Can examples of ancient human bone neoplasms inform current biomedical bone cancer research?

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Abstract

Whilst cancer is often considered to be a modern disease, examples of bone neoplasms can be seen in skeletal remains from ancient human populations. Such ancient examples suggest it is neither a distinctly modern, nor ancient, disease in humans. This essay evaluates the paleopathological study of metastatic carcinoma in relevance to modern biomedical studies, addressing whether the available evidence of these investigations can reliably be used in the development of new methods of bone cancer treatment.

Keywords

paleopathology, paleo-oncology, cancer

Introduction

Paleo-oncology, a term coined by Halperin (2004), refers to the study of paleopathological tumours in ancient human skeletal remains. Cancers originating from epithelial cells are referred to as carcinomas, whilst malignant sarcomas arise from connective tissues such as cartilage, bone, and nerves (Halperin 2004). Such tumours and abnormal growths in the skeleton are referred to as bone neoplasms (Marks and Hamilton 2007). This field of paleo-oncology falls more broadly under paleopathology, the study of evidence for the history of disease and trauma (Roberts 2016). A study of oncology throughout history is important in understanding the evolution of cancer, and may give insight into aetiology of different primary and secondary bone cancers. The field of paleo-oncology is increasingly important in the contemporary time, with over eight million cancer-related deaths per year occurring as recently as 2012 (Ferlay et al. 2015). It is thought that an increased understanding of ancient bone neoplasms and the aetiology of tumours may direct novel contemporary cancer treatments, and many are seeking to understand how the natural history of cancer is relevant to the modern disease (Capasso 2005).

This essay will address the research question of whether an understanding of paleo-oncology can make a meaningful contribution to modern biomedical bone cancer research, and whether any contribution is reliable enough to have impact on innovative methods of bone cancer treatment. Whilst examples of primary bone cancer exist in the archaeological record, discussion in this essay will be through the lens of metastatic carcinoma. At present, the prevalence of metastatic neoplasms is greater than that of primary sarcomas, and this area of paleo-oncology carries great potential impact on modern cancer treatments (Ragsdale et al. 2017; Halperin 2004). Examples will be discussed in light of the pathophysiology and skeletal pathology of ancient human bone neoplasms, including an evaluation of paleopathological methods, and with regard to the relationship between past and present bone cancers.

Pathophysiology and skeletal pathology of ancient human bone neoplasms

Bone neoplasms can manifest in several forms on the skeleton, depending on the type of cancer and if the tumour is primary or secondary (Coleman 2006). Metastatic carcinomas—secondary bone neoplasms resulting from primary tumours in the soft tissue—may be osteoblastic, osteolytic, or a combination of both (Guise et al. 2006; Luna et al. 2015). Cancerous cells affect bone through invasion

of the marrow stroma, and migration to the endosteal surface to stimulate either osteoblast or osteoclast activity (Mundy 2002). Cancerous cells travel to bone via haematogenous spread, either directly entering the blood flow from the primary tumour or by draining into systemic circulation from lymph (Suva et al. 2011). Osteoblastic metastatic carcinomas often arise from prostate cancer, whilst osteolytic lesions result generally from cancer of the thyroid, kidneys, uterus, gastrointestinal tract, and adrenal glands (Mundy 2002). Mixed lesions commonly occur as metastasis from cancers of the lung, breast, and ovaries (among other organs), but may also occur in some cases of prostate cancer (Mundy 2002; Luna et al. 2015). A case study on Hungarian skeletons from the Roman Period further suggested that osteoblastic lesions were formed from prostate cancers, whilst mixed lesions were observed in an example of breast cancer (Merczi et al. 2014). In a sample (G 1287) estimated to be from the second to third century from a civil town in Aquinicum (western Hungary), the characteristic lesions of osteoblastic carcinoma were found to be: periosteal bone apposition (with porous and striated lesions in foci), generally affecting the pelvis, vertebral column, and femora (Merczi et al. 2014). A case of a Cis-Bakal mobile forager from the Early Bronze Age in Eastern Siberia found that blastic lesions were often located in proximity to lytic lesions, where they were not specifically mixed lesions (Lieverse et al. 2014). An example of metastatic carcinoma from a second century subelite individual from Amara-West (Nubia) found that osteolytic lesions generally manifest as scalloped bone loss in cancellous bone, only becoming visible in cortical bone in advanced stages (Binder et al. 2014). In advanced cases of osteolytic bone loss, fractures are additionally a common pathology (Coleman 2006). The study from Eastern Siberia noted that lytic lesions ranged remarkably in size (Lieverse et al. 2014). Both studies from Nubia and Hungary concluded that macroscopic examination was inadequate in determining the extent of lesions affecting the skeleton, as most changes occur in cancellous bone before affecting cortical bone on the exterior (Binder et al. 2014; Merczi et al. 2014). A study of likely prostate cancer in a preIncaic individual from Pukara de la Cueva (northwest Argentina) agreed that radiographic examination gives more insight into the dispersion and characteristics of neoplastic changes to bone structure (Luna et al. 2015). Use of a scanning electron microscope and radiographic imaging is considered a key diagnostic tool in the positive identification of metastatic carcinoma in the skeleton, with osteoblastic cases showing the formation of an irregular network of sclerotic trabeculae and loss of original cancellous bone. Osteolytic lesions show resorption of trabeculae under scanning electron microscope (Merczi et al. 2014).

Often difficult to diagnose in the archaeological record, there is currently disagreement on whether traditional macroscopic and radiographic methods are sufficient in diagnosing metastatic carcinoma in ancient human skeletal remains (Schultz et al. 2007). The majority of studies on ancient bone neoplasms, and on metastatic carcinomas, are completed using macroscopic and radiological examination of the skeleton, as in Merczi et al.'s (2014) study. As no soft tissue is usually available to paleopathologists—except in the case of mummified remains—diagnosis relies solely on the observed skeletal lesions (David and Zimmerman 2010). This becomes problematic as the lesions of metastatic carcinoma are often nonspecific, particularly in early stages, with several other conditions also causing osteolytic or osteoblastic activity (Merczi et al. 2014). A study using proteomic methods on a Scythian king showed that biochemical analysis for a prostate specific antigen (PSA) and hydroxyapatite in the extracellular matrix of bone was reliable in diagnosing metastatic carcinoma from prostate cancer (Schultz et al. 2007). Bound PSA increased with malignancy in this case (Schultz et al. 2007). Whilst this molecular method is considered more reliable and may have more relevance to modern biomedical research, the approach is underdeveloped and relies on the successful isolation of ancient DNA from archaeological remains (Schultz et al. 2007). Furthermore, additional research into antigens for other primary cancers would need to be employed before this method could become standard in paleo-oncology (Schultz et al. 2007). Currently, detailed description of the characteristics and location of observed skeletal lesions, such as that seen in a study by Luna et al. (2008), is important in improving the differential diagnosis of metastatic carcinoma.

The relationship between past and present bone cancers

Many seek to establish and understand the relationship between historical and contemporary forms of cancer (Halperin 2004). In the case of metastatic carcinoma, it has been demonstrated that the skeletal manifestation in modern clinical cases is similar to that in ancient skeletal remains (Marks and Hamilton 2007). A study of metastatic carcinoma in a 62-year-old contemporary female was used as a comparative standard, as no medical intervention was given (Marks and Hamilton 2007). This modern study agreed that scalloped-edged lesions were characteristic of osteolytic perforations in the cortical bone, and that both osteoblastic and osteolytic lesions were focused in certain areas of each affected bone (Marks and Hamilton 2007). As suggested in paleopathological studies, neoplasms most commonly affected the pelvis, vertebral column, and femora (Marks and Hamilton 2007). The similarities between archaeological studies and this contemporary case study suggest that metastatic carcinoma is not distinctly an ancient or modern disease in humans (Marks and Hamilton 2007). It has additionally been documented that most types of modern neoplastic disease can be found in the archaeological record, thus suggesting that a relationship between ancient and contemporary cancers may exist (Capasso 2005).

In establishing cancer and metastatic carcinoma as an ancient disease, inferences can be made regarding aetiology and pathogenesis of modern metastatic carcinomas and bone cancers (David and Zimmerman 2010). It is argued that the rarity of metastatic carcinoma and other bone neoplasms in ancient times indicates that the conditions producing such lesions were rare (Capasso 2005; Binder et al. 2014). From this, conclusions can be made about the environmental factors contributing to metastatic carcinomas and cancers in the modern era (Faltas 2011). Studies of malignancies in European cases found that the low rate of neoplasms in historic samples tended to increase in time as social aggregation levels and levels of indoor activity rose (Capasso 2005). Of the recorded neoplasms, 43.2 per cent were found to be metastatic carcinomas (Strouhal 1998). This agrees with other studies that geography and increased ‘civilisation’ is progressively a risk factor in contemporary cancers (Capasso 2005). It is thought that such civilisation is linked to an aging population, where more metastatic carcinomas were recorded as life span increased (Nerlich et al. 2011). This is likely, as cancer is considered to be an age-progressive disease (Capasso 2005). Such a conclusion is supported by an understanding of paleo-oncology and the evolution of the disease, signifying a way in which examples of ancient human bone neoplasms can contribute to a modern understanding of cancer (Capasso 2005). Whilst not on a molecular level, this represents one contribution of paleo-oncology to contemporary biomedical bone cancer research.

Is it possible for an understanding of paleo-oncology to contribute to contemporary treatment of bone cancers?

Certain limitations into the paleo-oncological study of bone neoplasms exist, affecting many, if not all, case studies (Halperin 2004). It is widely documented that skeletal evidence for metastatic carcinoma—and indeed many other types of bone neoplasm—are rare in the archaeological record (Capasso 2005; Luna et al. 2008; Lieverse et al. 2014). It is questioned whether this rarity denotes a lack of evidence and inadequate diagnostic criteria, or whether it proves the rarity of cancer as an ancient disease (Marques et al. 2017). The limited skeletal evidence may be due to misdiagnoses of observed lesions, or underreporting cases of metastatic carcinoma based on incidental discovery in archaeological samples, and on the belief that it was rare in hunter-gatherer populations (Lieverse et al. 2014). The limited amount of conclusive skeletal evidence affects all studies of metastatic carcinoma, and limits the contribution that paleo-oncological studies can make to modern biomedical research (Capasso 2005). Whilst most paleopathologists recognise this limitation, relatively small sample sizes continue to present a large source of error in studies of ancient human bone neoplasms (Capasso 2005). Halperin (2004) discusses the difficulty in diagnosing cancer in ancient human remains due to pseudopathology, a postmortem effect on the skeleton that mimics lesions associated with an antimortem disease

(Halperin 2004; Lieverse et al. 2014). Soil erosion and pressure may result in the erosion of the cortical bone and warping of long bones, and the acidification of groundwater has further been shown to cause severe porosity on the bone surface (Halperin 2004). Bacteria and fungi, in particular, are able to induce dissolution of bone mineral of Haversian canals in a regular pattern, reminiscent of the osteolytic changes seen in metastatic carcinoma (Halperin 2004). Such taphonomic changes are central in the gross underestimation of the incidence of metastatic carcinoma in macroscopic and radiological studies of ancient human remains, such as those by Merczi et al. (2014) and Binder et al. (2014). A multidisciplinary approach including consultation by experts in taphonomy may help in the accurate distinction of pre- and postmortem lesions. Studies are further limited by the nonspecific nature of many lesions associated with metastatic carcinoma (Rothschild et al. 1998; Assis and Codinha 2009). A review on the methodological approach to studying ancient cancers by Faltas (2011) criticises macroscopic methods, and discusses the need to move to a modern molecular method in order to gain relevant and conclusive insights into the pathogenesis of the disease. Molecular methods include proteomic analysis and biochemical testing of bone neoplasms, such as those used by Schultz et al. (2007). Although considered more reliable, even molecular techniques are relatively underdeveloped and are met with issues such as cost and the successful extraction of ancient DNA (Schultz et al. 2007; Nerlich 2017). Ultimately, the little molecular evidence available from ancient metastatic carcinomas significantly limits the contribution that can be made to modern cancer research and new methods of cancer treatment at present (Faltas 2011).

Whilst Faltas (2011) argues that there is insufficient molecular evidence available from metastatic carcinoma and malignant bone neoplasms to make a meaningful or reliable contribution to modern biomedical research, the study of paleo-oncology should not be entirely dismissed. Studies of metastatic carcinoma in ancient skeletal remains are valuable in providing an insight into the history of cancer in human populations, and the anthropological context surrounding the disease (David and Zimmerman 2010). Capasso (2005) presents the argument that it is only through the study of the biological evolution of cancer that the concurrent social and cultural evolution of different populations can be understood. In looking to things such as the Medical Papyri of Ancient Egypt, or the early work of Hippocrates and the Ancient Greeks, an understanding of the social evolution of cancer can be gained (David and Zimmerman 2010). Although this does not directly impact modern biochemical research into bone cancers, its value should not be understated.

Conclusion

In conclusion to the research question, there is currently insufficient molecular evidence from ancient metastatic carcinomas for any reliably or significant contribution to modern biochemical research into bone cancer. Any information gained from the paleo-oncological study of metastatic carcinoma largely relates to aetiology of the disease, and does not yet have applications in innovative or targeted treatment therapies (Faltas 2011). The characteristic osteolytic and osteoblastic lesions of metastatic carcinoma were discussed, with either the formation of sclerotic periosteal tissue or loss of cancellous bone occurring (Merczi et al. 2014). The issues with macroscopic and radiological methodologies were established, including the difficulty in diagnosing metastatic carcinoma (Schultz et al. 2007). Although osteoblastic or osteolytic lesions can be observed in ancient skeletal remains, it can be difficult to distinguish both anti- and postmortem changes to skeleton, and whether cancer was the underlying causes of the lesions (Halperin 2004). Whilst molecular methods are considered more reliable and conclusive, they are still generally underdeveloped and are not yet widely applicable enough to have a substantial impact on modern bone cancer research (Schultz et al. 2007). In spite of this, paleo-oncology still contributes to the contemporary understanding of the evolution of metastatic carcinoma, and the related primary cancers. Contextual anthropological evidence has provided an insight into the social and cultural dimensions of ancient bone neoplasms, invaluable to the current knowledge of how cancer was approached in ancient societies (Capasso 2005).

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