Musculoskeletal Manifestations of Hemophilia: Imaging Features

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The purpose of this pictorial assay is to demonstrate the imaging features of the various musculoskeletal manifestations of hemophilia, an X-linked disorder. Depending on the site of recurrent bleeding, musculoskeletal manifestation can be in the form of hemophilic arthropathy and/or soft tissue, intraosseous, or subperiosteal pseudotumors. Radiography, sonography, computed tomography, and especially magnetic resonance imaging help in the evaluation of hemophilic arthropathy and pseudotumors, providing accurate diagnosis, thus avoiding inadvertent procedures and related complications. Treatment includes replacement of clotting factors either continuously or when indicated, radionuclide or open synovectomy in cases of disabling arthropathy.

Introduction

Hemophilia is an X-linked recessive disorder that occurs because of deficiency of clotting factors. The disease occurs predominantly in males and is transmitted through females. The two common forms of this disorder, hemophilia A and B (due to the deficiency of clotting factor VIII and IX, respectively), are similar in their clinical presentation and imaging findings. The classic presentation is bleeding into the joints leading to hemophilic arthropathy. Other locations of bleeding include soft tissues, subperiosteum, and within the bone, the latter two being rare. The radiographic features of these lesions may mimic many tumor and tumor-like conditions (hence called pseudotumors) and are not diagnostic. However, hemophilic pseudotumors should be kept in the differential diagnosis of well-defined osseous expansile lytic lesion(s) in a young male, especially in the presence of adjacent hemophilic arthropathy. The presence of various stages of hemorrhage surrounded by hemosiderin/sclerotic rim, appreciated on magnetic resonance imaging (MRI). This can help in differentiating these lesions from true neoplastic conditions.

FIG 1. Fourteen-year-old boy with hemophilia presented with swelling of right knee. Anteroposterior (A) and lateral radiographs (B) show widening of the intercondylar notch (arrowhead), epiphyseal overgrowth and destruction of the articular surface (black arrow), and associated soft-tissue swelling (asterisk) involving the right knee joint. Left knee joint is normal. These features are diagnostic of hemophilic arthropathy.

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MR imaging, points toward this diagnosis. In this pictorial assay, we intend to describe the various musculoskeletal manifestations of hemophilia with an emphasis on the characteristic imaging appearance on conventional radiograph, ultrasound, and MR imaging.

**Hemophilic Arthropathy**

Hemorrhage in hemophilic patients occurs most commonly in the musculoskeletal system, although it can occur anywhere. In the musculoskeletal system, joints are the most common site of bleeding followed by soft tissues and bones.\(^1\)\(^-\)\(^4\) Recurrent bleeds are common into the synovial joints and result in articular and periarticular abnormalities.\(^5\)-\(^7\) The usually affected joints are knee, ankle, elbow, shoulder, and hip in descending order of frequency.\(^8\) Early findings include joint effusion and hemarthrosis, followed by articular and periarticular changes (including synovial hypertrophy and hemosiderin deposition). In later stages, there is epiphyseal overgrowth and osteopenia (due to hyperemia), early closure of physeal plate, destructive changes like loss of cartilage, subchondral cyst formation, and bone erosions.\(^7\) Features that favor hemophilic arthropathy on radiograph include epiphyseal overgrowth and osteopenia, widened intercondylar notch, soft-tissue swelling, flattening of the condylar surface, squaring of the patella, and other destructive

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**FIG 2.** Sixteen-year-old male with hemophilic arthropathy. Axial gradient echo MR images (A, B) of the right knee joint show hypointense areas with blooming involving the femoral attachment sites of anterior and posterior cruciate ligaments (asterisk). The hypertrophied synovium (white arrow) also shows blooming. These hypointense areas with blooming represent hemosiderin deposition due to repeated hemarthrosis in a hemophilic patient. Sagittal gradient echo MR images (C, D) show hypointensity associated with blooming artifact involving the anterior cruciate ligament (white arrow) and posterior cruciate ligament (black arrow), suggesting hemosiderin deposition. Note, associated joint effusion is seen.
changes, as mentioned above (Fig 1). The radiographic mimic of hemophilic arthropathy is juvenile rheumatoid arthritis. The classical features on MR imaging include hemosiderin deposition (seen as hypointense foci on both T1-weighted and T2-weighted sequences, and showing blooming on gradient echo sequences) and synovial hypertrophy (best appreciated on T2-weighted fat-suppressed and postgadolinium T1-weighted sequences) (Fig 2). Hemosiderin may be deposited along the intra-articular ligaments and tendons as well (Fig 2). Cartilage is well evaluated on fat-suppressed proton density sequence or on dual echo steady-state sequence and thus MR imaging can pick up cartilage destruction and bone erosions at an early stage. MR imaging optimally demonstrates intra-articular blood products, synovial hypertrophy, and effusion and this information is instrumental in early treatment planning.

**Hemophilic Pseudotumor**

Pseudotumors are rare complication of hemophilia, occurring in 1%-2% of the patients with severe coag-

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**FIG 3.** Twenty-five-year-old hemophiliac presented with difficulty in walking and joint pain involving both knees. Anteroposterior radiograph of both knees [A] shows multiple expansile lytic lesion involving the right proximal tibia (white arrow), left distal femur (black arrowhead), and left proximal tibia (black arrow). Multiple osseous trabeculae (asterisk) are seen extending across the lesion in left proximal tibia. The same lytic lesion (white arrowhead) of the right proximal tibia is seen on lateral projection (B). Note, distal femoral lesion also shows pathologic fracture and associated soft tissue swelling.

**FIG 4.** MR images of the same patient as in Fig 3. T1-weighted coronal MR image (A) shows well-defined hypointense lesion admixed with areas of hyperintensity (asterisks) in right proximal tibia (black arrow), left distal femur (black arrowhead), and left proximal tibia (white arrow). On T2-weighted coronal MR images, non-fat-suppressed (B) and fat-suppressed (C), these lesions are heterogeneously hyperintense with hypointense areas within suggestive of blood breakdown products in various stages (white arrowheads). Note, a thin hypointense rim is seen around in all the lesions on T2-weighted MR images, suggesting hemosiderin/sclerotic rim.
ulation disorder. A hemophilic pseudotumor is a chronic, encapsulated, slowly expanding mass lesion occurring because of recurrent hemorrhage into the extra-articular musculoskeletal system. It may arise because of minor trauma or de novo. Usually these are painless expanding masses that may be detected incidentally. These may also present due to acute bleeding, which causes local and systemic signs or secondary complications (fracture or neurovascular compression). These may result in contractures and compartment syndromes, leading to profound loss of function. Superimposed infection, fistula formation to skin or bowel, and exsanguination due to pseudotumor rupture may complicate disease management. Although they may not be limited by anatomical boundaries, they are categorized into osseous and soft-tissue lesions. The imaging characteristics on various modalities depend on the site and extent and stage of bleeding. A pseudotumor consists of blood products in various stages of evolution and has a fibrous capsule that contains hemosiderin.

Just as repetitive bleeding into the joints leads to hemophilic arthropathy, recurrent bleeding into the bones results in osseous pseudotumor (intraosseous/intramedullary and subperiosteal). The most frequently implicated bones are femur, pelvis, tibia, and small bones of the hand in order of descending frequency. On radiograph, intraosseous pseudotumors appear as well-defined, unilocular or multilocular, expansile lytic lesions of variable size with geographic pattern of bone destruction (Fig 3). Osseous trabeculae or septa-like structures frequently extend across the osteolytic lesions (Fig 3). These can occur in any portion of the tubular bones, may be intramedullary or eccentric, and may show endosteal scalloping, cortical thinning, peripheral sclerosis, as well as dystrophic calcification. These lesions can be quite destructive and completely replace the involved segments of bone. Deformities and pathologic fractures may occur due to progressive expansion of the bone (Fig 3). The various radiographic differentials that merit consideration are primary and secondary bone neoplasms (giant cell tumor, plasmacytoma, telangiectatic osteosarcoma, metastasis, and malignant fibrous histiocytoma), tumor-like lesions (aneurysmal bone cyst, brown tumor, solitary bone cyst), and infection (echinococcosis). Computed tomography (CT) helps by better depicting crossing trabeculae, cortical change, periosteal reaction, and anatomical extent. MR imaging has the characteristic appearance of a multiloculated lesion containing fluid components having heterogeneous signal intensity on various sequences, reflecting the presence of blood
products in various stages of evolution\textsuperscript{15} (Fig 4). Fat-suppressed T1-weighted images depict methemoglobin and gradient echo images show areas of hemosiderin deposition. The lesions are surrounded by T1- and T2-hypointense rim (Fig 4), which is due to either hemosiderin or peripheral sclerosis/fibrous capsule or residual cortical bone, and shows thin nodular enhancement (if any) on postgadolinium images. MR imaging accurately assesses intramedullary and soft-tissue extension, neurovascular involvement, as well as monitoring the therapeutic response. Fluid–fluid levels may also be seen on MR imaging.\textsuperscript{17} Subperiosteal pseudotumors result because of elevation of the periosteum and pressure necrosis of the bone, caused by hemorrhage. Radiographic findings include soft-tissue mass in subperiosteal location, cortical erosions, subperiosteal new bone formation, and soft-tissue extension (Fig 5). These lesions may be associated with aggressive periosteal reaction. The presence of curvilinear calcific struts at the periphery, projecting into

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\caption{Twenty-four-year-old male with hemophilia presented with swelling in the right gluteal region. Anteroposterior radiograph of the pelvis (A) with a magnified image (B) shows increased soft tissue in the right gluteal location (asterisk). Grayscale and color Doppler sonography (C, D) images of the right gluteal location show an intramuscular heterogeneous lesion predominantly hypoechoic (black arrow). There is no vascularity (white arrow) within the lesion. These features suggest intramuscular pseudotumor in a hemophilic patient. [Color version of figure is available online.]
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\begin{figure}
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\caption{Thirty-year-old hemophilic patient presented with swelling in the left hip region. Axial contrast-enhanced CT images (A, B) show heterogeneous lesion (arrows) with peripheral enhancement involving the proximal left thigh with nonenhancing areas (asterisk) within. Note, variable attenuation areas are seen in the lesion, suggesting various stages of hemorrhages in a soft-tissue pseudotumor.
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soft tissues, is the most characteristic feature of hemophilic pseudotumors. Recurrent and nonresolving soft-tissue bleeding gets organized and causes joint contractures and soft-tissue pseudotumors. The latter are most common in the thigh, gluteal region, and iliopsoas muscle. Soft-tissue pseudotumors can be categorized into intramuscular or extramuscular (interfascial, subcutaneous).

Intramuscular hematomas usually remain localized, although they may produce pressure deformity or subperiosteal new bone formation. Pressure to adjacent soft tissues may lead to skin necrosis, pain, neurologic deficits, and restriction of movement. On radiographs, soft-tissue pseudotumors manifest as increased soft-tissue
density, with or without internal calcification (Fig 6). Adjacent bony structures may show focal new bone formation, extrinsic erosion, periosteal reaction, or medullary destruction. Secondary infection is rare and is suggested by the presence of gas within. Sonography helps to follow the progression or regression of hematoma after therapy. Depending on the different stages of the hemorrhagic event, variable patterns of echogenicity on ultrasound (anechoic or heterogeneously hypoechoic) and attenuation on CT (high, isodense, or low) may be seen. No internal vascularity is seen on color Doppler imaging (Fig 6). Contrast-enhanced CT shows peripheral enhancement and central nonenhancing variable attenuation areas (Fig 7). MR appearance is similar to the osseous pseudotumor, demonstrating blood products in various stages of evolution and hemosiderin rim.

Hemophilic pseudotumors may be complicated by superimposed infection, pathologic fractures, and fistula formation (Figs 3, 5, and 8).

Hemophilic pseudotumors may develop in soft tissues, in the bone, or in subperiosteum, in descending order of frequency and may coexist in these locations. The radiographic appearance is variable and has many differential diagnoses. MR imaging is superior for demonstrating different stages of hemorrhage, hemosiderin/sclerotic rim, and in displaying the soft tissues and intramedullary spaces. Accurate knowledge of the extent and character of pseudotumors gained through sonography, CT, and especially MR imaging is extremely valuable for optimal management. Apart from the clinical profile of recurrent bleeding, the presence of hemophilic arthropathy near the pseudotumor is frequent on conventional radiographs and serves as an important diagnostic clue, thus differentiating this entity from other mimickers. It is vital to make the diagnosis of hemophilic pseudotumor because percutaneous drainage or biopsy is contraindicated due to the risk of complications, including life-threatening bleeding, fistula formation, and infection.

Conclusions

Hemophilia, a bleeding disorder with X-linked inheritance, can present with varied musculoskeletal manifestation. A proper knowledge of the imaging appearances is essential for early diagnosis. Although many conditions may mimic hemophilic lesions, clinical details along with imaging features can narrow down the differential diagnoses. Early diagnosis is useful in planning therapy, such as synovectomy, radiosynarthroses, and/or prophylactic factor therapy.

REFERENCES