

ARTICLE

Malignant tumors in osteoarchaeological samples from Hungary

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ABSTRACT According to our current knowledge, tumors are the same age as mankind itself. The prevalence of tumorous diseases, however, was seemingly relatively low in the past and apparently increased dramatically in modern times. This theory is based on scattered case studies. However, the majority of these investigations were not carried out using modern diagnostic techniques. The scarcity of data concerning the antiquity of cancer demands new investigations in this field. Future paleopathological discoveries and the application of improved diagnostic techniques may enable „paleo-oncology” to make further contributions to our understanding of cancer. In this study, we present data on the occurrence of malignant bone tumors in 12 anthropological series (3967 individuals) from Hungary dated to the 3rd -16th centuries AD. All skeletons were subjected to a careful macroscopic investigation, complemented by radiological examination and in special case scanning electron-microscopic and histological analyses, too. We identified 13 cases of malignant bone tumors. In most instances, multiple osteolytic lesions with slight osteoblastic reactions, in characteristic skeletal distributions, were strongly suggestive of metastatic carcinoma. However, in some cases multiple myeloma cannot be excluded. A mature male with pronounced osteoblastic reactions, particularly on the hip bones, seemed to be most compatible with the diagnosis metastatic prostate cancer. These observations indicate that carcinomas were present in human populations living on the territory of present-day Hungary over the last two millennia.

KEY WORDS

paleopathology
osteoarchaeological samples
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metastatic carcinoma
multiple myeloma

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According paleopathological records, tumors have a great antiquity (Capasso 2005). The earliest known unequivocal neoplastic case was noted on the partial skeleton of a North American lower carboniferous (about 300 million years BP) fossil fish, *Phanerosteon mirabile*. The first clear, well-documented case of malignancy dates to the Jurassic, as does the first certain case of metastasis (Rotschild et al 1999; Capasso 2005).

Concerning ancient human populations both benign and malignant forms of tumors are well in evidence certainly from the Neolithic period (Schultz 1989; Brothwell 2008). The prevalence of cancer in ancient populations might have differed from that in modern humans, because of substantial differences in environmental factors (such as tobacco and alcohol use, diet, etc.), life expectancy, and the availability of treatment (Halperin 2004).

According to the generally accepted view, current high rates of malignant tumors in industrialized Western populations have been ascribed to an increase in life expectancy and increasing influence of environmental factors, particularly

nutritional intake of potentially carcinogenic substances and air pollution (e.g. Aufderheide and Rodriguez-Martin 1988; Ortner 2003; Capasso 2005; Józsa 2006; Nerlich et al. 2006; Thillaud 2006). It can be assumed that these factors have undergone substantial changes during various periods of time, which seem to have affected historical populations to variable extent.

Paleooncology - as a part of paleopathology - is a new term established by Halperin (2004) and refers to the study of malignant tumors in ancient human populations and their hominid ancestors. These populations provide information of crucial importance concerning the possible influences of morphological and functional evolution, diet, lifestyle, and other environmental factors on tumorous diseases. This new discipline may have deep impact on our knowledge of the natural history of cancer. The application of improved diagnostic techniques (such as paleohistology, micro-ct or proteomic analysis: Schultz 1993; Kuhn et al. 2007; Schmidt-Schultz and Schultz 2004; Schultz et al. 2007; Tóth et al. 2008) may enable paleooncology to make remarkable contributions to our understanding of cancer.

Several cases of bone tumors have been reported from historical anthropological materials, but the majority of pa-

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Table 1. Most important data of the affected individuals.

name of the cemetery (N)	dating of the site	affected individual	pathological alterations	supposed diagnosis	reference
1. Madaras-Halmok (635)	3rd-4th centuries AD	Grave No 216 - fragmentary skeleton of a mature (40-50 yrs) male	several lytic lesions of the cranium	metastatic carcinoma	Marcsik et al. 2002
2. Kiszombor B (55)	5-6th centuries AD	Grave No 45 - cranium of a mature male (40-50 yrs)	circular lytic defects of the cranium	metastatic carcinoma	Marcsik et al. 2002
3. Orosháza Béke-TSZ (100)	7-8th centuries AD	Grave No 8 - fragmentary skeleton of an elderly (60+ yrs) male	multiple osteolytic lesions of the calvarium	metastatic carcinoma	unpublished
4. Székkutas-Kápolnadűlő (518)	8th century AD	Grave No 209 - fragmentary skeleton of an elderly (60+) female	osteolytic defects and slight osteoblastic reactions	multiple myeloma or metastatic carcinoma	Pálfi, 1989
5. Székkutas-Kápolnadűlő (518)	8th century AD	Grave No 135 - fragmentary skeleton of a mature male	high number of small osteolytic defects (constant size)	metastatic carcinoma	Pálfi, 1989
6. Pitvaros Víztorozó (226)	7-9th centuries AD	Grave No 208 - fragmentary skeleton of a mature female (50-60 yrs)	circular lytic lesions overall on the skeletal remains	multiple myeloma or metastatic carcinoma	Molnár et al. 2006
7. Tiszafüred-Majoroshalom	7-9th centuries AD	Grave No 1092 - cranium and very fragmentary postcranial skeleton of a mature female (50-60 yrs)	lytic defects with a slight superficial, periosteal involvement	metastatic carcinoma	Marcsik et al. 2002
8. Nyíregyháza-Manda (42)	8-9th centuries AD	Grave No 40 - mature male (good state of preservation)	numerous lytic lesions with ragged margins (variable in size)	metastatic carcinoma	Marcsik et al. 2002
9. Hódmezővásárhely-Nagysziget (131)	10-11th centuries AD	Grave No 42 - mature female, (50-55 yrs) good state of preservation	large porous lesions and slight new bone formations on the calvaria	metastatic carcinoma	Bereczki et al. 2003
10. Homokmégy-Székes (195)	10-11th centuries AD	Grave No 94, mature male (50-60 yrs)	number of osteoblastic alterations - especially in the pelvis, vertebrae and ribs	metastatic carcinoma (prostate cancer)	Zink et al. 2004
11. Tiszalök-Köveshalom (270)	11-12th centuries AD	Grave No 42 - no cranium, fragmentary postcranial skeleton of a mature male (45-55 yrs)	several lytic defects without reactive bony margins, concentrated in the hematopoietic areas of each bone	multiple myeloma	Marcsik et al. 2002
12. Csongrád-Ellés (~300)	11-13th centuries AD	Grave No 126 - adult male (30-40 yrs), good state of preservation	large osteolytic lesion (destructive margin; superficial periosteal involvement)	metastatic carcinoma	unpublished
13. Baja-Pető (209)	11-16th centuries AD	Grave No 187-190 - well preserved cranium of a mature male	circular lytic defects of the cranium	metastatic carcinoma	unpublished

leoneological studies only deals with case histories without paleoepidemiological reconstruction of these conditions (e.g. Regöly-Mérei 1962; Pap 1985; Pálfi 1989, Strouhal 1991; Józsa and Pap 1994; Strouhal et al. 1996; Horáčeková et al. 1997; Šefčáková 2001; Józsa and Fóthi 2002; Marcsik et al. 2002; Bereczki et al. 2003; Zink et al. 2004; Molnár et al. 2006). The analysis of tumor frequencies in populations from different historical periods may reveal the role of environmental factors on carcinogenesis. To this regard, only few previous reports describe human remains with traces of malignant tumors in historical populations of different time and location (e.g. Schultz 1992; Ricci et al. 1995; Zink et al. 1999; Strouhal 2000; Nerlich et al. 2006; Farkas et al. 2007; Roumelis 2007).

The identification of specific tumor types in bone often depends on careful histological examination of soft tissue components and/or clinical test available to modern pathologists. This information will not usually be available to those engaged in differential diagnosis of tumors in archeological human remains and specific diagnosis of tumor type will not always be plausible. This is particularly the case with metastatic carcinomas affecting bone, which often have very similar skeletal manifestations regardless of the primary site of the tumor (Dorfman and Czerniak 1998; Greenspan and Remagen 1998). However, careful analysis of the variables available to paleopathologists, including the type and distribution of the lesions and other factors such as the age and sex of the skeleton, provide helpful clues. Paleohistology,



Figure 1. Lytic lesions of the cranium (Madaras Halmok cemetery; male, 40-50 yrs).



Figure 3. Radiograph - additional lytic loci localized in the diploë (Kiszombor B, male, 40-50 yrs).



Figure 2. Lytic defects of an intentionally deformed skull (Kiszombor B, male, 40-50 yrs)

paleoradiology, proteomic analysis and other new methods can contribute to a more precise diagnosis of the observed tumorous or tumor-like conditions in ancient osteological samples.

Materials and Methods

For the study, the skeletal remains of 12 anthropological series (3967 individuals) from Hungary dated to the 3rd -16th

centuries AD were investigated from paleopathological point of view.

All skeletons were subjected to a careful macroscopic investigation, which was complemented by radiological examination and in special case scanning electron-microscopic and histological analyses, too.

Results and Discussion

Skeletal signs of malignant carcinoma or bone metastases were identified in 13 cases in the investigated material. The most important data regarding the affected skeletons are summarised in Table 1.

Our first case is a mature male from the so-called Sarmatian Period of Hungary (Madaras Halmok cemetery). The cranium is affected by several lytic lesions (Fig. 1). The radiograph shows additional lytic loci localized in the diploë. The endocranial table of the frontal bone reveals a large destruction surrounded with reactive bone. The detected pathological alterations seem to fit the diagnosis of metastatic cancer.

The second case is a mature male from the Gepid Phase of Hungary (Kiszombor B cemetery). The intentionally deformed skull reveal lytic lesions on the frontal bone and on the left parietal bone (Fig. 2). The cranium was previously restored using a glue which disturbed the radiographic analysis. In spite of that some additional lytic defects are seen on the radiograph (Fig. 3). The mandible reveals postmortem enlarged circular lytic lesion. The detected alterations could be diagnosed as a possible case of metastatic carcinoma.

The following 7 cases came from the so called Avar Period of Hungary.

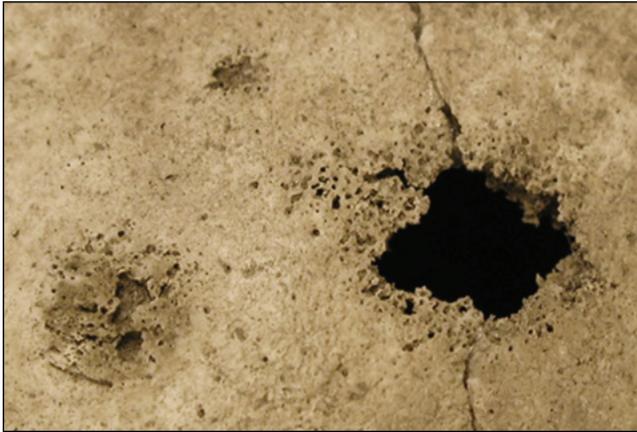


Figure 4. Porosity of the bone adjacent to the margin of the lytic lesion (Orosháza Béke TSZ, female, 60+).



Figure 6. Numerous small osteolytic lesions on the skull (Székkutas-Kápolnadűlő, male, mature).



Figure 5. Osteolytic defects on the hip bone (Székkutas-Kápolnadűlő, female, 60+).

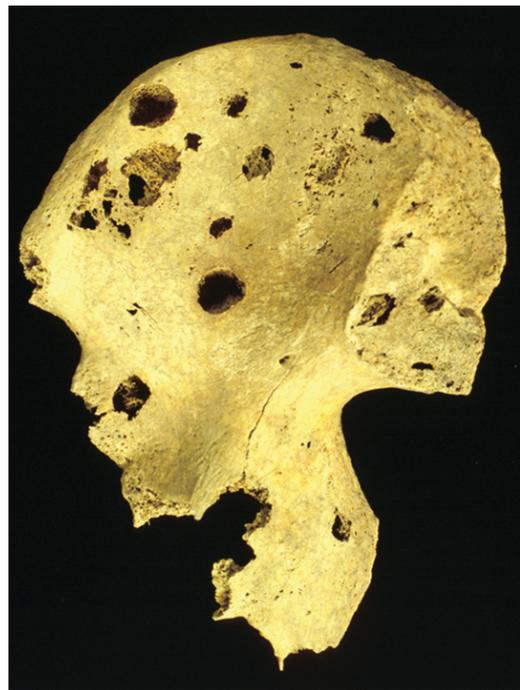


Figure 7. Circular osteolytic lesions of the right hip bone (Pitvaros-Víztározó, female, 50-60 yrs).

The cranium of an elderly male from the Orosháza Béke TSZ cemetery is affected by multiple osteolytic lesions. The defects vary greatly in size and some of them have not perforated the entire bone. The close up picture of the lesions shows the porosity of the bone adjacent to the margin (Fig. 4). On the radiograph more lytic loci localized in the diploe could be observed. The detected lesions are probable results of a metastatic carcinoma.

The fragmentary skeletal elements of an elderly female from the Székkutas cemetery reveal osteolytic defects on the frontal bone, on the ribs, on the vertebrae and on the hip bones (Fig. 5). The detected alterations suggest the diagnosis of metastatic cancer but the possibility of multiple myeloma cannot be completely excluded.

The fragmentary skeleton of a mature male comes from the same cemetery as the previous case. On the skull a number of small osteolytic lesions are seen which have not perforated the entire bone (Fig. 6). The high number, the small diameter and the constant measure of the lesions seems to fit the di-

agnosis of multiple myeloma but the diagnosis of metastatic carcinoma cannot be completely excluded.

The skeleton of a mature female (Pitvaros-Víztározó cemetery) is affected by widespread osteolytic lesions on the cranium and on the postcranial elements (Fig. 7). The majority of these lesions are circular (from 2 to 36 mm of diameter) and the edges are relatively irregular. Paleoradiological study



Figure 8. Radiograph - additional lytic defects localized in the trabecular bone (Pitvaros Víztorzó, female, 50-60 yrs)



Figure 9. Lytic alterations on the skull (Tiszafüred-Majoroshalom, female, 50-60 yrs)

using plain films and CT investigations, shows the osteolytical aspect of the lesions evidenced by gross examination and the lack of associated osteosclerosis (Fig. 8). The diagnosis is based on the morphological and radiological aspects of the lesions and on the gender and the elderly age of this individual, considering a metastatic process rather than a multiple myeloma.

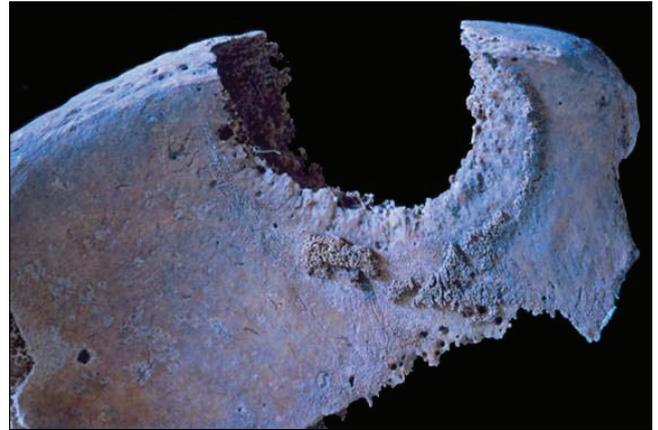


Figure 10. Large osteolytic defect surrounded by superficial periosteal involvement – hip bone (Nyíregyháza-Manda, mature, male).



Figure 11. Massive osteoblastic alterations on the hip bone (Homokméggy-Székes, 50-60, male)

Our next case is a mature female (Tiszafüred-Majoroshalom cemetery) whose skull reveals circular lytic lesions. Some of the defects affect only the external table of the cranium (Fig. 9). On the inner table of the skull lytic defects with a slight superficial periosteal involvement were observed. The radiograph reveal additional lytic defects in the diploe. The character of the lesions suggests the diagnosis of a metastatic carcinoma.

Our last case from the Avar Period is a mature male from the Nyíregyháza-Manda cemetery. The skeleton is in a very

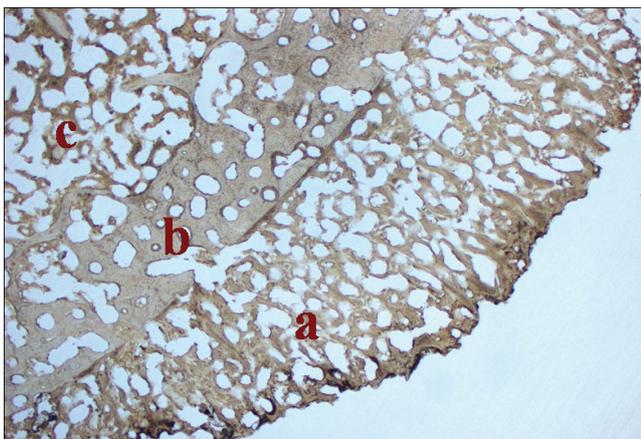


Figure 12. Cross section through a rib. Newly built bone formation (a), remains of original cortical bone (b), filled bone marrow (c), magnification X16 (Homokmégy-Székes, 50-60 yrs, male).

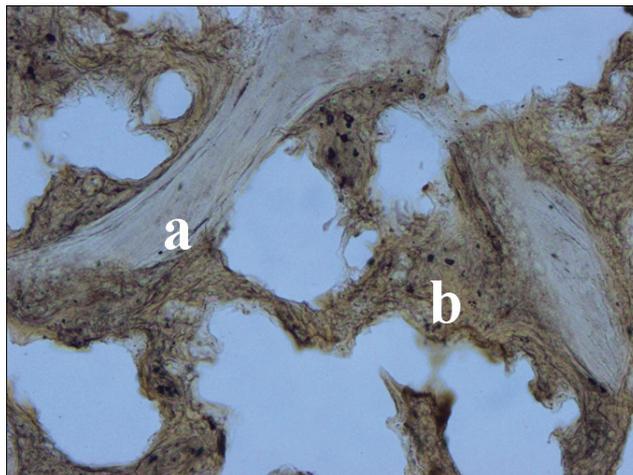


Figure 14. Cross section through a rib. Original spongy bone (a), newly built bone formation (b) magnification X100 (Homokmégy-Székes, 50-60 yrs, male).

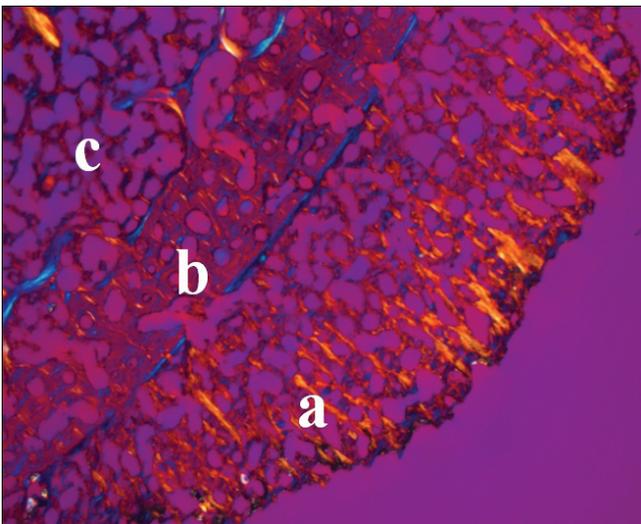


Figure 13. Cross section through a rib. Newly built bone formation (a), remains of original cortical bone (b), filled bone marrow (c), magnification X16, polarized light (Homokmégy-Székes, 50-60 yrs, male).

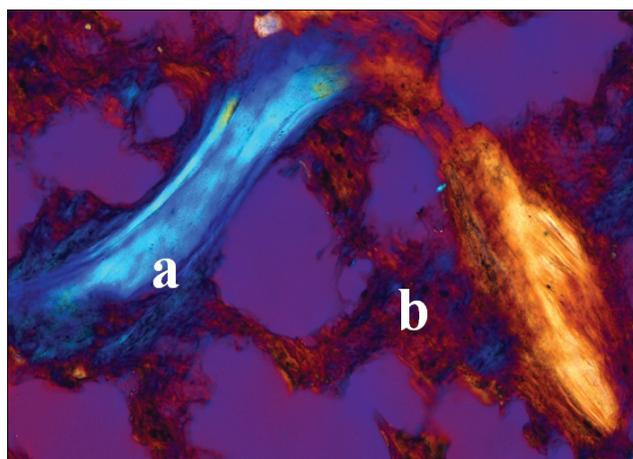


Figure 15. Cross section through a rib. Original spongy bone (a), newly built bone formation (b) magnification X100, polarized light (Homokmégy-Székes, 50-60 yrs, male).

good state of preservation. Numerous circular lytic lesions with ragged margin could be seen on the skull. The mandible shows severe erosive lesion surrounding with periosteal new bone formation. Concerning the detected pathological alterations of the postcranial bones, large osteolytic defects on both innominate bones (Fig. 10) and on the distal quarter of each femur should be noted. These lesions are suggestive of metastatic carcinoma.

The mature female from the 10-11th centuries cemetery of Hódmezővásárhely-Nagysziget reveals pathological alterations on the skull and on the postcranial bones. In spite of some post mortem damage large porous lesion of the calvaria

is seen. Another porous lesion surrounding with slight new bone formation could be detected on the temporal surface of the greater wing of the left sphenoidal bone. The radiograph of the frontal bone shows additional lytic lesions in the diploe. The postcranial bones are also affected by slight osteoblastic defects. The number, the character and the distribution of the observed lesions suggest the diagnosis of metastatic carcinoma.

The mature male from the Homokmégy-Székes cemetery reveals severe pathological alterations. A number of osteoblastic alterations are found in many bones of the postcranial skeleton, especially in the pelvis (Fig. 11), ribs and vertebrae. Osteolytic lesions are only present on the base of the skull.



Figure 16. Osteolytic defects of a lumbar vertebra (Tiszalök-Köveshalom, male, 45-55 yrs)



Figure 17. Close up view of a large osteolytic lesion on the skull – destructive margin; superficial periosteal involvement (Csongrád-Ellés, male, 30-40 yrs).

The skeletal lesions were studied using metrical, radiographic and gross morphological observation. Additionally, a detailed histological, immunohistological and CT analysis was performed. These investigations clearly reveal, that the alterations are mainly osteoblastic with the most massive involvement located in the pelvis. Histology shows that the alterations are due to metastasis of a carcinoma (Fig. 12-15). The distribution and the extent of the lesions are most indicative of prostate cancer.

The mature male skeleton from the 11-12th centuries cemetery of Tiszalök-Köveshalom reveal numerous small, purely osteolytic defects on their postcranial bones (Fig. 16). The cranium is missing postmortem. The absence of



Figure 18. Lytic defect of the right parietal bone (Baja-Pető, male, mature).

sclerotic margin of the defects is seen on the radiograph. The character, the size, the number and the distribution of these lesions seems to fit the diagnosis of multiple myeloma.

The skeletal remains of the adult male from the 11-13th centuries cemetery of Csongrád-Ellés are in a very good state of preservation. The skull reveals severe pathological alterations. Large osteolytic lesion with destructive margin in the left side of the coronal suture is worth mentioning (Fig. 17). Besides this alteration some porous lesions could be seen on the internal and external lamina of the skull. The radiograph shows additional lytic lesions in the diploe. Concerning the postcranial bones, the osteoblastic alterations of the 5th cervical vertebra is worth mentioning. The detected alterations suggest the diagnosis of metastatic cancer.

The last case is a mature male from the 11-16th centuries cemetery of Baja-Pető. The postcranial skeleton was missing postmortem. On the frontal bone circular lytic lesion (~16mm) without superficial periosteal involvement could be observed. Besides the frontal bone the right parietal bone is also affected by a circular lytic defect (Fig. 18). The intra vitam origin of the observed erosion of the mandibular ramus is questionable. The character of the lesions seems to fit the diagnosis of metastatic carcinoma.

Summary

We conducted the paleopathological analysis of the skeletal remains of 3967 individuals deriving from 12 archaeological sites of Hungary with special regards to malignant tumors. During the investigation skeletal evidence of malignant carcinoma or bone metastases were identified in 13 cases. No sign of primary bone tumors was found. Regarding the type

of the observed alterations the predominance of osteolytic lesions has to be mentioned. Concerning sex distribution of the affected individuals it has to be emphasized that males were more often affected (at a ratio of 9 to 4). Apart from one individual the observed cases belonged to older age categories. This observation fits to the generally accepted view that cancer is primarily a disease of old age.

Finally, we can conclude that carcinomas were present in the territory of present-day Hungary over the last two millennia.

Further investigations – applying modern diagnostic methods – in order to define the primary site of the tumors are planned to extend this study.

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