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A probable case of multiple myeloma from Bronze Age China

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ABSTRACT

Paleopathological evidence of cancer from past populations is rare, especially outside of Europe and North Africa. To begin to fill the gaps in the geographical distribution of neoplastic disease, this study presents a probable case of multiple myeloma in an adult male from the Qijia culture horizon (1750-1400 BCE) of the Bronze Age cemetery of Mogou (□□), located in Gansu Province, Northwest China. Multiple ovoid-shaped osteolytic lesions with sharply demarcated margins were assessed macroscopically and radiographically. The axial skeletal had the greatest involvement, specifically the vertebrae, ribs, and sternum. Radiographic imaging revealed more extensive destruction of hematogenous than cortical bone, indicating that the marrow was the focal point of the disease. Based on the nature, distribution, and radiographic appearance of the lesions, the most likely diagnosis is multiple myeloma. This is one of the only cases of cancer identified in archaeological human skeletal remains in East Asia. By placing case studies such as this into a temporal and spatial framework, it is possible for future research to begin to interrogate possible underlying causes of cancer in ancient populations within the context of changing environmental conditions and subsistence strategies.

Key words: cancer, hematopoietic malignancy, paleo-oncology, Qijia Culture, Mogou

1.0 Introduction

Evidence of cancer from past populations is rare: less than 300 cases have been identified in the archaeological record (Hunt et al., 2018; Riccomi et al., 2019). Though there has been considerable interest in the topic within the scientific community in recent years, there are notable gaps in the history of neoplastic diseases in populations outside of Europe and North Africa (Hunt et al., 2018; Riccomi et al., 2019). The analysis and publication of examples of neoplasia from areas that expand upon the current known temporal and spatial distribution is necessary in order to better reconstruct the history and evolution of cancer (Binder et al., 2014). To date, only a handful of cases of neoplastic disease have been identified from the study of human skeletal remains from mainland China (Hou, 2013; Pechenkina et al., 2019; Xiao, 2014; Zhang et al., 2019). This study expands upon the current literature by presenting a possible case of multiple myeloma from a Bronze Age cemetery located in Northwest China.

2.0 Materials & Methods

The human skeletal remains under investigation were recovered from the Mogou (□□) site in Lintan County, Gansu Province, China. The site, which covers more than 30 hectares, was excavated between 2008 and 2012 by the Gansu Provincial Institute of Cultural Relics and Archaeology and the School of Cultural Heritage of Northwest University. It is estimated that over 5000 individuals were interred in this cemetery. Radiocarbon dates indicate that the site was in use between 1750-1100 BCE, and the material culture shows it was occupied first by individuals associated with the Qijia material culture complex (from c. 1750-1500/1400 BCE) and later by those associated with Siwa cultural material (c. 1400-1100 BCE), with the two cultural horizons possibly overlapping (Mao et al., 2009; Xie et al., 2009; Zhang et al., 2014). All excavated materials are stored at the Gansu Institute's headquarters in the provincial capital of Lanzhou, where the analysis of the human skeletal remains and material culture from the site are ongoing.

The majority of the graves excavated at Mogou are vertical pits with side chambers (Qian et al., 2009). Many of these graves have multiple side chambers at different depths, as well as small niches in the walls. Burial practices at Mogou are particularly varied and include primary and secondary interments, with graves commonly containing between two and nine individuals of different ages and sexes. The individual that is the subject of this paper (M1187:R1) was buried inside a chambered tomb with at least six other individuals. The location of the tomb in the cemetery indicates that this individuals was associated with the Qijia cultural horizon.

The Qijia horizon (2300-1500BCE) is found across much of the upper Yellow River Valley drainage, spanning the early and middle Bronze Age of the northwest Loess Plateau, the eastern Hexi Corridor, and the eastern Qinghai-Tibet Plateau. Little is known about the specific way of life of the people buried at Mogou, as there has been no associated settlement found. Based on other Qijia sites, it is thought that the people associated with this widespread material culture led a sedentary life, living in small settlements of 5.3 to 7.5 ha (An et al., 2005). They practiced cereal agriculture supplemented by animal husbandry, though there was geographic variation in the mix of agriculture and pastoralism (Xie, 1981, 2002), and this may have also varied over time with climatic change (An et al., 2005, 2010). The staple crops at Qijia sites were millets (*Panicum miliaceum*, *Setaria italica)*, though they were early adopters of wheat (*Triticum* cf. *aestivum*) and barley (*Hordeum vulgare)* when these arrived in East Asia. Animal domesticates included sheep, pigs, dogs, donkeys, and cattle (Dong et al., 2014; Ma et al, 2016; Xie, 1981). They had both forged and cast bronze, though metal objects were mostly small tools and ornaments (Campbell, 2014; Xie, 1981).

The skeletal remains were macroscopically examined a\nd recorded according to the standards outlined in Buikstra and Ubelaker (1994) and Mitchell and Brickley (2017). The skeleton was approximately 50-60% complete (Figure 1). The ribs were more than 75% complete and the vertebral column was approximately 60% complete, with the majority of the vertebral neural arches intact. However, the state of preservation of the vertebral bodies did not permit precise identification of all fragments. The preservation of surviving elements in the axial skeleton was moderate to good, as was the *ossa coxae*, but the overall state of preservation of the appendicular skeleton was generally poor. The cortical bone on the long bones was very degraded and the epiphyses on most long bones were either very damaged or not present. Neither the cranium nor the mandible was present. Biological sex was estimated based on pelvic morphology (Buikstra and Ubelaker, 1994; Phenice, 1969) and age-at-death was estimated by assessing sternal rib ends (İşcan et al., 1984), as the iliac auricular surfaces and pubic symphysis were taphonomically damaged. The skeletal remains were estimated to be those of an adult male, 34-42 years of age at time of death (phase 5). Plane radiographs were taken using a HUARI-300HP portable industrial X-ray machine (100kV, 1.0mAs, 30 seconds) at a source-object distance (SOD) and source-image receptor distance (SID) of 100 cm.

3.0 Results

3.1 Description of pathological lesions

Multiple small, primarily circular-shaped osteolytic lesions with sharply demarcated margins were macroscopically observed in the axial skeleton, *ossa coxae*, and scapulae. The lesions ranged from 1 mm to 8 mm in diameter. Some coalescing of lesions was observed, particularly in the vertebrae. Vertebrae from the cervical, thoracic, and lumbar regions were affected. Due to the fragmentation of many of the vertebral bodies, it was not always possible to precisely identify the specific vertebra affected. No new bone formation or evidence of healing were observed surrounding the lesions. Lesions were located on the lateral borders of the scapulae, the coracoid process of the right scapula (Figure 2), the manubrium, the right hemipelvis, and the bodies and neural arches of the vertebrae (Figure 3). However, due to the state of preservation, the full extent of osteolytic lesions of the infracranial elements of this individual cannot be discerned.

Radiography revealed additional lytic foci in the cancellous bone of the ribs and vertebrae which were not identified macroscopically because the lesions had not yet penetrated the cortical bone. The radiographic imaging indicates more extensive destruction of the hematogenous bone compared with the cortical bone (see Figure 3, Figure 4, Figure 5). This suggests that the marrow was the focal point of the disease. Imaging also confirmed that the skeletal lesions are osteolytic without sclerosis.

Within this
lesion the trabecular bone is smoothed with
scooped-out region

4.0 Discussion

The diagnosis of specific conditions in ancient skeletal remains is complicated by a number of factors, including some that are not found in clinical cases. In this case, the differential diagnosis of the observed lesions was made more difficult by the poor preservation and the incompleteness of the skeleton. The poor state of preservation of the appendicular elements resulted in an inability to determine the extent and distribution of the lesions in the appendicular skeleton. There are also several taphonomic processes that can result in small holes in archaeological bone, including roots and insect activity (Huchet et al., 2011). Although there is substantial taphonomic damage, the round and oval-shaped osteolytic lesions observed in the axial skeleton are not congruent with taphonomic damage. This is supported by the radiographic imaging of the lesions, which shows more extensive destruction of hematogenous bone compared with cortical bone.

Macroscopic and radiographic assessments indicate that the disease process in this individual is characterized by osteolytic activity, with no evidence of new bone formation. The distribution of the observed lesions is similar to that of some types of neoplastic disease, as these conditions can produce widespread lytic lesions (Biehler-Gomez et al., 2019; Rothschild and Rothschild, 1995). There are, however, a suite of conditions that can mimic one another. First, we ruled out possible infectious diseases that cause similar lesions. The lesions observed in this case are inconsistent with those that typically result from tuberculosis, as there is no evidence of destructive remodeling or vertebral body collapse. Osteolytic lesions, such as those noted, can also be caused by certain fungal diseases, including histoplasmosis, blastomycosis, and coccidioidomycosis. However, these mycotic infections are not endemic to Northwest China. The remainder of the differential diagnosis will concentrate on the following more likely conditions: Langerhans cell histiocytosis (LCH), metastatic carcinoma, leukemia, and multiple myeloma.

4.1 Langerhans cell histiocytosis (LCH)

LCH represents a spectrum of rare disorders that are characterized by idiopathic infiltration and accumulation of abnormal histiocytes in various tissues (Windebank et al., 2009). The clinical manifestations of LCH are highly variable but typically differ in adults and children, (Götz and Fichter, 2004; Stockschlaeder and Sucker, 2006). Osseous involvement is more common in children than in adults, and in both adults and children unifocal skeletal involvement is more common than multifocal involvement (Stockschlaeder and Sucker, 2006). Both the axial and appendicular skeleton are commonly affected. LCH has a predilection for the thoracic spine, followed by the lumbar and cervical spine. In most cases, skeletal involvement is limited to vertebral bodies and mostly spares the neural arches (Khung et al., 2013). In patients with LCH, periosteal reaction is often associated with osseous lesions. The radiographic features are variable and although the majority of bone lesions have a characteristic "punched out," radiolucent appearance, the margins of lesions can appear either well or poorly defined (Khung et al., 2013).

The characteristics of the osteolytic lesions described on M1187:R1 have some similarities to those described in adults with LCH, specifically well-defined "punched out" margins. However, there is no evidence of periosteal reaction associated with the osteolytic lesions. As unifocal lesions are more common in LCH, it is unlikely that the lesions observed were the result of LCH.

4.2 Metastatic carcinoma

Metastatic carcinoma is the most common type of metastasizing tumor, with skeletal involvement occurring relatively late in the disease process (Dorfman & Czerniak, 1998).

Metastatic carcinoma is a malignant neoplasm that arises in epithelial tissues, and spreads from the primary tumor site to other organs via the lymphatic system, hematogenous dissemination, or direct extension from the primary site (Coleman, 1997; Czerniak, 2015; Nielsen et al., 1991). Although any tumor can metastasize to bone, carcinomas that originate in the prostate and thyroid glands, breasts, lungs, and kidneys account for the majority of skeletal metastases (Gerratana et al., 2015; Macedo et al., 2017; Sternberg et al., 2013). The axial skeleton is most often affected, particularly the skull, *ossa coxae*, and scapulae (Marks and Hamilton, 2006). The long bones, particularly the metaphyses of the femora, are also commonly affected. The osseous expression of metastatic carcinoma is variable and can involve osteolytic, osteoblastic, and mixed skeletal lesions (Coleman, 1997; Marks and Hamilton, 2007; Mundy, 2002; Rothschild and Rothschild, 1995). The type, distribution, and density of metastatic lesions are dependent on the primary source of the tumor, its duration, and the age of the patient.

In dry bone, it can be difficult to distinguish lytic metastatic carcinoma from multiple myeloma, as both can cause multifocal osteolytic lesions that primarily affect the hematopoietic-rich elements in the axial skeleton (Strouhal, 1991). The key diagnostic features differentiating lytic metastatic carcinoma and multiple myeloma are the number, size, and radiographic appearance of the lesions (Rothschild and Rothschild, 1995; Rothschild et al., 1998; Strouhal, 1991). Metastatic carcinoma produces multiple lytic lesions that may coalesce, similar to those observed in this case. The lesions that commonly occur in metastatic carcinoma, however, tend to be less numerous and discrete, and are medium to large in size. Furthermore, lesions from metastatic carcinoma tend to be irregularly-shaped, with denticulations and scallops, rather than oval and similar in size, like the lesions observed on M1187:R1. Moreover, the margins of osteolytic lesions of metastatic carcinoma tend to have new bone formation, and the area surrounding the lesion is usually porous, whereas the lesions observed on M1187:R1 are purely osteolytic with no osteoblastic reaction around the margins of the punched-out lesions.

4.3 Leukemia

Leukemia is a broad term for cancers of myeloid or lymphoid cells of the bone marrow, further subdivided as either acute or chronic depending on how quickly the disease progresses. Bone involvement most often occurs in the acute types of leukemia that occur during childhood (Navarro et al. 2017; Sinigaglia et al., 2008). Although less common, skeletal manifestations can occur in adults with various subtypes of acute leukemia (Angsubhakorn and Suvannasankha, 2018; Kishore et al., 2016; Rothschild et al., 1997). The most commonly reported radiographic finding in clinical contexts is osteopenia, but the osseus changes seen with leukemia are variable and can include osteosclerosis, bone marrow necrosis, vertebral compression fractures, periosteal new bone formation, and lytic or sclerotic lesions (El-Ashwash et al. 2018; Angsubhakorn and Suvannasankha, 2018; Ashwash et al., 2016; Kishore et al., 2016; Navarro et al. 2017; Ricccio et al., 2013). The osseous changes reported in adults tends to be abnormal porous lesions that range in size from 0.1 - 0.2mm in size (Rothschild et al. 1997). Although there are no pathognomonic characteristics for leukemia, the size (1-8mm in diameter) and the "punched out" nature of the lesions observed on M1187:R1 are inconsistent with those observed in most cases of leukemia in adults.

4.4 Multiple myeloma

Multiple myeloma is a primary malignant tumor characterized by proliferation of malignant bone marrow plasma cells. The pathogenesis of multiple myeloma remains unknown, but it likely arises as a result of a combination of genetic and environmental factors (Becker, 2011; Morgan et al., 2012). Males are more commonly affected than females, and incidence increases with age in both males and females (Becker 2011; Kim et al., 2014; Wang et al., 2020). Multiple myeloma is the most frequent cancer to involve bone, with osteolysis resulting from disrupted bone formation and resorption homeostasis (Adamik et al., 2018). Osteolytic lesions in multiple myeloma develop when malignant plasma cells secrete a substance that triggers osteoclast activity and inhibits osteoblasts (Adamik et al., 2018; Angtuaco et al., 2004; Rabb et al., 2009). These lesions are typically uniformly small to medium-sized (5 mm to 2 cm in diameter) and are circular or ovoid in shape, with well-defined margins and no evidence of osteoblastic response of surrounding bone. Multiple lesions may coalesce (Biehler-Gomez et al., 2019). Lesions can be located anywhere in the skeleton but are most commonly found on the cranium, ribs, *ossa coxae*, and vertebrae (Borggrefe et al., 2015).

The macroscopic and radiographic appearance of the observed lesions on M1187:R1 are consistent with hematologic malignancy, specifically multiple myeloma. The lesions are purely osteolytic in nature, with sharp, well-defined margins and no evidence of sclerosis or new bone formation in the surrounding bone. The distribution of the lesions reflects a predilection for highly vascularized areas in the skeleton. The individual described here has extensive osteolytic lesions affecting the neural arches and ribs, with less concentrated lesions of the scapulae, manubrium, and *ossa coxae*, which are all relatively consistent in size. The concentration of lesions on the neural arches of M1187:R1 is slightly atypical for multiple myeloma. Some research has suggested that vertebral lesions in multiple myeloma are restricted to the vertebral bodies and are not found on the neural arches, whereas neural arch lesions are commonly seen in metastatic carcinoma (Jacobson et al., 1958). However, a recent study on clinically diagnosed individuals with multiple myeloma has shown that osteolytic lesions can be present on the vertebral neural arches (Biehler-Gomez et al., 2019).

4.5 Multiple myeloma: Past and Present

Cases of multiple myeloma have been identified in many different geographic areas that span from the Neolithic to modern times (Hunt et al., 2018; Morse et al., 1974; Riccomi et al., 2019; Strohaul and Kritscher, 1990). Multiple myeloma is the second most common hemopoietic malignancy in modern times, but is still an uncommon cancer (Wang et al., 2020). The global distribution of multiple myeloma is uneven, with higher incidence in developed countries (Becker, 2011). The etiology is poorly understood. There is some evidence that occupational exposure to certain pesticides may be correlated with increased risk (Baris et al., 2004; Perrotta et al., 2012). Interestingly, clinical data reveal that many of the risk factors for malignant diseases, such as tobacco and alcohol consumption, are not associated with increased risk for multiple myeloma (Becker, 2011). To date, obesity is one of the only factors associated with increased risk (Birmann et al., 2017; Larsson, 2007). There is some evidence that diets with inflammatory or insulinemic potential may play a role in the development of multiple myeloma in men (Lee et al., 2019), but the evidence for an association between diet and multiple myeloma risk is limited and inconclusive.

In China, the only other possible case of multiple myeloma that has been identified from the study of archaeological human skeletal remains is in an adult male from the Neolithic period (c. 6000 BCE) that was excavated from the Houtaomuga Site in Northeast China (Xiao, 2014). Although it is not possible to extrapolate trends in mainland China based on so few cases, the wide geographical distribution and temporal span of multiple myeloma in past populations suggests that risk for developing this disease has persisted in human populations for thousands of years (see >>>>). As the etiology remains poorly understood, it is hoped that the identification and analysis of additional archaeological cases may enable researchers to better examine the relationship between the environmental and the known inherited genetic risk factors (see Morgan et al., 2012). As it is unlikely that exposure to pesticides was a contributing factor to these archaeological cases, a future avenue of investigation could include an examination of associated environmental conditions, subsistence strategies, and diets. Such research may be able to add clarifying data to the ongoing discussion about the association between diet and risk for multiple myeloma.

5.0 Conclusion

The numerous small, relatively uniform, ovoid osteolytic lesions located throughout the axial skeleton observed on this adult male are consistent with multiple myeloma. This is one of the only cases of cancer identified in archaeological human skeletal remains from East Asia, and is the first published case of a hematopoietic malignancy from China. With limited evidence to suggest that incidence increases with modern risk factors (i.e. smoking, diet, alcohol consumption), further research into the history and distribution of multiple myeloma may help clarify the etiology. By placing case studies such as this into a temporal and spatial framework, in the future it will hopefully be possible to begin to interrogate possible underlying causes of cancer in ancient populations within the context of changing environmental conditions and subsistence strategies. It is hoped that this case study will contribute to future research that may ultimately further understanding of the underlying mechanisms that can lead to cancer in modern times.

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Figures

Figure 1: Skeletal inventory of M1187:R1. Shaded area indicates present skeletal elements, diagonal lines indicate highly fragmented skeletal elements.

Figure 2: Osteolytic lesions, indicated by arrows, on the a) ventral surface of the right scapula and b) posterior surface of right scapula c) X-ray showing osteolytic lesions with no sclerosis. Image by Jenna Dittmar.

Figure 3: Photographs and X-rays of vertebrae showing osteolytic lesions with clearly defined margins and no evidence of sclerosis. Image by Jenna Dittmar.

Figure 4: Radiograph of ribs showing osteolytic lesions without sclerosis. X-ray taken by Jenna Dittmar.

Figure 5: Photograph and X-ray of rib shaft showing osteolytic lesions. Photograph and X-ray taken by Jenna Dittmar.