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Research article

Dry bone histology of bone tumours

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ABSTRACT

This article focuses on the application of dry bone histology in the diagnosis of a series of different bone tumours. It provides a short introduction on bone tumour classification and how tumours may affect the skeleton. To illustrate the value of dry bone histology in the diagnostic process we studied the 'fresh' and 'dry' bone histology of a series of well-documented, recent clinical cases of various benign and malignant bone tumours.

We show that histology is a valuable instrument to assess bone tissue architecture, which provides information on the biological behaviour of a tumour. Though histology may reveal the specific 'tumorous' bone deposition of high-grade conventional osteosarcomas, all other bone tumours display common, unspecific features. This holds for the following tumours: osteochondroma, hyperostotic meningioma, high-grade angiosarcoma, grade 2 chondrosarcoma, myoepithelial carcinoma, high-grade osteosarcoma and four carcinoma metastases.

We conclude that histology is useful in cases where the biological behaviour of a tumour is to be defined, and is particularly an aide in the diagnosis of high-grade conventional osteosarcomas. Nevertheless, the differential diagnosis on the bone tumours in our series should primarily be based on a combination of physical anthropological patient data (age, sex), gross anatomy (e.g. tumour morphology and location), and radiography.

1. Introduction

Paleopathologists study diseases in ancient remains. They reconstruct the medical history of deceased individuals, provide valuable insight in the living conditions of past populations, and utilise an unique opportunity to study the natural development of diseases in time (Rühli et al., 2016). In most cases the studied material is in such an advanced state of decomposition that only skeletonized or 'dry bone' tissue remains. This limits the range of diseases that can be analysed to those diseases that (eventually) affect the skeleton. In addition, because of the missing of the soft tissue component, it limits the reliability of a paleopathological diagnosis (Waldron, 2009). In an effort to maximize diagnostic reliability, paleopathologists tend to complement 'standard' gross anatomical analysis with other diagnostic tools, such as histology. However, due to various reasons, the diagnostic value of histological analysis is subject to discussion (De Boer et al., 2013a; Schultz and Schmidt-Schultz, 2015; Schutkowski and Fernandez-Gil, 2010; Strouhal, 1991; Van der Merwe et al., 2010; Waldron, 2009; Weston, 2009), one of them being the unavoidable tissue destruction from sample excision.

This article focuses on the dry bone histology of a specific group of diseases, namely neoplasms. A short introduction of their classification and how they may affect the skeleton is followed by the backbone of this paper, the difficulty of their diagnosis. To illustrate the latter, we compare the 'fresh' and 'dry bone' histology of specimens of a well-documented current series of clinical cases of neoplasms with bone involvement.

1.1. The classification of bone tumours

Neoplasms (ancient Greek: new formations) constitute a heterogeneous group of disorders with the common denominator: monoclonality. This means that, although neoplasms generally contain more than one cell type, they originate from a single population of cells with a shared genetic or epigenetic anomaly. Although originally used for any type of tissue enlargement, the term tumour is nowadays used as a synonym for neoplasm.

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Neoplasms are usually classified by their biological behaviour and their tissue type. Benign neoplasms are non-invasive and their name is customarily named an aggregation of their dominating tissue type and the suffix –oma. Benign neoplasms of bone tissue are for instance called osteomas whereas benign cartilaginous neoplasms are chondromas. Malign neoplasms, or cancers, are defined by their potential to spread (metastasise) to other parts of the body. Since almost every cell in the body has the potential to undergo malign transformation, the number of different types of cancers is enormous. The most relevant ones from a paleopathological perspective are derivatives of epithelial or mesenchymal tissue, which are respectively called carcinomas and sarcomas.

Alternatively, bone tumours (tumours situated in or near the skeleton), can be classified as being primary or secondary. Primary bone tumours are those neoplasms that originate from skeletal tissue itself (e.g. bone, cartilage) and can either be benign or malign. The current incidence of benign primary bone tumours is unknown as most of them grow (very) slowly or cause no clinical symptoms. Malign primary bone tumours are very rare, having an incidence of 0.8–2 cases per 100,000 individuals per year (Fletcher et al., 2003). Secondary bone tumours originate elsewhere in the body and have spread to the skeleton. As such they are malign by definition. Secondary bone tumours are much more common than primary bone tumours. In the USA an estimated 350,000 people per year die having metastases in their bones (Vigorita et al., 2016).

1.2. The effect of bone tumours on the skeleton

Only neoplasms that leave traces in the skeleton can be studied in dry bone tissue. Essentially these traces are limited to the formation of mineralised tissue, the resorption or destruction of bone tissue or a combination of the two.

Mineralised tissue is formed either by ossification or calcification (Vigorita et al., 2016). Ossification is the formation of new bone and requires the deposition of osteoid and its subsequent mineralisation by osteoblasts. If bone tissue is formed in a slow and organised manner it displays a distinct lamellar architecture and is referred to as lamellar bone. Accelerated bone deposition results in bone tissue with an irregular, disordered architecture and is referred to as woven bone. Subsequent remodelling may convert woven bone into lamellar bone. Given a certain time lapse, the degree of progress of the remodelling process is indicative for the growth speed of a neoplasm. A high growth speed is usually indicative of poor differentiation or immaturity and of (consequently) high malignity, although exceptions exist.

By definition, osteogenic bone tumours produce tumorous bone tissue by means of their tumorous osteoblasts. Benign osteogenic tumours produce bone tissue resembling the texture of normal bone, whilst the bone texture in malign osteogenic tumours (osteosarcomas) is markedly disordered and immature (less differentiated). Prompted by the growth of any bone tumour, locally also reactive, secondary bone tissue may be formed by normal, non-tumorous osteoblasts, the so-called 'wild type' osteoblasts.

Mineralisation (less accurately called 'calcification') is the deposition of calcium and a minority of other minerals in tissue. In contrast to bone tissue, the mineralised (or calcified) component in soft tissue displays as an amorphous acellular substance. Such mineralisations may be seen in a myriad of diseases and are by no means pathognomonic (Vigorita et al., 2016). They may dissolve, persist or develop into bone tissue. The mechanisms hereof are poorly understood. Due to the handling of paleopathological specimens, small in vivo fragments of mineralised tissue usually get lost (Steinbock, 1989).

Bone tissue is resorbed by large multinuclear cells from the monocyte-lineage; so-called osteoclasts. These cells adhere to the cortical or cancellous bone surface and dissolve the underlying bone tissue by excreting erosive substances. The resulting resorption bays, Howship's lacunae, remain visible in dry bone histology. According to the present state of science, osteoclasts do not undergo malign transformation. Their bone tissue resorption activity can be regarded as a secondary, reactive process.

1.3. The diagnosis of bone tumours

In current medical practice, the diagnosis of bone tumours requires a combination of clinical, radiographic, histological and presently in an increasing number of cases molecular analysis (Czerniak, 2016; Waldron, 2009). Especially primary bone tumours have a tendency to occur in specific age groups, in specific skeletal elements, and at preferential positions within a long bone (its diaphyseal, metaphyseal or epiphyseal part) (Fletcher et al., 2003). The location and size of the tumour, as well as its potency to produce extracellular matrix (e.g. cartilaginous or osseous tissue) is best assessed by radiography. Radiographic analysis also provides information on the biological behaviour of the tumour by showing its pattern of bone destruction and its related periosteal reaction (Fletcher et al., 2003; Miller, 2008; Priolo and Cerase, 1998). Histological analysis of tissue samples, sometimes combined with molecular analysis, is the final step of the clinical diagnostic process (Mangham and Athanasou, 2011).

Strategically, an analogous diagnostic approach is aspired in paleopathology (Rothschild and Rothschild, 1995; Waldron, 2009). Though frequently missing are selective data for diagnoses such as the age and sex of the diseased and the presence of soft tissues. In a clinical context the histological diagnosis is primarily based on soft-tissue features such as soft tissue architecture and cytonuclear morphology. A lack of soft tissue thus greatly hinders the application of histology as a diagnostic tool. Due to the focus on soft tissue features, pathology textbooks hardly mention the histology of the mineralised, 'dry bone' part of the various bone tumours.

There is a limited number of paleopathology case reports of bone tumours in which histology was used (Alt and Adler, 1992; Anderson et al., 1992; Campillo, 1991; et al., 1984Campillo and Marcí-Balcells, 1984; De La Rúa et al., 1995; Grupe, 1988; Merczi et al., 2014; Molnár et al., 2009; Plenk Jr., 1999; Schultz, 1993; Schultz et al., 2007; Šefčáková et al., 2001; Strouhal, 1991, 1993; Strouhal et al., 1996, 1997; Suzuki, 1987; Tkocz and Bierring, 1984; Vyhnánek et al., 1999; Wakely et al., 1995, 1998). These reports indicate that histology is especially valuable to exclude pseudopathology, which is best recognized by an irregular distribution that does not correspond with the normal distribution of disease. However, the value of histology to differentiate between different tumour types varies strongly (De Boer and Maat, 2012; De Boer et al., 2013a). As a result, the potential of histology in the diagnoses of bone tumours in dry bone tissue remains subject to debate.

This study therefore compares the 'fresh' and 'dry bone' histology of specimens of a well-documented current series of clinical cases of bone tumours. Such an approach has two important benefits. Firstly, all cases are diagnosed with state-of-the-art techniques and include clinical follow-up. The correct diagnosis is therefore no matter of debate. Second, the comparison between the fresh and dry bone histology enables us to focus on the mineralised tissue, of which the morphology is generally neglected in pathology textbooks.

2. Materials

A total of 13 tumour specimens of recent, thoroughly diagnosed cases were selected from the collection of the Department of Pathology of the Academic Medical Centre in the Netherlands. The series contains the following tumour types: osteochondroma,

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