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PROBLEMS OF DIFFERENTIAL DIAGNOSIS IN PALEOPATHOLOGY

GIUSEPPE CAROTENUTO, GIUSEPPE BELLOMO, GABRIELE LAURIA, ROBERTO MICCICHÈ, LUCA SÌNEO
Dept. STEBICEF Università degli Studi di Palermo;
LabHOMO Laboratori di Antropologia, Palermo, I
Corresponding author: luca.sineo@unipa.it

SUMMARY

PROBLEMS OF DIFFERENTIAL DIAGNOSIS IN PALEOPATHOLOGY

This work discusses on the problems of the differential diagnosis in paleopathology, describing one case of intense modification observed in a skeletal sample from the archaelogical site of Baucina (Sicily, VI century BCE). Difficulties in this setting originate mainly from the aspecificity or absence of pathological markers on ancient bones and confounding features arising from clinical phenocopies or taphonomic artifacts.
On the base of an in-depth morphological analysis of the find, with aid of CT scan imaging and wide revision of the medical and paleopathological literature, we arrived to a convincing diagnosis.

"… I now have a bum leg and foot and there isn't
any army in the world that would take me.
But I can be of service over here and I will stay here
just as long as I can hobble …"
(E. Hemingway, Selected Letters 1917-1961)

Key words: Paleopathology - Differential diagnosis - Ischemic bone necrosis - Anthropology

Paleopathology is the science that studies diseases of the past and their evolution over time[1]. The investigative activity of this discipline concerns the anatomo-pathological, epidemiological and etiological aspects of diseases in ancient historical periods, either in relation to biological evolution of man or in relation to the social, cultural and environmental characteristics of the human communities of the past[2,3].
However, the possibility to describe ancient scenarios of diseases is very often frustrated by the inconsistency of the sample and the "osteological paradox" is a dramatic reality[4].
The findings offered to the paleopathological study are generally represented by isolated or fragmented skeletal remains, sometimes profoundly modified by taphonomic factors. The pathological stigmata can be completely absent on the bones or, if present, they have generic diagnostic value. In this regard, mummified bodies certainly allow more in-depth and precise studies. As pointed out by Capasso[5], in paleopathology there is a clear separation between the description of the sample and the diagnostic phase. The diagnostic process is limited and consequently mostly interpretative, due to the lack of the whole series of clinical data, for example concerning soft tissues.
Bone tissue has a homeostasis in the context of continuous turnover.
This homeostasis can be disturbed by stress that may leave markers on the bone.
According to the adaptively model, as revised by Goodman and Armelagos[6], the markers of skeletal stress can be distinguished in three categories: general cumulative indicators, general episodic indicators and specific indicators.
The rate of mortality in a population is a general cumulative stress indicator.
The general episodic indicators are those limited at the moment where stress occurred (e.g. Harris lines at the metaphysis of a long bone, hypoplasia of the enamel).

Skeletal specific indicators are produced by identified pathological processes that leave marks on the bone.
Unfortunately, there are many pathological processes that leave no evidence on bone. These processes cause harm to soft tissue only or work so quickly that the bones or teeth do not have enough time to react. Furthermore, a rigorous differential diagnosis in paleopathology should always consider the limitation represented by the fact that the bone can respond to stresses in a limited number of ways: tissue production and proliferation and tissue erosion and destruction. The two events can occur simultaneously or be consequent to one another, depending on the nature and stage of the disease. Therefore, the markers of a specific disorder affecting the bone tissue can demonstrate convergence towards very different diseases[7].
Each of these possible pathological conditions represent a separate hypothesis, which has to be confirmed or refuted by an increasing series of evaluations that will be more efficacious in relationship to the availability of diagnostic instruments and the professional experience of the examiner. However, the Paleopathologists must sometime surrender to the evidence that it is not possible to suggest any confident diagnosis on the base of skeleton markers[8].
Some diseases are closely linked to an individual's sex, such as prostate cancer in the male, or are statistically more frequent in one sex, such as frontal hyperostosis in the female. Other diseases arise exclusively or predominantly in certain age groups, moreover with variable anatomo-pathological expressions, such as osteomyelitis[9].
Historical data can also be of great help in the differential diagnosis. In considering three diseases that can leave similar skeletal markers we must take in mind that, in Europe, leprosy mostly spread in the 13th century, syphilis from the end of 15th, and tuberculosis culminated in the 19th and beginning of the 20th century.
The differential diagnostic approach in paleopathology considers all the diseases that could have caused a response similar to the one ob-

served and proceeding comparatively and with an exclusion criterion leads to a probable diagnosis.

The differential diagnostic approach uses methodologies common to clinical practice, in particular radiological imaging.

Radiological imaging of ancient pathological specimens can enable comparison of a lesion with that can be visualized in living patients with known diseases.

Since radiography has been in use for more than 100 years, an extensive record of images is available, depicting cases of the diseases whose appearance did not meet the phenomena of pathomorphosis induced by medical treatment[10].

A known limitation of traditional radiology is represented by the fact that the three-dimensional anatomical features are projected on a single plane. The resulting overlap of images can therefore lead to difficulties in identifying relevant pathological details. Radiographic interpretation in paleopathology additionally presents specific issues. Postdepositional artifacts can alter the radiographic image. Soil intrusion can create areas of radiodensity that can limit or completely prevent the production of diagnostically useful images.

The current availability and ease of access to the CT imaging has improved the efficacy of the radiological survey applied to paleopathology, further eliminating the problem of superimposition.

MR imaging of hard tissues remains challenging due to low proton content in such tissues as well as to very short transverse relaxation times (T2).

Several attempts have been made, unfortunately, without success[11,12,13].

More sophisticated MRI techniques, such as sweep imaging with Fourier transformation (SWIFT), ultrashort echo time (UTE) imaging, and zero echo time (ZTE) imaging, have been developed with promising results reported[14].

However, technical problems and high costs still hinder the global deployment of this imaging tool.

It is also possible to proceed with electron microscopy, chemical and serological analysis of the bone, and combine them with the paleogenetic approach. In this regard, we start from the premise of having a material that meets the requirements of certain provenience (material correctly extrapolated from "ancient" contexts), which has not been polluted by improper manipulations (for example due to inadequate conservation) and that in any case it has not suffered from a deep diagenesis.

Here we present a case that illustrates the difficulties of differential diagnosis in paleopathology.

The pathological find comes from Baucina (Palermo, Sicily), a hilltop indigenous archaeological site in a water-shed between the Milicia and San Leonardo rivers, approximately 15 km from the Tyrrhenian coast. Archaeological excavations have discovered an artificial cave tomb, that has been used between the 6th and early 5th centuries BCE, which is distinguished among the other burials by its monumentality and number of occupants (at least fifty individuals)[15].

The sample, of truly impressive appearance, consists of the distal portion of the right tibia and fibula and of the corresponding talus (Fig. 1a).

The tibia and the fibula are fused at the level of their articulation; there is a bone proliferation of the posterior tibial cortex, with a candle-wax dripping aspect, partly interesting also the interosseous space, suggestive of metaplastic ossification of soft tissues (Fig. 1b).

The tibia and fibula articular faces are profoundly altered by erosion; it is possible to see eburnation of the malleolar articular faces (Fig. 1c).

The talus is severely deformed: the dome is flattened and eroded, marginal osteophytes are present, some of which in pseudo-articulation with corresponding formations on the tibia (Fig. 1d).

The sample was analyzed with CT scanning and 3D imaging approaches.

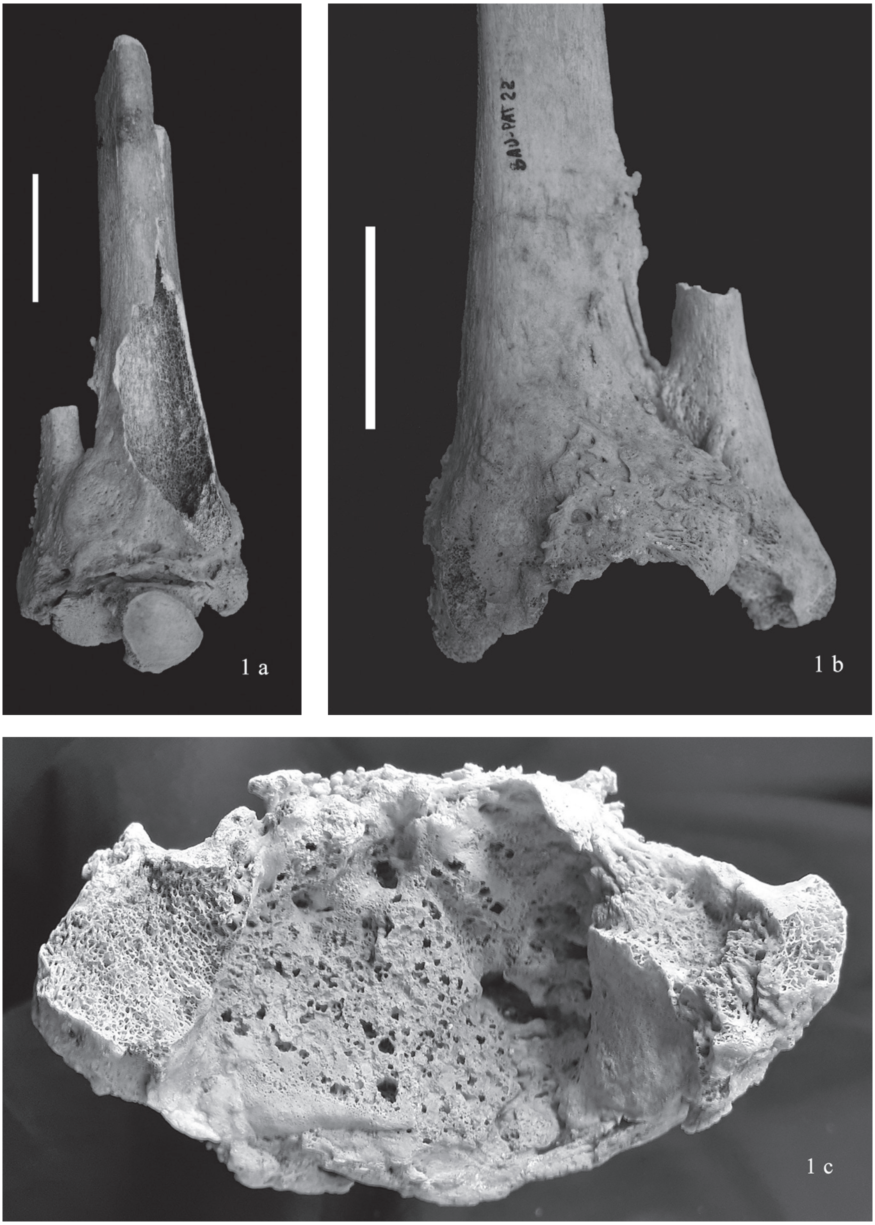
1 a
1 b
1 c

Fig. 1.

CT images were achieved using a General Electric Light Speed VCT 64 Slice CT scanner, with a gantry rotation time of 0.6 s, a slice thickness of 0.6 mm, and maximum intensity projection (MIP) utilized for integration. Data were saved as bitmap files in Digital Imaging and Commutations in Medicine (DICOM) format and treated and visualized using the open-source software 3D Slicer and Amira 6.0 software.

The images suggests a chronic disease, highly disabling but *per se* compatible with the survival of the individual.

Based on our observation and the medical and paleopathological literature, we suggest that the most probable diagnosis is the outcome of an ischemic necrosis of the talus bone, complicated by superimposed degenerative arthritis[16].

Nevertheless, the diagnosis of ischemic talus necrosis demands an articulated differential reasoning.
In fact, ischemic bone necrosis may be associated with a huge of conditions, including traumatic disruption of the blood supply, osteomyelitis or septic arthritis, autoimmune arthropaties, Sickle Cell Disease, corticosteroid therapy or Cushing's disease, alcoholism, irradiation.There are also a number of cases in which no clear condition is present or otherwise remains unknown ("idiopathic" or "spontaneous" osteonecrosis).
Some of the above-mentioned conditions, such as cortisone therapy or irradiation, can obviously be excluded, given the historical period of reference.
Traumatic avascular osteonecrosis (AVN) of the talus is a well known disabling condition[17]. Trauma is the leading cause of talar AVN, making up 75% of cases[18].
Displaced fracture of the neck of the talus is the most common traumatic precursor, though other ankle and hindfoot trauma may also precede the diagnosis. It is typically unilateral, involving the injured side. Risk of developing AVN of the talus is associated with the severity of the injury, since it is related to the failure of the blood supply to the talar body[19].
Blood supply to the talus is limited by the high proportion of its surface that is articular, limiting entry for perforating vessels, which may explain the relationship between traumatic lesions of this region and AVN.
One of the striking pathologic features of early stages of osteonecrosis is the intactness of the chondral surface despite the presence of adjacent severe osseous abnormality. Once patients with ischemic necrosis exhibit buckling or partial collapse of the articular surfaces, it usually is only a matter of time until superimposed degenerative arthritis becomes manifest[20,21].
Osteomyelitis and septic arthritis have been reported either as a cause or as a complication of osteonecrosis. Predisposing factors for infec-

tion are open fractures, penetrating injuries, necrosis of the skin, soft tissue infection and comorbidity like diabetes, and vascular disease.
The responsible pathogens are more commonly the bacteria; however, we must consider that similar bone alterations may have been caused also by fungi and parasites, that attack the bone both on the external face and in marrow cavities[22]. The pathological changes caused by many bacteria are relatively non-specific: infection by one bacterium is generally indistinguishable from that of another[23]. Bacterial infection can result in bone destruction, as well as bone proliferation, and both patterns in succession can be present in the same subject. In osteomyelitis, the bone is enlarged and deformed, the surface shows extensive pitting; the spread of infection moves via the Haversian systems and Volkmann's canals, with a possible coalescence of foci. The repairing process produce woven bone over and in between lesions, with a progressive osteoblastic action of building and melting of the new tissue to the mature lamellar bone. It derives that osteomyelitis alters the bone tissue at macroscopic and microscopic levels. The pus may extend into the epiphysis, where it can penetrate the articular surface or spread along capsular and tendon-ligamentous insertions into the joint. Consequently, septic arthritis develops, that is eventually associated with severe destruction of the articular cartilage.
Autoimmune arthropathies are a large group of a diseases triggered by the inability of the immune system to recognize and tolerate one's own tissues and are the most frequent post-cranial diseases in bone material, in both current and ancient human populations.
In general, autoimmune diseases do not cause visible lesions in bone tissue, except for some of these, preeminently Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis[24].
Pathologic features include joint space narrowing and erosive changes; the end-stage manifestation is ankylosis, most commonly seen in psoriatic arthritis.

Regarding the hypothesis of Rheumatoid Arthritis (RA), we should consider that on the basis of numerous cases of erosive arthropathy in archaic and present American native populations and the apparent absence of this disease in Europe before 1800, Rothschild and Woods have suggested that RA had its origins in the New World[25]. On the other hand, Rogers asserts that there was a low, but real, prevalence of the disease before the Columbian era in Europe[26].

Even Sickle Cell Disease is associated with localized areas of epiphyseal and metadiaphyseal bone infarction. Slugging of sickled erythrocytes within the sinusoidal vascular bed results in functional occlusion. In most cases, the foci of osteonecrosis are encountered in the epiphyseal and metadiaphyseal regions of long bones, especially the distal segments of the tibia and femur[27]. An additional diagnostic challenge is that sickle cell anemia is often complicated by superimposed osteomyelitis, mainly due to Salmonella organisms[28].

Conclusions

The case here discussed illustrates the difficulties encountered in the differential diagnosis in paleopathology. Indeed, paleopathological analyses of dried and ancient bones is often extremely difficult and rarely conclusive due to the aspecificity of markers and confounding situations arising from clinical phenocopies and taphonomic problems.

Furthermore, is not possible to state with certainty that currently known diseases cause the same anatomical-pathological alterations on the bones as those found in antiquity[29].

An accurate diagnosis in dry bones is possible only for some entities, such as fractures, which determine anatomical alterations similar to those observed even today.

In medical practice, the diagnosis is oriented by the patient's clinical history, by the results of laboratory investigations and by specific imaging methods, data which obviously are not available in the paleopatho-

logical context. Paleopathologists should therefore avoid diagnostic judgments of certainty based only on alterations to the normal anatomy of skeletal remains. According to Miller there are two main limitations: the scarcity of well-documented skeletal samples and the difficulty in finding patterns of pathognomonic anomalies for specific diseases[30].
In our case, another important limitation is represented by the lack of the remaining skeleton.
So we can only describe the severe deformation of the tibio-talar joint complex, but we are not able to formulate the diagnosis of a specific pathological entity. As pointed out by the Skeletal Database Committee of the Paleoanthropology Association, the descriptive data are nevertheless of primary importance, for the ordering into basic categories of the pathological conditions observed[31].
Considering the hard life and the social instability of the period to which the skeletal sample dates back, with a touch of imagination we would like to think that the bones belonged to a man, a private, who, although the victim of a severe traumatic event to his ankle, wanted to take action in defense of his community, at the cost of well imaginable sufferings.

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