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Differential diagnosis of a neoplastic condition in a prehistoric juvenile individual from La Falda site, Northwest Argentina☆

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ABSTRACT

Bone neoplasms or tumors are of great interest for paleopathological studies due to their close relationship with health and survivorship as well as for their epidemiologic and demographic relevance. However, the identification of these lesions in archaeological specimens is very uncommon. The aim of this paper is to report the case of skeleton R5 E#1 from the prehistoric cemetery La Falda, in the Northwest region of Argentina. During the osteopathological analysis of the skeletal series, proliferative lesions in several bones of the skeleton of a 7–10-year-old juvenile were observed (i.e., both scapulae; left clavicle, humerus, and ulna, both os coxae, femora, and fibulae, and right foot bones). Age-at-death estimation, location and distribution pattern, and morphological appearances of the lesions indicated that this juvenile suffered from a neoplastic condition. A comprehensive differential diagnosis was carried out, suggesting that these lesions were compatible with hereditary multiple osteochondromas. However, Ewing's sarcoma was not definitively ruled out as a probable diagnosis. Thus, this work adds new evidence to the existence of neoplastic conditions in the prehistoric populations of the Americas, and it contributes original data to perform a differential diagnosis for multiple proliferative lesions.

1. Introduction

Cancer is a major cause of morbidity and mortality in human populations worldwide. Nevertheless, there are relatively few studies about the expression of neoplastic conditions in past societies (Capasso, 2005; Halperin, 2004; Luna et al., 2015; Marques et al., 2013; Ortner, 2003). Disorders usually called cancer are characterized by an uncontrolled cell proliferation (tumors or neoplasms) (Aufderheide and Rodríguez-Martín, 1998; Ortner, 2003). The development of neoplasms is a complex process that can result from the interaction between mutations in oncogenes and tumor suppressors, host susceptibility factors, and cell ecology (Capasso, 2005; Toomey et al., 2010). The study of neoplastic conditions is of great importance for paleopathologists because it has the potential to provide information about the susceptibility to cancer of ancient populations and about how socio-cultural changes may have influenced in their expression and prevalence (Capasso, 2005; Halperin, 2004). However, the identification of lesions associated with neoplasms or tumors in ancient human populations is relatively rare (Capasso, 2005; Halperin, 2004; Luna et al., 2015; Marques et al., 2013; Ortner, 2003). This limitation could be associated to environmental factors that affected the preservation of the bones, as well as to characteristics of human populations of the past (i.e., idiosyncratic characteristics, shorter life expectancy, shorter survival of individuals with neoplastic diseases, lower concentration of carcinogens in the environment, etc.) (Aufderheide and Rodríguez-Martín, 1998; Capasso, 2005; Halperin, 2004; Marques et al., 2013; Ortner, 2003).

Neoplastic conditions in juveniles are not frequent in the paleopathological record (Weiss, 2000). Types of cancers that occur in juveniles are usually different from those observed in adults (Aufderheide and Rodríguez-Martín, 1998; Brothwell, 2012; Miller, 2008; Ortner, 2003). The most common cancers in juveniles are leukemia, brain and other central nervous system tumors, neuroblastoma, and some bone tumors (Dorfman et al., 2002; Miller, 2008; Rothschild et al., 1997). Among bone tumors, the most frequent are those that develop in metaphyseal areas, such as osteosarcoma, chondrosarcoma, and Ewing's sarcoma (Brothwell, 2012; Miller, 2008; Ortner, 2003; Wicklund et al., 1995; Wilkins et al., 1986). However, juveniles can also develop cancers that are more common in adults (Miller, 2008).

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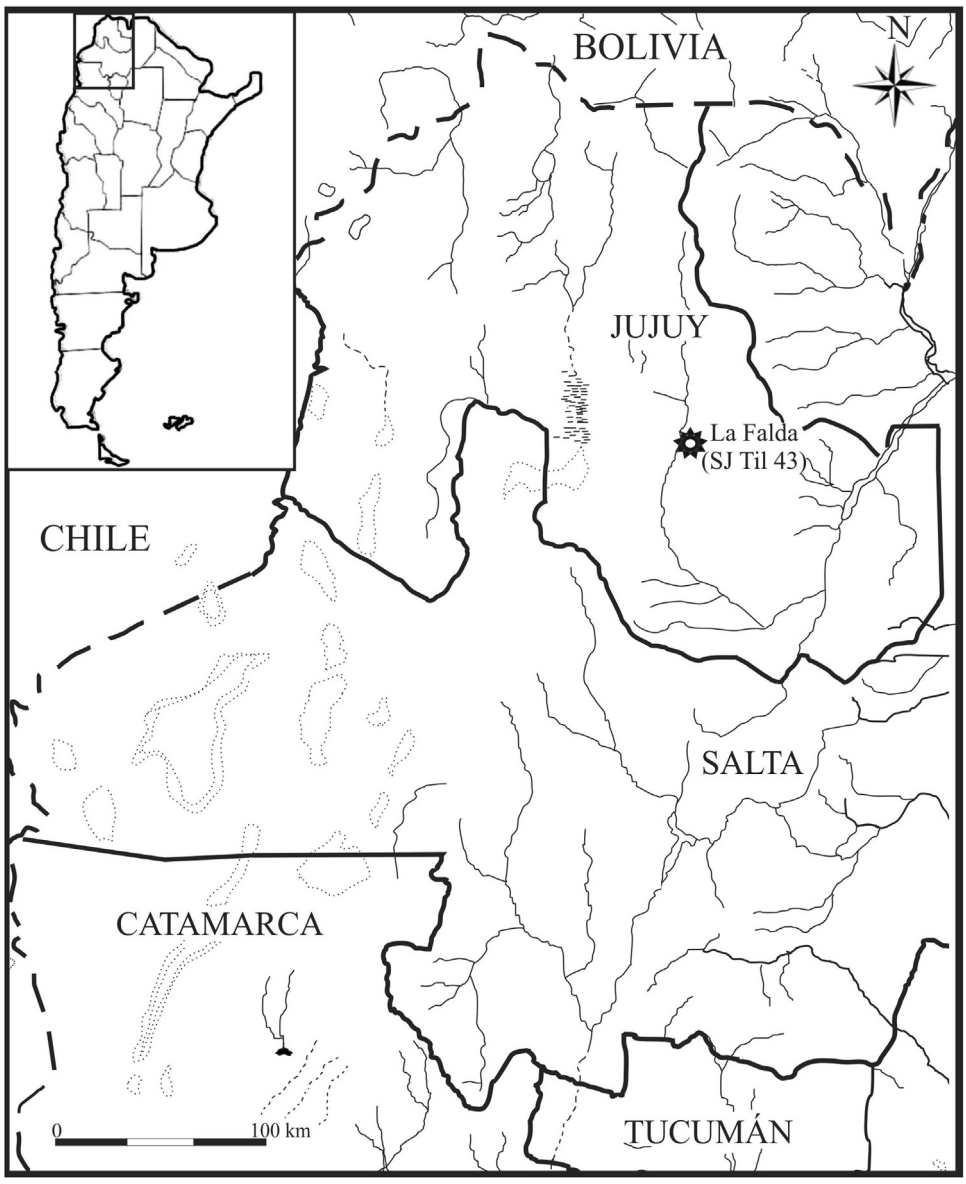

Fig. 1. Map of northwestern Argentina. Location of La Falda site (SJ Til 43).

Paleo-oncological studies have been carried out previously in Argentina. Luna et al. (2008) reported the presence of multiple lesions consistent with a neoplastic disease in the skeleton of an adult male from a prehistoric site at the western Pampean region. The authors concluded that the lesions could correspond to metastatic cancer, which could have provoked the death of the individual (Luna et al., 2008). Also Luna et al. (2015) reported multiple lesions in the skeleton of an adult male from prehistoric Northwest Argentina. Based on the type and distribution of lesions, the authors concluded that the lesions were consistent with a secondary carcinoma, specifically prostatic carcinoma.

The aims of this paper are to analyze multiple proliferative lesions recorded in an immature skeleton from prehistoric northwest Argentina and to perform a differential diagnosis. Lesions presented morpho-typological characteristics that seem to correspond to neoplastic diseases so far underrepresented in the paleopathological record. Thus, this work provides new evidence for the existence of neoplastic conditions in the prehistoric populations of the Americas.

2. La Falda cemetery (SJ Til 43)

La Falda is an Inca-Early Spanish Contact cemetery located in the present day city of Tilcara, in the middle sector of Quebrada de Humahuaca, Jujuy province, Argentina (Fig. 1). It is a site that was accidentally discovered during the construction of modern housing. The cemetery is characterized by the presence of funerary structures composed of a vertical shaft and a lateral chamber (Mendonça et al., 1997). Radiocarbon dates suggest that this cemetery was used for burial between cal CE 1460 and 1639 (Beta–153720 = 380 ± 40 BP; Beta–153721 = 370 ± 40 BP) (Mendonça and Bordach, 2001). In the past, the cemetery could have been spatially segregated from other sites of human occupation. The importance of SJ Til 43 is that it is a burial area belonging to the "Hispano-Indigenous period", a time of prehistoric development relatively little known in the region. It has both Inca cultural evidence and some very early signs of cultural exchange with the Spaniards (Bordach et al., 1998; Mendonça et al., 1997).

The tombs excavated in La Falda mostly contained single primary burials, although some tombs with multiple individuals were also discovered. The bodies were buried clothed, with gifts and personal items. The existence of gender-related inclusions was evident (Bordach, 2006). For example, in burials of women, items related to textile activity such as needles from thorns (*Cereus*), shuttles, bone spindles and whorls, and *topus* in bronze were found. By contrast, in burials of males, items related to combat or hunting activities (i.e., bone projectile points and wooden bows and arrows) or certain tools such as chisels, punches, and bronze hatchets were encountered (Mendonça and Bordach, 2001; Mendonça et al., 1997).

With regard to the spatial distribution of the tombs, the close relationship between funerary structures with unique contextual characteristics and wealthy grave goods suggested the existence of a burial area of individuals with high status (elite) within the prehistoric population of Tilcara (Bordach et al., 1998; Mendonça et al., 1997, 2003). Among the funerary inclusions, the presence of elements of local aboriginal tradition, elements with a clear influence of the Inca cultural pattern along with items of European provenience, was recognized (Mendonça et al., 1997).

A total of 25 tombs were excavated, 11 of which were found intact. The bone assemblage, whose state of conservation and integrity can be considered very good, is composed of 34 skeletons. The human remains studied here were found in Feature 5, a tomb in which the bones of three immature individuals were encountered. From this tomb, glass necklace beads, a topu with a circular head, as well as ordinary ceramic fragments and several pieces of worked wood, were also recovered.

The skeleton of one of these three individuals (an immature named R5E# 1) displayed multiple lesions. This skeleton showed a very good degree of integrity, presenting almost all the bones. The skull was almost complete, the left side was fragmented. Regarding the postcranium, only some vertebrae, the right clavicle and humerus, the left patella, and some bones of the hands and feet, were absent. The remaining bones were present, although with variable degrees of conservation and integrity (Fig. 2). From the outset, it was established that the proliferative lesions observed did not correspond to post-mortem changes caused by any taphonomic agent. Nor had the taphonomic processes significantly affected the structure of the bones. Thus, the described abnormalities can be reliably interpreted as pathological.

In order to achieve a reliable differential diagnosis, we performed an accurate description of the affected bones, along with age estimation of this individual. Age at death was established by tooth eruption status, epiphyseal fusion stages, and metrical dimensions of postcranial bones (Buikstra and Ubelaker, 1994; Fazekas and Kósa, 1978; Scheuer and Black, 2000; Ubelaker, 1989). To identify osseous pathologies, bones were analyzed by simple ocular inspection, using hand magnifying lens with different amplification factors, as well as a stereomicroscope. Anatomical elements displaying lesions were radiographed. The lesions were classified as proliferative, lytic or a combination of these two (Buikstra and Ubelaker, 1994; Luna et al., 2015; Marques et al., 2013; Miller, 2008; Ortner, 2003). From the results obtained by the osteopathological analysis, we followed the recommendations and indications published in the specialized literature (Aufderheide and Rodríguez-Martín, 1998; Brothwell, 1967, 2012; Chhem and Brothwell, 2008; Fletcher et al., 2002; Miller, 2008; Ortner, 2003; among others). This information was essential for the differential diagnosis.

3. Results

The sequence of tooth eruption, status of epiphyseal fusion and the length of the long bones suggested that this individual was between 7 and 10 years old at the time of death.

Pathologic lesions were primarily proliferative, mostly of the compact porous type, with varying degrees of mineralization. These bone proliferations did not show a regular shape and its distribution affected several skeletal elements (Fig. 2).

The left clavicle, on the upper aspect of the lateral end, presented the formation of “woven bone” periosteal new bone formation (PNBF). A higher elevation of the periosteum towards the acromial end was observed (Fig. 3A). Radiographic image suggested that it would be unilamellated PNBF, without cortical involvement (Fig. 3B).

The presence of PNBF was also observed in the subscapular fossa, near the medial border, of both scapulae. The lesions were located on both sides; these do not seem to have affected the epiphyses of the medial border. In both scapulae, the bone proliferations were clearly elevated from the surface of the bone. The lesions were much more noticeable in the left subscapularis fossa, which showed a tumor of considerable size (approximately 20 mm × 11 mm) and irregular shape (Fig. 4A). Radiological images revealed that the bone proliferations were distinctively opaque and showed an incipient formation of spicules (Fig. 4B).

The left humerus showed a proliferative lesion on the anterior distal third of the diaphysis above the coronoid fossa. This lesion presented a concave wall rising towards the lateral side of the bone. When the arm was flexed, this lesion might have come into close contact with the bone tumor developed in the ulna (Fig. 5). The proliferative lesion of the left ulna was located in the region of the brachial tuberosity; its dimensions were 16 mm high, 17 mm wide, and 16 mm deep, with well-defined borders (Fig. 6A). In both bones, the proliferations had irregular shape and texture, and the development of spicules was observed. In the case of the ulna, the periosteal reaction was perpendicular to the cortex, similar to the “hair-on-end” pattern (Fig. 6B). Radiographic analysis showed that these lesions affected neither the cortical bone nor the medullary cavity.

The left and right os coxae showed the presence of PNBF in ilia and ischia. In the ilia, the lesions were located on both sides of the bones, being mostly of the “woven bone” type. Regarding the ischia, the lesions were above the ischial tuberosity, both in the front and the back sides. The lesion of the left ischium was more noticeable, with a cloud-like appearance (Fig. 7).

Proliferative lesions were also observed in both femora. In the femoral neck, on the intertrochanteric line region, the presence of spicular PNBF was registered. Lesions of the left femur were more noticeable because its spicules had a greater length. This lesion had a cloud-like appearance (Fig. 7A). The radiological analysis showed that the lesions were poorly mineralized and some cortical involvement was apparent (Fig. 8B). The presence of PNBF in the region of the gluteal line of both femora was also observed.

Lamellar PNBF without defined borders was also recorded in the medial third of the diaphysis of both fibulae. In addition, proliferative lesions were also observed on the lateral aspect of the distal metaphysis of the right fibula.

Finally, osteoblastic lesions in the distal metaphysis of the right fifth metatarsal and right first proximal phalanx were registered.

4. Discussion

The individual R5E#1 shows compelling evidence for the presence of a disease that affected the skeletal system. The lesions observed were primarily proliferative, although lytic lesions were also apparent. The anatomic elements affected were the left clavicle, both scapulae, left humerus and ulna, both os coxae, femora, fibulae, and bones of the right foot. Lesions in the axial skeleton were not observed. The degree of development of the registered lesions varied, ranging from unilamellated PNBF to spiculated (type

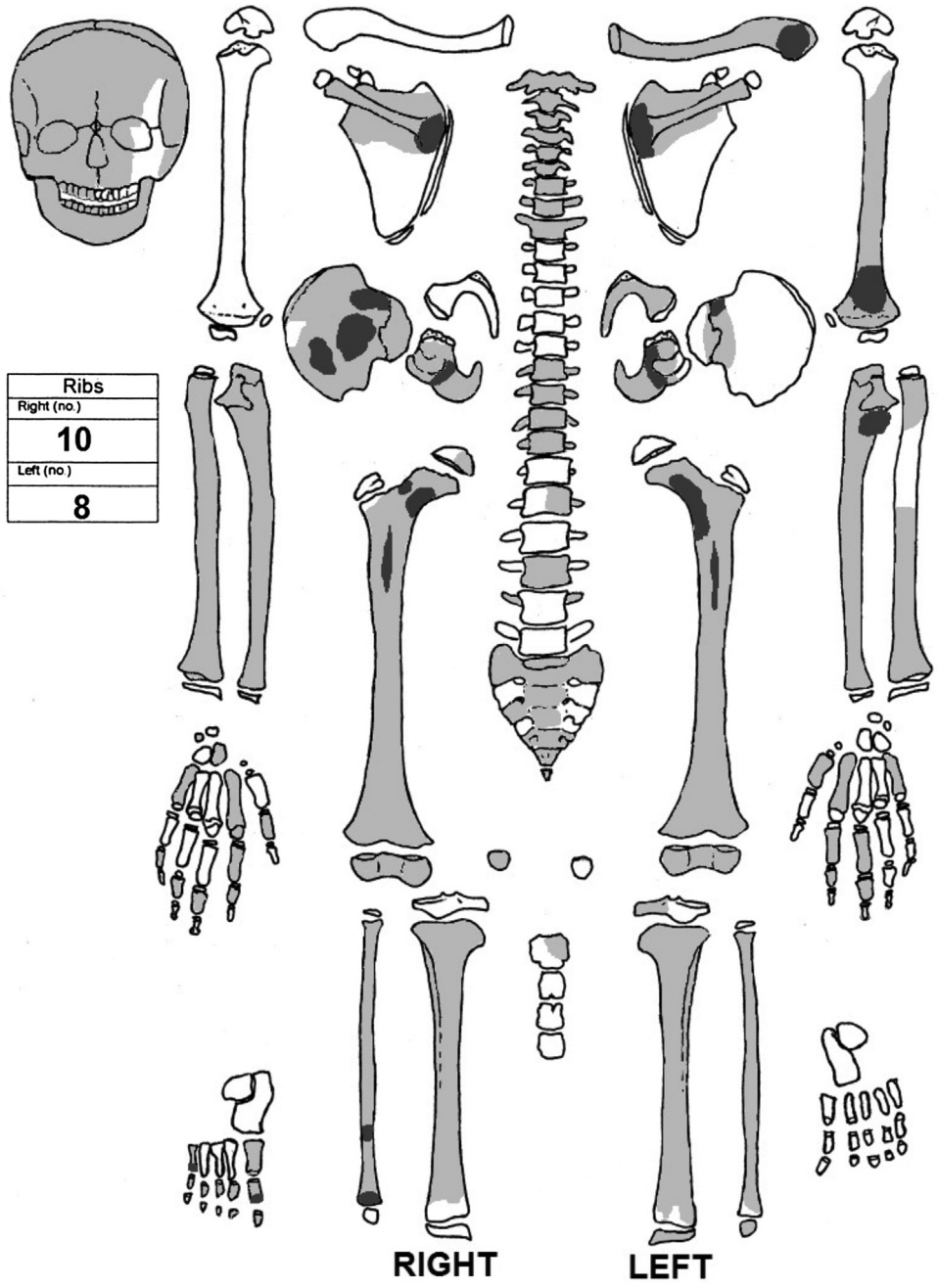

Fig. 2. Preserved elements of the skeleton R5E#1 (light grey) and bone sites affected by pathological lesions (dark grey).

hair-on-end) periosteal reactions. Such proliferative lesions have developed in sites of origin and musculoskeletal insertion in the skeleton (i.e., insertion of the brachialis muscle in the ulna, origin of the infraspinatus and subscapularis muscles in the scapulae, origin of the iliacus, gluteus minimus, rectus femoris muscles in the ilia, origin of the obturators muscles in the ischia, insertion of the gluteus maximus, gluteus minimus and illiacus muscles in the femora, etc.), which could suggest the possible involvement of the muscular system. The radiologic analysis of the affected bones showed the apparent existence of osteolytic lesions, although it was not possible to discriminate definitively between pathological and taphonomic changes.

Given the characteristics of the lesions recorded, we decided to perform a differential diagnosis, which included neoplastic or tumor-like conditions as well as other diseases.

4.1. Other than neoplastic conditions

Among the non-neoplastic conditions included in the differential diagnosis are fibrous dysplasia and infectious diseases. These conditions generally promote the development of proliferative lesions in different parts of the skeleton.

Fibrous dysplasia is a disease of unknown etiology that usually manifests during childhood or adolescence (Aufderheide and Rodríguez-Martín, 1998; DiCaprio and Enneking, 2005). This disease is characterized by the replacement of normal bone tissue by fibrous tissue (Lichtenstein, 1970; Lichtenstein and Jaffe, 1942). The lesions consist of islands of fibrous tissue developed in the medullary space, from which they generally expand, generating proliferative lesions with different degrees of ossification (Harris et al., 1962; Lichtenstein and Jaffe, 1942; Ortner, 2003). Because in its polyostotic form it affects multiple skeletal sites generating

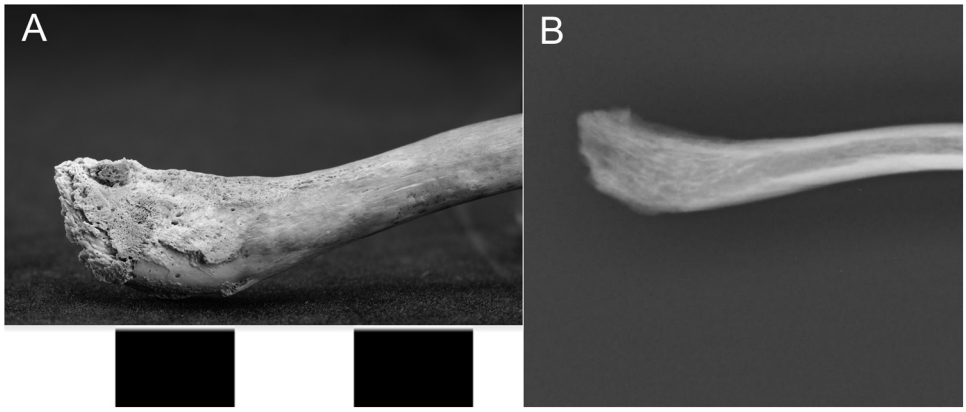

Fig. 3. Lesions in the left clavicle. A. Details of PNBF on superior aspect of acromial end. B: Radiological image of the corresponding area showing a unilamellated PNBF (white arrow) without cortical involvement.

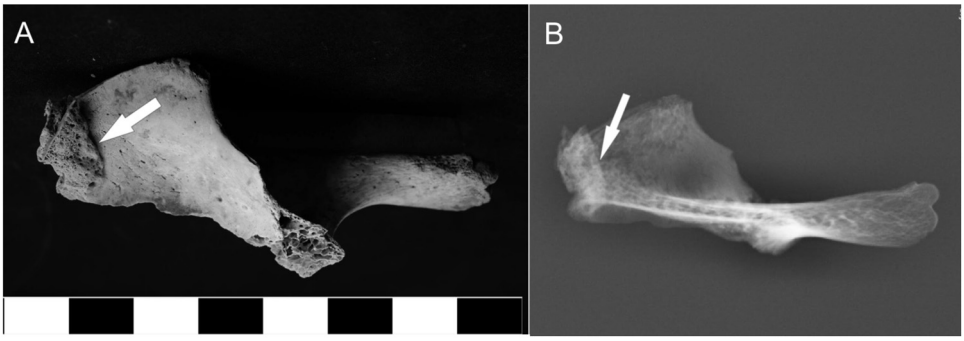

Fig. 4. Anterior view of left scapula. A. Detail of proliferative lesion (white arrow). B. Radiography showing a densely sclerotic lesion (white arrow).

Fig. 5. Anterior view of left humerus. Proliferative lesions on the coronoid region.

proliferative lesions, fibrous dysplasia was included in the diagnosis. However, this disease is mainly characterized by proliferative lesions of fibrous tissue rather than bone tissue. Furthermore, the presence of pathologic fractures caused by the weakening of bone, severe deformity, frequent involvement of the axial skeleton (Aufderheide and Rodríguez-Martín, 1998; DiCaprio and Enneking, 2005; Ortner, 2003), and radiolucent areas on radiological images (Waldron, 2009) are very common. For these reasons, fibrous dysplasia is discarded as a possible diagnosis.

Several diseases of infectious origin, such as tuberculosis, brucellosis, treponematosis, osteomyelitis, mycotic infections, among others, also have the potential to cause a marked osteoblastic activity and to generate proliferative lesions (Aufderheide and Rodríguez-Martín, 1998; Ortner, 2003; Waldron, 2009; among others). However, all these conditions are also characterized by a high osteoclastic activity, so the presence of osteolytic lesions is a very common manifestation in these diseases. Due to the fact that clear evidence of osteolytic lesions was not observed in the individual, infectious diseases were excluded from the differential diagnosis.

4.2. Neoplastic and tumor-like conditions

The number of pathological conditions included in this nosological group is very large and the pathological changes are manifested in a wide and varied range. Therefore, the differential diagnosis was a true challenge. However, it is only within neoplastic conditions where we found pathologies that match or correspond to those lesions recorded in the individual R5E#1. Furthermore, the multiplicity and morphological characteristics of the lesions recorded allowed us to significantly reduce the number of possible diagnoses. Following the recommendations of Miller (2008) and Marques et al. (2013), the differential diagnosis was performed taking into account: i) age of the individual; ii) location and distribution of the lesions; and iii) morphological characteristics of the lesions (i.e.; pattern of periosteal reactions, presence of osteolytic activity, size and number, radiographic visualization, etc.).

Among the neoplastic and tumor-like conditions that could have caused these lesions we include Ollier disease (or enchondromatosis), osteosarcomas, osteochondromatosis (or hereditary multiple osteochondromas), and Ewing's sarcoma, most of them being able to promote multiple proliferative lesions.

Ollier's disease (or enchondromatosis) is a developmental disorder that Jaffe (1958) defined as the presence of either circumscribed foci or large masses of cartilage in bones. This disease most frequently affects the bones of the hands, although bones of the feet,

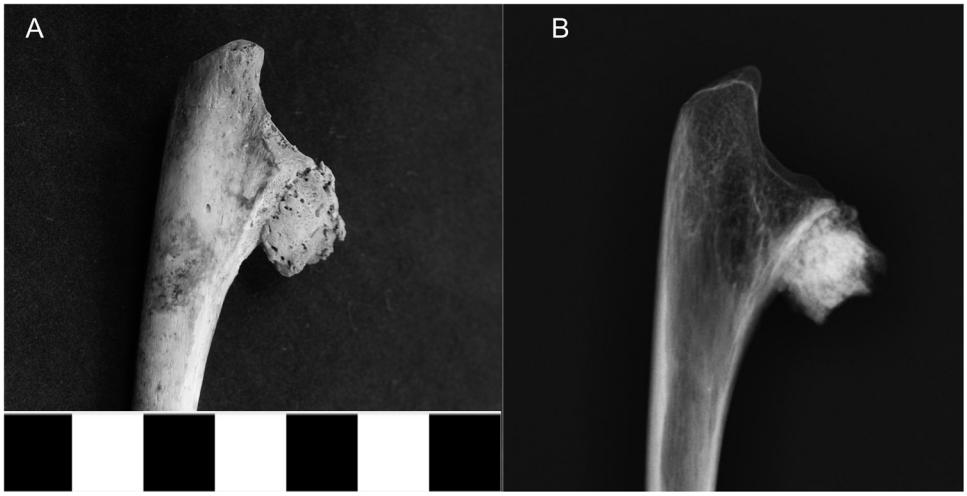

Fig. 6. Medial view of left ulna. A. Bone tumor on the brachial tuberosity area. B. Radiological image showing periosteal reaction without cortical involvement.

Fig. 7. Proliferative bone in periacetabular region of the left isquium.

femora, humeri, and forearm are also involved (Khoo et al., 2008; Lucas and Bridge, 2002). This disease is characterized by an asymmetric distribution of multiple cartilage lesions in metaphysis and adjacent regions of the shafts and flat bones (Lucas and Bridge, 2002; Shaheen et al., 2010). Such lesions can be extremely variable (in terms of size, number, location, evolution of enchondromas, age of onset and of diagnosis) (Shaheen et al., 2010). Roentgenograms typically show multiple, radiolucent, homogenous lesions with an oval or elongated shape and well defined slightly thickened bony margin (Whyte, 2003). Lesions in the ulna showed in the article of Hemraj et al. (2014) led us to include enchondromatosis in the differential diagnosis. In addition, multifocal involvement and metaphyseal location have also been registered in this disease. However, lesions are often limited to one limb or one side of the body (Lucas and Bridge, 2002). Moreover, lesions are mainly radiolucent and bone expansion is common (with cortical bone involvement), showing varying degrees of bone deformity (Lucas and Bridge, 2002). This is not the case in the individual of our study, who had primarily bilateral osteoblastic lesions and bone deformity was not observed.

Initially, we thought that the bone lesions observed in the individual R5E#1 were more compatible with osteosarcoma. This condition is a primary intramedullary malignant tumor, and is characterized by neoplastic cells that produce osteoid, even if only in small amounts (Raymond et al., 2002). Within osteosarcomas there is a category where the surfaces or juxtacortical lesions are grouped, which constitute 4–10% of all osteosarcomas (Mirra, 1989). These tumors affect young patients in the 2nd and 3rd decades of life and the femur and tibia are most frequently involved (85% –95%), followed by the ulna and humerus (5–10%) (Bertoni et al., 1982; Fechner and Mills, 1993; Murphey et al., 2004). Radiological analyses generally show thickening of the diaphyseal cortex, with scalloping and a perpendicular periosteal reaction extending into a broad-based soft-tissue mass, with or without invasion of the medullary canal (deSantos et al., 1978; Murphey et al., 2004). Although osteosarcoma is characterized by the production of massive sclerotic bone, as observed in our case study, most patients who develop this condition are over 25 years old, and the most common site of location is the distal femoral metaphysis (Murphey et al., 2004; Unni and Knuutila, 2002). Furthermore, Unni and Knuutila (2002) indicate that the flat bones are very rarely affected and it is common to observe invasion of the bone marrow and cortical thickening, a pattern that is not consistent with our results. Finally, only a very small number of patients with osteosarcoma (1.5%) develop multiple bone lesions, either synchronous or metachronous (Corradi et al., 2011; Fitzgerald et al., 1973). All these reasons led us to exclude osteosarcoma as a probable diagnosis.

Thus, after a comprehensive analysis, the most probable diagnosis in our case study is reduced to two neoplastic conditions: Ewing's sarcoma and hereditary multiple osteochondromas or (osteochondromatosis). Although both conditions have different etiologies, they are characterized by the presence of multiple bone lesions and the almost exclusive occurrence in persons less than 20 years old (Chhem and Brothwell, 2008; Peersman et al., 2007; Schmale et al., 1994; Stieber and Dormans, 2005; Wilkins et al., 1986).

Ewing's sarcoma (ES) is a malignant round cell tumor of bone that occurs mostly in individuals between 10 and 20 years old (Dahlin et al., 1961; Hoffmann et al., 1999; Peersman et al., 2007; Wilkins et al., 1986). Osseous ES represents the second most common primary tumor of bone in children and adolescents, and it is exceeded in prevalence only by osteosarcoma (Ushigome et al., 2002). ES is highly lethal, with a 5-year survival rate of approximately 20% in patients without treatment (Dahlin et al., 1961; Wilkins et al., 1986). Nearly 14–39% of patients with ES have

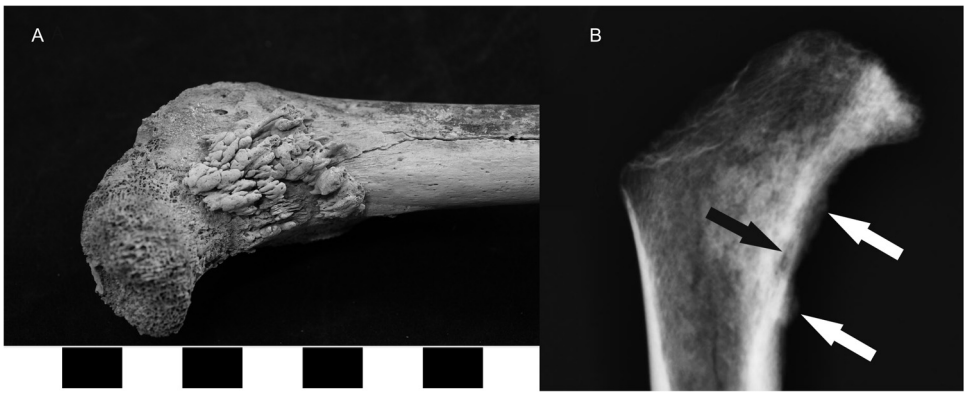

Fig. 8. Lesions in the left femur. A. Detail of spicules formation on femoral neck. B. Anterior radiograph showing a poorly sclerotic proliferative bone (white arrows) and apparent cortical involvement (black arrow).

more than one bone affected (Mendenhall et al., 1983; Peersman et al., 2007; Wilkins et al., 1986). This condition can affect any bone of the skeleton, but it is the pelvis that is most commonly affected (Hoffmann et al., 1999; Peersman et al., 2007; Wilkins et al., 1986). The fibula, femur, humerus and scapula can also be involved (Peersman et al., 2007; Wilkins et al., 1986). In long bones, the lesions are localized in the metaphyseal or diaphyseal regions, rarely involving the epiphysis (Peersman et al., 2007). While in the past it was considered that the radiological appearance of Ewing's sarcoma involved osteolysis without osteosclerosis and an onion-skin layering of periosteal new bone, presently it is known that the lesions are manifested in a non-specific and highly variable form (Wilkins et al., 1986). Thus, the age of the individual along with the multiplicity, location and distribution of the lesions registered seem compatible with this disease. Furthermore, the location of lesions in the pelvis corresponds to the most common pattern recorded by Hoffmann et al. (1999). Also the early age at death of the individual R5E#1 could be consistent with the high malignancy of ES, given the fact that before the improvement of the clinical treatments, the survival was very lower (Dahlin et al., 1961; Wilkins et al., 1986). However, although the presence of spicular periosteal reactions is not uncommon in this condition (Wilkins et al., 1986), Peersman et al. (2007) observed that the presence of exclusively sclerotic lesions is very rare (ca. 6% of patients with ES). The lesions are presented mostly as a mixed sclerotic-lytic (75%). Because in the present case study we observed the presence of proliferative lesions almost exclusively, this situation led us to consider that ES is a less likely diagnosis. Although ES cannot be definitively excluded, histopathological analysis is always necessary to confirm the diagnosis in clinical cases (Dahlin et al., 1961; Hoffmann et al., 1999). This procedure cannot be carried out only in dry bone.

Multiple hereditary osteochondromas (MHO) is a dominant autosomal disorder characterized by the formation of cartilaginous capped prominences (osteochondromas) that develop in the metaphyses of the bones during the first years of life (Boveé and Hogendoorn, 2002; Gordon et al., 1981; Stieber and Dormans, 2005; Wicklund et al., 1995). It is a very rare inherited condition that affects several bones, with an estimated prevalence of 1:50000 and 1:100000 (Stieber and Dormans, 2005). It has a very high penetrance, and it is manifested in several members and generations of families who have a history of this disease (Boveé and Hogendoorn, 2002; Legeai-Mallet et al., 1997). The lesions consist of multiple osteochondromas, which are bone protuberances, either sessile or pedunculated, surrounded by a cartilage layer (de Souza and Bispo Júnior, 2014; Gordon et al., 1981; Stieber and Dormans, 2005). These lesions arise from the external surface of the bone and contain cancellous bone mixed with calcified cartilage or densely sclerotic bone (Bovée and Hogendoorn, 2002; Ortner, 2003). Although the lesions are histologically benign, they can cause a variety of clinical complications, such as pain, restricted range of motion, deformities and shortening stature, and malignant transformation (Stieber and Dormans, 2005; Wicklund et al., 1995). Osteochondromas are always located in areas where bone growth is very active (Gordon et al., 1981; Stieber and Dormans, 2005). Although the number of osteochondromas and the number and location of involved bones are variable, the lesions occur more usually in the knee area (Boveé and Hogendoorn, 2002; Ortner, 2003; Schmale et al., 1994). However, in decreasing order, lesions are also commonly registered in humeri, scapulae, ribs, radii, ulnae, and proximal femora and fibulae (Boveé and Hogendoorn, 2002; Schmale et al., 1994). The lesions are usually bilateral and symmetrical (Porter et al., 2004; Schmale et al., 1994). Osteochondromas growth is uneven and it has been suggested that it could cause a stunting in bone growth (Boveé and Hogendoorn, 2002; Gordon et al., 1981; Porter et al., 2000; Stieber and Dormans, 2005). The differential diagnosis carried out here revealed that there is a high correspondence between the age of death of the individual R5E#1 and the age of diagnosis of the vast majority of patients with MHO (Schmale et al., 1994; Stieber and Dormans, 2005). Also, the lesions recorded are consistent with the type of lesions commonly reported for patients with MHO. As is commonly observed in osteochondromas, lesions grow away from the site of active growth, probably due to forces caused by tendons and adjacent muscles (Khurana et al., 2002). In addition, the lesions observed were almost exclusively characterized by the presence of sclerotic bone, although with varying degrees of mineralization. However, the distribution pattern recorded does not seem to correspond exactly with the one described above. Nevertheless, Murphy and McKenzie (2010), in a review of 16 paleopathological cases of MHO, report a distribution pattern similar to that observed by us. Although bilateral involvement was recorded, no presence of knee involvement was observed, a feature reported in more than 90% of patients with MHO (Murphey et al., 2000; Schmale et al., 1994; Stieber and Dormans, 2005). However, lesions in the scapula, elbow, pelvis, hip and feet are commonly present in patients with MHO (Boveé and Hogendoorn, 2002; Schmale et al., 1994; Murphey et al., 2000). Schmale et al. (1994) and Murphey et al. (2000) estimate that the scapula is affected in approximately 40% of patients with MHO. A similar prevalence was calculated for the elbow joint (Murphey et al., 2000; Schmale et al., 1994). In addition, morphologically similar lesions to that recorded in the proximal ulna have been reported for osteochondromas by other researchers (Abe and Koyama, 1998; Hamada et al., 2015; Kushner et al., 2015; Lyall and Mann, 1993). With regard to the lesions registered in both os coxae and femora, at least nine cases of acetabular dysplasia, caused by exostosis located in the acetabular region and/or on the femoral neck, have

Table 1
General characteristics of the pathological manifestations in Ewing's sarcoma and multiple hereditary osteochondromas (MHO) compared with the case reported here (R5E#1).

Characteristics	Ewing's sarcoma	MHO	R5E#1
Profile			
Age	< 20 years	Birth to 12 years	7–10 years
Sex prevalence	Male (1.4:1)	Male (1.5:1)	Undetermined
Lesions Typology			
Multiple lesions	4–25% of cases	Very common	Yes
Pattern of distribution	Variable (pelvis, femora, tibiae, humeri, fibulae, ribs, scapulae)	Variable (knee area, humeri, scapulae, ribs, radii, ulnae, proximal femora)	Pelvis, scapulae, ulna, humerus, proximal femora, fibulae, clavicle, right foot bones
Bone location	Meta-diaphyseal	Metaphyseal	Metaphyseal and diaphyseal
Symmetry	Non specific	Bilateral and unilateral	Bilateral and unilateral
Type of lesions	Mixed lytic-sclerotic	Sclerotic	Sclerotic
Onion-skin PO	Yes	No	No
Spicules PO	Yes	Variable	Yes
Cleavage plane	No	Yes	Yes
Cortical involvement	Very common	No	Apparent
Medullary involvement	Very common	No	No
Short Stature	Non specific	Yes	Probable
Hereditary Transmision	Non specific	Yes	Probable

been reported in patients with MHO (Felix et al., 2000; Garrison et al., 1982; Stieber and Dormans, 2005). Furthermore, Lyall and Mann (1993) reported a similar lesion in the proximal femur of an individual from ancient Jericho. Lesions in the bones of the feet were registered in approximately 10–25% of patients with MHO (Murphey et al., 2000; Schmale et al., 1994). Another important aspect to consider in the differential diagnosis is that patients with MHO often manifest a shorter stature than the average of individuals of the same age (Shapiro et al., 1979; Stieber and Dormans, 2005). In our case study, the estimated age was 9 years ± 24 months, considering the sequence of tooth eruption in skull and mandible (Buikstra and Ubelaker, 1994), while for the length of long bones (Scheuer and Black, 2000) the estimated age was slightly lower (8 years for the radius and ulna; 6.5-7 years for femora). However, in MHO, the shortening of stature has been attributed to the bowing of limb bones (Boveé and Hogendoorn, 2002; Schmale et al., 1994; Stieber and Dormans, 2005), which is not observed in our case study. Nevertheless, some authors (Ortner, 2003; Stieber and Dormans, 2005) propose that, in MHO, the growth of the osteochondromas might retard the growth of any closely associated metaphysis. Finally, taking into account the hereditary nature of this condition, characterized by its high penetrance, it is also noteworthy that, in this cemetery, another individual (R23), a male about 16 years old at the time of death, presented an osteochondroma in the medial aspect of the right tibia, near the proximal metaphysis. The lesion is approximately four centimeters long, and it is projected from the postero-inferior border of the lateral condyle of the tibial plateau. Assuming that, as in MHO, the development of solitary osteochondromas is also caused by mutations affecting genes EXT1 and EXT2, the presence of an osteochondroma in the individual R23 might enhance the probabilities of a possible MHO diagnosis. Moreover, if we consider the possibility that SJ Til 43 would be a funerary area of high status individuals within the prehistoric population of Tilcara (given the contextual features of the site: type of tombs, spatial proximity and sumptuous regalia) (Bordach et al., 1998; Mendonça et al., 1997, 2003), this situation could increase the probabilities of a close family relationship or filiation between individuals buried in this site.

Based on the data presented above, we conclude that MHO would be the most likely diagnosis for the lesions registered in the skeleton R5E#1. However, a histopathological analysis made on soft tissue would be necessary in order to confirm the final diagnosis for either of the two conditions, and ES cannot be completely excluded as a possible diagnosis. General features of the pathological manifestations (i.e.; age of individual, location and distribution of the lesions and morphological characteristics of the lesions) in ES and MHO in comparison with the case reported (R5E#1) are shown in Table 1

Ewing's sarcoma and MHO are relatively scarce in the paleopathological record. Regarding MHO, Murphy and McKenzie (2010) reviewed 16 cases of multiple osteochondromas from 14 published case studies identified in the international paleopathological record. The reports range in date from ca. BCE 1700 to the ca. post CE 1800, and the cases come from a total of eight countries (Zimbabwe, Poland, Gotland, Canada, England, Peru, Jordan, and Republic of Ireland) (Murphy and McKenzie, 2010). The pattern of distribution of the lesions is similar to that observed in our case and the authors suggest that individuals with MHO were more susceptible to early death (Murphy and McKenzie, 2010). With regard to Ewing's sarcoma, the number of reported cases is much lower. Campillo and Marí-Bacells (1984) reported a possible case in a young male from the Late Neolithic in Catalunya, Spain. The individual displayed 16 different tumor foci with irregular margins. Also Löwen (1998) described a medieval German skeleton with a lesion suggestive of Ewing's sarcoma. Finally, Brothwell (2012) reported a post-medieval femur from York, England, with irregular cortical destruction and PNBF. He proposed Ewing's sarcoma sarcoma as a possible cause of such lesion (Brothwell, 2012).

5. Conclusions

The individual R5E#1 from SJ Til 43 cemetery (northwest Argentina), chronologically assigned at Inca and early Hispano-Indigenous contact times (ca. CE 1441–1639), shows proliferative bone lesions that are mostly compatible with multiple hereditary osteochondromas. This disease is a very rare benign condition, although in some cases malignant degeneration is observed (Boveé and Hogendoorn, 2002; Gordon et al., 1981; Schmale et al., 1994; Stieber and Dormans, 2005). MHO usually affects several members of the same family (Boveé and Hogendoorn, 2002; Legeai-Mallet et al., 1997). Although it has been long debated whether MHO is a developmental disorder or a true neoplasm, it is now known that mutations in the EXT1 and EXT2 genes are strongly related with the disease in about 90% of cases (Boveé and Hogendoorn, 2002; Khurana et al., 2002; Stieber and Dormans, 2005). For this reason, MHO is recognized as a true neoplasm (Khurana et al., 2002).

Even though t Ewing's sarcoma is not definitively excluded of the diagnosis, the report of lesions registered in this skeleton might be an important contribution to the knowledge about the neoplastic diseases present among past societies.

As several authors have previously highlighted (Halperin, 2004; Luna et al., 2015; Marques et al., 2013), there is a relative paucity of studies about neoplastic conditions in the paleopathological record. Probably, this situation not only responds to a lower occurrence or prevalence of these diseases in past societies, but also to the fact that these findings are generally limited to isolated cases, which are not published (perhaps because these findings are not considered important at the population level). It is important to stress that when we work with dry bone, the performance of a differential diagnosis becomes much more difficult. This is because the diagnosis is usually performed from data of current clinical reports. In these studies, the researchers not only have a careful monitoring of the evolution of patients, but also patients receive specific treatments that slow the normal development of tumors. In addition, in clinical studies, diagnoses are performed and confirmed by biopsy as well as by histopathological analysis, a situation virtually impossible for paleopathologists working exclusively with dry bones. Thus, the establishment of comparisons among clinical and paleopathological cases suffers from limitations that could discourage paleopathological researchers.

For this reason, the growing development of a line of research in paleo-oncology will be of great help to the increase of paleopathological knowledge in general, since it will stimulate the increase in the number of reports about neoplastic conditions present in the archaeological skeletal series. Thus, we are deeply convinced that paleopathologists will reach a better understanding of the evolutionary and ecological relations between neoplasms and human populations.

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