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Research article

Neoplasm or not? General principles of morphologic analysis of dry bone specimens

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ABSTRACT

Unlike modern diagnosticians, a paleopathologist will likely have only skeletonized human remains without medical records, radiologic studies over time, microbiologic culture results, etc. Macroscopic and radiologic analyses are usually the most accessible diagnostic methods for the study of ancient skeletal remains. This paper recommends an organized approach to the study of dry bone specimens with reference to specimen radiographs. For circumscribed lesions, the distribution (solitary vs. multifocal), character of margins, details of periosteal reactions, and remnants of mineralized matrix should point to the mechanism(s) producing the bony changes. In turn, this allows selecting a likely category of disease (e.g. neoplastic) within which a differential diagnosis can be elaborated and from which a favored specific diagnosis can be chosen.

1. Introduction

A dry bone from antiquity is like a fossilized footprint left in solidified mud. From the print the foot can be modeled and is of more interest than the print. Similarly, in paleopathology, the goal is the identification of the disease as deduced from the residual bone imprint. During osteological examination, one's frame of mind must be to mentally "put the soft tissue that abutted solid substance back on the specimen" and thus find clues to the host response (mechanism) that produced the changes. Radiologic images can provide valuable information to supplement and increase the accuracy of macroscopic osteological analysis.

Pathologic bone morphology is the result of disease-related changes in circulation, metabolic factors, and/or mechanical stress, which stimulate the activity of the only three cell types that can modify bone structure: osteoclasts, osteoblasts and, to a much lesser extent, osteocytes. Due to the limitations of bony reaction, at times it can be difficult to distinguish between diseases that trigger similar cellular responses. Furthermore, in the analysis of paleopathology in dry bones, taphonomic processes, anthropogenic body modification, and even trauma can resemble neoplastic lesions and act as a pseudopathology. As a result, no differential diagnosis for skeletal remains is complete without consideration of all disease categories (Table 1) and pseudopathology.

Neoplasms, more commonly known as tumors, can be particularly tricky to diagnose from bone morphology as there are many types to consider. They may be malignant or benign, primary or secondary (metastases), slow or fast growing, manifesting in skeletal remains as lytic, blastic or mixed lesions, originating in, on, or beside bone from a variety of tissue precursors, and they may differentiate into more than one tumor pattern with products that may or may not preserve. Consequently, the ability to distinguish the mechanism(s) responsible for bony reactions through macroscopic and radiographic analysis can be a key factor in identifying the type of neoplastic disease that is represented.

This article provides a guide to the differential diagnosis of neoplastic disease in dry bones through macroscopic and radiologic

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Table 1
The categories (discussed below) overlap to some extent, since the inflammation includes repair, trauma is associated with circulatory changes, and metabolic disease may call forth mechanical compensation. The acronym "VITAMIN" assists in recalling the categories so that each of the Basic Categories of Disease is entertained as a differential possibility.

THE SEVEN BASIC CATEGORIES OF DISEASE		
I.	V	Vascular
II.	I	Innervation/Mechanical
II.	T	Trauma/Repair
IV.	A	Anomaly
V.	M	Metabolic
VI.	I	Inflammatory/Immune
VII.	N	Neoplastic

analysis of bone morphology, mainly by summarizing the relevant points of the publications by Madewell et al. (1981), Ragsdale et al. (1981), Sweet et al. (1981), and Ragsdale (1993). We will briefly address the disconnect between clinical and paleopathological terminology and standards for differential diagnosis, and the importance of radiographic analysis in the diagnosis of pathological dry bone. Following this, guides to the recognition of disease categories and specific diagnosis of neoplastic disease are presented, with a focus on lesion margins, periosteal reactions, and bone matrix patterns. The article concludes with discussions of the difficulties associated with the identification of spinal and cranio-facial neoplasms in skeletal remains and the specific challenges associated with the analysis of bioarchaeological remains. It is hoped that this complete classification of neoplastic evidence in dry bones will be useful in future assessments of bone pathology, and that pseudopathology and the six non-neoplastic disease categories (Table 1) will also be considered in future differential lists for suspected neoplasms.

2. Where are the standards?

Bone morphology exists on a spectrum from healthy normal bone to the manifestations of adaptive or pathological reactions. Clinicians regularly see patients in the early stages of bony change or even prior to the development of bony reactions, while most of the skeletal alterations that paleopathologists encounter are the result of chronic disease, trauma or infection, which may or may not have led to the death of the individual. Modern textbooks of orthopedic pathology and radiology include illustrations based on surgical specimens intercepted at some point short of their full natural history. Autopsy specimens may be more likely to represent more advanced expressions of disease than surgical examples, as the deceased is likely to have lived with the disease longer than a surgical patient, but the morphologic expression is generally modified by therapeutic manipulations, including surgery and pharmacology. The reference work by Ortner and Putschar (1981) is of great relevance; many of its illustrations are cases collected in the 19th century or come from Dr. Putschar's Third World experience.

The modern practice of pathology occasionally presents rare instances where, for one reason or another, treatment is delayed or not given. In such cases, radiographs taken over time present visual documentation of the evolution of a process with skeletal manifestations, carrying it to degrees approaching what might be analogous to the process in antiquity, in the absence of (most) effective treatment. Such cases are better, but not perfect, standards for the natural progression of the disease represented (Ragsdale, 1997). Of equal importance, these cases teach much about the mechanisms, tempo, and personal disability of specific disease states, although individual experience of pain and disability can vary widely.

An additional concern is the lack of standardization in terminology used by researchers referring to neoplastic diseases. Many popular terms and expressions are best avoided since they obscure or misrepresent disease mechanisms. This article will follow the terminology laid out in a series of articles: Madewell et al. (1981), Ragsdale et al. (1981), Sweet et al. (1981), and Ragsdale (1993). Though directed at today's pathologists, radiologists, and orthopedic surgeons, the terminology therein defined can be advocated without alteration for use in paleopathological descriptions.

3. Radiologic examination is an indispensable part of morphologic analysis

In modern diagnostics it has become axiomatic that the histologic diagnosis of bone tumors can be safely attempted when all of the clinical history and roentgenograms are available. This method of triangulation or triple diagnosis technique is essential in arriving at a reliable diagnosis. It gives equal weight to clinical, radiographic, and histopathologic data. Competent pathologists know it is hazardous to make final diagnoses without film review, even more so when attempting diagnosis of a dry bone from antiquity. Radiographs may also reveal lesions not visible macroscopically, meaning that systematic radiographic analysis of human remains is absolutely necessary for the comprehensive study of neoplastic disease in the past. Furthermore, radiologic studies can suggest the optimal plane for sampling or sawing through a gross specimen for destructive analysis. Excavated bones will not likely be exhumed with histories and microbiologic culture results that are of great help in diagnosing a non-neoplastic process simulating a bone neoplasm such as infection (especially Brodie's abscess and granulomatous osteomyelitis), trauma and repair (e.g., osteoporotic and stress fractures), and metabolic disorders (e.g., brown tumor of hyperparathyroidism). Assuming sufficient retention of matrix and mineral, specimen radiographs will be all that most paleo-oncologists can rely upon to test opinions based on surface examination and matrix histopathology; without them no opinion should be taken seriously.

As submitted in consultation to the Orthopedic Branch of the Armed Forces Institute of Pathology in Washington, D.C., Madewell et al. (1981), Ragsdale et al. (1981), Sweet et al. (1981), and Ragsdale (1993) determined that attention to the three parameters of **margins**, **periosteal reactions**, and **matrix patterns**, as disclosed in plain films, permits a diagnostic accuracy in excess of 90% for modern day bone tumors. Special imaging techniques (CT and today's MRI) can settle details of internal structure, however, only rarely do they modify the diagnosis proposed after experienced analysis of plain films. The aforementioned authors went on to point out that generally the most important areas for determining a specific diagnosis are those showing abnormal patterns of mineralization and that the more important areas for assessing biologic activity (benign vs malignant) are radiolucent. The plain film radiograph delineates the lesion's location (one or several bones), the segment of involvement (epiphysis, metaphysis, or diaphysis), growth characteristics, and the presence or absence of mineralized tumor matrix. Combinations of periosteal alterations, margins, and density changes can help refine an "Inflammatory Category" diagnosis into one of the three patterns of skeletal inflammation: suppurative, granulomatous, or angiitic. Post-traumatic and some metabolic (e.g., hyperparathyroid bone disease) changes are also succinctly described with these terms. Madewell et al. (1981), Ragsdale et al. (1981), Sweet et al. (1981), and Ragsdale (1993) emphasized that for accurate description and as a permanent record of a specimen, radiographs are indispensable since choice of descriptive terms in part relies on radiographic appearances.

Some radiographic configurations are distinctive, repetitive, and so typical as to represent radiologic clichés known to radiologists as 'Aunt Minnies'. Examples are: the honeycomb, spoke-wheel, and

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