

# Secondary hypertrophic osteoarthropathy caused by non-pleural or pulmonary tumors

Hans-Jonas Meyer, MD<sup>a,\*</sup>, Leonard Leifels, MD<sup>a</sup>, Andreas Gunter Bach, MD<sup>b</sup>, Alexey Surov, MD<sup>a</sup>

## Abstract

Hypertrophic osteoarthropathy (HOA) is a rare paraneoplastic syndrome characterized by digital clubbing, periosteal reaction, polyarthralgia, arthritis, and synovitis. Herein, we report a case series of patients with secondary HOA caused by non-pleural or pulmonary tumors.

The radiologic databases of 2 tertiary university hospitals were retrospectively screened for secondary HOA patients. In addition, a systemic review of the published case reports. Only HOA cases with non-pleural or pulmonary malignancies were involved into the study. HOA in primary pleural or pulmonary malignant or benign disorders, as well in inflammatory diseases were excluded. In all cases, plain radiography was performed and clinical signs were documented.

In our databases, 6 patients with secondary HOA were identified. In addition, the systemic review yielded 24 eligible patients. The most prevalent primary tumors were nasopharyngeal carcinoma and esophageal cancer in 6 patients (20%), respectively. In 17 patients, (56.7%) HOA was associated with lung metastases, and in 10 patients (33.3%), no lung metastases were detected. In 14 patients (46.7%), HOA was symptomatically before a tumor diagnosis was made. Plain radiography displayed typically features with periosteal enlargement in every case.

This study is the first report about secondary HOA caused by non-pleural or pulmonary tumors. Various primary tumors were identified, including several rare tumors such as sarcomas. HOA is a rare disorder with typically radiologically findings, which is not only associated with lung cancer or pleural mesothelioma and can even occur in tumor patients without lung metastasis.

**Abbreviation:** HOA = hypertrophic osteoarthropathy.

**Keywords:** hypertrophic osteoarthropathy, paraneoplastic syndrome

## 1. Introduction

Hypertrophic osteoarthropathy (HOA) is a rare syndrome, clinically characterized by digital clubbing, periosteal reactions of long bones, polyarthralgia, arthritis, and synovitis.<sup>[1,2]</sup> The primary type is rare with only 3% of all cases of HOA.<sup>[3]</sup> The secondary form occurs more frequently, namely in 95% to 97% of cases.<sup>[4]</sup> A wide variety of diseases is known for causing HOA.<sup>[2,4]</sup> Most prevalent is the neoplastic origin associated with lung cancer or pleural mesothelioma.<sup>[4]</sup> However, benign disorders such as pulmonary infections, chronic obstructive pulmonary disease, sarcoidosis, cyanotic heart disease, hepatic cirrhosis, vascular aneurysms, and inflammatory bowel disease

have also been identified causing secondary HOA.<sup>[1,2,4]</sup> Due to its rare incidence, only few case reports have been published to date. In previous retrospective studies, the prevalence of HOA ranges from 0.73% to 31.6% in lung cancer patients.<sup>[5-7]</sup> It is also known that other tumors can cause secondary HOA.<sup>[8]</sup> However, it occurs rarely in other malignancies.<sup>[4,8]</sup> There are also no reports providing systemic data about HOA in nonpulmonary or nonpleural malignant tumors.

Therefore, our aim was to estimate clinical and radiological features of HOA in nonpleural or pulmonary tumors in adult patients.

## 2. Methods

This retrospective study was approved by the institutional ethic committee and informed consent was waived.

The radiologic databases of 2 tertiary university hospitals were screened for secondary HOA patients caused by non-pleural or pulmonary tumors. Cases with HOA in different benign diseases were also excluded. Overall, 6 patients with the following malignancies were identified: non-Hodgkin lymphoma (n=2), esophageal cancer (n=1), renal cell carcinoma (n=1), nasopharyngeal carcinoma (n=1), and angiosarcoma (n=1).

In all cases, plain radiography of lower and upper extremities was performed as well as clinical signs were acquired.

Furthermore, a systematic review of the Medline database was performed by using the following keywords secondary HOA (135 results) and HOA (833 results). Only reports in English and German language published from January 1996 to April 2017 were evaluated to ensure homogeneity of the patient collective. Pediatric patients were excluded. After thorough review, 23 reports with 24 cases were included in this systemic review.<sup>[9-31]</sup>

Editor: Hisashi Oshiro.

The authors declare that they have no conflict of interest and have not received funding for this study.

<sup>a</sup> Department of Diagnostic and Interventional Radiology, University Hospital Leipzig, Leipzig, <sup>b</sup> Department of Diagnostic Radiology, Martin-Luther University Halle (Saale), Halle (Saale), Germany.

\* Correspondence: Hans-Jonas Meyer, Department of Diagnostic and Interventional Radiology, University Leipzig, Liebigstraße 20, 04103 Leipzig, Germany (e-mail: hans-jonas.meyer@medizin.uni-leipzig.de).

Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Medicine (2017) 96:36(e7985)

Received: 13 May 2017 / Received in final form: 9 August 2017 / Accepted: 13 August 2017

<http://dx.doi.org/10.1097/MD.0000000000007985>

**Table 1****Identified primary tumors causing secondary hypertrophic osteoarthropathy in this case series.**

Diagnosis	n (%)
Nasopharyngeal carcinoma	6 (20.0%)
Eophageal cancer	6 (2 neuroendocrine tumors, 1 adeno, 3 squamous) (20.0%)
Non-Hodgkin lymphoma	2 (6.7%)
Malignant melanoma	2 (6.7%)
Breast cancer	2 (6.7%)
Phyllodes tumor	2 (6.7%)
Renal cell carcinoma	2 (6.7%)
Hodgkin lymphoma	1 (3.3%)
Leiomyosarcoma	1 (3.3%)
Gastrointestinal stromal tumor	1 (3.3%)
Thymic carcinoma	1 (3.3%)
Sarcoma of the heart	1 (3.3%)
Thyroid carcinoma	1 (3.3%)
Hemangiothelioma	1 (3.3%)
Angiosarcoma	1 (3.3%)
Total	30

Altogether, the study sample comprises 30 patients (n=18 male (60%), n=12 female (40%)), with a mean age of 43.9±15.5 years, median 44.5, range 16 to 73 years.

Statistical analysis was performed using GraphPad Prism (GraphPad Software, La Jolla, CA). Collected data were evaluated by means of descriptive statistics. Continuous variables were expressed as mean±standard deviation (SD) and categorical variables as percentages.

### 3. Results

Several different primary tumors caused secondary HOA (Table 1). The most frequent tumors were nasopharyngeal carcinoma and esophageal cancer in 6 patients (20%), respectively.

In 17 patients (56.7%), HOA was associated with lung metastasis, and in 10 patients (33.3%), no lung metastasis was detected. The remaining 3 patients (10%) had thoracic located lymphomas.

Clinically, most patients presented with arthralgia and bone pain (n=27, 90%). In 2 patients (6.7%), clubbing was the only sign for HOA. In 1 patient (3.3%), HOA was detected incidentally by radiography.

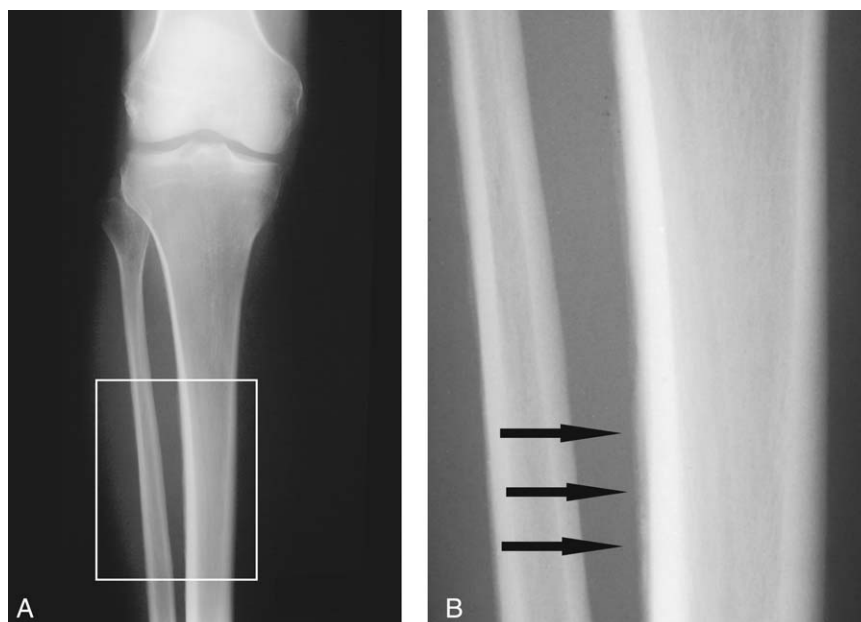
HOA symptoms were detected in several tumor stages. In 14 patients (46.7%), HOA symptoms were detected before a tumor diagnosis was made. In 16 cases (53.3%), HOA became symptomatically with already known diagnosis.

Serologically, there were no abnormalities. Regarding HOA therapy, 11 patients (36.7%) had no statement of therapy. Eleven patients (36.7%) were treated by nonsteroidal anti-inflammatories and opioids. In 5 of these patients (45.5%), it led to pain relief, and in 6 patients, (54.5%) no alleviation of pain was achieved. In 1 refractory case, methotrexate and hydrochloroquine led to symptomatic regression, in 2 cases pamidronate, and in 1 case zoledronic acid was administered. In 11 patients (36.7%), the HOA symptoms were regressive after tumor treatment.

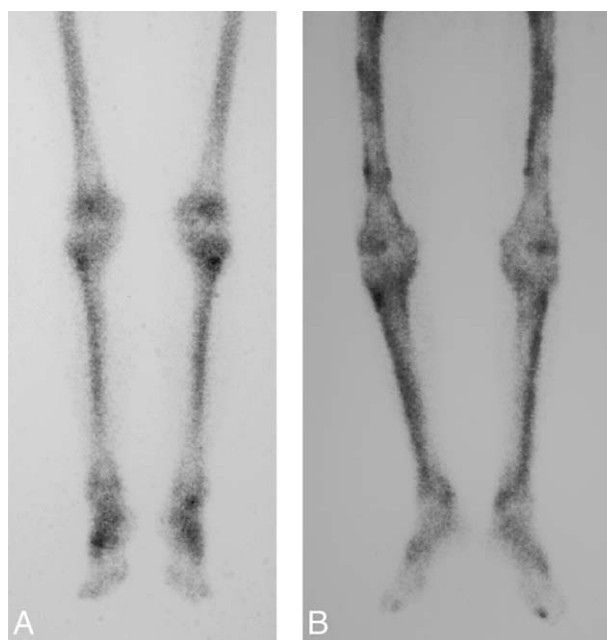
Radiologically, in all patients, a periosteal reaction of long bones was seen on plain radiography (Fig. 1). An exemplarily bone scintigraphy of 2 patients with different grades of tracer uptake is shown in Fig. 2.

### 4. Discussion

HOA was first described by von Bamberger in 1889 and 1 year later by Marie.<sup>[32,33]</sup> Since then, clinical examination is still most important in diagnostic evaluation of HOA. Clinically, HOA presents with symmetrical pain and swelling at the distal end of the limbs, arthralgia, and synovitis.<sup>[2,4]</sup> Histological features include prominent bone remodeling and proliferation of the periosteum with an inflammatory reaction with round cell infiltration.<sup>[2,4]</sup>



**Figure 1.** Periosteal reaction along the tibia in a patient with angiosarcoma. (A) A diaphyseal smooth periosteal thickening can be seen. (B) (zoomed in) the arrows point out the periosteal thickening of the lateral tibia.



**Figure 2.** Bone scintigraphy of secondary HOA. (A) Low-grade tracer uptake in a patient with renal cell carcinoma metastasized to the lungs. (B) Moderate tracer uptake in a patient with metastasized angiosarcoma.

It is most often associated with pulmonary disorders, mainly with lung cancer and pleural mesothelioma.<sup>[4]</sup> Nevertheless, only few studies investigated the prevalence of secondary HOA in malignancies. It ranges from 0.73% to 31.6% in patients with lung carcinoma.<sup>[5-7]</sup> Regarding pleural mesothelioma, finger clubbing can be detected in up to 30% of cases,<sup>[34]</sup> whereas the prevalence of HOA is still unclear.

In the present case series, secondary HOA was caused by non-pleural or pulmonary tumors, most patients suffered from esophageal cancer and nasopharyngeal carcinoma. Moreover, secondary HOA can be associated with carcinomas, sarcomas, and lymphomas, with a higher prevalence in carcinomas in our presented data. Interestingly, rare tumors such as phylloides tumor of the breast or sarcomas are more represented in this study than their rare incidence might reflect it. Yacoub et al<sup>[35]</sup> also described more sarcomas and nasopharyngeal carcinoma than more prevalent tumors in their systemic review in 1967. Contrary to the present study, they only investigated HOA cases with lung metastasis by extrathoracic tumors.<sup>[35]</sup>

Furthermore, HOA caused by nasopharyngeal carcinoma and malignant melanoma might only be associated with lung metastasis, whereas HOA caused by esophageal cancer was only found without lung metastasis. However, the underlying pathophysiological mechanisms are unclear. Regarding lymphomas, HOA was found in non-Hodgkin lymphomas as well as Hodgkin lymphoma. Interestingly, the described cases were all located thoracical, indicating that an extrathoracical lymphoma might not cause HOA.

Moreover, HOA can also occur in benign diseases. For example, it has also been described in inflammatory bowel disease, tuberculosis, endocarditis, chronic obstructive pulmonary disease, sarcoidosis, aortic aneurysm, chronic liver disease, and vascular prosthesis infection.<sup>[1,2,4]</sup>

We could not identify specific clinical or radiologically findings of HOA in our patient collective than in HOA cases by the abovementioned causes.

The exact pathogenesis of HOA is yet elusive. Recent molecular studies identified 2 possible pathophysiological mechanisms, namely a neurogenic pathway and a humoral pathway.<sup>[4]</sup> The humoral pathway is associated with high cytokines and growth factors serum levels, for example, platelet-derived growth factor and prostaglandine E2.<sup>[4]</sup> Presumably, this pathway might induce the effects in patients with tumors. It is well known that tumors secrete growth factors to stimulate angiogenesis maintaining their own growth capacities.<sup>[36]</sup>

Regarding the diagnostic evaluation of HOA, a clinical diagnosis is based upon digital clubbing, synovial effusion, arthralgia, and bone pain.<sup>[1,2,4]</sup> In our study, only 1 patient did not present any clinical sign and therefore HOA was an incidental finding in this patient.

The most important diagnostic modality is plain radiography because reliable serological tests are lacking.<sup>[4]</sup> Radiologically, HOA presents with a generalized or localized periosteal reaction.<sup>[4]</sup> The localized form was only described in patients with HOA caused by benign diseases such as aortic aneurysm or patent ductus arteriosus.<sup>[4]</sup> This finding is underlined by the present results with only generalized HOA forms identified.

Another imaging modality is bone scintigraphy, which is the most sensitive test for HOA.<sup>[4]</sup> In HOA patients, an increased paracortical uptake of radioactive tracer in the bones of the extremities can be detected.<sup>[4]</sup> Moreover, it can even display tracer uptake in bones with no periosteal reaction in radiography resulting in the higher sensitivity. Typically, the uptake is symmetrical, diffuse, affecting spine, pelvis, and ribs.<sup>[37]</sup> However, in some cases, it may be unilateral.<sup>[37]</sup> Therefore, discrimination of HOA from osseous metastases or osteomyelitis may be difficult in these cases.

There are only few reports regarding magnetic resonance imaging (MRI). MRI is able to display the periosteal as well as soft tissue changes.<sup>[38]</sup> These include muscle and septal edema as well as muscle swelling.<sup>[38]</sup> The periosteal reaction has a low to intermediate signal intensity on T1-weighted images and low

signal intensity on T2-weighted images.<sup>[4]</sup> Furthermore, periosteal contrast enhancement can be noticed.<sup>[4]</sup> The periosteal MRI findings correlate with radiography findings.<sup>[4]</sup> Finally, MRI findings cannot distinguish between primary and secondary HOA.<sup>[4]</sup>

There is no established specific therapy for HOA and the symptoms might regress after control of the primary disease. In our case series, one-third of cases also showed distinctly symptomatic regress after tumor treatment. Recently, several promising reports about treatment with bisphosphonate were published.<sup>[2]</sup> In our case series, this treatment led to pain relief in 3 patients, representing every patient treated with this drug group.

Regarding clinically representation, HOA may be the first sign of malignant disease and can even predict pulmonary metastasis.<sup>[4]</sup> In the present study, HOA was the first sign of tumor disease in almost half of the patients and in a smaller amount HOA symptoms led to further lung metastasis diagnostic. However, HOA was only detected incidentally by radiography in 1 patient.

There are several limitations of this study to address. First, it is a retrospective case study. Second, the patient sample is small caused by the rarity of this entity. Third, this study cannot provide systemic data regarding the real prevalence of secondary HOA in several primary tumors. Finally, possible publication bias might influence these data due to only clinically noticeable cases are published as case reports and some asymptotically HOA cases might not be diagnosed.

In conclusion, this study is the largest case series about secondary HOA caused by non-pleural or pulmonary tumors to date. The most prevalent primary tumors were nasopharyngeal carcinoma and esophageal cancer followed by various other tumors. A bigger account of sarcomas was identified than their rare incidence might reflect it. HOA was associated with lung metastasis and without metastasized tumors. Finally, it is a rare disorder with typically radiologically findings, which is not only associated with lung cancer or pleural mesothelioma.

## References

- Alonso-Bartolome P, Martinez-Taboada V, Pina T, et al. Hypertrophic osteoarthropathy secondary to vascular prosthesis infection. *Medicine (Baltimore)* 2006;85:183–91.
- Pineda C, Martínez-Lavín M. Hypertrophic osteoarthropathy: what a rheumatologist should know about this uncommon condition. *Rheum Dis Clin North Am* 2013;39:383–400.
- Diren HB, Kutluk MT, Karabent A, et al. Primary hypertrophic osteoarthropathy. *Pediatr Radiol* 1986;16:231–4.
- Yap FY, Skalski MR, Patel DB, et al. Hypertrophic osteoarthropathy: clinical and imaging features. *Radiographics* 2017;37:157–95.
- Ito T, Goto K, Yoh K, et al. Hypertrophic pulmonary osteoarthropathy as a paraneoplastic manifestation of lung cancer. *J Thorac Oncol* 2010;5:976–80.
- Izumi M, Takayama K, Yabuuchi H, et al. Incidence of hypertrophic pulmonary osteoarthropathy associated with primary lung cancer. *Respirology* 2010;15:809–12.
- Suțeanu S, Rohan C, Gherasim E, et al. Hypertrophic osteoarthropathy secondary to bronchopulmonary cancer (our experience). *Rom J Intern Med* 1992;30:281–4.
- Utine EG, Yalçın B, Karnak I, et al. Childhood intrathoracic Hodgkin lymphoma with hypertrophic pulmonary osteoarthropathy: a case report and review of the literature. *Eur J Pediatr* 2008;167:419–23.
- Ali N, Abbasi AN, Karsan F, et al. A case of finger clubbing associated with nasopharyngeal carcinoma in a young girl and review of pathophysiology. *J Pak Med Assoc* 2009;59:253–4.
- Andrés R, Saenz A, Mayordomo JL, et al. Case 4. Hypertrophic osteoarthropathy associated with pulmonary metastasis of uterine leiomyosarcoma. *J Clin Oncol* 2003;21:3540–1.
- Biswal BM, Kareem A, Ahmed NM. Hypertrophic osteoarthropathy: an unusual manifestation in nasopharyngeal cancer. *Australas Radiol* 2001;45:71–3.
- Chen YC, Tiu CM, Bai LY, et al. Hypertrophic pulmonary osteoarthropathy associated with disease progression in renal cell carcinoma. *J Chin Med Assoc* 2003;66:63–6.
- Collinson FJ, Bilous AM, Kefford RF. Hypertrophic osteoarthropathy from pulmonary metastatic phyllodes tumour of the breast. *Med J Aust* 2004;181:279.
- Goodyer MJ, Cronin MC, Ketsitile DG, et al. Hodgkin's lymphoma with digital clubbing. *J Clin Oncol* 2009;27:e95–6.
- Gregory RK, Chang J, Singh R, et al. Clubbing, arthralgia and haemoptysis in a patient with metastatic carcinoma of the breast. *Ann Oncol* 1996;7:756–7.
- Kim JH, Lee EB, Kim S, et al. A case of hypertrophic osteoarthropathy associated with epithelioid hemangioendothelioma. *J Korean Med Sci* 2004;19:484–6.
- Kim SJ, Seo JH, Choi CW, et al. Unusual presentation of thymic carcinoma: hypertrophic osteoarthropathy. *Korean J Intern Med* 2003;18:125–8.
- Landrum ML, Ornstein DL. Hypertrophic osteoarthropathy associated with metastatic phyllodes tumor. *Am J Clin Oncol* 2003;26:146–50.
- Manger B, Lindner A, Manger K, et al. [Hypertrophic osteoarthropathy. Bamberger-Marie disease]. *Z Rheumatol* 2011;70:554–60.
- Morita M, Sakaguchi Y, Kuma S, et al. Hypertrophic osteoarthropathy associated with esophageal cancer. *Ann Thorac Surg* 2003;76:1744–6.
- Murosaki T, Mori K, Nagashima T, et al. Hypertrophic osteoarthropathy associated with esophageal cancer. *Intern Med* 2015;54:357–8.
- Nobeyama Y, Nakagawa H. Case of metastatic malignant melanoma associated with hypertrophic osteoarthropathy. *J Dermatol* 2013;40:484–5.
- Saif MW, Vethody C. Poorly differentiated neuroendocrine tumor of the esophagus with hypertrophic osteoarthropathy and brain metastasis: a success story. *Cureus* 2016;8:e646.
- Silva L, Andreu JL, Muñoz P, et al. Hypertrophic osteoarthropathy associated with gastrointestinal stromal tumour. *Ann Rheum Dis* 2006;65:681–2.
- Sonthalia N, Mukherjee K, Saha A, et al. Treatment of hypertrophic osteoarthropathy in the case of pulmonary metastasis secondary to nasopharyngeal carcinoma with zoledronic acid: an enlightening experience. *BMJ Case Rep* 2012;2012:pil: bcr2012006759.
- Suppiah R, McQueen F. Hypertrophic osteoarthropathy associated with a left ventricular tumour. *Rheumatology (Oxford)* 2008;47:1277.
- Suzuma T, Sakurai T, Yoshimura G, et al. Pamidronate-induced remission of pain associated with hypertrophic pulmonary osteoarthropathy in chemoendocrine therapy-refractory inoperable metastatic breast carcinoma. *Anticancer Drugs* 2001;12:731–4.
- Tavarelli M, Sarfati J, De Gennes C, et al. Hypertrophic osteoarthropathy and follicular thyroid cancer: a rare paraneoplastic syndrome. *Eur Thyroid J* 2015;4:266–70.
- Thompson MA, Warner NB, Hwu WJ. Hypertrophic osteoarthropathy associated with metastatic melanoma. *Melanoma Res* 2005;15:559–61.
- Ulusakarya A, Gumus Y, Brahimi N, et al. Symptoms in cancer patients and an unusual tumor: Case 1. Regression of hypertrophic pulmonary osteoarthropathy following chemotherapy for lung metastases of a nasopharyngeal carcinoma. *J Clin Oncol* 2005;23:9422–3.
- Wechalekar MD, Kennedy NA, Ahern M, et al. Esophageal adenocarcinoma and hypertrophic osteoarthropathy with improvement following resection of esophageal cancer. *J Clin Rheumatol* 2011;17:323–4.
- von Bamberger E. Changes of long bones associated with bronchiectasis. *Wien Klin Wochenschr* 1889;2:226.
- Marie P. About pulmonary hypertrophic osteoarthropathy. *Rev Med Paris* 1890;10:1–36.
- McGavin C, Hughes P. Finger clubbing in malignant mesothelioma and benign asbestos pleural disease. *Respir Med* 1998;92:691–2.
- Yacoub MH, Simon G, Ohnsorge J. Hypertrophic pulmonary osteoarthropathy in association with pulmonary metastases from extrathoracic tumours. *Thorax* 1967;22:226–31.
- Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646–74.
- Ali A, Tetelman M, Fordham J, et al. Distribution of hypertrophic pulmonary osteoarthropathy. *AJR Am J Roentgenol* 1980;134:771–80.
- Capelastegui A, Astigarraga E, Garcia-Iturraspe C. MR findings in pulmonary hypertrophic osteoarthropathy. *Clin Radiol* 2000;55:72–5.