



Early Imaging Findings of Hypertrophic Osteoarthropathy Mimicking Bone Metastasis from Extrathoracic Malignancy

뼈 전이로 오인될 수 있는 흉강 외 악성 종양으로 인한 비대성 골관절증의 초기 영상 소견

Ji Yeon Hwang, MD¹ , Jang Gyu Cha, MD^{1*} ,
Yu Sung Yoon, MD¹ , Ahrim Moon, MD²

Departments of ¹Radiology, ²Pathology, Soonchunhyang University College of Medicine, Bucheon Hospital, Bucheon, Korea

Hypertrophic osteoarthropathy (HOA) is a syndrome characterized by digital clubbing, periosteal bone formation, and synovial effusions. Secondary HOA is associated with intrathoracic malignancy in most cases; however, in rare cases, HOA can be caused by extrathoracic conditions. We report early ultrasound, computed tomography, magnetic resonance imaging, and bone scintigraphy findings of HOA in a patient with breast cancer. Its ambiguous clinical and imaging findings that mimicked malignant conditions are particularly interesting and informative.

Index terms Hypertrophic Osteoarthropathy, Secondary; Breast Neoplasms; Neoplasm Metastasis; Magnetic Resonance Imaging; Ultrasonography

INTRODUCTION

A wide variety of conditions causes secondary hypertrophic osteoarthropathy (HOA) such as malignancy, infection, inflammation or chronic hypoxia. Among them, secondary HOA is highly associated with malignancy as a form of paraneoplastic syndrome, mostly with lung cancer (1). Since pulmonary origin malignancy is a major cause of secondary HOA, extrathoracic conditions are rarely associated with secondary HOA. Although the radiographic findings of secondary HOA are widely known, only a few reports present ultrasonography (US) and MRI findings of secondary HOA. We

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*Corresponding author

Jang Gyu Cha, MD
Department of Radiology,
Soonchunhyang University
College of Medicine,
Bucheon Hospital, 170 Jomaru-ro,
Bucheon 14584, Korea.

Tel 82-32-621-5851
Fax 82-32-621-5874
E-mail mj4907@gmail.com

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ORCID iDs

Ji Yeon Hwang
<https://orcid.org/0000-0002-1047-5304>
Jang Gyu Cha
<https://orcid.org/0000-0002-3803-4850>
Yu Sung Yoon
<https://orcid.org/0000-0003-2349-5256>
Ahrim Moon
<https://orcid.org/0000-0001-6587-0013>

present a case of early US, CT, MRI, and bone scintigraphy findings of HOA mimicking bone metastasis in a 59-year-old woman with past history of breast cancer.

CASE REPORT

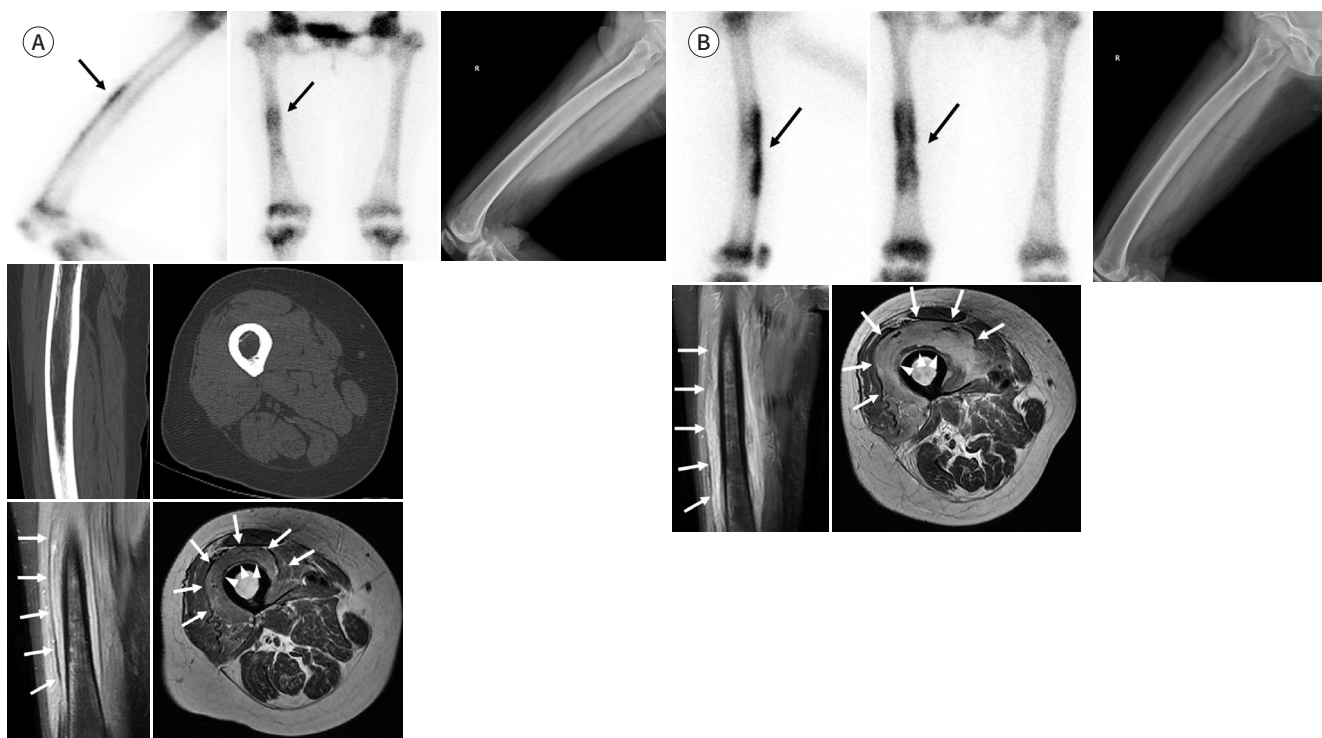
A 59 year-old woman presented with a one-week history of right thigh pain with no orthopedic history. She had a medical history of left breast cancer (invasive ductal carcinoma) with bone metastasis in the sternum and had undergone left modified radical mastectomy 2 years prior. She had been treated with Docetaxel as chemotherapy and human epidermal growth factor receptor 2 (HER-2) target therapy (Herceptin) for HER-2 positive breast cancer. Laboratory tests including complete blood count, electrolytes, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, and CA 15-3 were within normal limits.

Bone scintigraphy using technetium-99m-3,3-diphosphono-1,2 propanodicarboxylic acid (^{99m}Tc -DPD) revealed newly identified increased cortical uptake of the right mid-femoral shaft compared to the previous bone scintigraphy performed 3 months prior, which was needed to differentiate between traumatic lesion and bone metastasis. There was no change of known sternal metastasis. However, plain radiograph and CT scan of the right femur showed no abnormalities of bone and soft tissue. Eventually, the patient was admitted to our hospital complaining of aggravated right thigh pain that persisted for one month. Contrast enhanced MRI of the right thigh was performed using a 3.0-T MRI scanner (Signa HDxt, GE Healthcare, Waukesha, WI, USA) for further evaluation. The MRI revealed diffuse periosteal thickening at the anterior aspect of the right mid-femoral diaphysis. This lesion corresponded with the increased uptake area on bone scintigraphy. There were no signal changes of bone marrow or cortical disruption. Vastus medialis, vastus lateralis, and vastus intermedius muscles exhibited diffuse enhancement on contrast-enhanced T1-weighted image and diffuse increased signal intensity on T2-weighted image. No definite swelling of these muscles was observed (Fig. 1A). We suggested diagnosis of periosteal reaction in the femoral diaphysis by stress injury combined with adjacent muscle strain even though the femoral diaphysis is not a frequent location for stress injury. The patient was discharged and informed to make note of any further pain.

Two months after the initial pain, she was readmitted for pain that persisted in the same area. Laboratory data were similar to the previous test results. Bone scintigraphy demonstrated an increase in the extent of bone uptake in the right femoral shaft, but plain radiograph of the right femur still exhibited no abnormal findings (Fig. 1B). Therefore, we repeated MRI to exclude malignant bone lesion. The periosteal thickening was aggravated compared to the previous study, but there were no abnormal findings of the bone marrow. Follow-up MRI also revealed greater increase in extent of diffuse enhancement on the contrast-enhanced T1-weighted image and signal intensity of the vastus intermedius muscle on the T2-weighted image compared to the previous MRI. Moreover, the contour of the muscle was bulging to the anterior side, indicating swelling (Fig. 1B).

Consequently, a US-guided juxtacortical biopsy of the right femur was performed to exclude malignant conditions. The US image showed an abundant, periosteal, low echoic lesion surrounding the outer cortex of the right femoral diaphysis, measuring up to 8 mm with an

Fig. 1. Secondary hypertrophic osteoarthropathy in the right femur mimicking bone metastasis in a 52-year-old woman with right thigh pain. **A.** Initial ^{99m}Tc -DPD bone scintigraphy shows increased cortical uptake in the right mid-femoral shaft (black arrows). However, plain radiograph and CT images of the right femur show no abnormalities in the bone or soft tissue. On MRI, the fat-suppressed contrast-enhanced T1WI (lower left image) shows diffuse enhancement of the vasti muscles, predominantly, the vastus intermedius muscle (white arrows). The T2WI (lower right image) shows periosteal thickening of the anterior aspect of the right mid-femoral diaphysis (arrowheads), corresponding with the area of increased uptake on bone scintigraphy and diffuse increased signal intensity of the muscles (white arrows). **B.** Follow-up bone scintigraphy two months after the initial onset of pain shows increased ^{99m}Tc -DPD uptake in the right femoral shaft (black arrows) compared with that in the earlier bone scintigraphy (**A**). Plain radiograph of the right femur shows no remarkable findings. On follow-up MRI two months after the initial onset of pain, the fat-suppressed contrast-enhanced T1WI (lower left image) shows a much greater increase in the enhancement of the vastus intermedius muscle (white arrows). The T2WI (lower right image) shows increased periosteal thickening (arrowheads) compared to that in the previous study shown in (**A**) and a much greater increase in the signal intensity of the muscle (white arrows). T1WI = T1-weighted image, T2WI = T2-weighted image, ^{99m}Tc -DPD = technetium-99m-3,3-diphosphono-1,2 propanodicarboxylic acid



intact cortex. Diffuse swelling and decreased echogenicity of the vastus intermedius muscle also were observed. The power Doppler image did not reveal increased vascularity of the periosteal lesion or the muscle (Fig. 1C). At this point, we made a differential diagnosis more favorable to malignant lesions such as bone metastasis, leukemia, and lymphoma because of aggravated periosteal reaction and soft tissue swelling. And it was our major concern to exclude bone metastasis since the patient had a history of bone metastasis. The microscopic findings were unmineralized lace-like woven bone formation without malignant cell infiltration, resulting in the final diagnosis of secondary HOA from extrathoracic malignancy (Fig. 1D). The patient was discharged and followed-up for secondary HOA.

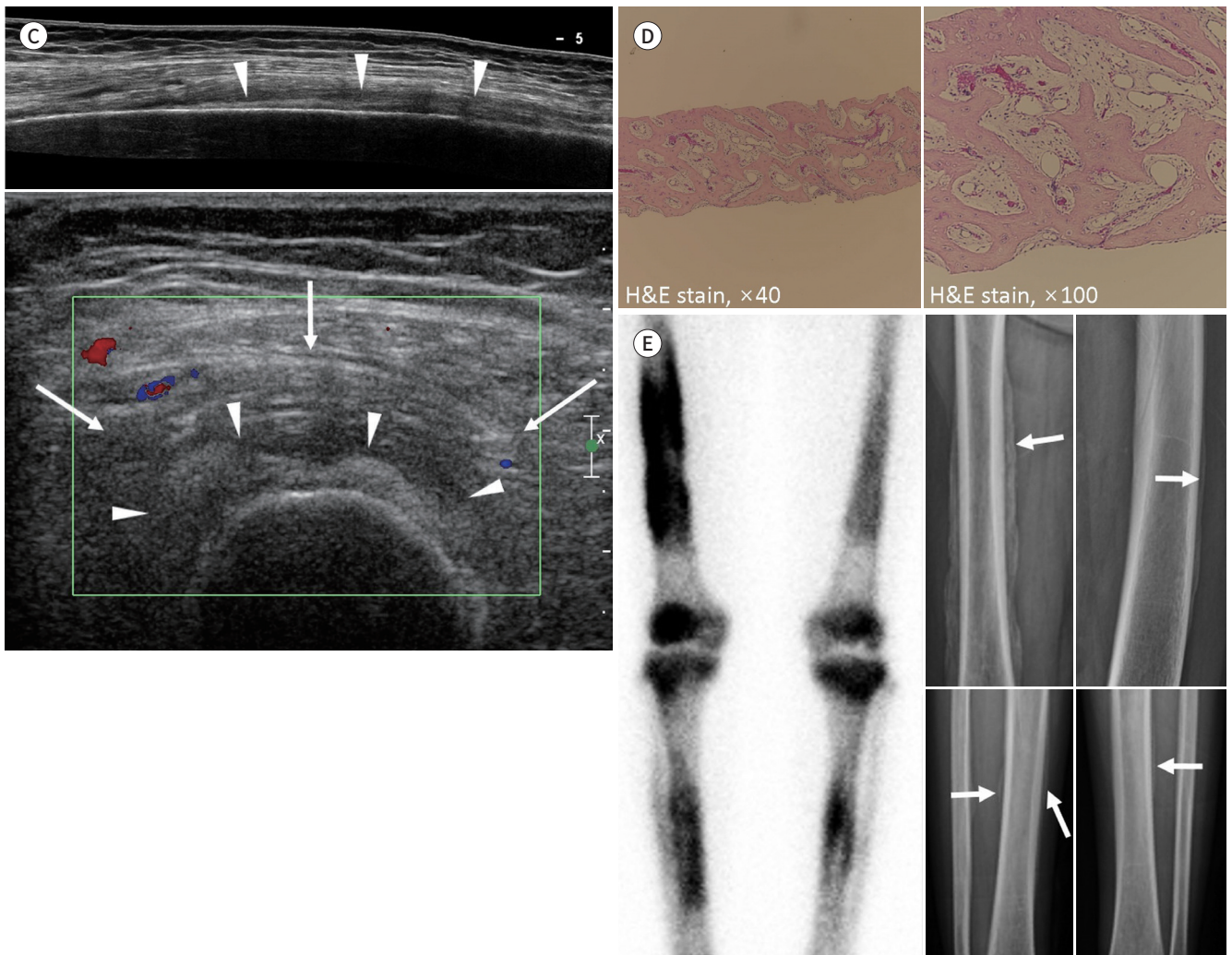
The symptoms progressively resolved while the patient was avoiding weight bearing and intense physical activity. Follow-up MRI 4 months after the onset of pain was performed, revealing no significant change of the periosteal reaction. The vastus intermedius muscle exhibited improvement in swelling but no significant change in signal intensity. Plain radiography revealed no positive findings. However, the 7-month follow-up plain radiography after the initial

episode of pain showed bilateral, broad-based, cortical ossification in the diaphysis of both femurs, tibias, and fibulas. In addition, bone scintigraphy demonstrated bilateral linear increased periosteal and cortical uptake areas, corresponding to the plain images (Fig. 1E).

DISCUSSION

HOA is a syndrome with a clinical triad of digital clubbing, periosteal bone formation, and

Fig. 1. Secondary hypertrophic osteoarthropathy in the right femur mimicking bone metastasis in a 52-year-old woman with right thigh pain.
C. Longitudinal ultrasonography image obtained two months after the initial onset of pain shows abundant periosteal low echoic lesions (upper image, arrowheads) with a broad base on the outer cortex of the femur. The vastus intermedius muscle (lower image, white arrows) shows diffuse swelling and decreased echogenicity. The power Doppler image did not reveal increased vascularity of the periosteal lesion (arrowheads) or muscle.
D. Histologic specimen shows lace-like woven bone and medulla. No lamellation or mineralization is observed within the specimen (left image). Osteoblastic proliferation is present, but no osteoblastic rim formation is observed within the lesion (right image). These findings reflect an immature bone matrix without zonal architecture, suggesting the early stages of new bone formation.
E. Follow up bone scintigraphy after seven months shows bilateral linear increased periosteal and cortical uptake in both lower extremities. Plain radiographs of femur, tibia, and fibular show bilateral broad-based cortical ossification (arrows).
 H&E = hematoxylin and eosin



synovial effusions owing to abnormal skin and periosteal proliferation of the extremities, typically symmetrical in appearance. Secondary HOA is more frequent than primary HOA, accounting for 95–97% of cases. Secondary HOA is associated with various pathologic conditions such as infection, inflammation or chronic hypoxia, but a high prevalence of malignancies in secondary HOA, up to 90%, exists as a form of paraneoplastic syndrome. Intrathoracic tumor, especially lung cancer, is a predominant neoplastic cause of secondary HOA, accounting for approximately 80% of cases, in which the HOA condition is referred to as hypertrophic pulmonary osteoarthropathy (1).

Extrathoracic tumors associated with secondary HOA are rare, but a variety of neoplasms is associated with secondary HOA. It is mostly reported in patients with esophageal cancer and nasopharyngeal carcinoma (1). Secondary HOA-associated breast cancer is extremely rare, but a previous report of secondary HOA by pulmonary metastatic phyllodes tumor of the breast has been published (2).

The exact pathogenesis of HOA is not clear, but neurogenic and humoral pathways have been suggested (1). Recently, vascular endothelial growth factor (VEGF) has been proposed to play a major role in this syndrome. This cytokine promotes angiogenesis, stimulates new bone formation, and increases vascular permeability. These activities may explain the pathologic findings of vascular hyperplasia, osteoblastic proliferation, and edema. The levels of plasma and serum VEGF were significantly higher in a patient with lung cancer who presented with HOA (3). In breast cancer, HER-2+ cases exhibited higher expression of VEGF compared to HER-2- cases, leading to an aggressive phenotype (4, 5). In addition, patients with metastasis from underlying breast cancer had a higher level of circulating VEGF compared to those with localized breast cancer (6). Our patient had HER-2+ invasive breast cancer with known sternal metastasis, hypothetically causing the high level of circulating VEGF. Therefore, even though there was no primary lung cancer or intrathoracic metastasis in our case, there was a considerable possibility of HOA given the disease mechanism related to VEGF. Further studies are needed to evaluate the association between secondary HOA and circulating VEGF in a large number of patients with breast cancer.

The diversity and nonspecificity of the clinical and radiologic manifestations of HOA complicate accurate diagnosis (1, 7). Furthermore, there is no reliable diagnostic serologic test for HOA, making radiologic evaluations even more important (1).

Plain radiographs are commonly used as the initial assessment tool for HOA. Symmetric periosteal bone formation in the shafts of long bones with a wide involvement of underlying bone is a typical finding of HOA. HOA has a spectrum of radiologic presentations in association with disease stage. Its early phase involves the diaphysis, but spares the epiphysis, with a minimal number of affected bones. As it progresses, the extent of periostosis can be increased to the epiphysis, involving more bones, and widening the connection to the underlying bone (1). Our case is considered an early stage of HOA from an underlying malignancy because the periostosis initially exhibited unilateral and eccentric cortical involvement and progressed upon follow-up.

Adams et al. (8) reported the first case of sonographic findings of primary HOA in a pediatric patient. US revealed a layer of echogenic periosteal tissue based on the outer cortex of underlying bone. There was no increased vascularity of this lesion on power Doppler image. The

authors believed that the low vascularity may have resulted from the relatively small size of the vascular channels in a young patient. These imaging findings in our case were consistent with a previous report (8).

MR imaging of HOA exhibits periosteal reactions with reactive changes of the surrounding soft tissues (1, 7). Periosteal reactions are classically seen as hypo- to isointense on T1-weighted images and hypointense on T2-weighted images. Thickened periosteum can be observed in contrast enhancement. Reactive change of adjacent soft tissue may be presented as hyperintensity on T2-weighted image, which is correlated with the degree and location of parosseous swelling (1). It is important to evaluate the presence of abnormal cortical and intramedullary signal change to exclude underlying osteomyelitis or malignancy (1). There was no cortical disruption or marrow abnormality in our patient. Moreover, the periosteal reaction was uniform in shape. These findings are more compatible with HOA rather than metastasis.

Bone scintigraphy demonstrates the typical “tram line” or “double stripe sign,” presented as symmetric increase of cortical uptake of long bones (1). This typical radiologic finding was shown on follow-up bone scintigraphy 7 months after the onset of pain (Fig. 1F).

Our initial radiologic differential diagnosis included malignant conditions such as bone metastasis, leukemia, and lymphoma. It was our major goal to exclude bone metastasis since the patient had a history of bone metastasis from an underlying malignancy. There are several reasons that favor secondary HOA compared to malignant conditions. First, the periosteal reaction exhibited a circumscribed uniform appearance in our case, while an aggressive shape is observed in leukemia and lymphoma. Second, there was no osseous destruction or intramedullary signal change in the MR images. In cases of malignant conditions, intramedullary osteolytic or osteoblastic lesion with associated periosteal soft tissue mass are often observed (1). Third, there was no increased vascularity on the power Doppler image. Malignant lesions are more likely to show increased vascularity than benign lesions (9).

Even through retrospective review, it was challenging to make a correct diagnosis of HOA in the initial stage for several reasons. First, the patient exhibited no intrathoracic lesion, and the bony involvement was initially unilateral as it is in early phases of HOA. Second, in our case, mineralization of the periosteal reaction was exceptionally delayed. Mineralization of the periosteal reaction must be present for HOA to be demonstrated on plain radiography and typically requires a maximum of 10 days to 3 weeks to be mineralized from the initial cause (10). Our microscopic examination 2 months after the initial pain revealed unmineralized woven bone formation and required 7-month follow-up plain radiography to demonstrate mineralization.

There is a lack of literature on secondary HOA associated with invasive ductal breast cancer without intrathoracic metastasis. As a result, our case is significant for radiologic multimodality evaluation of the early manifestation of HOA in underlying breast cancer.

Radiologists should consider the possibility of the early phase of HOA as a differential diagnosis when US and MR findings show an evident periosteal reaction in a symptomatic region of long bone, even in patients with extrathoracic pathology.

Author Contributions

Conceptualization, C.J.G.; data curation, all authors; investigation, H.J.Y., Y.Y.S., M.A.; supervision,

C.J.G., Y.Y.S.; validation, C.J.G., Y.Y.S.; visualization, H.J.Y.; writing—original draft, H.J.Y., Y.Y.S.; and writing—review & editing, all authors.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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REFERENCES

1. Yap FY, Skalski MR, Patel DB, Schein AJ, White EA, Tomasian A, et al. Hypertrophic osteoarthropathy: clinical and imaging features. *Radiographics* 2017;37:157-195
2. Collinson FJ, Bilous AM, Kefford RF. Hypertrophic osteoarthropathy from pulmonary metastatic phyllodes tumour of the breast. *Med J Aust* 2004;181:279
3. Silveira LH, Martínez-Lavín M, Pineda C, Fonseca MC, Navarro C, Nava A. Vascular endothelial growth factor and hypertrophic osteoarthropathy. *Clin Exp Rheumatol* 2000;18:57-62
4. Pegram MD, Reese DM. Combined biological therapy of breast cancer using monoclonal antibodies directed against HER2/neu protein and vascular endothelial growth factor. *Semin Oncol* 2002;29:29-37
5. Nasir A, Holzer TR, Chen M, Man MZ, Schade AE. Differential expression of VEGFR2 protein in HER2 positive primary human breast cancer: potential relevance to anti-angiogenic therapies. *Cancer Cell Int* 2017;17:56
6. Adams J, Carder PJ, Downey S, Forbes MA, MacLennan K, Allgar V, et al. Vascular endothelial growth factor (VEGF) in breast cancer: comparison of plasma, serum, and tissue VEGF and microvessel density and effects of tamoxifen. *Cancer Res* 2000;60:2898-2905
7. Sainani NI, Lawande MA, Parikh VP, Pungavkar SA, Patkar DP, Sase KS. MRI diagnosis of hypertrophic osteoarthropathy from a remote childhood malignancy. *Skeletal Radiol* 2007;36 Suppl 1:S63-S66
8. Adams B, Amin T, Leone V, Wood M, Kraft JK. Primary hypertrophic osteoarthropathy: ultrasound and MRI findings. *Pediatr Radiol* 2016;46:727-730
9. Griffith JF, Chan DP, Kumta SM, Chow LT, Ahuja AT. Does Doppler analysis of musculoskeletal soft-tissue tumours help predict tumour malignancy? *Clin Radiol* 2004;59:369-375
10. Lin PP, Patel SR. *Bone sarcoma*. New York: Springer 2013:14

뼈 전이로 오인될 수 있는 흉강 외 악성 종양으로 인한 비대성 골관절증의 초기 영상 소견

황지연¹ · 차장규^{1*} · 윤유성¹ · 문아림²

비대성 골관절증은 곤봉지, 근막골형성 및 윤활막 삼출액을 특징으로 하는 증후군이다. 이차성 비대성 골관절증은 대부분의 경우 흉부 내 악성 종양과 연관이 있으나, 드물게 흉강 외 악성 종양에 의해 발생할 수 있다. 이에 우리는 유방암의 과거력이 있는 환자에서 발생한 비대성 골관절증의 초음파, 전산화단층촬영, 자기공명영상 및 뼈 스캔그래피의 초기 영상의학적 소견에 대해 서술하고자 한다. 악성 종양으로 오인된 본 증례의 모호한 임상 및 영상 소견은 독자에게 흥미롭고 유익할 것으로 생각된다.

순천향대학교 의과대학 부천병원 ¹영상의학과, ²병리과