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Three-dimensional printed titanium pseudo-prosthesis for the treatment of a tumoral bone defect

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Langerhans cell histiocytosis (LCH) is a proliferative disease of histiocytic cells with a granulomatous appearance that generally affects children. The etiology of LCH is still unknown. However, it has been associated with exposure to certain solvents, smoking, and a family history of cancer, thyroid disease, or LCH.[1] Its estimated annual prevalence is of 1 case per 560,000 adults.[27] Three forms of presentation have been described: located in the skeleton as solitary or multiple eosinophilic granuloma, chronic disseminated disease such as Hand-Schueller-Christian disease, and acute subacute diffuse disease such as Letterer-Siwe disease.[8]

In the adult population, LCH frequently presents as a lytic bone lesion.[13,27] It may appear in short bones, ribs, pelvis, vertebral bodies, clavicle, and scapula. It may also develop in the diaphysis of long bones. However, the location of LCH in the hands and feet is very uncommon, and its presence in the clavicle is extremely rare.[27]

The diagnosis can be confirmed with a core needle biopsy. An extension study should be made to detect any systemic diseases or dissemination. Various therapeutic options have been used in the management of LCH depending on the severity of the disease. These options have ranged from observation to chemotherapy, surgery, radiotherapy, photodynamic therapy, immunotherapy, and stem cell transplant.[1,16]

The use of low doses of radiotherapy has been found to achieve good results.[10] A combination of vinblastine and steroids has also been used for the treatment of LCH; however, no standard chemotherapy has been established for the management of LCH in adults.[25] Nevertheless, a surgical resection with clean margins is usually the recommended treatment.

On the other hand, the use of three-dimensional (3D) printing represents a technological advance that is progressively becoming more popular in orthopedic surgery and traumatology. This technique is increasingly being used in surgical planning and in the reproduction of predesigned templates that serve as osteotomy guides in joint replacement procedures.[6,15,17,20,24]

In this study, we present a novel application for 3D printing in orthopedic surgery, using a 3D printed porous titanium graft for the treatment of a bone defect after an extensive resection of the middle third of the clavicle in a patient with LCH.

Case report

The patient was a previously healthy 37-year-old man who worked as a maintenance laborer, with no known drug allergies, and smoker of 20 cigarettes per day. He previously attended the emergency department of another hospital presenting with a 3-week history of shoulder pain. An x-ray of the clavicle was performed in which a small lytic lesion appears on the middle third of the clavicle (Fig. 1, *A*). However, this lesion was not initially detected, and the patient was treated with oral analgesics and discharged. Two months later, the patient presented in our center with a 3-month history of left clavicular pain and swelling without previous trauma. Clinical examination revealed a tender mass located on the left supraclavicular fossa associated with local edema. The patient was febrile, and the active and passive mobilization of his left shoulder was painful. However, the neurovascular examination of the left upper extremity was

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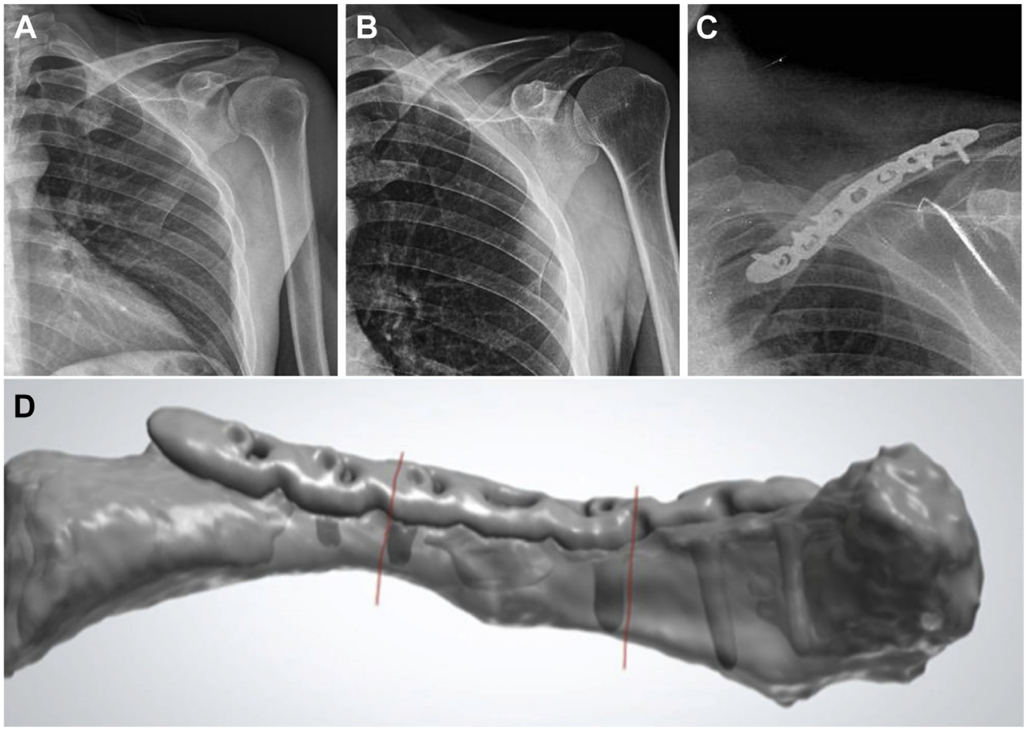

Figure 1 (**A**) A well-defined lytic lesion involving the middle third of the left clavicle. (**B**) This lesion evolved into a pathological fracture. (**C**) Postoperative radiological control after initial intralesional resection, curettage, and osteosynthesis. (**D**) A 3D reconstruction of the clavicle which included the previously synthesized fracture and the tumoral lesion; the red lines mark the planned resection margins. *3D*, three-dimensional.

normal. This patient provided consent for publication of this case report.

Plain x-rays revealed an evolved and displaced pathological fracture involving the middle third of the left clavicle associated with a well-defined 2.5-cm lytic lesion. The tumor appeared to spare bone cortices (Fig. 1, *B*). The blood tests showed a mild white cell count increase (23 × 10 ˆ 9 / L), an unaltered c-reactive protein, and negative tumor markers.

Given the pathological nature of the fracture and the smoking history of the patient, our initial differential diagnosis was of metastasis vs. bone cyst. Accordingly, a chest x-ray was performed showing no evidence of any pulmonary disease.

The patient was then subjected to an intralesional resection and curettage, and samples were collected for pathological analysis. The bone defect was then filled with synthetic and bioactive bone graft substitute (GlassBONE, Noraker, France), and the fracture synthesized with an anatomical clavicular plate (DePuy Synthes, Raynham, MA, USA). Postoperative x-rays showed a satisfactory reduction of the fracture (Fig. 1, *C*). The pathological analysis confirmed the diagnosis of LCH (ie, eosinophilic granuloma subtype). Then, a positron emission tomography–computer tomography was performed to detect any other possible lesions. The positron emission tomography–computer tomography revealed the presence of pathological trace uptake in the middle third of the left clavicle (SUV max 4.15). No other metabolic abnormalities were detected.

The case was then presented in our institutional musculoskeletal tumor committee to determine the best therapeutic strategy. Several options were considered including observation, wide resection with oncological margins followed by reosteosynthesis using an autologous bone graft, radiotherapy, and wide resection followed by a clavicular reconstruction using a 3D printed porous titanium graft "pseudo-prosthesis". After taking in consideration the patient's age and the tumor's location and after discussing the available options with the patient, we decided to proceed with the clavicular reconstruction using a 3D printed "pseudo-prosthesis".

Description of the surgical technique

Implant design

We contacted the 3D design company 4DiMedical (Ortoplus, Malaga, Spain). A fine-cut computer tomography scan was then performed to make a detailed 3D reconstruction of the clavicle which included the previously synthesized bone and the 2.5-cm tumoral lesion (Fig. 1, *D*). Then, a customized cutting template was printed to perform the clavicular osteotomy with clean 14-mm proximal and distal oncological margins. The cutting template was adapted to a 1.3-mm saw blade and included holes for its fixation with 1.8-mm Kirschner wires (Fig. 2, *A* and *B*).

We then printed a 3D porous titanium pseudo-prosthesis resembling the size and shape of the resected area. Its trabecular titanium structure was designed to facilitate bone growth through the implant (Fig. 2, *C* and *D*). This pseudo-prosthesis also included a medial and lateral intramedullary fin to provide additional rotational stability.

Surgical intervention

The patient was subjected to a brachial plexus block of the left upper extremity. The patient was then positioned in a "chair bed" position. A longitudinal incision was made over the previous scar. A progressive dissection was made to expose the previously used anatomical clavicular plate (DePuy Synthes, Raynham, MA, USA). The plate was then extracted, and the clavicle was exposed. A 3D printed biocompatible resin (MED610) radio-opaque cutting guide

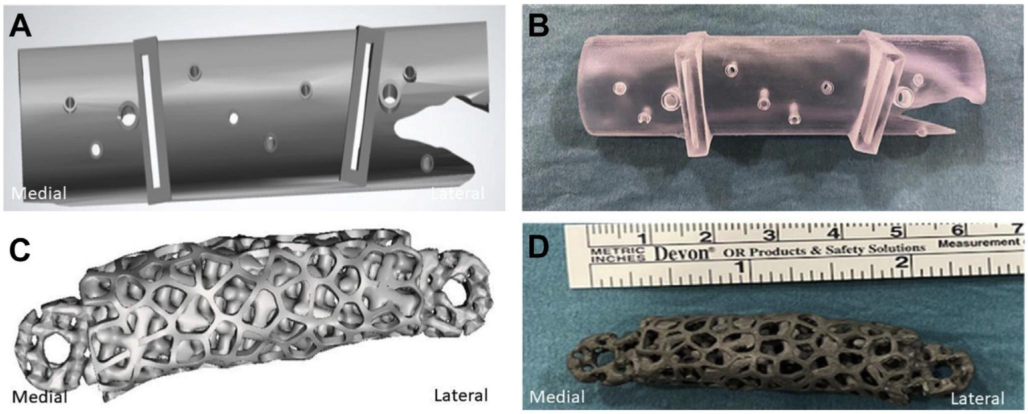

Figure 2 (**A** and **B**) The customized cutting template was designed and printed to perform the clavicular osteotomy with clean 14-mm proximal and distal oncological margins. (**C** and **D**) A 3D porous titanium pseudo-prosthesis with the size and shape of the resected area was designed and printed. It included a medial and lateral intramedullary fin to provide additional rotational stability. *3D*, three-dimensional.

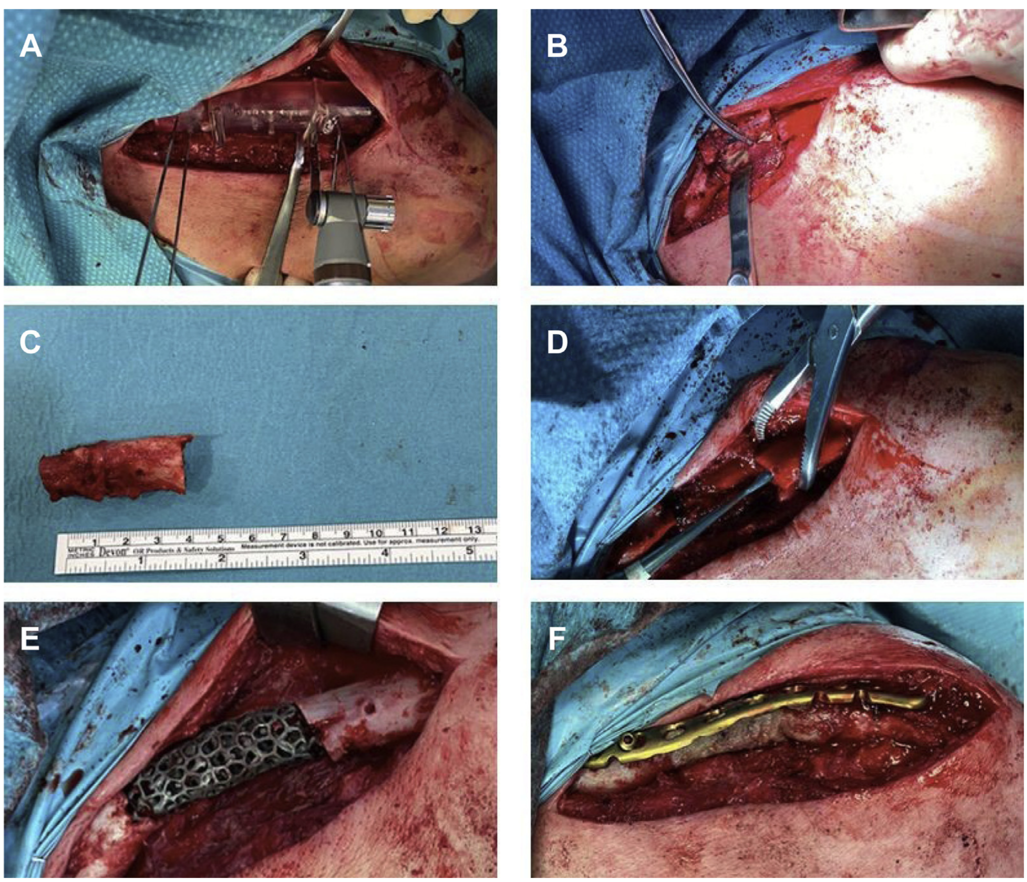

Figure 3 (**A**) The cutting template was fixed on the clavicle with four 1.8-mm Krischner-wires. (**B** and **C**) The selected bone segment was removed and measured. (**D**) The intramedullary canal was drilled proximally and distally using a 2-mm burr. (**E**) The titanium implant was placed in the bone defect. (**F**) The clavicle was fixed using an anatomic clavicular plate; the implant's trabeculas were filled with a bioactive bone graft substitute.

was positioned on the clavicle and fixed with four 1.8-mm Kirshner wires. A 62-mm long osteotomy was performed, achieving a complete excision of the tumor with oncological margins (Fig. 3, *A*–*C*). Then, the intramedullary canal was drilled proximally and distally using a 2-mm burr. The titanium implant (Ti6AL4V) was positioned following the "press-fit" method. Once the implant was stabilized, the clavicle was fixed using an anatomical clavicular plate (DePuy Synthes, Raynham, MA, USA) and locking screws. The implant's trabeculas were filled with bioactive bone graft substitute (GlassBONE, Noraker, France) (Fig. 3, *D*–*F*). Finally, the wound was washed with normal saline, and the wound was closed with 2-0 and 3-0 Vicryl.

Evolution

The final histopathology report confirmed the diagnosis of LCH with disease-free margins. The operated extremity was immobilized in a sling until the removal of the sutures 2 weeks after

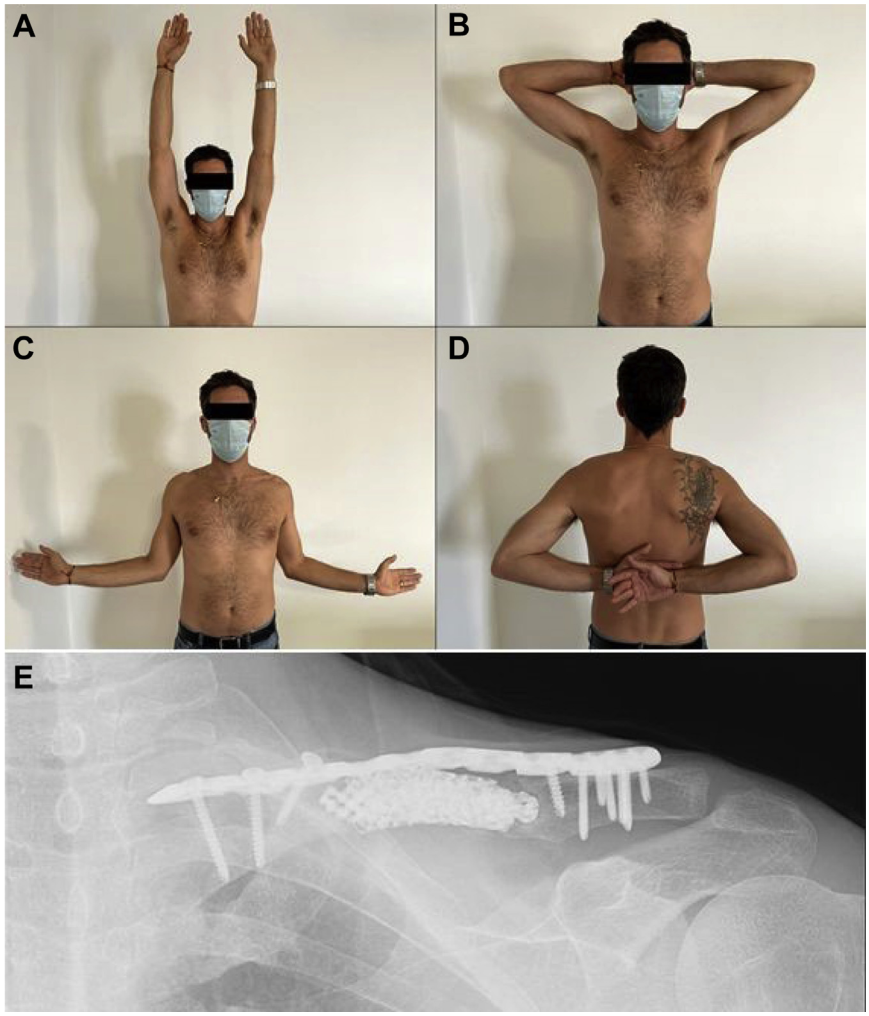

Figure 4 (**A-D**) Two years after surgery, the patient had a complete range of motion of the left shoulder. (**E**) The follow-up x-ray 2 years after surgery.

surgery. Then, pendular exercises of the shoulder and passive physiotherapy were initiated. The operated extremity was kept non–weight-bearing, and efforts were avoided. No postoperative complications were observed, and the evolution of the wound was satisfactory.

At 3 months after surgery, the patient presented with a complete range of motion and no pain on palpation or mobilization. The patient was authorized to initiate progressive loading of the operated extremity and to resume his regular physical activities. On his last follow-up appointment, 2 years after surgery, the patient led a normal life without any type of functional limitation; he had a Constant score of 100 and a disabilities of the arm, shoulder, and hand score of 2.5 (Fig. 4, *A–D*). His follow-up x-ray was also satisfactory (Fig. 4, *E*).

Discussion

Langerhans histiocytosis is a rare disease in adults.[13] It is difficult to determine its incidence in this age group because most of the published reports have been focused on the pediatric population. In children, LCH has been found to be more common in males (male-female ratio of 2:1). However, in the adult population, this ratio may vary depending on the series. According to the Rizzoli Institute,[18] the diagnosis of LHC progressively decreases with age (ie, 55% of the cases with LHC occur between 0 and 9 years, 30% between 10 and 19 years, 8% between 20 and 29 years, and 5% between 30 and 39 years). The treatment of LHC depends on the extent of the disease and may range from curettage and corticosteroid injection, polymethyl methacrylate filler, to local radiotherapy and systemic chemotherapy in certain cases.

The clavicle is a rare site of LHC.[26] Most of LHC reports in the literature involving this bone were treated by curettage of the lesion, steroids, and plate fixation. However, relapses often require adjuvant radiotherapy.[10,27] Some authors have postulated that a combination of surgery with localized radiotherapy would be the best therapeutic if the presence of residual disease is confirmed.[3,4]

In our case, the presence of residual disease would have been an indication for local radiotherapy. However, we believed that the eradication of the tumor was possible without exposing the patient to radiation if the lesion was completely resected. Therefore, we decided to perform a second excision with oncological margins and a subsequent reconstruction of the clavicle with the intercalary titanium pseudo-prosthesis. The location of the lesion required a resection that could have compromised the anatomical function of the left upper limb.[2] However, the titanium pseudo-prosthesis provided adequate mechanical stability and continuity and preserved the functionality of the clavicle.

The use of the titanium pseudo-prosthesis avoided exposure to radiotherapy in our relatively young patient. In a previous study, Kriz et al determined that the possible indications for radiotherapy in LHC would be in case of unresectable lesions, if the resection compromised the anatomical function, recurrent or progressive lesions, adjuvant treatment followed by incomplete or marginal resection, as well as pain or symptoms that compromise the quality of life.[10] However, radiotherapy can induce secondary leukemias, malignant meningiomas, osteosarcomas, and breast, lung, and thyroid malignancies over time.[5,14,21,23] This risk may persist up to 25 years after exposure. In head and neck tumors, the rates of radiation-related tumors have been reported to be of 15% within 5 years. This prevalence is even higher in patients with breast cancer reaching up to 50%, mainly involving the contralateral breast.[5] Moreover, radiation is also associated with numerous side effects such as sore skin, fatigue, hair loss, nausea, vomiting, esophagitis, mucositis, diarrhea, urinary and bladder changes, and headaches.[19] In our opinion, the negative effects of radiation are not unremarkable, and its use should be individualized in each case and reserved for situations in which no other viable options are viable. Nevertheless, in our study, radiotherapy would have been considered if the tumor recurred after the second surgical procedure.

The treatment of bone defects faces significant challenges to preserve the functionality of the affected extremity. In this case, the inadequate management of the bone defect could have hindered the mobility and strength of the operated extremity and altered its cosmetic appearance.[12] Several methods have been traditionally used for the reconstruction of bone defects in orthopedic surgery. These include leaving the bone defect and the use of bone allografts and vascularized bone grafts. However, the risk of bacterial infection has been estimated to be of 11.7% for large allografts and 0.7% for small grafts.[28] The use of bone allografts could also result in nonunion rates in approximately 21% of the cases.[22] Moreover, vascularized bone allografts are technically demanding and are associated with a significant morbidity on the donor site.[7,9,11] Thus, the use of 3D printing in orthopedic surgery and traumatology could become an additional surgical option in the management of complex fracture reconstructions. Moreover, this technique could provide accurate bone cutting guides in oncological surgery that could help perform precise osteotomies with disease-free margins based on preoperative imaging. It could also help produce customized osteosynthesis plates and print replicates of the operated bone.[17] In addition, it could be used to replace bone segments with implants of an equal size, shape, and volume. This could be particularly easier to achieve in cases affecting small bones, exposed to lower mechanical demands. In this case, the implant successfully replaced the bone defect of the clavicle, preserving its continuity and original length. Consequently, the strength and functionality of the affected extremity were preserved. Moreover, the empty spaces within the trabecular structure of the implant could facilitate the formation of woven bone. These spaces may be also filled with bone substitutes to enhance the osteogenesis process.

Finally, the use of 3D printing to reproduce intercalary segments for the replacement of bone defects is a promising field that needs further development. This new technique could provide an additional therapeutic tool that could minimize the morbidity associated with other conventional treatments.

Conclusion

The use of a 3D printed pseudo-prosthesis achieved an excellent clinical and functional outcome in the treatment of a large bone defect, after a resection of an LCH of the clavicle. 3D printed pseudo-prostheses could be useful instruments for the treatment of bone defects after large bone resections in musculoskeletal tumors.

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Patient consent: Obtained.

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