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The probable evidence of leprosy in a male individual unearthed in medieval Armenia (Angeghakot)*

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Abstract

The objective of this study is to present the paleopathological lesions relevant to the discussion of the differential diagnosis of leprosy. Macroscopic, histological and X-ray observation of the bones and scrutiny of lesions according to the paleopathological literature allowed the identification of a probable case of leprosy in an adult male from Angeghakot (Early Middle Age, skeleton 4). The skeleton of a male (50–55 years) revealed several bony changes indicative of leprosy with clear rhino-maxillary syndrome. There is a scarcity of information in the osteoarchaeological literature of leprosy in ancient Armenia. The significance of this case is that it adds to an understanding of the history of the disease in Armenia and to the data set necessary to understand the epidemiological dynamics in the South Caucasus during the Early Middle Ages.

Keywords: Armenia; Angeghakot; Early Middle Age; leprosy; paleopathology

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Introduction

Leprosy (Hansen's Disease), is a chronic infectious disease caused by Mycobacterium leprae which attacks the skin, mucous membranes and peripheral nerves, resulting in destructive skeletal manifestations (1). The Mycobacterium was discovered by Dr. G.H. Armauer Hansen in 1873, and was the first pathogenic micro-organism to be associated with a specific disease (2). Leprosy occurs in a variety of forms, causing diverse responses depending on an individual's immunity, with lepromatous leprosy being the most severe and tuberculoid leprosy being the least (3). Although leprosy largely affects humans, the disease is zoonotic, having been noted to occur in Armadillos (4) and several primate species (5). Despite being one of the most widely studied communicable diseases, the exact mode of transmission of leprosy is unknown due to the difficulties of studying the disease in vitro, although droplet inhalation (6) or close repeated contact with infected skin (7) are widely considered as primary causes of transmission. A distinctive trait of leprosy is the diseases long and varied incubation period, lasting up to 6 years in humans (8), although incubation periods of up to 30 years have been observed in wild chimpanzees (9).

Bone resorption associated with leprosy is the direct result of nerve damage and circulatory obstruction, causing progressive sensory and motor loss, which can then give way to ulceration and secondary infection of the overlying dermal and muscular tissues (8, 3). In the cranial skeleton, rhinomaxillary syndrome is the combination of several destructive proliferative lesions, which include loss of the anterior nasal spine, endonasal inflammation and recession of the alveolar process, resulting in the loss of the anterior dentition (10, 8). In the post-cranial skeleton, the bones of the hands and feet are most commonly affected (11). The highly vascular bone of the epiphyses results in bilateral diaphyseal remodelling, resorption of the distal phalanges and pitting on the tarsals and metatarsals of the feet and the carpals and metacarpals of the hands (12). Some skeletons showed more facial lesions whereas others showed more postcranial lesions and these differences appear to have had an influence on the treatment of the victims of leprosy (13, 14).

Through an examination of the geographic distribution of leprosy, it appears that climate does not play a major role in the epidemiology of the disease. In general terms, the countries with the highest incidence of leprosy are situated in the tropics, in areas characterized by a high annual rainfall (15). It is less commonly present as an endemic disease in temperate regions such as the Mediterranean littoral, as well as amongst the Australian Aborigines and native-born Americans in Louisiana and Texas (16, 17).

The rise of leprosy is documented through skeletal, documentary and material evidence. Leprosy is an old disease (18). Manchester and Roberts (6) highlighted the traditional view that leprosy originated in Asia, citing Indian and Chinese medical texts dated to the late second half of the first millennium BC as offering dependable descriptions of advanced leprosy. Hulse (19) suggested Egyptian texts, dated to 1550 BC, allude to leprosy and references to leprosy are widely associated with the book of Leviticus from the Old Testament, 1500-1400 BC. However, the condition mentioned in the Bible as leprosy was probably not related to the disease as we know it from the present and from the Middle Ages (20).

Robbins et al. (21) demonstrated that lepromatous leprosy was present in India as early as 2000 BC, pushing the date back for the earliest occurrence of the disease. Analysis of a Middle-Aged male individual at Balathal, India, exhibiting osteological lesions comparable to rhinomaxillary syndrome supports the textual evidence for an eastern origin for the pathogen. Possible skeletal lesions associated with leprosy observed in four individuals at Dakhleh Oasis, Egypt, dating to the second century BC (22), suggest that leprosy may have least spread east to west during the second and first millenniums BC. Lepromatous leprosy also was present in Armenia. The earliest case of Mycobacterium leprae (M. leprae) is found in the Middle Bronze age. Resorption of the alveolar bone in the anterior maxilla was in individual with lepromatous leprosy in Aragatsavan (23). The Lchashen series (Late Bronze and Early Iron Ages) of Sevan pool represents a remarkable material for the study of past mycobacterial infections and very rich in leprous cases (four men and two women) (24). The morphological aspects of the rhinomaxillary changes are characteristic of a facies leprosa. and one individual from Karmir (Early Iron Age) has nasopharyngeal lesions, including significant remodeling of the nasal aperture margins (25). Paleopathological analysis indicates that lepromatous leprosy was present and in Ancient Age (Vardbakh, 1st century BC - 3rd century) (26). At woman (20-25 years) from Dvin (Early Middle Age) had bony signs that were possibly

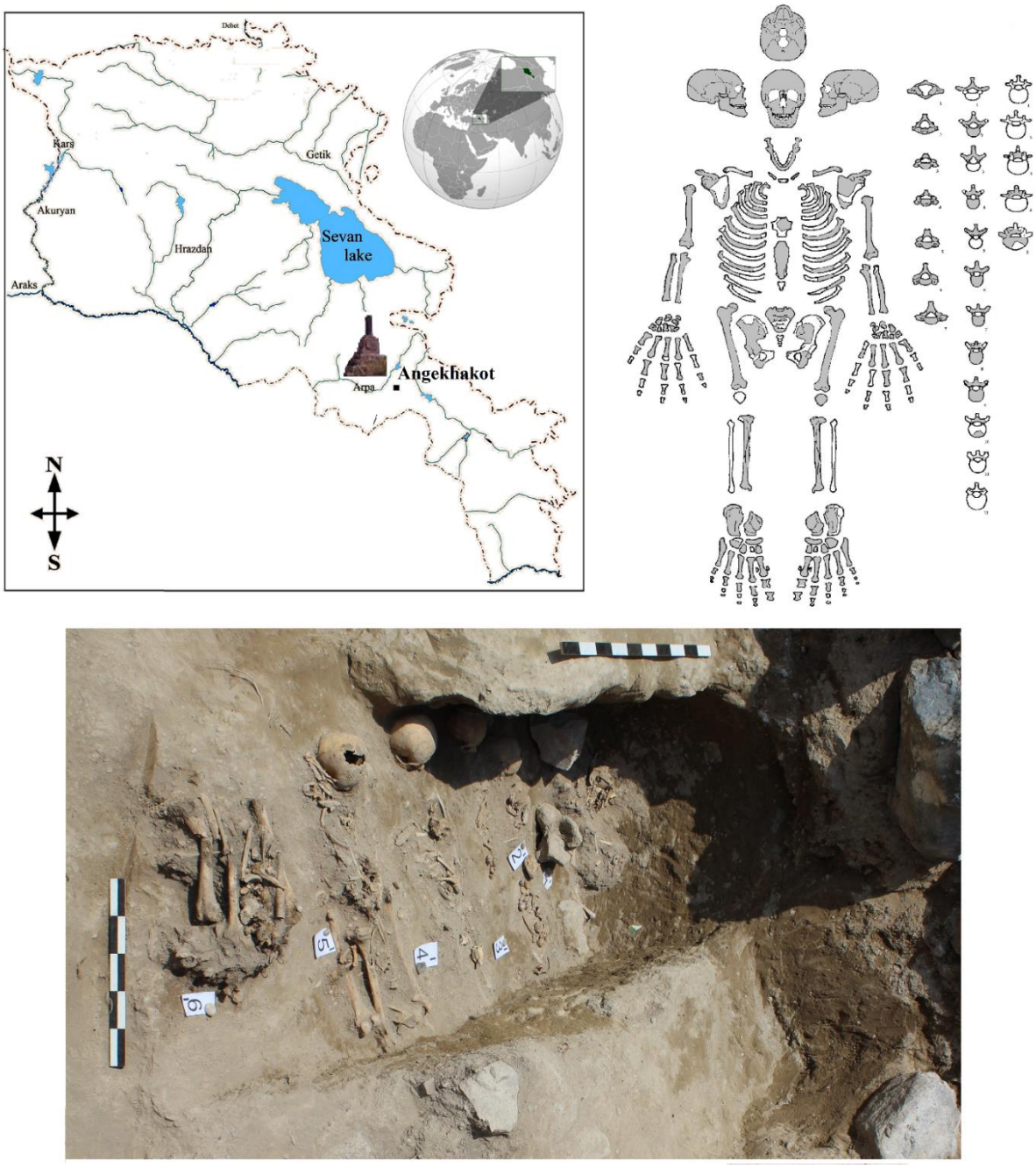

Figure 1. Armenia, Angeghakot burial, excavations 2018, preservation of skeleton No. 4.

related to facies leprosa (the skull unearthed by archaeologist Nyura Akopyan in 1978) (27). Destructive lesions were observed of the nasal cavity, and atrophy of the margin of the nasal bone (certain degree of pitting). The nasal condition in particular points to this disease rather than any other known to have occurred in medieval Armenia. Excavation and analysis of the human remains from Dvin revealed some evidence of decapitation (27).

The westward spread of leprosy was confirmed by molecular analysis of European and Middle Eastern strains of the disease (28). It is traditionally considered that that leprosy was brought westward by the armies of Alexander the Great on return from their Indian Campaign (356-323 BC) (3), however, Mark (29) argued that the westward spread of leprosy was related to seafarers involved in the Indo-Egyptian slave trade routes. Although, the discovery of a

possible leprous individual in Bologna, Italy (30), from the fourth to third century BC, Abony-Turjányos dűlő site, located in Central Hungary (31) and medieval Denmark (32) and in four individual medieval inhumations from the St. Mary Magdalen, Winchester leprosarium (33) has shed doubt on the Alexandrian theory.

Figure 2. Individual No 4. X-ray: inferior view, left lateral view. Right lateral view, frontal view, superior view.

From Greece, the disease's thought to have spread around the Mediterranean basin, with the Romans introducing leprosy into the Western part of Europe. Little is known about its presence in sub-Saharan Africa. From India, leprosy is thought to have spread to China and then to Japan, reaching Pacific Islands like New Caledonia (19th century). Monot et al. (34) leads two alternative conclusions for the global spread of leprosy that differ from classic explanations. In the first, SNP type 2, from East Africa/Central Asia, preceded type 1, which migrated eastward, and type 3, which disseminated westward in human populations, before giving rise to type 4. In the second scenario, type 1 was the progenitor of type 2, with SNP types 3 and 4 following in that order. The researcher believes that leprosy was most likely introduced into West Africa by infected explorers, traders, or colonialists of European or North African de-scent, rather than by migrants from East Africa, because SNP type 4 is much closer to type 3 than to type 1 (34). From West Africa, leprosy was then introduced by the slave trade in the 18thcentury to the Caribbean islands, Brazil, and probably other parts of South America, because isolates of M. leprae with the same SNP type, 4, are found there as in West Africa. The strain of M. leprae responsible for disease in most of the Americas is closest to the European/North African variety (34), which indicates that colonialism and emigration from the old world most probably contributed to the introduction of leprosy into the new world.

Historically, leprosy was well recognized both by the medical profession and by the general public earlier than virtually any other specific disease. It was particularly the establishment of leprosaria that prompted and documented this development. During the period of early Christianity, leprosaria already existed in Armenia. Princess Agvida Salahuni (wife of Naharar Suren Salahuni) opened the first of the world leprosaria in Armenia (35).

Throughout the Middle Ages, to be diagnosed with the disease had major social and medical implications for the individual. Some communities, knowing the importance of accurate diagnosis, established multidisciplinary groups to review suspected cases. Representatives from the church, physicians, and people with the disease were typically

members of these groups. Medieval diagnosis of leprosy, Brody (36, p. 59) wrote, "… was a prediction of disfigurement and death, and what is perhaps more terrifying, it separated a man from society because of the infection he carried outwardly and the moral corruption that lay within him."

The aim of the current paper is to report the pathological lesions with relevance to the differential diagnosis of leprosy in individual No 4 from the Angeghakot. The significance of this case is that it adds to an understanding of the history of the disease in Armenia and to the data set necessary to understand the epidemiological dynamics in the South Caucasus during the Early Middle Ages.

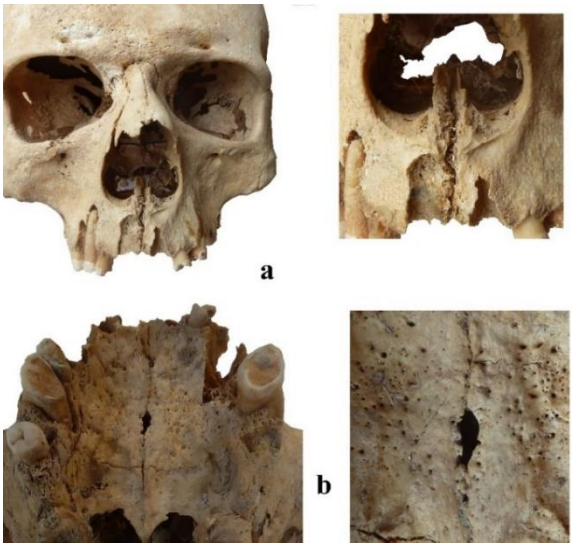

Figure 3. Atrophy of the anterior nasal spine (a), destructive and proliferative bony lesions on the oral and nasal surfaces, osteoporosis and hole around the palatine suture(b), on the surface hard palate also an intense pitting process is present (b).

Material and methods

In August of 2018 a collective burial was discovered at an altitude of 1 800 m in the district of Angeghakot in the valley of the Vorotan (South-Eastern Armenia). Angeghakot is a village and rural community (municipality) in the Syunik Province of Armenia. Excavation at the Angekhakot site was conducted archaeologist by Tigran Aleksanyan. The burial was probably dated from the Early Meddle Age and the contained secondary burials. Despite all efforts it was not possible to match these bones with the primary inhumations. However, this possibility cannot be completely discarded due to post-mortem fragmentation. Using the excavation photographs (Figure 1), it was possible to determine that the primary burials were consistently layed on the decubitus dorsalis. During the excavation, 9 skeletons were discovered. Of the 9 individuals, 4 are male, 4 are child, and 1 are an indeterminate sex. Age estimations ranged from 1.5 to 48-55 years old. A skeleton No 4 discovered in burial was unique as it bore traces of rare pathologies.

The age-at-death and sex of adults were assessed through the use of multiple indicators: morphological features of the pelvis and cranium were used for the determination of sex (37, 38); a combination of pubic symphysis (39, 40, 41), auricular surface changes (42), degree of epiphyseal union (38), and cranial suture closure (41) were used for adult age estimation.

The paleopathological analysis followed the generic recommendations detailed in standard textbooks (38, 8, 12). An important element in the diagnosis of leprosy in past individuals is a recognition of the specific pattern of osseous change that occurs in this condition.

The degree to which the bone is affected results from a number of related factors such as the age of the individual, the degree of nerve involvement, and the level of trauma and secondary infection that occurs in the extremity (43). According to Steinbock (2), the bone changes resulting from lepromatous leprosy have been divided into three main types: a. specific destructive changes: resulting from the direct action of the leprosy bacilli, characterized by localized destruction. facies leprosa, enlargement of the nutrient foramen, and localized cortical destruction of the bones of the hands and feet due to lepromatous granulomas; b: non-specific absorptive changes: involving the bones of the hands and feet almost exclusively, and often leading to fracture, subluxation of the joints, arthritic changes and ankylosis. Secondary pyogenic infection and periostitis may be associated with these changes; c. osteoporosis: a degenerative process characterized by enlarged areas of bone with decreased density and increased porosity. Osteoporosis occurs as a result of disuse and is present only in severe cases. In cases of advanced leprosy in the skeletal record, it is likely that one will find a combination of all three categories of osseous change.

The osseous change which occurs in the cranium is restricted to the rhino-maxillary region of the face, and has been divided into three distinct categories: atrophy of the anterior nasal spine

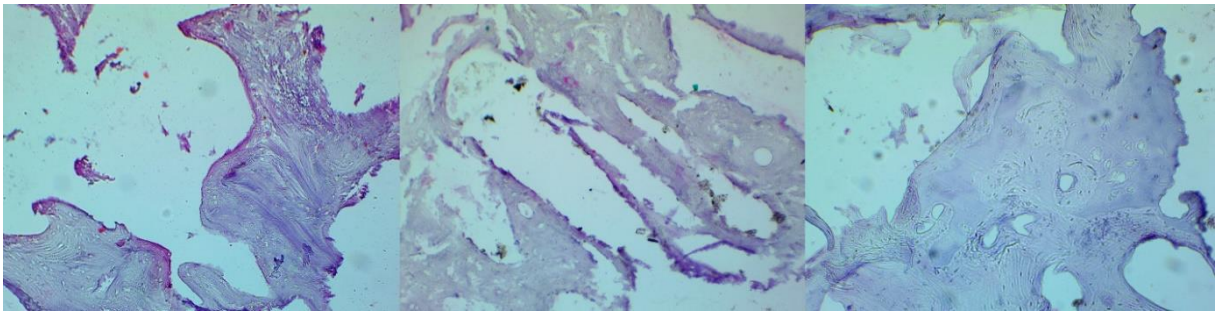

Figure 4. Histopathology of the lepromatous lesion (the samples taken from affected areas).

associated with atrophy of the pyriform aperture, atrophy and recession of the alveolar process of the maxilla, and endonasal inflammatory changes involving the hard palate, vomer and turbinate bones (44, 45, 46, 47).

According to E. Schrnitz-Cliever (cited in 44), facies leprosa should be divided into three distinct types: a. facies leprosa nasalis: which involves atrophy of the anterior nasal spine in combination with inflammatory changes of the nasal surface of the palatine process, vomer, and/or of the conchae, turbinate bones; b. facies leprosa maxillaris: involving atrophy of the alveolar process of the maxilla accompanied by inflammatory changes of the oral surface of the palatine process; c. facies leprosa nasaiis et maxillaris: involving atrophy of the anterior nasal spine and the alveolar process of the maxilla, combined with inflammatory changes of the oral and nasal surfaces of the hard palate, or of the vomer and/or turbinate bones. The manifestation of the disease in the infracranial skeleton primarily involves the bones of the hands and feet. The most common osseous changes in these regions involve non-specific absorptive changes. The bones of the hands and feet undergo various degrees of bone destruction, which range from distortion of the digits with subsequent deformation, to eventual reduction in size, with little to no reactive bone formation. In most cases the distal phalanges become thinned due to 'concentric bone atrophy', and the bones take on a 'pencilling' or 'sucked candy stick' appearance (16). This process in turn compromises the joint, leading to collapse and a cupping deformity in the joint area (48). In the initial stages, the claw-hand deformity is associated with soft tissue, involving the skin, subcutaneous tissue and joint capsule. The bone change involves "extension, even hyperextension, at the rnetacarpo-phalargeal joints, and hyperflexion at the interphalangeal joints. Because of sustained hyperflexion there may be volar subluxation at the interphalangeal joints" (11, p. 77). The metacarpophalangeal and interphalangeal joints undergo a series of osseous change characterized by; juxta-articular dorsal inflammatory change, septic arthritis due to pyogenic sepsis, subluxation and dislocation, ankylosis resulting from pyogenic septic arthritis, and cupping, with or without associated peg deformity (49). In the feet the change begins in the proximal phalanges and distal metatarsals, at the metatarsophalangeal joint, and often spares the distal phalanges.

The tibia and fibula change are destructive and proliferative, and is characterized by irregular subperiosteal deposits. Although these deposits may occur on any portion of the tibial or fibular shaft, they are usually concentrated in the distal third (2). The inflammatory change is typically bilateral, and most marked on the adjacent surfaces of the tibia and fibula (49). In addition to the bone changes which directly result from the invasion of leprosy bacilli, there are bone changes that have been identified in affected individuals, which may, or may not, be related to the disease itself. In most cases, these are secondary changes resulting from the destruction of specific bones or the invasion of the peripheral nerves by the bacilli. These changes include enlargement of the nutrient foramina, erosive joint lesions observed as osteochondritis dissecans-type lesions, and bone cysts.

The bones had been cleaned and restored in our laboratory of physical anthropology of Institute of Archaeology and Ethnography, National Academy of Science (Yerevan). The X-ray and histological analysis were performed at the Armenia Republican Medical Center (Yerevan). Suspected leprosy cases can be confrmed by the detection of M. leprae ancient DNA (aDNA). Further study will provide a report looked at M. leprae using aDNA methods (ancient DNA laboratory at the Department of Anthropology, University of Vienna).

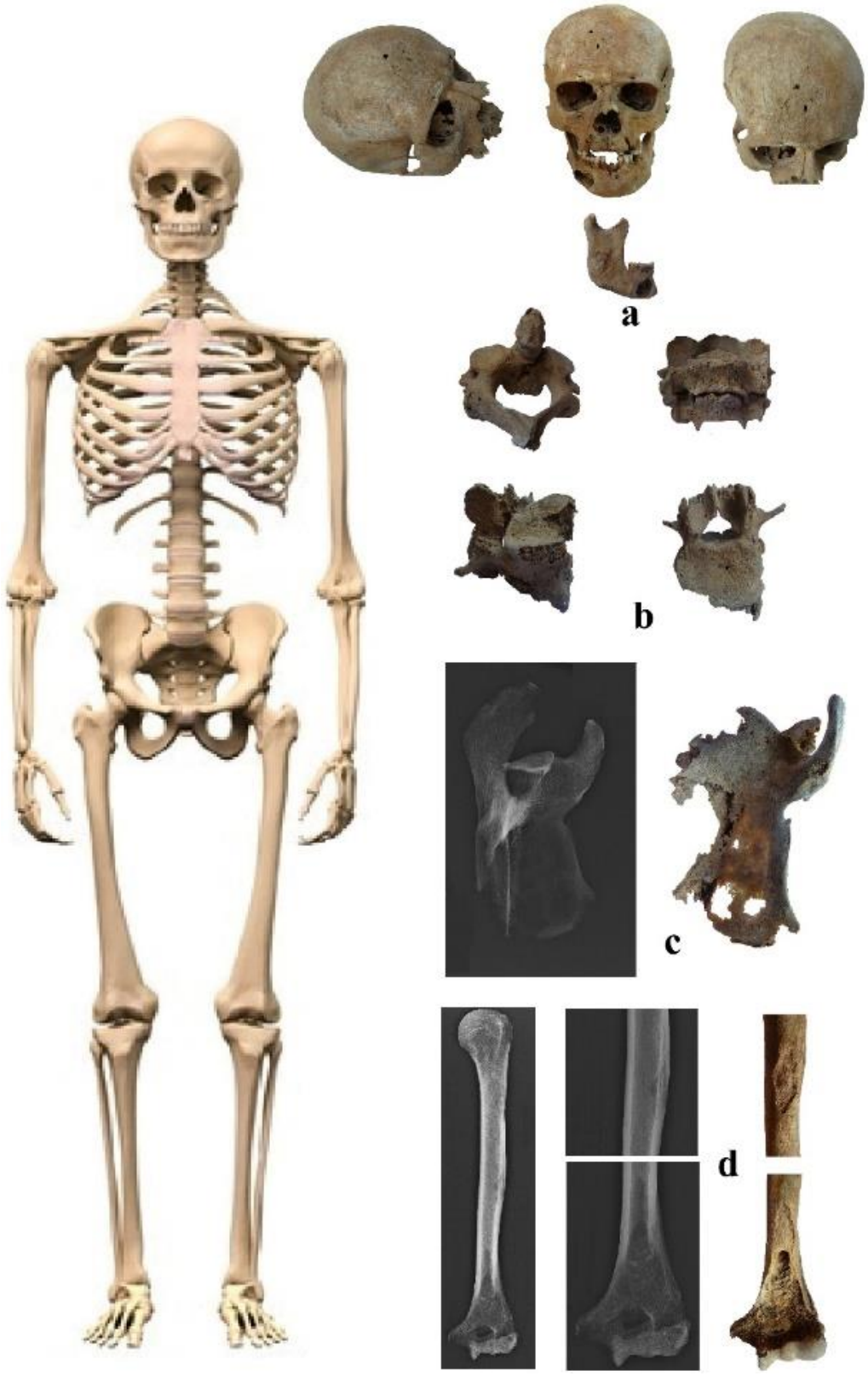

Figure 5. Elements demonstrating pathological conditions in the skeleton: lytic and blastic lesions, vertebrae demonstrate degenerative changes including osteophytosis and spondylolysis.

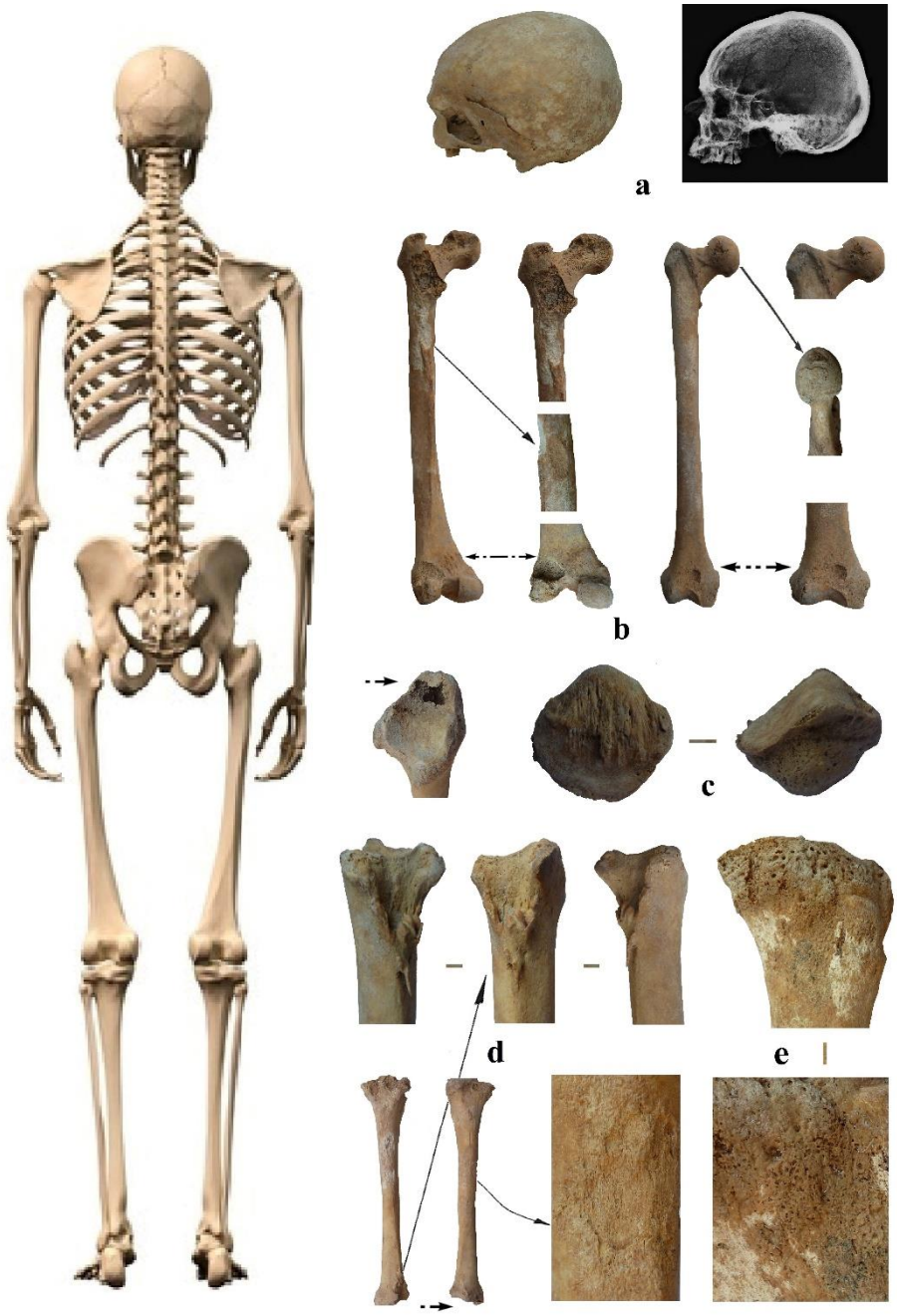

Figure 6. Cradle deformation (a), lytic and blastic lesions (b), kneecap (c), injury (d), periostitis (e).

Results

The skeleton in N 4 was and incomplete. The bone inventory of the analyzed skeleton can be seen in Figure 1. Analysis suggests that the skeleton was a man's (Figure 2), based on morphological characteristics of the skull and pelvis, approximately 50 to 55 years old based on dental wear, stage of fusion of the cranial sutures, and auricular surface morphology scoring system. His height was 170 cm.

The examination of the skeleton No 4 revealed bone alterations of both cranial and infra-cranial bones. Rhinomaxillary changes are conspicuous and can be summarized as follows: 1) atrophy of the anterior nasal spine (Figure 3a); 2) tentative evidence for destructive remodelling of the alveolar process of the anterior maxilla; 3) the alveoli of the anterior teeth show an irregular shape in the lingual edge (Figure 3a). The cortical bone of the nasal aperture the displayed

hypertrophy, especially remarkable in the area inferior edge. The alveoli are slightly damaged, making it difficult to observe the extent of the lesions (Figure 3a).
3) Destructive and proliferative bony lesions were observed on the oral and nasal surfaces of the palatine process (Figure 3b). The edges of the hard palate have been resorbed. The area of reaction extending to the alveolar bone of the premaxilla and anterior maxilla. Osteoporosis and hole were observed around the palatine suture (Figure 3b). Atrophy of the nasal spine, atrophy of the alveolar bone around the prosthion and inflammatory changes in the surface of the cortical bone on the anterior teeth were confirmed. The histopathology of the lepromatous lesion includes an extensive, diffuse cellular infiltrate (more details will be provided in future works) (Figure 4).

Figure 7. Claw-finger deformity in leprosy.

On the skeleton No 4 exhibited diffuse lesions on the skull, scapulae, humerii, ulnae, radii, pelvis, femora, tibia, foot. These lesions consisted of a mix of lytic and blastic activity that were observed throughout the skeleton (Figures 5-6). On the skull, periosteal lesions were seen on the frontal bone and mandible. On the frontal a large lesion was located along the midline, a smaller lesion was on the left portion of the squama close to the coronal suture and on the right side of the lower jaw (Figure 5). These lesions consisted of a mixed periosteal reaction where the bone had been destroyed and developed in a number of areas. Lytic porosity could be seen along the margins and overall these lesions were round. On the infra-cranial skeleton, visible lesions are concentrated in the upper and lower limbs. The most common lesions and location are exemplified in Figures 5-6.
Skeleton also presented bone changes on the foot (Figure 7). Exostosis at the medial and dorsal aspects of the head of the first metatarsal were discovered. Ankylosis between a middle and distal left phalanx was noticed. An additional incomplete left phalange presented diaphyseal concentric remodeling.
On the tibiae are evidence for infection (periostitis) and injury is present (Figure 6d,e). Evidence for injury to a lower extremity is also commonly associated with a side effect of lepromatous leprosy.
In the postcranial skeleton, marginal osteophytes effected most of the joint surfaces present, including of the scapulae, humerus (proximal epiphysis: head and trochanters), ulnae (lunar and radial notches), radius (distal epiphysis), the vertebral ends of the right and left ribs, left innominate (around the perimeter of the acetabulum), the right and left femoral heads, and the proximal end of the tibia (lateral condyle). The cervical and thoracic vertebrae had severe degenerative changes including osteophytic lipping on the margins of the centra and on the superior and inferior articular surfaces, and spondylolysis (Fig 5b). Similar changes were noted on the lumbar vertebrae. Osteoporosis of bones is observed, characterized by a structural deterioration of bone tissue leading to an increased risk of fracture, porosis.
As shown in Figure 8b, enamel hypoplasia often appears linearly on the enamel surface. There was bilateral periostitis of the alveolar bone supporting the teeth (Figure 8a). Periostitis was severe in the areas with first molar /right/, and there was mild periostitis in all other areas, which was almost the entire maxilla and mandible. Pathology also includes multiple abscesses and infection on the maxillae (Figure 8a). Continuous ridges (exostosis) with a thickness of less than 1 cm (maxilla: M2 and M3) were given a moderate score (Figure 8a). He had caries on the left II incisor (maxillary) and second molars (mandibular) (Figure 8c). The individual had lost two teeth ante-mortem (M1 /mandibular, Figure 8c/, M3 /maxillary/). Cradle deformation (Figure 6a) also is observed on the skull.

Discussion

Differential diagnosis includes granulomatous diseases such as sarcoidosis and treponemal diseases and fungal infections such as aspergillosis and mucormycosis (phycomycossis), actinomycosis (a bacterial rather than a true fungal disease), and lupus vulgaris (tuberculosis of the facial skin and soft tissue).
Sarcoidosis is a systemic disease of unknown etiology characterized by the presence of

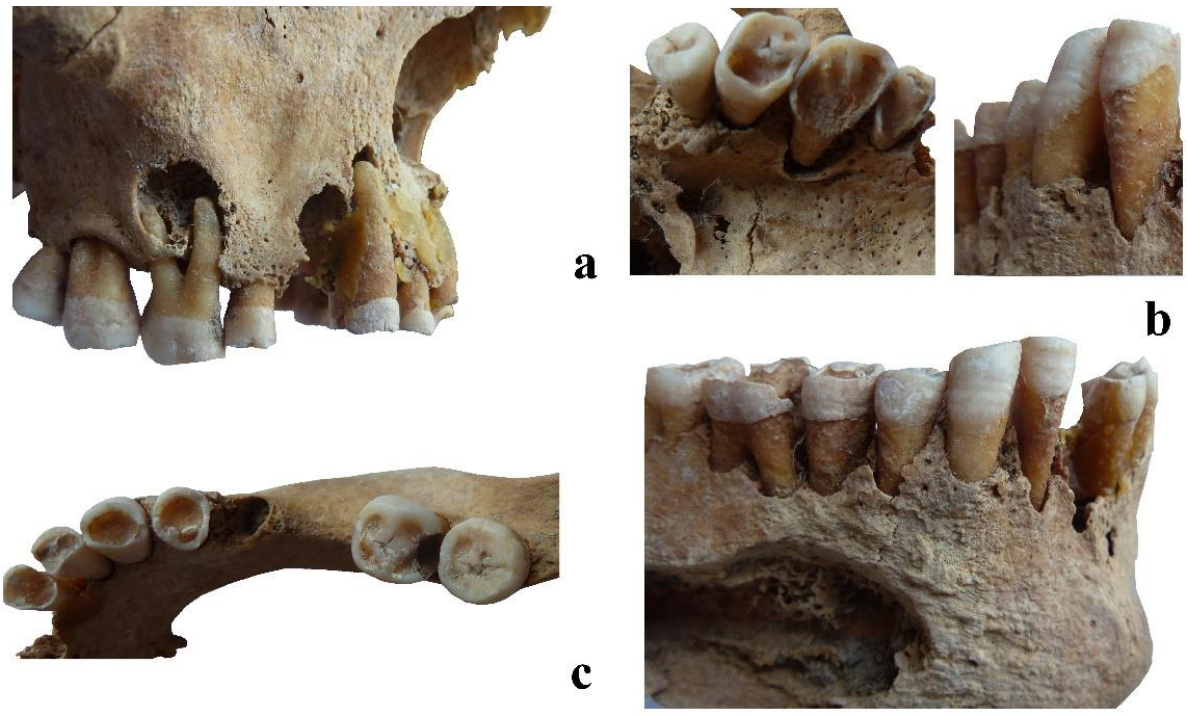

Figure 8Figure 8. Abscesses, bilateral periostitis of the alveolar bone (a), enamel hypoplasia (b), caries and ante-mortem tooth (c).

noncaseating granulomas in any organ, most commonly the lungs and intrathoracic lymph nodes. Like leprosy, it tends to affect the phalanges of the fingers and toes, causing lytic lesions and no reactive bone formation (12). However, in the skull, it causes mainly the destruction of the nasal bones while only rarely of the anterior nasal spine and never of the crest (50). Thus, we can exclude this disease as an explanation for the bony lesions in Angeghakot.

Clinicians categorize human treponemal diseases as syphilis (venereal and endemic), yaws, pinta, which are granulomatous infections caused by spirochetes of the genus Treponema. Excluding pinta, which does not affect bones, in the tertiary stage these diseases can involves the skeleton, and they tend to be associated with inflammatory bony changes accompanied by extensive bone regeneration, often resulting in alteration of the bone morphology and in some cases destruction of the nasal-palatal area may occur (12). Yaws is characteristically an infection acquired during childhood through skin contact. In yaws disorder, the last stage can be characterized by widespread bone, joint, and soft tissue destruction, which may include extensive destruction of the bone and cartilage of the nose (rhinopharyngitis mutilans or “gangosa”). Joints may stiffen, and chronic osteitis and periostitis can lead to deformed leg bones (sabre tibiae). A close relative of the syphilis and yaws treponemes is T. pallidum subsp. endemicum, which causes bejel (also known as endemic syphilis). The involvement of the skull is very rare, with gummas of the soft palate and nose developing in the last stage (50). The “gangosa” condition may occur rarely. In venereal syphilis, the most commonly affected bones are (in order of importance) tibia, frontal and parietal (with caries sicca on the outer tables), nasal-palatal region, clavicle, sternum, vertebrae, fibula, femur, humerus and radius, and ulna. The teeth may also be involved, showing a screwdriver shape (Hutchinson teeth). No specific involvement of the feet is observed in this pathology (12, 50). The most common bones afflicted during the tertiary stage of the disease are the tibia (with sabre-shaped deformity) and the skull. According to Ortner (12), the calvarial lesions are the most specific diagnostic features. Although the nasal cavity is often enlarged, producing the characteristic “saddle nose,” the nasal spine is usually spared (51). Furthermore, the anterior alveolar change process is uncommon in yaws and syphilis (52). Therefore, the pathogenetic picture of our skeleton does not correspond to that of treponemal diseases.

Aspergillosis continue to be an important cause of life-threatening infection in immunocompromised individuals. Aspergillosis is

marked by inflammatory granulomatous lesions in the skin, ear, orbit, nasal sinuses, lungs, and sometimes bones and meninges. It affects the paranasal sinuses and orbit or the anterior cranial fossa (50). Most infections are caused by Aspergillus fumigatus. The organism is capable of invading across all-natural barriers, including cartilage and bone. Mucormycosis is an infection caused by fungi belonging to the order Mucorales, which tends to affect people who have poorly controlled diabetes (53). The skin barrier represents a host defense against cutaneous mucormycosis, as evidenced by the increased risk for developing mucormycosis in individuals with disruption of this barrier. However, burns, traumatic disruption of the skin, and persistent maceration of skin enables the organism to penetrate into deeper tissues. Mucormycosis attacks the nasal cavity with involvement of the paranasal sinuses and their walls (12). A diagnosis of aspergillosis and mucormycosis can be ruled out.

Actinomycosis is a chronic, and slowly progressive granulomatous disease. Multiple different clinical features of actinomycosis have been described, as various anatomical sites (face, bone, joint, respiratory tract, skin, soft tissue structures) can be affected. When affected of skull, the mandible rather than the maxilla is more involved (12, 54).

Lupus vulgaris is a chronic tubercular infection of the skin involving soft yellow swellings, ulcers, and abscesses. Lupus vulgaris and tuberculous dactylitis (which occurs predominantly in young children) are rare clinical entities (55). Long-standing tuberculosis of the facial skin and soft tissues can lead to the destruction of the nasal bones (50). The anterior alveolar process, however, is rarely affected (52), which discounts lupus vulgaris as a diagnosis. Thus, a tuberculous origin for the skeletal lesions observed in skeleton 4 seems highly improbable. Frostbite, also known as freezing cold injury, may also be ruled out (56).

Skeleton 4 from Angeghakot displays a pattern of skeletal involvement highly compatible with a diagnosis of leprosy. The pattern of pathological changes observed, which includes rhinomaxillary lesions and lower limb bone lesions. This skeleton also presented fused foot phalanges, indicating that it may have suffered from claw foot deformity. This condition develops after the peripheral neuropathy often found in leprosy patients (57, 58). Post-cranial bones demonstrate a variety of irregular bone formations due to healing of bone lesions, or small pitting when unhealed. This is due to infection of the skin progressing into the underlying bone. Infection in the feet spreads to the lower leg, the tibia through the nerves, causing periostitis. Periostitis is a non-specific infection of the periosteum of bone occurring as new bone buildup on the surface of the bone. It is the overall pattern of infection, in addition to temporal and spatial location, that lead to diagnosis since a number of these pathologies can be due to other infections.

Leprosy represents one of the most interesting of all diseases. Many myths and misperceptions about the disease have shaped social perceptions and reactions to people with the disease. Medieval citizens feared the person with leprosy out of uncertainty, misinformation, self-preservation, and ignorance. By virtue of being considered an evil outcast, people with the disease were symbolic representations of evil. Leprosy was a warning to all living that their sinful lives might result in God's punishment. Medieval communities developed sets of rituals that were used to diagnose, segregate, and label people with leprosy. Under Pope Alexander III, the Third Lateran Council (1179) issued a decree that urged their segregation, building separate chapels, and burying them in separate cemeteries (59). Communities sequestered people with leprosy by forcing them outside community boundaries. Individuals from Angeghakot were reburied (secondary burials) outside the cemetery. Amongst the skeletal material unearthed the Angeghakot, only (at this stage) in skeleton 4 can a probable diagnosis of leprosy be established. A study of the bone remains of the remaining 8 individuals will determine the cause of their death. Which will open the key to understanding their reburial outside the cemetery. The case under study enrich the scanty osteoarchaeological documentation of leprosy in Armenia in the early Middle Ages.

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References

1. Martin EA. Concise Medieval Dictionary. Oxford, Oxford University Press, 2010
2. Steinbock RT. Paleopathological Diagnosis and interpretation. Springfield, C.C. Thomas, 1976.
3. Roberts C, Manchester K. The Archaeology of Disease, 3rd edn., Stroud, The History Press. 2010.
4. Lumpkin LR 3rd, Cox GF, Wolf JE Jr. Leprosy in five armadillo handlers. J Am Acad Dermatol. 1983 Dec;9(6):899-903. doi: 10.1016/s0190-9622(83)70206-9. PMID: 6643788..
5. Hubbard GB, Lee DR, Eichberg JW, Gormus BJ, Xu K, Meyers WM. Spontaneous leprosy in a chimpanzee (Pan troglodytes). Vet Pathol. 1991 Nov;28(6):546-8. doi: 10.1177/030098589102800617. PMID: 1771747..
6. Manchester K, Roberts C. The palaeopathology of leprosy in Britain: a review. World Archaeol. 1989 Oct;21(2):265-72. doi: 10.1080/00438243.1989.9980105. PMID: 16470999..
7. Job CK, Jayakumar J, Kearney M, Gillis TP. Transmission of leprosy: a study of skin and nasal secretions of household contacts of leprosy patients using PCR. Am J Trop Med Hyg. 2008 Mar;78(3):518-21. PMID: 18337353..
8. Auferheide AC, Rodriguez-Martin C. Cambridge Encyclopedia of Human Paleopathology, Cambridge, Cambridge University Press, 1998.
9. Suzuki K, Akama T, Kawashima A, Yoshihara A, Yotsu RR, Ishii N. Current status of leprosy: epidemiology, basic science and clinical perspectives. J Dermatol. 2012 Feb;39(2):121-9. doi: 10.1111/j.1346-8138.2011.01370.x. Epub 2011 Oct 4. PMID: 21973237.
10. Anderson J, Manchester K. The rhinomaxillary syndrome in leprosy: A clinical, radiological and palaeopathological study. Int J Osteoarch. 1992, 2(2): 121–129.
11. Andersen JG. Grooving of the proximal phalanx in leprosy : a paleopathological and radiological study. J Archaeol Sci. 1987;14:77-82. doi: 10.1016/s0305-4403(87)80007-9. PMID: 17265601.
12. Ortner DJ. Identification of Pathological Conditions in Human Skeletal Remains. London, Academic Press, 2003.
13. Christensen VB, Boldsen JL. Aeblekassereglementet [Medieval leprosy]. Ugeskr Laeger. 2001 Dec 17;163(51):7248-50. Danish. PMID: 11797556.
14. Boldsen JL, Mollerup L. Outside St. Jørgen – Leprosy in Medieval Odense. Am J Phys Anthropol. 2006, 115:380-387.
15. Badger LF. Epidemiology. In Cochrane RG, Davey TF. (eds), Leprosy in Theory and Practice, 2" edition. Bristol, John Wright and Sons, pp. 69-97, 1964.
16. Jopling W. Handbook of leprosy. London, William Heinemann Medical Books, Redwood Burn Ltd, 1971.
17. Hargrave JC. Leprosy in Northern Temtory Aborigines. Northern Territory Medical Service of the Australian Deportment of Health, Canberra, 1970.
18. Zias J. New evidence for the history of leprosy in the Ancient Near East: an overview. In: Roberts C.A., Lewis M.E., Manchester K. (eds.), The Past and Present of Leprosy. Archaeological, historical, paleopathological and clinical approaches. BAR International series 1054, Archaeopress, Oxford, pp. 259 – 268, 2002.
19. Hulse EV. Leprosy and ancient Egypt. Lancet. 1972 Dec 2;2(7788):1203-4. doi: 10.1016/s0140-6736(72)92636-0. PMID: 4117634.
20. Andersen JG. Studies on the medieval diagnosis of leprosy in Denmark. An osteoarchaeological, historical and clinical study. Costers Bogtrykkeri, Copenhagen, 1969.
21. Robbins G, Tripathy VM, Misra VN, Mohanty RK, Shinde VS. Ancient Skeletal Evidence for Leprosy in India (2000 B.C.). PLoS ONE 2009, 4(5): e5669. doi:10.1371/journal.pone.0005669
22. Dzierzykray-Rogalski T. Paleopathology of the Ptolemaic inhabitants Dakhleh Oasis (Egypt). Journal of Human Evolution 1980, 9(1): 71–74.
23. Khudaverdyan AYu, Manukyan SV, Vardanyan BV, Shakhmuradyan MS. Resorption of the alveolar region in Facies leprosy: a paleoanthropological and paleopathological analysis (Aragatsavan, Armenia). Bull. Int. Assoc. Paleodont.2019, 13(1): 1-17.
24. Khudaverdyan AY. Pattern of disease in II millennium BC–I millennium BC burial from Lchashen, Armenia. Anthropologie (Brno). 2010;48(3):248-9
25. Khudaverdyan AYu. The anthropology of infectious diseases of Bronze age and early iron age from Armenia. Dental Anthropol. 2011, 2 (2): 42–54
26. Khudaverdyan AYu. Pattern of disease in three 1st century BC - 3rd century ad burials from Beniamin, Vardbakh and the Black Fortress I, Shiraksky plateau (Armenia). Journal of Paleopathology 2010, 22: 15-41.

27. Khudaverdyan AYu. Decapitation in the Dvina (Armenia): an analysis of the skulls of Middle Ages. Journal of Paleopathology 2015, 25 (1-3): 25-34
28. Schuenemann VJ, Singh P, Mendum TA, Krause-Kyora B, Jäger G, Bos KI, Herbig A, Economou C, Benjak A, Busso P, Nebel A, Boldsen JL, Kjellström A, Wu H, Stewart GR, Taylor GM, Bauer P, Lee O, Wu H, Minnikin DE, Besra GS, Tucker K, Roffey S, Sow SO, Cole ST, Nieselt K, Krause J. Genome-Wide Comparison of Medieval and Modern Mycobacterium leprae. Science 2013, 341 (6142): 179–183.
29. Mark S. Alexander the Great, Seafaring, and the Spread of Leprosy. Journal of the History of Medicine & Allied Sciences 2002, 57(3): 285–310.
30. Mariotti V, Dutour O, Belcastro MG, Facchini MG. Probable Early Presence of Leprosy in Europe in a Celtic Skeleton of the 4th-3rd Century BC (Casalecchio di Reno, Bologna, Italy). Int J Osteoarch. 2005, 15: 311–325.
31. Köhler K, Marcsik A, Zádori P, Biro G, Szeniczey T, Fábián S, Serlegi G, Marton T, Donoghue HD, Hajdu T. Possible cases of leprosy from the Late Copper Age (3780-3650 cal BC) in Hungary. PLoS ONE. 2017, 12(10): e0185966.
32. Matos VMJ, Santos AL. Leprogenic odontodysplasia: New evidence from the St. Jørgen's medieval leprosarium cemetery (Odense, Denmark). Anthropological Science. 2013,121:43-47.
33. Taylor GM, Tucker K, Butler R, Pike AWG, Lewis J, Rofey S, Marter P, Lee OY-C, HHT W, Minnikin DE, Besra GS, Singh P, Cole ST, Stewart GR. Detection and strain typing of ancient Mycobacterium leprae from a medieval leprosy hospital. PLoS ONE. 2013, 8:e62406.
34. Monot M, Honoré N, Garnier T, Araoz R, Coppée J-Y, Lacroix C, Sow S, Spencer JS, Truman RW, Williams DL, Gelber R, Virmond M, Flageul B, Cho S-N, Ji B, Paniz-Mondolfi A, Convit J, Young S, Fine PE, Rasolofo V, Brennan PJ, Cole ST. On the origin of leprosy. Science. 2005, 308: 1040 -1042.
35. Vardanyan SA. History of medicine in Armenia. From ancient times to the present day. Yerevan, 2000 (in Russian).
36. Brody SN. The Disease of the Soul: Leprosy in Medieval Literature. Ithaca, NY, Cornell University Press, 1974.
37. Phenice TW. A newly developed visual method of sexing the os pubis. Am J Phys Anthropol. 1969; 30: 297–302.
38. Buikstra JE, Ubelaker DH. Standards of data collection from human skeletal remains. Fayetteville: Arkansas Archaeological Survey Research Series, 44, 1994.
39. Gilbert BM, McKern TW. A method for aging the female os pubis. Am J Phys Anthropol. 1973; 38:31–38.
40. Katz D, Suchey JM. Age determination of the male os pubis. Am J Phys Anthropol 1986; 69:427–435.
41. Meindl RS, Lovejoy CO. Ectocranial Suture Closure: A Revised Method for the Determination of Skeletal Age at Death Based on the Lateral-Anterior Sutures. Am J Phys Anthropol 1985; 68:57–66.
42. Lovejoy CO, Meindl RS, Pryzbeck TR, Mensforth RP. Chronological metamorphosis of the auricular surface of the ilium: A new method for the determination of adult skeletal age at death. Am J Phys Anthropol. 1985, 68:15–28.
43. Brothwell D, Sandison AT. Diseases in Antiquity. A Survey of the Diseases, Injuries and Surgery of Early Populations. Springfield, Ill., C. C. Thomas, 1967.
44. Møller-Christiansen V. Leprosy Changes of the Skull. Odense, Odense University Press, Denmark, 1978.
45. Boldsen JL. An epidemiological approach to the paleopathological diagnosis of leprosy. Am J Phys Anthropol. 2001, 115:380-387.
46. Boldsen JL. Leprosy and mortality in the medieval Danish village of Tirup. Am J Phys Anthropol, 2005, 126:159-168.
47. Andersen J; Manchester K. The rhinomaxillary syndrome in leprosy: a clinical, radiological and palaeopathological study. Int J Osteoarch. 1992, 2(2):121-129.
48. Ortner DJ, Putschar WGJ. Identification of Pathological Conditions in Human Skeletal Remains. Washington D.C . Smithsonian Institution Press, 1981.
49. Manchester K. Bone Changes in Leprosy: Pathogenesis and Paleopathology. Bradford, England: Calvin Wells Laboratory, School of Archaeological Science, University of Bradford. Unpublished, 1989.
50. Robbins SL, Cotran RS. Pathologic Basis of Disease. W.B. Saunders Company, Philadelphia, 2002.
51. Rogers J, Waldron T. Infections in palaeopathology: the basis of classification according to most probable cause J. Archaeol. Sci. 1989; 16 (6): 611–625
52. Møller-Christensen V. Evidence of leprosy in earlier people. In: Brothwell D, Sandison AT (eds.), Disease in Antiquity. A Survey of Diseases, Injuries and Surgery, Charles C. Thomas, Springfield, Ill, USA, pp. 295–306, 1967.
53. Hibbett DS, Binder M, Bischoff JF, Blackwell M, Cannon PF, Eriksson OE, Huhndorf S, James T, Kirk PM, Lücking R, Lumbsch HT, Lutzoni F, Brandon MP, McLaughlin DJ, Powell MJ, Redhead S, Schoch CL, Spatafora JW, Stalpers JA, Vilgalys R, Aime MC, Aptroot A, Bauer R, Begerow D, Benny GL,

Castlebury LA, Crous PW, Dai Yu-Ch., Gams W, Geiser DM, Griffith GW, Gueidan C, Hawksworth DL, Hestmark G, Hosaka K, Humber RA, Hyde KD, Ironside JE, Kõljalg U, Kurtzman CP, Larsson K-H, Lichtwardt R, Longcore J, Miadlikowska J, Miller A, Moncalvo J-M, Mozley-Standridge S, Oberwinkler F, Parmasto E, Reeb V, Rogers JD, Roux C, Ryvarden L, Sampaio JP, Schüssler A, Sugiyama J, Thorn RG, Tibell L, Untereiner WA, Walker C, Wang Z, Weir A, Weiss M, White MM, Winka K, Yao Y-J, Zhang N. A higher-level phylogenetic classification of the Fungi. Mycol Res. 2007, 111:509–47

54. Rothschild B, Naples V, Barbian L. Bone manifestations of actinomycosis. Ann Diagn Pathol. 2006 Feb;10(1):24-7. doi: 10.1016/j.anndiagpath.2005.09.017. PMID: 16414541..
55. Ormerod P. Non-respiratory tuberculosis. In: Davies PDO, Gordon SB, Davies G. (eds.), Clinical Tuberculosis., 5th ed. CRC Press, Taylor & Francis Group, London, pp. 167–187, 2014.
56. Golant A, Nord RM, Paksima N, Posner MA. Cold exposure injuries to the extremities. J Am Acad Orthop Surg. 2008 Dec;16(12):704-15. doi: 10.5435/00124635-200812000-00003. PMID: 19056919.
57. Yawalkar S. Leprosy for medical practitioners and paramedical workers. Novartis Foundation for Sustainable Development, Basle, Switzerland, 2002.
58. Sehgal A. Leprosy. Chelsea House Publishers, Philadelphia, 2006.
59. Le Goff J. Medieval History: 400–1500. New York, Basil Blackwell, 1990.