

Surgical Treatment for Patients With Hemophilic Pseudotumor-Related Femoral Fracture: A Retrospective Study

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Abstract

Purpose: Hemophilic pseudotumor (HPT)-related fracture is a rare but severe complication in patients with HPTs. These fractures often occur in femurs. There is no consensus on the standard surgical protocol for HPT-related femoral fracture. The aim of this retrospective study is to evaluate the outcome of these patients treated with surgical interventions.

Methods: Ten patients with HPT-related femoral fractures who were treated with 12 surgical procedures in our hospital from Jan 2014 to April 2020 were retrospectively evaluated. Demographic data, fracture location, complications after operation and follow-up outcomes were recorded and analyzed with a mean follow-up period of 39.7 months.

Results: Bone union was observed in five patients, an adequate callus was visible in two patients, and three patients underwent amputation. Both of 2 patients with closed reduction external fixation (CREF) had pin infection. Nonunion combined with external fixation (EF) failure occurred in one of whom, and the plate was broken after open reduction internal fixation. Three patients underwent autogenous or allogeneic cortical strut grafting. Three patients had HPT recurrence.

Conclusion: It is necessary to perform surgery in patients with HPT-related femoral fractures. Surgical treatments must take both fracture stabilization and HPT resection into account. Internal fixation is preferable and EF should be dismissed unless for the purpose of temporary fixation. If the HPT erodes more than one-third of the bone diameter, strut grafts are necessary for mechanical stability. Amputation is a proper curative method in certain situations.

Introduction

Hemophilia is an X-linked hereditary bleeding disorder caused by a deficiency or lack of coagulation factor VIII (FVIII), leading to hemophilia A (HA), and factor IX (FIX), leading to hemophilia B (HB)[1]. This deficiency results in recurrent bleeding episodes in the musculoskeletal system. Hemophilic pseudotumor (HPT), a result of recurrent bleeding from extra-articular bone or soft tissues, develop in severe hemophilia with a prevalence of 1–2%[2, 3]. HPTs usually progress asymptotically for years, causing symptoms when pathological bone fracture or neurovascular compression occurs[4]. Gilbert has described two clinical types, including proximal pseudotumors and distal pseudotumors. Proximal pseudotumours occur in the proximal skeleton of adult patients, especially around the femur and pelvis, develop slowly and do not respond to conservative treatment. Distal pseudotumours occurring distal to the wrist and ankle, developing rapidly, which are seen mainly in children and adolescents[4, 5]. Besides, according to the imaging features and location of HPTs, they can be classified into 3 types: soft-tissue, subperiosteal and intraosseous types[6]. HPTs will normally involve adjacent bone, result in massive bone destruction[7].

Patients with hemophilia often have osteoporosis or low bone density[8]. When combined with HPTs, pathological fractures are more likely to occur, and these fractures are caused by minimal trauma or have

no obvious cause. The femur is the most susceptible long bone to HPTs; accordingly, most HPT-related pathological fractures occur in the femur[9–11].

Surgical procedure is viewed as an effective treatment for HPTs, especially for cases complicated by HPT-related fractures. However, there is no consensus on the standard surgical protocol because of the complexity and variety of HPTs and fractures. Surgeons may encounter many challenges during operation, such as abnormal anatomy and multiple fixation options and bone reconstruction programs. In addition, complications including nonunion, infection, fixation failure, inhibitor development and pseudotumor recurrence should not be ignored, as they exert a profound influence on patient outcomes[7, 12]. Due to the rarity of these fractures, reports of surgical treatment for patients with HPT-related femoral fractures are scarce. In this retrospective study, we pooled our experience to evaluate the outcome of orthopedic surgery for patients with HPT-related femoral fractures.

Materials And Methods

In this study, we retrospectively reviewed patients with HPT-related femoral fractures who underwent orthopedic surgery in our Hospital between January 2014 and April 2020. Patients with conservative treatment or defective medical records were excluded from the study. Hemophilia was classified as either severe (< 1%), moderate (1 ~ 5%) or mild (> 5%) depending on the level of FVIII/IX activity.

The units of coagulation factor use were dynamically adjusted according to the concentration of factors during the perioperative period. Patients with hemophilia A received plasma-derived or recombinant FVIII throughout the entire treatment phase. Patients with hemophilia B received recombinant FIX only on the day of surgery, and the rest of the time, they received prothrombin complex concentrate due to economic considerations. Preoperatively, all patients received coagulation factor replacement to maintain a peak factor level of over 100% during surgery, a factor level of 80% on postoperative days 1–2, 40–60% on postoperative days 3–6, and 30–40% on postoperative days 7–14; a factor level of 20–30% was maintained until the end of the rehabilitation period.

All surgical procedures were performed by same surgical team. For HPT excision, a single incision was made to reduce the fractures and expose the pseudotumor. Pseudotumor resection began with as much normal tissue as possible. If the pseudotumors were adjacent to nerves and blood vessels, the surrounding cyst wall could be only partly incised, and the fibrosed tissue and clotted blood contained within the cyst were drained. The remaining wall was closed with sutures. The cyst cavity within the soft tissue was eliminated with biodegradable gelatin sponge and hemostatic gauze, and the bone cavity was filled with autologous or allogeneic cancellous bone grafts, combined with manual compression of the grafts into the cavity. Elastic bandages were used to wrap the affected area with compression for 2 weeks. HPT curettage and bone grafting were performed for cystic lesions originating within the bone. If a massively eroded unilateral cortex was present, allogeneic or autogenous bone strut graft was used for mechanical stability. For fracture management, closed reduction external fixation (CREF), open reduction internal fixation (ORIF), screw fixation, brace immobilization and amputation were performed according

to the fracture situation and patients' willing. All patients or patients' parents provided informed consent of permitting their anonymous data for research purposes and this study was approved by the Ethics Committee of our Hospital.

Results

Of 14 patients, 4 were excluded from the study because they were treated conservatively. Therefore, data from 10 patients were available for the study. All patients were male, with an average age of 31 years (11 to 46). The mean follow-up period was 39.7 months (6 to 82). According to the severity, 5 patients were classified into the severe group, and 5 patients were classified into the moderate group. Four fractures were caused by falling, and the rest did not have an obvious cause. The general characteristics of the patients are shown in Table 1.

Table 1
General characteristics of the patients

Patient (No.)	Age	Diagnosis	Severity	Fracture Location	Type of treatment	Follow-up(mo)	Outcome
1	46	HA	Severe	L Shaft	CREF	6	Pin infection after 3 mo combined with visible adequate callus, and inhibitor developed after 4 mo, patient refused further intervention. Died due to severe bleeding and infection 6 mo later.
2	23	HA	Severe	L Distal	HPT excision, ORIF	83	Bone union, no HPT recurrence
3	44	HA	Moderate	R Shaft R Shaft (revision)	CREF HPT excision, ORIF	61	Pin infection after 2 weeks, treated with dressing change and discontinuous use of antibiotics, was not resolved until fixation failure, HPT excision performed after 2 mo. Fixation failed with fracture nonunion after 13 mo. HPT recurrence, plate broken 3 mo after ORIF, high-thigh amputation was performed finally.

Abbreviations: HA: hemophilia A; HB: hemophilia B; HPT: hemophilic pseudotumor; ORIF: open reduction internal fixation; CREF: closed reduction external fixation; R: right; L: left.

Patient (No.)	Age	Diagnosis	Severity	Fracture Location	Type of treatment	Follow-up(mo)	Outcome
4	20	HA	Moderate	R Shaft	HPT excision, ORIF, allogeneic cortical strut graft	30	Bone union, no HPT recurrence
5	31	HB	Severe	L Distal	HPT excision, ORIF, allogeneic cortical strut graft	31	Bone union, no HPT recurrence
6	38	HA	Severe	L Shaft	High-thigh amputation	45	No HPT recurrence
7	26	HB	Moderate	L Shaft R Shaft	Hip disarticulation, HPT excision in another thigh R high-thigh amputation	77	HPT recurrence after 3 mo in another thigh, femoral fracture caused by HPT compression after 4 yr No HPT recurrence
8	11	HB	Moderate	R Distal	HPT curettage, allogeneic cancellous bone graft, immobilization with brace	27	Bone union, no HPT recurrence
9	28	HA	Severe	R Distal	HPT excision, autogenous cortical strut bone graft, allogeneic cortical strut bone graft, screw fixation	29	Bone union, thigh HPT recurrence after 1 year was treated with coagulation factor replacement without further progress. Tibial shaft fracture resulted from trauma 1 year later, was treated with ORIF

Abbreviations: HA: hemophilia A; HB: hemophilia B; HPT: hemophilic pseudotumor; ORIF: open reduction internal fixation; CREF: closed reduction external fixation; R: right; L: left.

Patient (No.)	Age	Diagnosis	Severity	Fracture Location	Type of treatment	Follow-up(mo)	Outcome
10	48	HA	Moderate	R Shaft	HPT excision, ORIF	8	Visible adequate callus was observed, no HPT recurrence
Abbreviations: HA: hemophilia A; HB: hemophilia B;HPT: hemophilic pseudotumor; ORIF: open reduction internal fixation; CREF: closed reduction external fixation; R: right; L: left.							

The mean operative time was 195.5 minutes (82 to 268). The mean hospital stay was 21.9 days (9 to 32). One patient developed postoperative hematoma, which was resolved by ultrasound-guided puncture and drainage. One patient had abnormal postoperative wound aseptic exudation, which was resolved by dressing changes.

Seven fractures occurred in the femoral shaft, and the other 4 occurred in the distal femur. For fracture management, CREF was originally performed in 2 patients, ORIF in 4, screw fixation in 1, brace immobilization in 1 and amputation in 3. All patients treated with ORIF underwent fixation with anatomically locking plates. Three patients underwent autogenous or allogeneic cortical strut graft implantation. Grafts include fabula and allogeneic femoral head (Fig. 1). Bone union was observed in five fractures, and adequate callus was visible in two fractures.

Both patients treated with CREF had pin infections. Although an adequate callus was visible in one patient, he developed high-tier coagulation inhibitor, refused further intervention, and died due to severe bleeding and infection 6 months after surgery. Another patient was treated with dressing changes and the discontinuous use of antibiotics, and the infection was not resolved until fixation failure occurred. In this patient, fixator failed combined with fracture nonunion after 13 months; the patient underwent revision surgery of HPT excision and ORIF. However, the plate was broken and HPT recurred 3 months later, high-thigh amputation was performed to ultimately resolve the symptoms (Fig. 2).

Three patients had recurrent pseudotumors. Except one mentioned above, one of them had a recurrent pseudotumor in the other thigh at 3 months after excision, and pseudotumor progression and bone erosion occurred, which resulted in another femoral fracture 4 years later. The other patient had HPT recurrence 1 year after the primary surgery, and HPT progression was halted with the use of coagulation factor replacement therapy.

Discussion

In patients with hemophilia, poor musculature and reduced bone mineral density may predispose them to the risk of fractures[9]. HPT-related fractures are a severe complication of HPTs and may be caused by minimal trauma or have no obvious cause[13]. Jensen et al. demonstrated that bone may be affected by HPTs through pressure necrosis and the femur is the most common site of involvement[11]. Usually, HPTs

progress asymptotically until pathological bone fractures or neurovascular compression occurs[4]. Literatures recommend surgical treatment for HPTs combined with bone erosion or fracture[12, 4]. There is no consensus on the standard surgical protocol because of the complexity and variety of HPTs and fractures. Thus, surgery is very challenging for surgeons.

Seven patients received internal fixation: 1 with screws and 6 with plates. Plate breakage occurred in 1 patient because of HPT recurrence, who eventually underwent amputation. Bone union was observed in 5 patients and visible adequate callus was observed in 1 patient. Intramedullary nails are reported to be preferable fixation method for HPTs combined with fractures[14], but the locking plate was used in the most of patients in our study. Because HPT resection, fracture reduction and internal fixation could be completed with a single incision. Moreover, because pseudotumors usually erode the bone cortex, the extramedullary blood supply is affected during pseudotumor resection, and the reaming required for intramedullary fixation may affect the intramedullary blood supply[15], which would aggravate the damage to the bony blood supply. Although studies have illustrated the effect of metal internal fixation on stress shielding, which will cause peri-implant fractures and nonunion[12], in order to provide support for fractured bone to facilitate union at an appropriate position and to allow patients to perform early functional exercises, rigid internal implants are necessary. The use of long plate can reduce risk for fixation failure and spread the stress to the whole bone[16, 17].

When the pseudotumor is large and difficult to remove or the bone is massively eroded, amputation can be an effective treatment option. The advantage of amputation is that it can completely eliminate pseudotumors and reduce the cost of surgery and the risk of readmission. In fact, when severe bone deconstruction occurs, pseudotumors almost completely erode the bone, and the affected limb loses its bony support, making it very difficult to reconstruct the limb. Jacob et al. reported that reconstruction with a custom total femoral prosthesis is a valuable alternative to amputation in massive pseudotumors of the femur and soft tissues of the thigh[18]. However, the long-term outcome of custom total femoral prostheses is not clear. In our study, 3 patients with pathological fractures caused by pseudotumors ultimately chose amputation. No HPT recurrence was observed among them. Due to the presence of pseudotumors, the surrounding tissues including blood vessels and nerves are anatomically abnormal, and there is a risk of excessive bleeding during amputation. Accordingly, the operation should be performed delicately to avoid iatrogenic vascular damage and excessive bleeding, especially when tourniquets are not applied. In our study, patients who undergo amputation usually use crutches to walk because poor economic situation. Attention should be paid to the additional bleeding risk of the upper limbs caused by the long-term use of crutches.

EF procedures are typically used for temporary fracture fixation, deformity correction, limb lengthening, etc. For fracture treatment, a major benefit of external fixators is that they can stabilize a fracture without the need for open reduction or invasive surgery at the fracture site[19]. In theory, EF can stabilize the fracture in a minimally invasive way and simultaneously avoid interfering with the pseudotumor. In this study, two fracture patients underwent CREF, and both developed pin infections. Similar to conservative treatment, EF does not fundamentally solve the cause of the fracture; that is, EF does not remove the

pseudotumor. Even when fractures have been stabilized, it is difficult to prevent HPT progression through conservative treatment, and uncontrolled progression will affect both the pins and bone, resulting in pin infection, bleeding and bone erosion. In addition, to avoid pseudotumors, the entry points of the pins are located far from the fracture site, which means that fixation may not be powerful enough to control fracture displacement. Therefore, we do not recommend EF for patients with HPT-related fractures. However, when a patient's overall condition is not suitable for open surgery, EF may be able to provide temporary fixation. After the situation is corrected, the external fixation should be replaced with an internal fixation.

For HPT-related fractures, the main purpose of surgery is to remove the pseudotumors while providing stable conditions for bone union. Zhai reported the use of structural bone grafts for bone defects > 5 cm caused by HPTs[12]. Similarly, we used structural internal fixation with bone graft for patients with massive bone defects. Graft incorporation was observed in all patients. When autologous grafts are not sufficient, allogeneic structural bone can also be used. Bastiaan C et al. used allogeneic strut bone grafts for the treatment of fibrous dysplasia of the proximal femur with a mean follow-up of 13 years. They argued that cortical allografts were less prone to be affected by pathological fibrous dysplasia bone and therefore less prone to resorption and failure[20].

For patients without actual fracture, we recommend that if the HPT has eroded more than one-third of the bone diameter, struct grafts are necessary for mechanical stability. However, whether prophylactic internal fixation is performed should be based on radiographic and intraoperative findings according to the surgeon's decision. Mirels et al. analyzed 78 metastatic long bone lesions from 28 patients, and the results showed that when the size of the lesion was measured as more than two-thirds of the diameter, the rate of fracture significantly increased[21].

There are some limitations in this study that should be noted. This study had a retrospective design and involved only a small number of patients. In addition, because the patients in this study were from different cities, sometimes it took several months for them to return to the hospital for review, which made it difficult for us to accurately evaluate the time of bone union. Furthermore, our follow-up period was relatively short.

Conclusion

In conclusion, it is necessary to perform operation in patients with HPT-related femoral fractures. Surgical treatments must take both fracture stabilization and HPT resection into account. Internal fixation, especially the plate, is preferable and EF should be dismissed unless for the purpose of temporary fixation. If the HPT erodes more than one-third of the bone diameter, struct grafts are necessary for mechanical stability. When a pseudotumor is large and difficult to remove and bone reconstruction is complex, amputation is a suitable surgical option.

Abbreviations

FVIII: coagulation factor VIII; FIX: coagulation factor IX; HA: hemophilia A; HB: hemophilia B; HPT: hemophilic pseudotumor; ORIF: open reduction internal fixation; CREF: closed reduction external fixation; CE: closed reduction

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Nanfang Hospital on 19 December 2019 (approval number: NFEC-2020-177) and all patients or patients' parents provided informed consent of permitting their anonymous data for research purposes.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The author(s) declared no potential conflicts of interest with respect to the research.

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Authors' contributions

Keyu Chen: Designed the study, Collected the data, Reviewed the literature, Wrote the manuscript.

Guiyong Jiang: Designed the study, Edited the manuscript, Provided support and guidance.

Yaowen Xu: Collected the data, Checked the manuscript, Reviewed the literature.

Yunping Yang: Checked the manuscript, Reviewed the literature.

Zexiong Mao: Checked the manuscript, Reviewed the literature.

Jiaxin Lv: Checked the manuscript, Reviewed the literature.

Fei Liu: Checked the manuscript, Reviewed the literature.

Bin Chen: Designed the study, Wrote and edited the manuscript, Provided support and guidance.

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Figures

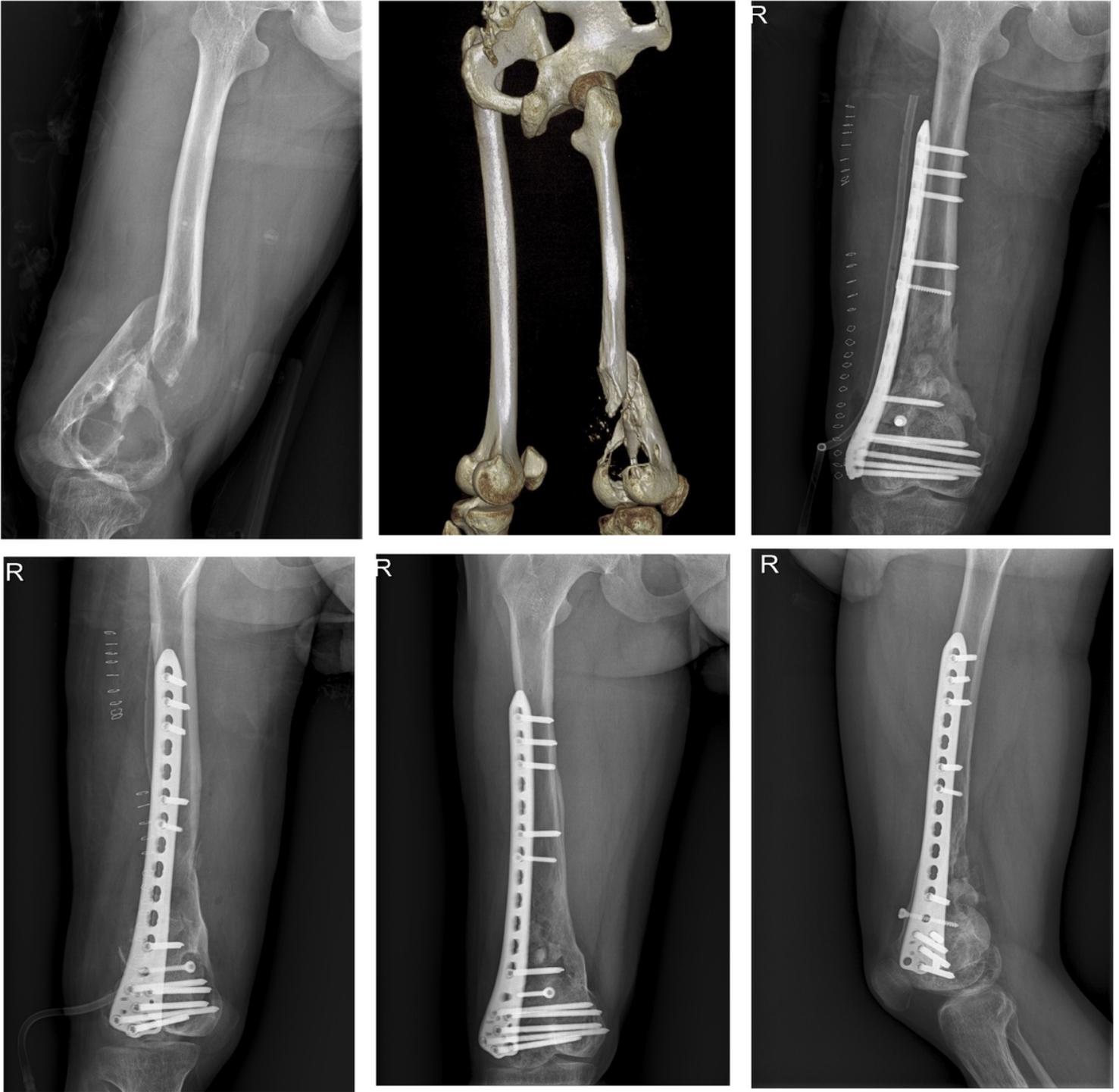


Figure 1

Surgical treatment with locking plate and allogeneic cortical strut graft was applied to 23-year-old man (Case4) with a right distal femoral HPT-related fracture. Radiographs were taken at the a,b) preoperative, c,d) postoperative, and e,f) 20-month-postoperative timepoints.

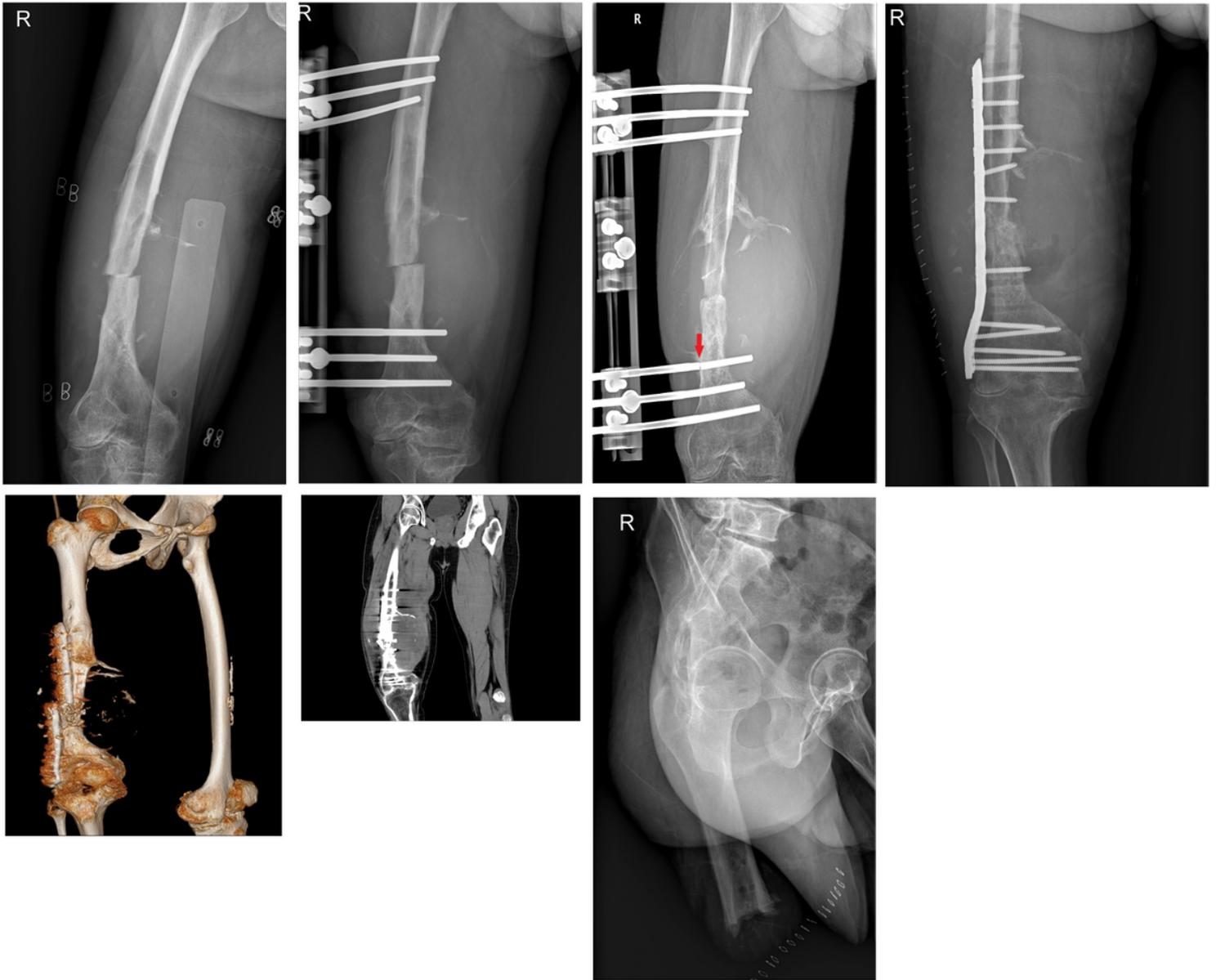


Figure 2

Surgical treatment with CREF to 46-year-old man (Case2) with a right femoral shaft HPT-related fracture. a,b) preoperative and postoperative radiograph of CREF c) Bone nonunion combined with fixator failure (red arrow) 13 months later d) ORIF performed and HPT excision 14 months later, e,f) HPT recurrence and plate broken 6 months after ORIF, g) amputation performed finally.