Pathol. Oncol. Res. (2017) 23:583–587
DOI 10.1007/s12253-016-0153-7

ORIGINAL ARTICLE

Rare Case of an Ancient Craniofacial Osteosarcoma with Probable Surgical Intervention

Erika Molnár[1] · Michael Schultz[2] · Tyede H. Schmidt-Schultz[2] · Antónia Marcsik[1] · Krisztina Buczkó[3] · Péter Zádori[4] · Gergely Biró[4] · Zsolt Bernert[5] · Daniel Baumhoer[6] · Tamás Hajdu[5,7]

Received: 25 April 2016 / Accepted: 13 November 2016 / Published online: 19 November 2016

Abstract Osteosarcoma is the most common primary malignant bone tumor both today and in antiquity. Nevertheless, it is a comparatively rare tumor. This paper describes a case of a highly aggressive craniofacial lesion from the 11th–12th centuries AD, most likely representing osteosarcoma. During the paleopathological study, macroscopic, endoscopic, radiological, scanning-electron and light microscopic investigations were performed. The skull of the approximately 40–50 year-old female revealed several pathological findings. The most impressive macroscopic feature was an extensively spiculated periosteal reaction ("sunburst" pattern) in combination with a massive bone destruction most likely derived from a highly aggressive tumor originating in the ethmoidal area of the medial wall of the orbit. The central parts of the lesion showed excessive new and most probably neoplastic bone formation indicating an underlying high-grade osteosarcoma. The light microscopic examination revealed three different levels of bony structures representing different qualities of bone tissues. Besides the mass lesion, signs of a healed multiple incomplete trephination of the left parietal bone was observed. This case represents a unique example in which the concomitance of a tumor and an incomplete trephination could be observed from the skeletal remains of an ancient individual. The case opens new considerations as to whether surgical interventions, such as incomplete trephination, might have been used already in the Middle Ages as a therapeutic approach.

Keywords Craniofacial osteosarcoma · Paleopathology · Incomplete trephination

Michael Schultz is a shared first author of the manuscript.

Electronic supplementary material The online version of this article (doi:10.1007/s12253-016-0153-7) contains supplementary material, which is available to authorized users.

✉ Erika Molnár
balinte@bio.u-szeged.hu

1 Department of Biological Anthropology, University of Szeged, Közép fasor 52, Szeged H-6726, Hungary

2 Department of Anatomy, University Medical School Göttingen, Kreuzbergring 36, D-37075 Göttingen, Germany

3 Department of Botany, Hungarian Natural History Museum, Könyves Kálmán körút 40, Budapest H-1097, Hungary

4 Health Center, Kaposvár University, Guba Sándor utca 40, Kaposvár H-7400, Hungary

5 Department of Anthropology, Hungarian Natural History Museum, Ludovika tér 2, Budapest H-1083, Hungary

6 Bone Tumor Reference Center at the Institute of Pathology, University Hospital Basel, Schönbeinstrasse 40, D-, 4031 Basel, Switzerland

7 Department of Biological Anthropology, Institute of Biology, Eötvös Loránd University, Pázmány Péter sétány 1/c, Budapest H-1117, Hungary

Introduction

Cancer is the second leading cause of death after cardiovascular diseases in industrialized societies today [1, 2]. The occurrence and frequency of neoplastic lesions in ancient populations, which seem lower in human antiquity than observed nowadays, are still a subject of debate for both paleopathologists and medical historians [3]. However, using innovative methods and techniques, neoplastic diseases can be diagnosed reliably on archaeological specimens [4]. Human skeletal paleopathology provides important insights into the antiquity of malignant tumors in ancient human populations and their hominid ancestors [5, 6].

Osteosarcoma is the most common primary bone malignancy, with a high incidence rate in children and adolescents compared to other age groups. Although any bone may be affected, osteosarcomas show a predilection for the metaphyses of long bones, particularly the distal femur, the proximal tibia and the proximal humerus [7]. However, the fourth most common site of presentation are the bones of the face and jaws [8, 9]. Generally, osteosarcomas are high grade neoplasms often causing aggressive periosteal reactions, in about 25% of cases presenting with a "sunburst" pattern [10].

In the paleopathological literature, there are only a few reports of osteosarcomas [11]. Until recently, only four cases of ancient osteosarcomas in Hungary have been published. In all four cases, the lesions affected young adults and were localized in the long bones [12–14].

Trephination represents one of the oldest surgical procedures, and its practice was widespread in many ancient cultures and several parts of the world [15, 16]. Two types of trephination have been performed in living persons: complete (or surgical) and incomplete (or symbolic) trephination. Surgical trephination is a process in which a hole is drilled or cut into the skull vault, exposing the intracranial content without affecting the dura mater, for either medical or ritual purposes [17].

A special form of trephination was the incomplete trephination. During this procedure, only the external lamina of the cranial vault was removed, exposing the diploë. After the procedure, the exposed surface relatively quickly generated a thin, secondary cortical layer of bone. However, even after complete healing, a shallow cavity usually remained [18, 19]. Some authors interpret incomplete trephinations as ritual intervention while others suppose that they may be related to an ancient cauterization practice documented by the Turkish doctor, Sabondjü-oğlu in the 15th c. AD [17–19]. Incomplete trephinations were very common in the territory of recent Hungary during the 9th–11th century AD, and are found particularly in those skeletal series connected to early Hungarians [18, 19].

This paper describes a case of a highly aggressive craniofacial lesion from the 11th–12th centuries AD, most likely representing osteosarcoma, which additionally exhibits vestiges of an incomplete trephination.

The study aims to present this interesting phenomenon and to call for similar investigations of ancient specimens from different periods and geographical locations to be conducted and shared for the purpose of obtaining a larger scale analysis that will shed light on past cancer epidemiology.

Materials and Methods

The skeletal remains of a mature female were excavated in 1884 from the Pusztapáka-Nándorhalom site in Central Hungary and were analyzed first by Allodiatoris [20]. The cranium is well-preserved, but the postcranial skeleton was lost after the excavation. Recently the skull was re-examined and during this paleopathological study, macroscopic, endoscopic, radiological, scanning-electron and light microscopic techniques were applied. Computed tomography (CT) was performed using a Siemens Somatom Definition Flash Dual Source CT scanner. The primary axial CT images were obtained with 0.4 and 0.6 mm slice thickness. For better visualization three-dimensional volume rendering technique (VRT) and two-dimensional secondary image reconstructions were applied [21]. For light microscopy, resin-embedded thin-ground sections were viewed in polarized transmission light [22–24]. For scanning-electron microscopy, coating with gold/palladium was accomplished using a XC7620 Mini Sputter Coater for 120 s at 16 mA. A Hitachi S-2600 N scanning-electron microscope operated at 20 kV and 5–8 mm distance was used. Samples for scanning-electron microscopic and light microscopic investigations were taken from the tumorous bone of the orbital roof and the nasal cavity.

The dating of the skeleton was carried out by the AMS radiocarbon method in the Hertelendi Laboratory DeA-2798 [25] (two sigma ranges – cal AD 1021: cal AD 1155).

Results and Discussion

The skull revealed impressive pathological findings most likely caused by a primary bone tumor (Fig. 1a). The ethmoidal sinuses, both nasal cavities (mainly the left one), the frontal and the left maxillary sinuses, and the hard palate were involved. The lesion occupied one third of the left orbit (Fig. 1b).

The most characteristic macroscopic feature was the extensive and spiculated periosteal new bone formation indicating a highly aggressive causative lesion in combination with lytic parts in which a soft tissue component must have been located (Supplementary Material Fig. S1–3). The edge of the orbital roof was characterized by a porous surface which might be due to a secondary periostitis as a consequence of the periosteal reaction. Due to pressure atrophy caused by the lesion, pronounced bone loss of the frontal process of the left zygomatic bone was seen (thickness of about 2.5 mm and on the normal right side 5.5 mm) (Supplementary Material Fig. S1). The left lateral orbital wall was almost completely resorbed, resulting in a lengthened opening (Supplementary Material Fig. S3). The transverse width of the right orbit was 36 mm, while, theoretically, the available space for the left eyeball was reduced to 25 mm. The atrophy of the left lateral orbital wall was certainly provoked by pressure atrophy caused by the eyeball.

The medial two thirds of the left orbital floor and the medial wall of the left maxillary sinus were already missing *intra vitam*. Moreover, the almost complete dissolution of the

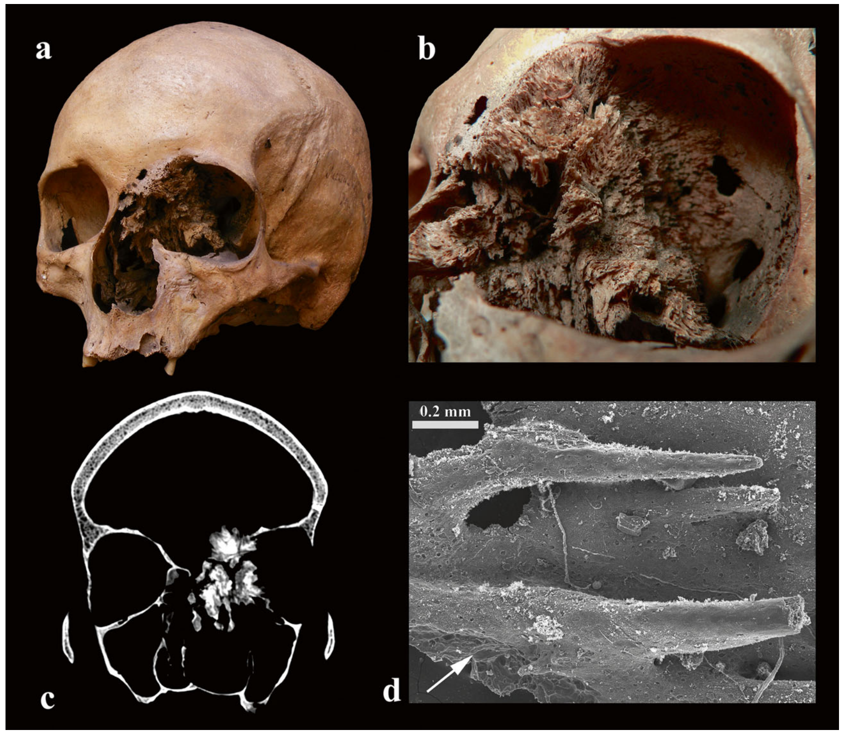

Fig. 1 Macroscopic, radiologic and scanning-electron microscopic views of the osteosarcoma. **a** Left anterolateral view of the cranium with facial osteosarcoma. **b** Close up of the tumor in the orbit. **c** Coronal CT image - Tumorous involvement of the ethmoidal, intraorbital, intracranial regions and the nasal cavity. **d** Scanning-electron microscopic image of the tumorous bone (arrow points to the area covered by Howship's lacunae)

posterior wall of the left maxillary sinus was striking (Supplementary Material Fig. S3). Additionally, the volume of the nasal cavity was considerably reduced. This resulted in a complete displacement of the nasal septum to the inner surface of the external wall of the right nasal cavity (Supplementary Material Fig. S4).

The wall of the frontal sinus was fenestrated and its remaining part was very porotic (Supplementary Material Fig. S5). The left supraorbital margin was partly destroyed. The anterior surface of the left maxilla was incompletely covered with a thin layer of porous bone. These vestiges of a slight periosteal reaction surrounded the pathologically widened piriform aperture (Supplementary Material Fig. S1).

During the course of the endoscopic investigation, a multiple bulging of the internal lamina was seen on the anteromedial part of the frontal bone which was bilaterally situated and was regarded as a vestige of *Hyperostosis frontalis interna*. The endoscopic analysis also showed that the newly formed bone had already penetrated into the endocranium (Supplementary Material Fig. S6).

The CT scans revealed the bony residues of an invasively growing facial tumor which protruded in its final stage into the left orbit, causing extensive bone destruction and spiculated periosteal new bone formation with the well-known "sunburst" appearance which often accompanies aggressive bone tumors. The lesion probably originated from the ethmoidal cells, affected the orbital wall, penetrated into the frontal and maxillary sinuses, besides the involvement of the anterior skull base on the left (Fig. 1c, Supplementary Material Fig. S7).

Based on the results of the scanning-electron microscopic investigation, the most characteristic morphological features of this mass lesion were slim bony spiculae and numerous Howship's lacunae which demonstrate a rapidly proceeding resorption process (Fig.1d).

Interestingly, the light microscopic examination revealed at least two different levels of bony tissue, apparently representing different qualities of woven bone (Fig. 2a). Small regions of lamellar bone which might represent residual autochthonous bone (i.e. remnants of the original bony wall of the nasal cavity or the conchae) were alternating with larger regions of woven bone (Fig. 2b). Strikingly and in contrast to the external macroscopic view, there were very small areas of lamellar bone which were situated close to the part of the bone sample where the bone had been cut for sampling (Fig. 2b).

Thus, the tumor already existed for a relatively longer time (probably several months) than the macroscopic investigation suggested. The peripheral bone formations mainly consisted of woven bone which might have been built relatively shortly before the death of the individual (Fig. 2b). Additionally, there were small areas of woven bone which show a morphological pattern similar to lamellar bone directly on the surfaces of the lamellar bone formations (Fig. 2b). This quality of woven bone had already been described by Franz Weidenreich [26]. In some small areas, this bone showed the morphological characteristics of "mosaic pattern" which can be explained by increased irregular appositional growth (Fig. 2b). Principally, it seems that the newly built immature bone coats the residuals of the autochthonous bone. However, as the taken sample is very

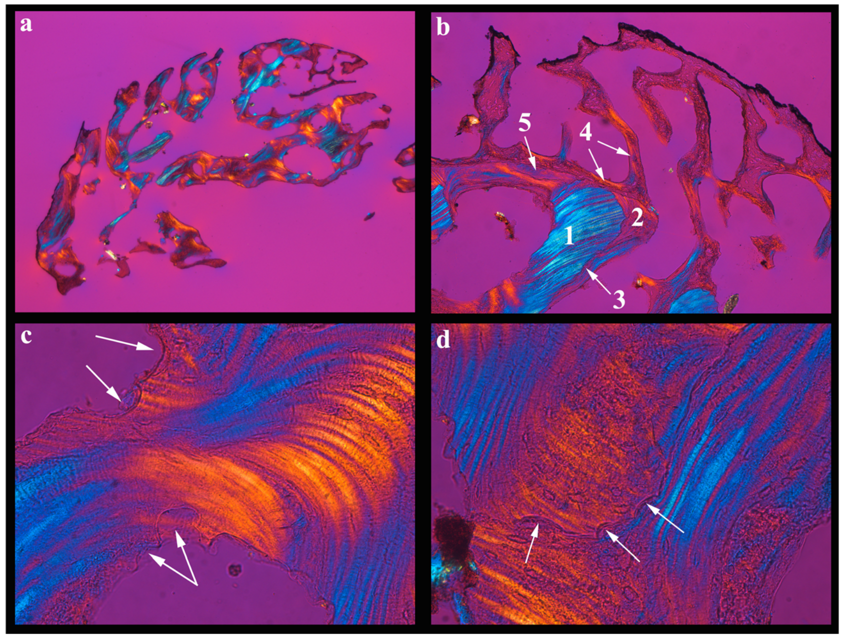

Fig. 2 Tumorous bone sample from the nasal cavity. Thin-ground sections (thickness 60 μm) viewed in polarized light using a hilfsobject red 1st order (quartz) as compensator. **a** Overview of the thin-ground section of the bone sample. Magnification 25x. **b** Different qualities of bone tissues: region of lamellar bone (*1*) regions of woven bone (*2–5*). Magnification 100×. **c** Pronounced osteoclastic resorption expressed by numerous Howship's lacunae (*arrows*). Magnification 400x. **d** Remodeled Howship's lacunae filled with woven bone (*arrows*). Magnification 400x

small, no additional observations can be conducted by light microscopy dealing with osteoblastic activities. Vestiges of pronounced osteoclastic resorption were expressed by numerous Howship's lacunae (Fig. 2c) which demonstrate a rapidly proceeding changeover from proliferation to resorption and back. Furthermore, there were also remodeled Howship's lacunae filled during a proliferative phase with woven bone (Fig. 2d). The rapid increase of bone proliferation might explain the formations of breccia-like lamellar bone (Fig. 2b). Taken together, we found evidence of a highly aggressive lesion in the midface that resulted in extensive bone destruction and demonstrated intralesional new bone formation as well. While other non-neoplastic (e.g. acute osteomyelitis) and neoplastic (e.g. Ewing sarcoma) lesions can cause excessive periosteal reactions, the destructive growth pattern and the most likely neoplastic bone formation inside the lesion clearly argues in favor of a high grade osteosarcoma.

In addition to the findings described the skull vault revealed two further lesions (Fig. 3a). One of them was situated along the sagittal suture (maximal length 35 mm, maximal width 21 mm). This lesion represented the vestige of a surgical intervention which might be interpreted as an incomplete trephination (Fig. 3b). During this operation, three facets were cut out, one after another. Additionally, a second, almost

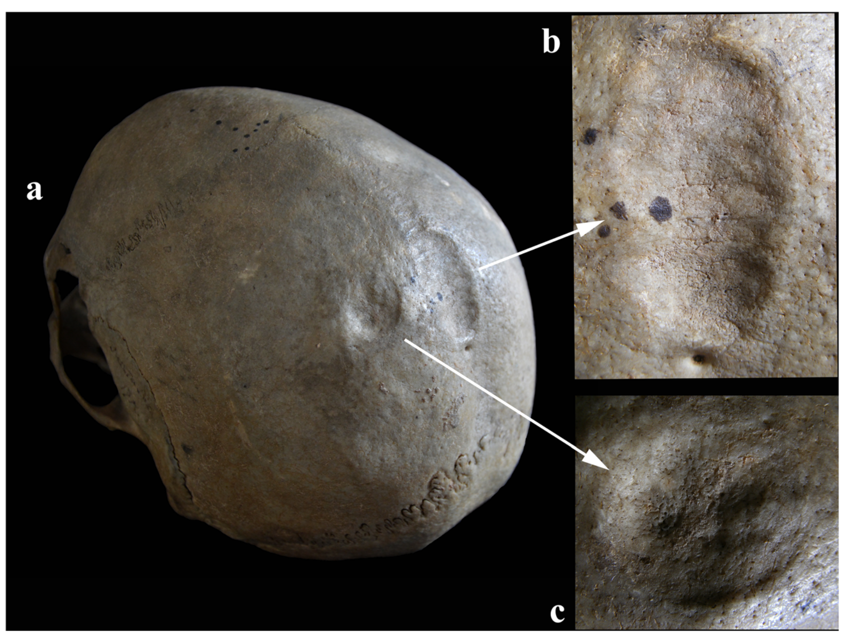

Fig. 3 Well-healed incomplete trephinations on the cranial vault. **a** Overview describing the position of the lesions. **b** Magnified view of the pronounced depression along the sagittal suture. **c** Magnified view of the roundish lesion

round, however slighter, depression was observed measuring approximately 20 mm in diameter (Fig. 3c). This lesion was situated 18 mm left of the sagittal suture on the parietal bone, near to the defect described above. Also this roundish lesion was seen as an incomplete trephination. The margins of these alterations were clearly defined and easily recognizable in the well-preserved external surface of the skull. The surfaces were smooth suggesting that both lesions healed very well without complications before the female died.

There is no way to establish whether there is a causal connection between the incomplete trephination and the tumorous lesion. However, it cannot be excluded that the surgical interventions might be regarded as a medical treatment.

This case is a unique example in which the concomitance of a primary malignant bone tumor (osteosarcoma) and an incomplete trephination are observed in the skeletal remains of a medieval individual. This fact supports the hypothesis that incomplete trephination could probably have served medical purposes.

Acknowledgements This research was supported by grants from the Hungarian National Scientific Research Foundation (OTKA) project number NN 78696, TÁMOP 4.2.4. A/1-11-1-2012-0001 „National Excellence Program – Elaborating and operating an inland student and researcher personal support system" and ELTE Talent Management Council.

We would like to acknowledge our debt of gratitude to Kendra Sirak for language editing of the manuscript.

The authors thank Michael Brandt for the production of the thin-ground samples and Ingrid Hettwer-Steeger for the preparation of the samples for scanning-electron microscopy, both Department of Anatomy, University Medical School Göttingen, Germany.

References

1. David AR, Zimmerman MR (2010) Cancer: an old disease, a new disease or something in between? Nat Rev Cancer 10:728–733
2. Capasso LL (2005) Antiquity of cancer. Int J Cancer 113:2–13
3. Thillaud PL (2006) Paleopathology of cancers. Bull Cancer 93: 767–773
4. Schultz M, Parzinger H, Posdnjakov DV, Chikisheva TA, Schmidt-Schultz TH (2007) Oldest known case of metastasizing prostate carcinoma diagnosed in the skeleton of a 2,700-year-old Scythian king from Arzhan (Siberia, Russia). Int J Cancer 121:2591–2595
5. Ortner DJ (2011) What skeletons tell us. The story of human paleopathology. Virchows Arch 459(3):247–254. doi:10.1007/s00428-011-1122-x
6. Halperin EC (2004) Paleo-oncology: the role of ancient remains in the study of cancer. Perspect Biol Med 47:1–14
7. Rosenberg AE, Cleton-Jansen A-M, de Pinieux G, Deyrup AT, Hauben E, Squire J (2013) Conventional osteosarcoma. In: Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F (eds) WHO classification of Tumours of Tumours of soft tissue and bone. IARC Press, Lyon, pp. 282–288
8. Gadwal SR, Gannon FH, Fanburg-Smith JC, Becoskie EM, Thompson LD (2001) Primary osteosarcoma of the head and neck in pediatric patients: a clinicopathologic study of 22 cases with a review of the literature. Cancer 91:598–605
9. Smith RB, Apostolakis LW, Karnell LH, Koch BB, Robinson RA, Zhen W, Menck HR, Hoffman HT (2003) National Cancer Data Base report on osteosarcoma of the head and neck. Cancer 98: 1670–1680
10. Beutel A, Tänzer A (1963) Röntgendiagnostik der Orbitae, der Augen und der Tränenwege. In: Olsson O, Strnad F, Vieten H, Zuppinger A (eds) Handbuch der Medizinischen Radiologie, Bd VII/2. Röntgendiagnostik des Schädels II, 1st edn. Springer, Berlin-Göttingen-Heidelberg, pp 673–818
11. Ortner DJ (2003) Tumors and tumor-like lesions of bone. In: Ortner DJ (ed) Identification of pathological conditions in human skeletal remains, 2nd edn. Academic Press, New York, pp. 503–544
12. Farkas LG, Józsa L, Paja L, Molnár J (2007) Bone forming tumors on skeletons from a medieval Hungarian cemetery (Bátmonostor). Paleopathol Newsl 140:14–22
13. Józsa LG, Fóthi E (2003) Juxtacortical osteosarcoma on tibia and fibula from a medieval cemetery of Budapest. J Paleopath 15:23–31
14. Bona A, Papai Z, Maasz G, Gabor A, Toth GA, Jambor E, Schmidt J, Cs T, Cs F, Mark L (2014) Mass spectrometric identification of ancient proteins as potential molecular biomarkers for a 2000-year-old osteogenic sarcoma. PLoS One 9(7):e103862. doi:10.1371/journal.pone.0103862
15. Russeva V (2012) Religion, Magic or Medicine? New finds of trepanned skulls from Southeastern Bulgaria, 11th–13th c. Archaeologia Bulgarica XVI:77–95
16. Mariani-Costantini R, Catalano P, di Gennaro F, di Tota G, Angeletti LR (2000) New light on cranial surgery in ancient Rome. Lancet 355:5–7
17. Jordanov J, Br D, Sp N (1988) Symbolic trephination of skulls from the middle ages (IXth-Xth century) in Bulgaria. Acta Neurochir 92: 15–18
18. Zs B, Évinger S, Fóthi E (2006) New symbolic trephination cases from Hungary. Annls hist-nat Mus nat hung 98:177–183
19. Bereczki Z, Molnár E, Marcsik A, Pálfi G (2015) Rare types of trephination from Hungary shed new light on possible cross-cultural connections in the Carpathian Basin. Int J Osteoarchaeol 25(3):322–333
20. Allodiatoris I (1937) Adatok az Árpádkori alföldi magyarság anthropológiájához (data to the anthropology of the lowland Hungarians from the Arpadian-age). University of Pázmány Péter, Dissertation
21. Zádori P, Bajzik G, Biró G, Lelovics Zs, Balassa T, Bernert Zs, Évinger S, Hajdu T, Marcsik A, Molnár E, Ősz B, Pálfi Gy, Wolff K, Repa I (2016) Koponyacsont-laesiók komputertomográfiás vizsgálata és paleoradiológiai aspektusai (Computed tomographic examination of cranial lesions, a paleoradiological approach) Ideggyogy Sz 69: (in press)
22. Schultz M (2001) Paleohistopathology of bone: a new approach to the study of ancient diseases. Yearb Phys Anthropol 44:106–147
23. Schultz M (2003) Light microscopic analysis in skeletal paleopathology. In: Ortner DJ (ed) Identification of pathological conditions in human skeletal remains, 2nd edn. Academic Press, New York, pp. 73–108
24. Schultz M (2011) Light microscopic analysis of macerated pathologically changed bone. In: Crowder C, Stout S (eds) Bone histology. An anthropological perspective. CRC Press, Taylor & Francis Group, Boca Raton, pp. 253–296
25. Molnár M, Janovics R, Major I, Molnár M, Janovics R, Major I, Orsovszki J, Gönczi R, Veres M, Leonard AG, Castle SM, Lange TE, Wacker L, Hajdas I, Jull AJT (2013) Status report of the new AMS $_{14}$C sample preparation lab of the Hertelendi Laboratory of environmental studies, Debrecen, Hungary. In: Jull AJT, Hatté C (eds). Proceedings of the 21st International Radiocarbon Conference. Radiocarbon 55:665–76
26. Weidenreich F (1930) Das Knochengewebe. In: v. Möllendorff W (ed) Handbuch der Mikroskopischen Anatomie des Menschen, Bd. II, Die Gewebe, Zweiter Teil, Stützgewebe, Knochengewebe, Skeletsystem. Verlag von Julius Springer, Berlin, pp. 391–520