PROBABLE PROSTATE CANCER IN A PRE-INCAIC INDIVIDUAL FROM PUKARA DE LA CUEVA, NORTHWESTERN ARGENTINA

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ABSTRACT

Prostate carcinoma is a common malignant neoplasia that mostly metastasizes to bone in males. Nonetheless, the number of paleopathological cases reported is very small and only two from South American individuals, almost of them being identified in Europe. The purpose of this paper is to document the lesions identified in a new Pre-Columbian (around 1400 AD) individual that corresponds to a middle-aged male from Pukara de la Cueva, Jujuy province, in the Northwest region of Argentina. The skeleton was found disarticulated but it is nearly complete and well preserved. The overall character of the lesions observed is predominantly proliferative in nature, but osteolytic and mixed patterns were also detected in both axial and appendicular skeleton. Macroscopically, this overall pattern and the distribution of the lesions are compatible with a secondary cancer. Radiological examination showed multiple dense areas with sclerotic borders in several bones, which confirm the previous diagnosis of prostate carcinoma. The exuberance and dissemination of the lesions all over the skeleton led infer individual cachexy implying that he would have been assisted by his family and/or social group during the chronic process. Carcinogenic risk factors are also discussed in order to ascertain the possible causes of the disease. This analysis adds a new evidence of a Pre-Columbian carcinoma in a South American native population and enhances the possibilities of an adequate differential diagnosis.

Key words: tumor, metastases, proliferative bone, osteolytic lesions, paleopathology.

INTRODUCTION

Prostate cancer is one the most aggressive malignant tumor that metastases in bone, with around 70-90% of the patients developing osteoblastic and osteolytic lesions in the skeleton (Aufderheide and Rodríguez-Martín, 1998; Coleman, 2001; Ortner, 2003; Keller and Brown, 2004; Resnick and Kransdorf, 2005; Marks and Hamilton, 2007; Waldron, 2009). Even so, there are few cases reported in the paleopathological bibliography. In South America, only two Peruvian skeletons with prostate metastases were identified, one from the Pre-Incaic site of Huaca Las Ventanas, dated 900-1100 AD (Baraybar and Shimada, 1993) and the other from Caleta de San José, dated ca. 1375-1475 AD (Klaus, 2008). In North America, only Ortner (2003) inferred the presence of prostate cancer in a 1500-1600 AD individual from Florida. Schultz and co-authors (2007) claimed to have morphological and biochemically diagnosed the most ancient case of the Old World in Siberia (2700 years old), although de la Rúa et al. (1995) studied an older Neolithic (ca. 5000 years BP) individual from the site of San Juan Ante Portam Latinam, in the Basque Country, using macroscopic, radiographic, microscopic and chemical analyses. Other skeletal evidences of prostate metastases in Europe are a cremated individual from the 1st century AD in Italy (Grevin et al., 1997) and five Medieval cases: one from a cemetery near Dubendorf, Switzerland (Ortner and Putschar, 1981), a skeletal specimen from Homokmégy-Székessite, Hungary (Zink et al., 2004; Molnar et al., 2009), another from Svendborg, Denmark (Tkocz and Bierring, 1984) and two recovered in England, one from Canterbury (Anderson et al., 1992; Wakely et al., 1995) and the other from Wharram Percy (Mays et al., 1996). Finally, there is a more recent case from the 19th century AD London analyzed by Waldron (1997), and an identified skeleton from the Lisbon collection was macroscopically and histologically studied by Assis (2013).

As can be seen from this bibliography survey, evidence of this condition is rare worldwide and not previously reported in the Argentinean territory. The goal of this paper is to analyze a pre-Incaic human skeleton temporally located within the local period known as *Período de los Desarrollos Regionales II* (PDRII; ca. 1250-1430 AD) that shows osteoblastic, osteolythic and mixed lesions compatible with a metastatic carcinoma of the prostate. The intense bone response consequence of the pathological development was probably responsible of the progressive physical weakness and health deterioration of this individual, interfering with his living conditions and the daily activities of the social group to which he belonged.

THE PUKARA DE LA CUEVA SITE

The term *pukara* relates to pre-Hispanic settlements, located in elevated, naturally defended places, usually with difficult access and very good visibility. They were frequently surrounded by a defense wall and included numerous conglomerated dwellings (Madrazo and Ottonello, 1966; Ruiz and Albeck, 1997; Tarragó, 2000). The Pukara de la Cueva is an archaeological site located in La Cueva gorge at Humahuaca district, Jujuy province, Northwestern Argentina. In this area, numerous archaeological sites with chronologies between the Later Formative and Inka Periods (from ca. 900 AD to 1536 AD) were identified (Nielsen, 2001; Ramundo, 2012). Pukara de la Cueva is located 3500 meters above sea level, has approximately 1000 square meters and more than 150 architectural structures along with internal circulation areas, several probable public areas, stockyards and access pathways (Basilico, 1998; Ramundo, 2012). The people who lived in this pukara were mainly potters, agriculturalists and long-distance pastoralists (Ramundo 2012).

In the first archeological surveys that took place in the 1930', primary inhumations of adult individuals in a seated flexed position were found under the floor of three residential units. Casanova (1933) very briefly described these findings, without further laboratory research. Since 1980's, this site has been subject of new investigations (Basílico, 1998). In 2008, a 3 m x 4 m excavation was done using modern archaeological methodologies and commingled human remains were found near the foundations of a pre-Hispanic wall (Fig. 1). During laboratory analyzes a minimal number of 6 individuals was estimated: three non-adults (two infants and one adolescent), two middle adult females and an adult male. During this process, it was observed that a group of bones with the same color, robustness and relative size showed similar massive pathological lesions, indicating that they belonged to the same male individual, called “skeleton number 5” (Aranda et al., 2012). Two radiocarbon dates were obtained from this individual (540 ± 60 and 549 ± 30 years BP in an humerus -LP 2268- and a rib -MTC-15600- fragment, respectively; Aranda et al., 2012), placing him just prior to the arrival of the Inca in the area.

Figure 1. Area of the excavation showing the commingled bones and the Pre-Hispanic wall.

MATERIAL AND METHODS

The human remains of the 6 individuals were studied and, beside oral pathology, 5 of them didn’t show macroscopic evidence of pathologies in their bones (Aranda et al., 2012). The specificity and the rarity of the conditions observed in the adult male (# 5) forced to the elaboration of a detailed examination, focus of this paper. This individual is a fairly complete skeleton (Fig. 2) with well preserved bones except for the skull which is very fragmented and incomplete. From the postcranial skeleton, only the left patella and several small bones such as those from feet were absent. According to standard methods (Buikstra and Ubelaker, 1994), this skeleton belonged to a middle-aged male (Aranda et al., 2012).

The bones were observed in detail, macroscopically and with a magnified lens. The lesions identified were both proliferative and osteolytic, but a mixed form was also detected. The distinction between woven and lamellar new tissues was stated taking into account the descriptions given by Ortner (2003) and Matos and Santos (2006). In order to observe the general distribution of the lesions, their location was recorded in a skeletal diagram (Fig. 2). After the description of the pathological manifestations sixteen bones, with and without osseous changes, and from different anatomic regions, were selected to radiological exam. Radiographs were taken in Imagen Test facilities with a Toshiba Monocomando Digital equipment, Dinar model, and the images were processed using a Digital Carestream program.

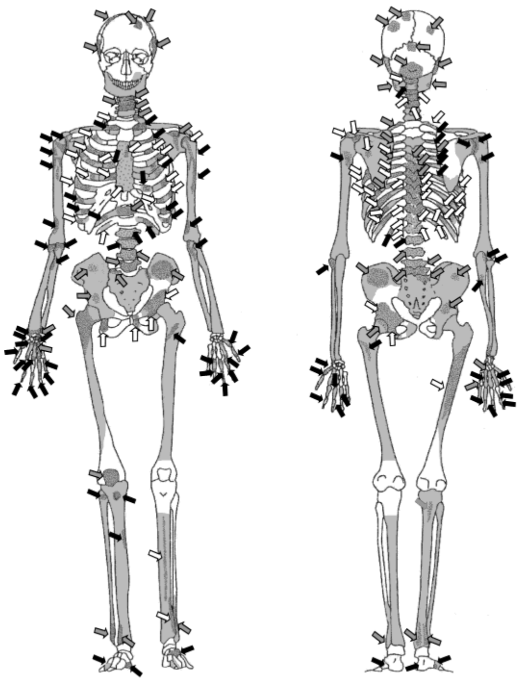

Figure 2. Skeletal sketches with the bones recovered in light grey and the pathological lesions signed in dark grey. Grey arrows point to proliferative lesions, black to osteolytic and white to both types of bone reactions.

RESULTS

The distribution of the lesions along the skeleton is provided in Table 1 and in Figure 2. Pathological manifestations are bilateral and present all over the skeleton. The intraskeletal distribution shows that only proliferative lesions occur alone in the skull. In the post cranial skeleton both types are present, with predominance of bone growth in the axial area (Fig. 3) and in the pelvis. New bone formation is visible in bones as the scapula (Fig. 4) and ribs (Fig. 5). Osteolytic defects are mostly present in the upper limb and in the distal ends of lower limb bones. The most outstanding lesions were recorded in both os coxae, especially in the left (Fig. 6). Both visceral (Fig. 6A) and posterior (Fig. 6B) surfaces are affected by pathological lesions. The iliac fossa is covered by a layer of new bone, reaching ca. 14 mm in high, with numerous spiculae perpendicular to the cortical surface (Fig. 6C), while in the posterior views of the ilium alae and in the ilioischial region (Fig. 6D) there are massive outgrowths of highly irregular spiculae. The proximal thirds of the femora show the same trend of bone growth (Fig. 7). The proliferative lesions observed in this skeleton are mainly spiculated, in disorganized (Fig. 5) or organized (Fig. 6C) patterns, although dense undulating periosteal reactions are also seen in areas such as the gonial region of the mandible and several rib epiphyses (Table 2). No laminate appearance is seen in the cortex of any bone.

The radiological examination revealed multifocal and geographic dense areas with sclerotic borders in fragments of the skull, scapula, vertebrae (Fig. 8), coxae (Fig. 9), femora and ribs (Fig. 10). In the radiographs, the ulna (Fig. 10) and the hand phalanges are apparently non-affected, despite the slight osteolytic lesions macroscopically visible in some of the proximal and distal epiphyses (Fig. 2).

DIFFERENTIAL DIAGNOSIS AND DISCUSSION

Malignant tumors are a major problem in nowadays societies. There are multiple factors attributable to its high incidence, but to understand the natural history of these conditions it is important to firstly trace their evolutionary pathways. Evidences of these diseases are rare in ancient populations, because paleoncology counts with very few cases as the identification and differential diagnosis are difficult in skeletal derived samples. In general, the most affected bones for any secondary cancer are those of the vertebral column, pelvis girdle, thorax, proximal epiphyses of humerus and femora, in concordance with the main location of the hematopoietic marrow (Thillaud, 1996). The dissemination may occur through the circulatory or lymphatic systems, promoting the proliferation of multiple lesions in the specific areas where lymphatics and arteries enter the bone structure (Marks and Hamilton 2007). Metastatic bone tissues, even in those cases predominantly osteolytic, may show a variable amount of bone reaction (Marques et al., 2011). Thus, the identification of the primary focus should be made mainly done considering the difference between proliferative or erosive nature of the lesions and their location (Ortner, 2003). An exuberant osteoblastic activity with very sclerotic borders and in occasions also with some bone destruction is, according to the specialized literature, mainly a response to prostate cancer in males, although primary tumors in the lung, kidney and thyroid cannot be ruled out (Rosenthal, 1997; Aufderheide and Rodríguez-Martín, 1998; Ostendorf Smith, 2002; Ortner, 2003; Chhem and Brothwell, 2008; Waldron, 2009). Secondary lesions to prostate cancer are more sclerotic and proliferative, while those provoked by lung carcinomas are mainly osteolytic (Schultz et al., 2007; Waldron, 2009). Recent studies had identified that the development of prostate cancer metastases produces osteoblastic new bone depositions associated with osteoclastic activity, both derived from the same whole process (Mundy, 2002; Keller and Brown, 2004). Thus, the case presented in this paper is more likely related to the first type of disease.

In PDR period, direct primary inhumations below the floors of the domestic dwellings were common in Northwestern Argentina (Lafón, 1967; Palma, 1998; Nielsen, 2001, among others) and secondary single or collective burials were also sometimes found (e.g. Nielsen 2001). In this case, despite the fact that the bones of the 6 individuals recovered are commingled and associated with some cultural items, such as decorated and non-decorated ceramic shreds of PDRII, some lithic artifacts, faunal bones, ochre and valve beads (Aranda et al. 2012), there is no evidence of important postmortem osseous deterioration caused by taphonomic agents. Thus, it is impossible to know if the spatial arrangement within the assemblage was a consequence of a cultural practice or due to a posterior sediment removal that affected the bone distribution. Beside this consideration, only the bones corresponding to the male showed the lesions previously described, considered to be the effect of the proliferation of a metastazing carcinoma with a prostatic primary focus.

According to Lastres and Cabieses (1959) malignant tumors, primary or metastatic, where commonly present in Pre-Columbian populations. In the present territory of Argentina, one case of metastatic carcinoma was previously reported, a pre-Hispanic hunter-gatherer middle-aged male from Western Pampas. As it only shows multiple osteoclastic activity in the axial skeleton and proximal epiphyses of femora and humeri, the primary focus could not be precisely identified (Luna et al., 2008). On the contrary, the male individual under analysis in the present paper exhibits striking new bone formations in specific areas of the skeleton, being the first case in which the soft tissue formerly affected was recognized. The concomitance among new bone formation, osseous destruction and mixed lesions, their distribution along the skeleton and the sex and age of the individual, is consistent to a metastatic carcinoma of the prostate (Ortner, 2003; Marks and Hamilton, 2007; Brothwell, 2008). The external contours of some of the affected bones, especially those of the visceral area of the pelvic girdle, are much altered as massive new subperiosteal bone is deposited in the form of mossy and dense spiculae. The lesions "typically display a mixture of osteolytic and osteoblastic reactions with sharp, distinct scallop-shaped borders and borders with attendant osteoblastic remodeling" (Marks and Hamilton, 2007: 228-229). Only the pathological signals recorded in fibulae and hand and foot bones are slight and mainly erosive in this case. Although rectal cancer tends to produce a rather similar pattern of strong new bone deposition, the overall distribution, the extreme and almost exclusively osteoblastic activity of the metastases and the compactness of the resulting secondary tissue usually deposited in the axial, pelvic and thoracic areas (Rosenthal 1997; Resnick and Kransdorf 2005; Assis 2013), is dissimilar enough to discard it as a primary focus of the neoplastic disease.

A spicular periosteal reaction is usually observed in rapid and aggressive conditions such as malignant tumors (Ortner, 2003; Assis, 2013) and has been categorized in three different subtypes depending on the size and orientation of the spiculae: hair-on-end and sunburst pattern, velvet, and disorganized (Wenaden et al., 2005; Rana et al., 2009; Assis, 2013). According to these authors, the hair-on-end pattern is characterized by parallel bone spiculae perpendicularly projected from the cortex of the bone, as the lesions present at the os coxae. The spiculae tend to be long and thin in the focus of the pathological activity, decreasing in height in the surroundings. In the sunburst appearance the proliferation of new bone shows radial outgrowths starting from a clear center point, and spiculae don't have the perpendicular orientation characteristic from hair-on-end. This is visible in the rib diaphyses (Fig. 5) and in the acetabular and pillar area of the coxae. The velvet reaction shows short and local oblique spiculae with a smooth appearance. This manifestation is present in several areas of the skeleton, such as in the mandible, the ribs, the scapulae and the ilia. The fourth subtype seen in this case, defined by disorganized spiculae leading to a non-patterned appearance, is present in elements from all the anatomic portions (see Table 2).

Bone response to disease is limited to formation or destruction and abnormalities in size, shape and density (Ortner, 2003). That's why many diagnoses of secondary tumors need radiological examination in paleopathological studies to adequately precise the primary focus of the malignancy (Brothwell, 2012). This was not mandatory in the case under analysis since the lesions were macroscopically evident; however, the radiographs clearly showed the dispersion and characteristics of the lesions in the inner structure of the bone, giving much more strength to the differential diagnosis. The massive replacement of the spongy cells of the marrow substance by dense new formed bone, inferred in the radiopaque radiograph signals, must have provoked chronic anemia during the final phase of the life of this man (see Schultz et al., 2007). Moreover, other systemic symptomatology suffered should have been bone pain, progressive physical weakness, impaired mobility and finally the systemic collapse (Keller and Brown, 2004). This process should have caused an incremental impairment related to the final phase of the disease (Dettwyler, 1991; Hawkey, 1998) and a consequently almost full assistance of some of his relatives or other members of the social group.

Direct aetiology of neoplasias is still not completely known and multificatorial (Brothwell, 2008). Risk factors are diverse and include genetic, epigenetic, demographic and environmental (mainly occupation and nutrition) aspects (Brothwell, 1967; Aufderheide and Rodríguez-Martín, 1998; Krtolica *et al.*, 2001; Hsing and Chokkalingam, 2006; Masoro, 2006; Waldron, 2009). According to Hsing and Chokkalingam (2006: 1388), "as much as 42% of the risk of prostate cancer may be accounted for by genetic influences", although dietary habits and lifestyle factors are also two of the main contributors of the occurrence of clinical prostate cancer (see e.g. Shen and Abate-Shen, 2010). Isotopes values obtained for this individual ($\delta^{13}C$ = -20.2‰) indicate a very low maize consumption and a diet based on C3 vegetables and herbivore animals (Aranda et al., 2012), so that diet seems not to have been a fundamental contributor in the development of the disease. Some authors also refer that endogamous groups are more susceptible to this diseases through mutation transmission due to small population size (v.g. Halperin, 2004). This is potentially the case of the societies in which the individual under study came from, because during the Pre-Incaic period, a process of endemic war was raised in the Humahuaca gorge area (Nielsen 2007). As the Pukara de la Cueva is the Northern strategically entrance to the gorge, we propose that different social changes may have occurred, mainly a higher population density inside the Pukara, the development of an overcrowded community and a diminution of the previous social interaction with neighbor societies. This process would have promoted more intense intermarriage linkages among the inhabitants of the Pukara, enhancing the chances of deleterious gene transmissions.

In general, tumors are very scarcely documented in paleopathological literature. One of the most common statements used to explain the low prevalence of metastatic cancer in ancient times is related to the supposed short life expectancy (i.e. Brothwell, 1967, 2012; Wakely et al. 1995; Aufderheide and Rodríguez-Martín, 1998; Ortner, 2003; Marks and Hamilton, 2007; Waldron, 2009; Shen and Abate-Chen, 2010; Prates et al., 2011). This proposal is especially important in this case because prostate cancer is more likely to affect men older than sixty (Waldron, 2009). Clinical research points that the single most significant risk factor for prostate cancer is advanced age and senescence. While men younger than 40 years old have a 1/10.000 chance of developing prostate cancer, this risk increases to 1/7 by the age of 60 (American Cancer Society 2009 in Shen and Abate-Chen, 2010). Nevertheless, studies in documented skeletal samples show that there are no accurate methods for age estimation, especially for elderly individuals, and that the current approaches tend to underestimate middle and older adult ages (Martins et al., 2012). Another important reason usually quoted for the explanation of the low prevalence of cancer in antiquity is the absence of many of the nowadays carcinogens developed mainly after the Industrial Revolution (Prates et al., 2011). However, in sedentary preindustrial societies, environmental pollution derived from the increase of population densities, the enhancing overcrowding and the less hygienic lifestyle could have had an important role in promoting the proliferation of malignant primary cells. This scenario would have been possible in Pukara de la Cueva since the beginning of a probable endemic warfare process must have derived in this settlement and sociocultural pattern.

Malignant neoplasias usually derive in a lethal condition. However, the macroscopic and radiographic lesions are so striking that led to wonder about the survival of this individual, following the statements previously put by authors like Ortner (1991) and Wood et al. (1992): was he able to survive for a long period with the disease that the skeleton could report the changes provoked by the uncontrolled bone growth, or his immune system was so weak that the bones were strongly affected in a short period of time? As prostate cancer could remain silent due to its slow and non-symptomatic development, sometimes during years (Keller and Brown 2004), the first hypothesis seems to be more likely in this case.

CONCLUSION

The scarcity of studies about neoplastic pathologies in ancient societies shows the need to make efforts to understand in depth the incidence of such diseases in the past. The paleopathological analysis of this skeleton allowed identifying the development of a metastatic prostate cancer in pre-Hispanic societies. This evidence is especially important because it is one of the first cases analyzed in detail in South America and the first of its kind in Argentina. The finding contributes to the discussion of the environmental and behavioral characteristics where these populations lived, which gave rise to the development of this very unusual disease before industrialization. It is possible to suggest that the basic socioenvironmental conditions (hygienic, demographic, climatic and/or genetic) were given for the appearance of malignant prostate cells, their proliferation and subsequent spread to the skeletal system. The detailed macroscopic and radiographic analyses allowed identifying osteoblastic, osteoclastic and mixed pathological manifestations, contributing to the differential diagnosis of the disease and to the characterization, in dry bones, of patterns systematically observed in clinical cases. This contributes to the understanding of neoplastic manifestations in the past and helps to outline a history of the disease, a significant fact for the full characterization of the variability of the processes of proliferation of malignant cells in the present.

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Table 1. Location and type (proliferative, osteolytic or mixed) of the lesions identified.

Anatomic portion	Bone	Area	Type of bone		
			Proliferative (P)	Osteolytic (O)	Mixed (P+O)
Skull	Temporals	Around the external auditory meatus	x	-	-
	Occipital	Inner and outer tables	x	-	-
	Parietals		x	-	-
	Mandible	Gonial region, medial and external surfaces	x	-	-
-	Hyoid	Anterior and posterior body	-	x	-
Thorax	Sternum	Manubrium	x	-	-
		Corpus sterni	-	x	-
	1^{st} rib	Costal tubercle	-	-	x
		Distal end	x	-	-
	2^{nd}-11^{th} ribs	Vertebral end	x	-	x
		Diaphyses	x	x	-
		Sternal end	-	x	-
	12^{th} left rib	Diaphysis, anterior surface	-	x	-
Vertebral column	Atlas	All bone	-	x	-
	Axis	Body	-	-	x
	3^{rd}-7^{th} cervical	All bone	-	x	x
	Dorsal		x	x	x
	Lumbar		x	x	-
Scapular girdle	Clavicles	Proximal epiphysis	-	x	-
	Scapulae	Acromion and coracoid process	-	x	-
		Posterior scapular neck	x	x	-
		Body	x	-	-
Upper limb	Ulnae	Proximal epiphysis	-	x	-
		Diaphysis and distal epiphysis	x	-	-
	Radius	Both epiphyses	x	x	-
	Carpals	All bones	x	x	-
	Metacarpals	Both epiphyses	x	x	-
	Hand phalanges		-	x	-
Pelvic girdle	Coxae	Anterior and posterior acetabular area	x	x	x
		Anterior surface of obturator foramen area	x	-	-
		Anterior view near the auricular surface	x	x	-
		Anterior view of greater sciatic notch	x	-	-

		Posterior iliac pillar	x	-	-
		Left iliac crest	x	-	-
		Left pubis (anterior)	-	x	-
		Left pubis (posterior)	x	-	-
	Sacrum	Left wing	-	-	x
Lower limb	Femora	Proximal half	x	x	-
	Right patella	Anterior surface	x	-	-
	Tibiae	All bones	x	x	x
	Fibulae	Proximal epiphysis	-	x	-
		Distal epiphysis	x	-	-
	Tarsal	All bones	-	x	-
	Foot phalanges	Both epiphyses	-	x	-

Table 2. Type of spiculated and solid proliferative periosteal lesions for each location.

Anatomic portion	Bone	Area	Type of spiculated periosteal reactions				Dense reaction
			Hair-on-end	Sunburst	Velvet	Disorganized	
Skull	Temporals	Around the external auditory meatus	-	-	-	x	-
	Occipital	Inner and outer tables	-	-	-	x	-
	Parietals		-	-	-	x	-
	Mandible	Gonial region, medial and external surfaces	-	-	x	-	x
Thorax	Sternum	Manubrium	-	-	-	x	-
	1st rib	Costal tubercle	-	-	x		x
		Distal end	-	-	-	x	x
	2nd-11th ribs	Vertebral end	-	-	x	x	x
		Diaphyses	-	x	x	x	-
	Axis	Body	-	-	-	x	-
	Dorsals	All the element	-	-	-	-	x
	Lumbars		-	-	-	-	x
Scapular girdle	Scapulae	Acetabulum	-	-	x	x	-
		Body	-	-	-	x	-
	Ulnae	Diaphysis and distal epiphysis	-	-	-	x	-
	Radius	Both epiphysis	-	-	-	x	-
	Carpals	All the element	-	-	-	x	-
	Metacarpals	Both epiphysis	-	-	-	x	-
Pelvic girdle	Coxae	Anterior and posterior acetabular area	-	x	x	x	x
		Anterior surface of obturator foramen area	-	-	x	x	-
		Anterior surface near auricular surface	x	-	x	x	-
		Anterior surface of greater	x	-	x	x	x

		sciatic notch					
		Posterior iliac pillar	-	x	x	x	x
		Left iliac crest	-	-	x	x	x
		Left pubis (posterior)	-	-	-	x	-
	Sacrum	Anterior left upper wing	-	-	-	x	-
Lower limb	Femora	Proximal half	-	-	-	x	x
	Right patella	Anterior face	-	-	-	x	-
	Tibiae	All the element	-	-	-	x	-
	Fibula	Distal end	-	-	-	x	-

Figure 3.

Figure 4a.

Figure 4b.

Figure 5.

Figure 6a.

Figure 6b.

Figure 6c.

Figure 7.

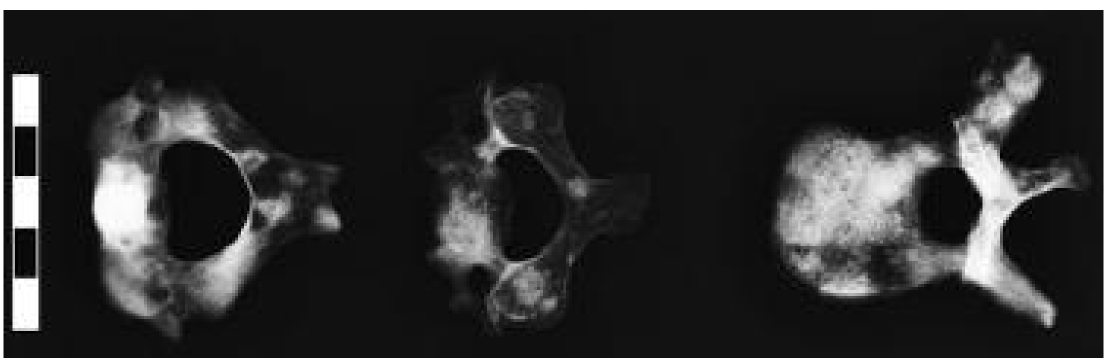

Figure 8.

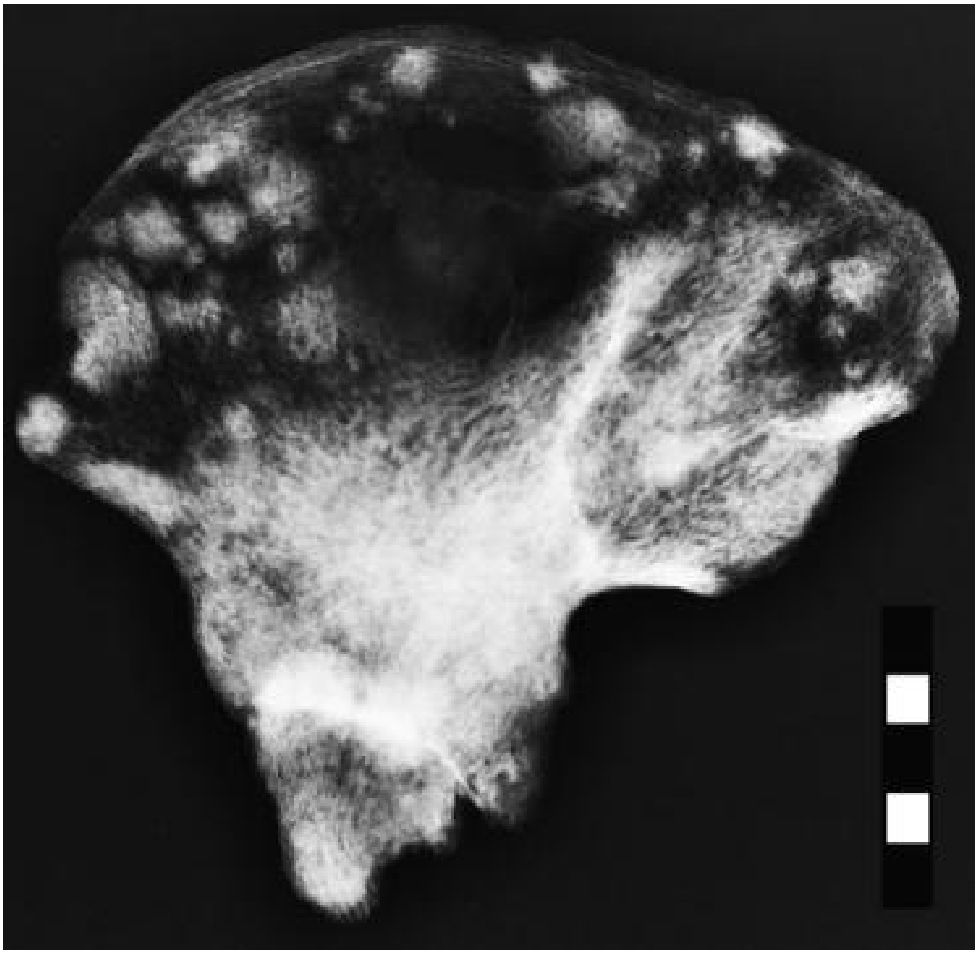

Figure 9.

Figure 10.