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Case Study

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Salvage of a femoral nonunion after primary non-Hodgkin's lymphoma of bone: A case report and literature review

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: With the advent of superb microsurgery techniques and advanced stabilization instruments, recent decades have seen great progress in treating nonunions secondary to traumatic fractures. However, those nonunions that are secondary to primary non-Hodgkin's lymphoma of bone and often related to irradiation still remain a challenging problem. The condition could be more perplexing when bone healing abilities are greatly compromised and reliable stabilization is difficult.

Case Report: We performed an operation using free vascularized fibular graft in combination with a locking plate on a 47-year-old female patient who had suffered from a three-year femoral nonunion after courses of radiochemotherapy for the treatment of primary non-Hodgkin's lymphoma of bone, a spontaneous femoral shaft fracture, an intramedullary nailing, and some nonoperative interventions in sequence. Primary union of the graft was obtained at 9 months without wound infection. No recurrence of lymphoma occurred in the 61-month follow-up, nor did a stress fracture or failure of fixation. Limb salvage was achieved and the range of motion of the adjacent joints was acceptable.

Conclusions: Free vascularized fibular graft in combination with a locking plate can effectively enhance bone union in compromised bone and soft tissue milieu. More cases have yet to be further investigated.

key words: **free vascularized fibular graft • nonunion • Non-Hodgkin's lymphoma • locking plate**

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Background

Primary non-Hodgkin's lymphoma (NHL) of bone is rare, accounting for less than 5% of extra-nodal NHL and 3% of all bone malignancy [1]. Classically, the treatment regime includes chemotherapy and radiotherapy, which may contribute to pathological fractures, or even nonunion [2]; then surgical interventions are required.

Conventionally, nonvascularized autografting is preferable for a bone defect less than 5-8cm secondary to a nonunion because of the slow and incomplete neovascularization of the graft [3]. Bone allografts diminish donor-site morbidity and enable the use for larger defects when compared with autografts [4]. However, allografts are limited to rare sources and the procedure runs risks of immunological rejection and spread of diseases. Also, the biological behavior of allografts is inferior to that of autografts [5]. Current advances in microsurgery make vascularized fibular graft (FVFG) available to deal with large skeletal defects. These grafts retain their intrinsic blood supply, which contributes to the promotion of bone union and graft hypertrophy [6].

Nevertheless, pathologic fracture nonunions after irradiation are frequently characterized by thin cortex, poor bone stock and extensive soft-tissue damage, which make it challenging to maintain the stability of the osteosynthesis following bone grafting until graft union is achieved. Locking-plate technology is believed to provide better purchase in poor quality bone and equivalent purchase with fewer screws, and also to prevent screw pullout due to its unique angular stabilization. We present the case of a female patient with a recalcitrant femoral nonunion after radiotherapy for primary non-Hodgkin's lymphoma of bone that we treated with FVFG in combination with a locking plate.

Case report

Patient

The 47-year-old woman complaining of worsening pain in her right thigh for months was diagnosed with primary non-Hodgkin's lymphoma of bone. Courses of chemotherapy and radiotherapy were administered, but the dose of irradiation was unknown. Months later, she heard a crack from her right femur and felt sudden pain when putting on trousers in the morning. She was sent to a local hospital, where she was diagnosed as having a pathological fracture in the right femoral shaft (Figure 1), which was then fixed with an intramedullary nail (Figure 2). The fracture, however, didn't heal (Figure 3), despite some nonoperative interventions such as low-intensity pulsed ultrasound, and extracorporeal shock wave therapy. Three years later she was referred to our institution. Neither metastasis nor lymph node involvement was revealed through a thorough examination.

Surgical technique

The operation was performed under general anesthesia. First, a radical debridement was performed to ensure the removal of all necrotic or nonviable tissue in the nidus up to the bleeding tissue. The debrided bone and soft tissue were immediately collected for pathologic examination as well as microbiological testing. The wound was copiously irrigated

Figure 1. Spontaneous fracture in the diaphysis of right femur. Roentgenograms showed some lytic changes around the fracture ends.

with normal saline. Second, the screws and broken nail fragments were removed, and a 9-cm-long trough was created in the lateral cortex. Third, contralateral FVFG was harvested through a lateral approach under tourniquet control according to our previous technique [7]. The graft was 9 cm in length, leaving at least 6 cm of the distal fibula to ensure ankle stability. Fourth, the graft was placed in the slot made in the femur cortex, and a 13-hole locking plate (LISS for femur) was applied to fix both junctions (Figure 4A). After fixation was completed, an end-to-end microvascular anastomosis of the peroneal vessels with the descending branch of lateral femoral circumflex vessels was performed under guidance of an operating microscope. Finally, the wound was closed directly after insertion of drain tubes.

Postoperatively, no micro-organisms were cultured from the excised specimen and no recurrence of lymphoma was revealed. The involved extremity had been restricted for weight-bearing ambulation until radiological union occurred between the fibular graft and the host femur. Consent was obtained from the patient to allow the data of her case to be submitted for publication in medical journals.

Results

The patient recovered uneventfully. Primary union of the fibular graft occurred at 9 months postoperatively and the patient experienced no pain. Although there was still residual nonunion in the medial cortex, the patient declined further treatment and started to ambulate with use of a walking stick, which she discontinued to use 2 years later. Until the

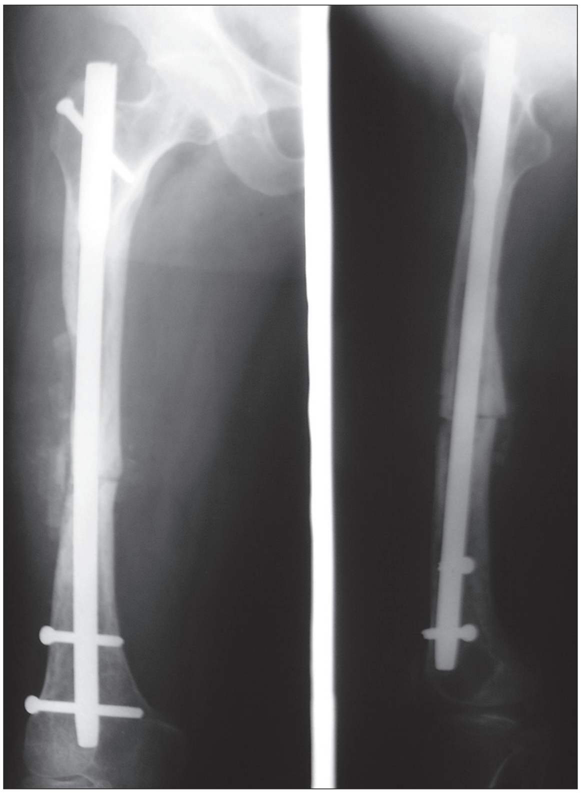

Figure 2. Postoperative film after fixation with an intramedullary nail. Open reduction and internal fixation was done followed by resection of bone lesion and bone grafting in the lateral cortex performed in a local hospital.

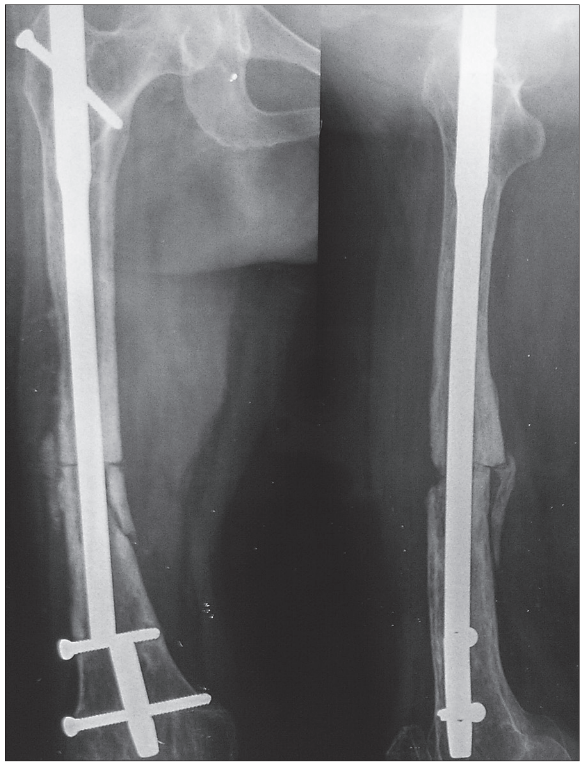

Figure 3. A radiograph is shown three years later, depicting the broken nail and fracture nonunion, with a segment of bone in the medial cortex.

61-month follow-up (Figure 4B,C), no stress fracture or fixation failure occurred. The range of motion of the adjacent joints, namely the hip and knee joints, were slightly limited, but she was satisfied since she could return to work at home.

Discussion

As demonstrated in the current literature, primary lymphoma of bone (PLB) is rather rare clinically, so there is a paucity of information regarding the management of pathologic fracture nonunions, which are distinct from those resulting from ordinary trauma. Possible reasons include the use of adjuvant chemotherapy, radiation therapy at the fracture site, and alterations in the biological milieu from prior surgical procedures. After radiotherapy, there is often a decrease of osteoclasts and osteoblasts [8]. Radiation generates free radicals and reactive oxygen species, which damage vital cellular targets such as DNA and membranes and affect the niches for stem cells [9]. Metabolic bone activity can also be decreased, which leads to radiation osteitis, atrophy and osteopenia. Specifically, animal studies after irradiation have demonstrated decreases in bone vascularity, cellularity of the cortex, rate of new bone formation and dry weight of bone [10]. Not surprisingly, bone healing abilities are greatly compromised and these fractures tend to have a high rate of nonunion in radiation-related fractures. Lin et al. [11] described the union of such fractures in only 4 out of 12 cases after open reduction and internal fixation and bone grafting. In all 4 cases, union was delayed beyond 12 months and 17 complications occurred in 10 patients. Helmstedter et al [12] reported on a series of 20 radiation-associated fractures, among which 12 occurred in femurs. The nonunion rate was 45% in those fractures. Furthermore, the authors identified a significant decline in functional outcome after surgical treatment of fractures involving femurs. Livi et al. [13] reported union in only 4 of 7 such fractures after surgery; the other 3 patients underwent amputation of the affected limb.

Currently, there is no clearly superior technique for the treatment of nonunion. Both autografts and allografts have been widely used. Nevertheless, revascularization of nonvascularized autografts and allografts is slow and restricted to the peripheral third of the graft [3]. They usually heal by creeping substitution, the prolonged process of simultaneous osteoclastic and osteogenic activity, which weakens these grafts and renders them susceptible to fracture, delayed union and nonunion [14]; therefore, their use is confined to defects shorter than 5 to 8 cm in length. Some physical methods, such as low-intensity pulsed ultrasound and extracorporeal shock wave therapy, which were previously used in our patient, have been shown to enhance bone formation in some nonunion cases, but their role is still controversial, and the currently available evidence suggests that hypertrophic nonunions show a better response than atrophic ones [15,16]. In other words, viable tissue or vascularized bone is probably a prerequisite for the success of these physical methods, and they were not able to facilitate bone union effectively before our procedure.

Unlike cortical allograft and nonvascularized autograft, vascularized bone grafts do not depend on gradual

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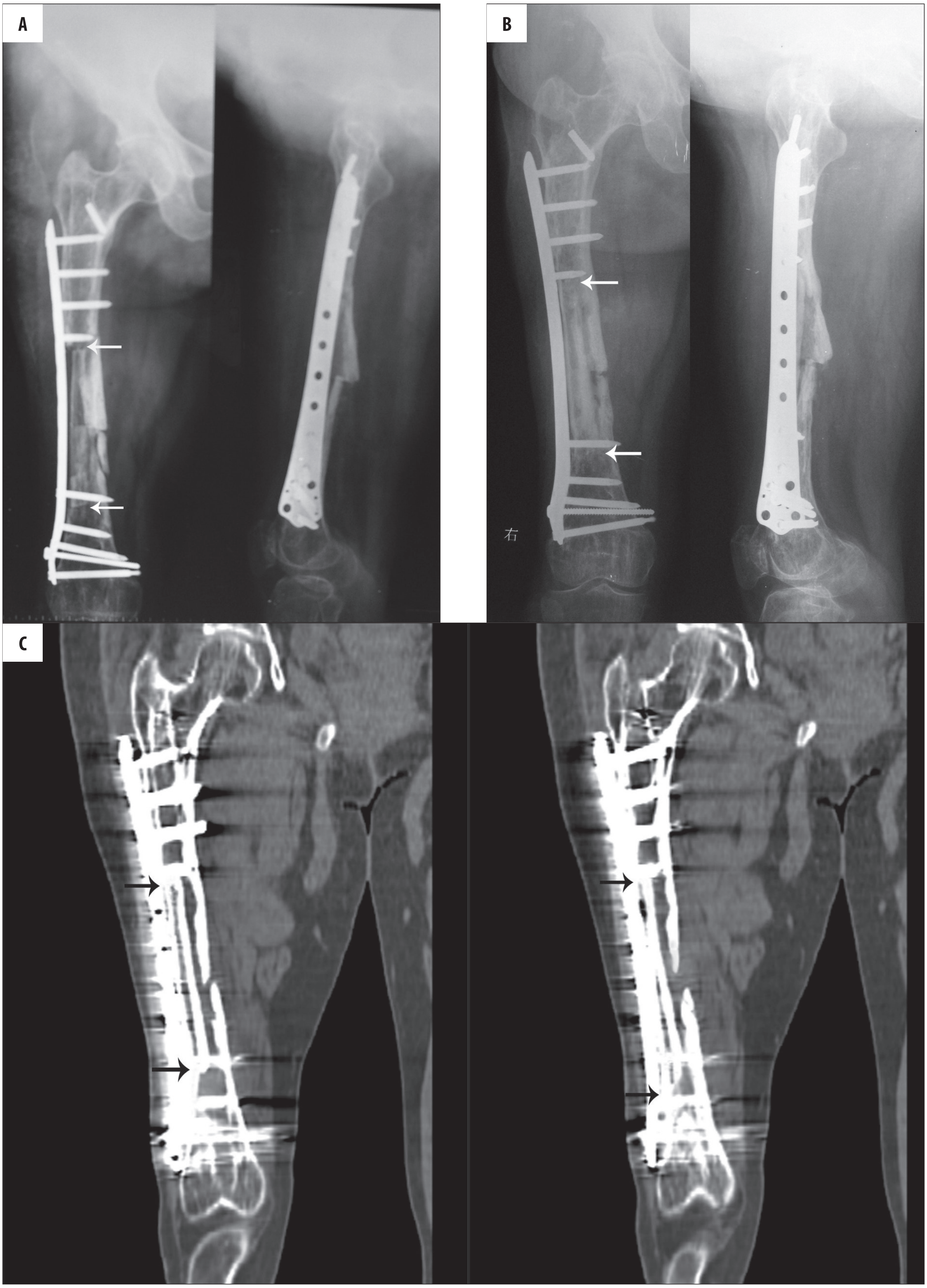

Figure 4. X-ray film following the revision performed in our institution. (**A**) A 9-cm FVFG and a femoral LISS plate were surgically implanted for reconstruction of the bone defect after debridement. The arrows indicate both ends of the fibular graft. At 61 months postoperatively, the X-ray (**B**) and coronal CT scan (**C**) demonstrated the gaps at graft-host junction sites disappeared and osseous continuity could be found (white arrows on X-ray films and black arrows on CT section). Hypertrophy of the fibular graft was also observed.

revascularization [17]. Of the multiple osseous donor sites, the FVFG, since its introduction in 1975, has become the most commonly transferred vascular autograft for reconstructing segmental bone defects after trauma, nonunion, osteonecrosis and tumor resection. The dual vascularity of the fibula, which derives from endosteal and periosteal vessels, is still viable when immediate and successful microvascular anastomoses are performed between fibular vessels and recipient vessels. Hence, bone healing occurs by simple fracture union rather than by a "creeping substitution" after transfer [17]. Reconstruction using FVFG often means a great potential for rapid union and is more resistant to infection and irradiation than nonvascularized counterparts [18,19]. This will minimize complications in patients whose underlying physiologic milieu may be compromised owing to chemotherapy, immunosuppression or radiotherapy. Additionally, because of its unique anatomic and biomechanical properties, the FVFG can provide a cortical strut for reconstruction up to 26 cm in length, meanwhile leaving less donor-site morbidity than vascularized ribs or iliac crest grafts [20].

As for fixation, there are numerous biological and mechanical obstacles present in oncology patients which make osteosynthesis more challenging than in common fracture patients [21]. Biological obstacles include chemotherapy, irradiation, and pathologic host bone. Mechanical obstacles consist of long pathologic segments, short residual host segments, multiple implants and the presence of polymethylmethacrylate. Thus, a nonunion resulting from a pathologic fracture like the patient mentioned presents many challenges to surgeons, as the bone quality is compromised from a previously destructive oncologic process and subsequent radiochemotherapy followed by a failed fixation, which create significant biological barriers for cellular response and tissue repair. Low bone mineral density, once regarded as a fracture risk [22], also indicates decreased strength and ability to hold fixation. This makes it difficult to obtain satisfactory stabilization when conventional fixation devices, such as traditional compression plates and intramedullary nails, are used. Thus, it is advised to treat these fractures in a manner similar to that used for severely osteoporotic fractures [23].

In recent years, locking-plate technology has gained popularity as an attractive option, especially for the stabilization of intractable fractures and nonunions. As a biomechanical internal fixation system, locking plates have integrated both the advantages of fixation techniques and the latest advances of the biological plating technique [24]. Studies have shown the efficacy of this technique to treat nonunion fractures with relatively low rates of complications [23]. Different from conventional plates, locking plates feature an angular stable interface between screws and plates, which allows plates to be placed without contact to bone underneath, thus preserving periosteal blood supply and bone perfusion. In addition, locking plates offer relative stability rather than absolute stability, therefore they are able to minimize stress shielding and further promote graft hypertrophy [6].

The literature regarding application of locking plates in orthopedic oncologic reconstruction is still limited. Virkus et al. [23] reported bone union in 23 of 25 oncologic reconstructions involving locking plates at mean follow-up of 18.2 months. The union rate is much higher than those mentioned above, although such comparison needs to be further investigated.

Stress fracture of fibular grafts is a special complication for large bone defects in the extremities. Possible mechanisms are excessive mechanical stimulation upon fibular grafts and misalignment following inappropriate fixation [25]. In our patient, no stress fracture or fixation failure occurred in postoperative 61-month follow-up. Its success can be attributed to reliable fixation in proper alignment with the suitable locking plate, which was proved to be effective by Sun et al. [26]. Another reason may be related to significant hypertrophy of the fibular graft. The exact mechanism is not completely understood, but mechanical loading of the graft appears to be a critical factor, and patients who received chemotherapy are believed to have a faster progression of graft hypertrophy than those who didn't [6]. These reasons may help explain why our patient with residual nonunion in the medial cortex could ambulate for over 5 years without occurrence of stress fracture or fixation failure, which mostly occurs within 1 year postoperatively [27]. A single report, nonetheless, cannot provide adequate data for sufficient interpretation.

Conclusions

This case report highlights the potential for successful reconstruction of a complicated femoral nonunion after primary non-Hodgkin's lymphoma of bone, using a FVFG in combination with a locking plate. This technique can effectively promote bone union in the compromised bone and soft tissue milieu. Additional cases have yet to be further investigated.

Conflicts of interest

The authors declare that there are no funding sources associated with this study.

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