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ARTICLE

Juvenile cases of skeletal tuberculosis from the Terry Anatomical Collection (Smithsonian Institution, Washington, D.C., USA)

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ABSTRACT In order to better define the variability of skeletal expression of tuberculosis, we studied 1728 skeletons from the Terry Anatomical Collection, Smitsonian Institution, dating from the first half of the 20th century. Among the numerous cases we studied there were three juvenile individuals who died from TB that are of particular interest. The spine of the first case exhibits lesions related to a multifocal cystic spondylitis, associated with rib lesions probably caused by a pneumo-pleural infection. The second skeleton has frontal and parietal endocranial lesions that can be attributed to TB meningitis. The associated multifocal vertebral and costal abnormalities apparent in this case may represent an early stage in the development of skeletal TB lesions. The skull vault of the third skeleton is perforated by lytic lesions compatible with a diagnosis of cranial tuberculosis. These lesions are associated with bone forming endocranial lesions that suggest TB meningitis. The postcranial skeleton shows mainly osteolytic lesions. These case-studies give an insight to different manifestations of skeletal TB and provide stronger basis for identifying this infection in archaeological human remains. The three juvenile skeletons from the Terry Anatomical Collection provide evidence that lesions like endocranial symptoms, vertebral hypervascularization, rib periostitis, diffuse periostitis of long bones and especially their association do have diagnostical value in the identification of tuberculosis.
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KEY WORDS

Terry Anatomical Collection
Smitsonian Institution
juvenile skeletons
skeletal tuberculosis
multifocal cystic spondylitis
TB meningitis

The paleopathological and evolutionary aspects of tuberculosis

Tuberculosis (TB) is one of the oldest known specific infections that has been coexisting and developing with mankind for several thousands of years. The disease is caused by members of the Mycobacterium tuberculosis complex (MTBC), namely M. tuberculosis, M. bovis, M africanum, M. canettii, M. microti, M. caprae, M. pinnipedii. Nowadays M. tuberculosis is the causative agent of most cases of human TB that most frequently spreads with droplet contact. Besides contagions of M. tuberculosis, the consumption of infected beef and dairy products resulting in alimentary infections of M. bovis must have accounted for a much larger proportion of tuberculosis of past human populations than it does today. However, the number of infection cases caused by M. bovis is still not negligible in certain developing countries.

One hundred years after the discovery of the TB bacterium in 1882, the spectacular development of modern medicine and bacteriology witnessed from the end of the 19th century encouraged the brave statement of the World Health Organization (WHO) that TB would be eradicated by 2000. Negative experiences of the last three decades, however, show that this was based on optimism beyond measure. Prevalence of tuberculosis has risen in almost every continent showing distressing rates especially in Africa and Asia, and multiresistant strains occur on a regular base. According to the WHO estimate, there are 1.7 billion people in the world infected with Mycobacterium tuberculosis, which is nearly one fourth of the total population including almost the whole population of the third world. 5% of all carriers may develope an active disease during their lives. Today, the number of people suffering from an active TB is estimated around 20 000 000. WHO reported 9.4 million new cases for 2009. The same year a total of 1.7 million patients died in TB-related conditions, about 1.3 million of which where HIV negative and 0.4 million HIV positive (WHO 2010). TB is the most lethal infectious disease in the world. Poverty, starvation, increasing alcohol consumption and drug use, the spread of HIV and the application of immunosuppressive drugs strongly facilitate the occurrence of new multidrug resistant variants and the propagation of TB.

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The increase in the number of TB cases brought new attention to the research of the disease and the causative Mycobacterium-species. The international efforts against TB have strengthened and created manifold and diverse scientific trends that are still linked up in many points. Studies dealing with evolutionary issues of the disease and its pathogens tend to gain more attention. The last decades brought extremely important new results in this field. Researchers succeeded in sequencing the complete Mycobacterium tuberculosis genome in 1998 (Cole et al. 1998). Subsequent investigations found that analyses of the deletions accumulated in the genome of the members of the MTBC provide reliable base for separating lineages and identifying certain species (Parsons et al. 2002). This led to the revision of earlier theories of the MTBC phylogeny (Brosch et al. 2002; Mostowy et al. 2002). According to recent molecular results TB as a disease occurred 2.5–3 million years ago in East Africa similarly to the oldest members of the Homo genus, and these ancient infections where caused by a hypothetical Mycobacterium ancestor M. prototuberculosis. As for the evolutionary aspects, the today known M. tuberculosis is an extremely successful human pathogen and it has only descended from the ancient lineage relatively late, some 30-40 thousand years ago (Guttiérrez et al. 2005; Brisse et al. 2006).

The above mentioned research directions in molecular genetics connected to researchers like Cristina Guttiérrez, Roland Brosch, Véronique Vincent and their co-workers and the new results of their investigations are overly important in historical and paleoanthropology and in paleopathology. This is especially true in the case of the latter where they also pose a great challenge at the same time. Paleopathology can provide a vast amount of data on TB and its various osteoarticular occurrence in human skeletal remains found in archeological sites (e.g. Aufderheide and Rodríguez-Martín 1998; Pálfi et al. 1999; Ortner 1999, 2003, 2008). Hungarian researchers have already contributed highly important data to the knowledge of the paleopathology and the epidemiological history (e.g. Marcsik 1972; Pálfi and Molnár 1994; Pálfi and Marcsik 1999; Pap et al. 1999, 2002; Józsa 2006; Marcsik et al. 2009). TB was known for over a hundred years to have been affecting mankind since the Neolithics (Bartels 1907). Paleopathological studies have been reporting thousand old TB cases from all over the world during the 20th century. Based on these evidences several paleoepidemiological review works have been completed (e.g. Dutour et al. 1998; Pálfi and Blondiaux et al. 1999; Marcsik 1999; Roberts and Buikstra 2003; Marcsik et al. 2009) at the turning of the millennia. The overwhelming majority of the paleoepidemiological works prior to the mid-1990's dealt with the so-called classical paleopathological criteria of TB. Basically, these include the most frequent and/or most well known osteoarticular changes observed in skeletal TB: tuberculous spondylitis (spondylitis tuberculosa) and TB arthritis of the great joints. TB spondylitis (Pott's disease) can result in complete destruction of the vertebral bodies and may cause ankylosis of several vertebrae and angular kyphosis of the spine in a chronic state. Among the highly pathognomonic tuberculous arthritis of the great joints (e.g. coxitis and gonitis tuberculosa) are the most frequent forms sometimes also causing full destruction of the joint and ankylosis in an advanced stage of the disease. In both locations morphological diagnosis of the osteoarticular destruction in chronic TB has also been furthered by the detection of cold abscesses in bioarcheological remains, which is again abundantly evidenced in the literature. Thus, earlier TB diagnostics in paleopathology only focussed on late, sometimes even healed symptoms of the chronic forms. Those cases remained literally unnoticed for the history of paleoepidemiology where the patients died in an earlier stage of the severe TB infection and hardly any or no bone changes developed. Infection rates and morbidity observed in paleopathology in many cases did not reflect the actual epidemiological tendencies of past populations.

The last decade of the 20th century brought a major breakthrough in the paleopathological diagnostics of TB. The first DNA evidence based molecular ("paleomicrobial") study on M. tuberculosis infection in old skeletal remains came out in 1993 (Spigelman and Lemma 1993) and was later followed by many others (e.g. Salo et al. 1994; Donoghue et al. 1998; Dutour et al. 1999; Haas et al. 2000). Paleomicrobiology has become a special interdisciplinary branch of paleopathology (Donoghue 2008), and most recently molecular paleoepidemiological studies based on bigger sample sizes have also been published in TB literature (e.g. Fletcher et al. 2003; Zink et al. 2007; Molnár et al 2010). Paleomicrobiological diagnostics is effectively supplemented by other molecular techniques (Gernaey et al 1999; Redman et al. 2009). Thanks to paleomicrobiology and paleobiochemistry, the earliest osteological evidence of human TB infection was recently identified in the Eastern Mediterraneum dating back to 7000 years BC (Hershkovitz et al. 2008). In case of these remains the DNA analyses and other molecular incvestigation techniques proved the presence of Mycobacterium tuberculosis in the bone samples.

Atypical or early-stage skeletal symptoms of TB infections also started to gain more attention in the last few years of the 20th century. Following earlier works by Kelley and El-Najjar (1980) and Kelley and Micozzi (1984), investigations of Roberts and co-workers in the Terry Anatomical Collection in Washington DC supplied evidence for the causal relationship between the osteo-periostitis of the visceral rib surfaces and pulmo/pleural TB (Roberts et al. 1994). A couple of years later Schultz published a paper on endocranial impressions in TB related meningitis (Schultz 1999), whereas Baker (1999) identified certain superficial changes of the vertebral bodies as manifestations of early TB. The molecular cross validation of these types of lesions in Hungarian skeletal series (Haas et al. 2000) was among the first studies in the paleopathological

Figure 1. The National Museum of Natural History, Washington DC, USA.

Figure 2. Donald J. Ortner (left) with Olivier Dutour (right) in the „Terry Anatomical Collection" (National Museum of Natural History, Washington DC, USA).

literature to confirm their diagnostical value. Maczel's study (Maczel 2003) gave an excellent review of early-stage and atypical TB lesions in osteoarcheology.

Materials and Methods

TB research in the skeletal remains of the Terry Anatomical Collection

For a better understanding of the skeletal manifestations of TB we studied human skeletal remains from the first half of the 20th century in the Terry Anatomical Collection (National Museum of Natural History, Smithsonian Institution, Washington DC). We have spent 3 research periods in Washington in the frameshift of a French-US-Hungarian co-operation (1999, 2000, 2010). The evaluation of the complete paleopathological database is already in progress.

The Terry Anatomical Collection consists of skeletal remains from 1728 individuals and is now housed in the Department of Anthropology, NMNH, Smithsonian Institution, Washington DC since 1967 (Figs. 1-2). The collection was founded by Robert J. Terry professor of anatomy, former dean of the Washington University Medical School (St. Louis, Missouri). The skeletons have been macerated from bodies of individuals who have died between the 1920's and the 1940's in US hospitals usually without any living relatives, and the skeletons are being used for educational and research purposes since then. The Terry Collection contains the skeletons Euro-American and Afro-American individuals in approximately the same proportion. The total sample size is 1728 including extremely well preserved, complete skeletons of 16 to 102 years old individuals.The collection consisting of mostly adults is of distinguished value in anatomical, anthropological and paleopathological studies. Among the 1728 individuals only 61 were below 20 years of age at the time of death (Hunt and Albanese 2005).

The collection is especially important in the research of palepathological diagnostics of infectious diseases, as these remains derive from the pre-antibiotic era representing manifestations of osteoarticular infections that are almost unknown in the contemporary medical practice of developed countries. The temporal origin of the collection also makes it an outstanding TB research data source: in accordance with the TB prevalency of the first half of the 20th century the archives of the collection report that more than 15% of these 1728 individuals have died in tuberculosis or TB-related conditions. In the present paper we would like to give detailed macromorphological analysis of lesions found in 3 extraordinary juvenile skeletons form the dataset of our on-going project and interpret these individual data with regards to their diagnostical value in paleopathological practice.

Results and Discussion

Manifestations of TB in 3 juvenile skeletons

Case no. 129 is a 19 years old Afro-American male whose death certificate states TB spondylitis as the cause of death – the only of its kind among the rather frequent pulmonal tuberculosis death causes in the Terry Collection's registry. The most characteristic feature of the spine is a dozen of spherical destructive lesions between the size of 10 to 30 mm in the thoracic, lumbar and sacral regions (Figs. 3-7). Vertebrae L1-3 in Figure 3 convincingly demonstrate how severely destroyed and almost unaffected vertebrae alternate in the spine referring to develepoment of independent destruction foci. The hight of vertebral bodies is maintained in all vertebrae even if the body itself is more than 50% destroyed (Figs. 4-5). Figure 5 shows that the rim of the lesions is slightly remodelled

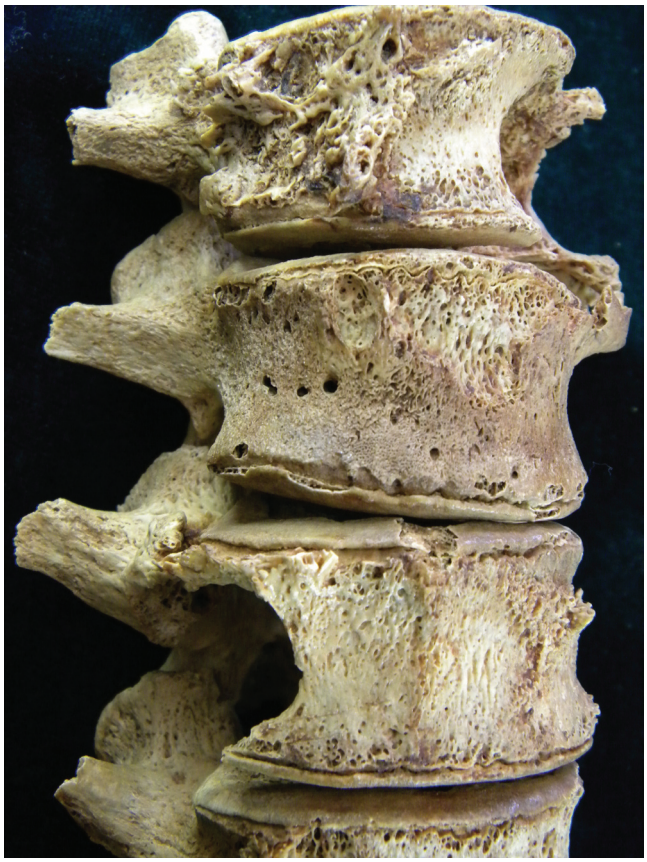

Figure 3. Cystic lesions and superficial new bone formations on lumbar vertebrae (Case No 129).

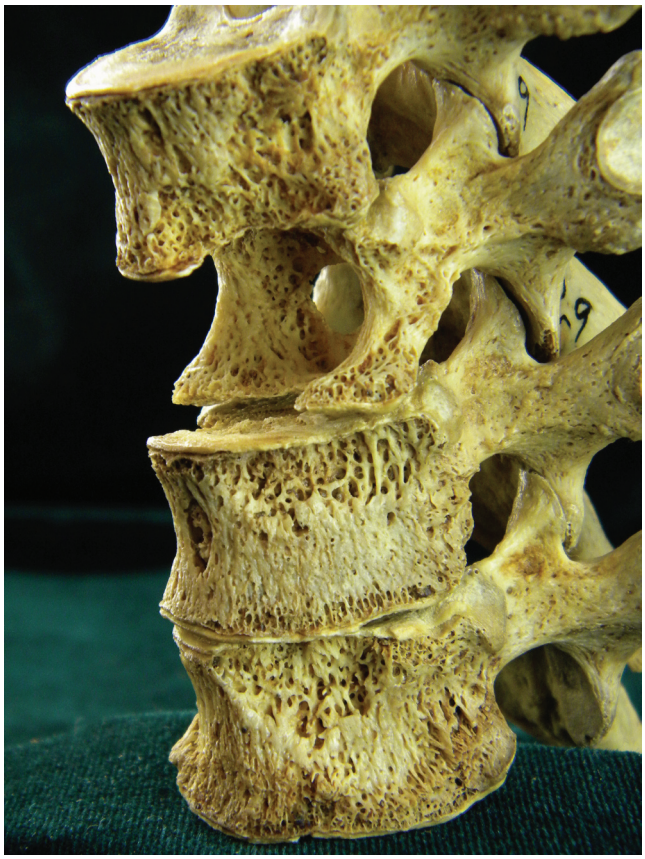

Figure 4. Serious destruction of a thoracic vertebral body (Case No 129).

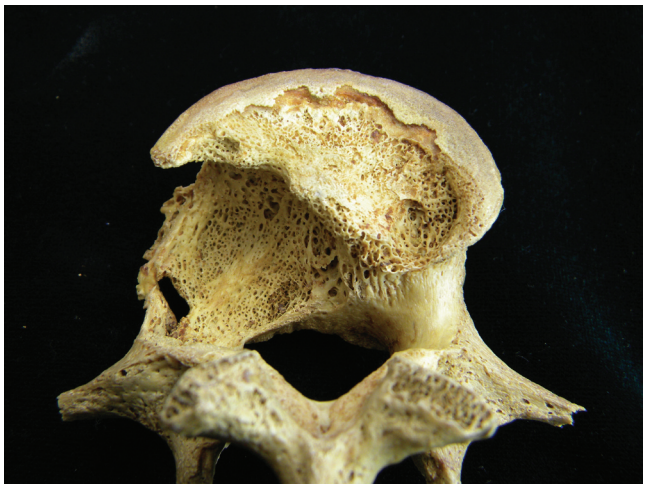

Figure 5. Destruction of a lumbar vertebral body (Case No 129).

Figure 6. Vertebral body destruction around the original TB granuloma (Case No 129).

with reorganization of the original trabecular structure but the bone renewal is by far less extensive than the destruction. The coloured plaques in the internal surface of the lesions (Fig. 6) may be imprints of soft tissue. Despite maceration desiccated organic matter has remained in a smaller lesion

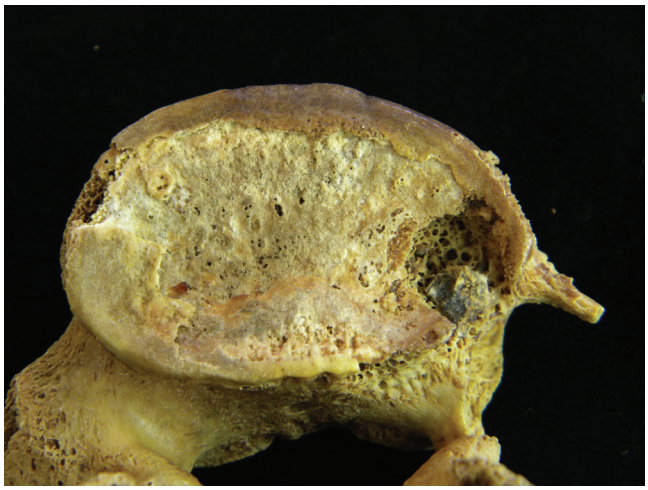

Figure 7. Small lesion of a vertebral body with the remnants of the original TB granuloma (Case No 129).

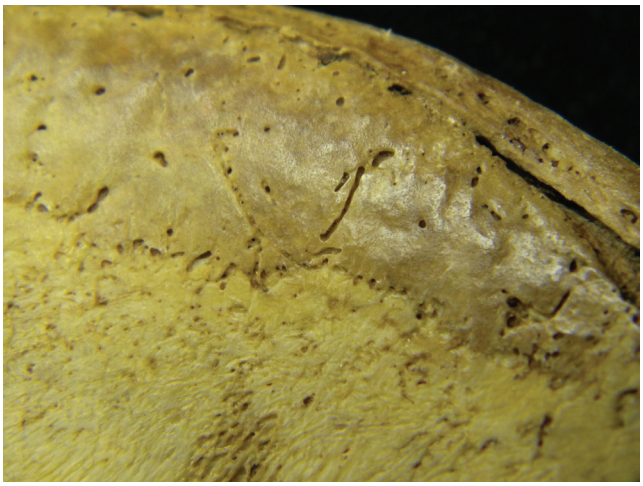

Figure 8. Periosteal new bone formation on right iliac bone indicating TB cold abscess (Case No 129).

Figure 9. Periosteal appositions and traces of an erosive osteitis on a rib (Case No 129).

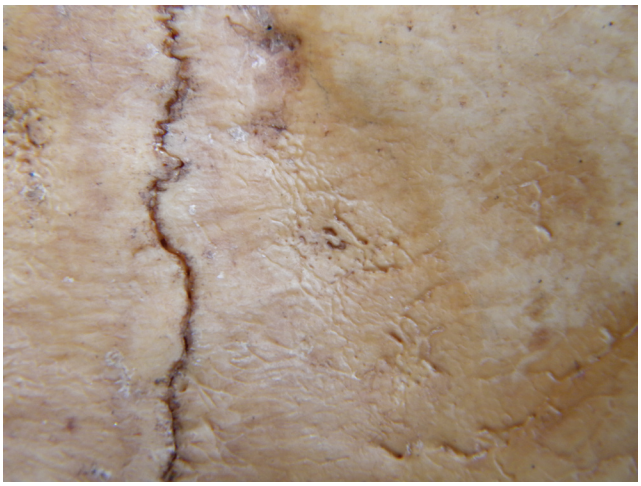

Figure 10. Early-stage endocranial alterations (Case No 129).

in the lumbar region (Fig. 7). Periosteal new bone formation (Fig. 3) has also occurred in the spine othervise dominated by destructive lesions. Abdominal surface of the right ilium (Fig. 8) and trochanters of the right femur are covered with continuous new bone layer. Several ribs show lytic lesions similar to those of the vertebrae, and also some remodelling on the visceral surfaces (Fig. 9). Numerous regions along the sagittal sinus exhibit signs of endocranial hypervascularisation and slight remodelling referring to inflammatory processes (Fig. 10).

The characteristics of the bone destruction observed in the vertebrae and the desiccated matter in the holes clearly indicate a granulomatous process. Even though many pathological conditions my initiate granuloma formation, the epidemiological context and the death certificate supports TB granuloma in our case. The superficial lesions of the vertebrae refer to paravertebral abscesses, while the new bone layer of the right ilium and the right femur must be in connection with psoas abscess (in accordance with the TB related process in the lumbar region). The periosteal appositions observed on the ribs refer to direct pneumo-pleural infection. The endocranial alterations in the skull of the young male indicate probable meningitis. We can conclude that the observed osteological lesions are in consonance with the casuse of death in the death certificate, even though the literature hardly ever mentions tuberculous destruction of the spinal elements could cause death. In our case the vertebrae exhibit such a multifocal,

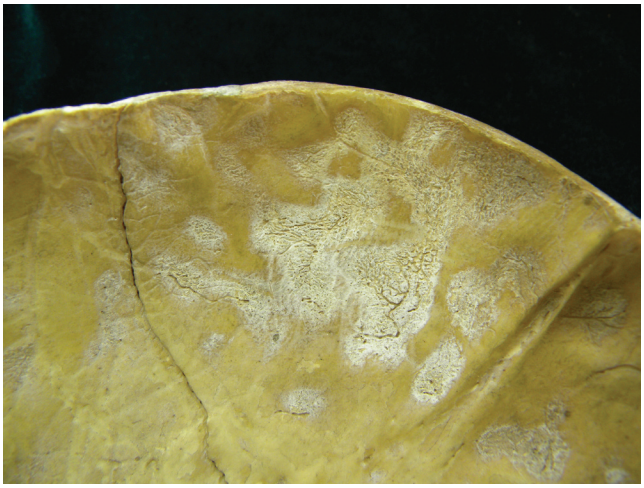

Figure 11. Endocranial lesions due to TB-meningitis (Case No 306).

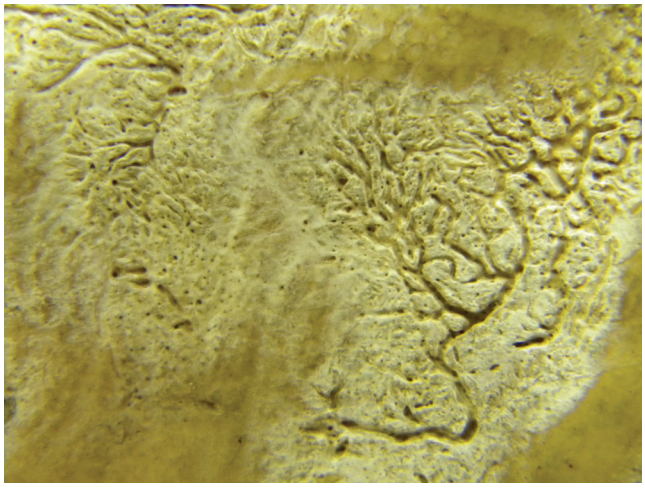

Figure 12. Endocranial lesions due to TB-meningitis (Case No 306).

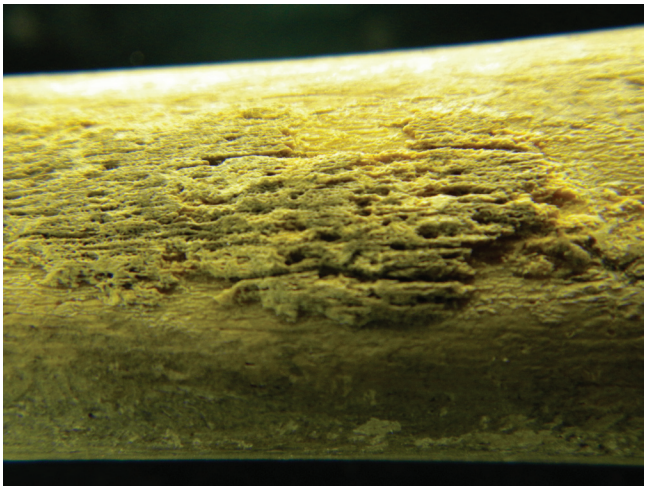

Figure 13. Periosteal new bone formations on long bone diaphysis (Case No 306).

Figure 14. Osteo-periostitis on visceral surface of a rib (Case No 306).

cystic and highly destructive form of TB spondylitis that is extremely rare both in the medical and the paleopathological literature (e.g. Sorrel and Sorrel-Dejerine 1932; Yalniz et al. 2000; Ortner 2003; Marudanayagam and Gnanadoss 2006). As long as the suspected cause of death is spondylitis it must be in connection with the abscess affecting the spinal marrow (together with a fast, multifocal destruction of vertebrae). Based on the early-stage endocranial lesions found in the skull, however, it may be presumed that the state of the patient was also aggravated by other factors and even TB meningitis may be proposed as the cause of death.

Case no. 306 is the skeleton of a 17 years old Euro-American female whose death resulted from pulmonary TB as the death certificate states. The most significant feature of the remains is the the extensive, asymmetrical, bilateral hypervascularisation in the endocranial surface of the skull, and superficial new bone appositions surrounding the vessel impressions (Figs. 11 and 12). Traces of diffuse periosteal new bone formation are observed in numerous postcranial elements (e.g.: long bone diaphyses (Fig. 13), visceral rib surfaces (Fig. 14). Vertebral bodies in the thoracic and upper lumbar region carry conspicuous, wide, pit-like vessel impressions (Fig. 15), accompanied by traces of superficial remodelling in most cases (Fig. 16).

The eye-catching endocranial lesions of the skull refer to severe inflammation of the meninges. Such manifestations have many times been reported in the literature since the 1990's concerning which Hershkovitz and co-workers suggested the name 'SES' (Serpens Endocrania Symmetrica) in

Figure 15. Hypervascularisation on thoracic vertebral bodies (Case No 306).

Figure 16. Hypervascularisation and cortical remodelling on a thoracic vertebra (Case No 306).

Figure 17. Large perforation in the left side of the frontal bone (Case No 329).

their 2002 paper (Hershkovitz et al. 2002). It must be noted that, despite the name, this phenomenon is not necessarily symmetrical, and the serpentine nature is not true in the early stages of the lesion development (see the other two cases introduced in this paper). The hypervasularization of abnormal measures observed in the thoracic vertebrae cannot be explained with anatomical features in connection with the developing state of the spine in this young individual. This case provides an excellent example of what paleopathological literature has been addressing as early-stage TB-related spondylitis (e.g. Baker 1999; Haas et al. 2000; Pálfi and Ardagna 2002; Maczel 2003). It is important to emphasize that similar osteological features have already been published in the medical literature at the end of 19th century (e.g. Ménard 1988), but they remained unnoticed for paleopathology for more than a century. In our case the generalized skeletal infection of this young female manifested in the long bones and the ribs, in the latter location most likely due to pulmo/pleural TB. These associated lesions reveal a highly aggressive, multifocal, early-stage skeletal TB.

Case no. 329 is the skeleton of a 17 years old Afro-American male who died of TB. The skeleton shows traces of both osteoblastic and osteoclastic processes. The death certificate mentions syphilitic skull lesions as the cause of death along with TB. This generalized pathology affected almost every part of the skeleton in the form of quite heterogenous lesions. One of the most remarkable symptoms is a perforation of the cranial vault (Figs. 17 and 18). The lesion with plain rims in the external table apparently flares out towards to endocranial surface surrounded by a halo of excessively remodelled, hypervasculralized bone layer and abnormal vessel impressions in the internal table (in different forms such as ‘pit-like’, ‘worm-like’, ‘spider-like’ etc lesions). The pathological symptoms of the postcranial elements include osteolytic perforations of the innominates surrounded by thin layers of

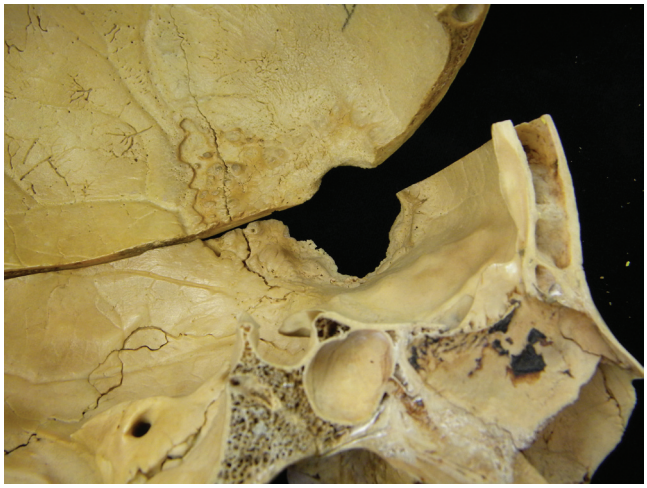

Figure 18. Endocranial view of the lesion presented in the Picture No. 17 (Case No 329).

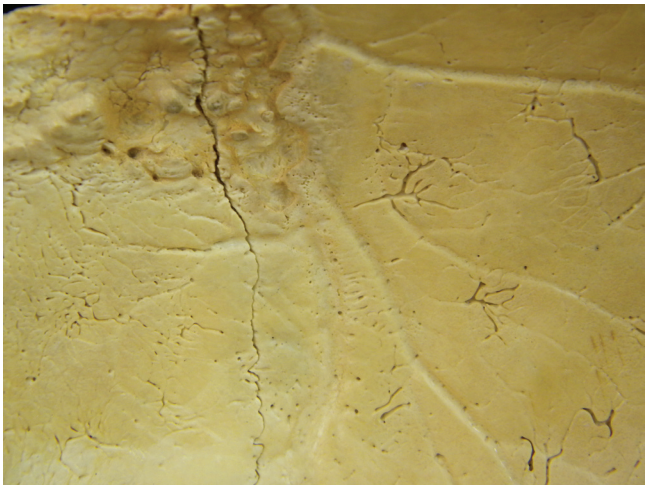

Figure 19. Endocranial changes – different types of abnormal vessel impressions - associated with the lytic lesion (Case No 329).

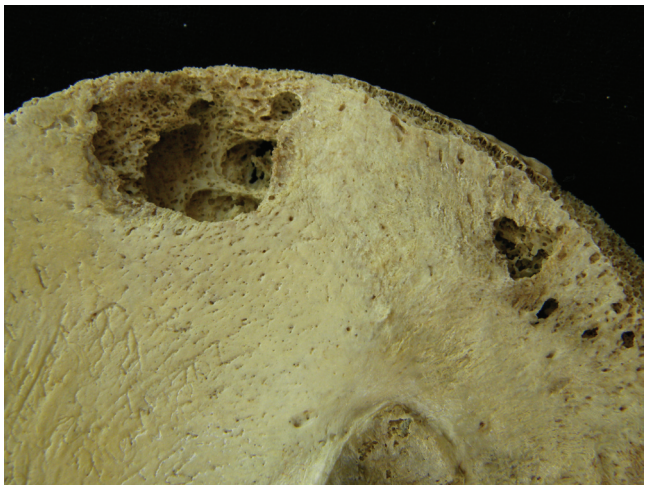

Figure 20. Tuberculous osteitis of the right iliac bone (Case No 329).

periosteal appositions (Fig. 20), thickening of the diaphyses of ulnae (spina ventosa) with cloacae (Fig. 21), remarkable destruction of the elements of the spine. All spinal regions are affected from the first cervical to the sacrum showing smaller perforations and extensive superficial new bone formations while the height if the vertebral bodies remained normal (Figs. 22-24). Articular surfaces of the cervical vertebra are also destroyed (Fig. 22). The ribs show both superficial osteoperiostitis and osteolytic zones cutting through the original and the newly built substance (Figs. 25, 26).

Having studied the remains we concluded that the skull lesions resembling syphilitic symptoms at first sight during the original autopsy are evident signs of a severe TB osteitis, and clearly differ from caries sicca pathognomonic to syphilis.

Figure 21. TB osteomyelitis in the diaphysis of the left ulna (Case No 329).

The tuberculous destruction of the calvarium gets very little attention in the medical literature of developed countries, but

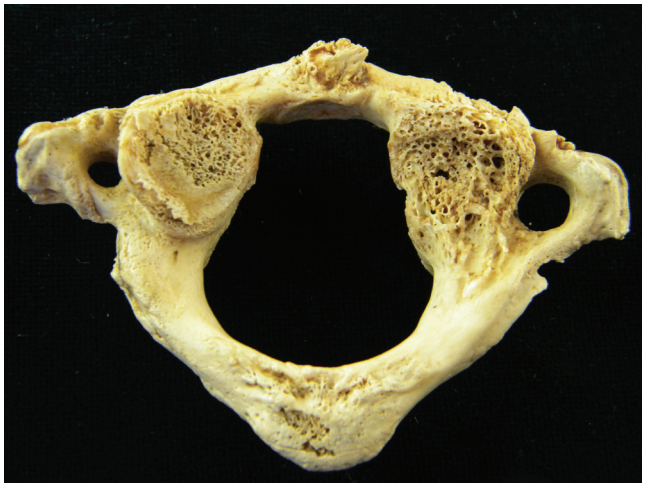

Figure 22. Destruction of the articular surfaces of the atlas (Case No 329).

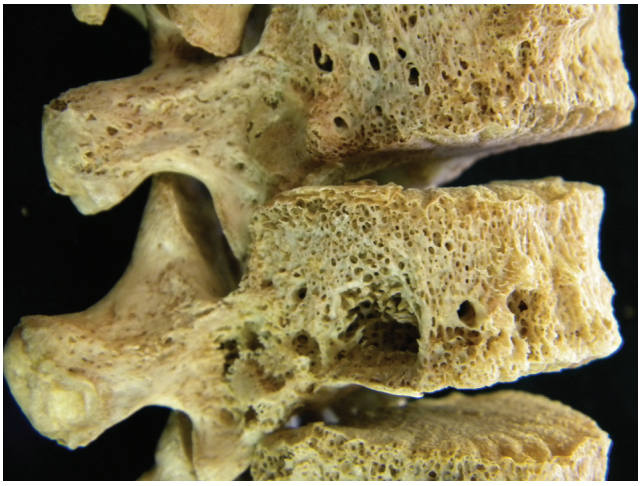

Figure 23. Destruction and cortical remodelling of vertebrae (Case No 329).

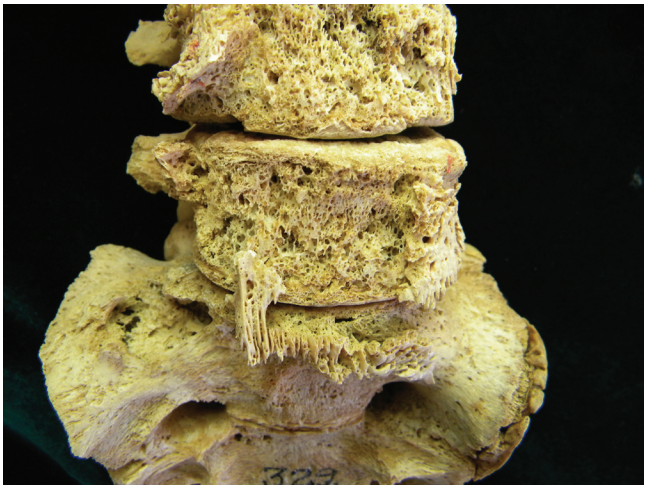

Figure 24. Severe inflammatory/infectious changes in the lumbo-sacral region (Case No 329).

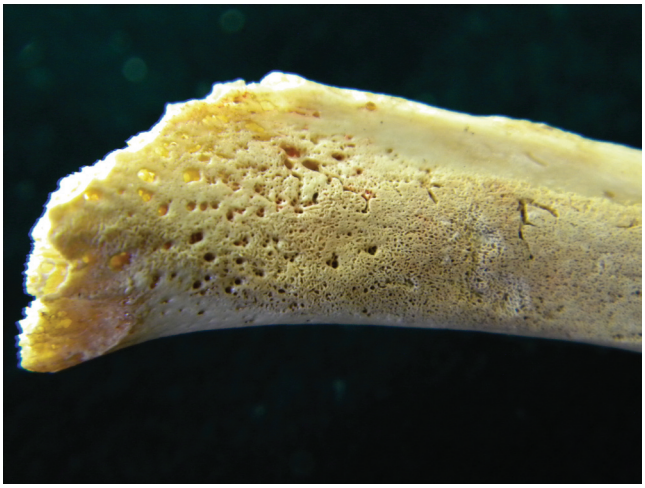

Figure 25. Periosteal new bone formation on visceral surface of a rib (Case No 329).

papers published in the first half of the 20th century provide sufficient comparison to our case (e.g. Sorrel and Sorrel-Dejerine 1932; Beatty and Russell 1940). Sadly, similar cases are still quite often found and published in Asian and African countries with high TB prevalence today (e.g. Amin et al. 2004; Diyora et al. 2009). In our case lytic processes are largely associated with lesions of different phases of TB meningitis in the endocranial surfaces ('pit'-, 'worm'-, 'spider'- and 'star'-shaped impressions). The postcranial skeleton shows signs of a multifocal, mostly destructive inflammatory process. Two more things have to be mentioned here: the rare osteomyelitis of the ulnae otherwise characteristic to TB and the TB-related ileitis. The original misdiagnosis of syphilis was also cleared up. In our opinion, this case exhibits a complex multifocal, partly cystic and highly aggressive, presumably fast-running yet atypical osteitits tubeculosa process.

Conclusion and Perspectives

First of all, these three cases represent extraordinary manifestations that are even though uncommon in the paleopathological literature, can be doubtlessly attributed of osteo-articular TB. All three cases are rather complex, with association of lesions the etiology of which is usually disputed. Therefore, these cases provide solid evidence that lesions like endocranial symptoms, vertebral hypervascularization, rib periostitis, diffuse periostitis of long bones and especially their

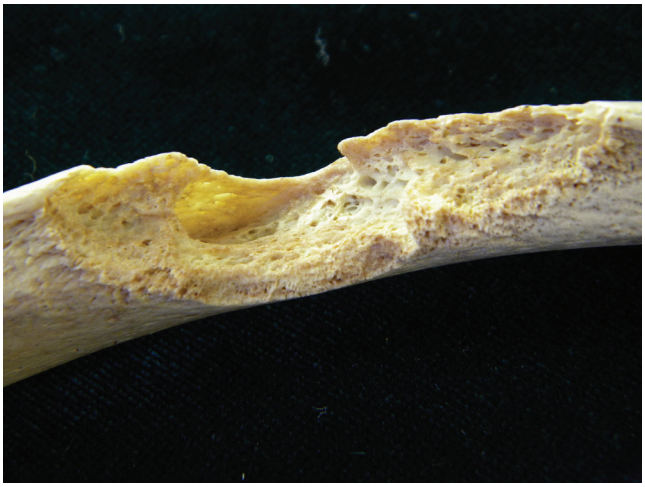

Figure 26. Large lytic lesion in a rib (Case No 329).

association do have diagnostical value in the identification of tuberculosis. The discussion of these scarce localizations of TB osteitis (skull, long bones, pelvis) and cystic appearances may contribute to more reliable diagnosis of similar TB cases in paleopathology, as a recently issued paper also rightly undertook (Dabernat and Crubézy 2010).

The case reports of these three juvenile skeletons from the beginning of the 20th century may provide help in the understanding and paleopathological interpretation of inflammatory symptoms of older humans remains unearthed in archeological excavations. Comprehensive analysis of possible osteo-articular manifestations of human TB is indispensable in human paleopathology if we are to achieve the aims introduced in the first part of our paper, namely the identification of potential pre-Neolithic tuberculosis cases for the research of Mycobacterium-evolution.

Morphology-based paleopathological investigations a couple of years ago provided unique but unfortunately controversial data in TB research. Approx. 500 000 years old Homo erectus remains from Denizli in Turkey showed endocranial changes similar to those observed in TB (Kappelman et al. 2008). This find would be overly important as no other data are available on TB infections from such ancient times. The lesions, however, are rather non-specific and no molecular results are yet available to prove their tuberculous origin. According to our current knowledge, the earliest evidence of Mycobacetrium infections supported by morphological and paleomicrobial data are the 9000 years old human remains of Atlit-Yam, Israel (Hershkovitz et al. 2008). The gap between the chronological estimates based on theoretical genetical calculations concerning Mycobacterium-evolution and the actual paleopathological + paleomicrobial data on TB occurrence is still enourmos: M**.** prototuberculosis is estimated to have occurred 2.5 – 3 million years ago while M. tuberculosis 35-40 000 years ago (Guttiérrez et al. 2005; Brisse et al. 2006) and we only have evidence based data for 9 000 years back. This huge gap necessitates further investigation in TB evolution. However, new multidisciplinary cooperation initiatives between the concerned fields of science raise hope. Refinement of morphological criteria in the paleopathological diagnosis of TB, the application of these in bioarcheological series and further development of paleomicrobial techniques may open new perspectives in the research of evolutionary issues of TB.

Dedication

We would like to dedicate this short paper to the loving memory of our coauthor, collaborator, colleague and friend, Dr Donald J. Ortner, who, for the deepest regret of all paleopathologists, left us some months before this paper was published. We will always keep the memory of the greatest paleopathologist and the very kind friend, who invited us to the Smithsonian Institution, who initiated this joint research, and who co-presided the first world congress on the evolution of tuberculosis in Hungary in 1997.

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