The Philippine Journal of Orthopaedics

CASE REPORT

The Use of Extended Curettage with Freezing Nitrogen Ethanol Composite for Giant Cell Tumor of Bone: A Case Report*

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ABSTRACT

Liquid nitrogen (LN) has been used successfully to treat benign-aggressive lesions such as the Giant Cell Tumor of bone (GCTB). However, its volatility has led to concerns regarding peri- and post-operative complications. A novel, semi-solid composite of liquid nitrogen and ethanol was developed to mitigate these risks, called freezing nitrogen ethanol composite (FNEC). We present the first application of this technique in the Philippines, for a 20-year-old male with a pathologic fracture of the proximal femur secondary to GCTB. FNEC was applied after extended curettage, followed by proximal femoral plating. At 4 years post-surgery the patient's functional status is excellent, with no evidence of local recurrence.

Keywords. FNEC, giant cell tumor of bone, liquid nitrogen

INTRODUCTION

In 1969, Marcove and Miller were the first to use liquid nitrogen as a palliative treatment for metastatic bone disease, via direct application into a bone lesion in the humeral shaft. Several authors since then have demonstrated liquid nitrogen as an effective cryogen. The minimum temperature range required for tumor cell necrosis is -50°C to -70°C. The temperature of liquid nitrogen in room air ranges from -195°C to -197°C, making it suitable for both tissue preservation and destruction.[1,2]

In the early 2000s, Tsuchiya et al., processed extremity bone sarcomas in situ via immersion in liquid nitrogen. Histology demonstrated complete tumor cell necrosis while retaining the bone's structural and osteoinductive properties, with local recurrence rates comparable to other limb salvage methods. Liquid nitrogen, however, boils at room temperature; its volatile state makes surgical handling difficult for smaller lesions. Unintended exposure increases the risk for complications such as nerve palsy, and skin and soft tissue necrosis.[3-5]

To address these risks, Wu and colleagues developed a novel material composed of liquid nitrogen and 95% ethanol and called it freezing nitrogen ethanol composite (FNEC). This composite assumes a semisolid state that aids surgical handling and accurate placement in smaller lesions, thereby minimizing complications. With a working temperature range of -114°C to -122°C, FNEC is comparable in terms of efficacy with liquid nitrogen when used to treat giant cell tumor of bone (GCTB).[5,6]

ISSN 0118-3362 (Print)
eISSN 2012-3264 (Online)
Printed in the Philippines.

Received: September 5, 2023.
Accepted: October 1, 2023.
Published Online: November 15, 2023.
https://doi.org/10.69472/poai.2023.09

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**Previous versions of this paper were presented in poster format at the 13th Asia Pacific Musculoskeletal Tumor Society (APMSTS) Meeting in April 2021, in Okayama, Japan, and in oral/ podium form at the 70th Annual Congress of the Philippine Orthopaedic Association (POA), November 2019 in Manila, Philippines.*

Giant cell tumor of bone (GCTB) is a benign-aggressive lesion with a relatively high prevalence among Asians, common in young adults during the second to third decades. Most patients are diagnosed at Campanacci Stage 2 or higher, with up to 50% affecting the distal femur or tibia. This emphasizes the need for a durable surgical option that preserves joint mobility, provides oncologic control, and low re-operation rate at an economic cost. This is relevant for developing countries such as the Philippines, where close to 20% of citizens live below the poverty threshold, and the majority of health expenditures are not subsidized.[7-10]

This surgical case report aims to discuss indications and procedure-related specifics following the first application of FNEC, according to the original description by its innovators, for the biologic reconstruction of a pathologic fracture secondary to GCTB.

CASE

A 20-year-old male consulted emergently due to severe left hip pain after a basketball game. Radiographs revealed a pertrochanteric fracture through a geographic, lytic lesion in the intertrochanteric region of the left proximal femur (Figure 1). An open biopsy was performed, which confirmed a diagnosis of GCTB (Figure 2). The patient was then started on Denosumab while preparing for surgery. The standard dosing regimen for GCTB was followed, with a subcutaneous 120 mg injection of Denosumab every 4 weeks following loading doses on the day of initiation, day 8, and day 15.[10] After

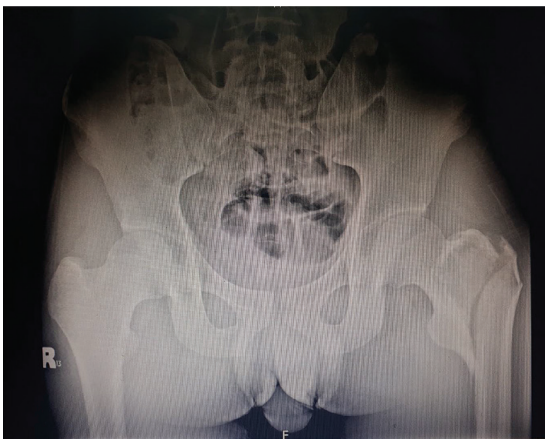

Figure 1. This antero-posterior (AP) radiograph of both hips shows a pertrochanteric fracture at the left proximal femur, through a lytic lesion at the intertrochanteric region with geographic borders, no apparent bone response, no matrix, thinned cortices, and no associated soft tissue mass. Correlation with biopsy findings are consistent with giant cell tumor of bone, Campanacci 3.

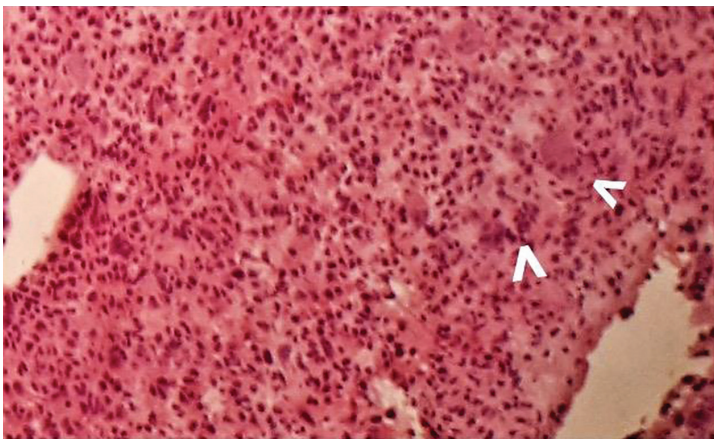

Figure 2. Histology slide on high power magnification shows layered nests of multi-nucleated giant cells *(arrowheads)* on a background of highly cellular stroma, consistent with giant cell tumor of bone.

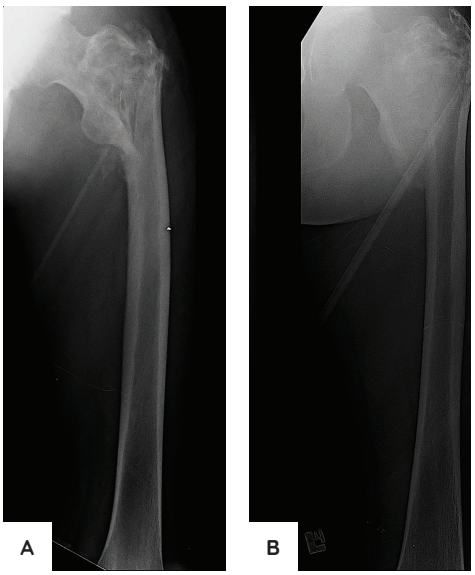

Figure 3. AP radiographs at 1 month **(A)** and 3 months **(B)** post-injury of the left hip show fracture site consolidation and development of a sclerotic rim around the lesion while on Denosumab.

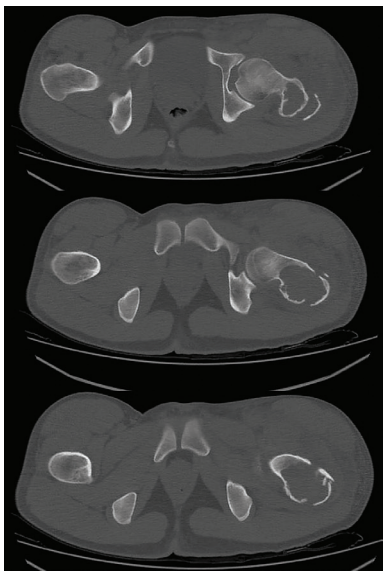

Figure 4. These representative axial cuts of computed tomography (CT) scans taken after the second month of Denosumab show an intact medial cortex.

four doses, repeat imaging showed fracture site consolidation, a sclerotic border around the lesion, and an intact medial cortex (Figures 3 and 4). The following surgical options were discussed in detail with the patient and his family: extended curettage with FNEC followed by polymethylmethacrylate (PMMA) application and plate fixation, tumor resection with subsequent hip fusion, and resection followed by reconstruction with tumor endoprosthesis. The latter constitutes the current standard of care internationally.[12] Citing a desire for a mobile joint, intention to resume high-impact activities, and monetary considerations, the family decided on extended curettage with FNEC. Government financial assistance for implants was obtained a month after the fourth dose of Denosumab.

All materials for storing, handling, and creating FNEC were provided for free by the musculoskeletal tumor service. Surgeries were performed by a team of two orthopedic oncologists and two residents in training. The patient was placed in the right lateral decubitus position and a direct lateral approach was used to expose the left proximal femur, making sure to include the previous biopsy site (Figure 5).

The team created a cortical window large enough to allow adequate curettage of all gross tumor (Figure 6). Approximately 150cc of tumor material was removed using curettes and sent for histologic confirmation. This was followed by mechanical extension of margins using a high-speed burr under fluoroscopy. The cavity was washed copiously with normal saline solution, and soft tissues were covered with gauze for protection before adjuvant application.

The liquid nitrogen-ethanol composite was prepared according to the protocol described by Wu et al.[5] A ratio of 1 part ethanol (95% formulation) was mixed with 2 parts liquid nitrogen to create a semi-crystalline solid (Figure 7A). Once the desired consistency was reached, osteotomes and forceps were used to insert FNEC into the bone cavity (Figure 7B). A total exposure time of 10 minutes was completed for 2 cycles. The residual fluid was suctioned and the cavity was washed with normal saline at room temperature.

Reconstruction was completed using PMMA and a 7-hole 4.5mm standard locking compression plate (Figure 8). Closure was performed by repairing the gluteus medius tendon and fascia proximally, and the vastus lateralis fascia distally. A surgical drain was placed to allow for the egress of excess fluid and removed on the third postoperative day. Intravenous antibiotics were continued for three days. The patient tolerated sitting up on the first day after surgery and standing bedside with a walker on the third day. He was able to do walker ambulation with partial weight-bearing on the affected side by the fifth day and was discharged from the hospital.

At two weeks post-surgery the surgical site healed without signs of infection, frostbite, or dehiscence. Physical therapy sessions were initiated three times a week for the first month,

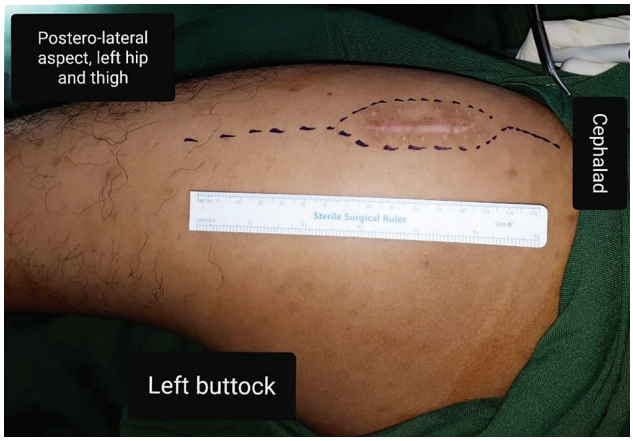

Figure 5. Image shows pre-operative markings for the surgical incision, including the previous biopsy site.

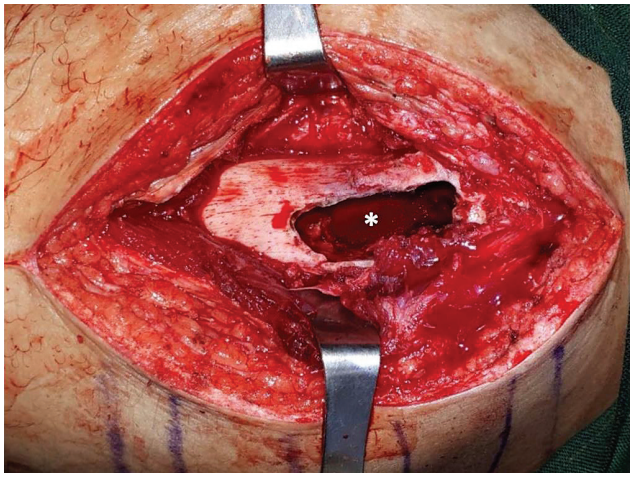

Figure 6. Image shows an ovoid cortical window on the lateral aspect of the left proximal femur, with an aperture* large enough to allow for access to entire area.

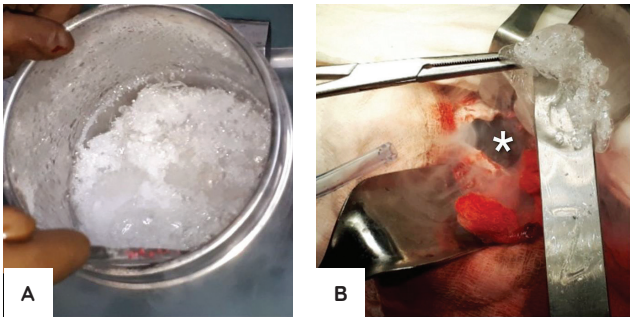

Figure 7. FNEC prepared using 1 part 95% ethanol and 2 parts liquid nitrogen, mixed to create a semi-crystalline solid **(A)** which was then placed into the tumor cavity* **(B)**.

focusing on strengthening the quadriceps and hip abductors and performing daily activities. The patient achieved full weight-bearing at two months, and had a Musculoskeletal Tumor Society Score (MSTS) of 28/30 at three months. Regular surveillance continued except for the year 2020, when COVID-19 restrictions made physical follow-up and

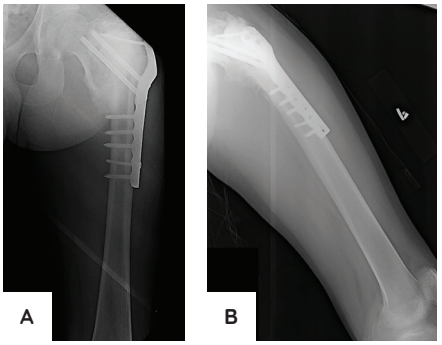

Figure 8. Femur AP **(A)** and lateral **(B)** radiographs showing PMMA and proximal femoral locking plate.

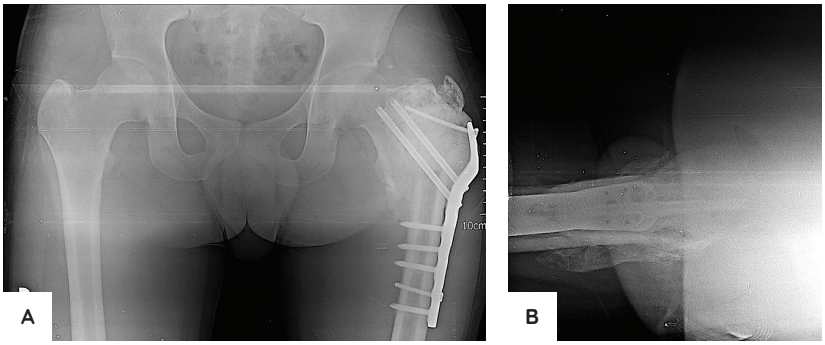

Figure 9. Bilateral hip AP **(A)** and left hip cross-table lateral **(B)** radiographs at 3 years' follow-up.

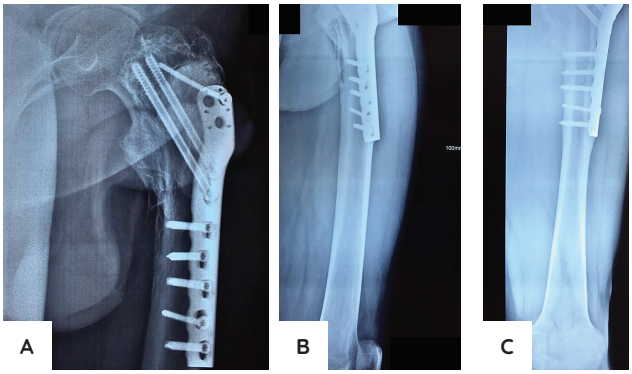

Figure 10. Left hip AP **(A)** and femur AP **(B)** and lateral **(C)** radiographs at 4 years' follow-up.

imaging inaccessible (Figure 9). At the latest follow-up at 48 months post-surgery, he has an MSTS score of 30/30 and no signs of local recurrence or distant metastases (Figure 10).

DISCUSSION

Giant cell tumor of bone is a benign-aggressive neoplasm with a predilection for the epi-metaphyseal region of long bones. Successful treatment of GCTB relies on a correct diagnosis and complete tumor removal, emphasizing the need for confirmatory biopsy and pre-operative planning. While en bloc resection has consistently produced excellent oncologic results, its higher surgical morbidity may affect long-term functional outcomes. Several authors emphasize the importance of balancing tumor eradication with joint preservation, particularly for GCTB in young, active patients. Related studies on tumor margins for GCTB over the past three decades have reported that a well-performed intralesional excision leads to comparable local recurrence rates while mitigating functional impairment.[7,8,12-17]

These findings are particularly relevant for low- and middle-income countries (LMICs) such as the Philippines, where economic considerations play a significant role in decision-making. With just six Southeast and East Asian countries achieving over 95% of healthcare coverage, surgery and implant costs remain prohibitive.[9,11,19,20] This novel procedure mitigates such limitations as it preserves bone and allows for the use of more affordable standard orthopedic implants such as plates, screws, and primary hip and knee prostheses, which are subsidized by the Philippine Charity Sweepstakes Office's Medical Access Program.[20]

Intralesional excision consists of mechanical curettage typically followed by a high-speed burr. Adequate exposure allows the surgeon to access all intraosseous crevices for complete tumor removal. Tumor seeding is minimized by avoiding contamination of surrounding soft tissues. With curettage alone, the reported local recurrence rate for extremity GCTB ranges from 25% to 54%.[7,12-14] Different adjuvants are used to extend margins and may decrease local recurrence rates, despite conflicting reports.[7,12-15,17] Chemical adjuvants such as phenol, ethanol (EtOH), and hydrogen peroxide (H_2O_2) denature proteins in GCTB stromal cells, causing tumor necrosis. Phenol has largely fallen out of favor internationally due to its systemic toxicity, difficult disposal, and carcinogenic potential. While more readily available, H_2O_2 and EtOH are seldom used alone as adjuvants due to the paucity of evidence-based publications.[5-7,10-17] One such paper has reported a local recurrence rate as high as 41% for H_2O_2 when administered as the definitive adjuvant following intralesional curettage.[18] The thermoelectric adjuvant argon beam exposure has replaced phenol due to its relative ease of application as a thermoelectric adjuvant to coagulate proteins in tumor cells. However, the equipment is expensive and not readily available in the Philippines.

Liquid nitrogen, a cryogenic adjuvant, uses ultra-low temperatures to induce intracellular crystallization in stromal cells via a process of fast-freezing and slow-thawing, causing cell membrane disruption and subsequent apoptosis. The fast-freeze phase induces the formation of ice crystals which expand intracellular volume and disrupt the cell membrane. As the cells slowly thaw, intracellular ice crystals coalesce and induce cell lysis and apoptosis.[1,5] It has a 2.3% recurrence rate among GCTB patients treated with intralesional excision. Because liquid nitrogen boils at room temperature, it releases significant amounts of vapor, which affects the visibility

of the surgical site particularly for smaller lesions. Worse, it can cause adjacent skin and soft tissue necrosis secondary to cold exposure.

FNEC has been found to have comparable local recurrence rates to phenol, argon beam, and liquid nitrogen while mitigating the risks.[5-7,10-18] Orthopedic oncologists in Taipei Veterans General Hospital developed this semi-solid composite of liquid nitrogen and 95% ethanol, with the same cryogenic action as liquid nitrogen. FNEC exists at a temperature range of -114°C to -122°C, which induces bone tumor necrosis while having fewer complications.[1,2,5,6]

The cryoablative effects on human GCTB tissue were confirmed *in vivo*, then clinically by Wu et al., in a 2017 study. Chicken chorioallantoic membrane models were used to grow primary GCT stromal cells from consenting patients, a method that has been validated for pharmacologic GCTB studies.[5,21] Following a 7-day incubation period, 15 specimens were divided into 3 groups. The first group was set aside as control, the second group was exposed to liquid nitrogen, and the third group to FNEC. Histologic analysis showed that both liquid nitrogen and FNEC significantly inhibited tumor progression and angiogenesis versus the control group, to a comparable degree. With this proof of concept, seven patients (mean age 39 years, range: 23 to 53) with non-recurrent GCTB of the distal or proximal tibia and distal femur (one patient classified as Campanacci Stage 1, four patients as Stage 2, and two as Stage 3) were treated with intralesional curettage followed by adjuvant FNEC. Within the follow-up period (mean: 24 months, range: 19 to 30 months), there were no recorded intraoperative nerve injuries, skin necrosis, fractures, infections, or local recurrences.[5]

Patient selection remains key to minimizing local recurrence following extended curettage with liquid nitrogen or FNEC. Treatment is more often successful with a minimal or absent soft tissue component, an expected subchondral bone margin of 1 cm or greater for articular areas, and/or at least 75% intact surrounding cortex beyond the cavity post-curettage. While pre-operative magnetic resonance imaging (MRI) better delineates soft tissue involvement and related bone edema, findings are non-specific and may mimic other tumors. The decision to perform a computed tomography (CT) scan instead of an MRI for this patient was influenced by the above recommendations, logistics, and socio-economic limitations. Pre-operative antibiotics, adequate exposure, and protecting the soft tissue envelope with warm saline irrigation all contribute to reducing complications post-surgery.[1,2,5,6]

CONCLUSION

Application of FNEC as an adjuvant cryogen for extended curettage of GCTB was successfully done for the first time in the Philippines, following the specifications of Wu et al. The patient has resumed all pre-morbid activities with an MSTS score of 30/30; he had no post-operative complications and no evidence of local recurrence at 4 years post-surgery. A larger sample size is recommended to determine long-term outcomes, technique modifications, and multi-center and multi-national comparisons that may improve and promote its use in the Philippine setting.

STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

AUTHORS DISCLOSURE

The authors declared no conflict of interest.

FUNDING SOURCE

None.

ACKNOWLEDGMENTS

The author wishes to acknowledge the patient and his family, as well as orthopedic oncology colleagues at the Therapeutical and Research Center of Musculoskeletal Tumors, Department of Orthopedics and Traumatology, Taipei Veterans General Hospital for their kind support.

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