Title

Better a broader diagnosis than a misdiagnosis: the study of a neoplastic condition in a male individual who died in early 20th century (Coimbra, Portugal)

Short title

Palaeopathological differential diagnosis in a neoplastic condition

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Keywords

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Abstract The paleopathological record of neoplastic conditions in the past is considered scarce. The detection of tumours in ancient populations is hindered by the quality and quantity of signs visible on the skeleton, the methodological approach, the preservation of remains, and by difficulties of differential diagnosis. The aims of this paper are to report the extensive and multiple osteolytic lesions observed in an adult male and to discuss the possible etiology of these lesions. The individual, a 71-year old male who died in 1932, is part of the Coimbra Identified Skeletal Collection. Records indicate that he died of a "heart lesion". The present study used macroscopic, radiological and computerized tomography examinations to analyse the skeletal remains of the individual number 439. The type and pattern of the lesions detected, which were most prominent on the skull, were compared with both clinical and paleopathological diagnostic criteria for different nosologic groups. The differential diagnosis addresses problems expressed both in clinical and in paleopathological literature with regard to the difficulties in distinguishing metastatic tumours from multiple myeloma. The nature of the lesions represented by this individual precludes an

exact diagnosis. Therefore, we employed a broader category, neoplastic condition, instead of choosing a more specific diagnosis that would likely have resulted in a misdiagnosis due to overlapping features on this individual's condition. Further investigations are necessary to establish more replicable indicators and to improve confidence in retrospective diagnosis of these types of conditions.

Introduction

The scarcity of malignant neoplastic conditions in the human skeletal record is a debated problem on the field of paleopathology (Strouhal, 1991; Capasso & Mariani-Costantini, 1994; Ricci *et al.*, 1995; Waldron, 1996; Weiss, 2000; Strouhal, 2001; Ortner, 2003; Halperin, 2004; Capasso, 2005; Thillaud, 2006; Brothwell, 2008; Waldron, 2009). The detection of malignant tumours in ancient skeletal remains relies on variable and often ephemeral signs of bone proliferation and/or destruction. The identification of these conditions is frequently constrained by the state of preservation of the skeleton, primarily due to higher susceptibility of lesional areas to bone destruction, or by the effect of diagenesis (which can mimic true lesions), but also, by the constraints on diagnostic parameters and paucity of systematic radiographic analysis of bones (Waldron, 1996; Weiss, 2000; Ortner, 2003; Capasso, 2005; Marks & Hamilton, 2007; Luna *et al.*, 2008; Waldron, 2009). Despite these clear limiting factors for assessing the past epidemiology of malignant tumours, some researchers still assert that the prevalence of cancer may have been extremely low in antiquity (David & Zimmerman, 2010). Contributing factors include: a) shorter life expectancy (age is a important epidemiological variable for the occurrence of certain types of malignant disease, such as carcinomas, which occur mainly in older individuals); b) preponderance of infectious conditions; and c) less exposure to environmental and occupational carcinogens*, e.g.* pollution, chemicals or radiation (Ricci *et al.*, 1995; Aufderheide & Rodríguez-Martín, 1998; Weiss, 2000; Ortner 2003; Halperin, 2004; Capasso, 2005; Thillaud, 2006; Brothwell, 2008; Waldron, 2009). However, it should be noted that even in antiquity humans were exposed to other natural environmental carcinogens such as natural light, infectious agents, heavy metals, and other natural carcinogenic chemical agents (Weiss, 2000; Halperin, 2004; Thillaud, 2006). The impact of intrinsic risk, such as genetic factors, should also not be minimized. For example, endogamous mating as a consequence of smaller population groups, may have favored the transmission of harmful mutations (Halperin, 2004; Greaves, 2008). Therefore, the true assessment of past oncological diseases is still rather limited. Although the paleopathological records of neoplasms span a wide chronological and geographical distribution (Capasso & Mariani-Costantini, 1994; Strouhal, 2001; Ortner, 2003; Capasso, 2005; Brothwell, 2008) their overall paleoepidemiology and the biocultural aspects

underlying the history of human vulnerability to malignant diseases, are still far from being clearly understood or described. The Portuguese paleopathological context does not differ from the general paucity of reported tumours, for example, only 6 cases of malignant neoplasms have been published to date (Marques & Matos, 2002; Assis & Codinha, 2010; Wasterlain *et al*., 2010).

The aims of this paper are to report the occurrence of extensive and multiple osteolytic lesions of the skull and destructive and proliferative processes of the postcranial skeleton of an adult male individual, and to explore the differential diagnoses. We intended to integrate both clinical and paleopathological diagnostic criteria, and explore the most common pitfalls and limitations to the study of malignant diseases of archaeological human remains.

The individual

The individual under analysis belongs to the Coimbra Identified Skeleton Collection from the University of Coimbra (Rocha, 1995). Skeleton number 439 is described in the collection record as a male photographer, 71 years of age at death, who died in Coimbra in 1932 from a "heart lesion". The skeleton is complete and well preserved, with slight effects of post mortem damage.

Methodology

Age estimation and sex diagnosis were conducted in accordance with anthropological methods (Ferembach *et al.*, 1980) in order to confirm the data registered in the collection records. For paleopathological analysis, the skeleton was observed in detail by naked eye and with the aid of a hand lens with a 10x amplification factor. The categorization and description of lesions was performed according to the methods of standard paleopathological procedure (Buikstra & Ubelaker, 1994; Ortner, 2003; Brickley & McKinley, 2004) and complemented by clinical radiological methods (Madewell *et al.*, 1981; Resnick, 1996a; Greenspan & Remagen, 1998; Miller, 2008). The proliferative new bone formation, particularly the distinction between woven *versus* lamellar typology, was categorized following the parameters described in Ortner (2003) and Matos & Santos (2006). The osteolytic foci observed on radiography were described according to published parameters (Madewell *et al.*, 1981; Resnick, 1996a; Greenspan & Remagen, 1998). The skull, vertebral column, ribs, scapulae, pelvic girdle, and long bones were submitted to conventional radiography by Philips Medical Systems equipment and computed tomography was performed on the skull (Santos & Cunha, 2001).

Results

The skull was the most affected skeletal element. A total of nine well defined perforating focal areas (Figure 1), affecting both the outer and the inner tables and the diplöe, are visible macroscopically: four in the frontal, two in the right sphenoid, one in each parietal and one in the occipital bone. Two additional smaller circular lesions affecting the outer table of the parietal were considered dubious in their pathologic or taphonomic nature. The osteolytic lesions dimensions ranged from 8 x 10 mm to 30 x 38 mm (with some surrounding post mortem bone damage), more frequently presenting a wider diameter in the outer cranial surface. The lesions main typology was roughly circular in shape with well-delimited boundaries, perfectly circumscribed margins and with tenuous indentation of the contour. There was no evidence of new bone formation at the margins or around the main osteolytic focus. The marginal areas were characterised by the presence of tenuous destructive activity, with tiny and smooth bordered pits (Figure 2). The osteolytic cortical destruction is accompanied by accentuated regression and destruction of the spongy bone (Figure 2). Additionally, the outer table of the left parietal presented two large areas of destruction translated by coalescent porosity (ca. 1 mm) (Figure 3). Macroscopically, the mandible shows no evidence of pathological alterations. On the radiographic exam of the skull (Figure 4) were observed multiple osteolytic foci with variable dimensions, circumscribed margins in a geographic pattern, i.e. represents a uniformly destroyed area usually within defined borders as defined by Madewell *et al.* (1981); Resnick (1996a) and Greenspan & Remagen (1998), and no evidence of sclerotic rim or new bone formation. These lesions created a relatively narrow to moderate zone of transition from normal to abnormal bone. The radiography and CT scan of the skull revealed areas of increased destruction of the diploe that was not assessed macroscopically.

The postcranial skeleton also exhibited affected anatomical elements. In the column only 11 thoracic vertebrae were present, with the 4th missing. The 6th thoracic vertebra (T6) showed a flattening of the vertebral body height, with a line of remodelled bone formation on the lateral body, indicative of a compression fracture. Areas of destruction were detected in the C3, T12, L1, L3, L5, left ala of the sacrum and between the 2nd and 3rd posterior sacral foramina. However, the characteristics of the outline of these destructions are dubious, therefore could have resulted either from taphonomic or pathological factors. Thus, the involvement of the vertebrae is not straightforward and should be considered only suggestive. Further examination using the radiological analysis did not clarify the etiology of the destructive areas.

The rib cage was preserved, except for the 10th right rib, yet some ribs were incomplete, fragmented and/or presenting taphonomic destruction. The 6th right rib show woven bone with intense porosity bordered by areas of bone remodelling and cortical integration on the posterior surface of the shaft, starting near the angle and extending along 61 mm towards the sternal extremity (Figure 5). The corresponding

visceral surface presented equally woven and lamellar bone (95 mm). The 7th right rib had an analogous process of new bone formation, similarly located and extending 66 mm over the posterior surface and 69 mm on the corresponding visceral one. These lesions were discrete at macroscopic level and imperceptible on the radiographic exam.

On the upper limbs, both clavicles and scapulae present minor post mortem destruction. On the right scapula a diffuse and poorly circumscribed zone of destruction (27 x 25 mm) was observed, comprised of small circular lesions located superiorly and medially adjacent to the base of the acromion, affecting both the posterior and anterior surfaces (Figure 6). The left scapular body presented a small lesion, on the medial border, which was radiologically characterized by small round osteolytic foci, with a round well-defined and regular margin and with a clear sclerotic rim (Figure 7). Other possible focal bone loss was noticed centrally under the acromion but without evidence of sclerosis.

The right innominate presented four demarcated areas of osteolytic destruction: in the lateral antero-superior iliac crest (28 x 13 mm), on the base of the pubic ramus (8 x 5 mm), pubis (10 x 13 mm), and ischium (7 x 8 mm). Only the lesion of the pubis did not extended through both cortical surfaces. This destruction presents some degree of trabecular regression. Nevertheless the borders were highly damaged by post mortem changes, prompting some caution with regard to their interpretation. Additionally, the radiologic examination exhibited a round osteolytic focus located centrally on the ilium. A macroporosity with active bone remodelling and patches of woven bone was located on the left innominate, inferior to the anterior inferior iliac spine (Figure 8a). Radiologically this area revealed increased radiopacity, associated with internal diffuse bone destruction, characterized by small, ill-defined osteolytic activity, culminating in a moth-eaten appearance (Figure 8b) as defined by Madewell *et al*. (1981). This pattern of the destructive process was not observable macroscopically.

In the lower limbs the only perceptible alteration was eburnation on the distal joint of the first left metatarsal. The remaining bones did not present any macroscopic changes. Furthermore, it is important to note the absence of endosteal scalloping on the x-ray survey of the long bones.

Discussion

The individual described herein exhibits indisputable osteolytic lesions on the skull, while the distinction of the lesions of postcranial bones is less clear due to the confounding effect of taphonomic factors. Regardless, the overall character of the lesions observed is predominantly osteolytic in nature. While there is clear evidence of osteolytic lesions of the skull, the postcranial skeleton showed a more heterogeneous pattern. This includes, osteolytic areas with no evidences of new bone formation, (namely in the superior and medial region of the scapula and pelvic bones), and signs of concomitance between new

bone formation and destruction (for example, the left innominate). Moreover, clear areas of exclusively new bone formation were present on the posterior and visceral surface of the 6th and 7th right ribs. Overall these lesions confer a multifocal, bilateral, asymmetric and predominantly axial distribution pattern.

According to Morse *et al.* (1974: 447) radiologic examination "is invaluable for the study of archaeological specimens, since it visualizes defects that have not yet reached the surface of the bone". This statement was corroborated by the present study, where the radiographic analysis was important to the detection of a destructive process associated with new bone formation on the left innominate. Radiological analyses were also useful in the assessment of zones of transition between lesion borders and normal bone, to testify to the sclerotic margin of the osteolytic focus on the scapula, and to clarify the absence of endosteal and medullary lesions on the long bones.

The nosological groups that may fit these types of lesions, particularly the intense osteolytic activity and the pattern of distribution, fall largely into broad categories of infectious diseases or neoplastic and tumor-like conditions.

Non-neoplastic conditions

Infectious diseases, namely tuberculosis, treponematosis, or fungal infection can promote the development of skeletal destructive lesions (Waldron, 1987; Mann & Murphy, 1990; Hershkovitz *et al.*, 1998**;** Rothschild *et al.*, 1997), yet these entities were excluded as the probable underlying mechanism of the above mentioned lesions on skeleton 439. The distinction of syphilitic cranial lesions from neoplastic ones can be challenging during the early stages of these diseases, since cranial pitting can be a common initial manifestation in both (Hackett, 1976). Syphilis tends to evolve to a typical crater-like depression with extensive sclerotic response and bone remodeling, and it is unusual to observe skull perforation or to have as numerous foci (Hackett, 1976; Ortner, 2003; 2008). The pattern of lesions observed on the postcranial elements of skeleton number 439 is also distinct from those common to treponematosis (Powell & Cook, 2005). Based on these diagnostic criteria, we have excluded this etiology.

Although fungal diseases can involve the skeleton, this is infrequent, especially in contrast with other human pathogens (Ortner, 2003; Arkun, 2004). Consequently, these conditions are seldom portrayed on paleopathological research (Ortner, 2003), and there is little information with regard to how these conditions impact the skeleton at a macroscopic level therefore making compromising the assessment of these conditions in archaeological remains (Hershkovitz *et al.*, 1998). In general terms, the morphological characterization of bone lesions caused by fungal infections is mainly of an osteolytic type, with reduced bone reaction, and can be similar to those produced by neoplasms or tuberculosis (Aufderheide & Rodríguez-Martín, 1998). Hershkovitz *et al*. (1998) and Schillaci (1999) have also noticed localized periosteal reactions associated with the destruction areas. Ortner (2003; 2008) emphasizes a more typical random pattern of lesion dissemination throughout the skeleton in mycotic disease. This is not the case

with skeleton 439 where the pathological changes have a predilection for the axial skeleton and a bilateral distribution.

The diagnosis of tuberculosis (TB) was also considered for the pattern of lesions herein described. Destructive lesions of TB on the skull do not appear to have pathognomonic features when compared with other diseases, namely neoplasms, at least using conventional radiography screening (Patankar *et al.*, 2000; Raut *et al.*, 2004). However, the skull is an uncommon anatomical site of involvement for TB, except in young individuals in the rare cases of disseminated infection (Aufderheide & Rodríguez-Martín, 1998; Patankar *et al.*, 2000; Ortner, 2003; Raut *et al.*, 2004; Diyora *et al.*, 2009), and frequently is a consequence of hematogenous spread of tubercle bacilli from a primary focus, such as pulmonary, renal or systemic tuberculosis or cervical or hilar lymphadenitis (Diyora *et al.*, 2009). In the pre-antibiotic period "calvarial tuberculosis was estimated to represent 0.2–1.3% of all cases of skeletal tuberculosis" (Raut *et al.*, 2004: 411) and it continues to be a seldom event in modern times (Diyora *et al.*, 2009). The clinical roentgenographic screening is characterized by small (not larger than 2 cm) circumscribed oval or round punched-out defect, usually solitary, with minimal sclerosis or zones of increased density, perforating the inner or outer table, or both, in which bony sequestra may be observed (Meng & Wu, 1942; Patankar *et al.*, 2000). In the paleopathological literature the descriptions also refer numerous small areas of destruction (less than 2 cm in diameter), with poorly defined margins and some surrounding reactive sclerosis, where abscess and fistula formation occur (Aufderheide & Rodríguez-Martín, 1998), or as a single focus with irregular margins, limited bony reaction, common existence of a sequestrum, and larger size on the inner table (Hackett, 1976; Roberts & Buikstra, 2003; Ortner, 2003). Pondering these clinical and paleopathological descriptions, it seems that the multifocal and large size osteolytic lesions in the skull, their irregular shape, the wider lesions on the outer table, and the age at death of the individual number 439, are arguments that do not sustain a case of tuberculosis. Furthermore, pure osteolytic foci on the ilium, ischium, and pubis are rarely caused by TB (Ortner & Putschar, 1981; Roberts & Buikstra, 2003). The type of rib lesions and their distribution on skeleton 439 also do not conform with the pattern described by Matos & Santos (2006) of individuals with pulmonary tuberculosis as cause of death. Therefore, a diagnosis of disseminated TB is improbable.

Neoplastic and tumour-like conditions

Amongst the neoplastic and tumor-like conditions, the key parameters used to narrow down the etiological possibilities and to perform a differential diagnosis are: 1) lesion morphology (*e.g.* the imbalance between bone formation and destruction; the pattern of the periosteal reaction; characteristics of the bone destruction and their margins typology); 2) the predilection of the lesion's anatomical distribution along the skeleton and on the bone; and 3) the age of the individual (Miller, 2008). This analytic approach is valid in clinical diagnosis and can be equally useful in paleopathology.

The presence of a multifocal pattern of skeletal affection and multiple osteolytic lesions, namely in the skull, is more frequently attributed to: metastatic disease (particularly originating from carcinomas), multiple myeloma (Resnick, 1996b; Greenspan & Remagen, 1998; Campanacci, 1999; Ortner, 2003), Langerhans cell histiocytosis (eosinophilic granuloma, Hand-Schüller-Christian disease, Letterer-Siwe disease) (Resnick, 1996b; Resnick, 1996c; Azouz *et al.*, 2005), and leukemia (Van de Casteele *et al.*, 1994; Ortner, 2003). One important factor that assists the differential diagnosis of these conditions is the distinct age-curves of incidence on these diseases (Miller, 2008). All except for multiple myeloma and metastatic carcinoma are more prevalent at younger ages (less than 20 years) and have a propensity for bone lesion development in earlier ages (Greenspan & Remagen, 1998; Ortner, 2003; Miller, 2008). However, is noteworthy the existence of adult chronic and acute forms of leukemia that has a peak age of onset of 35-55 years (Resnick & Haghighi, 1996). Age profile is therefore an important argument to consider and refutes the diagnoses of Langerhans cell histiocytosis and leukemia for individual number 439 that was 71 years old at the time of death. Moreover, considering the morphological characteristics of the lesions it could also be noted that for Langerhans cell histiocytosis, cranial lesions starts on the diplöe with subsequent extension, are round or oval in shape, are classically described as punched-out lesions, with well defined, sharp, and regular margins, and with a contour typically exhibiting a beveled appearance. This last feature is highly distinctive of this condition as well as a button sequestrum frequently observed (Resnick, 1996c; Greenspan & Remagen, 1998; Azouz *et al.*, 2005; Lloret *et al.*, 2009). Those important characteristics of lesion morphology are not evident in skeleton 439, sustaining the rule-out of this entity. As far as the chronic and acute adult forms of leukemia are concerned, they have a less common skeleton involvement compared with disease manifestation in children (Van de Casteele *et al.*, 1994). Osteolytic bone lesions are also extremely rare in chronic lymphocytic leukemia (Van de Casteele *et al.*, 1994). When bone involvement occurs, the radiographic features include diffuse osteopenia, discrete small focal osteolytic lesions (particularly on metaphyseal femur and humerus, but could also affect the skull or pelvis), and metaphyseal radiolucency bands (Resnick & Haghighi, 1996). Macroscopically the osteolytic destruction can achieve the form of a cortical pitting on the metaphysis of bones and diffuse multiple holes (Zimmerman & Kelley, 1982; Aufderheide & Rodríguez-Martín, 1998; Ortner, 2003) "with smooth edges, minimally remodeled edges […] or fronts of resorption" (Rothschild *et al.*, 1997: 491). These macroscopic lesions, the radiological metaphyseal radiolucency or the osteopenia are pathological signs absent on the specimen under analysis.

The lesions typology, the anatomical sites involved, and the epidemiological profile of the current case are more consistent with diagnosis of a predominantly osteolytic metastatic tumor (MT), or multiple myeloma (MM). These are the neoplastic conditions most frequently evoked when a pattern of multiple osteolytic defects, namely on the skull, appears in older individuals (Ortner & Putschard, 1981; Strouhal, 1991; Resnick, 1996b; Greenspan & Remagen, 1998; Lloret *et al.*, 2009), requiring a careful differential diagnosis and comparative analysis.

The spreading of tumor cells (via the blood stream, lymphatic system or adjacent invasion) from a primary site of involvement produces metastases, which are an important characteristic of malignant tumors, since most cases demonstrate their invasive potential over time from a precursor carcinoma, adenoma or disorders of epithelial proliferation (Liotta & Kohn, 2003). The radiographic broad categories of skeletal metastasis can be theoretically divided as: predominately osteolytic, predominately osteoblastic, and mixed [osteolytic-osteoblastic] lesions (Resnick, 1996a; Miller, 2008). Multiple myeloma is a systemic malignant hematological disorder characterized by the proliferation of atypical plasma cells and plasmacytoid cells in the bone marrow (Raje *et al.*, 2003; Lloret *et al.*, 2009). Both entities, MT and MM, are prone to bone affection. The incidence of skeletal metastases varies, and is strongly correlated, with the type of primary tumor and disease duration, been the most prevalent the skeletal metastases subsequent to carcinomas (most commonly breast, prostate, lung and kidney, that can account for nearly 80% of all metastatic cancer that affect bone) (Greenspan & Remagen, 1998; Campanacci, 1999, Coleman, 2001). Comparatively, for the MM approximately 79% of the individuals present radiological abnormalities and up to 90% develop bone lesions (Raje *et al.*, 2003; Roodman, 2010).

The distinction between MT and MM cannot be made based on distinctive age and sex profiles since both are more prevalent in mature or advanced aged individuals (Table 1) and the sex ratio in MM is fairly equitable, or manifesting a slight male predominance (Campanacci, 1999; Raje *et al.*, 2003; Altieri *et al*., 2006, Miller, 2010), while in metastases sex varies accordingly to the primary tumour location (Resnick, 1996b; Greenspan & Remagen, 1998; Campanacci, 1999). The distribution pattern on the skeleton also does not contribute to the differential diagnosis, due to a similar predominance in both diseases for the affection of anatomical sites richer in hematopoietic marrow such as the axial skeleton and the proximal segments of long bones. Both can present a range of different patterns, initially more focalized or spreading in a diffuse or multifocal pattern on the skeleton (Ortner & Putschard, 1981; Resnick, 1996a,b,d; Greenspan & Remagen, 1998; Campanacci, 1999; Lloret *et al.*, 2009).

Metastatic disease, from the predominantly osteolytic type, and multiple myeloma have many lesional characteristics in common and their distinctive features are often unclear. The typical roentgenographic signs of MM include a widespread multiple osteolytic and sharply defined foci, with absence of a sclerotic rim and reactive bone formation (Greenspan & Remagen, 1998; Raje *et al.*, 2003; Lloret *et al.*, 2009; Winterbottom & Shaw, 2009). The lesions are round in shape and the margins are well defined with a short transitional zone on x-ray that results in a punched-out appearance (Resnick, 1996d; Greenspan & Remagen, 1998; Rogers, 1998; Campanacci, 1999; Lloret *et al.*, 2009), and may be associated with diffuse osteopenia (Campanacci, 1999; Lloret *et al.*, 2009). The punched–out lesion arises in the medulla and extends to cortical bone (Campanacci, 1999; Winterbottom & Shaw, 2009). Involvement of the skull in MM, typically results in numerous small, round, uniformly sized punched-out defects, which are sharply demarcated (Rogers, 1998; Greenspan & Remagen, 1998) beginning in the diploic space and extending through the inner table, outer table, or both (Morse *et al*., 1974).

Multiple lesions of the skeleton are also a radiographic hallmark of skeletal metastases. Lesions with predominantly destructive character are initiated in the medullar cavity and can present a highly variable pattern of bone destruction (geographic, moth-eaten, permeative) (Madewell *et al*., 1981) translated either into well-demarcated or less defined defects (Pahade *et al*., 2008). The margins may also present poor or sharp demarcation, with a regular or irregular contour, and often with a moderate to wide zone of transition (Greenspan & Remagen, 1998; Rogers, 1998; Lloret *et al*., 2009). Even in predominantly osteolytic lesions there may be an observable osteoblastic response (Ortner & Putschard, 1981). Therefore, the presence of osteoblastic activity can be listed as a distinctive feature amongst these pathologies. Notwithstanding the fact that bone formation with diffuse or focal sclerosis or periosteal reaction can be present in virtually all malignant tumors, it is seldom seen in rapidly growing tumors as in multiple myeloma (Resnick, 1996b; Greenspan & Remagen, 1998; Campanacci, 1999; Raje *et al.*, 2003). This imbalance between the severe bone destruction and inhibition of osteoblastic activity is highly characteristic of MM and has been subject to intensive research over the last decades. Histology has revealed excessive "bone resorption in the vicinity of the myeloma cells, with severe inhibition of bone formation" and molecular research has also shed light into the mechanisms causing absence of bone formation in MM (Angtuaco *et al*., 2004: 13; Rodman, 2010). By contrast, metastatic disease, even when predominantly osteolytic, can frequently present a variable amount of bone reaction. The present skeleton showed a sclerotic rim on the osteolytic focus of the right scapular body, a concomitance of a destructive process with bone formation on the left hip bone, and new bone formation on the visceral and posterior surfaces of two ribs. This indicates a degree of bone proliferation and sclerosis that is not characteristic of MM. Strouhal (1991) suggests that any evidence of sclerotic bone formation probably excludes MM. In sum, considering the morphology of the lesions seen on skeleton 439, with a well defined margin typology, the round shape, and the short to moderate zone of transition are all characteristics consistent with either diseases, yet the more irregular contour or indentation can be more frequently seen in MT. From the above mentioned features, the most distinctive diagnostic aspect for the present case is the evidence of bone proliferation, therefore supporting a MT diagnosis.

It is evoked in the literature that lesion size can be used as diagnostic criterion for differential diagnosis of MT and MM, nevertheless is a characteristic that requires detailed discussion. In the majority of the clinical and paleopathological studies, osteolytic lesions in multiple myeloma are described as small and homogeneous in size (Ortner & Putschard, 1981; Zimmerman & Kelley, 1982; Resnick, 1996d; Greenspan & Remagen, 1998; Aufderheide & Rodríguez-Martín, 1998; Rogers, 1998; Campanacci, 1999; Lloret *et al.*, 2009). However it is also noted the possibility that smaller lesions may coalesce into larger segments, as seen in metastasis, and occasionally large and less well-defined lesions can appear (Resnick, 1996d; Greenspan & Remagen, 1998; Rogers, 1998; Campanacci, 1999). Also Morse *et al.* (1974: 447) states that in MM the tumors appear as "discrete rounded holes of *various sizes"*. We can conclude that the size of lesions is not a consensual aspect. For the metastases are generally larger lesions with more

heterogeneous dimensions (Resnick, 1996a; Pahade *et al*., 2008; Lloret *et al*., 2009). Rothschild *et al.* (1998) suggests that size differences are not a reliable diagnostic feature for differentiation multiple myeloma and metastatic carcinoma, nevertheless the authors reported a higher range of size variation in metastatic carcinoma than in multiple myeloma. Marks & Hamilton (2007: 228-229) describe, a modern specimen with a registered cause of death as breast cancer, in which "lesions, especially those of the skull, are large, coalesced and non-uniform in size" as opposed to multiple myeloma that "produce smaller, circular and more consistently sized", and in their report the skull lesions size ranged from 8 x 8 mm to 98 x 85 mm. Some researchers (Greenspan & Remagen 1998; Pahade *et al*. 2008) suggest a range between 20 and 40 mm for osteolytic metastases. For multiple myeloma, Ortner & Putschard (1981) report sizes ranging from 3 to 10 mm in diameter, Strouhal and Kritscher (1990) suggest a range of 5 to 10 mm, and Aufderheide & Rodríguez-Martín (1998) report a range of 5 to 20 mm. In the current study, we observed non-uniform dimensions of lesions, with the skull presenting the highest variation from 8 mm to 30 mm, and in general, the lesions on this skeleton may be considered larger than those typical for MM. If the heterogeneity of size is considered a distinctive feature, than this argument favors the diagnosis of a metastatic disease rather than MM.

Considering the number of lesions, Rothschild *et al*. (1998) suggests that in MM the lesions are generally more numerous than in metastatic carcinoma. These authors also refer the common existence of a cortical shell due to the more extensive destruction of trabecular bone in metastatic carcinoma. This accentuated trabecular affection was visible on the skeleton 439. Other lesions that Rothschild *et al*. (1998) attribute exclusively to metastatic tumor are circular defects comprised of confluent superficial pits, which they report as absent in MM. In current study, the coalescent superficial pitting was observed on the parietal bone only.

Another event that is noteworthy on the long bones refers to areas of medullary destruction with endosteal scalloping occurring in MM (Greenspan & Remagen, 1998), been less frequent on MT (Resnick, 1996d). This feature was not observable in the present case.

In sum, if the differential diagnosis of both conditions would rely exclusively on the cranial lesions, it would have been highly unlikely that osteolytic metastasis and MM could be distinguished from one another because of the overlapping features between these two diseases. If we assume that the remaining lesions on the skeleton are correlated to a common etiologic factor then the presence of proliferative rib lesions, a pattern of bone formation and simultaneous destruction on the hip bone, and the sclerotic margin of the osteolytic lesion on the scapula, all testify to the presence of a disease with manifested reactive bone formation. Therefore, a diagnosis of metastatic tumour etiology is more strongly supported. But, the possibility of other condition also manifesting on the skeleton cannot be irrefutably ruled out.

It is commonly mentioned in the medical literature some correlations between the primary tumor and the pattern of skeletal metastases, opening the possibility for the identification of the primary site of the tumor thorough analysis of the skeletal metastases. However, the pattern of metastases presents a

considerable variation and the challenge of this identification in paleopathology, especially in the absence of auxiliary clinical diagnosis tools, can represent a high probability of misclassification. Even in clinical settings, as Rosenthal (1997:1602) states: "previous studies have reported limited success in identifying the primary tumor when a patient presents with skeletal metastasis of unknown origin. In general the primary tumor is identified in less than 50% of these patients, even when they are followed to autopsy". Therefore, we did not attempt to identify the primary malignant tumour that resulted in these metastases.

Despite the skeletal evidence of a neoplastic condition, the cause of death recorded for this individual was "heart lesion". This may have been the result of misdiagnosis or from the registration of the direct cause of death instead the underlying condition. Even today, post mortem histopathology on patients who are thought to have died from non-neoplastic conditions exhibit "a strikingly high prevalence of covert malignant cancers or premalignant carcinomas" (Greaves, 2008:277). Additionally, it should be noted that skull metastases can be often asymptomatic or only mild uncomfortable, and less often are lead to neurologic dysfunction. This could be the reason that they are, seldom clinically diagnosed (Stark *et al.*, 2003). According to Coleman (2001: 168) "[h]ypercalcaemia is probably the most common metabolic complication of malignant disease", if left untreated it can cause relatively minor "symptoms related to dysfunction of the gastrointestinal tract, kidneys and central nervous system" to more significant symptoms such as death "as the result of cardiac arrhythmias and acute renal failure".

The attempts to reach a conclusively diagnosis for the lesions observed on this skeleton, establishing a distinction between MT and MM, were not fully accomplished. We attempted to expose the limits and pitfalls of performing a paleopathological diagnosis on extensive osteolytic processes. This result is in accordance with both clinical and paleopathological literature. For example, Resnick (1996d) states that the differential diagnosis of MM and MT is very intricate, and Ortner (2003: 537) states that "in the skeleton these two types of cancer reflect a morphological gradient, making differential diagnosis impossible in some cases". The typology of neoplastic lesions can overlap considerably (Strouhal, 1991; Brothwell, 2008).

Final comments

The worldwide scarcity of paleopathological cases of malignant neoplasms, demonstrates the need for more extensive research on paleoncology through the systematic scrutiny on human osteological collections and amelioration of the diagnostic tools. The adult male individual number 439 from the Coimbra Identified Skeletal Collection represents a paleopathological testimony of a neoplastic condition that culminated in skeletal involvement.

Despite the detailed description and differential diagnosis performed both macroscopically and radiologically for this skeleton, it was not possible to reach a definitive diagnosis. The most important

limiting factor is the overlap between the characteristic features of neoplastic lesions, especially those provoked by multiple myeloma and osteolytic metastases, which we attempt to expose on this work. Thus, this study supports previous works that ague that the paleopathological distinction between multiple myeloma and metastatic conditions requires further investigation using comparative analysis of cases with established clinical diagnosis (Marks & Hamilton, 2007), with identified skeletal collections (Rothschild *et al*., 1997), or with auxiliary techniques such as immunological diagnosis (Cattaneo *et al.*, 1994). Meanwhile, it is of major relevance the screening of these diseases (regardless of underlying specific etiology), research diagnostic tools, and the accumulation of reports of these conditions in variable chronological and geographical contexts, in order to contribute to a better portray of the natural history of neoplasms.

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References

Altieri A, Chen B, Bermejo JL, Castro F, Hemminki K. 2006. Familial risks and temporal incidence trends of multiple myeloma. *European Journal of Cancer* **42**: 1661-1670.

Angtuaco EJ, Fassas AB, Walker R, Sethi R, Barlogie B. 2004. Multiple myeloma: Clinical review and diagnostic imaging. *Radiology* **231**: 11-23.

Arkun R. 2004. Parasitic and fungal disease of bones and joints. *Seminars in Musculoskeletal Radiology* **8**: 231-242.

Assis S, Codinha S. 2010 Metastatic carcinoma in a 14th–19th century skeleton from Constância (Portugal). *International Journal of Osteoarchaeology* **20**: 603-620.

Aufderheide AC, Rodríguez-Martín C. 1998. *The Cambridge Encyclopedia of Human Paleopathology*. Cambridge University Press: Cambridge.

Azouz EM, Saigal G, Rodriguez MM, Podda A. 2005. Langerhans' cell histiocytosis: Pathology, imaging and treatment of skeletal involvement. *Pediatric Radiology* **35**: 103-115.

Brickley M, McKinley JI. 2004. *Guidelines to the Standards for Recording Human Remains*. BABAO, IFA: Southampton, Whiteknights.

Brothwell D. 2008. Tumours and tumour-like processes. In *Advances in Human Palaeopathology*, Pinhasi R, Mays S (eds). Chichester: John Wiley; 253-284.

Buikstra JE, Ubelaker DH. 1994. *Standards for Data Collection from Human Skeletal Remains: Proceedings of a Seminar at the Field Museum of Natural History*. Arkansas Archeological Survey Research Series 44: Fayetteville, Arkansas.

Campanacci M. 1999. *Bone and Soft Tissue Tumors: Clinical Features, Imaging, Pathology and Treatment*. Piccin Nuova Libraria: Padova.

Capasso L. 2005. Antiquity of cancer. *International Journal of Cancer* **113**: 2-13.

Capasso L, Mariani-Costantini R. 1994. Paleopatologia dei tumori umani. *Medicina Nei Secoli Arte e Scienza* **6**: 1-52.

Cattaneo C, Gelsthorpe K, Phillips P, Waldron T, Booth JR, Sokol RJ. 1994. Immunological diagnosis of multiple myeloma in a medieval bone. *International Journal of Osteoarchaeology* **4**: 1-2.

Coleman RE. 2001. Metastatic bone disease: Clinical features, pathophysiology and treatment strategies. *Cancer Treatment Reviews* **27**: 165-176.

David AR, Zimmerman MR. 2010 Cancer: an old disease, a new disease or something in between? *Nature Reviews Cancer* **10**: 728-33.

Diyora B, Kumar R, Modgi R, Sharma A. 2009. Calvarial tuberculosis: A report of eleven patients. *Neurology India* **57**: 607-612.

Ferembach D, Schwidetzky I, Stloukal M. 1980. Recommendations for age and sex diagnosis of skeletons. Workshop of European anthropologists. *Journal of Human Evolution* **9**: 517-549.

Greaves M. 2008. Cancer: evolutionary origins of vulnerability. In *Evolution in Health and Disease*, Stearns SC, Koella JC (eds.). Oxford University Press: Oxford; 277-288.

Greenspan A, Remagen W. 1998. *Differential Diagnosis of Tumors and Tumor-like Lesions of Bone and Joints*. Lippincott-Raven: Philadelphia.

Hackett CJ. 1976. *Diagnostic Criteria of Syphilis, Yaws, and Treponarid (Treponematoses) and of Some Other Diseases in Dry Bones*. Springer-Verlag: Berlin.

Halperin EC. 2004. Paleo-Oncology: The role of ancient remains in the study of cancer. *Perspectives in Biology and Medicine* **47**: 1-14.

Hershkovitz I, Rothschild B, Dutour O, Greenwald C. 1998. Clues to recognition of fungal origin of lytics skeletal lesions. *American Journal of Physical Anthropology* **106**: 47-60.

Liotta LA, Kohn EC. 2003. Invasion and metastasis. In *Holland-Frei Cancer Medicine 6*, Kufe DW, Pollock RE, Weichselbaum RR, Bast RC, Gansler TS, Holland JF, Frei E (eds.). BC Decker Inc: Hamilton, Ontario.

Lloret I, Server A, Taksdal I. 2009. Calvarial lesions: A radiological approach to diagnosis. *Acta Radiologica* **50**: 531-542.

Luna LH, Aranda CM, Bosio LA, Beron MA. 2008. A case of multiple metastasis in Late Holocene hunter-gatherers from the Argentine Pampean Region. *International Journal of Osteoarchaeology* **18**: 492-506.

Madewell JE, Ragsdale BD, Sweet DE. 1981. Radiologic and pathologic analysis of solitary bone lesions. Part I: internal margins. *Radiologic Clinics of North America* **19**: 715-748.

Mann RW, Murphy SP. 1990. *Regional Atlas of Bone Disease: A Guide to Pathologic and Normal Variation in the Human Skeleton*. Charles C Thomas: Springfield- Illinois.

Marks MK, Hamilton MD. 2007. Metastatic carcinoma: palaeopathology and differential diagnosis. *International Journal of Osteoarchaeology* **17**: 217-234.

Marques AC, Matos V. 2002. *Breast cancer and its palaeopathology. Four case studies from a Portuguese Human Skeletal Identified Collection (Lisbon, 20th century).* Program-Abstracts from the 14th European Meeting of the Paleopathology Association, 28-31 August 2002, (Coimbra, Portugal). Departamento de Antropologia, University of Coimbra: Coimbra; 97.

Matos V, Santos AL. 2006. On the trail of pulmonary tuberculosis based on rib lesions: Results from the human identified skeletal collection from the Museu Bocage (Lisbon, Portugal). *American Journal of Physical Anthropology* **130**: 190-200.

Meng CM, Wu YK. 1942. Tuberculosis of the flat bones of the vault of the skull: A study of forty cases. *The Journal of Bone and Joint Surgery* **24**: 341-353.

Miller E. 2010. Multiple myeloma past and present. *Paper presented at the 37th Annual Meeting of the Paleopathology Association.* Columbus, Albuquerque (abstract).

Miller TT. 2008. Bone tumors and tumorlike conditions: Analysis with conventional radiography. *Radiology* **246**: 662-674.

Morse D, Dailey RC, Bunn J. 1974. Prehistoric multiple myeloma. *Bulletin of the New York Academy of Medicine* **50**: 447-458.

Ortner DJ. 2003. *Identification of Pathological Conditions in Human Skeletal Remains*. Academic Press: Amsterdam.

Ortner D. 2008. Differential diagnosis of skeletal lesions in infectious disease. In *Advances in Human Palaeopathology*, Pinhasi R, Mays S. (eds). John Wiley: Chichester; 191-251.

Ortner D, Putschar W. 1981. *Identification of Pathological Conditions in Human Skeletal Remains*. Smithsonian Contributions to Anthropology, 28. Smithsonian Institution Press: Washington D.C.

Pahade J, Sekhar A, Shetty SK. 2008. Imaging of malignant skeletal tumors. In *Imaging in Oncology*, Blake MA, Kalra MK (eds.). Springer: New York; 367-422.

Patankar T, Varma R, Krishnan A, Prasad S, Desai K, Castillo M. 2000. Radiographic findings in tuberculosis of the calvarium. *Neuroradiology* **42**: 518-21.

Powell ML, Cook D. 2005. *The Myth of Syphilis: The Natural History of Treponematosis in North America*. University Press of Florida: Gainesville.

Raje N, Hideshima T, Anderson KC. 2003. Plasma cell tumors - multiple myeloma. In *Holland-Frei Cancer Medicine 6*, Kufe DW, Pollock RE, Weichselbaum RR, Bast RC, Gansler TS, Holland JF, Frei E (eds.). BC Decker Inc: Hamilton, Ontario; 2219-2244.

Raut AA, Nagar AM, Muzumdar D, Chawla AJ, Narlawar RS, Fattepurkar S, Bhatgadde VL. 2004. Imaging features of calvarial tuberculosis: a study of 42 cases. *American Journal of Neuroradiology* **25**: 409-414.

Resnick D. 1996a. Tumors and tumor-like diseases: radiographic principles. In *Bone and Joint Imaging*, Resnick D (ed.). W.B. Saunders Company: Philadelphia; 979-990.

Resnick D. 1996b. Skeletal metastases. In *Bone and Joint Imaging*, Resnick D (ed.). W.B. Saunders Company: Philadelphia; 1076-1091.

Resnick D. 1996c. Lipidoses, histiocytosis and hyperlipoproteinemias. In *Bone and Joint Imaging*, Resnick D (ed.). W.B. Saunders Company: Philadelphia; 607-624.

Resnick D. 1996d. Plasma cell dyscrasias and dysgammaglobulinemias. In *Bone and Joint Imaging*, Resnick D (ed.). W.B. Saunders Company: Philadelphia; 595-606.

Resnick D, Haghighi P. 1996. Myeloproliferative disorders. In *Bone and Joint Imaging*, Resnick D (ed.). W.B. Saunders Company: Philadelphia; 625-638.

Ricci R, Lama R, Tota G, Capelli A, Capasso L. 1995. Some considerations about the incidence of neoplasm in the human history. *Journal of Paleopathology* **7**: 5-11.

Roberts CA, Buikstra JE. 2003. *The Bioarchaeology of Tuberculosis: A Global View on a Reemerging* Disease. University Press of Florida: Gainesville.

Rocha MA. 1995. Les collections ostéologiques humaines identifiées du Musée Anthropologique de L' Université de Coimbra. *Antropologia Portuguesa* **13**: 7-38.

Rogers LF. 1998. Bone tumors and related condition. In *Paul and Juhl's Essentials of Radiologic Imaging*, Juhl JH, Crummy AB, Kuhlman JE (eds.). Lippincott-Raven: Philadelphia; 140-141.

Roodman GD. 2010. Pathogenesis of myeloma bone disease. *Journal of Cellular Biochemistry* **109**: 283-291.

Rosenthal DI. 1997. Radiologic diagnosis of bone metastases. *Cancer* **80**: 1595-1607.

Rothschild BM, Hershkovitz I, Dutour O, Latimer B, Rothschild C, Jellema L. 1997. Recognition of leukemia in skeletal remains: Report and comparison of two cases. *American Journal of Physical Anthropology* **102**: 481-496.

Rothschild BM, Hershkovitz I, Dutour O. 1998. Clues potentially distinguishing lytic lesions of multiple myeloma from those of metastatic carcinoma. *American Journal of Physical Anthropology* **105**: 241-250.

Santos AL, Cunha E. 2001. A severe myeloma which was not recorded as the cause of death of a male individual. In *Papers presented at the 28th Annual Meeting of the Paleopathology Association. Kansas City (Missouri)*, Powell ML (ed.). (abstract).

Schillaci MA. 1999. A case of coccidioidomycosis from the prehistoric southestern United States. *Journal of Paleopathology* **11**: 41-52.

Stark A, Eichmann T, Mehdorn H. 2003. Skull metastases: Clinical features, differential diagnosis, and review of the literature. *Surgical Neurology* **60**: 219 -226.

Strouhal E. 1991. Myeloma multiplex versus osteolytic metastatic carcinoma: Differential diagnosis in dry bones. *International Journal of Osteoarchaeology* **1**: 219-224.

Strouhal E. 2001. Malignant tumours in past populations in middle Europe. In *Proceedings of the XIIIth European Meeting of the Paleopathology Association,* Verghetta M, Capasso L. (eds.). Edigrafital S.P.A.: Chietti, Italy; 265-272.

Strouhal E, Kritscher H. 1990. Neolithic case of multiple myeloma from Mauer (Vienna, Austria). *Anthropologie* **28**: 79–87.

Thillaud PL. 2006. Paléopathologie du cancer, continuité ou rupture? *Bulletin du Cancer* **93**: 767-773.

Van de Casteele M, Verhoef GE, Demuynck H, Zachee P, Boogaerts MA. 1994. Hypercalcemia, monoclonal protein, and osteolytic bone lesions in chronic lymphocytic leukemia. *Annals of Hematology* **69**: 79-80.

Waldron T. 1987. Lytic lesions in a skull: A problem in diagnosis. *Journal of Paleopathology* **1**: 5-14.

Waldron T. 1996. What was the prevalence of malignant disease in the past? *International Journal of Osteoarchaeology* **6**: 463-470.

Waldron T. 2009. *Palaeopathology*. Cambridge University Press: Cambridge.

Wasterlain SN, Ascenso BF, Silva AM. 2010 Skeletal metastatic carcinoma: a case from 15th–20th century,Coimbra, Portugal. *International Journal of Osteoarchaeology* **21**: 336-346.

Weiss L. 2000. Observations on the antiquity of cancer and metastasis. *Cancer and Metastasis Reviews* **19**: 193-204.

Winterbottom AP, Shaw AS. 2009. Imaging patients with myeloma. *Clinical Radiology* **64**: 1-11.

Zimmerman M, Kelley M. 1982. *Atlas of Human Paleopathology*. Praeger: New York.

FIGURES

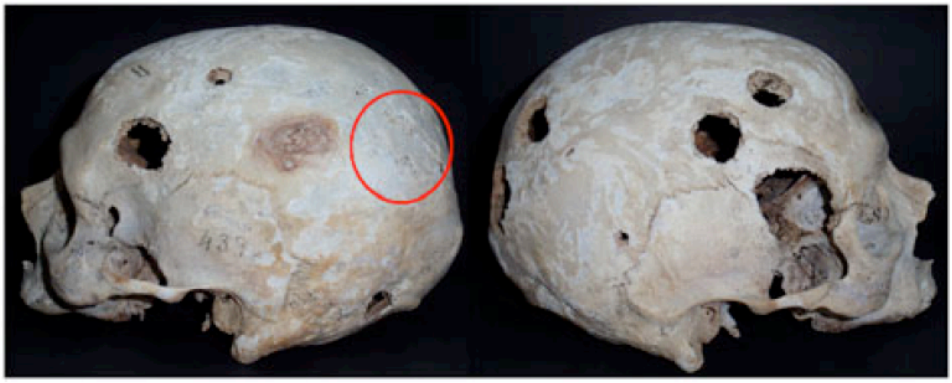

Figure 1. Lateral views of the skull with the osteolytic perforating lesions asymmetrically distributed. Also visible the area of coalescent porosity in the
left parietal (encircled).

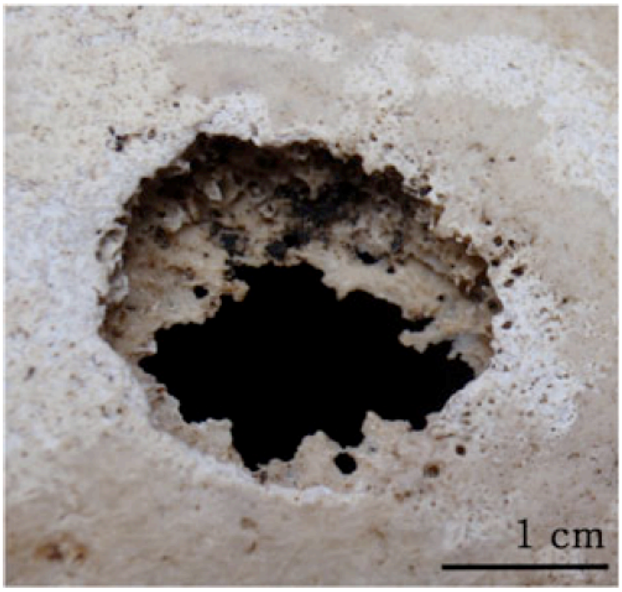

Figure 2. Close-up of the frontal osteolytic lesion showing the indentationof the margins, noticeable effaced trabeculae, and pitting bordering the lesion.

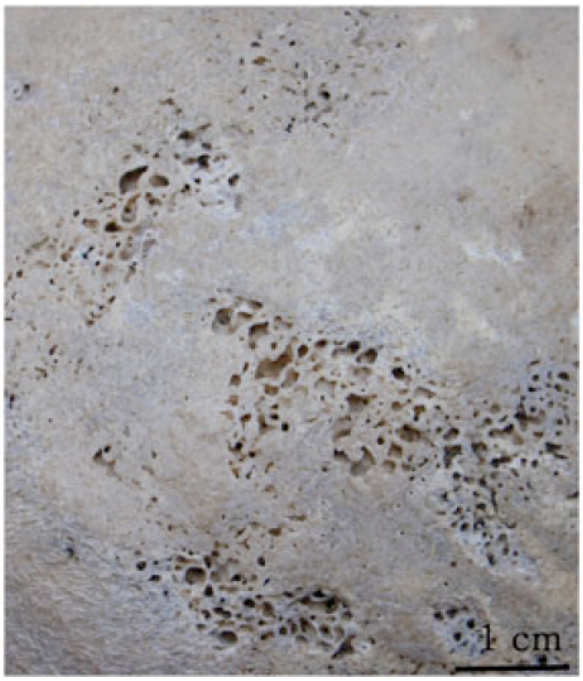

Figure 3. Detail of the cortical porosity on the left parietal.

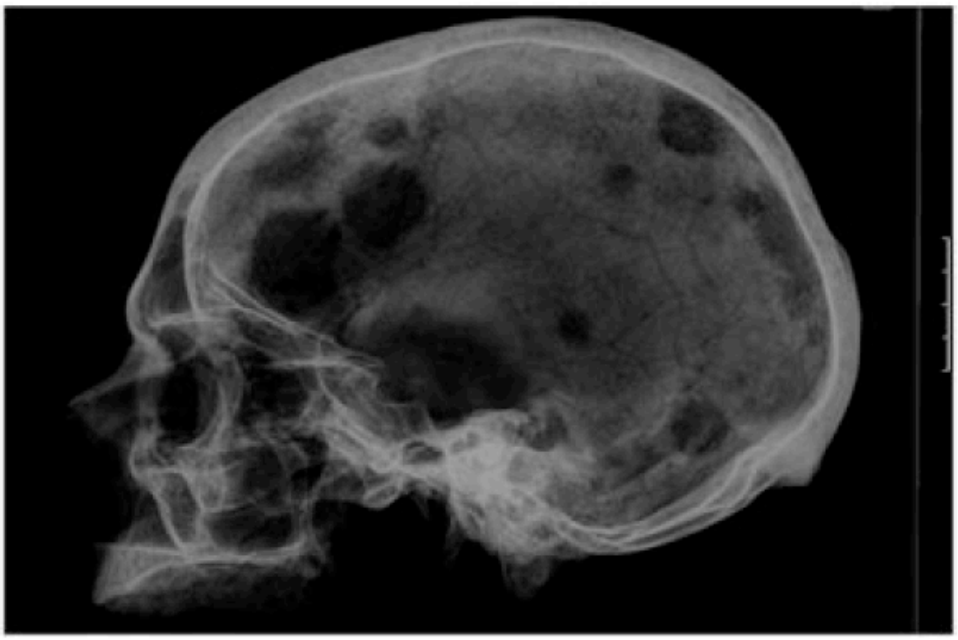

Figure 4. Radiography of the skull on lateral view, showing the osteolytic lesions [kV: 73.00; mAs: 1; ms: 2].

Figure 5. Sixth right rib with new bone formation on the posterior surface of the shaft, starting near the angle and extending through the diaphysis.

Figure 6. Posterior view of the right scapula, showing diffuse osteolytic activity located on the medial and upper region.

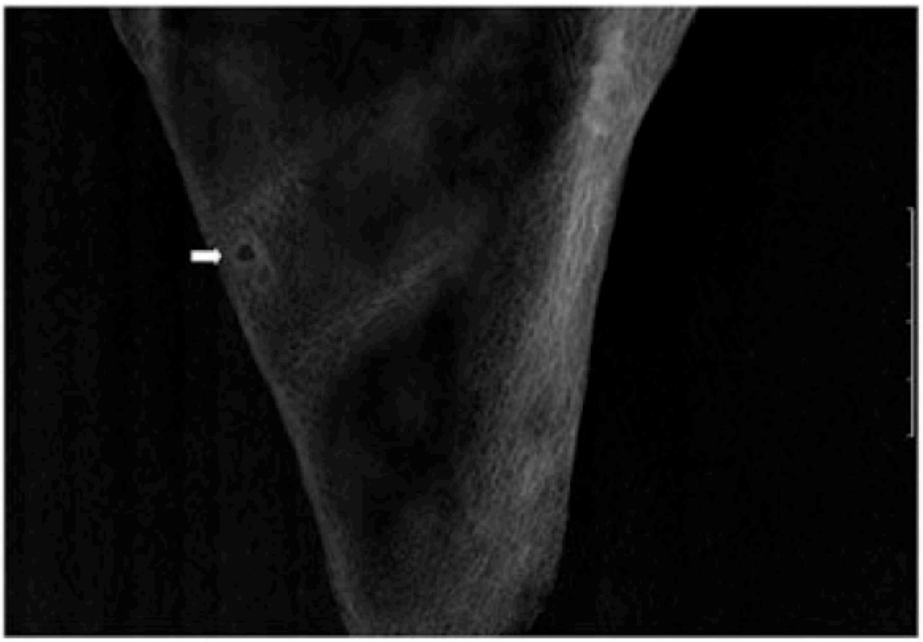

Figure 7. Left scapular body presents a round lesion (arrow) on the medial border, with a well-defined margin and with a clear sclerotic rim [kV: 73.00; mAs: 1; msec: 2].

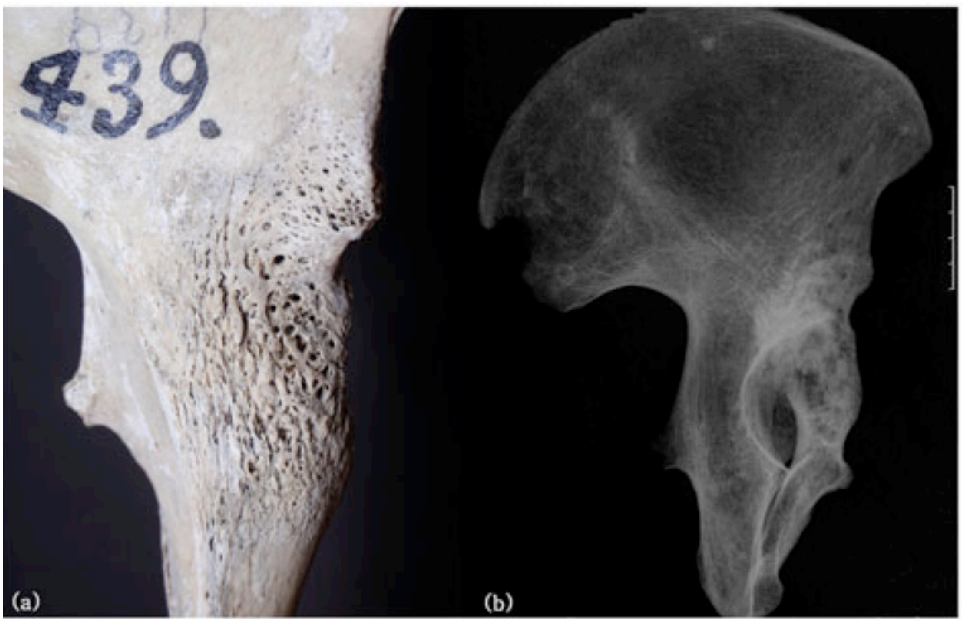

Figure 8. Left hip bone. (a) Anterior view with new bone proliferation and macroporosity located below the anterior inferior iliac spine. (b) Radiological

image of the corresponding area with signs of increased radiopacity with concomitant bone destruction [kV: 76.00; mAs: 1;ms: 2].

Table 1. General typology of lesions, topography and biodemographic profiles of the reported case (sk. Nr. 439), and in multiple myeloma and metastatic tumour.

FEATURES	SK. 439		MM	MT
Age	71		Middle aged - elderly (50-70)	Middle aged - elderly (45-90)
Sex prevalence	M		F = M or M > F	According to the primary tumor
Lesions				
Topography	• Multifocal • Skull, scapulae, ribs, pelvis		• Multifocal • Spine, skull, pelvis, ribs; humeri; femora; mandible; shoulder and elbow	• Multifocal • Spine, skull, pelvis, epiphysis of long bones (femur and humerus)
Symmetry	• Asymmetric/Bilateral		• Symmetric	• Asymmetric
Typologyy				
Type	**Purely *osteolytic*** skull, scapulae; right innominate ⬇	***Mix*** Left hip bone ***Proliferative*** 6th and 7th ribs	Purely ***osteolytic*** ⬇	Osteoblastic, ***osteolytic*** or mix ⬇
Zone of transition (on radiography)	• Narrow to moderate		• Narrow	• Narrow to wide
Margins	*Skull and innominate*: • Delimited, regular • No sclerosis *Scapulae*: • Well delimited; sharply defined, regular • With sclerosis • Poorly delimited		• Punched-out lesions • Well circumscribed • Sharp edges • No sclerosis	• Well or poorly circumscribe • Sharp or ill defined edges • Sclerosis can appear
Shape	• Circular		• Circular	• Variable
Contour	• Indentation		• Regular	• Variable
Size and number	• Multiple on bone (maximum 9) • Variable size *[8 to 38 mm]*		• Multiple on bone • Uniform size • Small size	• Multiple on bone • Varying size • Larger size

MM - Multiple myeloma; MT - Metastases

General characteristics educed from the clinical and paleopathological literature: Resnick (1996a,b,d), Aufderheide & Rodríguez-Martín (1998), Greenspan & Remagen (1998), Rogers (1998), Campanacci (1999), Raje et al. (2003), Ortner (2003), Marks & Hamilton (2007), Lloret *et al.* (2009).