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Extensive humeral defect secondary to humeral shaft nonunion and chronic osteomyelitis treated with induced membrane technique augmented with fibula autograft: a case report

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Incidence of chronic osteomyelitis in the humerus is relatively rare compared with the incidence in the lower limbs, with the humerus being the most commonly affected bone in the upper extremity.[2,31,35] Management of humeral osteomyelitis includes bone debridement, delayed defect reconstruction, and suppressive antibiotic therapy.[10] The chronic course of infections and repeated surgeries often lead to severe soft-tissue compromise, neurologic deficit (radial nerve), and poor functional results.[4,35]

The definitive treatment for chronic humerus osteomyelitis often includes removal of the compromised bone segment. Treatment of bone defects is a surgical challenge for orthopedic surgeons. Among the most used surgical alternatives are free vascularized fibula transfer, callus distraction with circular external fixation or rail fixator, and induced membrane technique (IMT).[7,13,17,27]

The IMT, otherwise known as the Masquelet technique, is a useful procedure[27] for bone regeneration in the metaphyseal and diaphyseal regions of long bones.[8] Since 2000, Masquelet et al[19-21] have used this technique for segmental bone loss, bone tumors, and septic nonunions. IMT allows the repair of large segmental bone defects without the application of distraction osteogenesis or microvascular surgery.[16] The IMT involves two stages. In the first stage, a polymethyl methacrylate spacer (with or without antibiotics) is placed into the bone defect to induce the formation of a vascularized membrane. The second stage is performed 6 weeks later and consists of filling in the gap with a bone graft.[9] This technique replaces almost any long bone defect in a fixed amount of time.[16]

This article presents a clinical case report of a patient treated with IMT augmented with fibula autograft for an 18-cm humerus shaft defect due to a pathologic fracture nonunion on chronic osteomyelitis. The patient provided informed consent.

Case report

The patient was a 39-year-old woman, a healthy adult patient, right-handed, who worked as a cook. In January 2016, she fell off a bicycle with a direct blow to the shoulder and right arm, for which she went to an emergency room where she was diagnosed with shoulder contusion (Fig. 1).

In February 2016 (25 days later), she was rushed to the emergency room for persistent pain that was not responding to oral analgesics. Previously, she had been evaluated by a general practitioner, including radiography (informed as normal) and ultrasound that revealed a subacromial and subdeltoid bursitis and long head biceps tendinitis (Fig. 2).

Upon physical examination, there was severe pain in the lateral aspect of the arm, with loss of active abduction, preserved active rotations, and painless passive shoulder rotations, without edema or erythema. Inflammatory parameters showed leukocytosis ($16.4 \times 10^3/\mu L$; normal range: $4.5–11.5 \times 10^3/\mu L$), increased erythrocyte sedimentation rate (ESR) (116 mm/h; normally less than 20 mm/h), and increased C-reactive protein (CRP) (124 mg/L;

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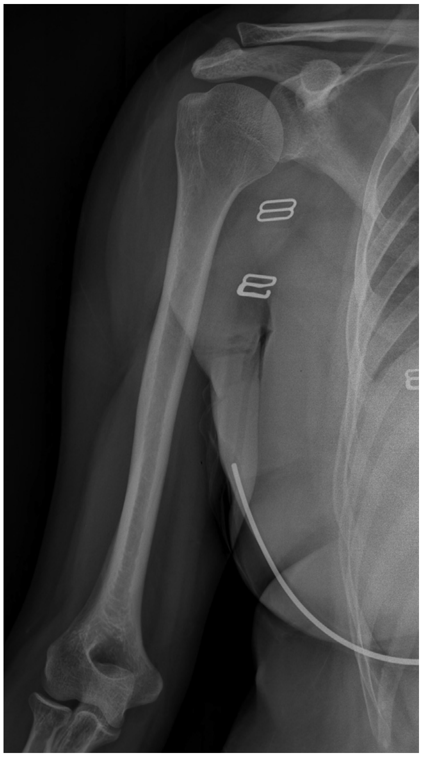

Figure 1 Anteroposterior humeral radiography (January 2006). No pathological findings.

Figure 2 Anteroposterior and lateral shoulder radiography (February 2006). At the junction of the *middle* and proximal third of the diaphysis, osteopenia, scalloping of the cortex, and loss of trabecular architecture of cancellous bone were observed, suggesting a permeative process.

normally less than 5 mg/L). Analgesia was optimized, and consultation was indicated in case of increased volume, erythema, fever, local heat, or increased pain.

In March 2016, she consulted for a sudden increase in pain and functional impotence without trauma. The radiography showed a proximal diaphyseal humerus fracture on the pathological bone with cortical disaggregation through the entire humerus, highly indicative of malignancy (Fig. 3).

Figure 3 Anteroposterior humeral radiography (March 2006). Diaphyseal fracture on the pathological bone with cortical disaggregation through the entire humerus, highly indicative of malignancy.

A shoulder immobilizer was placed, a humerus computed tomography scan was requested, and an evaluation by the orthopedic oncology unit was programed. This unit also requested a computed tomography scan of the chest, abdomen, pelvis, and bone scintigraphy (technetium-99m). The studies ruled out metastatic disease, with radioisotope hypercaptation at the level of the right humerus, so it was decided to perform a biopsy. Nevertheless, after 5 days, she consulted again because of a large increase in volume and purulent discharge from the medial right arm. The patient underwent a surgical cleaning through an anterolateral approach to the humerus, with debridement of necrotic tissue and abundant irrigation with physiological serum. The bone was biopsied, reported as chronic suppurative osteomyelitis with abscess, negative for neoplasia at the cytological examination, and negative for aerobic and anaerobic cultures. Endovenous antibiotics treatment was performed with cefazolin 1 g tid for 2 weeks, with a significant decrease in leukocytes ($8.2 \times 10^3/\mu L$), ESR (62 mm/h), and CRP (16 mg/L). Cloxacillin 1 g qid orally was prescribed, and a functional brace was installed to manage the fracture. Finally, the patient was discharged.

The functional brace was poorly tolerated because of the persistence of purulent discharge, with the patient's low adherence to the oral antibiotic treatment and without attending medical checkups. In June 2016, the patient was admitted to the emergency room because of an increase in volume (abscess), abundant purulent discharge, and altered inflammatory parameters (leukocytes $13.8 \times 10^3/\mu L$; ESR 50 mm/h.; CPR 122 mg/L) (Fig. 4).

She was hospitalized for a surgical cleaning; microbiological samples were taken, and intravenous antibiotic was administered (cefazolin 2 g tid and gentamicin 160 mg qd for 11 days). Bone cultures were negative, and inflammatory parameters had

Figure 4 Anteroposterior humeral radiography (June 2006). Diaphyseal fracture on the pathological bone with progressive displacement.

decreased (leukocytes, 8.5 × 10^3/μL; ESR, 30 mm/h; CPR, 6 mg/L). The patient was discharged again with long-term suppressive oral antibiotics (flucloxacillin 500 mg tid) and a functional brace. In serial radiography, a progressive area of compromise is evidenced, evolving to panhumerus osteomyelitis with the progression of bone loss (Fig. 5).

In February 2017, the patient was admitted to the emergency room because of increased volume (abscess) and a new draining fistula with purulent discharge. She was hospitalized again for a surgical cleaning; cultures were taken, and an intravenous antibiotic was administered (cefazolin 2 g tid and gentamicin 160 mg qd for 21 days). The patient was discharged once again with long-term suppressive oral antibiotics (flucloxacillin 500 mg tid).

After 12 months of irregular medical checkups and long-term suppressive antibiotic therapies with irregular adherence, an evaluation by the shoulder and elbow unit was requested because of persistent purulent drainage through two draining fistulas. The diagnosis was humeral shaft nonunion, extensive humeral bone defect, and chronic osteomyelitis Cierny-Mader IV secondary to nonaggressive management of the infection (Fig. 6).

In addition, an magnetic resonance imaging (MRI) study of the humerus showed complete diaphyseal involvement without compromise of the epiphysis (Fig. 7). The preoperative inflammatory parameters were leukocytes, 11.1 × 10^3/μL; ESR, 25 mm/h; and CPR, 22 mg/L.

Complete humeral resection of the devitalized and infected tissue was performed to decide definitively on reconstructive management. After surgical irrigation and debridement, all devitalized fragments were removed, and a proximal and distal bone resection, conserving the minimal humeral shaft bone stock for osteosynthesis, was performed (The minimal osteosynthesis was planned with an LCP Extra-articular Distal Humerus Plate [DePuy Synthes, Oberdorf, Switzerland]), considering a proximal molding to achieve the placement of two locked screws to the humeral head. At least one bicortical screw was considered for the diaphysis in the distal humerus, fixing the distal locked screws to the lateral column. The removed bone was biopsied and cultivated. The proximal and distal medullary canals were also cultivated. The biopsy showed nonspecific chronic osteomyelitis, with persistent acute activity without granulomas or tumor, on both ends. One bone culture of the distal humerus showed multisensitive coagulase-negative *Staphylococcus*. Other cultures (two distal and three proximal) were negative. Medullary canal cultures were also negative. After marginal resection of the main fragments, the bone defect was 18 cm (Fig. 8).

Among the treatment alternatives, the following were evaluated:

- Callus distraction osteogenesis with a circular external fixator (Ilizarov). Both proximal and distal fixation are scarce, and to perform the osteotomy in both foci, the fragment to be transported is exceedingly small. Thus, the reconstruction and bone transport unit considered this case not suitable for bone transport, with a high probability of failure due to scarce bone fixation.
- Free vascularized fibula transfer was a feasible alternative for this case, but fixation is scarce, and the team's experience with this technique was limited.
- The IMT was considered as an excellent alternative, but fixation with the plate alone would likely have been precarious.
- Nonvascularized fibula autograft was considered as another appropriate alternative. The team had vast experience, with excellent results, using autograft/allograft of the fibula. The use of a standardized technique reduces donor site morbidity, lowers costs, increases graft incorporation, and reduces other types of complications associated with allografts (eg, infection).

Finally, it was decided to perform a nonvascularized fibula autograft to augment the fixation of the segment (using the mechanical properties of the fibula and a plate) and maintain an adequate environment for the IMT (biological stimulation and new bone). Although the osteotomy did not show osteomyelitis-free margins, the maximum possible bone resection was considered adequate fixation for the final construct using the MRI study. In case of residual infection foci, the use of long-term suppressive antibiotic treatment on a better irrigated epiphyseal bone was also considered.

The intravenous antibiotic was administered (cefazolin 1 g tid), and a second surgical cleaning was performed at 72 hours. A polymethylmethacrylate antibiotic-loaded cement spacer was left (Simplex P with 1 g Tobramycin Stryker, Mahwah, NJ). Bone cultures were taken (three for each end), which were negative. After 14 days of intravenous antibiotics from admission, a third surgical cleaning was performed without suppurative wounds by placing a cement spacer with an endomedullary fixation (first reconstructive stage), thus completing 21 days of antibiotics by indication of the infectious disease service. The patient was finally discharged with downward inflammatory parameters (leukocytes 9.1 × 10^3/μL, ESR 61 mm/h, CRP 22 mg/L).

Surgical technique

First reconstructive stage (March-April 2018)

Cement spacer removal, a surgical cleaning involving the removal of necrotic tissue and irrigation, with 6-liter physiological saline and a pulsatile lavage system, was performed. After performing hemostasis, a cement spacer (Surgical Simplex

Figure 5 Humeral bone defect progression between June 2016 and February 2017.

P Stryker) of equal diameter as the diaphyseal humerus was installed with a central axis of a Steinmann 3.0 pin (Fig. 9). All intraoperative bone cultures were negative (three for each end). The patient was advised to attend the second stage in 6 weeks. Instead, she resumed follow-up 5 months after the first stage.

Figure 6 Anteroposterior and lateral humerus radiography (March 2018). Humeral bone defect and chronic osteomyelitis Cierny-Mader IV.

Second reconstructive stage (September 2018)

Preoperative inflammatory parameters were leukocytes, 11.3 10^3/μL; ESR, 15 mm/h; and CPR, 6 mg/L.

First surgical time

The patient was placed in a prone position, with a wide posterior humerus approach. Paratricipital dissection, identification, and protection of the radial and axillary nerves during surgery, all wrapped in scar tissue, were carried out. Cement spacer was removed, respecting the fibrous membrane envelope, and preserving the zone of the radial nerve (Fig. 10*A*). Proximal and distal humerus ends were checked without secretion. The necrotic bone was resected, and the remaining bone was curetted of bleeding (Paprika sign). Simultaneously, in a lateral leg approach, respecting superficial peroneal nerve and syndesmal ligament complex, proximal and distal fibula osteotomies were performed. They were harvested for autograft of length 20 cm, preserving the periosteum intact.

Second surgical time

Fibula autograft was positioned, checking adequate length according to surgical planning (Fig. 10*B*). The ends of the fibula were carved to achieve an endomedullary position at each end. The previously planned 10-hole plate (SYNTHES LCP Extra-articular Distal Humerus Plate, Oberdorf, Switzerland) was first molded at its proximal end and then placed inside the membrane. Three compression cortical screws were fixed into the fibula to compress it against the cortices of the humerus extremes (Fig. 11*A*). Then, definitive fixation was obtained with two locked screws proximal to the humeral head, with one cortical and four locked to the lateral column on the distal humerus, achieving adequate stability. Then, the membranous cavity was filled with a morcellated cancellous bone allograft from four femoral heads, mixed with 4 g of vancomycin (Figs. 11*B*–12*A*). The fibrovascular membrane was closed with self-locking running stitches of 3.0 Vicryl suture (Fig. 12*B*). Finally, closure by planes was performed.

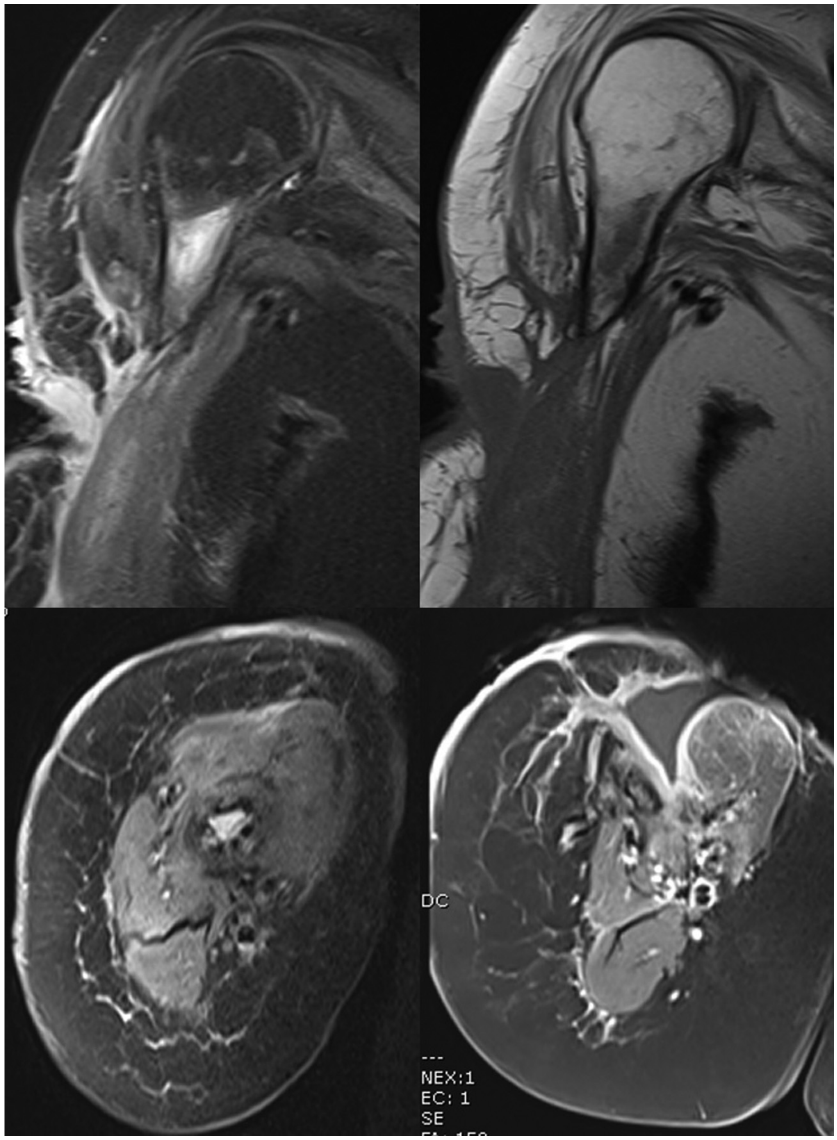

Figure 7 The proximal humerus and *middle* third humeral shaft, MRI study.

Postoperatively, the patient evolved with radial and axillary nerve paresis. All six intraoperative cultures were negative (two proximal bone humerus, one proximal medullary canal, two distal bone humerus, and one distal medullary canal). Postoperative radiographs showed adequate fixation (Fig. 13). The patient had an adequate perioperative evolution, so she was discharged after a week and given cefazolin 1 g tid and ciprofloxacin 500 mg bid. Upon discharge, she received oral antibiotic treatment of cefadroxil 1 g bid. The arm was immobilized with a sling and a dynamic extension orthosis for radial nerve neuropraxia.

Control at 10 days showed no complications of operative wounds or signs of infection, with tolerable pain. Progressive rehabilitation was started by both a physiotherapist and occupational therapist.

After 2 months, she had partial improvement in the function of the radial and axillary nerves. The use of cefadroxil 1 g bid was maintained for 12 months. Graft consolidation was noted on the postoperative radiograph after 12 weeks.

On the follow-up visit after 2 years, complete consolidation of the fibular autograft and morcellated cancellous bone allograft was observed (Fig. 14) without motor or sensory deficit in the radial territory and only mild hypoesthesia in the axillary territory.

Physical examination showed an adequate range of motion of the shoulder (170° anterior elevation; 130° abduction; 50° external rotation; internal rotation L2) (Fig. 15), elbow with normal range of motion, with isolated 15° loss of extension, and a Disabilities of the Arm, Shoulder and Hand Score (DASH Score) of 8.3. She will continue with annual checkups, or emergency consultations, in case of reactivation of the infection.

Discussion

Acute osteomyelitis of the humerus in adult patients is a diagnostic challenge. Suspicion and early diagnosis are key to adequate medical-surgical treatment to avoid associated complications, such as chronic osteomyelitis. Furthermore, when an infected nonunion and a large humeral defect are added, treatment alternatives become limited.

Acute osteomyelitis in adults is rare and generally linked to local and general comorbidities (trauma, bone surgery, joint

Figure 8 Extensive humeral bone resection for chronic osteomyelitis treatment.

replacement, immunodeficiency, diabetes, or vascular disease).[15] A hematogenous spread of bacteria leading to osteomyelitis is exceptional in adult patients but more frequent in the elderly.[15] The reported case presented blunt trauma to the arm, so a hyperemic area was probably generated with the consequent hematogenous bacterial spread.

Staphylococcus aureus and Coagulase-negative staphylococci are, by far, the most frequently involved microorganisms associated with bone osteomyelitis because of their ability to form biofilms, which are difficult to treat solely with antimicrobial agents.[5,26] Other resistant strains are not frequent and account for only 0.24%.[23] Identification of the microorganism involved is difficult. In the reported case, out of all the bone cultures taken, only one was positive for coagulase-negative staphylococci, which might have been a contamination. This fact makes it difficult to adjust antibiotic management, probably associated with the anticipated and remarkably diverse use of antibiotics before taking cultures in this case. According to recent treatment guidelines, the initial endovenous therapy of hematogenous osteomyelitis should last for 1–4 weeks and should be continued by oral therapy for 2–6 weeks.[28,32] Appropriate therapy requires a multimodal approach. Principles are aimed at the eradication of infection by thorough debridement and appropriate antibiotic coverage.[15,28,32] In this case, the infectious disease service decided on a 3-week endovenous therapy after humeral resection, considering that the patient significantly improved her adherence and radical surgical control of the infection.

Patients can present a variety of general symptoms: chills, fever, and malaise. Strong pain, local swelling, and bone tenderness on palpation are signs of a local infectious process.[15] Although our patient did not present fever during her entire clinical course, upon her second emergency consultation, she presented tenderness, functional impotence, and laboratory test results compatible with systemic inflammatory compromise. Also, the radiographic study, when compared with the first consultation (trauma), showed alterations compatible with osteomyelitis. In this consultation, the management had to be aggressive, with debridement and cleaning of the medullary cavity (ie, reamer irrigator aspirator system), taking cultures, biopsies, and intravenous antibiotic treatments. Complications could probably have been avoided at this point.

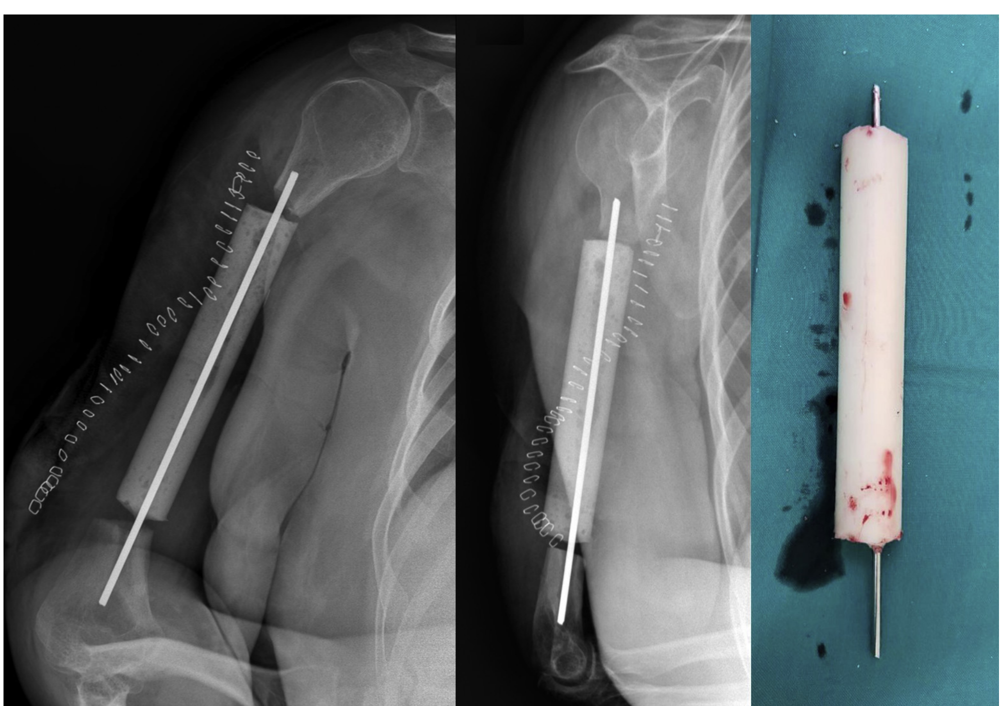

Figure 9 First reconstructive stage.

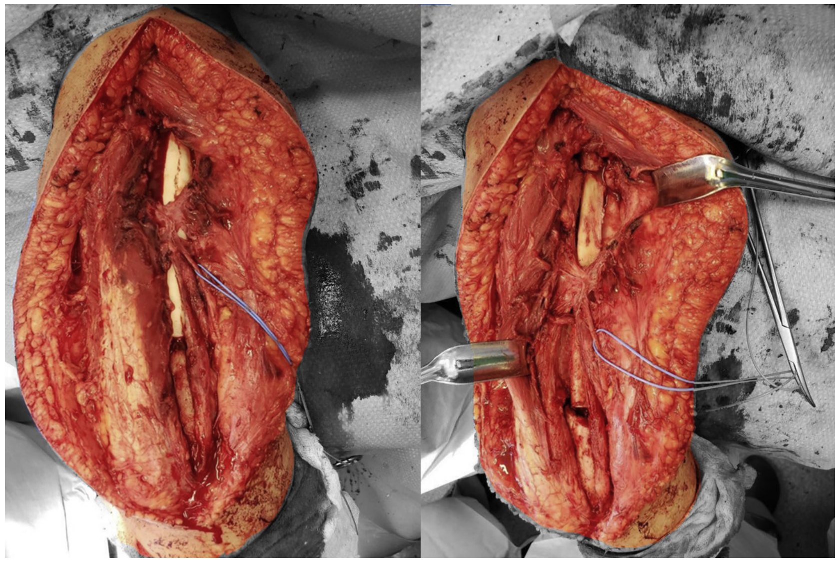

Figure 10 Cement spacer removal and fibula autograft length check.

Figure 11 Plate fixation and morcellated cancellous bone allograft.

Nevertheless, distinguishing between subclinical hematogenous osteomyelitis and primary or metastatic bone tumors by imaging can be challenging.[14,30] The earliest radiographic changes in osteomyelitis are swelling of soft tissue, periosteal thickening, or focal osteopenia, which are also frequently observed in malignant bone tumors.[11,30] Diagnosis supported by MRI would likely distinguish between infectious and tumor pathologies, but it has not yet provided enough pathognomonic findings for osteomyelitis. Therefore, the presence of a primary or metastatic bone tumor had to be excluded by biopsy.[11,30]

Humeral bone defects are an unsolved problem for orthopedic surgeons.[33] Its treatment is not standardized, and there are multiple techniques for its management: segment shortening, distractive osteogenesis, membrane induction technique, and vascularized fibula autograft.[25]

The membrane induction technique, originally described by Masquelet, is a surgical technique widely used to manage diaphyseal bone defects composed of two stages. In the first stage, a debridement and resection of necrotic bone tissue are performed to a bleeding bone bed known as the "paprika" sign, with the subsequent use of a polymethylmethacrylate spacer to fill the bone defect, which is stabilized with an external fixator or another osteosynthesis device. The spacer allows the filling of the bone defect and the development of a membrane in response to a foreign body by the host. This fibrovascular membrane, which has been studied in animals, is rich in osteoprogenitor growth factors (bone morphogenetic protein-2, vascular endothelial growth factor, and transforming growth factor-beta).[18,29,34]

In a second stage, 6 to 8 weeks later, an incision is made on the membrane, the spacer is removed, and the bone defect is filled with

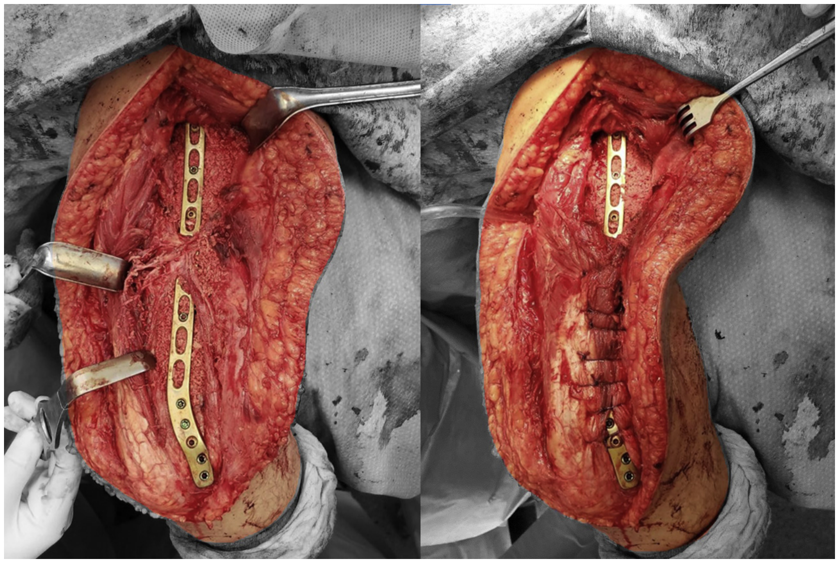

Figure 12 Membranous cavity filling with morcellated cancellous bone allograft and closing with self-locking running stitches.

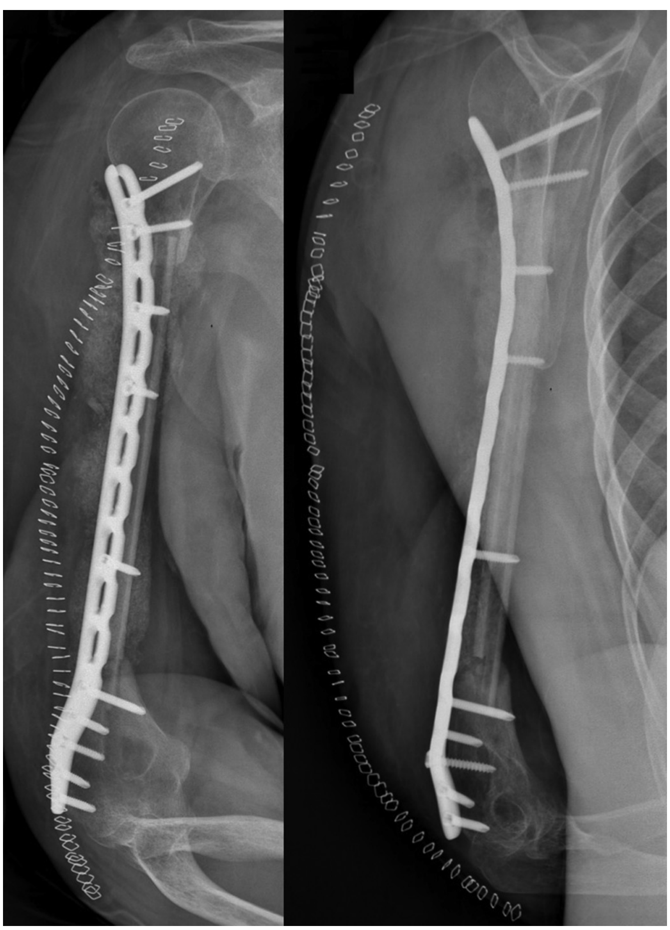

Figure 13 Anteroposterior and lateral humerus radiography (September 2018).

an autogenous morcellated iliac crest graft. Finally, stability is delivered to the construct with an endomedullary nail or plate. This technique has a variable success rate of approximately 80%, most of them on the femur and tibia and few on the upper limb.[25]

There is scarce literature regarding humeral bone defects, probably because of their low level of incidence. Zapaterra et al[36] described nine cases, all of them achieving thorough consolidation in an average of 14 months. Nevertheless, the average of these bone defects was 5 cm, the largest of which was 8 cm, much smaller than the humeral defect presented in this report. In another study, the humerus was involved in two of 11 cases treated with IMT, but the maximum defect was 3 cm.[12] Litvina and Semenistyy[16] describe this technique for the management of nonunion of a diaphyseal humerus fracture, with a bone defect of approximately 12 cm, secondary to multiple surgeries, achieving consolidation with the membrane induction technique at 8 weeks after a three-stage procedure.

To our knowledge, this is the first reported case of management of a practically complete bone defect of the humeral shaft, with a modified induction membrane technique and adding a structural fibula autograft. This technique modification enables to preserve the benefits of the IMT and adds the benefit of structural contribution (mechanical stability of the fibula graft), thus allowing a stable construct and a definitive synthesis, ensuring the contribution of osteoconductive graft, on a scaffold, and osteoinduction provided by the membrane and the morselized graft. As a disadvantage, morbidity is added at the time of fibula harvest; however, in our case, there were no sequelae after this procedure. An interesting element to highlight is that despite the lag between the first and second surgical time (greater than 8 weeks), the consolidation of the graft was achieved. The importance of not postponing the scheduled timing of the second stage has been widely described because of loss of the quality of the membrane envelope and deterioration of the osteoprogenitor capacities. The formed membrane has the most favorable osteogenic properties at 2–4 weeks, but at this stage, it is too thin and may be damaged during the operation. Although the membrane becomes thicker with time, it gradually loses its osteogenic properties. The optimal time for the second stage is 4–6 weeks, when the membrane becomes strong enough and, at the same time, maintains a high osteogenic capacity.[22] The vascularization of the membrane is at its greatest in 1-month-old patient samples and decreased to <60% in 3-month-old samples. One-month-old membrane samples had the highest expression of vascular endothelial growth factor, IL-6, and Col-1,

Figure 14 Anteroposterior and lateral humerus radiography at 2 years.

Figure 15 Anterior and posterior, cutaneous scar, and ranges of motion.

whereas 2-month-old membranes expressed <40% of the levels of the 1-month-old membranes.[1] Nevertheless, in this case, it did not impair consolidation. Aho et al[1] analyzed 35.7% of membranes, 3-month-old or more, and even a case with 22 months of evolution, which presented similar levels of vascularization and osteoprogenitor growth factors to cases closer to 3 months. The balance between the thickness of the membrane and its osteogenic capacity is controversial. It must be analyzed in conjunction with the type of bone graft and the use of structural graft.

Bone stabilization between the first and second stages of IMT is variable. Most cases use an external fixator, but this is more common in lower limbs or cases with minor defects. Litvina and Semenistyy[16] used the LCP Extra-articular Distal Humerus Plate for intermediate fixation, fixing the cement spacer with a screw, which appealed as an excellent technique to us. Litvina and Semenistyy[16] explained that the ends of the cement spacer should overlay the bone ends covered by periosteum. This allows the formation of a membrane that completely covers the created chamber, avoiding the appearance of scar tissue at the spacer-bone junction. Probably this detail led them to achieve complete consolidation for a third time. In our case, we cleaned the scar at both ends, and by using the intramedullary fibular autograft with a compressive technique, we were able to avoid this problem. Had we not used the structural allograft, the membrane would probably have been insufficient, and we would have had problems with consolidation. In addition, some authors recommend temporarily removing the spacer to avoid thermal damage to soft tissues or using a piece of a glove.[24]

Another alternative in the case of complex fixation could be a proximal and distal multiblock straight endomedullary nail. We have used them in some unpublished complex nonunion cases, but not yet in severe humeral defects such as this one. Nevertheless, the ideal fixation method remains an unsolved question. There is no evidence and consensus on the matter yet.

The origin of the graft (auto or allograft) and its harvesting technique (in the case of autograft) is a key issue. In a cadaveric study, the posterior iliac crest yields the highest amount of graft (33.8 mL).[3] In larger bone defects, this amount is usually insufficient. An alternative is to use the reamer irrigator aspirator system, which allows up to 90 mL of bone to be collected.[6] In cases with massive defects, it is necessary to amplify the autograft with osteoconductors, such as granulated b-tricalcium phosphate, or to use allograft (femoral heads of hip prostheses). Hydroxyapatite and tricalcium phosphate substitute, as well as bone morphogenetic proteins-7, have been used to increase the volume and osteoinductivity of the graft. Some authors even propose the use of the growth factor and osteoprogenitors cells to achieve consolidation. There is no evidence of the ideal graft, but the combination of these is likely to have a greater chance of success and consolidation.[22]

Finally, this technique makes it possible to address severe humerus bone defects, with few therapeutic alternatives that could be managed even with limb amputation. Although it is a highly demanding surgery, it has clear advantages over distractive osteogenesis, which requires long treatments, and is poorly tolerated in the upper limb, offering recovery of only acceptable functionality. The scope of this technique should not be limited to the management of posttraumatic bone defects (eg, exposed fractures, nonunion, and secondary osteomyelitis) but also as a reconstruction technique after resection in bone tumor lesions.

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