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Title: A possible case of Garre's sclerosing osteomyelitis from Medieval Tuscany (11th-12th centuries)

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Abstract: Archaeological excavations carried out at the castle of Monte di Croce near Florence brought to light a small cemetery complex belonging to the castle church, dated back to the 11th-12th centuries. A privileged stone tomb contained the skeletal remains of a male aged 35-45 years with an evident pathology of the right tibia. The bone appears massively enlarged in correspondence of the proximal metaphysis and of the upper half of the diaphysis as a result of a severe chronic periostitis. At transversal section complete obliteration of the medullary cavity by new spongy bone, with some large cavitations, is evident. The residual completely remodeled primitive tibial shaft is still recognizable. This finding and the strong sclerotic reaction with some central cavitations allowed us to rule out any form of bone tumor and to suggest a chronic inflammatory disease. The morphological and radiological picture and the tibial localization suggest a diagnosis of chronic sclerosing osteomyelitis of Garré, a rare form of chronic osteomyelitis characterized by small or by no suppuration, and by an intense periosteal reaction.

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Dear Editor,

we revised the manuscript, according to the referees' comments.

Here in bold type a detailed list of the changes and the rebuttal against each point. In the manuscript the changes are highlighted in yellow.

I have reviewed your manuscript, which I now attach as a WORD document. I have made numerous minor editorial changes, primarily copy-editing. I have a few questions inserted in the text.

Reply: we accepted all editorial changes and we answered all questions inserted in the text.

What this fine paper lacks, however, is an introduction. If you will please go to the advice for authors on the IJPP web site, you will see that Case Studies need to be justified in terms of the special nature of the disease, the rigor of the differential diagnosis, or other circumstances. Therefore, you need to discuss more specifically how "rare" the condition is in the literature on paleopathology. If reference to these cases (or if none exist, that should be noted as a rationale for the Case Study), is your differential diagnosis more extensive and convincing (which I suspect is the case). Also, how does this (or does it) condition enlighten us about the community in which this individual lived?

Reply: a new introduction was written.

Best regards

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3 **A possible case of Garre's sclerosing osteomyelitis from Medieval Tuscany (11th-**
4 **12th centuries)**
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Abstract

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2 Archaeological excavations carried out at the castle of Monte di Crocena near Florence brought to light
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4 a small cemetery complex belonging to the castle church, dated back to the 11th-12th centuries. An
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6 elite stone tomb contained the skeletal remains of a male aged 35-45 years with an evident pathology of
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8 the right tibia. The proximal metaphysis and the upper half of the diaphysis appear massively
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10 enlarged as a result of severe chronic periostitis. A transverse section illustrates complete
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12 obliteration of the medullary cavity by new spongy bone, with some large cavitations. The primary,
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14 but completely remodeled tibial shaft is still recognizable. This finding and the strong sclerotic
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16 reaction with some central cavitations rules out any form of bone tumor and suggests a chronic
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18 inflammatory disease. The morphological and radiological picture and the tibial localization
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20 suggest a diagnosis of chronic sclerosing osteomyelitis of Garré, a rare form of chronic osteomyelitis
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22 characterized by an intense periosteal reaction with little or no suppuration.
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36 **Article type:** Case study

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38 **Key words:** chronic periostitis, tibia, 11th-12th centuries
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1. Introduction

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2 Reports on sclerosingosteomyelitis of Garré, a chronic form of osteomyelitis characterized by an
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4 intense periosteal reaction with little or no suppuration, are absent in the paleopathological
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6 literature. To the best of our knowledge, only one paper mentions a tibia from Poland affected by
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8 this condition, but the diagnosis is not supported by a detailed description and no differential
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10 diagnosis was made (Prejzner and Gladykowska-Rzeczycka, 1997).
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12 This paper presents a possible case of sclerosingosteomyelitis of Garré, observed in the tibia of an
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14 individual from the Medieval church cemetery of Monte di Croce, in Tuscany. The purpose of this
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16 work is to describe in detail the case and evaluate the results of the imaging study; differential
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18 diagnoses, evaluating other possible conditions that can produce features similar to those seen in the
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20 tibia from Monte di Croce, such as some forms of bone tumors, syphilis and Paget's disease, are
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22 also discussed.
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2. Materials and Methods

2.1 Archaeological and Historical Context

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32 The archaeological site of Monte di Croce is located on a hill near the small town of Pontassieve
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34 (Florence) and is occupied by the ruins of a Medieval castle and of a church. The castle of Monte di
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36 Croce represented an important stronghold of the power of the Counts Guidi, as it controlled the
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38 commercial traffic of northern Tuscany in opposition to the nascent *comune* of Florence. It is well
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40 established that the castle was held by a local aristocratic family, the Galiga, strict ally of the
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42 Guidi (Cortese, 2005; Cortese, 2007). The army of Florence besieged Monte di Croce in 1143 and,
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44 after various vicissitudes, the castle was destroyed in 1154 (Repetti, 1839).
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51 A little church inside the castle was used as a private chapel. The building can be identified as the
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53 Church of Saints Miniato and Romolo, already attested at the end of the 11th century. The religious
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55 building (13m x 6.50 m) is reduced to the foundation level and consists in a single room with apse.
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1 The church was enlarged in the 12th century reaching the dimensions of 21.5m x10m, but the works
2 were never completed to the destruction of the castle (Francovich et al., 2003).
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4 Excavations of the church of Saints Miniato and Romolo, conducted in 2001-2002 by the
5 Department of Archaeology and Art History of the University of Siena, allowed full exploration of the
6 small cemetery complex of the castle, dated back to the 11th-12th centuries (Francovich et al.,
7 2003). The importance of the cemetery of Montedi Croce Castle derives from the fact that it is a private
8 cemetery, probably reserved to the burial of the bailiffs and *fideles* of the castle's
9 lords; paleonutritional analyses revealed in fact that the alimentation of this human group was based
10 on vegetables and was poor in animal proteins, suggesting that the individuals buried in the
11 cemetery did not belong to the aristocratic élite (Fornaciari et al., 2012). A total of 71 individuals,
12 including 35 subadults and 36 adults, were brought to light. This cemetery area included twelve stone
13 burials, coffins and many simple fossa burials (Fornaciari et al., 2003).
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28 Alithic tomb (n. 59), leaning against the south wall and made of square stones worked on the surface,
29 was found among the graves surrounding the church. The position and the unusual elaboration lead to
30 suppose that this was an elite tomb. It contained the remains of an adult individual still in connection
31 (n. 16), who showed an evident pathology of the right tibia (fig. 1).
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41 2.2 Skeletal Methods

42 Sex determination was performed on the basis of the morphologic features of the skull and pelvis
43 (Ferembach et al., 1977-79; Buikstra and Ubelaker, 1994). Age at death was estimated from the
44 examination of pubic symphysis morphology (Brooks and Suchey, 1990), dental wear (Lovejoy,
45 1985) and sternal rib end modification (Loth and Iscan, 1989). The stature was established by the
46 formulas of Trotter and Gleser (1977).
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55 Paleopathological study included both macroscopic and radiological examination. For conventional
56 X-rays a FCR Velocity by Fujifilm computed radiography equipment was used, with the following
57 parameters: 10-12 mAs with 54-60 keV, DFF 110 cm. Computed Tomography (CT) was carried out
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with a CT scanner Toshiba Aquilion 16, 100 kVp, 100 mA, rotation time 0,5 s, slice thickness 3 mm, DFOV 49,4x35,9 cm.

3.Results

The skeletal remains of individualn.16 belong to an adult male aged 35-45 years. The stature is about 177 cm.

The right tibia appears affected by a severe pathology. The bone is not completely preserved: the medial condyle with the underlying spongy bone and the distal epiphysis are missing. Post-mortem damage removed the cortical portion of the bone that included the medial central diaphysis, involving an area of ca 90 x 40 mm and exposing the underlying spongy bone; in addition, the bone is broken transversally, 25 mm under the nutrient foramen.

The tibia appears to be greatly enlarged in correspondence to the proximal metaphysis and the upper half of the diaphysis (fig. 2). Diameters at midshaft and at the nutrient foramen of the right tibia are significantly larger than those of the left unaffected tibia (table 1).

	Right tibia (mm)	Left tibia (mm)
Maximum diameter at midshaft	50	29
Transversal diameter at midshaft	44	23
Maximum diameter at the nutrient foramen	53	32
Transverse diameter at the nutrient foramen	51	25

Table 1 Diameters of the right and left tibia

The posterior and lateral surface of the proximal metaphysis appears altered by periostitic reaction consisting in plaques of new bone formation, porosities and bone spicules, irregularly disposed; the medial surface of the proximal metaphysis appears less irregular, with porosities and absence of bone spicules. A transverse section of the bone, due to post-mortem breakage, shows a thickened

1 cortex and total sclerotic obliteration of the medullary cavity by new spongy bone; a sub-cortical
2 large cavitation is present in correspondence of the superior-lateral portion of the bone. The posterior
3 portion of the earlier, normal tibial shaft, completely remodeled, is recognizable (fig. 3).
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5 Radiological examination showed heterogeneous sclerosis along the proximal to mid diaphysis,
6 with bone expansion; new bone levels are disposed parallel to the diaphysis. The cortical compact
7 bone appears to be locally thickened. The complete obliteration of the medullary cavity with
8 endosteal new bone formation is confirmed, along with cavitations and osteolytic phenomena. The
9 original diaphysis is reabsorbed but still recognizable. Bone sequestra, including drainage channels
10 (*cloacae*) are absent (fig. 4).
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12 The CT sections, at different levels, better defined partial (figs. 5a and 5b) and total obliteration
13 (fig. 5c) of the medullary canal; local circumferential cortical thickening and bone lacunae were
14 present. The residual original diaphysis, visible as cortical bone surrounded by abundant new spongy
15 bone, is recognizable.
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17 No bone lesions or traumatic injuries were observed in the left tibia. The other portions of the cranial
18 and post-cranial skeleton presented no additional evidence of pathology, including trauma.
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20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 **4. Discussion and conclusions**

40 The macroscopic and radiological features of the left tibia from Monte di Croce (Tomb 59, Skeleton
41 16) include a fusiform enlargement of the diaphysis caused by strong periosteal reaction, obliteration
42 of the medullary cavity and absence of sequestra and fistulisation. In differential diagnosis several
43 diseases need to be considered, in particular bone tumors, including osteoblastoma, Ewing sarcoma
44 and low grade osteogenic sarcoma, as well as other entities, such as syphilis, Paget's disease and
45 osteomyelitis.
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47 An osteoblastoma is considered a benign tumor, but locally aggressive. The tumor affects males more
48 than females, in a ratio of 2:1, and the age of occurrence is between 10 and 25 years. The most
49 common site of occurrence is the posterior portion of the column, but this tumor can also involve
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1 the long bones, in particular the femur and tibia in the medullary cavity and diaphysis,
2 whereasepiphysalinvolvementis rare.The tumor contains a central area usually larger than 2 cm
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4 and a sclerotic reaction circumscribing the lesion (Atesok et al., 2011). In our casethe ageisabove
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6 average, there are internal cavitations, and the involved segment is larger than in osteoblastoma.
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8 Ewing sarcoma is a malignant tumor of bone rarely occurring in patients older than 30 years. The
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10 tumorcan arise in any bone and the femur and tibia are the most commonly affectedlong bones
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12 (DorfmanandCerniak, 1998).Ewing sarcoma is highly aggressive, and it causes extensive
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14 destruction of the cancellous and cortical bone. Radiological examination reveals a permeative lytic
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16 lesion with periosteal reaction, frequently of the “onion-skin” type. In our case the age at onset, the
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18 absence of extensive destruction and the presence of the original diaphysis do not support the
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20 diagnosis of Ewing sarcoma.
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26 Low-grade centralosteosarcoma is a rare form of intramedullary osteosarcoma, whose average age
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28 of occurrence is 30 years. The most involved bones are the femur and tibia and the lesion originates
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30 in the metaphyseal tract, sometimes extending to the diaphysis (Kashima et al.,
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32 2013).Radiographically, both lytic andosteoblastic phenomenacoexist in the mixed form (Andresen
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34 et al., 2004). However, the structure of thescleroticlesion visible bothincompact andspongy bone,
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36 combined with preservation of tracts of theoriginaldiaphysis, allow the exclusion ofthis tumor.
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40 As for other entities, bone involvement is common in tertiary syphilis and the most affected bones
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42 are the skull and the tibiae.The lesions on the tibiae correspond to a non-gommatousosteomyelitis,
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44 including bone enlargement withnarrowing of the medullar cavity; there mayalso be an anterior
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46 bowing, as in“saber shin” tibia (Aufderheideand Rodriguez-Martin, 1998). However, in
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48 lueticosteomyelitis the lesions are commonly bilateral (Ortner, 2003); in our case the diagnosis of
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50 tertiary syphilis shouldtherefore be ruled out.
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55 Paget's disease of bone is a metabolic skeletal disease, characterized by excessive resorption
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57 followed by excessive formation of bone, with abnormal bone remodeling. Involvement is usually
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59 polyostotic and asymmetric, and the most affected bones are the pelvis, spine, skull, femur, and
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1 tibia. Mixed lytic and sclerotic changes are typical at X-ray examination (Griz et al., 2014). The
2 deformities in the tibia mainly consist in a marked expansion of bone and anterior bowing (Lee et
3 al., 2004). In the tibia from Monte di Croce (Tomb 59, Burial 16), the absence of bowing deformity
4 and atypical sclerotic and lytic lesions (“mosaic” aspect) exclude Paget’s disease.
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9 Osteomyelitis is an inflammatory process caused by pyogenic germs, such as staphylococcus,
10 streptococcus and pneumococcus, that can affect all skeletal segments (Resnick and Niwayama,
11 1989). The infection produces a local ischemia and subsequent necrosis of the bone segment,
12 forming a sequestrum. The periosteum is stimulated to produce new bone in order to enclose the
13 affected portion, forming an involucrum, that can be perforated by cloacae (Aufderheide and
14 Rodriguez-Martin, 1998).
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19 Amorphological pictures similar to our case could represent an acute osteomyelitis become
20 chronic. Chronic sclerosing osteomyelitis of Garré is a rare form of chronic osteomyelitis first
21 described by Carl Alois Philipp Garré in 1893; other names are chronic osteomyelitis with
22 proliferative periostitis, chronic sclerosing osteomyelitis, ossifying periostitis or non-suppurative
23 chronic sclerosing osteomyelitis (Moraes et al., 2014). This condition affects young children and
24 adults, predilecting the male sex (Vannet et al., 2014). The mandible is the
25 most commonly affected bone, but the disease can also affect the metaphyseal region of the long
26 bones (Belli et al., 2002); among the long bones, the tibia is the most preferred localization (Vannet
27 et al., 2014).
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32 Clinically, the onset of the condition is characterised by local pain and reaction in the affected bone,
33 whereas the symptomatology may persist for several months and in some cases even for years, with
34 an episodic non-progressive course and low mortality. During the acute phase the symptoms include
35 pain, heat, redness, tumor growth and deformity. The affected bone generally maintains its function,
36 and most patients appear to be healthy during the interval between episodic exacerbations,
37 (Bernard-Bonnin et al., 1987; Moraes et al., 2014). The radiographic changes consist in general
38 sclerosis, which can produce obliteration of the medullary canal, widening of the cortex and possible
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cystic changes. There is no evidence of abscesses and sequestra (Nikomarov et al., 2014; Vannet et al., 2014).

The etiology of this pathology has not yet been completely clarified. It seems to originate from an infection caused by low-virulent, anaerobic bacteria (Collert and Isacson, 1982), but in most cases no bacterial growth can be cultured; therefore, the chronic process may be maintained by a low-grade persistent infection (Vienne and Exner, 1997).

In conclusion, in clinical studies chronic sclerosing osteomyelitis of Garré presents as a general sclerosis of the involved segment due to the succession of periosteal reactions to persistent infectious stimuli, with possible areas of osteolysis. Medullary cavities, sequestra and cloacae are typically absent. In dry bone, this condition is described as characterized by regular fusiform shape of the involved portion, absence of medullary cavity, rough surface and absence of sequestrum and fistulisation (Prejzner and Gladykowska-Rzeczycka, 1997). The morphological and radiological features, as well as the tibial localization observed in the case from Monte di Croce (Tomb 59, Burial 16) are most compatible with the clinical and paleopathological features of chronic sclerosing osteomyelitis of Garré, thus making this diagnosis the most probable.

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Legend to the figures

1
2 Figure 1 Tomb 59 with skeleton 16 still in situ: the enlargement of right tibia is evident

3
4 Figure 2 Posterior view of both tibiae, with enlargement and fusiform shape of the right one

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6 Figure 3 Section of the right tibia, showing almost complete obliteration of the medullar cavity and
7 residual original diaphysis

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9 Figure 4 Radiography of the tibiae; heterogeneous sclerosis along proximal to mid shaft of the right
10 tibia with thickening of bone and immature but benign-appearing periosteal new bone formation

11
12 Figure 5 Cross-sections of the tibiae at CT: narrowing of the medullary canal by sclerotic new bone,
13 circumferential cortical thickening and areas of osteolysis are evident at the level of the metaphysis
14 (a) and superior third of the diaphysis (b); complete obliteration of the medullary canal is visible at
15 the level of midshaft (c); tracts of the original tibial diaphysis are well recognizable in all sections
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Figure 5

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