Diffuse Idiopathic Skeletal Hyperostosis (DISH): Palaeopathological Study on Human Remains from Parthian Cemetery, Liyarsangbon, Guilan, Iran; With a Special Reference to Metastatic Cancer as the Cause of Death

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Abstract

Diffuse Idiopathic Skeletal Hyperostosis (DISH) is a systemic noninflammatory condition that is characterized by unknown causes. It is closely associated with various factors including sex, age, environmental influences, genetic predisposition, and fluctuations in medication. Certain diseases, including gout, metabolic disorders such as type 2 diabetes as well as populations. Paleopathological studies of ancient remains indicate that it has been identified in various archaeological populations. The studied individual was discovered from Liyarsangbon cemetery, Amlash city, Guilan province, Iran. On the base of preliminary typology, the artifacts and grave types, the site was dated to the Parthian (247 BCE–224 CE) and in a few cases to the Sassanid period (224–651 CE). The remains of an individual with a potential case of DISH disease have attracted the interest of researchers. While there are other possible diagnoses such as spondyloarthropathies, Paget's disease, metabolic diseases, and POEMS syndrome. Following osteological examinations, advanced radiological imaging methods, in addition to visual inspection, were employed to differentiate between potential diagnoses. Based on criteria, the ultimate diagnosis was determined to be either DISH or eDISH. The presence of patchy sclerotic bone lesions in the majority of the pelvic, and spine, suggesting osteoblastic metastatic tumors that may have contributed to the individual's demise.

Introduction

Diffuse Idiopathic Skeletal Hyperostosis (DISH) is a systemic noninflammatory disease. It has been referred under different names such as Forestier-Rotes-Querol by(Resnick et al., 1978; Resnick et al., 1975). However, what seems certain is that DISH is closely related to sex and aging in humans(Forestier & Rotès-Querol, 1950);(Cassim et al., 1990; Hannallah et al., 2007; Julkunen et al., 1971; Navarro & Buckberry, 2022).

The prevalence of this disease among different ethnic groups shows that genetic factors play a role in the etiology of this disease(Julkunen et al., 1981; Kim et al., 2004; Kiss, O'Neill, et al., 2002)). Therefore, based on the researches, DISH disorder is more prevalent in White people with 25% compared to the blacks, as well as the Asian and Native American populations(Weinfeld et al., 1997). In fact, DISH is largely unknown in most of the Asian countries, ranging from between 2.9–15% 6,7 (Vaishya, Vijay, Nwagbara, & Agarwal, 2017). Based on limited scant statistical populations, the prevalence of DISH in the Eastern Mediterranean and Middle Eastern regions is rare. A prevalence of 10% was observed among the elderly in Oman Sirasanagandla et al., 2018) and 17.9% in Jerusalem (Bloom, 1984).

According to the paleopathological studies of ancient remains, it appears that this disease is not a recent disorder. Signs of DISH have even been observed in dinosaurs(Rothschild, 1987). It has been also reported as early as during the Middle Paleolithic on one of the Neandertal skeletons discovered at Shanidar in Iraq (Shanidar 1)(Crubézy & Trinkaus, 1992). Neandertal skeleton, the Kiik Koba 1, (Crimea) might also have been affected by DISH(Trinkaus et al., 2008).

Further, the occurrence of DISH is reported in different archaeological populations from different part of the world and all periods as well as in various contemporary respectively; in European populations(Mays, 1991, 2016; Müldner & Richards, 2007; Patrick, 2014; Rogers & Waldron, 2001; Waldron, 1985);(Paja, 2010; Verlaan et al., 2007); northern Chile(Arriaza, 1993); Meriotic Nubia(Arriaza et al., 1993); ancient Chinese(Hukuda et al., 2000); Japan(Oxenham et al., 2006); Botswana(Mosothwane & Steyn, 2009); Korea(Kim et al., 2012); pre-Columbian North America(Smith et al., 2013); ancient Egypt(Saleem & Hawass, 2014). As concerns Near Eastern post-Paleolithic prehistoric data is few in amount i.e., excavation report of three identified individuals, an adult male from Mallaha and two adult individuals from Hayonim cave of Israel in the Natufian population(Bocquentin, 2003). Base on the published manuscript, just a single study conducted in Middle East region during more than three last decades(Bloom, 1984).

The Etiology of DISH

The etiology of DISH is unknown, in most modern clinical investigations it is hypothesized to be associated with certain diseases such as gout, metabolic disorders, specifically obesity and type II diabetes mellitus(Denko & Malemud, 2006; Kiss, O'Neill, et al., 2002). Additionally, factors such as increasing age, exposure to environmental factors (retinol and fluoride), mechanical and genetic factors (human leukocyte antigen genes), excess growth factors (insulin-like growth factor), as well as drug fluctuations (vitamin A derivatives, acitretin, isotretinoin, and etretinate) have been implicated (Van der Merwe, Maat, & Watt, 2012).

Observation of DISH disease in people under 50 years old is rarely reported e.g., occurring in about 25% of males, and 15% of females; while instead, the rate is increased in patients over 80 years old, with 28% and 26% in men and women, based on the sex respectively(Mata et al., 1995). According to the available reports, up to 10% of patients over 65 years of age are affected by the disease as well(Matan et al., 2002).

The physical feature of DISH appears as a result of progressive ossification of the anterior longitudinal spinal ligament and bone proliferation in the enthesis, which produces a typical candle flowing wax appearance with large osteophytes that flow downward along the spine (Figs. 2 & 3)(Forestier & Rotès-Querol, 1950). New theories show that the change in the function and growth of osteoblasts is the reason for the calcification of the anterior longitudinal ligament(Atzeni et al., 2006).

Based on the circle of disease, it first affects the patient's spine. Although cervical spine involvement is not rare, but it is less common than lumbar or thoracic spine involvement. Ossification changes in the right side of the thoracic spine are greater than those in the left side; the main reason for this change may be the presence of the left-sided descending aorta(Rogers & Waldron, 1995). It is also closely related to ossification/calcification of capsule insertion (enthesis), ligament, and tendon, which occurs in several peripheral locations(Ghammam et al., 2019). The gradual ossification of the involved organs, i.e., the thoracic or lumbar spine, ultimately causes a decrease in movement operations, mild pain, or minor

stiffness in the patient(Resnick et al., 1975). In addition, patients with unstable spine fractures, permanent neurological deficits are often observed(Verlaan et al., 2007).

Methodology

During the years 2015 and 2016, a total of 49 human skeletons were unearthed from a cemetery situated in Liyarsangbon Amlash, Guilan province, as a result of two seasons of excavation(Eghdami et al., 2023). The bones were collected and transported to the biological anthropology laboratory, located at the Research Institute of Guilan Studies (RIGS), University of Guilan, Rasht, Guilan, Iran. Upon conducting initial studies, it was discovered that some of the exposed bones exhibited signs of infectious and chronic diseases(Eghdami et al., 2023). One of the most interesting examples that caught the attention of relevant researchers was the remains of an individual with the possibility of DISH disease, but, with many differential diagnoses. Soon after seeing the signs, a team composed of a human osteologist and several physicians with internist, radiologist, endocrinologist, and rheumatologist gathered together to investigate and discuss more about literature review and an update of the recent findings regarding the disease diagnosis more accurately.

The sex and age, both metric and nonmetric, of the arguing individual were determined by standardized criteria established by Rudolf Martin(Martin, 1928). This analysis was conducted using a dataset consisting of thirty-four cranial and forty-four postcranial measurements(Brothwell, 1963; Buikstra, 1994; Martin & Saller, 1957; Meindl et al., 1985; Stewart, 1979; Walker, 2008).

The use of basic and more advanced imaging techniques for investigating the pathogenesis and differentiation of DISH from other diseases with similar imaging properties and symptoms was argued(Mader et al., 2017). In order to diagnose the symptoms of DISH in the studying individual, two stated criteria (Resnick & Niwayama, 1976)and(Julkunen et al., 1975), were used. Typically, the identification of DISH is determined through the examination of a chest and spine plain film as well as CT scanning in recent times.

Following the identification of invisible factors that caused disorders in the bones such as, hyper osteosis and joint ankylosis or pseudo-fusion (Scholz et al., 2019) the skeletal specimens were transported to Golsar Hospital in Rasht, Guilan, for CT imaging. The imaging procedure was carried out utilizing a Philips Brilliance 16 Slice CT scanner, third generation, with the Rotate-rotate technique. The scanning parameters included 0.4**, 0.5, 0.75, 1, 1.5, and 2 seconds for complete 360° scans, as well as 0.28**, 0.33 seconds for partial 240° angle scans. Subsequently, the acquired images underwent enhancement using Medical Image Processing Software (MIPS) to enhance clarity and precision for improved diagnostic capabilities. Furthermore, to facilitate further analysis, the enhanced images were reconstructed in three dimensions using Virtual Reality (VR) software. To prevent errors in interpretation due to overlapping symptoms, the refined images were meticulously examined and analyzed with colleagues utilizing the iQ-VIEW / PRO version 2.6.0 software. This comprehensive approach ensured a

thorough evaluation of the images and facilitated accurate diagnosis and treatment planning for patients with DISH disease.

In order to further investigate paleopathological aspects, two distinct microscopes were employed: the KRUSS stereo zoom and metallurgical microscope, as well as a HD video borescope BS-280. These devices were utilized to observe parts of the bones that were otherwise inaccessible.

To determine the soil matrix's acidity, samples were initially collected from various areas of the excavated site of Liyarsangbon and examined on-site. Sodium bicarbonate and acetic acid were employed for this purpose. Additionally, in the laboratory, a Milwaukee Mi 151-m with ± 0.01 pH accuracy was utilized for further analysis.

Archaeological Materials

The archaeological site of Liyarsangbon, located in Amlash city, Guilan province. Through a preliminary typological analysis of artifacts and burial styles (Fig. 1), the site has been determined to date back to the Parthian era [247 BCE–224 CE] and occasionally to the Sassanid period [224–651 CE] (Eghdami, et al. 2023). Analysis of the soil samples collected from the area reveals pH values that vary between 7.70 and 8.67, with an average pH of 8.23, suggesting a soil composition that is moderately to strongly alkaline in nature (Table 1).

Table 1
showing all the individual information obtained from the excavated skeleton

Individual Information, Trench No. 9501 Cave No. 95501						
Date of Excavation: Summer, 2015			Site Director: V. Jahani			
Sex	Age	Soil pH	Burial Type	Burial Direction	Crave Type	Buried Goods
Male	~ 35–40	μ 8.46	Flexed	Northeast to Southwest	crypt	Bowl, Jar, Bayonet, Knife, Scissor, unknown metal and bronze object, an iron sword

Results and Discussions

Diagnostic observations were conducted through instrumental observations such as X-Ray and CT Scanning or visual observations using the naked eye. The choice between these methods depends on the researchers' objective, as the naked eye provides a broader perspective while instruments allow for more precise and detailed observations. Regardless of the method chosen, it is important to note that

each disease exhibits certain similarities with several other diseases which is called as differential diagnosis (DDx)(Henderson et al., 2012).

Drawing from the preliminary observations, certain regions of the skeletal structure exhibited indications of ossification and calcification, specifically the presence of syndesmophytes and calcification in the paravertebral ligaments (Figs. 2 & 3). One of the main diseases was DISH disease, but further extensive research was needed to issue a definitive opinion on this matter.

Description

A- Al. an abnormal round hole on parietal surface with dimensions of the outer surface measuring 5.7 × 5.7 mm and the inner surface measuring 1.7 × 4.7 mm without any vascular effects on its outer surface; B, B1, B2. complete bridging, ossification in the lower cervical spine (C6 to C8); C. costal cartilage of the right first rib completely ossified and fused to the sternal manubrium; D. bilateral hyperosteosis in supracondylar line of Homarus; E. Severe Syndesmophytes, paravertebral anterior and lateral ligament calcification throughout the spine without any skip lesion caused increased kyphosis in the thoracic vertebrae and lordosis in the cervical vertebrae C6 to C8 (Throughout the spinal disc, space is well preserved, the posterior portion of the vertebral bodies is less involved, and no grossly destructive pre-mortem evidence in vertebral bodies is observed) F. appearance of candle flowing wax; G. bony attachments of ilium, bilateral hyperosteosis in the tendinous attachments sites of iliac and bridging osteophytes in the right sacroiliac joint, caused the appearance of ankylosis of its joint; G1. posterior iliac spine hyperosteosis; G2. superior pubic margin hyperosteosis; G3. ischial tuberosity hyperosteosis; H. H1. bilateral hyperosteosis in intertrochanteric line and lateral medial lip of linea aspera of femur; J. prominent tibial tuberosity (right side); J1. An unusually large coarse osteophyte is seen at the proximal end of the fibular notch of the right tibia; M. patella anterior surface severe hyperostosis (left side); N. Prominancy of calcaneal tuberosity (Both sides); L. Thyroid and cricoid cartilage are completely ossified;

Overall, the bones do not show any evidence of osteoporosis, and there is also no evidence of premortem destruction and no evidence of destruction was observed in the cartilage surface of the joint; although evidence of extensive osteoarthritis was visible in the examination of most of the joint.

Description: A1, A3, A5, A6, A7. ankylosis/near fusion associated with bridging ossification in the anterior, posterior, and bilateral bodies resulting in neuroforaminal narrowing and DJD in end-plates (subchondral sclerosis & irregularity and marginal osteophytes in c6 to c8 levels as well as DJD in the right uncovertebral joint/near ankylosis in T1-T2 level; A2, A3. marginal osteophytes and schmorls nodes in thoracic and lumbar spines; B1, B2, B3. joint space narrowing, bridging osteophytes, and partial fusion in Right sacroiliitis (the anterosuperior portion of the joint) and Hyperosteosis and ossifications in the posterior tendinous attachment site of the ileum (especially on the right side). R/o enthesopathy; C. Hyperosteosis at lateral suprachondylar of Hemerus; D. Hyperosteosis and ossification in the anterolateral tibia at the tendinous attachment site (R/o enthesopathy); E. Cartilage ossification at the attachment site of the right first rib to the sternal manubrium resulting ankylosis; A3, B1, B3. Some round, oval, and lobulated/patchy sclerotic/blastic bone lesions are present in most of the spinal bodies and

appendages as well as bilateral ileum, pubis & left ischium. The largest lesion is found in the L3 body and T12 right pedicle/articular process.

Following preliminary investigations and extensive observations, it appeared likely that the hyperostosis condition in the individual could be attributed to the presence of various similar diseases, including DISH, spondyloarthropathies like Ankylosing Spondylitis (AS), and potentially psoriatic arthritis (PsA) and Reiter's Syndrome (ReS). Additionally, Paget's disease, metabolic disorders such as gout, primary and secondary hyperparathyroidism, and POEMS syndrome were also considered as potential causes. Moreover, the identification of sclerotic lesions in CT scan images can indicate the presence of osteoblastic metastatic tumors.

Differential Diagnoses between related diseases and symptoms found in the affected person

Ankylosing Spondylitis (AS)

AS, the most common of the spondyloarthropathies (SpAs) (Reveille, 2004), has many similarities with the symptoms found in the individual under study, although there are some differences. It predominantly affects Caucasians and native American males (Rogers, 1995) with an age of onset between 15 to 35 years which the sex matches to our sample while the age is not exactly (Table 1). In AS, there is bilateral involvement of the sacroiliac joint, commonly leading to fusion and the production of syndesmophytes. Spinal fusion always occurs in the lowest part of the spine and may progress inexorably upward without any normal vertebral intervening(Reveille, 2004). Costovertebral joint changes in AS involve a similar process to the sacroiliac joint, with the breakdown of articular cartilage and ankylosis across the margins of the joint via ossification of the enthesis(Roberts & Manchester, 2010). In the present study, existence of the involvement the entire spine without skip lesions, as well as sacroiliac joint faced the diagnosis towered AS, while the more severe involvement of the upper parts of the spine, as well as the nonsymmetry of the sacroiliac joint involvement, goes against the diagnosis of AS (Fig. 2. G & E). Additionally, discovered by CT imaging, the fusion of the right sacroiliac joint is caused by the convergence of osteophytes around the joint and the joint itself remains intact, which is contrary to AS (Fig. 3. B1). Although, except around the calcaneum, extra-spinal enthesophytes are not common in AS(Dj, 2003), but, presence of diffuse extra spinal hyperostosis including extensive osteophytes at the joint of tendons and bones, ossification of the cricoid and thyroid and costal cartilage of Rt 1st rib, turns the view against AS (Fig. 2. L, M, N).

Reiter’s Syndrome (Reactive spondyloarthropathy) (ReA)

ReA refers to acute non-purulent arthritis complicating an infection elsewhere in the body(Loscalzo et al., 2022). This disease has the typical characteristics of SPA, but the sacroiliac joint is usually affected asymmetrically and the fusion of the spine is uncommon, which is in the form of skip lesions(Loscalzo et al., 2022). Enthesitis and proliferation of new bone are more common in ReA than in some of the other SPAs and may also be observed in the metatarsal shafts and around the calcaneum. Another

distinguishing feature of ReA is that the changes tend to primarily affect the joints in the lower extremities rather than the upper(Grauer, 2016).

Considering the involvement of the spinal column with course desmophytes and asymmetric involvement of the sacroiliac joint in our case, and since ReA is common at older ages than AS (up to 40 years old), ReA diagnosis should be considered. In ReA, unlike our case, the syndesmophytes are asymmetric and comma-shaped, and they arise from the middle of the vertebral body, and progression to spinal fusion is uncommon(Loscalzo et al., 2022). Also, widespread desmophytes and ossifications in our case are also against the ReA diagnosis (Fig. 2).

Psoriatic Arthritis (PsA)

PsA involves the cartilaginous joints of the axial skeleton (Dj, 2003). PsA affects a subset of those who suffer from the skin disease psoriasis. Sacroiliac joints and spine are involved, with the latter showing the presence of skip lesions as in ReA. The principal distinguishing feature between ReA and PsA is that in the latter, the joints of the upper limbs tend to be preferentially affected. A fine subset of PsA is its destructive form, especially affecting the distal phalanges, known as the "cup in pencil" sign. Proliferation of new bone, especially on the metacarpal or metatarsal shafts, can be found. One feature of PsA is that the cervical spine is frequently involved (Grauer, 2016).

Considering that the cervical spine is more involved in our case than other areas of the spine, the closest SpAs to our case is PsA. In PsA, the cervical vertebrae are frequently involved, as well as asymmetric sacroiliac involvement and extra spinal joint involvement (Fig. 0–0). However, there is no evidence of marginal erosions with adjacent bony proliferation (Whiskering), small joint ankylosis, or osteolysis of phalangeal and metacarpal bones, which are common in PsA. Additionally, compared to the marginal syndesmophytes in our case, syndesnophytes in PsA are non-marginal and less symmetric(Loscalzo et al., 2022).

Paget's disease

Paget's disease can be defined as a progressive pathological reconstruction of bones, where normal bone is destroyed and replaced by mechanically defective osseous tissue. It is most commonly found in men between 50 to 60 years of age (Grauer, 2016), which matches our sample. This disease is rare in the native population of Asia and the Middle East and is not common in the explored area of our case. Pagetic bone is expanded, less compact, and more vascular(Loscalzo et al., 2022). The characteristic findings of Paget's disease include diffuse radio-dense enlargement of vertebrae referred to as ivory vertebrae, disruption or fusion of the sacroiliac joint, porotic and radio-dense lesions of the ilium, iliopectinal line (brim sign), and bowing deformity of long bones, which do not match the radiological findings of our case.

Related Metabolic Disease

Gouty Arthritis

Gout is a disease caused by a disturbance in purine metabolism, characterized by the accumulation of its end product, sodium, in the body(Shepherd-Wilson & Gelfand, 1962). Cystic change, well-defined erosions with sclerotic margins (often with overhanging bony edges) are a characteristic feature of advanced gout(Loscalzo et al., 2022). In addition, fusion of the fifth through twelfth ribs to the vertebrae, as well as the sacroiliac and diarthrodial and amphiarthrodial joints, may also be seen(Shepherd-Wilson & Gelfand, 1962).

Except for the characteristic of joint fusion in gout, which is present in our case, our other findings, including extensive osteophytes and extraosseous ossification and lack of evidence of joint erosions, are against the diagnosis of gout.

Primary and secondary Hyperparathyroidism

Hyperparathyroidism is a generalized disorder of calcium, phosphate, and bone metabolism due to increased secretion of PTH. Radiological changes include resorption of the phalangeal tufts and replacement of the bone in the digits by an irregular outline (subperiosteal resorption). Cortical bone density is reduced, while cancellous bone density, especially in the spine, is relatively preserved(Loscalzo et al., 2022). Although extensive extraskeletal ossification can be justified by hyperparathyroidism, in the radiological examination of our case (Fig. 3), subperiosteal resorption is not observed and cortical bone density is not reduced, which is contrary to the diagnosis of hyperparathyroidism.

Infectious Disease

At first glance, the involvement of cervical vertebrae (C6 to C8), especially those fused (Fig. 2 - B), seems to be osteomyelitis caused by infections. Spinal TB (Pott's Disease) often involves two or more adjacent vertebral bodies that commonly occur in the lower thoracic and upper lumbar vertebrae in adults(Loscalzo et al., 2022). Lytic lesions affecting the vertebral bodies with resulting ankylosis, body collapse, and kyphosis, extraspinal unifocal lytic lesions with absence of new bone formation; single joint ankylosis, especially localized in the hip, knee, and wrist; and new bone formation on the internal surface of the ribs(Donoghue, 2016; Waldron, 2008).

Another infection that can involve the bones is brucellosis, which is a zoonotic bacterial infection caused by Brucella species, spreading from animals (Zhang et al., 2021). The most complicated forms are osteoarticular involvement, especially spondylitis and vertebral osteomyelitis(Corbel, 2006; Young, 1995). Skeletal involvement in brucellosis usually includes the lower thoracic and lumbar vertebrae and sacroiliac joint with one or more focal osteolytic lesions(Dj, 2003).

Bacterial osteomyelitis and mycotic infections can be differentiated from TB due to their lack of complete destruction of affected vertebral bodies(Dj, 2003; Resnick & Kransdorf, 2005).

However, in our radiological studies (Fig. 3), evidence of bone destruction, vertebral collapse, and subsequent new bone formation, which indicate infection involvement, is not observed. Additionally, the

location of more involvement in the cervical vertebrae and diffuse osteophytes and diffuse extraskeletal ossification cannot be justified with the mentioned infectious disease.

Sclerotic/Blastic Bone Lesions

In the radiological study of this case, some round, oval, and lobulated patchy sclerotic/blastic bone lesions were found in the spine and pelvis areas, which was a surprising issue. The relationship between these lesions and the clinically visible lesions should be determined to consider them as a set of findings of a single disease or if they are symptoms of two diseases occurring simultaneously in this person. The only disease that can justify both bone sclerotic lesions and hyperostosis and ossification in our case is POEMS syndrome.

Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes (POEMS) Syndrome

In POEMS, as a monoclonal plasma cell disorder, it represents osteosclerotic lesions in conventional radiographs in 97% of patients, while 47% have only sclerotic lesions. The pelvis, spine, ribs and proximal extremities were most often involved (Dispenzieri et al., 2003). It could justify hyperostosis in the present case.

Although POEMS syndrome is a good explanation for sclerotic bone lesions and, to a lesser extent, for hyperostosis and the overall condition of bone health in the case being studied (without evidence of malnutrition), it does not align with a debilitating multisystem disease like POEMS syndrome. This weakens the diagnosis in relation to the case. The more logical way to justify the findings of two hyperostosis and bone sclerotic lesions in the CT scanning images of one person (Fig. 3) is that the sclerotic lesions are another separate disease, the most common of which is known as bone tumor metastasis. The tumors that predominantly have osteoblastic metastasis include: prostate, carcinoid, small cell cancer, Hodgkin's lymphoma, medulloblastoma(Suer & Sehgal, 2021).

Among the mentioned tumors, only prostate cancer has a slower progression and longer survival. As a result, it has a higher chance of coinciding with other diseases and also provides less suffering compared to other tumors. This is more consistent with the bone condition of this case.

Bone is a common site of metastasis for carcinoma of the prostate, and radiographic appearance may show increased bone density or sclerosis. The sites most often involved are the vertebrae, proximal femur, sternum, proximal humerus, and skull(Loscalzo et al., 2022), which almost correspond to the sclerotic area of our case.

Diffuse Idiopathic Skeletal Hyperostosis (DISH)

DISH stands out as the most apparent alternative diagnosis for the examined case. The main characteristic of DISH disease is new bone formation, particularly in the anterolateral longitudinal

ligaments of the thoracic spine. However, the lumbar and cervical vertebrae are often affected by this process(Forestier & Lagier, 1971). In the examined case, the highest level of engagement was detected within the cervical vertebrae. Additionally, indications of involvement in the lumbar and thoracic vertebrae were also documented.

Usually, the posterior longitudinal ligament is not involved. In this case, aside from C6 to C8, the remaining posterior longitudinal ligament of the spinal region is not involved. DISH disease is characterized by the development of a candle flowing wax shape in front of the vertebrae, as described by Jacques Forestier and Rotès-Querol in 1950. Exactly like the characteristic observed in the vertebral regions of the studying sample in this research (Fig. 2. F).

In the study conducted by Holton et al. (2011), it was observed that DISH disease leads to the development of extraspinal entheseal ossification. Interestingly, the subject under investigation also exhibited a comparable extraspinal entheseal ossification (Fig. 2).

Ossification of ligament attachment points can lead to pseudo-fusion in the sacroiliac joint, such as in the case of the sacroiliac ligaments. This phenomenon can be observed through imaging techniques(Kiss, Szilagyi, et al., 2002). A similar occurrence was observed in the sacroiliac joint of the examined sample (Fig. 2. G & Fig. 3. B1-2).

Researchers utilize a principle or benchmark to assess or determine a certain matter. Various authors have put forth varying standards with respect to the diagnosis of DISH disease. The prevalent criteria outlined by (Resnick & Niwayama, 1976) delineate DISH characteristics in the following manner: initially, continuous ossification of the anterior longitudinal ligament, encompassing a minimum of four contiguous vertebrae in the thoracic area; the subsequent criterion involves the preservation of vertebral disc space due to the ossification process. The last criterion is the noninvolvement of the apophyseal and sacroiliac joint by features of inflammation(Resnick & Niwayama, 1976). Another criterion has been described by(Julkunen et al., 1975). Based on their criterion, bridging ossification involves two adjoining thoracic vertebrae. The remaining two criteria mentioned by (Julkunen et al., 1975) are similar to the criteria declared by(Resnick & Niwayama, 1976).

Furthermore, a separate study conducted by(Schmidt et al., 2002), revealed that the fusion of vertebrae occurs less frequently when compared to the criteria outlined by Donald Resnick and Niwayama (1976). According to them, there is a possibility of reducing the number of fused vertebrae at the early stage of DISH disease, which they refer to as "eDISH".

Based on the observations made on the CT scanning images, the intervertebral space in the fused area - detected from the ossification of the longitudinal ligaments - is still preserved; Correspondingly, by checking through instrumental imaging the apophyseal and sacroiliac joints do not show any involvement. This specification is consistent with most of the characteristics mentioned in (Resnick & Niwayama, 1976) and (Julkunen et al., 1975) criteria. However, the number of three fused vertebrae in the present research is different from the criteria of (Resnick & Niwayama, 1976) and corresponds to the

criteria provided by (Julkunen et al., 1975) in terms of number. On the other hand, if it is necessary to diagnose based on the criteria of(Resnick & Niwayama, 1976), the number of fused vertebrae fewer than four in the studied person can be assigned to the early stage of DISH disease (eDISH).

The only variation identified between the findings of the investigated case and the established criteria pertains to the location of complete fusion. In this instance, the fusion involves the three cervical vertebrae, whereas the existing criteria predominantly discuss fusion occurring in the thoracic vertebrae (Fig. illustrated in both radiology and photograph).

The current study sample aligns with demographic and biological characteristics, including age and sex, that are consistent with DISH disease, suggesting a higher likelihood compared to other differential diagnoses outlined in Table (1 & 2).

The etiology of DISH can be related to obesity and consequently type 2 diabetes(Hajkova et al., 1965; Inamasu et al., 2006; Julkunen et al., 1966). Hence, an investigation was conducted on the symptoms of diabetes in the excavated individual. Upon assessing the completeness of the skeletal structure, there was no indication of limb amputation resulting from diabetes. Conversely, the individual exhibited adequate bone density, indicating the absence of significant distress caused by malnutrition and reduced bone density associated with severe diabetes. Consequently, the current specimen does not align with the diagnosis of severe type 2 diabetes, although the possibility of mild type 2 diabetes and early stages of the condition cannot be completely disregarded.

Conclusion

There are several reasons based on which it can be concluded that the individual was suffering from DISH disease rather than other diagnoses. The current case is more likely to be associated with DISH disease rather than other related differential diagnoses, considering demographic and biological factors such as age (above 40 years old), sex (male), and race (Caucasian).

The studying sample displays several characteristic features of DISH, such as the candle-like flow of wax down the spine, ossification of paravertebral ligaments, increased thoracic vertebrae kyphosis, absence of vertebral skip lesions, hyperostosis in the attachment sites of the ilium tendons, diffuse bilateral extra spinal hyperostosis, and sternal ankylosis resulting from cartilage ossification of the first right rib to the sternal manubrium. Furthermore, the presence of hyperosteosis in the anterolateral longitudinal ligaments of the cervical vertebrae, rather than the thoracic vertebrae, does not exclude the potential diagnosis of DISH disease in the patient.

Radiographic examinations reveal that, with the exception of the C6 to C8 vertebrae, the posterior longitudinal ligament remains unaffected. Furthermore, the presence of comparable extraspinal entheseal ossification and pseudo-fusion in the sacroiliac joint directs attention towards DISH as the more likely diagnosis, as opposed to alternative conditions.

Hence, the existence of intervertebral space within the fused region leads to the opposition of infectious ailments like TB. Additionally, despite AS disease and osteoarthritis being the closest differential diagnoses in the current sample, the presence of thick spinal flowing osteophytes, extensive extraspinal enthesopathy, and the lack of inflammatory involvement evidence of the apophyseal and sacroiliac joints lead to the preference of DISH diagnosis over AS. Moreover, engagement in joint distant areas of the bone cartilage junction, including the tibial tubercles and calcaneal spur(Nascimento et al., 2014; Vaishya et al., 2017), indicates a diagnostic inclination towards DISH rather than osteoarthritis.

Therefore, according to the most common criteria, it can be concluded that the individual being examined either had DISH disease or was in the early stage of DISH known as eDISH due to the gradual fusion of vertebrae.

In addition, some round, oval, and lobulated/spotted sclerotic/blastic bony lesions were observed in most of the spinal bodies & appendages and in the pelvis on CT scan images, suggestive of metastatic osteoblastic tumors; at the top of it; prostate and with less prevalence; carcinoid, small cell lung cancer, Hodgkin lymphoma, medulloblastoma. The existence of such a process shows that the mentioned person, in addition to DISH, was suffering from another disease, which probably caused the death of this person due to cell metastasis in the whole body.

Declarations

Author Contribution

A. Mohammad Reza Eghdami: Bone excavator and extractor, responsible for studying the osteological factors of the sample, writing reports, and coordinating the collected materials for possible differential diagnoses. 1- Corresponding AuthorB. Majid Gholamzadeh Roudbordeh: Internist, colleague, and main consultant for the current study.C. Maryam Bozorgnia: Professional radiologist for the current study, providing diagnoses based on radiological images and CT scans.D. Internist, endocrinologist, and consultant specializing in differentials related to glands.E. Habib Zaieni: Rheumatologist and project consultant.

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Figures

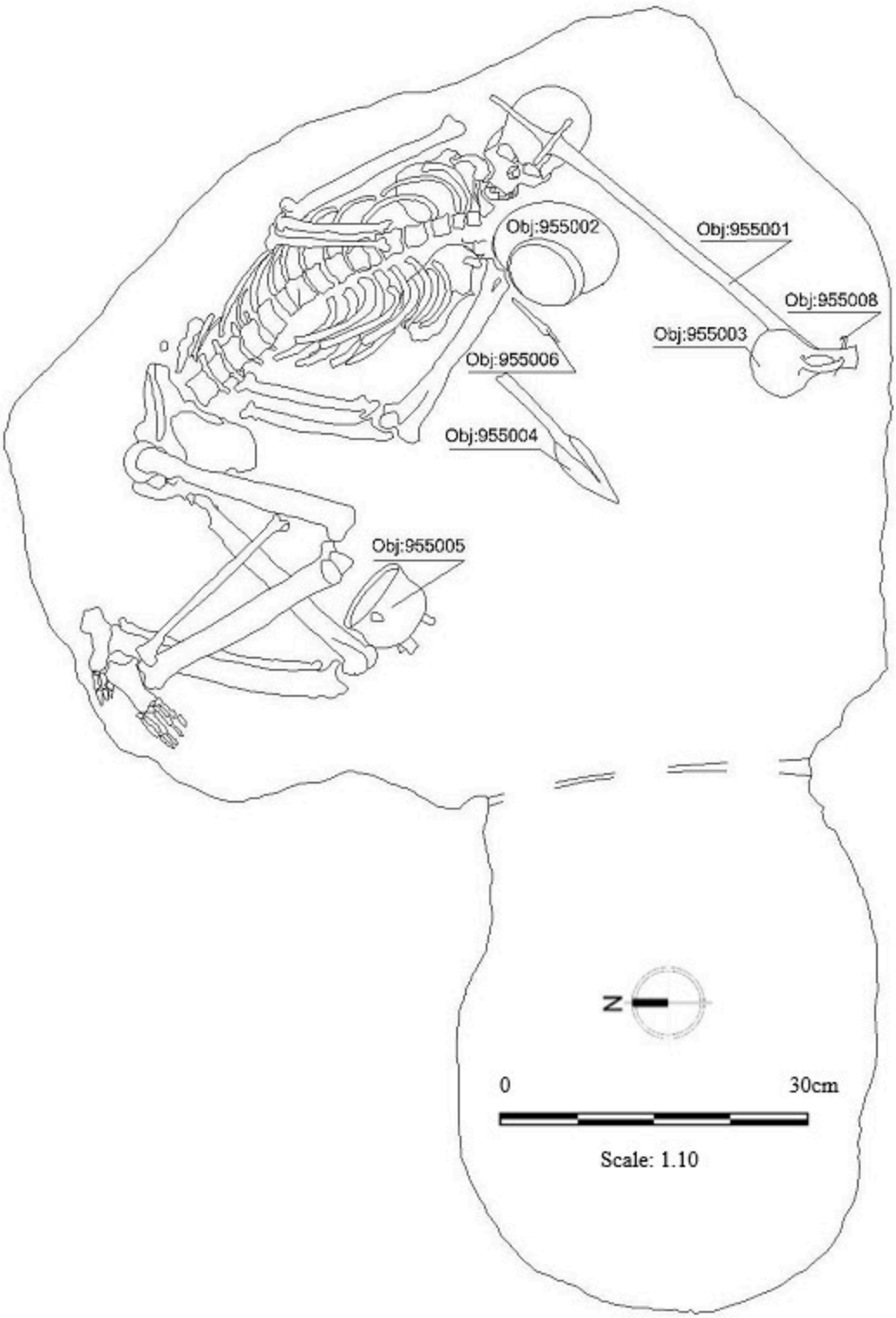

Figure 1

The situation and manner of burial of the person discovered from trench 9501, crypt grave 95501
Drawing by: Reza Shiargar

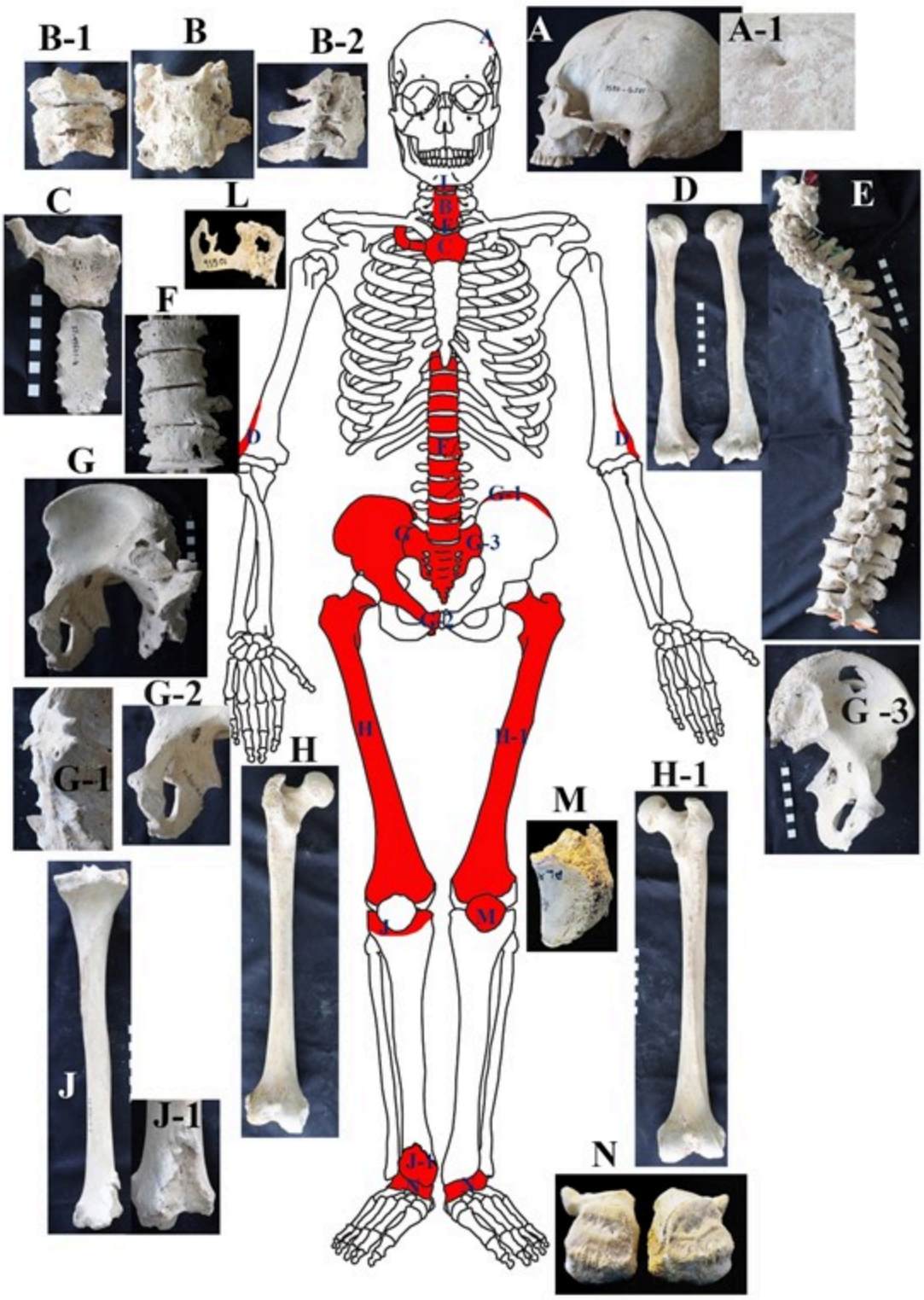

Figure 2

The excavated skeleton displays symptoms that are indicative of the affected organs, with the suspected parts highlighted in red on the accompanying graphic image. Photography & drawing by: Mohammad Reza Eghdami.

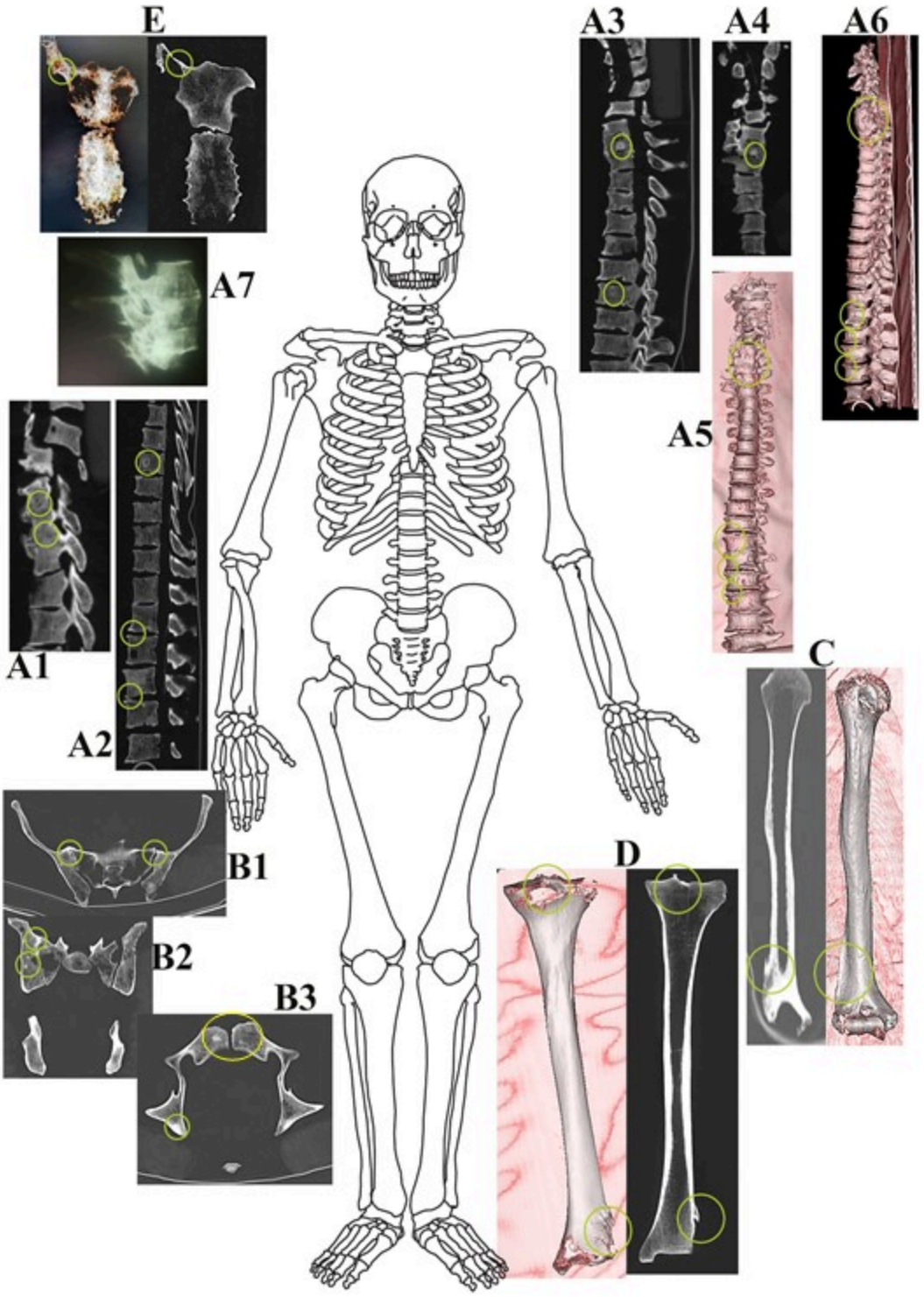

Figure 3

Radiological findings (CT scan & X-ray) are used to obtain a precise diagnosis of the disease. The yellow circle shows the involved part of the bone. Imaging by Maryam Bozorgnia; Drawing by: Mohammad Reza Eghdami.