function of normal bone tissues.

5. Conclusion

The results of this case showed that TEB combined with induced membrane could effectively repair ulna large segmental bone defects as long as 14 cm in adolescents. The applied seed cells were autologous BMSCs, the culture medium was autologous serum, and the cytokines promoting cell growth and differentiation had not been used in the whole process. The scaffold of TEB was β-TCP, which is a biomaterial approved by the SFDA for clinical application. Therefore, there had no immune-rejection; no need to use anti-rejection drugs, and the safety was higher. TEB combined with induced membrane technique might be used as one alternative method for the repair of segmental bone defects in juveniles caused by osteomyelities or trauma in the future. Due to the small number of cases, more clinical cases are needed to verify the effectiveness of this technique next.

Provenance and peer review

Not commissioned, externally peer reviewed.

Consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the signed written consent form is available for review by the Editor-in-Chief of this journal on request. We decide that color should be used for all figures in print.

Ethical approval

Ethical approval was not needed for writing a case report in our settings.

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Guarantor

Guolin Meng.

Research registration number

Not applicable.

CRediT authorship contribution statement

Guolin Meng: corresponding author, performed the operation and wrote the paper; Zhengyu Li: co-corresponding author, followed up the patients and analyzed the data; Yang Gao, Jiangang Cheng and Zhuoyu Long: have made consistent contributions to this paper, managed the treatment for the patient and wrote the paper; Pengzhen Cheng and Shuaishuai Zhang: cutured MSCs; Guoxian Pei: corrected the paper.

All authors reviewed the manuscript.

Declaration of competing interest

None of the authors have any conflicts of interest.

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