



Pulmonary Embolism after Core Decompression of the Femoral Head Using Injectable Bone Graft Substitute: A Case Report

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The authors report a rare complication regarding the case of an 18-year-old female with bilateral osteonecrosis of the femoral head (ONFH) secondary to the treatment and hematopoietic stem cell transplant (HSCT) of an acute lymphoblastic leukemia (ALL). The patient underwent a bilateral necrotic bone debridement and core decompression (CD) surgery with injectable synthetic bone graft, which unfortunately caused a pulmonary injectable bone graft substitute embolism.

Key Words: Femur head necrosis, Core decompression, Postoperative complications, Embolism, Bone substitutes

Many disorders and risk factors are associated with osteonecrosis, consisting of bone cell apoptosis which leads to bone destruction and end-stage osteoarthritis. Although any bone may be affected, the most commonly affected site is the femoral head¹. Pediatric hematologic malignancies are causes of osteonecrosis of the femoral head (ONFH)². Some components of antileukemic treatment, conditioning therapy prior to hematopoietic stem cell transplantation

(HSCT) or management of post-HSCT complications, especially corticoids, play a critical role in its onset. In the context of acute lymphoblastic leukemia (ALL), the overall incidence of osteonecrosis is 1-5% (as high as 16-29% in older children)³⁻⁵. An even higher incidence has been reported in pediatric patients who undergo HSCT after leukemia (reaching up to 30-44%)⁶. Survival rates for hematologic malignancies have improved with current treatments; therefore, increasing emphasis is placed on prevention, recognition, and management of this potentially disabling long-term complication^{4,7,8}.

In management of ONFH the primary goal is preserving the biological hip joint for as long as possible while also considering the patient's quality of life. Operative management in early stages of the disease, before femoral head collapses, is based on joint-preserving procedures⁹. Relief of intraosseous pressure and restoration of blood supply is the aim of core decompression (CD) of the femoral head^{7,10}. Several authors have recently proposed furthering the simple CD with complete necrotic bone debridement using an expandable reamer, and refilling it with cement, bone graft or injectable synthetic composite graft¹¹⁻¹³. To the authors' knowledge, no other

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articles reporting a pulmonary injectable bone graft substitute embolism have been published. We discuss the clinical relevance of this rare complication.

CASE REPORT

In 2016, a 14-year-old female was diagnosed with common B-ALL. Treatment was administered according to the therapeutic guidelines of the Spanish Society of Pediatric Hematology and Oncology, which includes prolonged high-dose systemic corticosteroids. Unfortunately, the patient suffered an early isolated marrow relapse shortly after completion of treatment. Treatment was reinstated and she received an HSCT in 2019. The patient suffered multiple complications, particularly thrombotic microangiopathy, graft-versus-host disease, and opportunistic infections. Multiple lines of treatment were administered, including high-dose systemic corticosteroids.

In November 2020, when the patient was 18 years old, she was referred for progressive atraumatic bilateral hip pain, without fever or other concomitant symptoms. Intense bilateral hip pain with preserved range of motion (although painful in passive rotations) and a refusal for weight bearing was observed upon physical examination. A diagnosis of bilateral ONFH was made after performing a hip magnetic resonance imaging. The left femoral head maintained its spherical contour (grade II on the Ficat and Arlet scale), while the right head had partially collapsed (grade III).

The case was debated in a multidisciplinary committee (involving orthopedic surgeons, a hematology-oncologist, and radiologists), and surgical treatment using a CD with necrotic bone debridement was regarded as the best option. After decompression, debridement of the necrotic bone was performed using a percutaneous expandable reamer, X-REAM[®] (Wright Medical Technology, Memphis, TN, USA). Samples were taken for histological analysis. Irrigation and aspiration were performed to clear the cavity. Finally, it was backfilled with 15 mL of an injectable composite calcium-sulfate/calcium-phosphate bone graft substitute, PRO-DENSE[®] (Wright Medical Technology). To avoid bone graft extravasation, fluoroscopy was performed to check the process. Partial weight-bearing with crutches was allowed. Anticoagulation prophylaxis using low doses of low-molecular-weight heparin was started routinely. Postoperative X-rays images showed correct placement and containment within the femoral head of the bone graft substitute (Fig. 1A).

Two days after surgery, the patient suddenly presented mild dyspnoea, desaturation (89%), and tachycardia (110 bpm). However, she did not suffer hypotension. Examination of the lower limbs showed neither wound complications nor signs of deep vein thrombosis. Due to the previous bilateral hip surgery and the patient's symptomatology, thrombotic pulmonary embolism was initially suspected. A computed tomography (CT) angiogram was performed. Images showed a 2 cm, hyperdense (934UH) lineal image in the

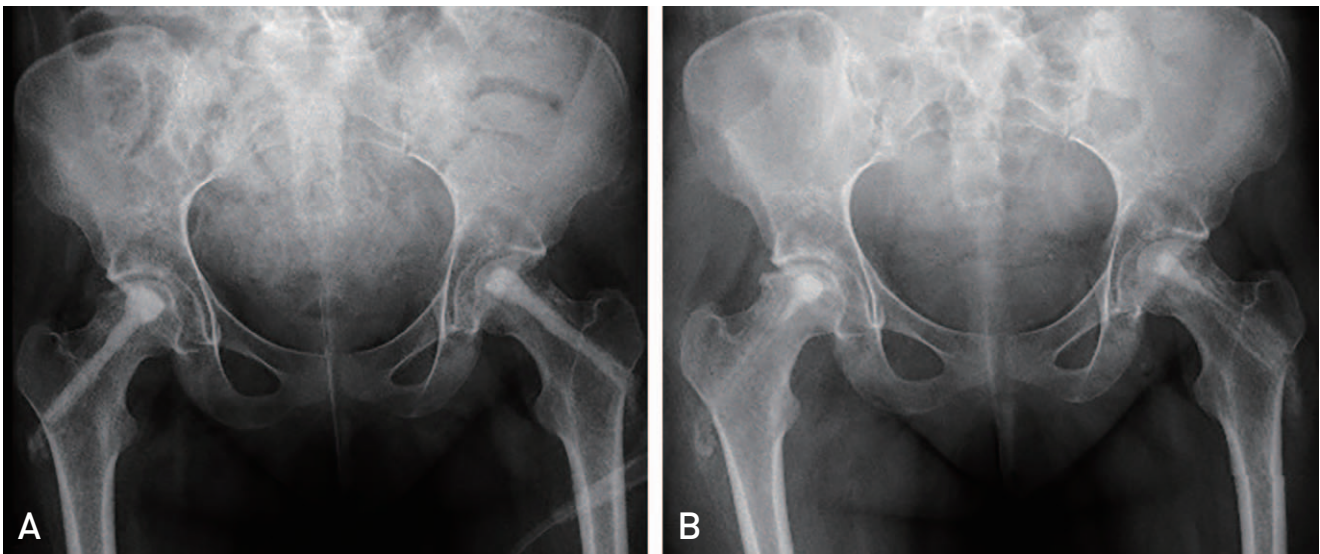


Fig. 1. (A) Postoperative anteroposterior (AP) X-ray of the pelvis after core decompression with necrotic bone debridement and backfilling with injectable bone graft substitute. (B) Two-month follow-up AP radiograph demonstrating partial synthetic bone graft reabsorption with apparent bone ingrowth. While no progression was observed in left femoral head collapse, minimum progression could be detected in the right femoral head.

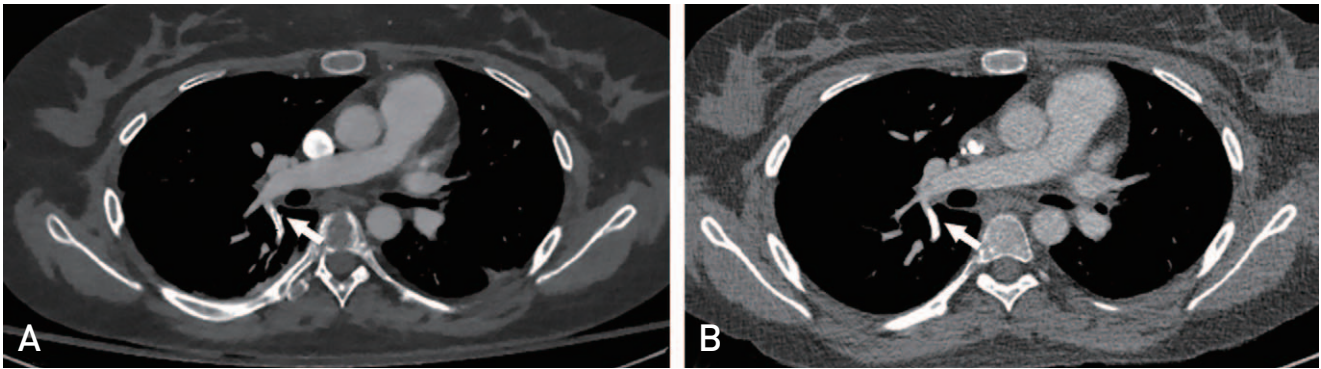


Fig. 2. (A) Computed tomography [CT] thoracic angiogram (vascular window) showing a 2 cm, hyperdense, lineal image in the right lower lobe of the superior segment branch, corresponding to a pulmonary bone graft embolism (white arrow). (B) Two-month follow-up control CT imaging demonstrates no changes in embolism size or density (white arrow).

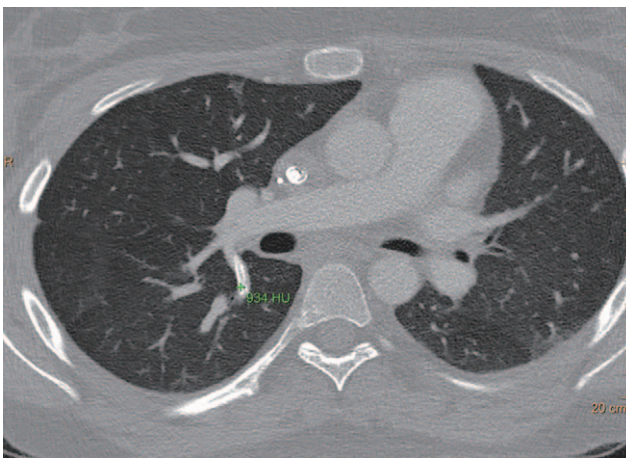


Fig. 3. Computed tomography thoracic angiogram (pulmonary window) showing the same embolism and demonstrating the Hounsfeld Unit (HU) measurement (934 HU).

superior segment branch of the right lower lobe: a pulmonary injectable bone graft substitute embolism (Fig. 2A, 3). The patient was monitored and supplemental oxygen was administered as required. Anticoagulation therapy using therapeutic doses of low-molecular-weight heparin was started. Fortunately, symptoms and saturation showed progressive improvement during the following 24 hours. Finally, one day later, oxygen therapy was no longer needed, as the patient returned to normal blood oxygen saturation (>93%) without any respiratory symptoms. Nonetheless, anticoagulation therapy was prolonged over three months. No further complications were observed and the patient was discharged.

At two-month postoperative follow-up, a pelvis X-ray image showed partial bone graft substitute reabsorption (Fig. 1B) and, surprisingly, the CT angiogram showed no changes regarding the size and density of the embolism (Fig. 2B).

At four-month follow-up, the patient was referred for occasional mild hip pain (3/10), good functionality (modified Harris hip score 45) and was satisfied with the procedure. The patient had no respiratory symptoms during follow-ups; therefore, no specific treatment was deemed necessary.

DISCUSSION

There are no definitive clinical guidelines for the treatment of ONFH in pediatric hematologic patients. Operative management in early-stages of the disease is based on joint-preserving procedures; CD is a widely accepted treatment for such conditions^{5,8}. According to several articles, these procedures could be recommended even in partially collapsed femoral heads^{7,8,11,13}. Although favourable results of arthroplasty have also been published¹⁴, there are major concerns regarding prosthesis longevity and the need for multiple revision surgeries in these young patients³⁹. For this reason, in the case of our patient, we decided to perform a CD with necrotic bone debridement in both hips.

After removal of necrotic tissue, bony defects can be filled safely using different materials. Polymethylmethacrylate (PMMA) cement does not preserve bone stock, and its biomechanical properties are different than those of bone. Allografts have the risk of disease transmission, deep infection and non-union, and the biological properties vary after preparation. Autografts generate donor-site morbidity, and availability is limited¹⁵. Injectable bone graft substitutes were introduced during the last decade in an effort to minimize such limitations. Among them, PRO-DENSE[®] (Wright Medical Technology) is a synthetic composite combining 75% calcium-sulfate (CaSO₄) and 25% calcium-phosphate (CaPO₄: brushite and granular tricalcium phosphate). This composite, in addition to providing structural support, cre-

ates an excellent osteoconductive environment. Calcium-sulfate reabsorbs rapidly through simple dissolution creating porosity and stimulating bony ingrowth, while calcium-phosphate offers a robust scaffold. Several authors insist that the use of this substitute is safe, provides pain relief and in some cases prevents ONFH progression^{11-13,16}. In addition, good results without composite related complications when refilling lytic bone tumors have also been reported^{15,17}. Similarly, our experience with previous patients with ONFH who underwent CD with necrotic bone debridement combined with PRO-DENSE[®] refilling is also satisfactory.

Previously, one case report showed vascular extravasation of injectable bioresorbable bone cement without pulmonary symptoms while refilling a calcaneal bone cyst¹⁸. Another study reported three cases of symptomatic fat embolism during CD and bone grafting for ONFH¹⁹. However, no previous cases presenting a pulmonary injectable bone graft substitute embolism have been reported; therefore, there are no specific treatment recommendations. As a result, after extensive literature review, we guided patient's management based on a very similar complication. Pulmonary cement embolism (PCE) associated with percutaneous vertebroplasty or kyphoplasty is relatively frequent²⁰, and so much more information is available.

Management is based on the severity of the patient's symptoms and the location and size of the emboli. Besides clinical follow-up no specific treatment is needed for patients with asymptomatic peripheral PCEs²¹. In cases of symptomatic or central embolisms, standard treatment guidelines for thrombotic pulmonary embolisms should be followed; including anticoagulation therapy during 3-6 months. However, in exceptional cases of very symptomatic and central PCEs, surgical embolectomy should be considered. If symptoms were to suddenly appear while the procedure is being performed, recommendations state that cement injection should be interrupted and supplemental oxygen should be administered²². Our patient's symptoms started two days after surgery, presenting mild dyspnoea, desaturation (89%), and tachycardia (110 bpm). As her embolism was peripheral (affecting the superior segment branch of the right lower lobe), acute management consisted of monitoring and supplemental oxygen. Anticoagulation therapy was initiated, and maintained over three months. Fortunately, the patient's symptoms showed progressive improvement during the following 24 hours until complete remission. The patient did not present any further respiratory symptoms despite the radiological persistence of the embolism; therefore, no more specific treatment was needed besides fol-

low-up.

However, there are clinically relevant differences between cement and bone graft substitutes that should be highlighted. PCE can trigger an inflammatory reaction causing cellular injury and increased capillary permeability, ultimately ending in acute respiratory distress syndrome²³. Besides, use of thrombogenic cement can additionally lead to progressive occlusion of pulmonary vessels²². In contrast, bone graft substitutes are biocompatible, so that a less aggressive local response could be expected. While PMMA is a non-degradable cement²⁴, calcium-sulfate/calcium-phosphate composite presents complete resorption in a multi-phase pattern when it is in bone^{11-13,16}. Partial resorption can be seen in radiographs from the first month, and complete resorption with new bone incorporation is demonstrated five months after surgery²⁵. In our patient's case, normal progressive composite resorption was observed in hip control images. However, unexpectedly, no changes in the size and density of the embolism were observed on the control pulmonary CT angiogram. One possible explanation may be that bone metabolism is necessary to allow a normal resorption pattern, and more time could be needed to complete the procedure in other tissues. The chronological radiographic absorption rate for this composite in other locations than bone is not known.

Although pulmonary injectable bone graft substitute embolism is an exceptional complication, the authors believe it is something to be aware of when using this composite. It seems reasonable to extrapolate embolism risk reducing techniques described in PCE when using such substitutes for ONFH treatment. Previous reports have suggested that early injection of cement in the liquid phase or using a lower-viscosity cement increases the risk of embolisms. Thus, ensuring the viscosity of calcium-sulfate/calcium-phosphate and sufficient polymerization prior to injection is recommended²². However, as viscosity is usually determined subjectively, one proposed option is to inject the composite in stages (first injecting an initial small volume, then waiting 20-30 seconds to occlude eventual leakages, and continue with the procedure)²³. In addition, because higher pressures are linked to leakage, injection should not be performed quickly. Limiting the volume of the material used can also help reduce such risk²⁴. According to some authors, saline lavage for preparation of the bone prior to injection provides a better filling distribution and reduces leakage incidence²⁶. Fluoroscopic control while filling the cavity is also recommended in order to promptly detect extravasations. As most of these tips are potentially ben-

eficial and relatively simple, we encourage their application. After careful reassessment of our patient's history and extensive literature review, we have not been able to identify any direct cause or surgical error leading to this very rare complication.

In conclusion, the authors report the first case of a pulmonary injectable bone graft substitute embolism associated with the use of CD in the treatment of ONFH. Although the safety and usefulness of calcium-sulfate/calcium-phosphate has been reported, surgeons should be aware when using this composite. Due to the exceptionality of this complication, its potential repercussion is not known and no management guidelines are available. In consequence, we recommend following the PCE principles summarized in this article to minimize risks and manage an injectable bone graft substitute embolism.

CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest relevant to this article.

REFERENCES

- Lespasio MJ, Sodhi N, Mont MA. *Osteonecrosis of the hip: a primer. Perm J.* 2019;23:18-100.
- Mont MA, Pivec R, Banerjee S, Issa K, Elmallah RK, Jones LC. *High-dose corticosteroid use and risk of hip osteonecrosis: meta-analysis and systematic literature review. J Arthroplasty.* 2015;30:1506-12.e5.
- Vora A. *Management of osteonecrosis in children and young adults with acute lymphoblastic leukaemia. Br J Haematol.* 2011;155:549-60.
- Biddeci G, Bosco G, Varotto E, et al. *Osteonecrosis in children and adolescents with acute lymphoblastic leukemia: early diagnosis and new treatment strategies. Anticancer Res.* 2019;39:1259-66.
- Heneghan MB, Rheingold SR, Li Y, et al. *Treatment of osteonecrosis in children and adolescents with acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk.* 2016;16:223-9.e2.
- Sharma S, Leung WH, Deqing P, et al. *Osteonecrosis in children after allogeneic hematopoietic cell transplantation: study of prevalence, risk factors and longitudinal changes using MR imaging. Bone Marrow Transplant.* 2012;47:1067-74.
- Jones LC, Kaste SC, Karol SE, et al. *Team approach: management of osteonecrosis in children with acute lymphoblastic leukemia. Pediatr Blood Cancer.* 2020;67:e28509.
- Te Winkel ML, Pieters R, Wind EJ, Bessems JH, van den Heuvel-Eibrink MM. *Management and treatment of osteonecrosis in children and adolescents with acute lymphoblastic leukemia. Haematologica.* 2014;99:430-6.
- Atilla B, Bakircioğlu S, Shope AJ, Parvizi J. *Joint-preserving procedures for osteonecrosis of the femoral head. EFORT Open Rev.* 2020;4:647-58.
- Rajagopal M, Balch Samora J, Ellis TJ. *Efficacy of core decompression as treatment for osteonecrosis of the hip: a systematic review. Hip Int.* 2012;22:489-93.
- Civinini R, De Biase P, Carulli C, et al. *The use of an injectable calcium sulphate/calcium phosphate bioceramic in the treatment of osteonecrosis of the femoral head. Int Orthop.* 2012;36:1583-8.
- Bednarek A, Atras A, Gągała J, Kozak L. *Operative technique and results of core decompression and filling with bone grafts in the treatment of osteonecrosis of femoral head. Ortop Traumatol Rehabil.* 2010;12:511-8.
- Sionek A, Czwojdzinski A, Kowalczewski J, et al. *Hip osteonecroses treated with calcium sulfate-calcium phosphate bone graft substitute have different results according to the cause of osteonecrosis: alcohol abuse or corticosteroid-induced. Int Orthop.* 2018;42:1491-8.
- Bernhard ME, Barnes CL, DeFeo BM, et al. *Total hip arthroplasty in adolescents and young adults for management of advanced corticosteroid-induced osteonecrosis secondary to treatment for hematologic malignancies. J Arthroplasty.* 2021;36:1352-60.
- Evaniew N, Tan V, Parasu N, et al. *Use of a calcium sulfate-calcium phosphate synthetic bone graft composite in the surgical management of primary bone tumors. Orthopedics.* 2013;36:e216-22.
- Yu PA, Peng KT, Huang TW, Hsu RW, Hsu WH, Lee MS. *Injectable synthetic bone graft substitute combined with core decompression in the treatment of advanced osteonecrosis of the femoral head: a 5-year follow-up. Biomed J.* 2015;38:257-61.
- Fillingham YA, Lenart BA, Gitelis S. *Function after injection of benign bone lesions with a bioceramic. Clin Orthop Relat Res.* 2012;470:2014-20.
- Wood D, Mollabashy A. *Vascular extravasation of injectable bioresorbable bone cement during aspiration and injection of calcaneal bone cyst. Proc (Bayl Univ Med Cent).* 2020;34:189-90.
- Schaffer JC, Adib F, Cui Q. *Intraoperative fat embolism during core decompression and bone grafting for osteonecrosis of the hip: report of 3 cases and literature review. Am J Orthop (Belle Mead NJ).* 2014;43:275-9.
- Singh V, Mahajan R, Das K, Chhabra HS, Rustagi T. *Surgical trend analysis for use of cement augmented pedicle screws in osteoporosis of spine: a systematic review (2000-2017). Global Spine J.* 2019;9:783-95.
- Kang HR, Kim TH, Chung CK, Lee CH. *The impact of incidental pulmonary cement embolism on mortality risk. J Thromb Thrombolysis.* 2020;49:468-74.
- Krueger A, Bliemel C, Zettl R, Ruchholtz S. *Management of pulmonary cement embolism after percutaneous vertebroplasty and kyphoplasty: a systematic review of the literature. Eur Spine J.* 2009;18:1257-65.
- Wang LJ, Yang HL, Shi YX, Jiang WM, Chen L. *Pulmonary cement embolism associated with percutaneous vertebroplasty or kyphoplasty: a systematic review. Orthop Surg.* 2012;4:182-9.
- Ignacio JMF, Ignacio KHD. *Pulmonary embolism from cement augmentation of the vertebral body. Asian Spine J.* 2018;12:

- 380-7.
25. Kotnis NA, Parasu N, Finlay K, Jurriaans E, Ghert M. *Chronology of the radiographic appearances of the calcium sulphate-calcium phosphate synthetic bone graft composite following resection of bone tumours--a preliminary study of the normal post-operative appearances. Skeletal Radiol. 2011;*
- 40:563-70.
26. Trost M, Schmoelz W, Wimmer D, Hörmann R, Frey S, Schulte TL. *Local osteo-enhancement of osteoporotic vertebra with a triphasic bone implant material increases strength--a biomechanical study. Arch Orthop Trauma Surg. 2020;140:1395-401.*