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Case Study
Forensic Anthropology

Differential diagnosis of metastatic bone disease: A case study from the CEAF Identified Skeletal Collection of the University of Pernambuco, Brazil

Diagnóstico diferencial da doença óssea metastática: um estudo de caso da Coleção Esqueleto Identificado do CEAF da Universidade de Pernambuco, Brasil

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ABSTRACT

This study aims to discuss the occurrence of pathological changes found in a skeleton from the Center for Studies in Forensic Anthropology (CEAF) Identified Skeletal Collection, Faculty of Odontology, University of Pernambuco (FOP/UPE), Brazil. The skeleton of a 47-year-old male that died in 2014 was macroscopically examined, and the differential diagnosis was performed based on clinical and paleopathological criteria. Lesions that were predominantly osteoclastic were observed in a multifocal pattern, mainly on the skull (29.6% of the total of lesions observed), pelvic bones (22.2%), and vertebrae (25.9%). The lesions morphology consists of elliptical osteolytic foci and areas of coalescent porosity, with lesional diameters ranging from 2.9 mm to 40.1 mm. Considering the individual's biological profile, the distribution pattern, the shape, size, margin, and appearance of the lesions, we consider that metastatic bone disease is the most likely etiology. Furthermore, an epithelial origin of this neoplasm seems more plausible than a hematological malignancy. However, this case study illustrates the difficulty of distinguishing between bone lesions resulting from a plasma cell myeloma or a carcinoma in the presence of predominantly osteolytic lesions. Since the distinction of these entities has the potential to be relevant for identification in Forensic Anthropology, we suggest that further research on the skeletal manifestation of these entities is needed.

Keywords: Neoplasms; Bone Metastases; Multiple myeloma; Metastatic carcinoma; Cancer.

RESUMO

Este estudo visa a discutir a ocorrência de alterações patológicas encontradas num esqueleto da Coleção de Esqueletos Identificados do Centro de Estudos em Antropologia Forense (CEAF), Faculdade de Odontologia, Universidade de Pernambuco (FOP/UPE), Brasil. O esqueleto de um homem de 47 anos de idade que morreu em 2014 foi examinado macroscopicamente e o diagnóstico diferencial foi realizado com base em critérios clínicos e paleopatológicos. Foram observadas lesões predominantemente osteoclásticas num padrão multifocal, principalmente no crânio (29,6% do total de lesões observadas), ossos pélvicos (22,2%), e vértebras (25,9%). A morfologia das lesões consiste em focos osteolíticos elípticos e áreas de porosidade coalescente, com diâmetros lesionais que variam entre 2,9 mm e 40,1 mm. Considerando o perfil biológico do indivíduo, o padrão de distribuição, a forma, tamanho, margem e aparência das lesões, admitiu-se que a doença óssea metastática é a etiologia mais provável. Além disso, uma origem epitelial desta neoplasia parece mais plausível do que uma malignidade hematológica. Contudo, este estudo de caso ilustra a

dificuldade de distinguir entre lesões ósseas resultantes de um mieloma de células plasmáticas ou um carcinoma na presença de lesões predominantemente osteolíticas. Uma vez que a distinção destas entidades tem o potencial de ser relevante para a identificação em Antropologia Forense, sugerimos que são necessárias mais investigações sobre a manifestação esquelética dessas entidades.

Descritores: Neoplasmas; Metástases ósseas; Mieloma múltiplo; Carcinoma mestastático; Câncer.

Introduction

Neoplasms result from the abnormal growth of cells that acquire particular genomic and/or epigenomic traits. Malignant neoplasms tend to invade adjacent tissues, and cells migrate to other body regions, forming satellite neoplasms (metastases).[1,2] The occurrence of metastatic bone diseases (i.e., metastatic spread to the skeletal system through the bloodstream, lymphatic system, or direct extension) is relatively common due to the intrinsic properties of the bone microenvironment.[3,4] Metastatic bone disease (MBD) exhibits three common patterns: predominantly osteolytic lesions, due to exacerbated osteoclastic activity, as seen for example in multiple myeloma; predominantly osteoblastic lesions, often seen in prostate cancers; and a mixed pattern, with concomitant osteoblastic and osteolytic lesions, which can occur, for example, in bone metastases of breast or bladder cancers.[3,4,5] In most cases, the effect of MBD on individuals is associated with severe pain, morbidity, pathological fractures, hypercalcemia, and nervous compressions.[6]

Even if virtually all cancers have the potential to develop MBD, some cancers exhibit higher metastatic potential (e.g., prostate, breast, or thyroid cancers) than others (e.g., colorectal, ovary, or stomach). Furthermore, there is also a potential relationship between an individual's survival time and the likelihood of developing MBD. Slowly progressing and less aggressive cancer types will induce a greater chance of metastatic lesions in bone tissue.[7]

The detection of evidence of malignant neoplasms based on the analysis of human skeletal remains is always challenging due to constraints associated with skeletal preservation, difficulties in the diagnosis, lack of systematic

radiological survey, and other sources of bias. However, the record of neoplasms in skeletal remains from past populations is far to be rare, with more nearly three hundred cases of malignant neoplasms published so far in the paleopathological literature.[8] These paleopathological records can function as important reference studies to forensic anthropology since similar diagnostic criteria to detect neoplastic diseases in skeletonized remains can be applied in both subfields of Biological Anthropology.

Furthermore, studies in reference collections with biodemographic data can also be useful for comparative analysis and relevant for ulterior identification of diseases in unidentified skeletons.[9,10]

Based on macroscopic analyses of a human skeleton from a contemporary Brazilian Identified Skeletal Collection of the University of Pernambuco (CEAF/FOP/UPE, Brazil), this paper aims to discuss the possible etiology of multifocal osteolytic lesions observed in a middle-aged male individual that died in 2014. The morphology of the lesions and pattern of distribution suggest metastatic bone disease (MBD). The case herein present shows the very characteristic biodemographic and lesional patterns of MBD and thus can serve as a comparative case study in forensic anthropology.

Thus, we intend to contribute to the knowledge about skeletal neoplasms' characteristics. Such information is relevant to the extent that it can provide subsidies for establishing the circumstances of death and as a paramount criterion to achieve positive identification.[11]

Material and Methods

This research was carried out at the Center for Studies in Forensic Anthropology (CEAF), Faculty of Odontology, University of Pernambuco (FOP/UPE), located in the city of Recife, State of Pernambuco, Northeast Brazil, and was approved by the Research Ethics Committee (Opinion No. 2284094; CAAE: 72907917.8.0000.5207). All procedures followed the guidelines and rules that regulate research involving human beings in the country.

The skeleton examined (nr. 152) integrates the CEAF Identified Skeletal Collection, University of Pernambuco (UPE), Brazil. The collection consists of

identified human skeletons of both sexes, administratively exhumed after two years of burial[12], from the Santo Amaro Cemetery, located in the central region of the city of Recife. The 427 skeletons are aged 0 to 109 years, buried between 2011 and 2016, and exhumed between 2013 and 2018. Individual data on sex and age at death are available, and there is information on the cause of death for 188 skeletons.[13]

The skeleton under analysis (nr. 152) is a male, aged 47 at death that died in 2014 and was exhumed in 2016. However, this individual does not have documentary information regarding the cause of death. As the contact information of possible relatives was not available, it was impossible to access medical records, as this would require authorization from the decedent's family.

In general, the skeleton examined has a good state of preservation, but it is not complete. Some facial bones such as the lacrimal, vomer, left maxilla, nasals, left malar, as well as the hyoid, most of the ribs, the right clavicle, coccyx, right ischium, both pubis, all cervical vertebrae, a few thoracic vertebrae, right femur, left fibula, and the left patella are absent.

It was impossible to perform radiological or histological exams due to the inexistence of the necessary equipment in our Lab. The macroscopic examination was conducted with the careful inspection performed on each bone. The structural changes identified were measured using a digital caliper, photographed, and described considering the affected anatomical sites, the number, shape, and margins of the lesions, as well as the morphological characteristics of the bone changes, following standard paleopathological protocols described in Marques (2019).[4]

Results

Twenty-seven bone lesions were observed in different anatomical sites, showing variable diameters (Table 1), with the following overall characteristics:

• Bone lesions were predominantly osteolytic;

• The areas of osteolysis mainly were characterized by sharp and defined focal lesional areas, with a narrow zone of transition, compatible with "geographic" (Type I) margins [4]

• Irregular contour of the margins; and

• The size of the lesions was variable.

Bone lesions were found in several regions of the skull, such as the right and the left parietal bones (Fig. 1A, 1B, and 1C), the right orbital region of the frontal bone (Fig. 2A, 2B, 2C, and 2D), the right and lower lateral portion of the occipital (Fig. 3A and 3B), the right mastoid process (Fig. 4), the basilar region of the occipital bone, and the right greater wing of the sphenoid, as well as the right mandibular angle (Fig. 5). With the aid of a magnifying glass, one lesion involving only the inner table of the skull in the right frontal region was also visualized. Regarding the finding shown in Fig. 3, it was decided not to measure it and, consequently, not to classify it as a lesion due to the coloring of its edges, which was probably related to post mortem changes.

The lesions in the parietal bones present scalloped contour and a narrow area of transition (Fig. 1A and 1B). The lesions in Figures 1A and 1B show involvement of inner and outer tables of the skull and diploë. The close-up in figure 1C shows an area of intense porosity associated with an osteolytic process. The lesion present in the right orbital edge and the right mandibular angle have osteolytic characteristics, with regression of the trabeculae(Fig. 2A, 2B, 2C, and 2D).
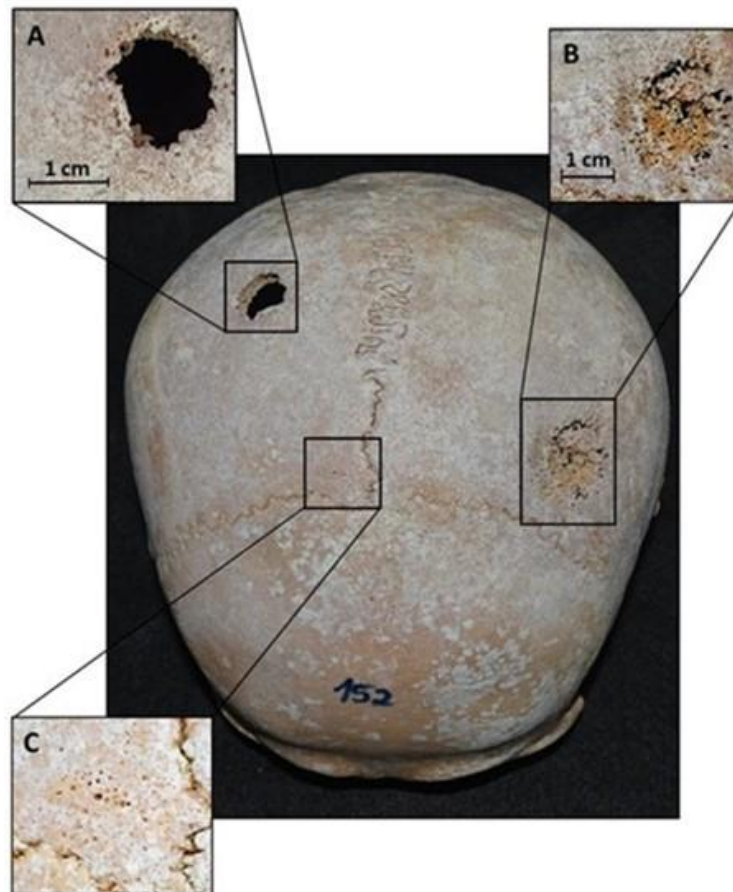
Fig.1. Neurocranial lesions (superior view) of the skeleton. A: Close-up of the lesion on the right parietal. B: Close-up of the lesion on the left parietal. C: Close-up of an initial osteolytic lesion.
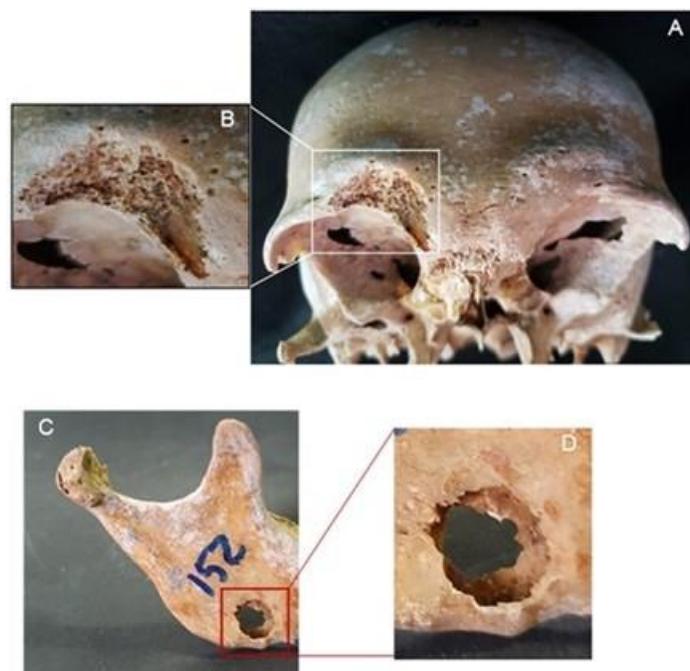

Fig.2. Cranial and facial bones (anterior view). A and B: An osteolytic lesion on the right orbital edge. C and D: Osteolytic lesion affecting the right mandibular angle.
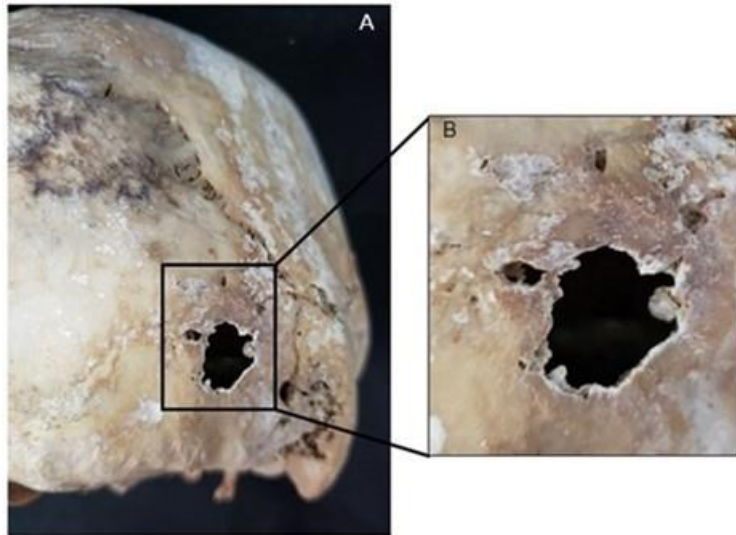
Fig. 3. Occipital bone. A: Posterior view. B: The close-up highlights the white margins, which are usually associated with post mortem changes.

There is a lesion in the posterior portion of the right mastoid process, with an irregular shape and notched edges, which involves the external bone surface and the underlying trabeculae (Fig. 4A, 4B, and 4C). The sphenoid's larger wing contains two irregularly shaped lesions (Fig. 5A and 5B). The occipital basilar process shows a bone lesion of irregular shape and edges, affecting only the outer bone plate measuring 6.1 x 10.8 mm (Fig. 5C).
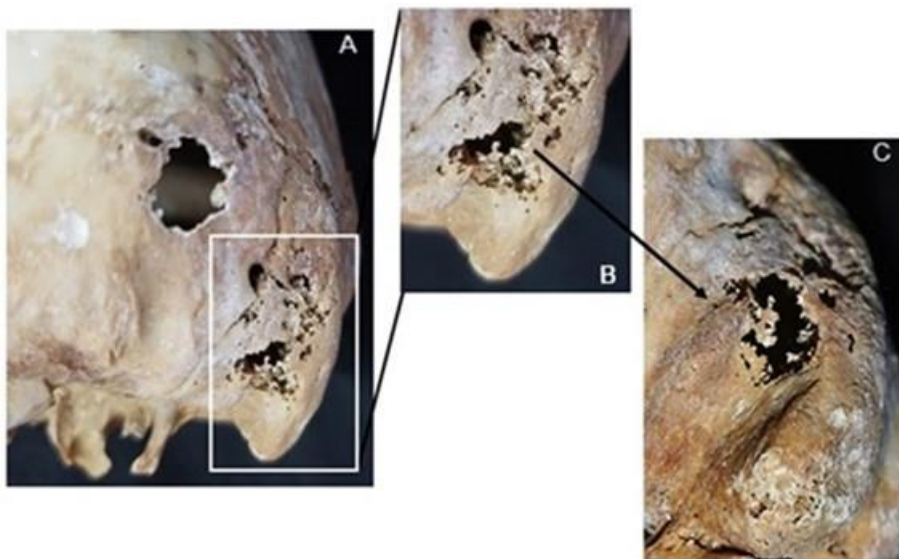

Fig. 4. A: Osteolytic lesion on the right mastoid process (posterior view). B and C: Close-up of the osteolytic lesion.

Fig. 5. Lesions A and B on the right greater wing of the sphenoid (inferior view). Lesion C: osteolytic lesion at the basilar portion of the occipital bone.

Only the sternum showed bone damage in the thoracic region, located in the proximal third of its body (Fig. 6), measuring 9.3 mm in sagittal diameter, 9.0 mm in transverse diameter.

The seventh, eleventh, and twelfth thoracic vertebrae, as well as the second, third, and fifth lumbar vertebrae, presented osteolytic lesions that varied in size and were located in the vertebral bodies (Table 1, Fig. 7A, 7B, 7C, and Fig. 8A and B). L5 vertebra presented two bone lesions, being one on the body's superior surface and the other on the left side of the vertebral body.
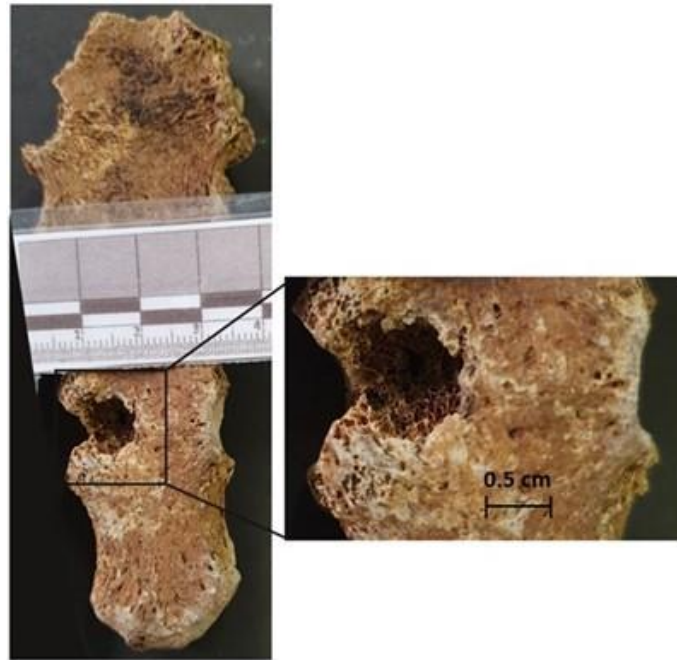
Fig. 6. Osteolytic metastasis on the body of the sternum (anterior view).
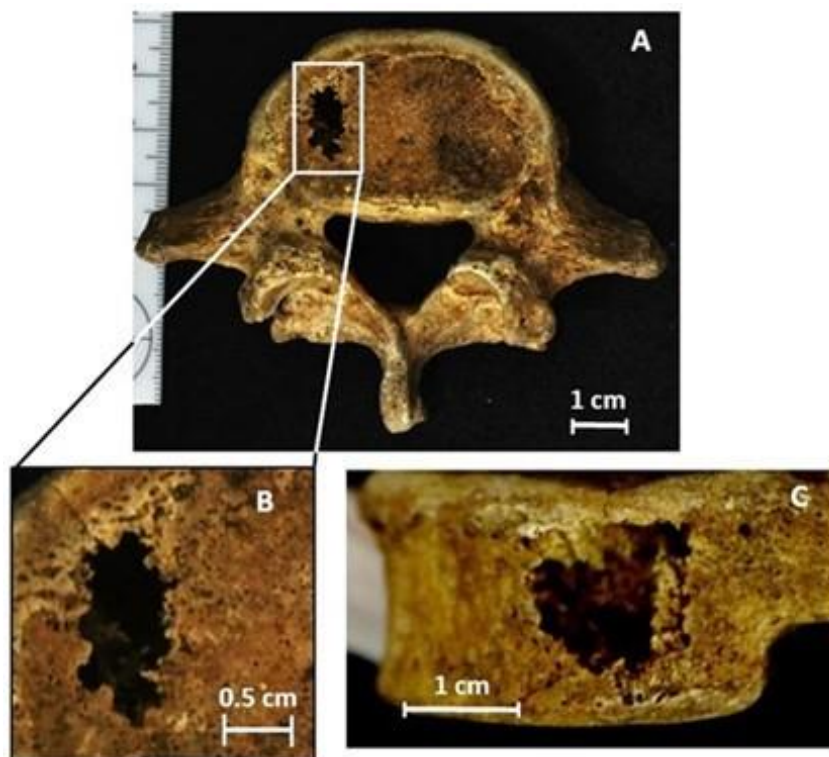

Fig. 7. A: Superior view of the 4th lumbar vertebrae. B- Close-up of the osteolytic lesion measuring 14.1 x 12.8 mm. C- Osteolytic lesion on the lateral of the vertebral body measuring 13.8 x 10.0mm. Note the scalloped borders on both lesions.

Fig. 8. A- Superior view of the 3rd lumbar vertebrae. Osteolytic lesion measuring 10.8 x 9.2 mm showing scalloped borders. B- Superior view of the 5th lumbar vertebrae. Osteolytic lesion measuring 14.0 x 15.0 mm.

There were only five complete ribs available for examination in a good state of preservation. The sixth left rib presented an osteolytic lesion in its middle third (Fig.9).

Perforating bone lesions were also seen in the right and left iliac bones (Fig.10). The right hip bone was affected close to the region of the anteroinferior iliac spine (Fig.11).

Fig. 9. osteolytic lesion in its middle third of the sixth left rib (anterior view).
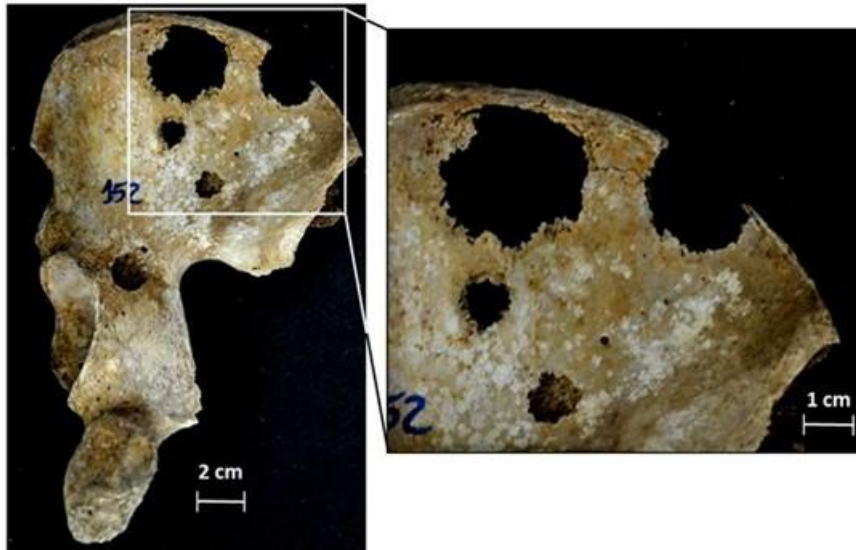
Fig. 10. Left ilium shows four osteolytic lesions, the largest measuring 31.0 mm x 33.0 mm, and the smallest measuring 11.3 x 11.9mm.

Fig. 11. Osteolytic lesion on the right ilium with 8.9 x 6.7 mm.

Regarding the long bones, it was possible to observe lesions on both humeri at different locations. A bone lesion was located on the proximal third of the diaphysis of the right humerus (Fig. 12A), presenting scalloped borders with maximum dimensions of 14.6 x 6.4 mm (Figure12B). The osteolytic lesion was circular on the distal epiphysis on the left humerus, in its anterior portion. The affected region included part of the trochlea and the medial epicondyle, measuring 25.0 x 23.4mm (Figure 12C). Only the second left metacarpal showed a lesion among the hand bones, located in the proximal third, measuring 2,1 x 4,0 mm (Figure 13).

The left femur showed bone changes in its distal epiphysis; however, as it is also similar to taphonomic changes, we decided not to include it in the list of purely metastatic lesions.

Fig. 12. A- Anterior view of the proximal right humerus showing the osteolytic metastasis location with scalloped margins. B- Close up of this lesion. C- Osteolytic metastasis on the distal left humeral epiphysis. Note the thickened trabecular bone.

Fig.13. Osteolytic lesion on the proximal left metacarpal epiphysis.

Discussion

Considering that, in the present study, the analysis of bone structures occurred exclusively through macroscopic visual inspection, the absence of radiographic images may imply a sub-estimation on the identification of the minimum number of bone metastases present on the bone surfaces.[14] However, using visual examination only, Marques et al.[7] classified malignant neoplastic lesions unequivocally in about 17.6% of their sample of skeletons with a malignant neoplasm as the cause of death, which in summary, shows a diagnostic method that, despite the low sensitivity, can be effective in diagnosing neoplasms.

Aspects such as the distribution pattern, severity, and extent of bone lesions made it possible to link such changes to characteristics pointed out in the literature referring to malignant neoplastic diseases.[4,7,10] Thus, the information obtained about the lesion's morphology and its distribution in the skeleton may provide the basis for identifying the nature of pathological processes in unidentified human skeletal remains through a comparative method between clinically diagnosed cases and paleopathological diagnostic criteria.[7] We argue that the paleopathological record and knowledge can be of use in the field of

forensic anthropology in what concerns the process of disease identification based on skeletonized remains.[7]

There are also taphonomic factors to consider, capable of causing structural damage simulating a pathological condition. Among these, we can mention the action of insects, cadaveric fauna, salt precipitation, the action of algae, bacteria, and fungi. The color of the lesions is similar in all affected areas, except for the alteration found in the posterior region of the occipital (Fig. 3), which justifies its exclusion of the classification as a lesion.[15] However, we could not completely rule out its possible lesional origin with increased size caused by post mortem changes.

Concerning the observed lesions, it is a fact that such changes may result from several nosological entities, such as infectious or metabolic diseases, which can modulate the action of bone cells.[4,16] However, the multifocal pattern and the predominantly osteolytic activity are compatible with a neoplastic origin for the lesions observed in skeleton nr 152.

Among the neoplastic nosologic category, the differential diagnosis falls mostly in the distinction between bone metastasis from a carcinoma and plasma cell myeloma (PCM), which overlap in the way they can manifest in the skeletal system, and their characteristics and, therefore, may present similar bone destruction, distribution pattern, and biodemographic profile; thus, the distinction is challenging.[10]

Some studies on reference skeletal collections can be enunciated to illustrate the potential similarity between these entities. Gomez et al.[17] selected two skeletons from the Identified Osteological Collection of the University of Milan, diagnosed in life with multiple myeloma. All lesions observed were purely osteolytic, with "perforated" margins and a shape similar to soap bubbles, ranging from 1.58 to 4.32 mm in diameter. The lesions were spread over the skeleton, especially in hematogenous areas. In part, the results are compatible with the skeleton of this study concerning the predominance of osteolytic reactions. However, the regularity of the size of lesions expected in plasma cell myeloma is inconsistent with those observed in our study.

Rothschild, Hershkovitz, Dutour[18] analyzed a male skeleton, aged 50 years old, diagnosed with PCM while living from the Terry Collection. Twenty-four well-defined spherical lesions were found on the skull, with relatively uniform

diameters (0.7 mm) and without evidence of bone formation. More than 100 lesions were found in the post-cranial skeleton, ranging from 1.5 to 12 mm in diameter, presenting the same characteristics as those of the cranial regions, predominantly affecting areas of high vascularization. As with the study of Gomez et al.[17], the regularity in size of the lesions, the spheroid shape, and the absence of new bone formation are traits that are often associated with PCM. Rothschild et al.[18] also studied macroscopically 140 skeletons diagnosed with bone metastases. Among these, osteolytic lesions were found in six cases. The lesions ranged from 1 to 45 mm, with irregular and ellipsoid geographic shapes. The bone defects had a rough surface on the skull due to the confluence of small lesions. Marques et al.[9] also refer to the irregularity in size of the osteolytic lesions in cases of metastatic bone disease in a study of 131 skeletons with cancer as the cause of death from the Lisbon and Coimbra identified collections.

Despite the similarity between the skeletal manifestation of PCM and bone metastases from a carcinoma (CM), a revision of the literature shows that some authors suggested criteria for their differentiation. Ortner[5] pointed out that the PCM lesions are more proportional, varying from small to medium, whereas in CM the lesions are disproportionate. The quantitative difference is also noticeable, where bone lesions of the CM are less numerous than multiple myeloma. PCM often does not show signs of new bone formation. The lesions found in the present study are compatible with those described for metastatic bone disease and provide elements that enhance the possible diagnosis for such neoplasia.

As we did not have an antemortem diagnosis, these reported characteristics could assist in possible differential diagnoses between neoplasms, but they are insufficient to establish them. The importance of the collections of skeletons is emphasized, especially if data on the cause of death is available, which, despite not being synonymous with the cause of the injury, is potentially helpful to provide the necessary subsidies for the differential diagnosis.[19]

Finally, it is worth noting that the significant variability of primary tumors capable of producing metastases in bone tissue, as well as the recognized overlaps, similarities, and multiplicity of characteristics between metastatic

lesions, makes it unlikely that a specific and objective diagnosis will be made regarding the original pathological site, based exclusively on skeleton findings.[4]

In an interdisciplinary context, descriptions and discussions of the pathologies observed in bones can significantly support human identification forensics. The information about the presence of pathology in bones allows the expert to assist in comparatively analyzing the antemortem information with all the forensic investigation methods used, confirm the victim's identity, and provide an answer for possible family members.

Conclusions

Based on the comparison between the information provided by the studies mentioned and the skeleton examined, it was possible to classify the lesions found as the most likely result of metastatic bone disease. However, as the overlapping of morphological characteristics and anatomical location of bone damage caused by metastases is recognized, this similarity usually does not allow evidence of traces that may link the bone lesion to the primary tumor when only visual inspection is performed. For this reason, considerations and conclusions about bone metastases to identify the organ of origin should be made with caution, being aware that an objective diagnosis is not always possible. As a result, the primary origin of the tumor was not classified in this study, as there are not sufficient subsidies for this.

Detailed macroscopic analysis, supported by radiographic, molecular, and histological exams, may help establish future diagnoses more safely. Finally, the importance of pathological descriptions on dry bones lies in enhancing information on the biological profile, reducing the spectrum of possibilities for finding unknown individuals when they have the antemortem record of the information necessary for collation.

Conflict of interest

There are no known conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome.

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