Skeletal Radiol (2012) 41:203–208
DOI 10.1007/s00256-011-1214-3

SCIENTIFIC ARTICLE

Radiologic findings of osteoarticular infection in paracoccidioidomycosis

Lucas Moretti Monsignore · Roberto Martinez · Marcelo Novelino Simão · Sara Reis Teixeira · Jorge Elias Jr · Marcello Henrique Nogueira-Barbosa

Received: 15 April 2011 / Revised: 9 May 2011 / Accepted: 18 May 2011 / Published online: 5 June 2011

Abstract
Objective To report the radiological abnormalities of osteoarticular involvement in paracoccidioidomycosis (PCM).
Materials and methods After institutional board approval, the medical records and conventional radiology findings of 19 patients with osseous PCM were retrospectively reviewed. Number, distribution, and lesion characteristics were evaluated in consensus by two experienced musculoskeletal radiologists.
Results The mean age of patients was 16.1 years (range 4–49 years), 11 male and eight female. MSK involvement was the only or the primary presentation of the disease in eight of 19 patients (42.1%). In total, 51 focal bone lesions were detected, being 41 in long bones. In long bones lesions, 19 of 41 (46.4%) were metaphyseal, 12 of 41 (29.3%) meta-epiphyseal, and 12 of 41 (29.3%) diaphyseal. The most common presentation was a geographic osteolytic bone lesion (62.7%), without marginal sclerosis (82.4%) and without periosteal reaction (90.2%). Articular involvement was present in six of 19 patients (31.6%), being two cases of primary arthritis.
Conclusions All encountered bone lesions were osteolytic. Metaphyseal or meta-epiphyseal osteomyelitis of a long bone was the most prevalent osteoarticular manifestation of paracoccidioidomycosis. PCM osteoarticular involvement could be solitary or multifocal, occurs almost exclusively in the acute/subacute clinical form, and it is more common in children and in juvenile patients. Axial skeleton involvement, arthritis, or a disseminated osseous pattern of infection may occasionally occur in this fungal disease.

Keywords Paracoccidioidomycosis · Fungal · Osteomyelitis · Radiography · Osteoarticular · Infection

L. M. Monsignore · M. N. Simão · S. R. Teixeira · J. Elias Jr · M. H. Nogueira-Barbosa (✉)
Division of Radiology of the Internal Medicine Department, Faculty of Medicine of Ribeirao Preto, University of São Paulo, Av. Bandeirantes, 3900 CEP, 14049–090 Ribeirao Preto, Brazil
e-mail: marcello@fmrp.usp.br

R. Martinez
Division of Infectious Diseases of the Internal Medicine Department, Faculty of Medicine of Ribeirao Preto, University of São Paulo, Ribeirao Preto, Brazil

Introduction

Paracoccidioidomycosis (PCM) is a systemic granulomatous disease caused by the dymorphic fungus *Paracoccidioides brasiliensis*, usually found in South America, especially in Brazil, Venezuela, Colombia, Ecuador, and Argentina, where it is considered an endemic disease and a public health problem [1, 2]. Some cases have been reported outside Latin America, and all these patients had lived or visited these endemic areas [2, 3]. PCM can be classified in acute/subacute and chronic forms [1]. The acute/subacute (or juvenile) form of PCM accounts for 3–5% of all cases and is frequently seen in children and adolescents, without difference between sexes. It is characterized by a fast progression with lymphadenopathy, gastrointestinal manifestations, hepatosplenomegaly, osteoarticular involvement, and cutaneous lesions. The chronic (or adult) form is most commonly seen in male adults, between the third and sixth decades, and can affect only the lungs, denominated unifocal, or lungs, mucosa, and skin, called multifocal [1, 2]. This infection is successfully treated with oral antifungals, and the most commonly prescribed are itraconazole or trimethoprim-sulfamethoxazole, used daily for a long period (from 6 to 24 months) [1].

Table 1 Information about the 19 patients: sex, age, clinical classification; osteoarticular location, involvement of other organs or systems, and symptoms. (*n*=patient number; *A*=acute/subacute; *C*=chronic)

n	Gender	Age	Clinical classification	Tissue	Region	Other sites	Osteoarticular initial or unique involvement	Osteoarticular symptoms
1	F	4	A	Osseous	Multiple	Lymphatic; skin/mucosa	No	Asymptomatic
2	M	23	A	Osseous	Vertebra	Lymphatic; skin/mucosa; abdominal viscera	No	Asymptomatic
3	F	17	A	Osseous	Clavicle	Lung; lymphatic; skin/mucosa	No	Asymptomatic
4	F	13	A	Osseous	Sternum	Lung; lymphatic; skin/mucosa	No	Asymptomatic
5	F	4	A	Osseous	Multiple	Lung; lymphatic	No	Diffuse osseous pain
6	M	5	A	Osseous	Clavicles	Lymphatic	No	Asymptomatic
7	F	15	A	Osseous	Clavicles; rib	Lung; lymphatic; skin/mucosa; abdominal viscera; central nervous system	No	Shoulder and hip pain
8	F	28	A	Osseous; articular; soft tissue	Acromioclavicular joint	Lymphatic; skin/mucosa; abdominal viscera	No	Asymptomatic
9	M	15	A	Osseous	Ulna	-	Yes	Acute elbow pain
10	M	33	A	Osseous	Multiple	Lung; lymphatic; skin/mucosa; abdominal viscera	No	Diffuse articular pain
11	M	7	A	Osseous	Multiple	Lymphatic	Yes	Shoulder pain linked to previous trauma
12	M	6	A	Osseous	Clavicles; humerus	Lymphatic; abdominal viscera	No	Asymptomatic
13	F	10	A	Osseous; soft tissue	Cuneiform	-	Yes	Right foot pain linked to previous trauma
14	F	21	A	Osseous; articular	Hip joint	-	Yes	Pregnant; acute right hip pain
15	M	17	A	Osseous; articular; soft tissue	Radius	-	Yes	Extension deficit of the right elbow
16	M	27	A	Osseous	Clavicles	Lymphatic	No	Shoulder pain
17	M	10	A	Osseous; articular; soft tissue	Femur	-	Yes	Acute right knee pain
18	M	11	A	Osseous; articular; soft tissue	femoral neck with articular extension	-	Yes	Acute left hip and knee pain
19	M	49	C	Osseous; articular	Knee joint	-	Yes	Chronic left knee pain

There are few publications on PCM osteoarticular involvement and some of them are controversial about the most common features [4, 5]. Bone lesion prevalence in the literature range from 2 to 30% [6–8], and articular [9–11] and muscular lesions are very rare [12]. The published literature data about PCM bone involvement originates mainly from case reports [9–20]. A case series included 20 proved cases of PCM osteoarticular involvement but it was not published in English [21]. To our knowledge, this is the largest series reporting PCM osteoarticular involvement in the English literature.

Materials and methods

This study was approved by the Research Ethics Committee in the University Hospital. The radiological and pathological reports databases were reviewed and a cross search was performed for patients with diagnostic of PCM and any osteoarticular lesion described. Cases were included in this study only when: (1) there was a positive culture from osseous or articular tissues or; (2) histopathology showed typical fungal cells in osteoarticular tissues or; (3) X-rays were available and there was radiological evidence of osteoarticular infection, the pathogen isolated from other tissues, and the osteoarticular lesion healed by clinical and radiological criteria after specific treatment. The clinical information obtained included sex, age, disease classification, other organs or systems involved in addition to the MSK system, and the site of the lesions in the MSK system.

The radiological pattern of each lesion and the imaging findings were classified in consensus by two experienced musculoskeletal radiologists. All lesions were identified and characterized considering the involved bone, location in the bone (when in a long bone), contour definition, presence of marginal sclerosis, and periosteal reaction. Lesions were evaluated and classified only when they were identified in at least two orthogonal available X-ray views.

Results

The study group consisted of 19 patients (11 male and eight female), with a mean age of 16.1 years (range 4 to 49 years) (Table 1). The disease was classified as the acute/subacute clinical form for 18 patients. Only one patient was clinically classified in the chronic form.

In eight patients, the MSK system was the exclusive site of the disease. In seven of 19 patients (36.8%) there were no symptoms related to the MSK system, and the osseous lesions in these cases were incidentally encountered. From the symptomatic patients, osteoarticular involvement was the unique or the primary presentation of the disease in eight of 12 (66.7%), and all of them were classified into acute/subacute form.

In this series, 51 distinct bone focal lesions were identified and characterized by conventional radiography. All the encountered bone lesions were osteolytic. The majority of bone lesions occurred in long bones 41 of 51 (80.4%). There was a predilection for the scapular girdle and upper limbs (27.5% clavicle, 15.7% humerus, 13.7%

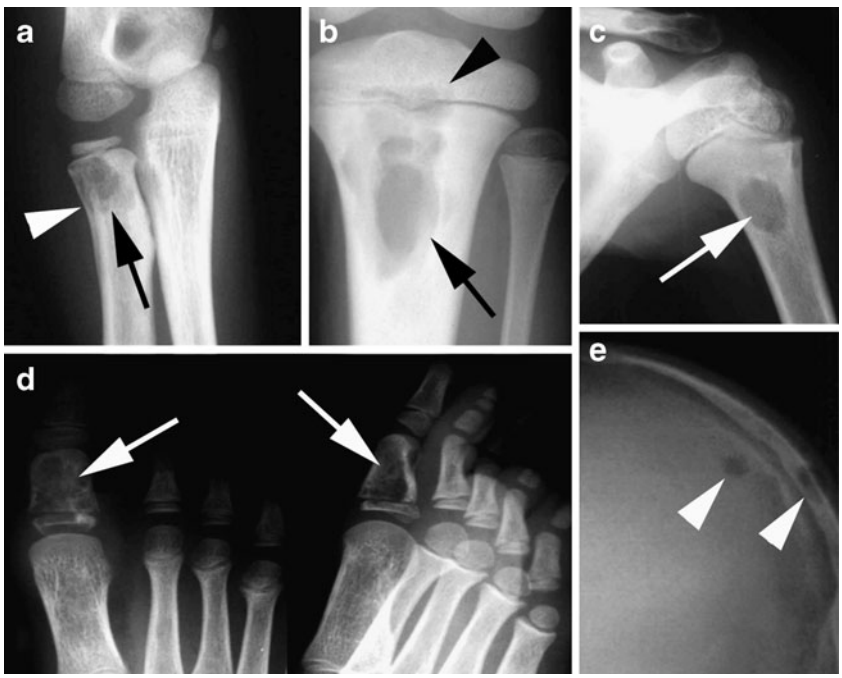

Fig. 1 A 7-year-old male with multiple bone lesions and cervical adenomegaly. Bone marrow biopsy and lymph node cytology were both consistent with paracoccidioidomycosis. Diagnosis also confirmed by the biopsy of the tibial lesion. **a** Metaphyseal osteolytic radius lesion (*black arrow*). Continuous and laminar periosteal reaction (*white arrowhead*). **b** Metaphyseal osteolytic tibial lesion (*black arrow*) with epiphyseal extension (*black arrowhead*). **c** Metaphyseal osteolytic humerus lesion (*white arrow*). **d** Osteolytic lesion at the hallux proximal phalanx (*white arrows*). **e** Two cranial vault osteolytic foci (*white arrowheads*)

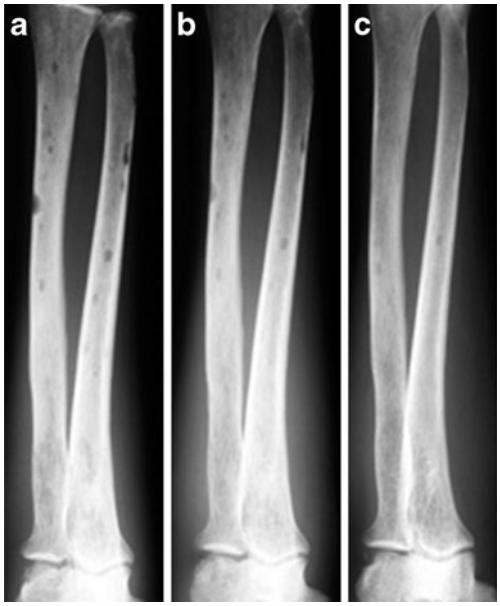

Fig. 2 A 33-year-old man with the acute form of PCM and HIV co-infection. Radiographs of the right forearm showed multifocal bone involvement. **a** 1996; the time of the PCM diagnosis. **b** 1997; 1 year after the beginning of specific treatment. **c** 2001; the lesion is almost completely healed

radius, and scapula 3.9%). In long bones, 12 of 41 (29.3%) lesions were meta-epiphyseal, 19 of 41 (46.4%) were metaphyseal and 10 of 41 (29.3%) diaphyseal. Focal lesions were identified in the cranial bones (3/51) and in a vertebra (1/51).

The margins were sharply defined in 32/51 (62.7%) of the bone lesions, and there was no marginal sclerosis in 42

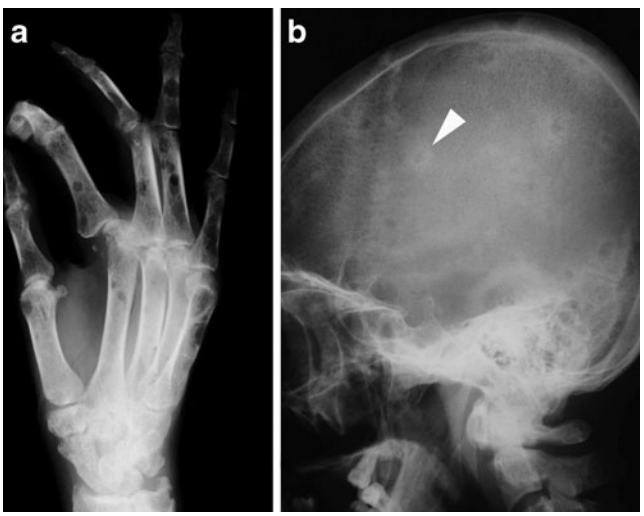

Fig. 3 A 33-year-old man, the same patient of Fig. 2. **a** Before treatment multiple "punched-out" osteolytic lesions in metacarpals and phalanges and articular misalignment of the second metacarpophalangeal joint. **b** Sparse osteolytic lesions in the cranial vault. Reactive bone sclerosis was present surrounding the cranial lesions (*arrow*) in this radiography obtained during treatment (*arrowhead*)

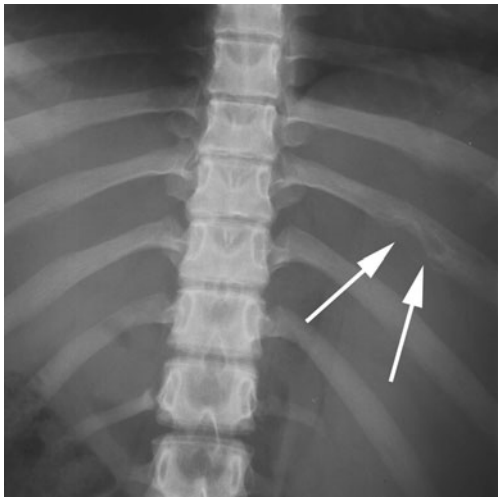

Fig. 4 A 15-year-old girl. Osteolytic lesion with cortical erosion in the inferior aspect of the costal arch (*arrows*)

of 51 (82.4%). When marginal sclerosis was present, it was discrete. Lesions without periosteal reaction were the majority (46/51; 90.2%).

A solitary bone lesion was identified in eight patients of this case series. In the remaining patients, two or more bones were involved (42.1%).

Discussion

People at the greatest risk for *P. brasiliensis* infection are male, especially in their third and fourth decades of life [6, 7]. *P. brasiliensis* reach the lungs by respiratory route and can infect persons exposed to the rural and suburban environment where the fungus survives in the saprophytic

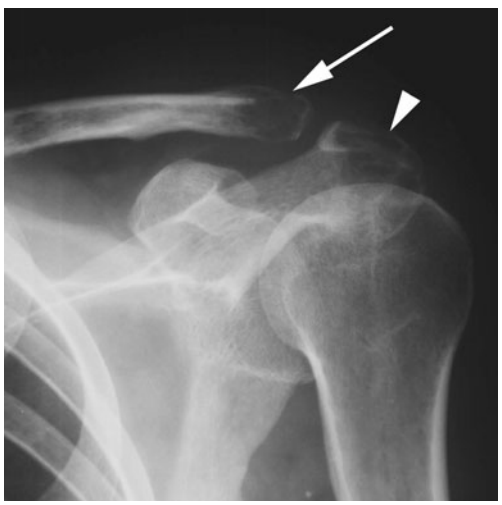

Fig. 5 A 28-year-old woman with cervical, axillary, and supra-clavicular lymphadenomegaly. Shoulder conventional x-ray showed osteolytic lesions in the acromion (*arrowhead*) and in the left clavicle extremity (*arrow*)

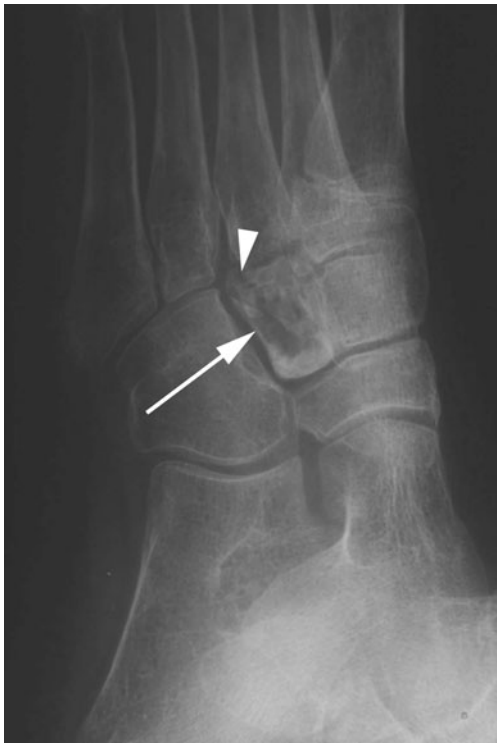

Fig. 6 A 10-year-old girl with foot pain for 3 months. Osteolytic lesion (*arrow*) with pathologic fracture and cortical interruption (*arrowhead*) in the lateral cuneiform bone. A bone tumor was suspected and bone biopsy confirmed paracoccidioidomycosis

form. The host usually controls the primary infection but PCM dissemination may occur to other tissues by blood and lymphatic route.

The majority of patients in the present series (94.7%) were classified in the acute/subacute form, which is the most prevalent in younger patients. According to our results, osseous involvement is almost exclusively of the acute clinical form of the disease and it was more often found in children and juvenile patients. In only one patient of this case series did PCM infection present as an opportunistic infection in an AIDS patient (patient no. 10 from Table 1).

The prevalence of osteoarticular involvement in PCM is variable as has been reported in the literature. A retrospective study comprised of 173 consecutive cases with PCM diagnosis found 4% of osseous involvement [7]. In the disseminated form of the PCM, osteoarticular involvement could reach up to 20% of cases [6]. It is important to note that osteoarticular involvement can be the first or the only system involved in this disease [10, 11, 14, 15, 20]. In the present case series, bone involvement was the unique or the primary presentation of the disease in eight patients (42.1%).

The bone lesions in PCM patients have often been studied with conventional radiography, and they have been described as sharply defined osteolytic lesions without marginal sclerosis and typically without periosteal reaction [4–8, 13, 21, 22]. The results of this series of cases are, therefore, in accordance with the literature. Geographic bone pattern of osteolysis was the most frequent type of presentation on radiographic investigation. In the present case series, the long bones were by far the most affected but virtually any bone can be involved [6, 7, 21]. Cranial, vertebra, rib, scapula, sternum, tarsal bone, and phalangeal lesions were documented. Figures 1, 2, 3, 4, 5, 6, and 7 illustrate the features and distributions.

The prevalence of clavicle focal lesions (Figs. 5, 7) observed in this case series may appear exaggeratedly high but this is accordance with the previous literature [6, 7]. The authors hypothesize that these could be the result of asymptomatic or subclinical involvement detected by routine chest x-rays. The appendicular skeleton is not evaluated in paracoccidioidomycosis patients unless there are symptoms, but chest radiographs are indicated in the baseline and follow-up assessments for both acute and chronic forms of lung disease [1]. In the present case series, lesions of the clavicle extremity or acromioclavicular joint destructive changes were found in four asymptomatic patients.

The current study had several limitations. First, the number of cases was relatively small and the study was limited to descriptive statistics. Second, radiographic evaluation of osseous involvement on PCM patients is not a routine and therefore the prevalence of bone and joint involvement could not be evaluated. In addition, this was a

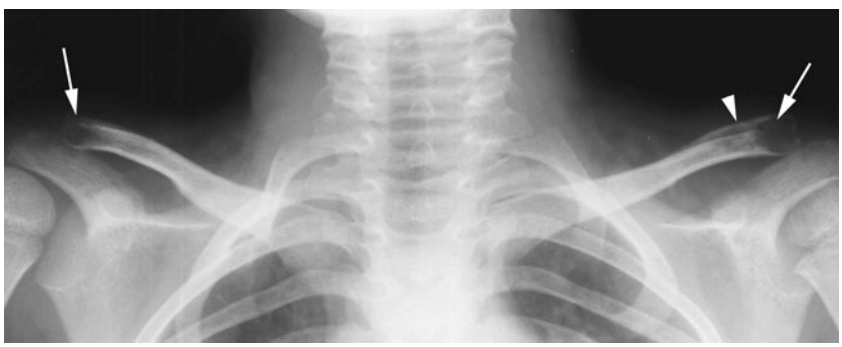

Fig. 7 A 5-year-old boy with clinical presentation of cervical, inguinal, and thoracic adenomegaly. Osteolytic lesions are seen at both clavicles extremities (*arrows*). On the left side, the lesion was accompanied by periostitis (*arrowhead*)

retrospective study and not all the lesions were proved pathologically in patients with multifocal bone lesions.

The differential diagnosis of the bone involvement in paracoccidioidomycosis would depend on the disease pattern and on the patient's age. Osteomyelitis of other etiologies would be important to consider in differential diagnosis when a focal metaphyseal osteolytic lesion is encountered. When osteolysis of the distal clavicle is present, it would be necessary to differentiate PCM involvement from post-traumatic osteolysis, hyperparathyroidism, and rheumatoid arthritis. Eventually, a focal and solitary bone PCM lesion may be misdiagnosed as a neoplasm [23]. In the case of multiple punched-out osteolytic lesions, it would be necessary to differentiate PCM from multiple myeloma for older patients and from Langerhans' cell histiocytosis, disseminated bone tuberculosis, and cystic angiomatosis in the younger patients and children.

Although pulmonary diagnostic imaging features of PCM have been better discussed in the literature [7, 24, 25], PCM osteoarticular involvement information is derived mostly from case reports and this is justified by the rarity of musculoskeletal manifestations. Osteoarticular involvement in PCM is infrequent but it may be the unique or the primary presentation of the disease.

Conclusions

All encountered bone lesions were osteolytic. Metaphyseal or meta-epiphyseal osteomyelitis of a long bone was the most prevalent osteoarticular manifestation of paracoccidioidomycosis. PCM bone involvement could be solitary or multifocal and it is more common in children and in juvenile patients. Axial skeleton involvement, arthritis, or a disseminated osseous pattern of infection may occasionally occur in this fungal disease.

References

1. Shikanai-Yasuda MA, Telles Filho Fde Q, Mendes RP, Colombo AL, Moretti ML. Guidelines in paracoccidioidomycosis. Rev Soc Bras Med Trop. 2006;39:297–310.
2. Brummer E, Castaneda E, Restrepo A. Paracoccidioidomycosis: an update. Clin Microbiol Rev. 1993;6:89–117.
3. Van Damme PA, Bierenbroodspot F, Telgtt DS, Kwakman JM, De Wilde PC, Meis JF. A case of imported paracoccidioidomycosis: an awkward infection in the Netherlands. Med Mycol. 2006;44:13–8.
4. Doria AS, Taylor GA. Bony involvement in paracoccidioidomycosis. Pediatr Radiol. 1997;27:67–9.
5. Rosario-Filho NA, Telles-Filho FQ, Costa O, Marinoni LP. Paracoccidioidomycosis in children with different skeletal involvement. Rev Inst Med Trop São Paulo. 1985;27:337–40.
6. Costa MAB, Carvalho TN, Araújo Júnior CR, Borba AOC, Veloso GA, Teixeira KS. Extra-pulmonary manifestations of paracoccidioidomycosis. Radiol Bras. 2005;38:45–52.
7. Trad HS, Trad CS, Elias Jr J, Muglia VF. Radiological review of 173 consecutive cases of paracoccidioidomycosis. Radiol Bras. 2006;39:175–9.
8. Amstalden EM, Xavier R, Kattapuram SV, Bertolo MB, Swartz MN, Rosenberg AE. Paracoccidioidomycosis of bones and joints. A clinical, radiologic, and pathologic study of 9 cases. Medicine (Baltimore). 1996;75:213–25.
9. Scheinberg MA, Cohen M, Abdalla RJ, Guidule J. Arthroscopy in the blastomycosis arthritis of the knee: report of a case. Rev Bras Ortop. 1994;29:577–8.
10. Silvestre MTA, Ferreira MS, Borges AS, Rocha A, Souza GMd, Nishioka SA. Monoarthritis of the knee as an isolated manifestation of paracoccidioidomycosis. Rev Soc Bras Med Trop. 1997;30:393–5.
11. Picado CHF, Garcia FL, Marcondes CRR. Late outcome of *Paracoccidioides brasiliensis* isolated infection on the hip. Acta Ortop Bras. 2006;14:97–100.
12. Neves MT, Livani B, Belangero WD, Tresoldi AT, Pereira RM. Psoas abscesses caused by *Paracoccidioides brasiliensis* in an adolescent. Mycopathologia. 2009;167:89–93.
13. Petlik MEI, Porta G, Kiss MHB, Oselka GK. Paracoccidioidomicose Generalizada com Comprometimento Ósseo em Crianças: Relato de Dois Casos. Pediat (S Paulo). 1980;2:65–72.
14. Severo LC, Agostini AA, Londero AT. Bone involvement in chronic disseminated paracoccidioidomycosis. A report on the first cases in Rio Grande do Sul. Rev Soc Bras Med Trop. 1996;29:241–4.
15. David A, Telöken MA, Dalmina V, Oliveira GKd, Oliveira RKd. Bone paracoccidioidomycosis: report of a case. Rev Bras Ortop. 1997;32:254–6.
16. Miranda Aires E, Costa Alves CA, Ferreira AV, Moreira IM, MC SMP, Peluso D, et al. Bone paracoccidioidomycosis in an HIV-positive patient. Braz J Infect Dis. 1997;1:260–5.
17. Maeda L, Hara MH, Sabedotti IF, Montandon C, Torriani M, Nanni L. Bone paracoccidioidomycosis associated with acquired immunodeficiency syndrome: a case report. Rev Imagem. 1999;21:21–4.
18. Nogueira SA, Guedes AL, Wanke B, Capella S, Rodrigues K, Abreu TF, et al. Osteomyelitis caused by *Paracoccidioides brasiliensis* in a child from the metropolitan area of Rio de Janeiro. J Trop Pediatr. 2001;47:311–5.
19. Castro G, Martinez R. Images in clinical medicine. Disseminated paracoccidioidomycosis and coinfection with HIV. N Engl J Med. 2006;355:2677.
20. Cassone AE, Mello A, Junior W, Alvarenga M, Moreira MP. Patellar paracoccidioidomycosis. Case report. Rev Bras Ortop. 2005;40:288–94.
21. Marchiori E. Aspectos radiológicos das lesões osteoarticulares na paracoccidioidomicose: considerações sobre 20 casos. Radiol Bras. 1989;22:5–22.
22. Sampaio SAP. Manifestações Clínicas da Blastomicose Sul-Americana (Paracoccidioidomicose). An Bras Dermatol. 1972;47:253–63.
23. Valera ET, Mori BM, Engel EE, Costa IS, Brandão DF, Nogueira-Barbosa MH, et al. Fungal infection by *Paracoccidioides brasiliensis* mimicking bone tumor. Pediatr Blood Cancer. 2008;50:1284–6.
24. Souza Jr AS, Gasparetto EL, Davaus T, Escuissato DL, Marchiori E. High-resolution CT findings of 77 patients with untreated pulmonary paracoccidioidomycosis. AJR Am J Roentgenol. 2006;187:1248–52.
25. Marchiori E, Valiante PM, Mano CM, Zanetti G, Escuissato DL, Souza Jr AS, et al. Paracoccidioidomycosis: high-resolution computed tomography-pathologic correlation. Eur J Radiol. 2009;77:80–4.