First case of juvenile bone malignant neoplasm in ancient China: A subadult skeleton from the Northern Wei Dynasty (386-534 CE)

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First case of juvenile bone malignant neoplasm in ancient China: A subadult skeleton from the Northern Wei Dynasty (386-534 CE)

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Abstract Discoveries of juvenile bone malignant neoplasm in archaeological settings have been rare. This study presented the first case of a juvenile aged 14 to 16 years from Datong, China (386-534CE) with signs of bone malignant neoplasm. The skeleton was macroscopically examined with the aid of computed tomography imaging. Results demonstrated that a bony outgrowth was found on the distal one-third of the diaphysis of the left femur; periosteal new bone reaction was found on the adjacent cortex; the medullary cavity was invaded by the lesion. Osteosarcoma was considered the most likely diagnosis, with differential diagnoses of Ewing's sarcoma and chondrosarcoma. This rare case enriches our knowledge of the epidemiological pattern of osteosarcoma and other malignant neoplasms in the past.

1. INTRODUCTION

Bone neoplasms are neoplastic growth of tissues in bones with the specific etiology unknown in most cases (de Boer and Maat, 2018). Bone neoplasms can be divided into two categories, namely benign and malignant neoplasms (de Boer & Maat, 2018; Miller, 2008). Benign bone neoplasms are localized, without invading adjacent tissues or spreading to distant organs (Qiu and Zhang, 1987: 100-101). They usually develop slowly and are not life-threatening (Qiu and Zhang, 1987; Kirkpatrick et al., 2018). Benign bone neoplasms mainly include osteoma, osteoid osteoma, osteochondroma, chondroma, and chondromyxoid fibroma (Kan, 2012; Fang et al., 2020). In contrast, malignant bone neoplasms often grow rapidly and can infiltrate and metastasize, causing death ultimately (Qiu & Zhang, 1987; Kirkpatrick et al., 2018). Osteosarcoma, chondrosarcoma, Ewing's sarcoma, malignant fibrous histiocytoma, fibrosarcoma, and chordoma are common malignant bone neoplasms (Kan, 2012; Yang et al., 1992).

In archaeological settings, because soft tissues are difficult to preserve in archaeological contexts, bioarchaeological data of neoplasms are mainly bone neoplasms (Kirkpatrick et al., 2018). The majority are benign bone neoplasms (e.g., osteoid osteoma and osteochondroma), while malignant bone neoplasms have been rarely reported (Ruffano and Waldron, 2018). In China, bioarchaeological evidence for malignant bone neoplasms has only been found on one skeleton. It is an adult skull dated to 500-221 BCE from Nilka, Xinjiang with a diagnosis of parosteal osteosarcoma on the posterior of the left temporal bone (Zhang et al, 2019). However, a number of historical written records might have indicated the presence of bone neoplasms in ancient China (Table 1). For instance, a medical text dated from the Spring and Autumn to the Warring States periods (the eighth to third century BCE) described “hard mass on bones”. These medical suggest that the bone neoplasm might not be rare. In the rest of the world, malignant bone neoplasms have also been reported sporadically in archaeological settings. In relation to subadult skeletons, only osteosarcoma (n=9) and Ewing's sarcoma (n=1) have been reported to date (Table 2).

This study presented a possible malignant bone neoplasm on a subadult skeleton from the Dongxin cemetery (386-534 CE) in Datong, China. It is the earliest bioarchaeological evidence for juvenile malignant bone neoplasm found in Asia to date should it be verified.

2. MATERIAL AND METHODS

The individual of interest in this study (Museum catalogue number: 13DDXM799, referred as M799 thereafter) was excavated from the Dongxin cemetery (东信) in Datong (大同) of Shanxi Province, China (N 40°03'32", E 113°17'24") (Fig. 1). The typology of the grave goods found has indicated a time period of the early and middle Northern Wei (T'o-pa Wei) Dynasty (386-534 CE). In total, 1129 skeletons were excavated from the Dongxin cemetery, among them there were 11 juveniles (< 15 years), 154 youths-young adult (15-23 years), plus 90 subadults with age unidentified (< 18 years).

Since the excavation report has not been published, detailed archaeological data were unavailable yet. Briefly, Datong was the capital of the Northern Wei Dynasty, a regime established by the Xianbei (鲜卑) people. Xianbei initially were nomadic pastoralists on the Mongolian plateau. They entered and ruled North China during 386-439 CE, and adopted to the Han Chinese culture and customs through a self-imposed sinicization and assimilation (Tsiang, 2010; Wang, 2015; Frankopan, 2016; Zhang et al., in press).

Stable isotope analysis suggested that residents in Datong, along with individuals buried in the Dongxin cemetery, subsisted on a millet-based diet with the consumption of animal proteins ($\delta 13C$: -18.2‰~-7.8‰; $\delta 15N$: 8.6‰~13.3‰) (Hou et al., 2017). Millet agriculture, livestock rearing, and hunting provided the major food supplies.

The grave size and the quantity and quality of grave goods found in the Dongxin cemetery have indicated that people buried here were ordinary citizens with a similar socioeconomic status (Datong Institute of Archaeology, unpublished). Nevertheless, historical records and archaeological findings have indicated that people from different heritages co-lived at Datong, including the Han ethnic Chinese, the nomads from northwestern and northeastern China and the Mongolian Plateau. The individual of interest in this study was buried in a rectangular pit grave, with a pottery vessel and a lime pillow (Fig. 2a). As the lime pillow was a typical grave good for people with of Xianbei origin (Wang, 1960; Xv and Sun, 1985; Qiao, 2015; Zhang et al., in press), it was believed that this individual belonged to the Xianbei population.

The skeleton of M799 was well-preserved in the tomb, yet part of the skeletons were too fragile to be collected (Fig. 2b). Both right and left parietal bones and the mandible were complete, while other bones of the skull were damaged during collection. The clavicle and upper limb bones were well-preserved, along with most of the vertebrae. Bony outgrowth was found at the left femur (Figs. 2,3). The scapula, os coxae, sacrum, and lower limb bones were preserved. The sternum, most of the ribs, and most of the hand and foot bones were missing postmortem.

Sex and age at death were estimated by population-specific standards. Specifically, age at death was estimated by the fusion of the epiphysis and tooth eruption, and sex was estimated according to the features of the pelvis and the skull (Shao, 1985). The diameter of the middle femur was measured following Shao (1985) too.

All bone elements were macroscopically observed according to Roberts and Connell (2004: 35). Bone formation and destruction, along with the distribution, were investigated and recorded with the aid of CT imaging. Neoplasms related bone changes were recorded following both clinical (Greenspan et al., 2007; Huang, 2010; Wu & Liu, 2014; Chen et al., 2018) and paleopathological criteria (Mann, & Hunt, 2012; Ragsdale et al., 2018; Marques, 2019). Differential diagnosis of the pathologies observed were attempted, and then the implications of case were discussed from a historical perspective.

3. RESULTS

3.1 Estimates of Age at Death and Pathological Observations

The maxillary second molar had erupted indicates that the individual was at least

14 years old. Unfused long bones (humerus and femur) implied the individual was younger than 19 years old. Os coxae was also unfused, indicating that the individual was no more than 16 years old. Collectively, the status of the fusion of the epiphysis and dental eruption would indicate that an age at death 14-16 years for M799. Since the individual was a subadult, sex estimation was not carried out.

3.2 Pathological profile

3.2.1. General description of the lesion

M799 manifested massive bony outgrowth on the distal one-third of the diaphysis of the left femur (Figs. 2, 3). The bone mass protruded from the posterior aspect of the diaphysis (about 50 mm) and grew around it (Fig. 3). The adjacent cortex was largely destroyed, and the remaining bone surface was cancellous and porous (Figs. 3a, 4). Meanwhile, grey woven bone formed circumferentially as a thick layer on the middle one-third of the left femur, indicating an active pathological process at the time of death (Fig. 4). Furthermore, bone destruction was observed on the posterior aspect of the left patella, as indicated by irregular appearance (Fig. 3c). Although both left and right tibiae and fibulae were partially damaged postmortem, no abnormality was found on these bones. The right femur was found to be normal, and the comparison between the right and left lower limb bones showed no sign of asymmetry (Fig. 3a). No signs of pathology or anomaly were observed in the rest of the M799 preserved skeleton.

3.2.2. CT images

In CT images, a well-defined, high-density lobulated exophytic mass, or a cauliflower-like lesion, was present on the left femur (Fig. 4e-h). The density of the diaphysis was unevenly distributed, with the density of the dis-eased site being higher than it of the rest of the bone (Fig. 4e-f). The presence of the "string sign" - the cortex separating the lesion from the medullary cavity of the affected bone suggested that the mass was separated from the affected diaphysis of the left femur (Fig. 4g).The medullary cavity was invaded by the lesion (Fig. 4h).

4. DISCUSSION

4.1. Differential diagnoses

The pathological manifestation in M799 was a massive bony outgrowth on the distal one-third of the diaphysis of the left femur. CT images confirmed a "cauliflower-like" lesion with high density. These features suggested a malignant bone neoplasm. As the lesion observed in M799 was mainly osteoblastic, bone neoplasms that are predominantly osteoblastic were considered for differential diagnosis (Table 4).

4.1.1. Osteochondroma

Osteochondroma, also known as osteocartilaginous exostosis, is the most common benign bone neoplasm (Marques, 2019; Sekharappa et al., 2014; Kang et al., 2017). It often results from abnormal proliferation and differentiation of chondrocytes (Marques, 2019; Varotto et al., 2021). Osteochondroma tends to affect males rather than females (1.8:1 ratio), with an incidence peak at the age of 10-30 years (Wu and Liu, 2014; Marques, 2019). It most commonly occurs on the metaphysis of the long bones and pelvises, while the hand and foot bones can also be affected (Marques, 2019). The lesion usually appears as a cartilage-capped bony outgrowth (however, cartilage was difficult to preserve in archaeological settings), yet the medullary continuity between bony outgrowth and the affected bone can be observed (Kitsoulis et al., 2008; Marques, 2019). In M799, massive bony outgrowth was found at the distal one-third of the diaphysis of the left femur, rather than the metaphysis; it was separated from the medullary cavity of the left femur by the cortex. Meanwhile, no pathological signs of the pelvic skeletons of M799 were observed. Thus, osteochondroma could be ruled out.

4.1.2. Chondrosarcoma

Chondrosarcoma is a malignant neoplasm occurring in chondrocytes and mesenchymal tissue (Huang, 2010). Chondrosarcoma may occur at any age, although the majority of the individuals affected are adults aged 30-60 years. Males are more likely to be affected than females (Kufterin et al., 2018; Marques, 2019). Chondrosarcoma mainly affects the metaphysis of the long bones, pelvises, and ribs (Marques, 2019), causing osteolytic lesions with ill-defined margins and cortical penetration (Arnay-de-la-Rosa et al., 2015; Marques, 2019). In contrast, the lesion observed in individual M799 was bony outgrowth rather than osteolysis. It occurred on the distal one-third of the diaphysis of the left femur rather than the metaphysis. Moreover, there were no signs of pathology observed on the pelvis and ribs in M799. Thus, chondrosarcoma might be possible yet less likely.

4.1.3. Ewing's sarcoma

Ewing's sarcoma is one of the most common bone sarcomas in children, and it is rarely found in adults in contemporary populations (Smith-Guzmán et al., 2018; Marques, 2019). The age interval between 8 and 20 years is most frequently affected (Marques, 2019). Ewing's sarcoma mainly affects the long bones and pelvis, while on the long bones it commonly occurs on the diaphysis and proximal metaphysis (Wu & Liu, 2014; Marques, 2019). These are consistent with the age and lesion distribution in M799. However, Ewing's sarcoma often causes osteolytic lesions with ill-defined margins (“moth-eaten” or permeative), which are absent in M799. Thus, Ewing's sarcoma might be possible yet less likely.

4.1.4. Osteosarcoma

Osteosarcoma is the most common malignant neoplasm seen in children and young adults in contemporary populations (Vallejo, 2020). It mainly affects individuals aged 15 to 25 years old. The most commonly affected sites are the distal femur, the proximal tibia, and the proximal humerus (Wu and Liu, 2014). Osteosarcoma can be osteolytic or osteoblastic. Cortical destruction or thickening can be observed. Viewing from CT images, osteosarcoma tends to have a high density and grows around the diaphysis (Wu and Liu, 2014). Osteosarcoma rarely shows continuity with the medullary cavity of the affected bone (Hang and Chen, 2014). The lesion distribution and characteristics observed in M799, along with the estimated age at death, are consistent with those of osteosarcoma. Therefore, osteosarcoma is likely the diagnosis.

4.2. Impact of the malignant bone neoplasm on the individual M799

Modern medical research shows that patients with osteosarcoma often experience pain, localized swelling, and joint dysfunction (e.g., claudication or pathological fracture), while metastasis can occur (Wu et al., 2006; Guo and Xiong, 2014). Before 1970s when the chemotherapy had not been introduced, and the five-year survival rate of osteosarcoma was only about 20% (Botter et al., 2014). Therefore, osteosarcoma could be very fatal in ancient time.

Osteosarcoma often occurs in the metaphysis of the long bones, which could affect patients' joint function and daily life (Zhao, 2005). In M799, there was no difference in diameter between the two sides (Table 3), indicating that the disease has no asymmetric effect on the individual's femurs. Moreover, woven bone in grey color formed on the middle one-third of the left femur, indicating an active pathological process at the time of death. Thus, it was reasonable to argue that M799 might die within a short period of time. It is clinically found that osteosarcoma may have lung metastasis in 4-9 months (Guo and Xiong, 2014). Extrapulmonary metastasis mostly occurs in the vertebrae and pelvis, and the time of metastasis is 9-10 months (Zhang, 1977). Except for the left femur and patella, there was no bone abnormality in this individual, suggesting that this individual might not have bone metastasis. The devastating disease might have developed very quickly and the youth died shortly. This youth was buried properly, during a time and area where evidence of "tenderness of burial" was found (Zhang et al., in press) . It was believed that the youth had received terminal care as well.

4.3. Rare malignant bone neoplasms in subadults

Malignant bone neoplasms have been reported sporadically among children (Table 2). Among all cases being reported, osteosarcoma has been the most common

(Suzuki, 1987; Strouhal et al., 1997; Alt et al., 2002; Ortner, 2003; Capasso, 2005; Nerlich et al., 2006; CRAB, 2018; Ruffano and Waldron, 2018; Smith-Guzmán et al., 2018;). Ewing's sarcoma is very rare, and other malignant bone neoplasms (such as chondrosarcoma, chordoma, etc.) have not been reported in children yet. The tumor-like lesion observed in M799 was likely to be osteosarcoma. Meanwhile, the published bioarchaeological data on osteosarcoma have shown that the long bones of individuals aged 8-25 years are most commonly affected. The age and lesion distribution in M799 are consistent with the pattern of osteosarcoma. This is the first bioarchaeological evidence for juvenile malignant bone neoplasm found in China should it be verified.

According to the Database of Cancer Research in Ancient Bodies (CRAB), most individuals with malignant neoplasms were from Northern Europe (18.7%, 51/272), followed closely by Northern Africa (16.9%, 46/272). In Asia, however, only a few skeletons were reported to have malignant neoplasms (2.6%, 7/272) (Hunt et al., 2018). Such uneven distribution of data may result from the poor preservation of the skeletons, lack of paleopathological studies, and lack of standard terminologies and diagnostic criteria in some regions (Marques, 2019; Marques et al., 2021). These problems are especially prominent in China and Asia, where paleopathology is undeveloped (Tayles et al., 2012; Berger and Pechenkina, 2020). Bioarchaeological data of malignant neoplasms in mortuary populations were extremely rare in China, which makes further interpretations currently impossible. Thus, to advance bioarchaeological research on neoplasms, standard recording and diagnostic criteria should be adopted, and multiple analytical methods should be used (e.g., biochemical analysis of bone neoplasms) (e.g., following Hunt et al., 2018; Nerlich, 2018), and a big data project is warranted (Wang and Zhang, 2020). Nonetheless, this rare case enriches our knowledge of the epidemiological pattern of osteosarcoma and other malignant neoplasms in the past.

5. CONCLUSION

A subadult skeleton (14-16 years of age) excavated from the Dongxin cemetery in Datong, China and dated to 386-534CE, manifested massive bony outgrowth on the diaphysis of the left femur. Osteosarcoma was most likely diagnosis, with differential diagnoses of Ewing's sarcoma and chondrosarcoma. This is the first bioarchaeological evidence for subadult malignant bone neoplasm found in China, which enriches our knowledge of malignant bone neoplasms among subadults in the past. Further intensive analysis of archaeological skeletons in Asia using standard recording and diagnostic criteria is warranted.

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Research data and images will be available in public domain after the completion and publication of the findings. Entities include Jilin University and Texas A&M University.

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FIGURE LEGENDS

FIGURE 1 Location of the Dongxin cemetery, Datong, Shanxi Province, China

FIGURE 2 The grave (a) and collected skeleton (b) of M799

FIGURE 3 Comparison of the right and left femur (a). Woven bone formation on the middle one-third of the diaphysis of the left femur (b). Bone destruction on the posterior aspect of the left patella (c).

FIGURE 4 The mass of bony outgrowth in M799. (a-d) Multi-angle-view showing bony outgrowth on the distal one-third of the diaphysis of the left femur. (a) Anterior view, (b) Posterior view, (c) Medial view, and (d) Lateral view. (e-h) Multi-angle CT images of the left femur showing a well-defined, high-density lobulated exophytic mass. (e-f) The density of the diaphysis was unevenly distributed, with the density of the diseased site being higher than it of the rest of the bone. (g) Blue arrows point to the "string sign". (h) Red arrow points to the mass; blue arrow points to the new bone formation within the medullary cavity. The cortical bone around the mass was destroyed.

TABLE 1 Chinese historical records regarding tumor-like lesions on bones (Jiang, 2018; Liu, 2012)

Ancient Chinese Medial Documents	Date	Records of bone diseases
Ling Shu: Ci Jie Zhen Ye 《灵枢·刺节真邪》	Warring States Period (5th-3rd century BCE)	Gangrene
Wu Shi Er Bing Fang 《五十二病方》	Warring States Period (5th-3rd century BCE)	Bone gangrene; treated by white berry
Bei Ji Qian Jin Yao Fang 《备急千金要方》	Tang Dynasty (7th-10th century CE)	Eight categories of tumors: gallbladder tumor, osteoma, lipoma, pomegranate, sarcoma, abscess, hematoma, and polyma
Wai Tai Mi Yao 《外台秘要》	Tang Dynasty (7th-10th century CE)	Symptoms and treatments of bone diseases
Qian Jin Yi Fang·Ying Bing Di Qi 《千金翼方·瘿病七》	Tang Dynasty (7th-10th century CE)	Symptoms and treatments of bone diseases
Wai Ke Shu Yao 《外科枢要》	Ming Dynasty (14th-17th century CE)	Symptoms and etiologies of bone diseases
Wai Ke Zheng Zong·Duo Gu Ju Lun 《外科正宗·多骨论》	Ming Dynasty (14th-17th century CE)	Symptoms and etiologies of bone diseases
Wai Ke Shu Yao·Lun Liu Zhui 《外科枢要·论瘤赘》	Ming Dynasty (14th-17th century CE)	Symptoms and etiologies of bone diseases
Yi Xue Ru Men 《医学入门》	Ming Dynasty (14th-17th century CE)	Symptoms and etiologies of bone diseases

TABLE 2 Subadult malignant neoplasms found in archaeological contexts

Sex	Age	Time period	Area	Lesion distribution	Neoplasm type	Reference
Male	15+	700 CE	Switzerland	Humerus	Osteosarcoma	Capasso, 2005; Ortner, 2003
Unknown	15-18	Historic	Canada	Proximal end of the left tibia, distal end of the femur, and proximal end of the fibula	Osteosarcoma	CRAB, 2018
Unknown	12-14	800-900 CE	Germany	Distal end of the right humerus and proximal end of the ulna	Osteosarcoma	CRAB, 2018
Unknown	8-10	1100-1200 CE	Germany	Proximal metaphysis of the right femur	Osteosarcoma	Alt et al., 2002
Unknown	14-16	1265-1380 CE	Panama	Midshaft of the right humerus	Osteosarcoma	Smith-Guzmán et al., 2018
Unknown	16-23	Pre-contact	Hawaii, US	Distal femur	Osteosarcoma	Suzuki,1987;Ortner, 2003
Unknown	18-20	Bronze Age	Spain	Left side of the skull	Ewing's sarcoma	CRAB, 2018
Female?	18-20	1400-1800 CE	Germany	Skull	Osteosarcoma	Nerlich et al., 2006
Male	16-18	6th-8th century CE	Germany	Femur	Osteosarcoma	Ruffano & Waldron, 2018
Male	15-25	13-17th century CE	Czech Republic	Skull	Osteosarcoma	Strouhal et al., 1997

TABLE 3 The diameters of the femur at diaphysis. Unit: mm

	Sagittal diameter of the femur at middle shaft	Transverse diameter of the femur at middle shaft
Left femur	21.84	28.46
Right femur	22.53	28.86

TABLE 4 Differential diagnoses for the lesions observed in Dongxin M799

	Age distribution	Sex	Bone elements involved	Periosteal new bone reaction	Cortical destruction	Lesion characteristics	Diagnosis
Dongxin M799	14-16	Unknown	Left femur only	+	+	Lesion margins are well-defined.	Most likely osteosarcoma
Osteosarcoma	15-25	Majorly males	The metaphysis or diaphysis of long bones	+	+	Lesion margins are variable.	Most likely
Ewing's Sarcoma	8-20	Majorly males	The metaphysis or diaphysis of long bones and pelvises	+	+	Lesion margins are moth-eaten/ permeative	Possible yet less likely
Chondrosarcoma	30-60; although any age can be affected	Majorly males	The metaphysis of the long bones, pelvises, and ribs	+	+	Lesion margins are ill-defined	Possible yet less likely
Osteochondroma	10-30	Majorly males	The metaphysis of the long bones, pelvises, and hand and foot bones	-	-	Lesion margins are well-defined and bony outgrowth continues with the host bone.	No

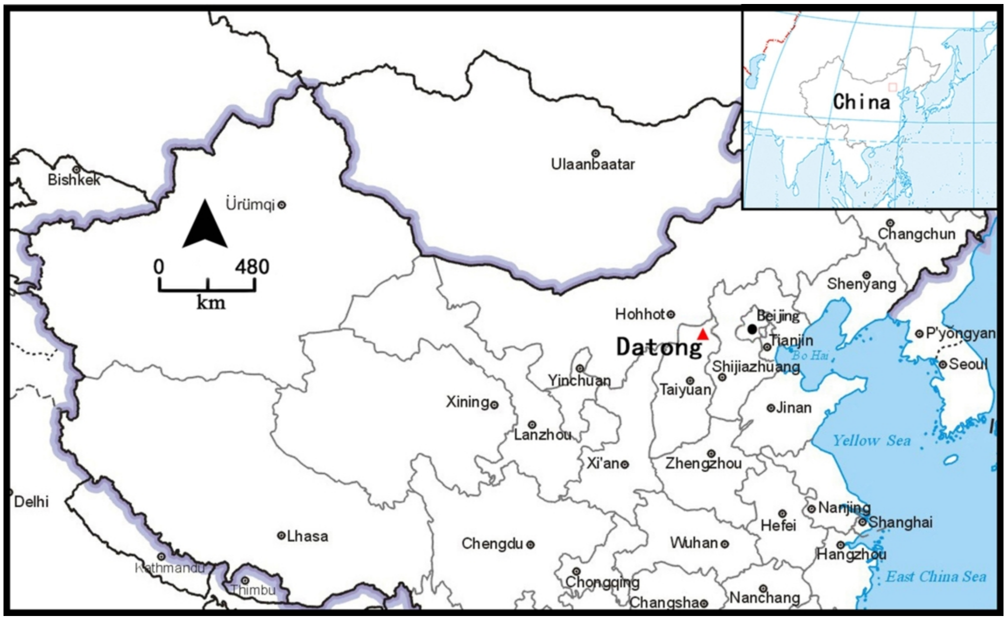

FIGURE 1 Location of the Dongxin cemetery, Datong, Shanxi Province, China

102x63mm (600 x 600 DPI)

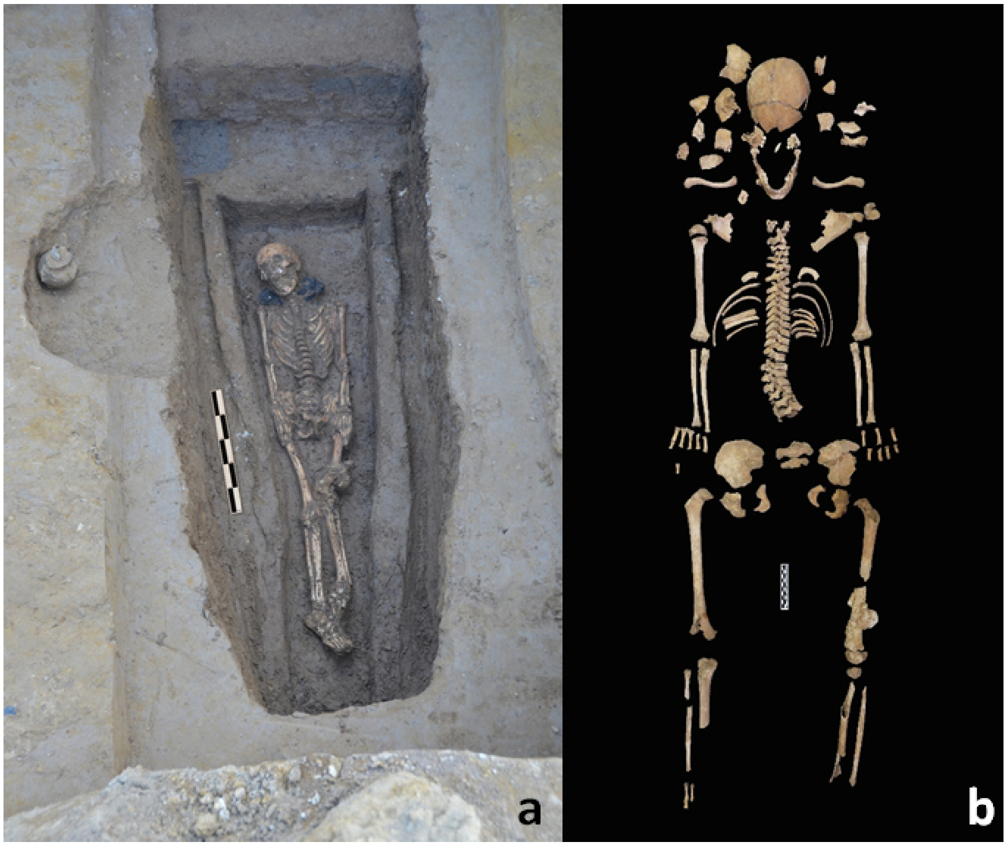

FIGURE 2 The grave (a) and collected skeleton (b) of M799

179x150mm (96 x 96 DPI)

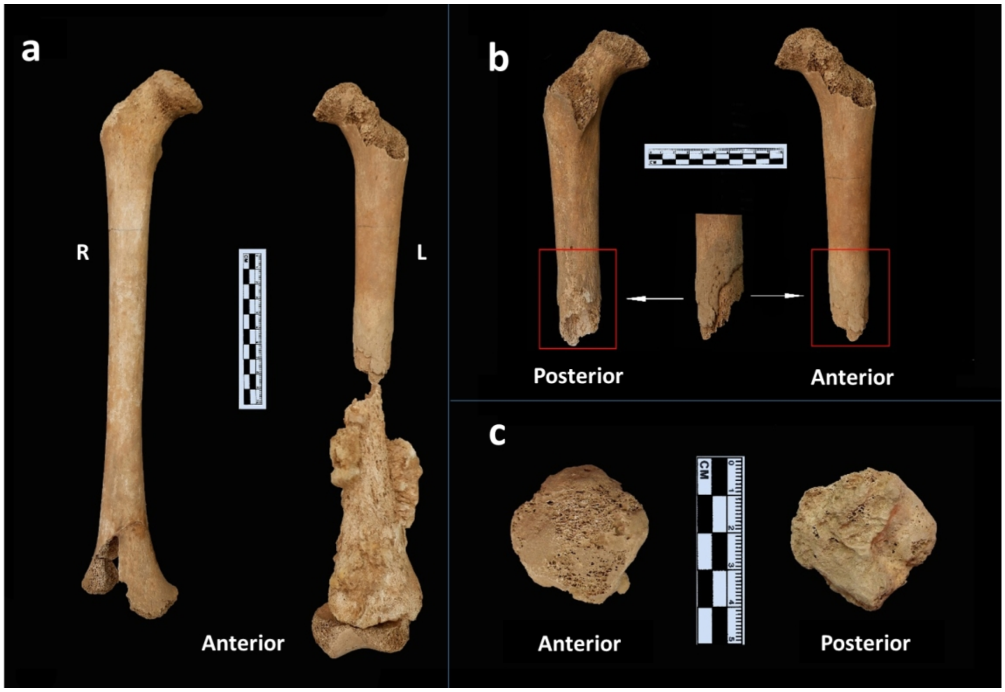

FIGURE 3 Comparison of the right and left femur (a). Woven bone formation on the middle one-third of the diaphysis of the left femur (b). Bone destruction on the posterior aspect of the left patella (c).

416x284mm (96 x 96 DPI)

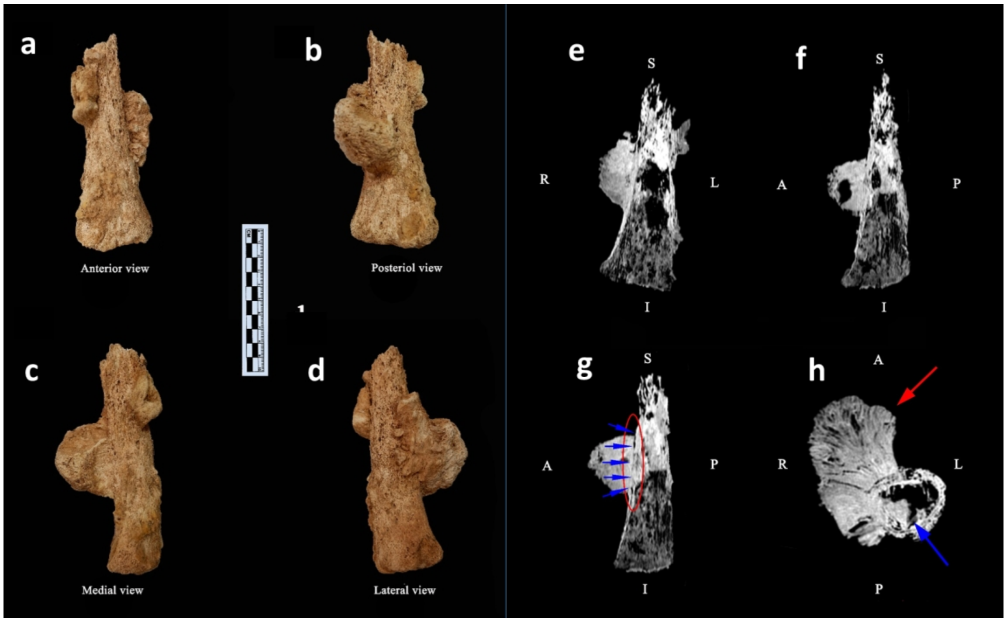

FIGURE 4 The mass of bony outgrowth in M799. (a-d) Multi-angle-view showing bony outgrowth on the distal one-third of the diaphysis of the left femur. (a) Anterior view, (b) Posterior view, (c) Medial view, and (d) Lateral view. (e-h) Multi-angle CT images of the left femur showing a well-defined, high-density lobulated exophytic mass. (e-f) The density of the diaphysis was unevenly distributed, with the density of the diseased site being higher than it of the rest of the bone. (g) Blue arrows point to the "string sign". (h) Red arrow points to the mass; blue arrow points to the new bone formation within the medullary cavity. The cortical bone around the mass was destroyed.

445x273mm (96 x 96 DPI)