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A probable case of metastatic carcinoma in the medieval Netherlands

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Abstract
Despite recent considerable gains, our knowledge of cancer in antiquity is still limited. This paper discusses an adult individual from a Dutch medieval hospital site who demonstrates osteoblastic and osteolytic lesions on the ribs, scapula, clavicle, and vertebrae. The morphology, radiographic appearance, and distribution of the skeletal lesions suggest that this individual was affected by metastatic carcinoma. This case increases the number of publications that present an osteoblastic and osteolytic response to cancer and contributes to the body of evidence for archaeological neoplastic disease. For the Netherlands, this individual presents the first published case of probable metastatic carcinoma with mixed skeletal lesions.

Keywords: cancer, osteoblastic lesions, osteolytic lesions, Middle Ages, paleo-oncology

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1. Introduction

In modern times, cancer is the second leading cause of death worldwide (WHO, 2018). In 2015, the disease was responsible for 8.8 million deaths, meaning that one in six deaths was due to cancer (Bray, 2014; WHO, 2018). As a result of the second epidemiological transition many countries witnessed a decrease in infectious disease and a concomitant increase in mortality associated with chronic, non-communicable diseases, such as cancer (Bray, 2014; Harper and Armelagos, 2010). In the last decades, cancer prevalence has also increased in low-income countries as a result of population growth and increasing ages-at-death as well as the adoption of certain behavioural and lifestyle habits common in industrialised countries such as the consumption of calorie-dense foods, smoking, and physical inactivity (Bray, 2014). This has drastically increased the global cancer burden (Bray, 2014; Jemal et al., 2010).

Even though more knowledge on neoplastic diseases is gained every day, still little is known about cancer in antiquity (Binder et al., 2014; Capasso, 2005; Marques et al., 2017). Its infrequent observation in archaeological human remains from past populations has resulted in the misconception that neoplastic diseases are only associated with modern living conditions and longer life spans (Binder et al., 2014; Lieverse et al., 2014; Marques et al. 2007). Although indeed an uncommon encounter in past populations, cancer is not a solely modern disease. Bony lesions associated with cancer in hominins appear to date back to 1.7 million years ago (Odes et al., 2016) and in the last 20 years there has been an increase in reported cases from archaeological remains dating to various time periods (Assis and Codinha, 2009; Binder et al., 2014; Caruso et al., 2017; Lieverse et al., 2014; Marques et al., 2017; Melikian, 2006; Schultz et al., 2007; Smith, 2002; Wasterlain et al., 2011). However, publications on neoplastic diseases in archaeological skeletons remain scarce. To contribute to the growing body of evidence for cancer in past populations, this paper presents a case of probable metastatic carcinoma from the medieval Netherlands.

2. Materials and methods

The individual (S4051V1051) with lesions suggestive of metastatic carcinoma was found in a cemetery belonging to a medieval hospital in Kampen, the Netherlands (figure 1). The infirmary, dedicated to St. Gertrude, was established in AD 1382 and was in use until 1598. Historical records indicate that the hospital initially functioned as a place where travellers and the sick were cared for temporarily. Later however, the infirmary also offered permanent housing to the chronically ill and elderly (Klomp, 2016). In preparation for construction on the site, the area of the infirmary and the associated cemetery were excavated in 2014 by archaeologists from the municipality of Zwolle and a team from the Laboratory for Human Osteoarchaeology, Leiden University. Although a large part of the cemetery was already disturbed by previous construction, a total of 89 primary inhumations and many unassociated human skeletal elements were recovered (Klomp, 2016; Schats, 2016). All primary inhumations have been analysed osteologically (see table 1). The individual who is the subject of this paper was poorly preserved and incomplete; only fragments of left scapula, left clavicle, ribs, and one thoracic neural arch remain (table 2). Therefore, reliable estimations of age-at-death and sex were not possible. However, the morphology of one unidentified sternal rib end (phase 5-6, (Işcan et al., 1984)) indicates that the individual was probably a middle to old adult (35+ years of age-at-death).

Fig. 1: Map of the Netherlands. Kampen is indicated in red.

Table 1: Sex and age-at-death distribution Kampen osteological collection (n=89).

The skeletal remains were examined using gross inspection following the standard palaeopathological guidelines (Ortner, 2003; Waldron, 2009). The pathological changes were described, photographed, and measured whenever possible. Additionally, radiographs were taken of the skeletal remains using a handheld Nomad Pro x-ray (75 kV, 2.0 µA, exposure: 0.1-0.2 sec.).

3. Results

3.1 Gross examination

All surviving bones of this individual display osteolytic lesions and new bone formation located both subperiosteally and intramedullary. An overview of all skeletal lesions is presented in table 2. The left scapula (figure 2) shows diffuse and small osteolytic lesions with sharp margins, ranging from 0.5-1 mm in size, with surrounding reactive bone on the anterior and posterior lateral border and on the inferior angle resulting in an irregular surface appearance. The supraspinous, infraspinous, and subscapular fossae also display new subperiosteal bone formation which has a spiculated appearance, but with fewer osteolytic lesions (figure 2). The patches of new bone formation range from 15 to 23 mm in size. The glenoid fossa, besides showing early indications of osteoarthritis, does not appear to be affected by this pathological process.

Table 2: Characterisation of all skeletal lesions.

Fig. 2: Left scapula, anterior (left) and posterior aspect (right), showing irregular and spiculated new bone formation as well as osteolytic lesions.

In total, 21 rib fragments were recovered, all of which appear to be from the left side of the body, although not every piece can be sided due to the substantial fragmentation. The rib fragments demonstrate subperiosteal and intramedullary new bone formation and show destructive lesions on both visceral and exterior surfaces. The appearance of the exterior surface is less irregular and mainly displays a diffuse osteolytic process with ill-defined margins (figure 3a-b). The small osteolytic lesions on the exterior surface perforate the cortex and are sharp and rounded, ranging in size from 1 to 6 mm. The visceral surface shows more reactive bone deposition extending across the complete fragment, as well as larger osteolytic lesions (8-10 mm) with round margins, which are mainly concentrated in the costal groove (figure 3c-e). Additionally, four of the rib fragments show transverse fractures of the body (figure 3f), most of which are healed, with possible non-union in one instance but this difficult to determine due to taphonomic damage. Although impossible to judge definitively, the many rib fractures may be related to the pathological process responsible for the other skeletal lesions.

Fig. 3a-f: Rib fragments (vertebral end to right side of the image. Fragment numbers correspond to table 2). a) Fragment 8: exterior surface, b) Fragment 12: exterior surface, c) Fragment 22: visceral

surface, d) Fragment 18: visceral surface, e) Fragment 16: inferior surface, f) Fragment 20: exterior/superior surface, healed transverse fracture visible on right.

An unidentified neural arch fragment, most likely thoracic, shows major destruction of the cortical bone surface as well as marked new bone formation (figure 4a). The posterior surface is mainly affected but the anterior surface also shows a small area of destruction. The lateral end of the left clavicle (figure 4b) also appears affected by the pathological process. The superior aspect shows only a few small osteolytic lesions (0.5-1 mm), while the inferior aspect is irregular with multiple, slightly larger osteolytic lesions with rounded margins (1-2 mm).

Fig. 4: a) Thoracic neural arch: posterior aspect, b) Acromial/lateral end clavicle: superior aspect.

3.2 X-ray examination

The x-ray images confirm that the skeletal lesions have a mixed character: the radiographs show areas of bone loss and clear regions with increased radiodensity. There is an overall loss of definition in the internal bone architecture. Osteolytic lesions (with moth-eaten margins) are especially apparent on the images from the rib fragments, however, there are also clear areas with sclerosis (figure 5a-b). Radiographs show destruction of most of the original cortex of the rib fragments and the mottled appearance of the ribs points to disorganised bone formation in the medullary cavity. In comparison to a non-pathological rib from another individual from the same site, there appears to be an increase in radiodensity (figure 5c). The scapula also shows strong evidence for both osteolytic and osteoblastic lesions. On the inferior portion of the lateral border, osteolytic lesions are particularly apparent, but the entire bone shows evidence for the deposition of disorganised new bone on the internal aspect (figure 5d). The clavicle fragment shows retention of normal cortical structure in most parts, however, the internal bone architecture appears disorganised and demonstrates increased radiodensity and osteolytic foci (figure 5e). The neural arch fragment (figure 5f) also has a mixed character on x-ray with clear areas of increased radiodensity.

Fig. 5a-f: X-ray images (75 kV, 2.0 µA, exposure time indicated in brackets). a) Fragment 8: exterior surface (0.15s), b) Fragment 15: superior surface (0.18s), c) Non-pathological rib fragment, same site (0.18s), d) Scapula: anterior aspect (0.15s), e) Lateral/acromial end clavicle: superior aspect (0.1s), f) Thoracic neural arch: posterior aspect (0.2s)

4. Discussion

4.1 Differential diagnosis

The disease process in this individual is characterised by osteolytic activity as well as marked irregular periosteal and endosteal new bone formation. On x-ray, it is clear that there is an increase in radiodensity of all bones and deposition of disorganised bone. The rough, disorganised and occasionally spiculated appearance suggests that the responsible disease was fairly aggressive (Rana et al., 2009). A differential diagnosis is challenging since this skeleton is poorly preserved and incomplete. Therefore, commenting on the distribution of the lesions and the extent of the

pathological process is problematic. Nevertheless, based on the appearance and location of the observed lesions certain diagnostic options can be excluded.

Owing to the fact that the ribs and vertebrae were affected, tuberculosis or another chronic infectious lung disorder might be suggested as a possibility (Roberts et al., 1998; Santos and Roberts, 2006). However, tuberculosis typically causes osteolytic lesions on the anterior vertebrae (the bodies) and rarely affects the posterior vertebral segments (Steyn et al., 2013). While poor preservation prevents assessment of the anterior vertebrae in this individual, the posterior neural arch is clearly affected and demonstrates new bone formation which is unlikely for tubeculosis (Lovász et al., 2010; Steyn et al., 2013). Moreover, while the osteoblastic reponse on the ribs seen in this individual fits with a diagnosis of tuberculosis or another infectious lung disorder, usually only the visceral (internal) surface of the ribs are affected in lung conditions (Roberts et al., 1998; Santos and Roberts, 2006), in contrast to the internal and external rib lesions seen in this individual.

Syphilis, a disease known to occur in the skeletal collection from Kampen (Schats 2015, 2017), causes mixed lesions on the skull and long bones characterised by a combination of destruction and healing, especially on the cranium (Hackett, 1975). Although the skull and long bones are missing in this case, the fact that the ribs are heavily affected makes syphilis an improbable diagnosis since this disease rarely affects the bones of the thorax (Park et al., 2014). Moreover, lesions diagnostic of syphilis, i.e., expansion of bones with superficial cavitation and gummatous lesions (Hackett, 1975) are not present in this individual. Therefore, the roughened, occasionally spiculated, skeletal lesions present in this individual are not deemed typical of syphilis. A similar argument can be made for haematogenous non-specific osteomyelitis. While this infection can result in osteoblastic and osteolytic lesions, the bones of the thorax are rarely affected (Aufderheide and Rodríguez-Martín, 1998). Moreover, osteomyelitis causes irregular, densely thickened surfaces with cavities (cloaca), which are absent in the Kampen individual (Aufderheide and Rodríguez-Martín, 1998; Ortner, 2003).

Although skeletal involvement is rare (Ortner, 2003), there are several fungal (mycotic) infections which could result in the type of lesions seen in this skeleton (Hershkovitz et al. 1998). Fungal diseases, such as histoplasmosis, blastomycosis, and coccidioidomycosis are known to cause similar (osteolytic) skeletal lesions, yet, these infections, while common in the Americas and Africa, are unknown to occur in the Netherlands (Aufderheide and Rodríguez-Martín, 1998; Ortner, 2003). Cryptococcosis, on the other hand, has a worldwide distribution (Aufderheide and Rodríguez-Martín, 1998; Ortner, 2003) and may therefore have been responsible for the skeletal pathology observed in this skeleton. A cryptococcosis infection can cause multiple, disseminated, discrete osteolytic lesions like those seen in the skeleton discussed here. However, new bone formation is very rare in this fungal disease (Aufderheide and Rodríguez-Martín, 1998; Behrman et al., 1990) and because this is clearly present in the individual studied here, cryptococcosis is considered an unlikely diagnosis.

Paget's disease of bone is a condition that initially causes skeletal lesions that are mainly osteolytic and osteoporotic in nature, after which mixed lesions can occur with the deposition of large amounts of irregular new bone (Mirra et al., 1995; Ortner, 2003). Therefore, the skeletal lesions observed in this individual could be attributed to Paget's disease. The new bone formation associated with Paget's disease is usually widespread and often results in a marked thickening of the cortex which is not observed in the individual discussed here where the new bone formation is more patchy (Brickley

and Ives, 2008; Mirra et al., 1995). While the classic radiographic characteristics of Paget's disease such as cutting cones in the long bones, cotton wool appearance of the skull, and picture-frame and ivory vertebrae cannot be observed due to the incomplete nature of the skeleton, the x-rays of this individual do not show the marked cortical thickening and the accentuated pattern of trabecular bone expected in Paget's disease (Brickley and Ives, 2008; Doyle et al., 2002; Mirra et al., 1995), making it an improbable diagnosis.

Multiple myeloma, a malignant disorder of the plasma cells, has frequent skeletal involvement (Ortner, 2003). The disease usually starts in a single location in the bone marrow, but quickly disseminates to multiple sites and can affect all parts of the skeleton (Giuliani et al., 2006; Ortner, 2003; Rothschild et al., 1998). The disease is characterised by diffusely distributed, small osteolytic lesions with no new bone formation (Roodman, 1997; Rothschild et al., 1998). Therefore, the clear osteoblastic component and irregular size and shape of the lesions in this individual argue against this diagnosis. A similar argument can be made for melanoma, a type of skin cancer. While bone metastases are relatively uncommon compared to other cancers (14-45%, Coleman, 1997), this cancer can cause metastases, predominantly in the spine and ribs (Brountzos et al., 2001). However, while mixed lesions can occur on rare occasions, most patients will present with solely osteolytic lesions (Brountzos et al., 2001), not fitting with the combined osteoblastic and osteolytic lesion in the individual discussed here.

Metastatic carcinoma refers to malignant neoplasms that arise in epithelial tissue and have spread to other organs such as the skeleton (Coleman, 2001). While the cancer cells can reach the bone through the lymphatic system or as a result of direct extension from a primary soft tissue tumour, most commonly they spread to the skeleton through haematogenous dissemination (Coleman, 1997; Nielsen et al., 1991). Thus, metastatic carcinoma commonly affects areas rich in bone marrow, such as the vertebrae, pelvis, ribs, scapulae, skull, and long bones (Coleman, 1997; Mundy, 2002; Nielsen et al., 1991). Carcinomas that metastasise to bone often osteolytic, osteoblastic, or mixed skeletal lesions, depending on the original location of the tumour (Coleman 1997; Mundy 2002). The irregular shape, distribution, and appearance of the lesions in this individual support the diagnosis of metastatic bone disease from a carcinoma. Moreover, pathological fractures are likely to occur as a result of bone metastases, especially when there is both and osteoblastic and osteolytic response (Keller and Brown, 2004). While new bone is produced, its mechanical properties are actually reduced since the bone is woven in nature and of inferior quality. The combination of this suboptimal woven bone production with osteolysis promotes pathological fractures (Coleman, 2006; Keller and Brown, 2004), which frequently occur in the ribs or vertebrae (Coleman, 2006). This individual has several rib fractures, which would therefore fit the diagnosis of metastatic carcinoma.

Carcinomas that commonly metastasise to bone can arise in many soft-tissue structures including the prostate, breast, lung, thyroid, kidney, and gastrointestinal tract (Aufderheide and Rodríguez-Martín, 1998; Coleman, 2006, 2001; Mundy, 2002, Ortner, 2003). While the poor preservation and incompleteness of this individual make it very difficult to identify the primary site of the carcinoma, it is clear that the lesions are both osteoblastic and osteolytic in nature which can help to narrow down the soft-tissue origin. Skeletal metastases associated with a primary origin in the thyroid, kidney and gastrointestinal tract are predominantly lytic in nature and only very rarely have an osteoblastic

response (Coleman, 1997, 2006). Those originating in the prostate, breast, and less likely lung, can give rise to a mixed response in the skeleton (Coleman 1997).

From those three diagnostic options, it is clear that prostate cancer is the most likely to cause skeletal metastases. Recent studies have shown that 90% of individuals present with bony metastases at autopsy (Bubendorf et al., 2000; Keller and Brown, 2004). While prostate cancer is generally associated with osteoblastic lesions (Mundy, 2002), clinical studies show that bone metastases associated with this type of cancer promote both osteolytic and osteoblastic activity (Guise et al. 2006; Keller and Brown 2004). Bone lesions associated with prostate cancer are generally located in the spine and pelvic boens, but also the ribs, long bones, and the skull can be a site were lesions occur (Bubendorf et al., 2000). Breast cancer is also very likely to cause skeletal lesions; 69% to 80% of individuals with advanced disease have skeletal involvement at autopsy (Coleman and Rubens, 1987; Guise and Mundy, 1998; Kozlow and Guise, 2005). Breast cancer is generally associated with osteolytic lesions, however, up to 25% of individuals with breast carcinoma will develop osteoblastic lesions similar to those seen in prostate cancer (Mundy, 2002), although lower numbers of 10% (Nielsen et al., 1991) and 15% (Kozlow and Guise, 2005) are also reported. Skeletal metastases associated with breast cancer are usually found in the vertebrae and pelvis, followed by the ribs, skull, and femur (Hamaoka et al., 2004). Lung cancer is associated with skeletal metastases in 10-40% of cases which are located most commonly in the spine and ribs (Ebert et al., 2004; Morgan et al., 1990; Tsuya et al., 2007). Generally these are osteolytic in nature but occasionally osteoblastic lesions can occur as well (Resnick and Kransdorf, 2005). Considering the similar morphology and distribution of the three primaries, it is not possible to distinguish between them at this time. Therefore, metastatic carcinoma, originating either in the prostate, breast, or lung, is considered the most likely diagnosis for the skeletal lesions observed in this individual.

4.2 Social and historical context

The town of Kampen was a thriving urban centre in the medieval period. As one of the cities in the Hanseatic League, trade was flourishing and the city most likely experienced a substantial influx of people and goods from outside (Klomp 2016). Unfortunately, very little is known about the individual discussed here apart from his or her final resting place. Interestingly however, the fact that he/she was recovered in a hospital cemetery, which suggests that this individual sought help for his/her disease. Skeletal metastases are associated with considerable morbidity and debilitating symptoms; one of the most common is pain (Coleman, 1997). While there is unfortunately limited information available about medieval health care in the Netherlands, we may assume that the staff were able to provide some pain relief and care until he/she died.

As in the rest of the world, cases of cancer are rare in the Dutch archaeological record. From the medieval period onwards, only a handful of cases are reported in the (grey) literature (e.g., Aten, 1989; Maat et al., 2002; Onisto et al., 1998; Rijpma and Maat, 2005). To best of the authors' knowledge, there are no documented cases of cancer predating the medieval period. Although the descriptions of Dutch cases are limited, they appear to be solely osteolytic in nature, which would, tentatively, make this individual the first published case of metastatic carcinoma with mixed lesions in the Netherlands. This case emphasises the importance of careful recording and consideration of both osteolytic and osteoblastic lesions in differential disease diagnoses. Moreover, this example

showcases that even in poorly preserved and incomplete skeletons much information may still be evident that improves our understanding of past populations.

5. Conclusion

An adult individual from medieval Kampen presented with osteoblastic and osteolytic lesions in the thoracic region. The morphology, radiographic appearance, and distribution of the skeletal lesions suggest that this individual was affected by metastatic carcinoma with a most likely origin in the prostate, breast, or lung. Most of the publications on metastatic carcinoma describe cases that are osteolytic in nature; this is especially true for Dutch publications. Therefore, this case increases the number of publications that discuss a mixed response to cancer and ultimately contributes to the body of evidence for archaeological neoplastic disease. For the Netherlands, this individual is the first published case of probable metastatic carcinoma demonstrating mixed skeletal lesions.

Although the preservation of the skeleton may limit biomolecular research, future research should include ancient DNA analysis to attempt to identify the sex of the individual which may shed light on the primary origin of the carcinoma. Additionally, proteomic research specifically focused on retrieving tumour markers (Schultz et al., 2007) could substantially improve the diagnosis.

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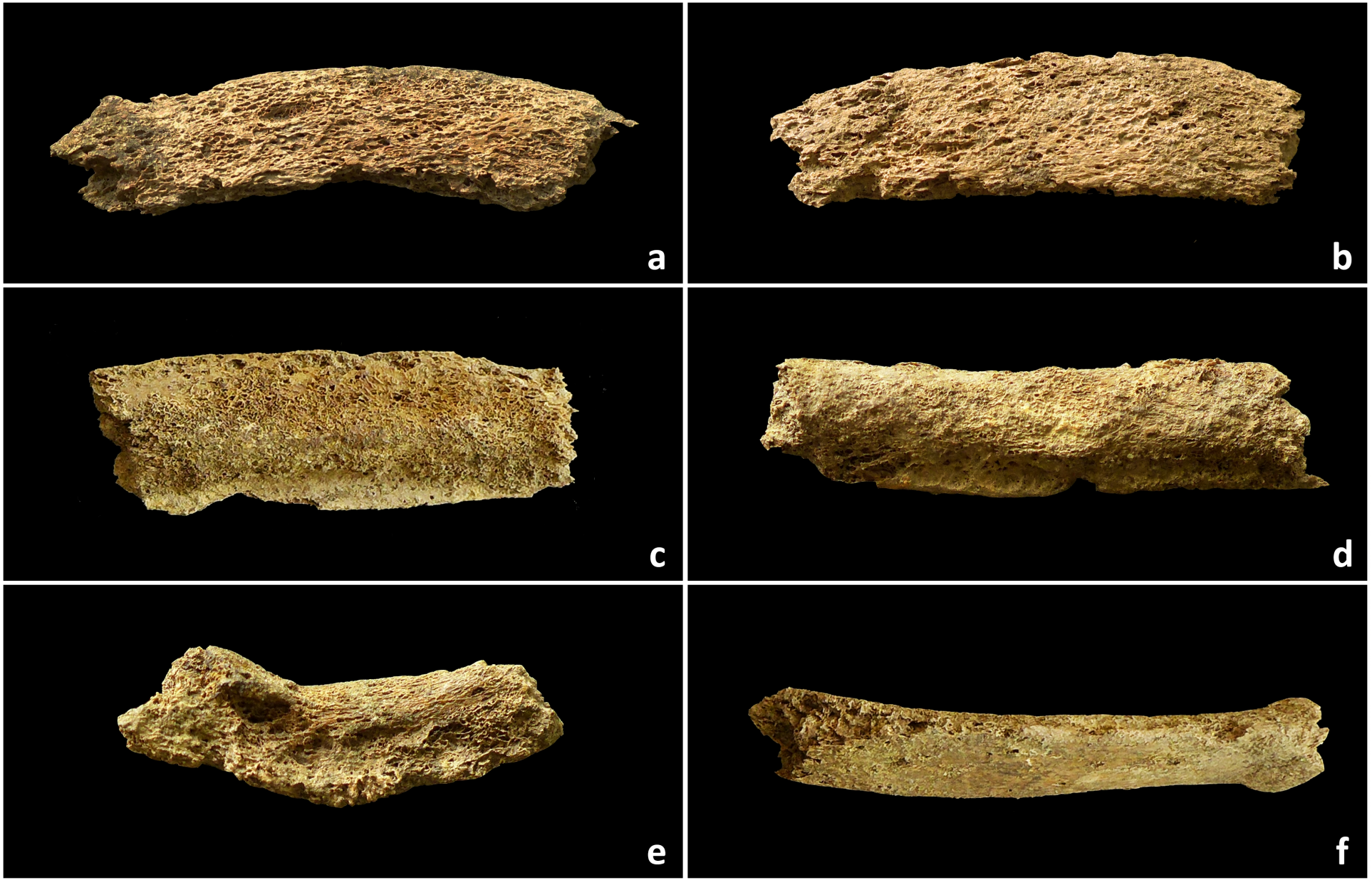
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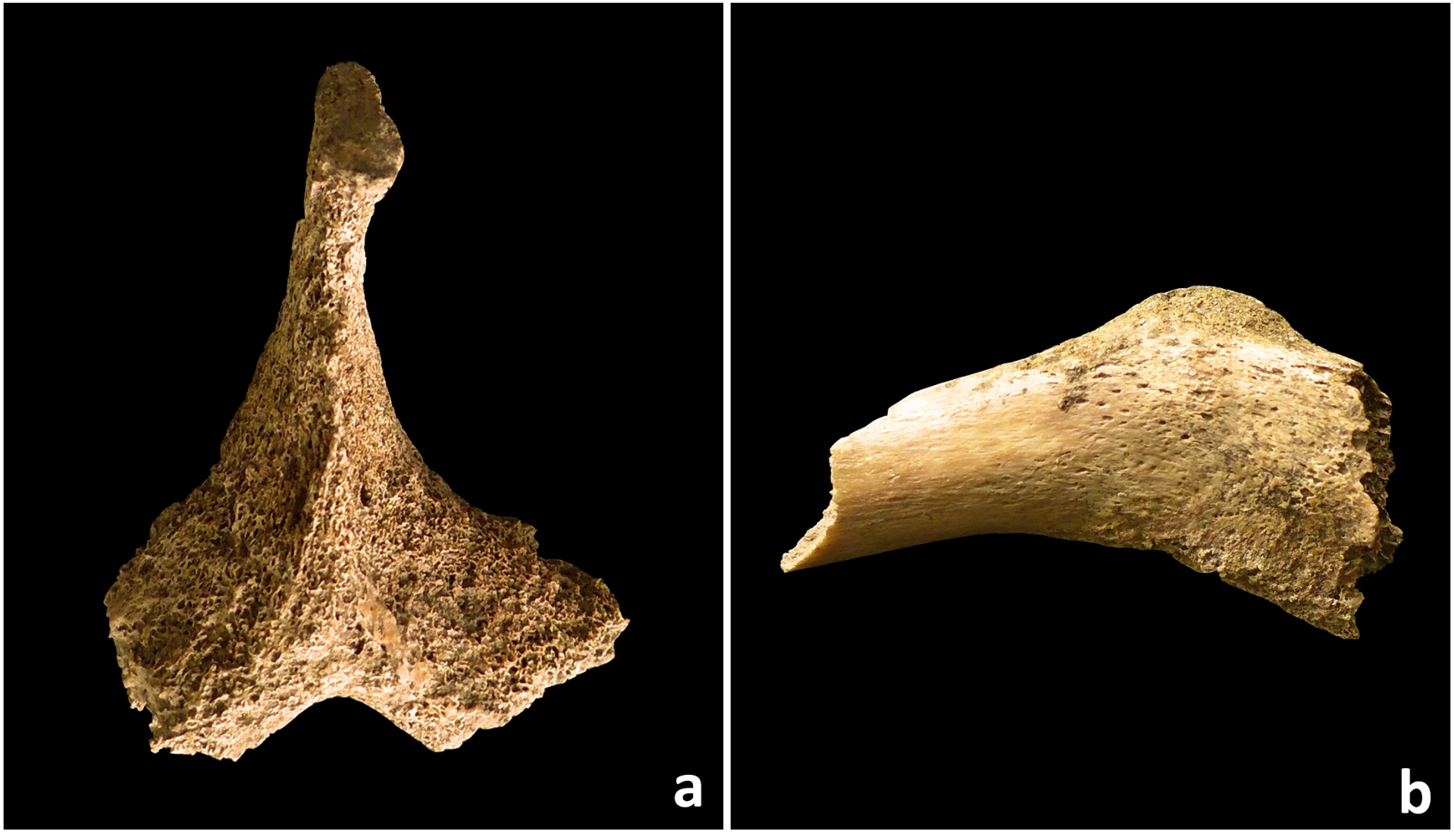
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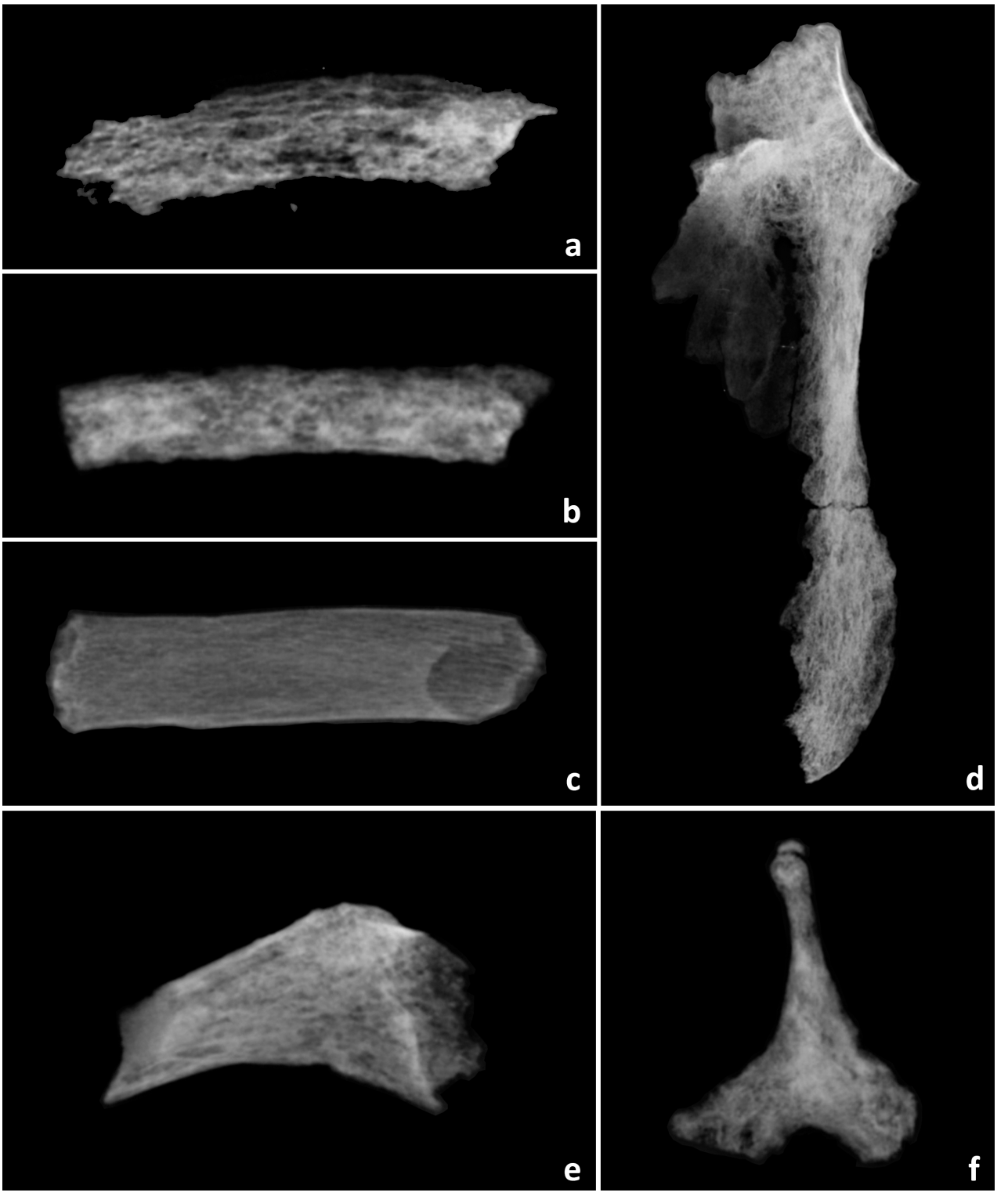
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Age-at-death in years	Males		Females		Indeterminate		Total	
	n	%	n	%	n	%	n	%
<0							0	-
0-3							0	-
4-12					5	-	5	5.6
13-18					6	-	6	6.7
19-25	5	33.3	7	46.7	3	20.0	15	16.9
26-35	12	75.0	3	18.8	1	6.3	16	18.0
36-45	10	52.6	7	36.8	2	10.5	19	21.3
46+	8	72.7	3	27.3	0	-	11	12.4
Indet.	7	41.2	4	23.5	6	54.5	17	19.1
Total	42	47.2	24	27.0	23	25.8	89	100

Lesion/ fragment	Bone	Side	Aspect	Type	Remarks
1	Scapula	L	Lateral border (ant. + post.)	Mixed	
2	Scapula	L	Inferior angle (ant. + post.)	Mixed	
3	Scapula	L	Infraspinous fossa	Mixed	
4	Scapula	L	Supraspinous fossa	Mixed	
5	Scapula	L	Subscapular fossa	Mixed	
6	Clavicle	L	Lateral portion (sup. + inf.)	Mixed	
7	Thoracic vertebra	-	Neural arch (post.)	Mixed	
8	Rib fragment: Rib 3?	L	Vertebral end (exterior + visceral surface)	Mixed	
9	Rib fragment: Rib 3?	L	Body (exterior + visceral surface)	Mixed	
10	Rib fragment: Rib 3?	L	Body (exterior + visceral surface)	Mixed	
11	Rib fragment: Rib 4?	L	Vertebral end (exterior + visceral surface)	Mixed	
12	Rib fragment: Rib 4?	L	Body (exterior + visceral surface)	Mixed	
13	Rib fragment: Rib 4?	L	Body (exterior + visceral surface)	Mixed	
14	Rib fragment: Rib 5?	L	Vertebral end (exterior + visceral surface)	Mixed	
15	Rib fragment: Rib 5?	L	Body (exterior + visceral surface)	Mixed	
16	Rib fragment: Rib 6?	L	Vertebral end (exterior + visceral surface)	Mixed	
17	Rib fragment: Rib 6?	L	Body (exterior + visceral surface)	Mixed	
18	Rib fragment: Rib 6?	L	Body (exterior + visceral surface)	Mixed	Healed transverse fracture
19	Rib fragment: Rib 7?	L	Body (exterior + visceral surface)	Mixed	
20	Rib fragment: Rib 7?	L	Body (exterior + visceral surface)	Mixed	Healed transverse fracture
21	Rib fragment: Rib 8?	L	Body (exterior + visceral surface)	Mixed	
22	Rib fragment: Rib 8?	L	Body (exterior + visceral surface)	Mixed	
23	Rib fragment: unid.	?	Body (exterior + visceral surface)	Mixed	
24	Rib fragment: unid.	?	Body (exterior + visceral surface)	Mixed	Healed transverse fracture, callus visible
25	Rib fragment: unid.	?	Body (exterior + visceral surface)	Mixed	Healed transverse fracture, callus visible
26	Rib fragment: unid.	?	Body (exterior + visceral surface)	Mixed	
27	Rib fragment: unid.	?	Body (exterior + visceral surface)	Mixed	
28	Rib fragment: unid.	?	Sternal end (exterior + visceral surface)	Mixed	Healed transverse fracture, slight callus