

Original Article

Adjacent bone changes caused by hemophilic pseudotumor using 3T MRI scan

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Abstract: Objective: This study was to investigate the factors involved in bone changes of hemophilic pseudotumor (HP) in soft tissues and their clinical value. Methods: The study included 32 patients with HP. All lesions were scanned multi-dimensionally with T₁ weighted Imaging (WI), T₂WI Imaging conventional scan and T₂/PD fat suppression (FS) sequences of 3.0T magnetic resonance imaging (MRI). Bone condition was observed in all patients. Four factors on T₂WI FS or PDWI FS sequences, including largest transverse diameter (LTD) of HP, the scope of bone wrapped (SOBW) by HP, the distance (D) between HP and bone and the largest longitudinal diameter (LLD) were measured. Results: Among all 32 patients, a total of 39 HPs were detected. Twenty-four lesions had periosteal edema or proliferation. There were significant differences in LLD, D and SOBW between cases with and without periosteal edema or proliferation (P<0.05). Fifteen lesions had marrow edema, and there were significant differences in LLD and SOBW between cases with and without marrow edema (P<0.05). Conclusion: LLD, D and SOBW are important factors involved in bone changes of HP in soft tissues. Abnormal changes of skeleton can be revealed clearly on T₂/PD FS sequences, which could provide reliable information for the decision of surgical plan preoperatively.

Keywords: Hemophilia, pseudotumor, skeletomuscular damage, magnetic resonance imaging, T₂/PD fat suppression sequences

Introduction

Hemophilia is a group of hereditary hemorrhagic diseases, in which the shortage and inactivity of clotting factors lead to coagulation dysfunction of patients. According to the deficiency of the clotting factor, hemophilia is divided into three types: type A (FVIII), type B (FIX) and type C (FXI). The type A and type B are generally congenital hemophilia, while the type C is acquired hemophilia. Hemophilic pseudotumor (HP) is a rare complication of hemophilia [1-3]. It usually occurs in the surrounding soft tissues of thigh and pelvis of patients with hemophilia A or B, greatly challenging the clinical treatment of hemophilia [4, 5].

According to the location of lesions, HP is divided into three types [6]: type I, HP in soft tissues; type II, HP under periosteum; and type III, HP in the bone. Type I HP had decreased bone density and strength, such as premature changes in trabecular, cortical microarchitecture, arthropathy and immobility [7, 8]. Generally, there are

various degrees of osteoporosis in the bone structure near type I HP. The bone effect of HP in soft tissues often begins from periosteal edema or proliferation, and then invades bone cortex or bone marrow gradually. Marrow edema appears earlier than periosteal change in some particular cases [9]. The impact of type I HP on bones is various due to the different sizes and locations of pseudotumors whereas huge lesions, especially in pelvic cavity, will become more serious and even lethal [10, 11].

The definite underlying mechanism of HP is not completely understood, and its occurrence has no obvious correlation with the order of severity or the type of hemophilia [12]. Considering most patients had traumatic history before, some researchers suggested that trauma could be the etiologic factor [13]. Some studies have been conducted to obtain medical imaging findings about HP [9, 14-16]. However, the factors involved in bone changes of HP in soft tissues have not been reported.

Bone changes by hemophilic pseudotumor

Table 1. Main laboratory results of patients (n=32)

Item	No. (cases)	Normal scope	Results (range)
Prothrombin (s)	32	9.80~12.10	12.04 ± 0.93 (10.60~13.50)
Thrombin (s) part activated	32	14.00~21.00	16.35 ± 1.24 (13.70~17.40)
Thromboplastin time (s)	32	22.70~31.80	76.04 ± 18.48 (47.70~116.60)
Fibrinogen (g/L)	32	1.80~3.50	4.39 ± 2.14 (1.96~8.90)
Blood coagulation factor VIII activity (VIII:C) (%)	27	50~150	2.76 ± 1.88 (0.83~9.60)
Blood coagulation factor IX activity (IX:C) (%)	5	80~120	3.74 ± 1.23 (2.60~5.80)
Erythrocyte sedimentation rate (ESR) (mm/h)	32	0-15	37 ± 33 (6-131)
C-reaction protein (CRP) (mg/l)	32	0-3	32.97 ± 34.25 (2.5-137)
Factor VIII antibody	3	-	+
Factor IX antibody	1	-	+

Note: "-", negative; "+", positive.

The magnetic resonance imaging (MRI) system has many advantages, such as high-speed scan, high tissue-contrast, high signal-to-noise ratio and large scanning range [17]. Multi-direction scan with T₂/PD fat suppression (FS) sequences of MRI can remove interference of high signal of fat tissue in marrow, intermuscular and subcutaneous tissues [18]. Therefore, the size, location and capsule of HP can be clearly revealed. Additionally, these sequences are sensitive to detect edema of the surrounding soft tissues, periosteum and bone marrow, accurately displaying the periosteal proliferation and abnormal changes of bone cortex [19]. Therefore, images acquired from this system are reliable and can be used for lesion analysis.

In this study, 32 patients with HP in soft tissues of thigh and pelvis were included. All lesions were scanned multi-dimensionally with T₁WI, T₂WI conventional scan and T₂/PD FS sequences of 3.0T MRI. The largest transverse diameter (LTD), scope of bone wrapped (SO-BW), distance (D) between HP and bone and the largest longitudinal diameter (LLD) of HP were observed and measured on T₂/PD FS sequences. We aim to analyze the skeletal changes or damages following HP, which could further be used for making reasonable therapeutic plans for HP patients.

Material and methods

Patients

A total of 32 patients with hemophilia A or B were enrolled from Jan, 2014 to Dec, 2016 in Qianfoshan Hospital. HP was confirmed by clinical

history, laboratory and medical imaging examinations, and no other lesions in thigh or pelvis were found. They all had type I HP. The patients who had surgery or any other diseases in thigh or pelvis were excluded. All Patients were male and aged from 11 to 58 years old (the average age was 32.4 years old). Twenty-seven patients were diagnosed with hemophilia A (27/32, 84.4%) and the other five were hemophilia B (5/32, 15.6%). Among the 32 cases, there were 2 (6.3%) cases with mild hemophilia (5% or more of the normal activity of blood coagulation factors), 23 (71.9%) cases with moderate hemophilia (1% to 5% of the normal activity of blood coagulation factors) and 7 (21.8%) cases with severe hemophilia (1% or less of the normal activity of blood coagulation factors). Of the 39 lesions, 8 (20.5%) lesions located in gluteus, 24 (61.5%) were in thigh muscles and 7 (18%) were in iliac muscle. Twenty-three (62.5%) cases had history of trauma, 15 (46.9%) cases had pain, 23 (71.9%) cases were lower limb dysfunction. Main laboratory results were shown in **Table 1**. Prior written and informed consent were obtained from every patient and the study was approved by the ethics review board of the Shandong University.

MRI scan

The examination was performed on SIEMENS Magnetom Skyra 3.0T Superconducting Magnetic Resonance Imaging system with abdomen coil (Siemens Healthcare GmbH, Germany). T₂/PD FS sequences of Turbo Spin Echo (TSE) were adopted except for T₁WI and T₂WI conventional scan. The transverse (TRA), coro-

Bone changes by hemophilic pseudotumor

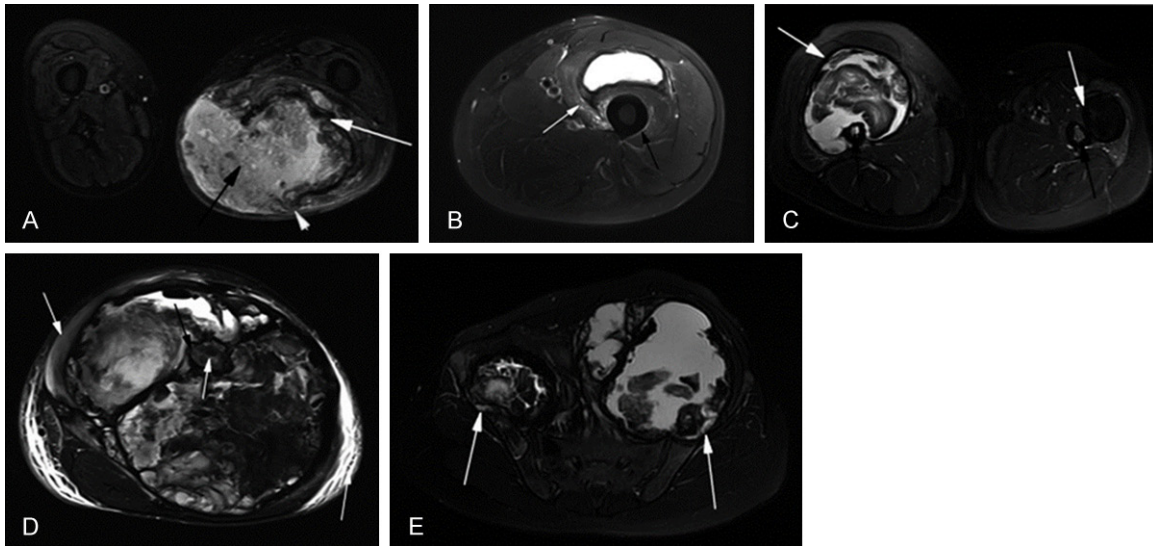


Figure 1. TRA FS-T₂ weighted images. A. Bilateral thigh image of a 33-year-old man with hemophilia A. High/low mixed signal in the soft tissue of media and posterior area of left thigh (black arrow) and capsule in the edge of lesion (white arrow) were found. Local capsule was incomplete (arrowhead), but all parts of left femur is normal. B. Left thigh image of a 43-year-old man with hemophilia B. The lesion's signal was high, while edema of soft tissue around HP showed moderate high signal (white arrow). Periosteal edema without obvious thickening also showed high signal (black arrow). C. Bilateral thigh image of a 20-year-old man with hemophilia A. Mixed signals of HP in both thighs (white arrow), the pseudotumor in right thigh surrounded bone and edema of bilateral marrows were discovered (black arrow). D. Left thigh image of a 34-year-old man with hemophilia A. HP with irregular cortex wrapped the femur completely (black arrow). The muscles, subcutaneous tissues and skeletal marrow had edema (white arrow). E. Pelvic cavity image of a 41-year-old man with hemophilia B. HP were found in bilateral iliacus areas. The iliac bones were eroded and the parts of local cortex were disappeared. The marrow cavity was occupied by high/low mixed signals (white arrow).

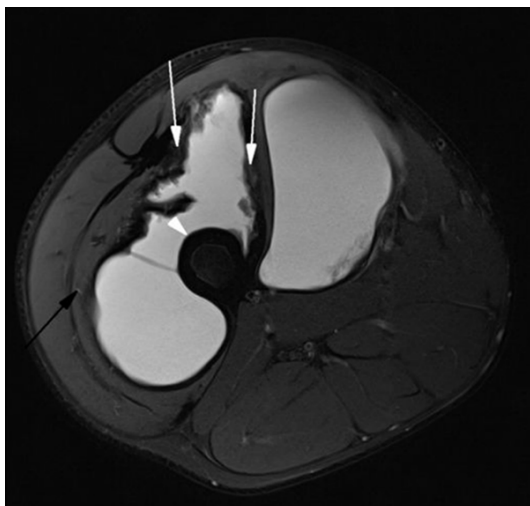


Figure 2. TRA FS-PD weighted images. Right thigh image of a 31-year-old man with hemophilia A. Honeycomb-like fibrous capsule of HP (white arrow) and the pressed muscles (black arrow) were found. The high signal of pseudotumor and periosteal edema (arrowhead) can be seen.

nary (COR) and sagittal (SAG) scan planes were used in all cases. Main scan parameters were

as follows: excitation frequency, 2; layer thickness, 5 mm; interlayer spacing, 6 mm; field of view, 380-400 mm; repetition time/echo time (TR/TE) of T₂ FS sequence, 5000-5500 ms/80-86 ms; and TR/TE of PD FS sequence, 3500-3800 ms/38-42 ms.

Measurement of lesions

LTD, SOBW, D and LLD of HP were measured. The first three parameters were measured on TRA, and the last one was measured on COR or SAG. If HP invaded or overlapped bone, the D value would become negative. The measurement of SOBW was as follows: two lines were made from the center of the bone to two lateral borders of the tumor on the transverse slice with largest area of the tumor, and SOBW was obtained by dividing the angle formed by these two lines by 360. The condition of periosteal edema/proliferation, the cortical thinning/disappearance and the edema of the bone marrow were observed simultaneously. LLD and LTD included pseudotumor itself and the capsule. The multiple pseudotumors in the same position were treated as a whole lesion. Mea-

Bone changes by hemophilic pseudotumor

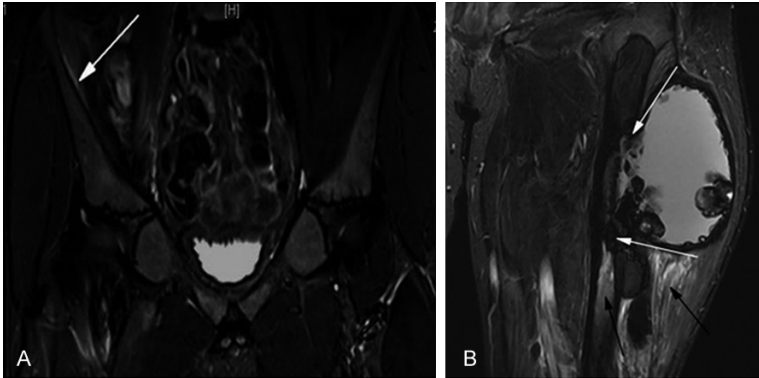


Figure 3. COR FS-T₂ weighted images. A. Pelvis image of a 14-year-old teenager with hemophilia A. High signal of thickening edematous periosteum, which was located in the medial area of the right ilium (white arrow) was found. B. Left thigh image of a 34-year-old man with hemophilia A. HP eroded femur and led to the cortex defect (white arrow); the marrow cavity became narrow, and the edematous marrow and soft tissue showed high signals (black arrow).



Figure 4. SAG FS-PD weighted images. Right thigh image of a 36-year-old man with hemophilia A. Both the thickening periosteum (short white arrow) and the edematous marrow had high signal (long white arrow), and the corresponding cortex became thinner (black arrow).

sured data and observed results were double-blindly evaluated by two imaging doctors. Data

were collected upon the consensus of the two doctors.

Statistical analysis

Data were expressed as mean \pm standard deviation (SD) and analyzed using SPSS 17.0 statistical software. The independent samples t test was used for comparison. The difference was considered significant when $P < 0.05$.

Results

Image analysis

By MRI scan, we detected the influence of these lesions on bone, cortex and soft tissues.

Among the 39 lesions, there were 24 lesions with periosteal changes (edema or proliferation) and 15 lesions with marrow edema. Seven lesions had periosteal changes and marrow edema simultaneously. The cortex became thinner or defect in 8 lesions. Low signal was present in the edge of 37 lesions (6 lesions with incomplete capsule). The edema of soft tissue was found in 34 lesions.

To further recognize of the imaging appearances of HP, we examined the MRI images of patients. Overall, the signal of HP was inhomogeneous or high (**Figure 1A**). The signal of both swollen limbs and edema periosteum was high (**Figure 1B**), and marrow edema also had high signal (**Figure 1C**). Low signal was shown by proliferated periosteum, similar as that of cortex. The growing trend of pseudotumor tended to be in the form of surrounding bone and towards longitudinal axis (**Figure 1D**). Local cortex was invaded, pressed, became thinner, and even disappeared, and the local marrow cavity became narrow (**Figures 1E** and **3B**). Moreover, TRA FS-PD weighted images showed that the thickness of the capsule was different in the different pseudotumors, and some lesions with thicker capsule showed honeycomb-like shape (**Figure 2**). From COR FS-T₂ or SEG FS-PD weighted images, we found that the adjacent tissues of capsule were pressed and distorted, showing structure disturbance. Involved limbs became swelling, accompanied with or without obvious periosteal thickening (**Figures 3A** and **4**).

Bone changes by hemophilic pseudotumor

Table 2. The values of HP with or without periosteal changes

HP (n=39)	LTD (cm)	LLD (cm)	D (cm)	SOBW (round)
With periosteal changes (n=24)	8.61 ± 3.56	14.81 ± 7.15	0.18 ± 0.28	0.42 ± 0.24
Without periosteal changes (n=15)	6.82 ± 1.87	11.32 ± 2.90	0.61 ± 0.48	0.29 ± 0.16
T	1.823	2.316	-3.077	3.347
P	0.076	0.026	0.006	0.002

Table 3. The values of HP with or without marrow edema

HP (n=39)	LTD (cm)	LLD (cm)	D (cm)	SOBW (round)
Edema group (n=15)	10.22 ± 3.83	21.08 ± 6.55	-0.02 ± 0.53	0.56 ± 0.28
No edema group (n=24)	8.15 ± 3.05	12.31 ± 3.96	0.15 ± 0.16	0.29 ± 0.12
T	1.861	5.253	-0.999	3.368
P	0.071	0.001	0.333	0.004

Lesion measurement

The lesions of pseudotumor were detected in 39 limbs from all the 32 cases of HP, among which 25 lesions were in unilateral limbs and 14 lesions in double limbs. The values on T₂ FS and PD FS weighted images, including LLD, LTD, SOBW and D, were unanimous with no statistical difference. To investigate the characteristics of these lesions, LTD, SOBW, D and LLD of HP were measured. The values of all the 39 lesions were as follows: the scope of LTD was 3.4-16.4 cm (9.04 ± 3.08 cm); the scope of LLD was 4.5-34.39 cm (16.13 ± 7.01 cm); the scope of D was -1-1.2 cm (0.07 ± 0.38 cm) and the scope of SOBW was 0.14-1 round, (0.45 ± 0.44 round). Periosteal edema/proliferation were found in 24 lesions (61.5%) and bone marrow edema in 15 lesions (38.5%). In addition, these values of lesions in HP were compared between cases with or without bone changes. LLD and SOBW were significantly higher in lesions with periosteal changes whereas D was significantly lower in these lesions compared with lesions without periosteal changes (**Table 2**). Similarly, LLD and SOBW were significantly higher in lesions with marrow edema compared with those without marrow edema (**Table 3**). These results indicate that there is a relationship between LLD, D, SOBW and periosteal edema/proliferation, and a relationship between LLD, SOBW and marrow edema.

Discussion

HP is not a real tumor but just a kind of chronic or subacute hematoma, which is not effectively

or completely absorbed in bleeding soft tissue and bone [1]. It mainly occurs in hemophilic patients with moderate or severe deficiency of clotting factor VIII or factor IX, and some HPs can exist for even more than ten years [20]. HPs occur commonly in the soft tissue of pelvis and lower limbs [5, 14], and sometimes in other positions, such as phalanx, mandible, humerus, ulna, radius, heel bone, orbit, temporal bone, psoas, iliopsoas, and so on [10, 14, 21-26]. The HPs can erode and destroy the integrity of skeletal structure and reduce bone quality reduce, thus inducing fracture or deformity. Sometimes HPs also cause joint dysfunction or destructive osteoarthropathy and final disability [26]. Therefore, early diagnosis and accurate assessment of HP are essential for proper surgical intervention and comprehensive treatment of this disease. It is believed that MRI is superior to CT in early judgment of bone destruction [10].

In this study, MRI was performed to evaluate the bone changes caused by type I HP. The results showed that marrow edema was found in 15 out of 39 lesions, and there was a significant relationship between marrow edema and LLD or SOBW of HP. In the cases with marrow changes, the mean size of LLD was 21.08 cm, and the mean value of SOBW was 0.56. Bone marrow edema may result from either backflow or obstruction of marrow vessels as the vessels in soft tissue are squeezed or reduced physical activity or functional limitations, capillary or venous congestion within the bone marrow [27]. If the LLD and SOBW of HP constantly increase, the marrow vessels would be continuously blocked and marrow edema would

Bone changes by hemophilic pseudotumor

become irreversible damage [28]. Bone marrow edema may occur either in the proximal or distal area of involved bone [29], but the possible cause and the underlying mechanism still need to be investigated.

There was also a relationship between LLD, D or SOBW and periosteal changes. Periosteal edema or proliferation was found in 24 of 39 lesions, which may be caused by direct stimulation of pseudotumors or the nearby tissue edema. Therefore, a continuous stimulation may result in periosteal proliferation, and thickening periosteum may merge with the cortical bone, resulting in irregularly thickening in the cortex. According to the results of this study, the pseudotumor had a trend of growing along the longitudinal axis of the bone or encasing the bone. The cortex became thinner or defect in 8 limbs because of the invasion of HP, and the cortical damage showed that pseudotumor was out of control and periosteum failed to prevent the lesions from development. Once HP is diagnosed, a treatment plan should be made right away, and regular reexamination for the evolution of lesions, especially focusing on the LLD, D and SOBW of HP for judging and assessing development of lesions is also needed [30]. Therefore, preventive or timely MRI T₂/PD FS examinations may be beneficial to early assess and treatment.

The whole lesion of HP has typically imaging features of the chronic and subacute hematoma, which reflects the evolution of hematoma in various stages. Many HPs experience a long history, and the capsule is formed in rim of most pseudotumor [11]. The capsules can be thick, and it is honeycomb-like in some cases, indicating small bleeding or generation of granulation tissue in the thick capsules. These characteristics are helpful in diagnosis and differential diagnosis. The formation of the capsule reveals a feature of slow-growth of HP, which can lead to destruction of adjacent structures [31]. In this study, edema of soft tissues in 34 lesions also had damage of the surrounding tissues. Fibrotic contracture and muscle atrophy may decrease elasticity and mobility of the soft tissue, and finally the dysfunction of limbs may occur. The possible mechanisms [11, 32] include: HP presses and destroys capillaries and causes dysfunction of microcirculation; hemosiderin in the hematoma can induce and activate neutrophils, which can release oxygen free

radicals and some cell factors, such as interferon- γ , interleukin-1, tumor necrosis factor.

There were 4 patients with antibodies to clotting factor VIII or IX in our study. This kind of patients should be treated more carefully because of the more complex and difficult therapeutic schedule. The presence of the antibodies might be associate with excessive therapeutic substitutes and their congenital susceptibility. High-titer of the antibody to clotting factor VIII may be related to the complete genetic disorders [33]. Surgical and medical comprehensive treatment should be performed on such patients [34]. Larger lesions should be given selective vessel embolism, radiotherapy or surgical intervention (resection of pseudotumor, bone graft and internal fixation or amputation) [35].

A study suggested that the most effective solution of bone severely damaged by pseudotumor was bone reconstruction and blood coagulation factor replacement [36]. Bone damages, such as periosteal edema/proliferation, marrow edema and pressed destruction of cortex, are responsible for clinical symptoms [15]. In addition, how to treat HP should also depend on changes of surrounding soft tissues and skin. In short, the treatment of HP is a project with multidisciplinary consultation that needs considering multiple factors.

Taken together, with the help of 3.0T T₂/PD FS sequences, we found that LLD, D and SOBW of HP were important factors involved in bone changes. However, owing to our limited samples, there were still some deficiencies. Henceforth, future studies with more cases are needed to further evaluate the pathological changes and potential damages of soft tissue/bone involved by HP. Our findings may offer meaningful help to clinical treatment of HP.

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Disclosure of conflict of interest

None.

Bone changes by hemophilic pseudotumor

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Bone changes by hemophilic pseudotumor

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