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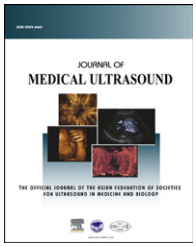

CASE REPORT

Serial Ultrasonography for Early Detection and Follow-up of Heterotopic Ossification in Stroke

Tian-Shin Yeh [1], Chueh-Hung Wu [2*], Wen-Shiang Chen [1], Tyng-Guey Wang [1]

[1] *Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital, School of Medicine, National Taiwan University, Taipei, Taiwan, ROC, and* [2] *Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital Yun-Lin Branch, Yunlin, Taiwan, ROC*

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Heterotopic ossification (HO) is a common complication in patients with neurologic deficits. Once developed, limited range of motion may occur and interfere with rehabilitation programs. Early diagnosis is crucial but difficult because radiographs may be negative, and similar clinical symptoms could appear in deep venous thrombosis, cellulitis, and osteomyelitis. A three-phase bone scan can detect the disease early, but it has high radiation and low specificity. Magnetic resonance imaging (MRI) may also assist in diagnosis, but is costly and has some contraindications. Ultrasonography has been used in HO detection and is safe, economical, easily accessible, and involves no radiation exposure. However, a few studies have described its use in HO, especially in serial follow-ups. We report a case with HO clinical symptoms, but the MRI results created a necrotizing fasciitis suspicion. Serial ultrasonography images implied the formation of HO rather than necrotizing fasciitis. Ultrasonography images serve as a good initial screening tool for HO and are useful for following up such dynamic disease processes.

Introduction

Heterotopic ossification (HO) is true bone formation in extraskeletal ectopic sites. The early clinical manifestations share similar features with deep venous thrombosis, infection, trauma, and arthritis. Low specificity of laboratory exams such as alkaline phosphatase (ALP) and erythrocyte sedimentation rate (ESR) makes it difficult to differentiate from other diseases without image studies.

* Correspondence to: Dr. Chueh-Hung Wu, Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital Yun-Lin Branch, Number 579, Yunlin Road, Section 2, Douliu City, Taiwan, ROC.
E-mail address: b88401062@ntu.edu.tw (C.-H. Wu).

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Magnetic resonance imaging (MRI) may assist in detecting soft tissue lesions, but is costly and has contraindications such as patient claustrophobia or obstructed imaging caused by instrument implants. Ultrasonography has recently been proposed as a useful tool for early HO diagnosis, but its application for serial follow-up has rarely been reported. We present a case with neurogenic HO and consecutive ultrasonography findings demonstrating the ectopic bone maturation process is shown to assist in the early diagnosis of this disorder.

Case report

A 56-year-old man without major systemic diseases was admitted to our rehabilitation ward with the diagnosis of left putaminal intracranial hemorrhage with right hemiplegia on November 7, 2009. After intensive training, he could walk with a quad cane and an ankle-foot-orthosis under moderate assistance for 20 m. He was administered massage therapy over his right lower extremity by a private massage therapist on November 24, 2009.

Right hip pain developed on December 8, 2009, especially during passive range of motion (ROM) exercises. Swelling and local heat in the right upper-anterior thigh were also noted, without obvious erythematous change. A right hip radiograph (Fig. 1A) showed no hip joint fracture or dislocation. Leg circumference was recorded periodically with the right side exceeding the left by 5 cm. Deep venous thrombosis (DVT) or early-stage cellulitis was suspected. A venous duplex ultrasonography was performed on December 10, 2009, which showed no evidence of DVT. Swelling improved mildly, but local heat and pain persisted, despite symptomatic treatment with diclofenac (100 mg) administered at one tab per day. Another ultrasonography on December 15, 2009, showed disarrayed muscle fibers of the right iliopsoas, with perifocal swelling and increased vascularity (Fig. 2A), and a 21.2 $\times$ 5.6 mm hypoechoic mass without internal vascularity between the right sartorius and the iliopsoas muscles (Fig. 2B). Myositis with possible abscess formation was suspected; thus, further imaging study was suggested.

The patient's body temperature reached 38°C once on December 16, 2009, with laboratory findings of white blood cells (WBC) exceeding 20,000/μl, segment 84.1%, C-reactive protein (CRP) 14.19 (mg/dL), ALP 309 (U/l), and creatine kinase (CK) 44 (U/l). Urine WBC was more than 100/high power field (HPF), urine culture later grew *Escherichia coli*, and blood culture was negative. An MRI (Fig. 3) taken on December 16, 2009, showed an intermuscular infiltrative mass-like lesion, approximately 17.5 $\times$ 5.5 $\times$ 3.0 mm of abnormal signal and heterogeneous enhancement with internal loculated foci of abnormal signal and rim enhancement between the right iliacus, sartorius, rectus femoris, iliopsoas, vastus medialis, and intermedius muscles, causing edema and mild hyperemia of the adjacent muscles and fasciae at the right pelvis, hip, and upper to mid-thigh. Necrotizing fasciitis (NF) was highly suspected. A plastic surgeon was consulted immediately, and he suggested that non-surgical treatment occur first with piperacillin/tazobactam and vancomycin. Another ultransound was done on December 17, 2009 (Fig. 2C), and it showed an enlarged hypoechoic homogeneous mass (30.5 $\times$ 7.3 mm) located between the iliopsoas and gracilis muscles. Follow-up WBC on December 19, 2009, was 5060/μl, segment 53.2%, CRP 3.69 (mg/dL), and urine WBC 0-2/HPF. Piperacillin/tazobactam and vancomycin were discontinued after 7-day and 5-day courses, respectively.

Although evidence of infection subsided, his right hip pain and ROM limitation persisted. On December 21, 2009, another ultrasound (Fig. 2D) showed septa formation within the mass, and hyperechoic lesions with acoustic shadows around the iliopsoas muscle. An HO diagnosis was highly suspected. A passive ROM limitation was obvious at this time, and severe pain during joint ROM persisted. Another ultrasound on December 23, 2009 (Fig. 2E and F) showed blurred muscle echotexture with increased vascularity and multiple hyperechoic lesions with a strong acoustic shadow obscuring the underlying bone cortex, but a hip radiograph on the next day (Fig. 1B) showed no evidence of ectopic bone formation. The rehabilitation program for neurological deficits was hampered after HO developed. Although ROM exercise and tilt table training resumed later, the

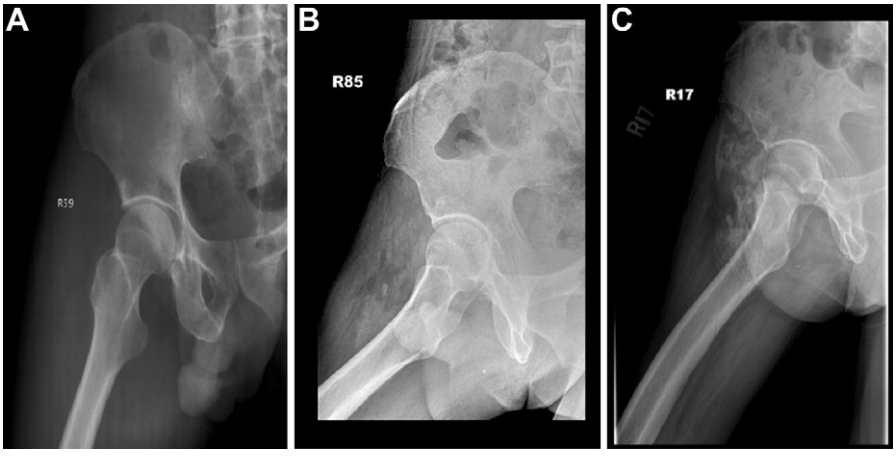

Fig. 1 (A) Right hip radiograph, anteroposterior view taken on the date of symptom onset, no focal bony or joint lesion was shown; (B) 2 weeks after symptom onset, there was no evidence of ectopic bone formation, although there seemed to be heterogeneous soft tissue density around the hip; (C) 3 months after symptom development, the radiograph showed varying-sized amorphous ossified shadows over the anterolateral periarticular area of the right hip joint.

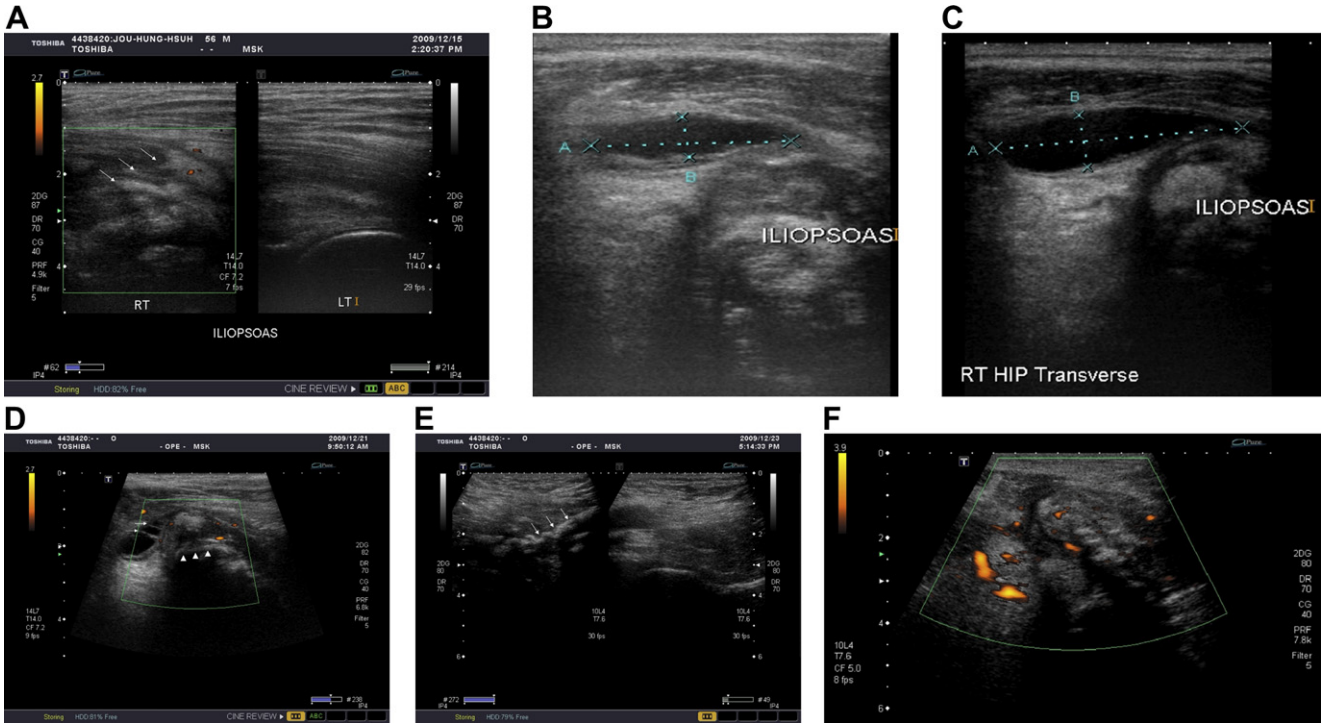

Fig. 2 Serial ultrasonography pictures. (A) left picture: 1 week after symptom onset, longitudinal ultrasonography imaging showed disarrayed muscle fibers (arrows) of right iliopsoas with perifocal swelling and increased vascularity. Right picture: Normal muscle texture on the sound side; (B) a 21.2 × 5.6 mm hypoechoic mass without internal vascularity between the right sartorius and iliopsoas muscles seen 1 week after initial symptoms (transverse view); (C) 9 days after symptom onset, an enlarged hypoechoic mass (30.5 × 7.3 mm) located between the iliopsoas and gracilis muscles was seen (transverse view); (D) 13 days after initial symptoms, a septa formation (arrows) within the mass and the appearance of hyperechoic lesions (arrowheads) with acoustic shadows around the iliopsoas muscle were shown (transverse view); (E) left picture: on Day 15, blurred muscle echotexture and multiple hyperechoic lesions (arrows) with strong acoustic shadow obscuring the underlying bone cortex. Right picture: normal muscle echotexture (longitudinal view); (F) marked increase of vascularity 15 days after symptom onset (transverse view).

patient could not tolerate weight bearing in his right lower extremity, and passive ROM of the right hip was limited (flexion: 90°; extension: 30°; abduction: 60°; adduction: 15°). He was discharged on January 18, 2010; Brunnstrom's stage remained stage II at the right upper limb, and stage III at the right lower limb. Three months after symptom onset, a hip radiograph (Fig. 1C) showed mature ossified shadows over the right hip joint's anterolateral periarticular area.

Discussion

HO is mature trabecular bone formation in extraskeletal soft tissues. It can be classified into post-traumatic, non-traumatic or neurogenic, myositis ossificans progressiva, or fibrodysplasia ossificans progressiva [1]. The neurogenic form is associated with neurologic conditions such as traumatic brain injury and spinal cord injury [2]; stroke without

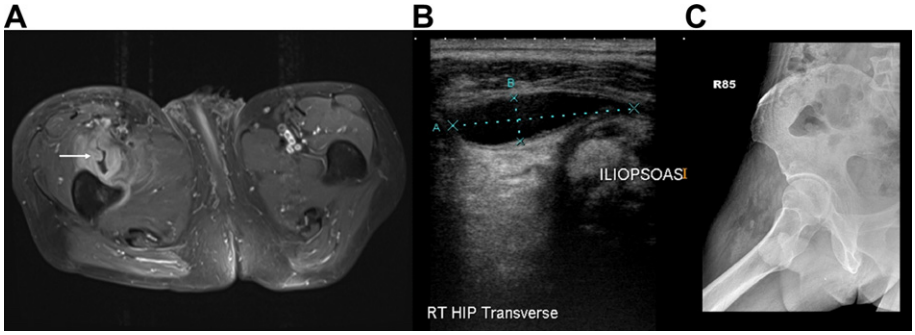

Fig. 3 (A) Transverse magnetic resonance imaging 8 days after initial symptoms showed an intermuscular infiltrative mass-like lesion 17.5 × 5.5 × 3 mm (arrow). The area with no enhancement among edematous muscles represented the area of necrosis and hemorrhage; (B) ultrasonography and MRI were performed almost simultaneously, which showed muscle fiber disruption and also a hypoechoic mass between muscle planes; (C) the radiograph at that time did not show ectopic bone formation. MRI = * magnetic resonance imaging.

coexisting trauma is generally not considered an independent risk factor [3]. Although the exact pathophysiology remains unclear, many have proposed that the presence of osteogenic precursor cells, inducing agents, and a permissive environment are required for HO formation [4]. Systemic inducing agents including bone morphogenetic protein, prostaglandins, growth factors, and hormones are keys for poly potential mesenchymal cell induction into osteoblasts; local inducing agents are potentially responsible for causing favorable alkalosis and hypoxic environments.

Whereas most HO are subclinical, 10%–20% of patients may experience painful swelling, erythematous change, and ROM limitation of the involved joint [4]. Mild-grade fever may also occur. The presentation timing may range from 2 weeks to 12 months after the injury [3]. Early HO diagnosis is largely based on these clinical symptoms. Conditions that may share similar manifestations include cellulitis, osteomyelitis, arthritis, DVT, trauma, and impending pressure ulcers. These should be ruled out because each has its own treatment options. The laboratory finding's diagnostic value remains controversial. The more frequently reported are serum ALP and CK [5–7]; CRP and ESR may also be elevated [8], but the rise in each is nonspecific [9–11]. In the present case, ALP and CRP were elevated, whereas CK was within normal limits. The coexisting urinary tract infection may also contribute to elevated CRP and WBC. Laboratory testing alone cannot finalize the diagnosis, and imaging modalities may provide further information.

Different imaging techniques can assist diagnosis depending on the stage of the disease. Plain films often fail to show positive findings until 4–8 weeks after initial symptoms, and they are used to rule out fractures or dislocations [3]. A three-phase bone scan is regarded as the standard criterion for early detection, and may serve as an index for following up on HO maturity [4]. However, patients experience radiation exposure during the exam, and its low specificity makes it difficult to differentiate HO with other traumatic, inflammatory, or degenerative skeletal system processes [12,13]. Originally used only for preoperative structure evaluation, MRI was recently found to be sensitive for approximately 20 days after disease onset. Findings include areas with no enhancement in regions of diffuse muscle edema, representing areas of necrosis and hemorrhage [14]. However, these findings are not specific [15,16]. Increased intramuscular signals and peripheral band-like contrast enhancement of muscles (>80% in prevalence) are also seen in necrotizing fasciitis; diffuse contrast enhancement of muscles is also found in pyomyositis (100% in patients with pyomyositis) [15,17]. These signals are shown in Table 1. The MRI is also time-consuming and costly. Therefore, ultrasonography may play an important role in dynamic disease process diagnosis and follow-up.

Kramer's report [18] is among the first to use ultrasonography for HO detection, describing the sonographic pictures of an ovoid, relative echo-free mass and a center core of calcification. Thomas and colleagues [19] later stated that the "zone phenomenon," the centrifugal maturation fashion of HO, can be seen with ultrasonography. The initial inner hypoechoic zone is also compatible with the area of no enhancement in an MRI. However, the use of ultrasonography for HO diagnosis was rarely described in the literature until recently, when Falsetti and others [12,13] performed bedside ultrasonography for 6 patients with neurogenic HO and concluded that

Table 1 Comparison of MRI and ultrasonography findings among heterotopic ossification, necrotizing fasciitis, and pyomyositis.

	Ultrasonography	MRI
HO	Zone phenomenon [19] Power Doppler ultrasonography: vascular signals within mineralized area of HO and in the outer hypoechoic area [12,13] Maturation: mineralized tissue ring thickens, shelly hyperechoic rim with a postacoustic shadow form [19]	Area with no enhancement in regions of diffuse muscle edema, sensitive approximately 20 days after disease onset [14]
Necrotizing fasciitis	Deep fascia thickening	Band-like hyperintense signal in muscles on fat-suppressed T2-weighted images (73%)
	Overlying fatty tissue diffuse thickening	Peripheral band-like contrast enhancement of muscles (82%)
	Fluid layer ≥4-mm thick along the deep fascia. Subcutaneous emphysema spreading along the deep fascia [22]	Thin enhancement of the deep fascia (82%) [15]
Pyomyositis	A focal, complex fluid collection of mixed echogenicity may be surrounded by a thick hyperechoic wall, which is often hyperemic.	Diffuse hyperintense signal in muscles on fat-suppressed T2-weighted images (100%)
	Edematous and hyperemic change in adjacent tissues	Diffuse contrast enhancement of muscles (100%)
	Septations: frequently present	Intramuscular abscess (88%)
	Air bubbles: small, hyperechoic foci with dirty shadowing [17]	Thick irregular enhancement of the deep fascia (75%)

HO = heterotopic ossification; MRI = magnetic resonance imaging.

ultrasonography is a useful tool for neurogenic HO diagnosis. The authors found that the classic "zone phenomenon" was always evident in hip HO, which was described as an inner hypoechoic core surrounded by a ring of hyperechoic mineralized islands, and then an outer hypoechoic zone adjacent to normal muscle [12,13]. A power Doppler ultrasonography demonstrates vascular signals within mineralized areas of HO, and in the outer hypoechoic area adjacent to normal muscle, but not in the central hypoechoic core [12,13].

Ultrasonography use for serial follow up of HO is even less reported. Because ultrasonography is economical, easily accessible, and without radiation, it can be an ideal tool in serial following up on a disease's progress. According to Thomas and coauthors [19], as the disease progresses, the mineralized tissue ring gradually thickens, and zone of differentiation is lost at approximately 7 weeks after symptom onset, representing total maturation of the heterotopic bone. Pan and others [20] used ultrasonography to follow seven cases with ectopic bone formation within muscles, and divided its course into three stages. In the first stage, an ill-defined hypoechoic lesion can be seen in the swollen muscle. In the second stage, the central area remains hypoechoic, but some shelly or spotted hyperechoic calcification appears in the periphery with a thin hypoechoic rim. In the third stage, a prominent shelly hyperechoic rim with a strong post-acoustic shadow can be observed.

Conversely, ultrasonography findings suggesting NF includes thickening of the deep fascia, diffuse thickening of the overlying fatty tissue, and a fluid layer at least 4 mm in thickness along the deep fascia. This criterion has the sensitivity of 88.2% and specificity of 93.3% for diagnosis of NF [21]. One pathognomonic feature for NF is the presence of gas within the soft tissues [22], which can further aid the diagnosis. These features were not seen in our case. Therefore, by ultrasonography findings, NF was not the tentative diagnosis.

In the present case, ultrasonography at 1 week led to a tentative myositis diagnosis, and an MRI was suggested, which was performed on Day 8. Because of peripheral band-like hyperintense signals, diffuse swelling and contrast enhancement of multiple muscle groups, necrotizing fasciitis was highly suspected by a radiologist. Prompt antibiotic treatment with piperacillin/tazobactam and vancomycin were initiated as suggested by the plastic surgeon, and surgical intervention was to be planned if further deterioration occurred clinically. Follow up laboratory data showed improvement, but symptoms persisted. Ultrasonography simultaneously showed a lobulated mass located between muscle planes. No typical US findings of necrotizing fasciitis such as gas formation in the soft tissues and fluid collections dissecting the deep fascia were seen, making necrotizing fasciitis less likely to be the diagnosis [22]. Subsequent ultrasonography depicted clear disease progression, with calcification visible on Day 15 of onset. The maturation process of ectopic bone and increased vascularity demonstrated by power Doppler ultrasonography in this case were similar to that described in previous studies. The ultrasonography findings combined with clinical presentations eventually allowed us to form the correct diagnosis. Therefore, ultrasonography can be a good screening tool suggesting further imaging modalities, and it also serves as a good tool for following up when the patient does not respond to the initial treatment.

In conclusion, during the process of HO maturation, positive findings can be seen in bone scans and ultrasonography approximately 2 weeks after symptom onset; MRI signal alternations may appear in 2—4 weeks. Ectopic bone formation generally does not show on plain film until Weeks 4—8 after the initial symptoms. Because of its cost-effectiveness, lack of radiation, and easy accessibility, ultrasonography serves as a useful initial screening tool for HO, and a safe and convenient modality for following up on progression in such patients.

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