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ARTICLE

Skeletal manifestation of tuberculosis in a late medieval anthropological series from Serbia

Gabriella Lovász[1, 2]*, György Pálfi[1], Antónia Marcsik[1], Annamária Pósa[1, 3], Endre Neparáczky[1, 3], Erika Molnár[1]

[1]Department of Biological Anthropology, University of Szeged, Szeged, Hungary, [2]Municipal Museum of Subotica, Subotica, Serbia, [3]Department of Genetics, University of Szeged, Szeged, Hungary

ABSTRACT The aim of this study is to present the results of the paleopathological investigation of tuberculosis (TB) in the late medieval (16th-17th c. AD) anthropological series of the Zombor-Repülőtér site from Serbia. The paleopathological analysis of TB was carried out in two phases during which macromorphological methods were used. The first phase of the investigation focused on classical/advanced stage skeletal TB alterations. In the second phase the atypical/early-stage TB lesions and 3 stress factors were also taken into consideration. The first phase of the investigation revealed two cases of tuberculosis in the series. However, in the second phase of the investigation additional 32 probable TB cases were recognized. The association of different tuberculous lesions (both classical and atypical/early stage alterations) as well as stress indicators were found in most of these cases, which rises the probability of the diagnosis of tuberculosis. The remarkable difference between the prevalence in the two phases of the investigation shows that the detection of diagnostic criteria related to atypical/early-stage tuberculosis raises the possibility of identifying TB cases. **Acta Biol Szeged 54(2): 83-91 (2010)**

KEY WORDS

tuberculosis
Pott's disease
early-stage TB lesions
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Human tuberculosis is an infectious disease affecting a number of organs, especially the lungs. It is caused by pathogens of the *Mycobacterium tuberculosis* complex, most often the *Mycobacterium tuberculosis* and the *Mycobacterium bovis*. The manifestation of symptoms depends on several factors, such as the type of the pathogen, the infected individual's age and the condition of the immune system (Bloom 1994; Madkour 2004). The pathogens might spread from the place of the primary infection (e. g. lungs) either by haematogenous route or in a direct way to other organs and tissues where they may trigger inflammatory reactions. The bones can also be affected, though only 3% of all the tuberculous infectious cases occur in the skeletal involvement (Resnick and Niwayama 1988; Aufderheide and Rodríguez-Martin 1998; Ortner 2003).

In the case of anthropological findings, usually only dry bones are available, thus we can observe only skeletal TB. Classically, the lesions used to identify tuberculosis in skeletal material are characteristic lytic lesions, with little reactive bone formation. These alterations occur particularly in areas of cancellous bone, especially in vertebrae, as well as metaphysis and epiphysis of long bones, but virtually any bone can be affected (Resnick and Niwayama 1988; Ortner 2003).

The most common "classic" representation of skeletal tuberculosis affects the vertebral column (tuberculous spondylitis, Pott's disease), causing cavitation in the vertebra as well as sharply angulated kyphosis of the spine or rarely "cold abcess" on the ventral surface of the vertebrae (Resnick and Niwayama 1988; Aufderheide and Rodríguez-Martin 1998; Ortner 2003). Tuberculosis of the hip joint (tuberculous coxitis) is the second most frequent skeletal lesion after vertebral involvement, but the knee (tuberculous gonitis) or other joints (e. g. elbow, wrist, ankle) can also be affected with the consequences of the erosion of the articular surface, subluxation and bony ankylosis (Resnick and Niwayama 1988; Aufderheide and Rodríguez-Martin 1998; Ortner 2003). Beside these lesions tuberculous osteomyelitis in the diaphysis of the long bones and the short tubular bones of the hands and feet (spina ventosa), lytic, rounded lesions in the skull and pulmonary calcifications might also occur, but these conditions are relatively rare (Resnick and Niwayama 1988; Molnár and Pálfi 1994; Pálfi et al. 1999; Haas et al. 2000; Ortner 2003).

However, the classical skeletal TB changes indicate a more or less developed stage of tuberculosis. Early-stage TB is not recognizable on the basis of the previously listed lesions and this causes the underestimation of the prevalence of tuberculosis in the examined historical populations. Since the recognition of the importance of establishing diagnostic criteria for early-stage TB a number of studies have been focusing on searching for atypical/non classical bone alterations linked to tuberculous infection. These researches are mainly

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*Corresponding author. E-mail: lovaszg@bio.u-szeged.hu

based on the study of skeletal collections with known causes of death. As the result of these surveys 3 different groups of alterations seem very likely to be linked with TB:

a) rib lesions: sharply circumscribed lytic lesions and/or diffuse periostitis on the visceral surface of ribs, particularly in pulmonary tuberculosis (e. g. Kelley and Micozzi 1984; Roberts et al. 1994; Santos and Roberts 2001, 2006; Pálfi 2002; Maczel 2003; Matos and Santos 2006; Raff et al. 2006);

b) superficial vertebral alterations: irregular pitting and holes especially on the ventral surface of the vertebral bodies, but with no cavitation and collapse of the bodies (e. g. Baker 1999, Haas et al. 1999, 2000; Pálfi 2002; Maczel 2003; Molnár et al. 2005; Zink et al. 2007; Nerlich and Lösch 2009);

c) endocranial lesions: small granular impressions or abnormal blood vessel impressions with branched or reticulated course as well as plates of new bone in the inner surface of the skull vault found in the cases of tuberculous meningitis (Schultz 1999, 2001; Hershkovitz et al. 2002; Pálfi 2002; Maczel 2003; Lewis 2004).

The analyses of ancient microbial DNA in samples showing any of these alterations confirmed the presence of MTB complex organisms in a significant number of the examined cases (e.g. Spigelman and Lemma 1993; Haas et al. 1999; 2000; Maczel 2003; Molnár et al. 2005; Raff et al. 2006; Zink et al. 2007; Nerlich and Lösch 2009). On the basis of these examinations, these minor pathological conditions are suggested to be indicative of early stage of tuberculosis, and are named Minor Osseous Lesions Attributable to Tuberculosis – "MOLAT" (Maczel 2003).

Apart from the above mentioned changes, the correlation between tuberculosis and stress indicators, such as porotic hyperostosis, linear enamel hypoplasia and long bone periostitis, were also recognized in some studies (Stuart-Macadam 1989; Santos and Roberts 2001; Pálfi 2002; Maczel 2003).

Although several studies showed correlation between TB and the above mentioned alterations, it should be noted that these lesions are not always TB specific. Other conditions, such as infections, malnutrition, neoplastic conditions or traumas might also cause similar changes; therefore these new criteria should be used cautiously. Nevertheless, based on the association of these lesions we can presume the tuberculous origin in a higher probability. In order to justify the diagnosis of TB, biomolecular examinations (DNA, protein and mycolic acid analyses) are also required (Fletcher et al. 2003; Maczel 2003. Hershkovitz et al. 2008; Donoghue 2009; Redman et al. 2009; Boros-Major et al. 2010).

The aim of this study is to present the results of the paleopathological investigation of TB in the late medieval (16th-17th c. AD) anthropological series of the Zombor-Repülőtér site from Serbia. The examinations were carried out in two phases. Focusing on classical TB lesions, the first phase of the investigation revealed only two cases of tuberculosis (Lovász et al. 2008). However, the examination of the Bácsalmás-Óalmás anthropological series originating from a similar geographic region and the same historical period showed a number of tuberculous cases based on atypical/early-stage TB lesions (e. g. Pálfi and Ardagna 2002; Maczel 2003; Marcsik et al. 2006, 2007; Pálfi and Molnár 2009). Ancient DNA analyses also confirmed the presence of MTB complex organisms in a significant number of these cases (Molnár et al. 2005; Zink et al. 2007; Nerlich and Lösch 2009). Considering these results and paying special attention to the lesions attributed to early-stage tuberculosis, in the second phase of the pathological investigation we re-examined the skeletal material of Zombor-Repülőtér. On the one hand, we wanted to know whether the prevalence of TB had changed in the second phase of the investigation. On the other hand, we wanted to find out if there was any association among TB related lesions and which alterations appeared together the most frequently. With the results of our research we wish to provide a basis for further paleoproteomic and mycolic acid analyses and especially ancient DNA examinations, in order to find more evidence of the connection between these alterations and TB infection.

Materials and Methods

The graveyard of Zombor-Repülőtér near the Northern-Serbian town of Sombor was excavated during World War II. The excavation was led by László Wollner with the help of the Anthropological Institution (today: Department of Biological Anthropology) of the University of Szeged, Hungary. The series consists of 196 skeletons, and after the time of the excavation it was stored in Szeged, where the archaeological and basic anthropological examinations were carried out. The archaeological findings of the graveyard suggest that this population emigrated from the southern part of Serbia or Montenegro during the Turkish occupation. After the war, the material from this site was moved back to Serbia, first to the Museum of Vojvodina (Novi Sad), later to the Municipal Museum of Sombor (Bartucz 1960; Korek 1994). Unfortunately the data of the anthropological investigations had been lost therefore the reinvestigation of the material became essential.

During the palaeopathological investigation 130 adults (60 males, 66 females, 4 individuals with undetermined sex) and 66 subadults were examined (Lovász et al. 2008). The pathological analysis of TB was carried out in two phases during which macromorphological methods were used. The first phase of the investigation focused on classical/advanced stage skeletal TB alterations (tuberculous spondylitis, tuberculous arthritis). In the second phase the atypical/early-stage TB lesions (rib lesions, superficial vertebral changes, endocranial alterations, early-stage spondylodiscitis) were also taken into consideration. In addition, the association of tuberculosis related lesions and 3 stress factors (long bone periostitis, cribra

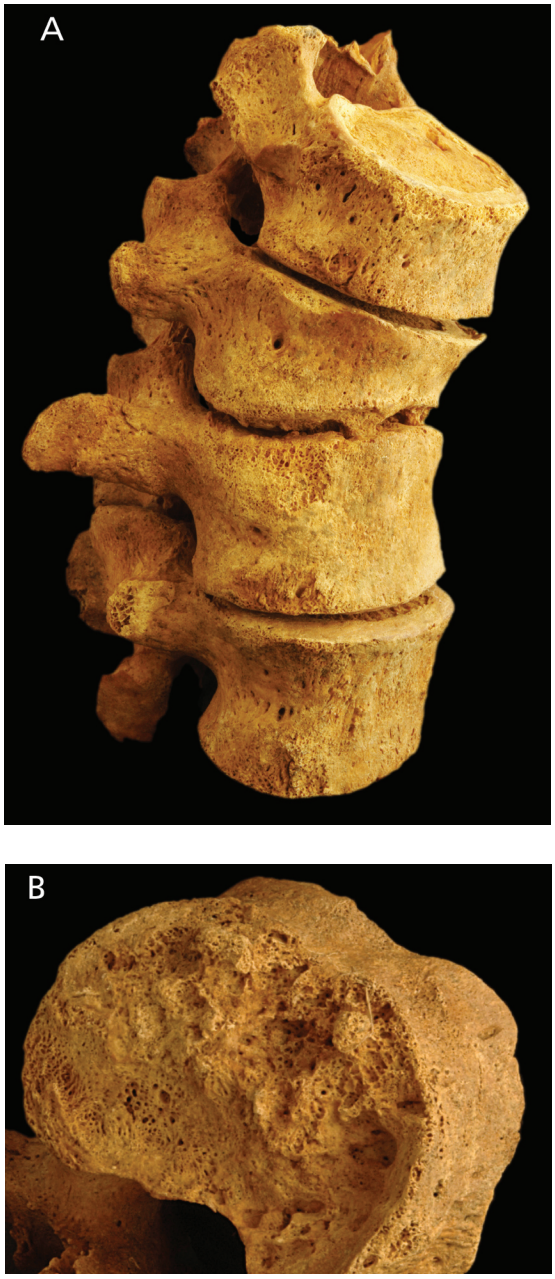

Figure 1. Tuberculous spondylitis: a) kyphotic angulation of the lumbar region (T12-L3); b) lytic focus in the body of the L1 vertebra (Grave no. 84, 23-25 year-old male).

orbitalia, cribra cranii) were also detected.

Results

The first phase of the investigation revealed two cases in the series showing alterations of an advanced stage of TB.

The skeletal remains of a young male adult (Grave no. 84) revealed severe pathological lesions on the 1st and 2nd lumbar vertebrae (Fig. 1). In the lower part of the body of the first lumbar vertebra lytic focus and some reactive bone formation were seen. In addition, on the ventral surface of the body periosteal reactions were observed too. The second lumbar vertebra also showed deep cavitation in the upper part of the body accompanied by reactive bone formation as well as periostitis on the ventral surface. As a consequence of these lesions, the angulation of the spine was also recognizable. These changes correspond to the diagnostic criteria of tuberculous spondylitis. Beside these alterations, the anterior surface of the bodies of the lower thoracic and third lumbar vertebrae revealed superficial inflammatory alterations. Moreover, periostitis on the right tibia and both fibula was found (Lovász et al. 2008).

Figure 2. Healed lumbo-sacral tuberculosis with L5-sacrum fusion and cold abscess (Grave no. 51, 45-50 year-old male).

The mature male individual of Grave no. 51 also showed serious alterations on the vertebral column: the 5th lumbar vertebra fused to the sacrum (Fig. 2). On the body of L5 vertebra remodelled bone formation and osteophyts were also seen. In addition, the ventral surface of the sacrum showed lytic lesions accompanied by extensive but also remodelled reactive bone formation probably in response to an overlying abscess. Moreover, inflammatory changes were observed in both sacroiliac joints as well. These alterations refer to healed lumbo-sacral tuberculosis accompanied by bilateral

Table 1. Skeletal manifestations of advanced and potential early-stage TB in the anthropological material of Zombor-Repülőtér site – individual data.

Grave No.	Reg. No.	Age at death	Sex	Classical TB alterations		Potential TB lesions (atypical or eraly-stage alterations)				Associated stress indicators			Other inflammatory lesions
				Tuberculous spondylitis	Tuberculous arthritis	Rib lesions	Superficial vertebral changes	Endocranial alterations	Early stage spondylodiscitis	Long bone periostitis	Cribra orbitalia	Cribra cranii	
5	191	35-40	Male	-	-	-	Thoracic region	Blood vessel impressions	-	2 tibiae	-	-	2 clavicles: periostitis
7	180	16-18	-	-	-	-	-	Blood vessel impressions	-	-	-	-	-
8	194/a	23-25	Female	-	-	-	-	Blood vessel impressions	-	2 femora, 2 tibiae, 2 fibulae	-	-	-
10	196	50-55	Male	-	-	Rough texture	-	-	-	-	-	-	T12-L5: disc lesions not related to TB
11	197	23-25	Male	-	-	-	Thoracic and lumbar region	-	-	-	-	-	Manubrium of sternum: porous appearance of the dorsal surface
13	199	45-50	Male	-	-	Rough texture	-	-	-	2 femora, 2 tibiae	-	-	-
24	211	30-35	Female	-	-	Rough texture, blood vessel impressions	-	-	-	2 tibiae	-	-	L2-L3: disc lesions not related to TB
25	212	12-14	-	-	-	-	-	Blood vessel impressions	-	-	-	-	2 rami of mandible: periotitis
26	215	18-20	-	-	-	-	Thoracic and lumbar region	-	T12: shallow cavitation in the distal disc	-	porotic	-	Manubrium of sternum: porous appearance of the dorsal surface
28	217	55-60	Male	-	-	Rough texture	-	-	-	2 tibiae, 2 fibulae	-	-	L4: disc lesions not related to TB
29	218	4-6	-	-	-	-	-	Blood vessel impressions	-	2 femora	trabecular	-	-
33	222	25-30	Female	-	-	-	-	Blood vessel impressions	-	-	porotic	-	-
40	229	23-25	Female	-	-	-	Thoracic and lumbar region	Blood vessel impressions	-	2 femora, 2 tibiae, 2 fibulae	-	-	-
46	235	16-18	-	-	-	Periosteal appositions	-	-	-	2 tibiae, 2 fibulae	-	-	-
48	237	23-25	Male	-	-	Periosteal appositions	Lumbar region	Blood vessel impressions	-	2 femora, 2 tibiae, 2 fibulae	-	-	-
51	240	45-50	Male	L5-sacrum fusion, cold abcess	-	-	-	-	-	-	-	-	sacroiliac joint (bilateral): athritis; left metatarsals: periostitis, possibly caused by malleolus medialis fracture

Table 1. continued

55	244	23-25	Female	-	-	Periosteal appositions	Thoracic region	-	-	2 tibiae, 2 fibulae	-	-	-
58	247	18-19	-	-	-	-	Thoracic and lumbar region	-	-	2 femora, 2 tibiae	porotic	-	-
69	265	23-25	Female	-	-	Rough texture, blood vessel impressions	Thoracic region	-	-	-	-	-	-
70	266	2-3	-	-	-	-	-	Blood vessel impressions	-	-	porotic	-	-
84	280	23-25	Male	L1-L2: cavitation of the bodies	-	-	Thoracic and lumbar region	-	-	right tibia, 2 fibulae	-	-	-
95	394	2-3	-	-	-	-	-	Blood vessel impressions	-	-	trabecular	-	-
97	294	23-25	Female	-	-	-	Thoracic region	Granular impressions and blood vessel impressions	-	2 femora, 2 tibiae	-	-	Manubrium of sternum: porous appearance of the dorsal surface
98	295	25-30	Female	-	-	-	Thoracic and lumbar region	-	-	2 tibiae	-	-	-
100	297	25-30	Male	-	-	Rough texture	-	-	-	2 femora, 2 tibiae	porotic	-	-
102	299	45-55	Male	-	-	Rough texture	-	-	-	2 tibiae	-	-	L1-L2: disc lesions not related to TB
108	406	0,5-1,5	-	-	-	-	-	Periosteal appositions	-	-	-	-	-
113	411	9-10	-	-		-	-	Blood vessel impressions	-	-	cribrotic	porotic	-
118	327	1-3	-	-	-	-	-	Blood vessel impressions	-	-	trabecular	-	-
szórvány	250	9-10	-	-	-	-	-	Blood vessel impressions	-	-	porotic	-	-
szórvány	252	5-6	-	-	-	-	-	Blood vessel impressions	-	-	porotic	-	-
szórvány	310	23-25	Male	-	-	-	Thoracic and lumbar region	-	-	2 femora, 2 tibiae	-	-	-
szórvány	341	Infant	-	-	-	-	-	Periosteal appositions	-	-	porotic	-	-
szórvány	349	45-50	Female	-	-	-	Lumbar region	-	-	2 femora, 2 humeri	-	-	-

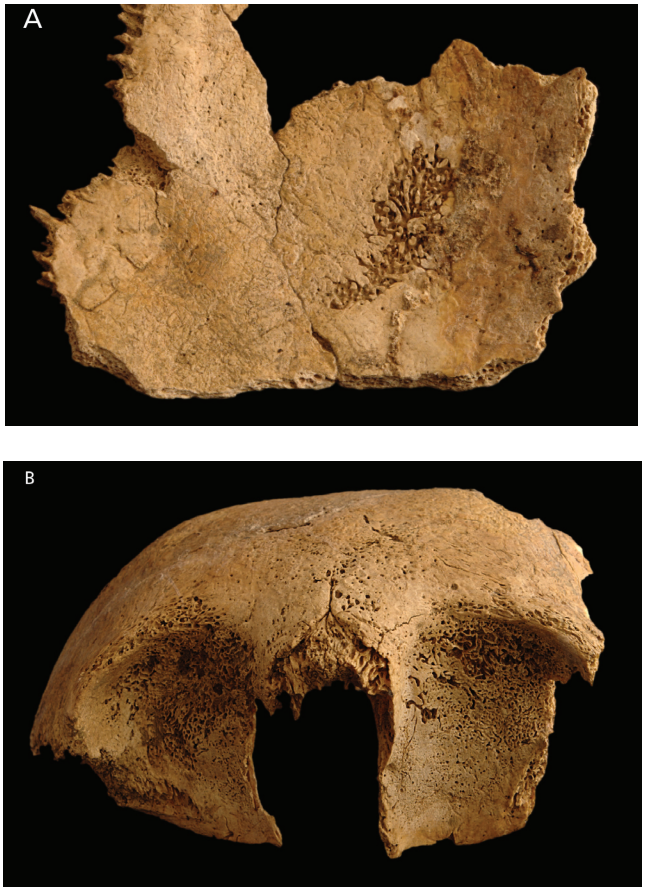

Figure 3. Potential early-stage TB showing association of: a) blood vessel impressions on the internal surface of the left parietal bone; b) bilateral trabecular cribra orbitalia (Grave no. 29, 4-6 year-old infant).

sacroileitis (Lovász et al. 2008).

The second phase of the investigation revealed 32 other probable TB cases, thus their total number rose up to 34 (see Table 1). Among these individuals 14 belong to subadults and 14 to young adults (6 males, 8 females), furthermore 6 mature individuals (5 males, 1 female) were also affected. As far as early-stage TB lesions are concerned, except for Grave no. 51, every individual showed at least one type of the alterations mentioned above.

In most of the cases (17 cases) endocranial lesions were seen. The majority of the alterations appeared in subadults (11 cases), but 6 young adults were also affected (2 males and 4 females). Abnormal blood vessel impressions on the internal surface of the skull vault were seen in the largest number (15 cases), and in one of the cases these lesions were accompanied by granular impressions as well. Two other individuals showed only periosteal appositions on the endocranium.

Superficial vertebral alterations were recognized in a smaller number of individuals (13 cases). The lesions were found mainly in young adults (5 males and 5 females), though

Table 2. Number of cases showing association of classical and atypical/early stage tuberculous lesions as well as stress indicators (TS: Tuberculous spondylitis, RL: Rib lesions, SVCh: Superficial vertebral changes, EA: Endocranial alterations, ESS: Early stage spondylodiscitis, LBP: Long bone periostitis, CO: Cribra orbitalia, CC: Cribra cranii).

	TS	RL	SVCh	EA	ESS	LBP	CO	CC
TS								
RL	0							
SVCh	1	3						
EA	0	1	4					
ESS	0	0	1	0				
LBP	1	8	10	6	0			
CO	0	1	2	9	1	3		
CC	0	0	0	1	0	0	1	

a mature female and two juvenile individuals also showed changes on the vertebral bodies. As mentioned before, one of the individuals showing tuberculous spondylitis (Grave no. 84) also belonged to this group.

As for rib lesions, alterations were found in 10 cases. A juvenile and two young adults (1 male and 1 female) showed signs of periosteal appositions on the visceral surfaces of the ribs, indicating an active inflammatory process. In seven other cases rough texture of the visceral surfaces of the ribs was detected, which was probably due to healed and remodelled periosteal bone formation. This alteration was found mainly on mature male skeletons: 4 mature and 1 young male adults as well as 2 young female adults were affected.

Beside these atypical alterations, in one of the juvenile cases (Grave no. 26) spondylodiscitis was found: shallow cavitation and inflammatory reactions were observed in the body of the 12th thoracic vertebra. This lesion is probably due to TB infection, and might be the sign of an early stage of tuberculous spondylitis. In addition, superficial vertebral lesions and cribra orbitalia were also detected in this case.

Potential early-stage TB lesions were accompanied by stress factors in a number of cases. Long bone periostitis was found in most of the cases (18 cases), mainly in young adults: 3 subadults, 5 young male adults, 6 young female adults, 3 mature male and 1 mature female individuals were affected. The lesions appeared only on the lower extremities (mostly on tibiae and femora) except for one case, where the humerus also showed periostitis. Porotic hyperostosis was also frequently seen in association with tuberculous changes. The orbital roof (cribra orbitalia) was affected in 12 cases (10 subadults, 1 young female adult and 1 young male adult) and mainly the porotic form was detected. However, cribra cranii was found in the case of one subadult.

As for the prevalence of TB cases in the skeletal material of the Zombor-Repülőtér site, we could state that it was quite different in the two phases of the examination. In the first phase the prevalence was P1=2/196*100%=1,02%, and in the sec-

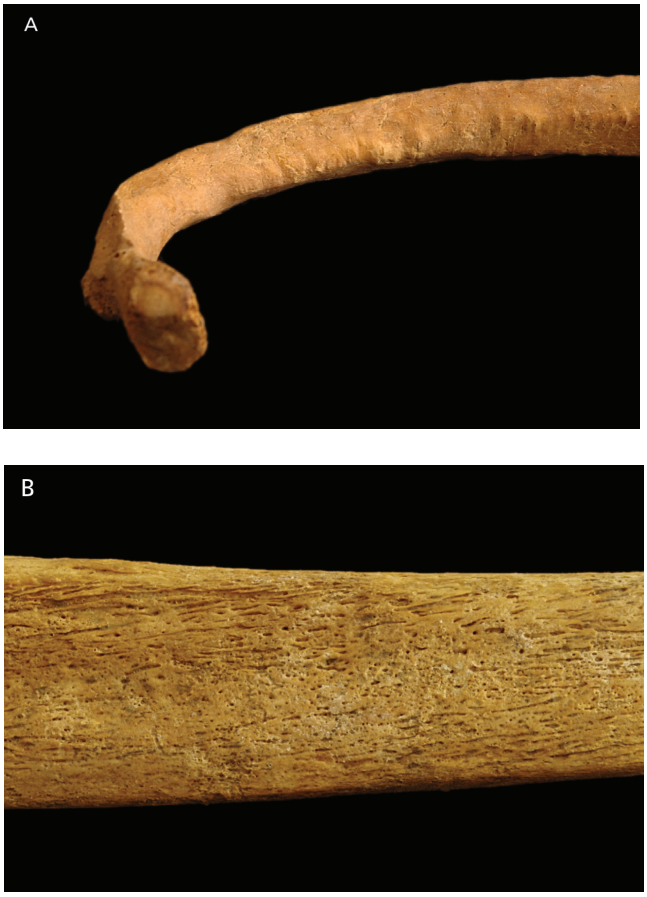

Figure 4. Potential early-stage TB showing association of: a) remodelled lesions on the visceral surface of the right 8th rib; b) remodelled periosteal reactions on the left tibia (Grave no 28, 55-60 year-old male).

ond phase this value rose up to P2=34/196*100%=17,35%.

Concerning the association of different tuberculous lesions (both classical and atypical/early-stage alterations) as well as stress indicators, we found that these changes occurred together in 28 cases (82,35% of all tuberculous cases). The majority of the cases showed two types of these lesions (19 cases). Moreover, in 8 cases we found the association of three lesions and in one case we recognized as many as four of these changes.

The most frequent association was the co-occurrence of a potential early-stage TB lesion and one of the stress indicators (Table 2). Superficial vertebral alterations and long bone periostitis association were observed in the highest number of the cases (10 cases). Furthermore, the combinations of endocranial alterations and cribra orbitalia (9 cases; Fig. 3) as well as rib lesions and long bone periostitis (8 cases; Fig. 4) were often found. The co-occurrence of potential early-stage TB lesions were also recognized, but in a relatively low number. Superficial vertebral changes and endocranial alterations were found together in 4 cases, the association

Figure 5. Potential early-stage TB showing association of: a) superficial vertebral changes on the T10-12 vertebrae; b) periosteal apposition on the visceral surface of the left 9th rib (Grave no. 55, 23-25 year-old female).

of rib lesions and superficial vertebral changes occurred in 3 cases (Fig. 5). Endocranial alterations accompanied by rib lesions were detected in a single case.

Discussion

Regarding the results of the first phase of the investigation, we could state that in the Zombor-Repülőtér skeletal material the characteristic, advanced-stage tuberculous alterations (e. g. tuberculous spondylitis), on which diagnosis was mainly based even some years ago, were present only in 2 cases.

However, taking into consideration the atypical/early-stage TB changes beside the classical alterations, the second phase of the examination revealed additional 32 potential tuberculous cases. Among all TB related cases, 33 showed at least one type of early-stage TB lesions, even in the case where an advanced-stage bone lesion was also present. The remarkable difference between the prevalence in the two phases of the investigation shows that the detection of diagnostic criteria related to atypical/early-stage tuberculosis raises the possibility of identifying TB cases. Therefore, it could also be concluded that for a more appropriate estimation of TB frequency, the application of new criteria and detection methods is inevitable.

Although there are many evidences about the connection of these atypical/early-stage lesions and tuberculosis, it is important to note that these alterations are not always TB specific. Thus, in the cases where the diagnosis was based on these atypical lesions, the tuberculous origin is only presumed, although the association of these changes raises the probability of the diagnosis. However, in addition to the frequent and simultaneous appearance of the supposed tuberculous changes, biomolecular confirmation (*i.e.* DNA, mycolic acid) of TB infection might justify the tuberculous aetiology of the lesions.

The TB related atypical bone changes appeared in almost all age groups (except for elderly individuals), particularly in subadults and young adults. Moreover, a certain tendency can be noted when considering the distribution of these lesions. The endocranial alterations appeared especially in subadults – this result corresponds with medical data from the pre-antibiotic era, which reports that a relatively high number of tuberculous children suffered and died from meningitis (Datta and Swaminathan 2001). Superficial vertebral changes were found mainly in young adults. These data might suggest particular, age-specific skeletal responses to the infection. However, in the case of rib lesions this tendency is not as clear as in the case of other atypical changes: the active form was observed in young (juvenile and young adults) individuals, but the remodelled, probably healed form was found in similar numbers, both in young adult and mature skeletons.

The activity of the tuberculous infection at the time of death was also recognizable in most of the cases. Endocranial lesions, superficial vertebral changes, as well as periosteal appositions on the ribs are suggested to be signs of active inflammation. These lesions were observed in 26 cases indicating an active tuberculous process and a possible cause of death. One of the individuals showing tuberculous spondylitis (Grave no. 84) also revealed an active form of the inflammation. The remodelled bone formations found in the other case of classical TB (Grave no. 51) and 6 cases with rib lesions are suggested to be the result of recovery process. However, a young adult female individual revealed both superficial vertebral changes and remodelled rib lesions. This phenomenon might be explained by the possibly faster recovery of periosteal apposition on the ribs in comparison with the vertebral changes or by assuming that there was no connection between the healing of these lesions. We do not have any data about the precise chronology of the healing process, therefore the use of new technologies of medical imaging (e. g. micro CT) in comparative examinations between skeletal material and recent samples may be able to solve this question.

The association of the different tuberculous lesions as well as stress indicators was recognized in a great number of the cases. This association by itself raises the probability of the diagnosis of tuberculosis. In addition, our results show that the most common combination of these alterations is a potential early-stage TB lesion accompanied by one of the stress indicators. Furthermore, the co-occurrence of potential early-stage TB lesions was also detected. These results suggest a specific pattern in the occurrence of TB related lesions and draw our attention to the importance of further examinations regarding the association of these lesions. However, the investigation of collections with known causes of death can give us reliable data in this matter.

The palaeopathological investigation of TB also gave us an insight into the life of the population of the Zombor-Repülőtér site. Our results showed that tuberculosis occurred in high frequency there, which might indicate a poor state of health in the examined population. This may have several possible reasons. As we mentioned before, the population of the Zombor-Repülőtér site probably emigrated from the Southern regions of Serbia or Montenegro, and the migration in itself probably caused stress as that population had to adapt to a new environment. In addition, as in the rest of Europe, the climate of the Carpathian basin was becoming extremely cold in the 16th-17th centuries (called "small ice-age") and that climate meant adverse conditions for agriculture (Rácz 2001), therefore famine was frequent during that period. The political and military crisis due to the Turkish occupation could also have contributed to the frequent starvation of the people living in that region. All these conditions had negative effects on this population, and could have resulted in their decreased resistance against diseases.

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