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A rare case of a patient with hemophilia presenting elbow-ankylosing heterotopic ossification: surgery and functional outcomes

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Hemophilia is a recessive X-linked inherited coagulopathy caused by absence or dysfunction of clotting factor VIII, for hemophilia A, and factor IX, for hemophilia B. This bleeding disorder has an incidence of 1:5000/10,000 male births.¹⁰ Clinical manifestations are generally secondary to recurrent bleeding episodes mainly in the musculoskeletal system (>80% of hemorrhages). Bleeding symptoms appear early in life and, when the disease is severe (when plasma factor VIII or IX activity is <1% of normal), joint bleeding may occur spontaneously.¹⁵ Following joint hemorrhages, spontaneous bleeding into muscle is the most frequent bleeding feature in these patients. Despite the relevant involvement of the musculoskeletal system, muscular heterotopic ossification (HO) is rarely reported in hemophilia.¹³ Therefore, there are no reliable epidemiologic data on the incidence, localization, and natural history of HO. HO is a diverse pathologic process, defined as the formation of extraskeletal bone in muscles and soft tissues. This kind of lesion can be thought of as aberrant tissue repair and is increasingly recognized as a common complication of trauma, surgery, and other local or systemic injuries.^{14,21}

We report a rare case of massive muscular HO of the elbow in a 31-year-old patient, affected by severe hemophilia A, who underwent surgical excision at our institution. To our knowledge, this is the first case of atraumatic massive elbow muscular HO described in a hemophiliac patient without joint involvement.

Case presentation

Clinical history and instrumental assessment

A 31-year-old man reported a progressive, almost complete, right elbow ankylosis. No traumatic events were reported. Symptoms appeared approximately 15 years ago and were referred as moderate localized elbow pain followed by a progressive and increasing limitation of range of motion.

Patient's medical history includes congenital severe hemophilia A complicated by chronic hemophilic arthropathy, type 1 diabetes, and high level of cholesterol. The patient underwent total right knee arthroplasty in 2014 followed by selective arterial embolization⁶ associated with articular arthroscopic synovectomy in 2019 owing to recurrence of chronic synovitis at that site. The patient was on regular secondary prophylaxis with 50 IU/kg of efmor-octocog alfa every 72 hours for 22 months before elbow surgery. No previous muscle hematoma of the upper right limb was reported.

The patient referred to the multidisciplinary outpatient clinic for hemophilia of our clinic complaining of severe right elbow dysfunction with limited range of motion. Physical examination showed 30° of arc of motion (70° of flexion, 40° of extension) and pronation and supination of, respectively, 80° and 90°. The Mayo Elbow Performance Score¹⁶ was 45, and the Disabilities of the Arm, Shoulder, and Hand questionnaire score⁷ was 47.5, reflecting important limitations in daily life activities.

Radiographic investigations showed a well-developed bony bridge between the volar surface of the distal humerus and proximal ulna with a nonfusion area at the middle third (Fig. 1). No elbow joint abnormalities were found, and the contralateral elbow radiography was normal.

Institutional review board approval was not required for this case report.

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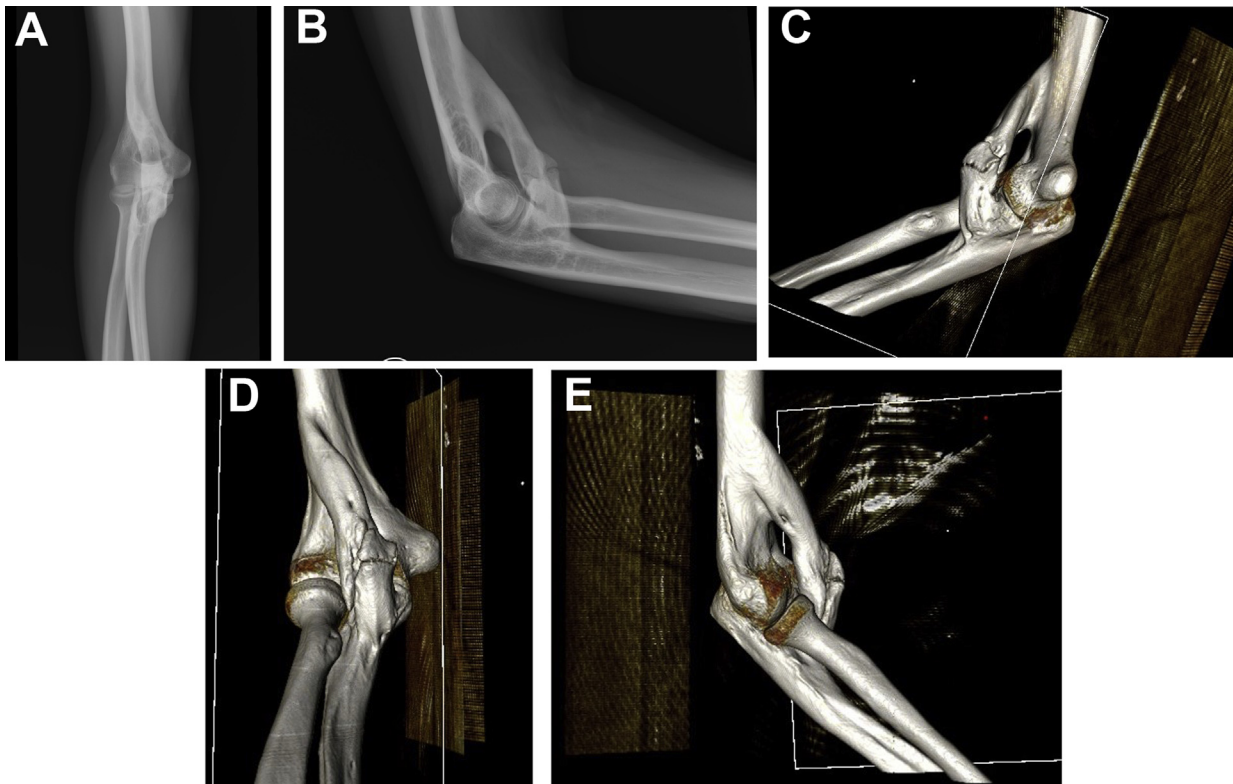


Figure 1 Preoperative radiographs (A, B) and 3D reconstruction (C-E) of right elbow heterotopic ossification; note the nonfusion area at the middle third.

Considering the important functional limitations, surgical removal of the calcification was proposed and discussed with the patient.

Surgery

The patient was placed supine with the right upper limb on an accessory surgical table; no tourniquet was applied to the right upper limb. Just before general anesthesia, a supplementary intravenous bolus of 60 IU/kg of efmoctog alfa was administered in association with 1 g tranexamic acid to prevent perioperative bleeding complications.

An anterior approach to the elbow was performed using a lazy italic-S incision. Care was taken to locate and protect the brachial artery and the median nerve. The bicipital aponeurosis was sectioned, and the flexor-pronator mass was retracted medially. By

spreading the brachialis muscle, and following longitudinally the direction of its fibers, the ulnar edge of the bony bridge was exposed just before brachialis muscle insertion to the ulna. Electrocautery was used to reduce bleeding. Approximately one-third of the ossification was removed piecemeal using a combination of rongeur and osteotomes: the removed material appeared as mature cortical bone tissue, with chondral tissue in the middle third (Fig. 2). The histopathologic report confirmed intraoperative observations. No interventions on the capsule or ligaments were performed. Meticulous hemostasis was performed, the wound copiously irrigated with saline solution, a drain placed, and the incision closed with separate silk stitches.

At the end of the procedure, the range of motion was as follows: flexion 111°, extension 14°, pronation 80°, and supination 90°. No elbow-manipulation was performed. A bulky dressing was applied.

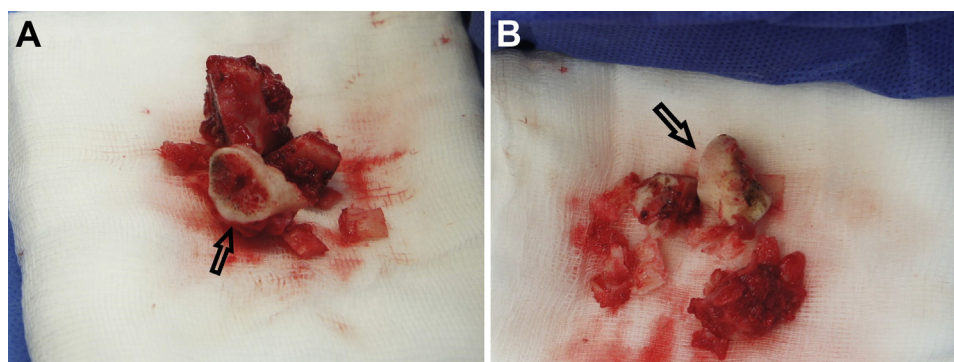


Figure 2 Removed material, peripheral compact bone tissue resembling cortical bone with central trabeculae of lamellar bone ⇒ (A), portion of chondral tissue in the middle third portion ⇒ (B).

Postoperative period

Physical therapy was started from day 1 after surgery and continued during the hospital stay; then it was performed at home. A 3-day hospital stay was necessary in order to achieve optimal hemostatic treatment. Celecoxib 200 mg once daily was prescribed for 20 days to prevent HO recurrence.^{18,22}

After surgery, to prevent postsurgical bleeding, the patient underwent the following protocol: 30 IU/kg efmoctocog alfa through bolus injection plus 1 g oral tranexamic acid, administered every 8 hours up to the third postsurgery day. Afterward, tranexamic acid was administered every 12 hours and efmoctocog alfa 30 IU/kg every 24 hours up to the seventh postsurgery day. From the 8th to the 14th postsurgery day, 30 IU/kg efmoctocog alfa was administered every 48 hours, followed by resuming the regular preoperative prophylaxis regimen (ie, every 72 hours).

No postoperative irradiations were performed. No hemorrhagic complications occurred, and the drain was removed in day 2 after surgery. The postoperative radiograph showed the removal of the middle third of the HO (Fig. 3).

Six months after surgery, the patient had no neurovascular deficits and could achieve flexion to 111°, extension to 14°, pronation to 80°, and supination to 90°. At the 6-month follow-up visit, the Mayo Elbow Performance Score¹⁶ was 80 and the Disabilities of the Arm, Shoulder and Hand score⁷ was 13.3. Radiographs performed 6 months after the surgery did not show recurrence of the excised HO, nor the presence of new HO among other areas involved during surgery (Fig. 4).

Discussion

The most common pathophysiological process reported in hemophilic patients is that of joint destruction owing to intra-articular bleeding, the condition known as hemophilic arthropathy.¹² Intramuscular hemorrhage is the second most common site of bleeding in patients with hemophilia. Despite this fact, HO is rarely reported in hemophilia even if its incidence may be underestimated, as suggested by one review²³ of radiographs of 60 hemophilia patients in which 9 (15%) showed ectopic new bone formation. Many of these reports are of lower limbs, specifically peripelvic bone growth.^{1,2,5,8,12,24,25} Loss of motion is the most common functional limitation in HO; however, significant restriction in the range of motion or bony ankylosis are relatively rare and only reported in some 2%–7% of patients with HO.¹²

A report by Mortazavi et al¹⁷ described the operative treatment of a brachialis muscle HO in an 8-year-old hemophilic boy causing complete elbow ankylosis (fixed elbow in 80° of flexion). The HO described in the report is a continuous bony bridge formed between the distal humerus and proximal ulna, very similar to the

one in our present report: localized in the bulk of brachialis muscle but with a nonfusion area at the middle third. Contrary to our case, in the report by Mortazavi et al, the HO was related to a specific traumatic event with joint involvement (swelling and hemarthrosis) followed by a period of elbow immobilization 16 months before surgical excision. Intramuscular hematoma inside the right brachialis muscle followed by HO seems likely in our patient. The bony bridge path developed in line with the main brachialis muscle fibers, and the referred localized pain without bruising, is compatible with the hypothesis of intramuscular bleeding.^{4,23}

HO classically forms without connection to the periosteum. However, if the muscle has a broad-based attachment to bone by Sharpey fibers, the hemorrhage may extend to involve the periosteum with subsequent periosteal new bone formation.²³ HO with connection to the bone surface may pose a diagnostic challenge to osteosarcoma that arise on the bone surface (periosteal or parosteal OS).¹¹ In our case, osteosarcoma was unlikely. Histopathologic examination of removed tissue showed thickened trabeculae of lamellar bone with central fatty marrow and peripheral compact bone tissue resembling native cortical bone; these are typical findings of more mature HO lesion. Moreover, 6-month radiographs did not show any evidence of recurrence. Histopathologic examination also reported the presence of chondral tissue situated in the middle third of the bony bridge, which is still compatible with HO. Indeed, focal areas of metaplastic cartilage and endochondral ossification are described among nongenetic intramuscular HO.¹⁴ The presence of this nonfusion area is probably related to the absence of elbow immobilization contrary to the case described by Mortazavi et al¹⁷ mentioned above.

Current consensus seems to suggest that the best treatment option appears to be conservative management with factor replacement, or a combination of radiotherapy and mobilization.¹³ Nevertheless, surgical treatment of mature HO has also been described.^{1,2,17,19}

Surgery in high-risk patients requires perioperative blood loss reduction thanks to a multimodal approach to coagulopathy and hemorrhagic risk. Appropriate liaison between the surgical, anesthetic, and hematology teams is mandatory to improve the patient outcome thanks to the patient blood management strategy.³ In accordance with the Association of Anaesthetists of Great Britain and Ireland guidelines, the administration of tranexamic acid should be considered in all nonobstetric patients where blood loss >500 mL is possible and in traumatic and obstetric major haemorrhage.⁹ Considering all surgical procedures, tranexamic acid has been shown to reduce blood loss by approximately one-third.²⁰ For these reasons, the administration of tranexamic acid preoperatively should always be considered in patients with hemophilia or other bleeding disorders.

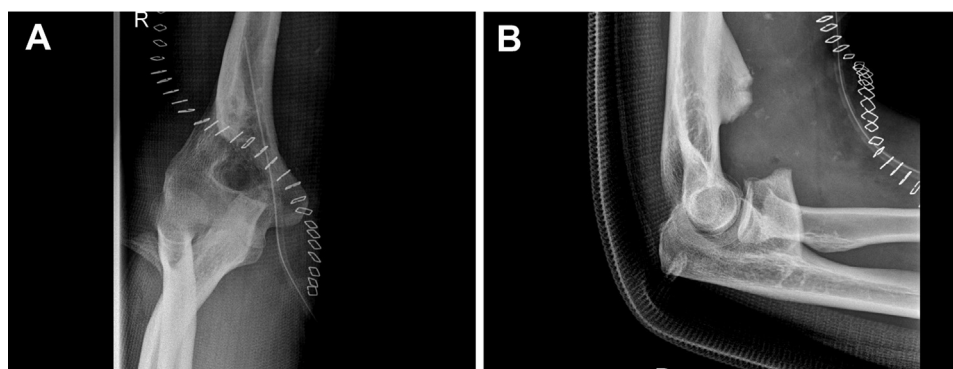


Figure 3 Postoperative radiograph in antero-posterior projection (A); postoperative radiograph in lateral projection (B).

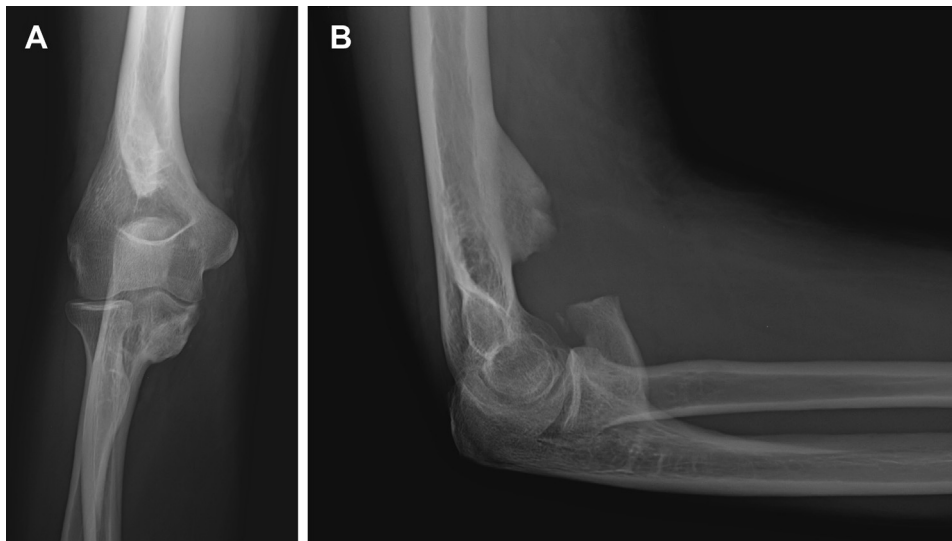


Figure 4 Six-month postsurgery radiographs shows no evidence of heterotopic ossification recurrence; antero-posterior projection (A), lateral projection (B).

Moreover, in recent years, an increasing number of patients are continuing antiplatelet or anticoagulant therapy into the perioperative phase to reduce the risk of major cardiovascular and thrombotic events. In their recent review, Shah et al²⁰ have proposed that aspirin can be continued for most procedures; bridging therapy for warfarin should be considered only in patients with the highest risk of thrombosis; postoperative bridging should not be started until at least 48 hours after surgery with a high bleeding risk; direct oral anticoagulants can be stopped 48 hours before most surgery in the presence of normal hepatic and renal function, adenosine 5'-diphosphate receptor antagonists, such as clopidogrel, should be stopped 5-7 days before operation; and that the use of tranexamic acid should be considered in patients undergoing urgent surgery with a high risk of bleeding who are on antiplatelet agents or where a residual anticoagulant effect of direct oral anticoagulants is suspected.

In our patient, full assessment of hematologic function and coagulation profile was performed in order to schedule surgery with hematologic optimization. Tourniquet was not used to achieve a better real-time hemostasis thanks to electrocautery and to minimize postoperative pain and increased risk of thrombotic events.²⁰ Just before surgery and up to the seventh postsurgery day, tranexamic acid was administered.

The cause of HO remains unclear but is more common in patients who have undergone large bone resection or massive soft tissues dissection. Intraoperative muscle ischemia and trauma have also been implicated.¹⁴ Considering the severe disability in such a young patient, we choose to perform surgery despite the risk of new HO formation and the risk of joint stiffness. The 6-month radiographs did not show recurrence of the excised HO nor the presence of new HO among other areas involved during surgery. These findings, associated with the absence of perioperative bleeding complications, are probably related to the combination of meticulous intraoperative hemostasis, well-dosed factor replacement and antifibrinolytics therapy, and prophylaxis with celecoxib.

Functional outcomes immediately after surgery and 6 months after surgery were excellent compared with the preoperative ones. The recovery of range of motion was remarkable considering the almost complete immobilization period of about 15 years, especially in a joint highly susceptible to stiffness such as the elbow joint. The Disabilities of the Arm, Shoulder, and Hand score decreased from 47.5 points (presurgery) to 13.3 points (at 6 months); that indicates a

considerable improvement in the patient's quality of life, allowing him to get his hand to his mouth, to wash his hair, to perform all personal hygiene activities, and almost all normal social activities with no or mild difficulty. These functional outcomes are in line with those reported by Mortazavi et al,¹⁷ with a restoration of normal range of motion at the 5-year follow-up visit.

Conclusions

To our knowledge, this is the first case of massive atraumatic muscular HO in the elbow without articular involvement and the second case of a similar elbow HO surgical excision described in a hemophilia patient. However, considering that the incidence of HO in hemophilia is probably underestimated, HO should be considered as a plausible musculoskeletal complication in patients affected by hemophilia, especially when the decrease in range of motion arises in the absence of evident acute joint bleeding or traumatic events. Despite the long-lasting near-complete elbow immobility, functional outcome was considerably better compared with the preoperative one. The short-term result is very satisfactory and suggests that surgery may be a good option to treat patients with mature HO lesion and severe disability. However, long-term results and possible recurrence are still unknown.

Disclaimer

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