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Abstract

Objective: To evaluate and differentially diagnose erosive skeletal lesions located on multiple joints of an individual archaeologically recovered in 2017. Materials: Skeletal remains of a well-preserved skeleton dating to the 12th-13th centuries from the Medieval church of San Biagio in Cittiglio (Varese, northern Italy). Methods: Macroscopic and radiographic imaging. Results: Erosive marginal symmetrical lesions are present on the metatarsophalangeal, metacarpophalangeal and interphalangeal joints of an adult male, aged 55-75 years. Osteolytic changes, in the form of pocket erosions, surface resorptions, and pseudocyst formations, are also macroscopically observed on some carpal and tarsal bones and on several large peripheral joints. Conclusions: A careful differential diagnosis of the lesions and their macroscopic and radiological appearance are suggestive of a case of rheumatoid arthritis-like polyarthropathy. Significance: This case contributes to the debate regarding the antiquity of erosive polyarthropathies, providing additional evidence for the existence of these diseases in the Old World prior to the discovery of the Americas. Limitations: Small sample size limits the discussion of the scope of the disease in antiquity. Suggestions for Further Research: This case highlights the need for further macroscopic, radiographic, and biomolecular studies of pre-modern European skeletal samples to investigate the hypothesized pre-existence of these pathological conditions in Europe prior to 1492.

Keywords	Erosive polyarthropathy; Rheumatoid-like arthritis; Remission phase; Osteoarthritis; Northern Italy; Middle Ages

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We are sending herewith a manuscript entitled: **"A case of erosive polyarthropathy from Medieval northern Italy (12th-13th centuries)"**, which we should like to submit for publication.

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Thank you for your time and assistance

Kind regards,

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Dear Editors,

We have followed the editor’s suggestion, shortening and revising the manuscript.

Sincerely,

Chiara Tesi

A case of erosive polyarthropathy from Medieval northern Italy (12th-13th centuries)

ABSTRACT

Objective: To evaluate and differentially diagnose erosive skeletal lesions located on multiple joints of an individual archaeologically recovered in 2017.
Materials: Skeletal remains of a well-preserved skeleton dating to the 12th-13th centuries from the Medieval church of San Biagio in Cittiglio (Varese, northern Italy).
Methods: Macroscopic and radiographic imaging.
Results: Erosive marginal symmetrical lesions are present on the metatarsophalangeal, metacarpophalangeal and interphalangeal joints of an adult male, aged 55-75 years. Osteolytic changes, in the form of pocket erosions, surface resorptions and pseudocyst formations, are also macroscopically observed on some carpal and tarsal bones and on several large peripheral joints,
Conclusions: A careful differential diagnosis of the lesions and their macroscopic and radiological appearance are suggestive of a case of rheumatoid arthritis-like polyarthropathy.
Significance: This case contributes to the debate regarding the antiquity of erosive polyarthropathies, providing additional evidence for the existence of these diseases in the Old World prior to the discovery of the Americas.
Limitations: Small sample size limits discussion of the scope of the disease in antiquity.
Suggestions for Further Research: This case highlights the need for further macroscopic, radiographic, and biomolecular studies of pre-modern European skeletal samples to investigate the hypothesized pre-existence of these pathological conditions in Europe prior to 1492.

Keywords: Erosive polyarthropathy, Rheumatoid-like arthritis, Remission phase, Osteoarthritis, Northern Italy, Middle Ages

Abbreviations: AS, ankylosing spondylitis; DIP, distal interphalangeal joint; EOA, erosive osteoarthritis; OA, osteoarthritis; PIP, proximal interphalangeal joint; PsA, psoriatic arthritis; RA, rheumatoid arthritis; ReA, reactive arthritis; SIJ, sacroiliac joint; SpAs, spondyloarthropathies

1. Introduction

In the field of paleopathology, there are many limitations associated with the diagnosis of rheumatoid arthritis (RA) in skeletal remains. This is due, in part, to the difficulty in applying clinical tests and diagnostic methods to the study of skeletal remains. Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease characterized by synovitis and destruction of joints that leads to severe disability (Aletaha et al., 2010). ~~The disease produces symmetric erosive lesions in both small and large joints that initially develop in the feet and/or hands simultaneously, and then spread to the other joints in subsequent years after the onset of the disease (Van der Heijde, 1995).~~ The etiology of RA is uncertain, but multiple genetic (~~Fontecchio et al., 2006;~~ Fontecchio et al., 2007; Fornaciari et al., 2012) and environmental factors have been associated with its development (Deane et al., 2017). The incidence of RA among modern populations has been reported to vary between environments and geographic areas. A recent study has investigated the epidemiology of the disease in the Italian peninsula (Rossini et al., 2014), finding a RA incidence of 35/100.000, with a peak during the eighth decade of life and a prevalence for the female sex, which tends to be similar to that of males during later life stages.

A topic under intense debate in the scientific community is the presence of RA in the Old World before 1492. Based on the first early robust description of this pathology by Landré- Beauvais in 1800, supported by the apparent absence of the disease in osteoarchaeological reports, it was suggested that rheumatoid arthritis was of recent origin (Short, 1974). Then, on the basis of the increasing number of studies conducted on archaeological samples in the USA and Europe during the 1980s (Rogers et al., 1981; Thould and Thould, 1983; Bennike, 1985; Leden et al., 1988; Kilgore, 1989), and the wider number of paleopathological cases among Pre-Columbian American populations compared to those found in Europe, researchers hypothesized that the disease had a New World origin (Rothschild et al. 1988; Woods and Rothschild, 1988; Rothschild and Woods 1990; Buchanan, 1994). However, in the last few decades, new paleopathological cases dating to the period prior to the European discovery of the Americas have multiplied in Europe and Asia (Hacking et al., 1994; Blondiaux et al., 1997; ~~Clavel et al., 1999;~~ Inoue et al., 1999; Kacki, 2012; Mckinnon et al., 2013; Mays et al., 2016) Unfortunately, the majority of cases reported date to the Medieval and Post-Medieval periods, leading to the uncertainty of the antiquity of the disease in the different regions of Europe.

Here, we present a case of erosive polyarthropathy in a medieval elderly individual whose lesions are suggestive of a diagnosis of RA-like disease. This case contributes to the debate on the antiquity of this disease, as it provides additional evidence of its presence in Europe before the European discovery of the Americas.

2. Materials and methods

The medieval church of San Biagio in Cittiglio (Varese, northern Italy) has been under investigation since 2006 ~~as part of a project on this historic building and the archaeological~~

~~stratigraphy of the site~~. The excavated area revealed 71 burials and 3 ossuaries located within five successive archaeological layers dating from the 11th to 16th centuries. The skeleton under study (T.052, SU 353) was located immediately outside the church, oriented W-E ~~with the head to west~~ and, according to the archaeological stratigraphy, dates ~~to the Medieval period~~ to a time between the 12th and 13th centuries. The skeleton is well preserved and most anatomical parts are represented: the bones present and those displaying erosive lesions are shown in Figure 1.

Sex was determined on the basis of the morphological features of the *os coxae* (Phenìce, 1969; Acsadi- Nemeskéri, 1970; Bruzek, 2002) ~~and specifically of the ischio-pubic region~~. Age at death was assessed through degenerative changes of the auricular surface and pubic symphysis (Lovejoy et al., 1985; Brooks and Suchey, 1990), sacrum (Passalacqua, 2009), and of the auricular surface and acetabulum (Rougé-Maillart et al., 2009). Stature was calculated using the formulae for white males from Trotter and Gleser (1958).

Every bone was examined under good light using a magnifying lens; furthermore, radiographic examination was conducted on the bones that displayed the more evident lesions. For X-ray and CT examinations, conventional medical radiological equipment was used (GE Healthcare Revolution-GSI 128 Layers). Imaging parameters were as follows: 100 kV, 80 mA. The slice thickness used was 2.00 mm.

For the description of the resorptive lesions, the criteria proposed by Blondiaux et al. (1997: 492) was employed to score their position, shape, size (small 1 - 3 mm, medium 3 - 5 mm and large > 5 mm in diameter), and depth (superficial 1 – 2 mm, deep 2 – 5 mm and cystic > 5 mm).

The Data Collection Codebook by Steckel et al. (2005) was employed to record the extent of osteoarthritis of the appendicular skeleton, scoring the presence of osteophytes, changes to the joint surface contours, eburnation of the articular surfaces, and degeneration of the intervertebral joints.

3. Results

Individual T.052 was a male aged 55-75 years, measuring approximately 165 cm tall. The skeleton exhibits many symmetrical and bilateral ~~resorptive~~ erosive lesions in the peripheral and marginal areas of the small joints of hands and feet, and also of major joints, such as the shoulder, elbow and hip (Fig. 1). Involvement of subchondral bone in the extremities is never observed, while the synovial membrane-lined bone space is most commonly affected. The erosive lesions observed are roughly circular or elliptical in shape, ranging in size from pits or small pinholes, giving the bone a “porous” appearance, to larger “scooped” pits, of greater depth (> 5 mm). The majority of lesions penetrate deeply into the bone tissue, displaying cortical destruction and undercut edges, with either sharp or rounded margins and smooth floors. ~~The bone changes are located in the periarticular area of joints, predominantly affecting the appendicular skeleton (Figs. 2-6).~~

As for the macroscopic distribution of the lesions (Table 1), in the hands there is evidence of erosive arthropathy in the proximal end of the right first metacarpal (Fig. 2A), in the right and left second metacarpal heads, on the margins of the distal articular surfaces of the left third proximal phalanx (Fig. 2C), of the left third interproximal phalanx (Fig. 2B), and of the right fourth

interproximal phalanx; on carpal bones, bony changes are observed in the right hamate (Fig. 2D) and triquetral. Lesions are also seen symmetrically in the feet, on the medial side of the right and left first metatarsal heads (Fig. 3A), in the margin of the distal articular surface of the left first proximal phalanx (Fig. 3B), and laterally in the proximal end of the right second metatarsal (Fig. 3C); in the tarsal bones, erosive areas are observed in the left and right cuboids.

In the major joints, polyarthritic signs are observed on the bones of the shoulder girdles: both clavicles are affected by resorptive changes on the margins of the acromial ends; the right scapula presents many large deep lesions around the margin of the glenoid cavity (Fig. 4C). Both humeral heads are affected by many small areas of resorption (Figs. 4-5A,B), superficial erosive lesions, and some confluent lesions located around the supero-anterior and the dorso-lateral margins of the articular surfaces, and within the intertubercular grooves. Some erosive lesions are located on the lesser and greater tuberosities. On the left humerus, a deep circular lesion is present on the lateral peripheral area of the capitulum (Fig. 5C). On the right *os coxae*, one large circular cystic cavity with sharp margins and a smooth floor is observed under the posterior cornus of the articular surface of the acetabulum (Fig. 6).

In the axial skeleton, there are minor bony resorptive changes: the manubrium of the sternum is affected by small deep circular resorptive lesions on the margin of the left clavicular notch. The cervical region of the vertebral column displays bony fusion of the third and fourth cervical vertebrae, with complete filling of the intervertebral space by the deposition of irregular bone (Fig. 7A); also, the zygapophyseal joints are ankylosed (Fig. 7B), while ligamentous ossification or osteophytic bridging are not present. The sub-cervical region of the vertebral column is only marginally involved: one deep circular area of resorption is located on the margin of the right transverse costal facet of the first thoracic vertebra. ~~Each lesion is described in detail in Table 1.~~

X-ray and Computed Tomographic (CT) examinations reveal evidence of reduced bone density, with radiolucent areas observed in the upper appendicular skeleton (Fig. 8). The extremities display a decrease of cancellous bone and some radiologically visible thinning with “dashed” interruptions of the cortical bone, along with points of greater radiolucency (dot-and-dash appearance). The erosive lesions observed on dry bones are recognizable on radiographic images as radiolucent shadows with slightly defined edges, or with a thin outer radiopaque border. Furthermore, CT-scans reveal the existence of periarticular internal erosive lesions that were not visible macroscopically. Two circular subcortical erosive lesions are found, respectively, at the medial and lateral margins of the base of the fourth and fifth interproximal phalanges of the right hand (Fig. 9B). Other lesions include a small circular subcortical lesion at the lateral margin of the base of the left third proximal phalanx, and an elliptical subcortical resorptive lesion along the proximal edge of the left hamate body. In the feet, particularly in the metatarsal heads, lesions are macroscopically identifiable, and include circular and irregularly-shaped subcortical lesions of variable dimensions, permitting observation of the extent and the internal development of the erosive process (Fig. 10A-F).

The radiograph of cervical vertebrae C3 and C4 shows reduction of the intervertebral joint space, while joint margins of the two individual vertebrae are still visible as well-defined radiopaque lines (Fig. 11).

Areas of calcified nodules and plaques of consolidated new bone formation are observed in several

areas of the diaphysis of the tubular bones of the hands and feet (Figs. 2 and 3). These outgrowths, in the form of nodular excrescences of lighter colour, are located on the medial and lateral sides of the shafts and in marginal areas of joints, even in some of the bones affected by erosive lesions. The calcifications do not overlap the erosive lesions.

Osteoarthritis (OA) is diffusely spread throughout the entire skeleton, with marginal lipping of most articular surfaces, and osteophyte formation and eburnation in the most severe cases. The appendicular skeleton shows generalized severity changes of stages 2-3. Moderate degeneration (stage 2) is observed in the preserved bones of hands and feet, except for the first right metacarpal, which presents more severe changes to the proximal joint contour (stage 3), including heavily polished and grooved eburnation on the carpal surface. More moderate signs are visible at both the metatarso-sesamoid joints. Extensive lipping and osteophytes are seenon both the shoulder and knee joints (stage 3), with severely flattened areas of eburnation on the medial condyles of the left femur and tibia. Moderate signs are also present in both hip joints (stage 2), with small polished areas of eburnation. A unilateral bony ankylosis of the right antero-superior sacroiliac joint is also observed: the fusion is shown to be para-articular, occurring via an anterior "bridging-osteophyte" (Resnick and Niwayama, 1988), while there is no evidence of intra-articular ankylosis. ~~The bony bridge appears to have been broken during the excavation, causing the separation of the bones, but the fusion of the two elements is recognizable due to the lighter colour of the break compared to the surrounding cortical bone.~~

The vertebral column exhibits generalized stage 3 degeneration, with extensive osteophyte formation and several curved projecting spicules, especially in the lower thoracic and lumbar regions of the vertebral column. The vertebrae show occasional asymmetrical changes due to the presence of slight degenerative scoliosis affecting the cervical, thoracic and lumbar regions, with at least three compensatory curves associated with a modest mid-thoracic kyphosis. Some signs of eburnation are also present on several zygapophyseal joints and vertebral bodies of the vertebral column, especially in the atlanto-odontoid joint. Schmorl's nodes are present in thoracic (n=5) and lumbar vertebrae (n= 3).

4. Discussion

The skeleton of T.052 shows evidence of symmetrical, bilateral polyarthritis, with erosive marginal lesions (affecting the so-called "bare areas" (Martel et al., 1965)), diffuse juxta-articular osteopenia and cortical thinning; bony changes predominantly involve the appendicular skeleton and extremities and the axial skeleton, to a lesser extent. To determine the specific type of polyarthropathy, a detailed differential diagnosis of inflammatory diseases of joints is essential. ~~For the interpretation of the other lesions observed in individual T.052, a variety of disease manifestations must be considered, which make the differential diagnosis challenging.~~

For an accurate differential diagnosis of the polyarthritis present in T.052, osteoarthritis (OA), erosive osteoarthritis (EOA), gout, arthropathies belonging to the group of seronegative spondyloarthropathies (SpAs), such as ankylosing spondylitis (AS), psoriatic arthritis (PsA) and reactive arthritis (ReA), and rheumatoid arthritis (RA), must be taken into consideration.

~~A diagnosis of OA may be dismissed due to the presence, location and distribution of erosive lesions in T.052, which are not found in the clinical presentation of OA. Chronic osteoarthritis can be excluded because bone proliferation is more common than resorption in the disease (Waldron, 2009).~~ In OA, osteopenia and marginal erosions are not present (Jacobson et al., 2008), whereas osteoarthritic cysts mainly occur in relation to weight-bearing joints (Ondrouch, 1963; Kosuge et al., 2007), and frequently develop on opposing sides of the same joint ("kissing cysts", as described in Landells, 1953). All these features are absent in the current case.

EOA presents both proliferative and erosive changes of the proximal and distal interphalangeal joints ~~(PIPs and DIPs)~~ of the hands, while other joints are rarely affected (Ehrlich, 2001). In addition, this arthropathy is asymmetric and may lead to bone ankylosis (Punzi al., 2004). ~~The erosive lesions initially appear centrally in the joints, producing two convex lesions on the surfaces that, when associated with marginal sclerosis and osteophytes, lead to a "seagull-wings" appearance, which is distinctive evidence of the disease (Martel et al., 1980; Jacobson et al., 2008; Waldron, 2009).~~ In our case, due to the lack of these combined proliferative and erosive lesions, and the different distribution, this possibility can be ruled out.

Gout ~~is a metabolic disorder in which urate crystals accumulate in granulomatous masses~~ produces arthritic erosion of the joints of the hands and feet, with large lytic lesions located both intra- and para-articularly. These erosive lesions usually appear "punched out", often show signs of remodeling, and are associated with new peri-lesion dense bone accretion, visible radiographically (Rothschild and Heathcote, 1995). The lesions, usually monoarticular, can be polyarticular, but are asymmetric~~, marked by sclerotic borders, and display overhanging margins oriented along the long axis of the bone. Osteoporosis does not occur (Waldron, 2009: 67-70)~~. These features are not present in the skeleton from Cittiglio, since here, the polyarticular resorptive lesions show a clear symmetrical distribution. ~~Thus, a diagnosis of gout can be rejected.~~

SpA are a group of inflammatory joint diseases that share many clinical features, especially asymmetrical peripheral joint involvement, vertebral fusion and enthesitis. ~~Distinguishing between the pathological signs of the diseases belonging to this group is only occasionally possible in very severe or advanced cases (Rogers et al., 1987).~~

AS is the best known of the group, having symmetrical ankylosis of the sacroiliac joints, vertebral new bone formation and fusion as common features (Waldron, 2009: 57-60). The vertebral bodies begin to fuse from the lumbar region upwards, with calcification of ligaments and formation of vertebral syndesmophytes, until the ultimate appearance of "bamboo spine" is achieved, with

vertebral body squaring and no skip lesions (Roberts and Manchester, 2005: 158-159). Osseous erosive lesions of the hands and feet bones are asymmetrically distributed and associated with periarticular bone proliferation, producing poorly defined and fuzzy osseous contours on X-ray (Resnick and Kransdorf, 2004). In the current case, the lesions observed show a symmetrical distribution, while bone proliferation is slight. Moreover, the skeleton shows a fusion between two cervical vertebrae, but there is no evidence of syndesmophytes or vertebral body squaring, while the thoracic and lumbar regions are not affected, permitting the rejection of a diagnosis of AS.

PsA ~~is a joint disorder that develops from primary psoriatic autoimmune skin disease: it~~ involves the synovial joints, either monoarticularly or polyarticularly, and is generally asymmetrical, but it may also be symmetrical, thus resembling RA (Hagihara et al., 2015). The resorptive lesions are best seen in the DIP joints of the hands, proceeding from the joint margin to the centre~~, with shortening of the phalanx producing the so-called "cup-and-pencil" deformities visible on X-rays.~~ Hallmarks of the disease are bilateral sacro-iliitis and vertebral fusion by paravertebral bony bridges, joint ankylosis, generalized enthesitis, and proliferative new bone deposition on the shafts and around eroded joints (Waldron, 2009: 62-65) in the form of increased sub-periosteal density of the cortex that widens the diaphyses (Forrester and Kirkpatrick, 1976). Moreover, erosive lesions in PsA are often less sharply defined due to concomitant juxta-articular new bone apposition (Martel et al., 1980), sometimes producing the "ivory phalanx" sign (Sudoł-Szopińska et al., 2016). In the skeleton under study, there is no evidence of commonly occurring PsA traits~~, such as diaphyseal cortical widening, inflammatory sacro-iliitis, bony ankylosis, paravertebral fusion or generalized enthesitis, and erosive lesions occurring diffusely and symmetrically in areas not associated with entheses (McGonagle, 2005; Hagihara et al., 2014).~~ Hence, this diagnosis may be excluded.

In ReA ~~is an inflammatory condition, known as Reiter's syndrome, which is a combination of symptoms that are known to be stimulated by a variety of infections.~~ joint symptoms include asymmetric fusion of the sacroiliac joint (SIJ), vertebral fusion with paravertebral bridging with skip lesions (Cawley and Paine, 2015), extra-vertebral erosive changes, enthesopathy, and periosteal new bone growth on shafts and around joints, especially in the lower limbs. Indeed, in ReA the erosive lesions develop asymmetrically, the feet, ankle and knee being especially involved (Rogers et al., 1987). Vertebral bridges are formed in paravertebral locations as bony outgrowths, beginning from the lower thoracic or upper lumbar regions and proceeding upwards, with normal vertebrae being interspersed between fused ones (Waldron, 2009: 61). The absence in the present case of paravertebral bridges or intra- articular fusions of the SIJ ~~which are common features of ReA,~~ rules out this disease.

RA is a generalized inflammatory disease of connective tissues that develops into a chronic deforming arthritis, especially of the hands and feet. The chief lesion is a synovitis, with intensive production of protoinflammatory cytokines and antibodies that stimulate osteoclastic resorption of synovial membrane-lined bone, while inhibiting bone tissue repair (Martel et al., 1965). The disease is clinically recognized as a symmetrical polyarthritis involving almost the entire appendicular skeleton (Rothschild et al., 1990), with erosive lesions located initially in the marginal area of joints and, with the sequelae of the pathology, also involving the intra-articular space, eventually producing joint ankylosis in the most severe cases. The axial skeleton is affected to a lesser extent: the cervical

spine is known to be generally involved in rheumatoid spondylitis (~~Shichikawa et al., 1978;~~ Rogers et al., 1987; Bywaters, 1981; ~~Mallory et al., 2014;~~ Hacking et al., 1994), possibly producing fusion of the upper cervical vertebrae that, according to Jensen and Steinbach (1977), occurs in about 17% of RA patients. Juxta-articular osteopenia, resulting from erosive lesions and osteoclast activation, is another common feature of the disease (Aufderheide and Rodríguez-Martín, 1998; Roberts and Manchester, 2005; ~~Waldron, 2009;~~ Biehler-Gomez and Cattaneo, 2018). Necessary for the diagnosis is the presence of bones of hands and feet that exhibit early manifestations of the disease (Waldron, 2009). In skeleton T.052 ~~from Cittiglio~~, the pattern and distribution of erosive lesions, characterized by periarticular erosions and diffuse trabecular porosis, and the absence of distinctive features at the major sites of predilection of the other disorders considered, suggest rheumatoid arthritis as a possible candidate (Table 2). Nevertheless, some evidence found in this case leaves the diagnosis uncertain. Thus, in the absence of more confirmatory tests and diagnostic methods, a diagnosis of a more generic RA-like polyarthropathy can be suggested. ~~A summary of the wide range of evidence and features taken into consideration for the differential diagnosis is listed in Table 2.~~

The ankylosis of the third and fourth cervical vertebrae, but with retention of the ring apophysis (Figs. 7, 11), appears not to be related to a congenital cause, as would be the case in Klippel-Feil syndrome (Fernandes and Costa, 2007), but more likely to be the clinical appearance of RA. Involvement of the cervical trait ~~region of the vertebral column~~, with erosive lesions of disc space and intervertebral and facet joint ankylosis, has been reported by several authors, both in clinical (~~Jensen and Steinbach, 1977;~~ Shichikawa et al., 1978; ~~Bywaters, 1981;~~ Mallory et al., 2014; ~~Calleja and Hide, 2015;~~ Gillick et al., 2015) and archaeological findings (Hacking et al., 1994).

One lytic lesion in the transverse process of T1, on the margin of the costovertebral facet, was also noted. This finding would be contra-indicative for a diagnosis of RA. ~~the manifestations of which are normally thought to exclude axial involvement (Rothschild, 1990; Waldron, 2009), except for the cervical region of the vertebral column.~~ Nevertheless, numerous clinical and archaeological findings report axial involvement with erosive lesions and fusion in sub-cervical regions ~~of the vertebral column~~ (~~Lorber et al., 1961; Lawrence et al. 1964; Shichikawa et al., 1978;~~ Heywood and Meyers, 1986; Hacking et al., 1994; Inoue et al., 1999; Kawaguchi et al., 2003; Lee et al., 2010; Kim et al., 2011). Therefore, the slight involvement of the thoracic region ~~of the vertebral column~~ in the present skeleton does not exclude RA as a possible diagnosis.

In our case, evidences of sub-periosteal new bone apposition are observed ~~in the present skeleton~~ in the form of several calcified nodules and consolidated bone formation on long bone diaphyses and around the joints displaying erosive lesions. These findings are usually considered to be contradictory to the diagnosis of RA (although this phenomenon is attested to occur in a small number of cases, as noted by Dilsen et al., 1962), and suggest, rather, the presence of PsA or AS. Nevertheless, sub-periosteal calcifications have also been found in connection with connective tissue degeneration of the periosteum due to the aging process, as reported in clinical data (Zagba-Mongalima et al., 1988). In the present individual, these bony outgrowths are located near the joint sites but do not overlap with the observed periarticular erosive lesions, and thus must not be confused with the rugosities and bony ossifications of the tendons of muscles attachments (~~as reported by~~ Touraine et al., 2014). Further, these formations are milder than those one would expect in cases of SpA, since there is no

evidence of substantial new layer apposition with diaphyseal widening and thickening of the cortex, or presence of the ivory phalanx sign. Therefore, ~~regarding the evidence of sub-periosteal apposition,~~ a hypothesis of periosteal degeneration associated with the aging process is plausible.

Osteoporosis is evident from the trabecular thinning and rarefaction visible as radiolucent areas on radiographic images (Fig. 8). This finding has sometimes been considered diagnostic of RA (Rothschild et al., 1990; ~~Aufderheide and Rodríguez-Martín, 1998;~~ Roberts and Manchester, 2005; Waldron, 2009; Biehler-Gomez and Cattaneo, 2018), although it is probably non-specific evidence of the condition (as reported by Fletcher and Rowley, 1952).

In our case ~~from Cittiglio~~, the diagnosis is complicated by the mild manifestation of the lesions, which suggests a case of early onset pathology. The individual does not show severe destruction or ankylosis of joints, ~~nor evidence of extensive erosive destruction of long bone ends,~~ which can be diagnostic of advanced cases of RA (Inoue et al., 1999; Kim et al., 2011; Mckinnon et al., 2013). Previously identified cases of early stages of RA have been published in the paleopathological literature, showing similar patterns and distributions of lesions to T.052 (Bennike, 1985; Kilgore, 1989; Kacki, 2013).

The presence in this individual of some rounded borders of the lesions, visible macroscopically (Figs. 2D, 3B) and sclerosis visible radiographically (e.g. as shown by the arrow in Fig. 8), can be interpreted as a possible remission phase of the disease, which is reported to occur in 10-30% of cases (Waldron, 2009). According to Jensen and Steinbach (1977), the margins of the erosions are fuzzy and irregular during the acute phase and become smoother with the regression of the pathology. Rau (2006) reports that during inflammatory inactivity erosions go through healing, eventually developing recortication, filling and restoration. The erosions observed generally present rounded borders with sclerotic outlines visible on radiographic images, except for the lesions observed near the acetabulum (Fig. 6) and on the proximal end of the first right metacarpal (Figs. 2A, 9A), which show sharp cortical margins and no rounding of the rims. Moreover, one of the observed lesions presents apparent complete recortication at the margin of the distal articular surface of the left third interproximal phalanx and a loss of bone substance with the appearance of a circular cortical depression is observed (Fig. 2B). This lesion may be interpreted as a completely healed erosion due to the absence of exposed trabeculae and compact bone covering ~~(as described by)~~, while the others with rounded rims ~~according to the same reference,~~ may represent a phase in the healing process (Rau, 2006). Moreover, CT-scans of the joints involved permit observation of marginal sclerosis of most the erosive lesions (Figs. 9C, 10F), that supports a quiescent phase of the polyarthropathy.

The presence of co-existing osteophytic growths, joint surface pitting, areas of eburnation and joint surface contour changes recorded from moderate to severe stages, implies a co-morbid, generalized OA, co-existence that is reported by other authors in clinical (Jacob et al., 1986; Abbott et al., 1991), autopsy (Rothschild et al., 1990) and archaeological cases (Klepinger, 1972; Kilgore, 1989; Mckinnon et al., 2013). Generalized OA is compatible with the advanced age of the individual ~~since the degenerative process is commonly associated with aging~~. Furthermore, according to Ortner (2003), the superimposition of OA on pre-existing RA manifestations is common if joint mobility is maintained. With regard to the unilateral fusion of the sacroiliac joint, a degenerative interpretation is justified, since this type of ankylosis is reported in many studies of the aging process and weight

transmission at the SIJ in males (Resnick, 1977; Vogler et al., 1984; ~~Waldron and Rogers, 1990;~~ Parmar et al., 2003; Dar and Hershkovitz, 2006; Imamura et al., 2014; Pialat et al. 2016).

After a detailed differential diagnosis, by which the other possible inflammatory pathological conditions producing erosive features were discounted, the diagnosis of more generalized rheumatoid arthritis-like disease is hypothesized in this case, and possibly RA.

~~As suggested by the possible diagnosis, the skeleton presented here provides additional evidence for the existence of forms of RA-like erosive polyarthropathies in the Old World before the discovery of the Americas, and thus enters the debate on the origin and antiquity of these diseases. This case highlights the need for further studies of pre-modern European skeletal samples to investigate the hypothesized pre-existence of these pathological conditions in Europe before 1492, as previously suggested following the discoveries of other cases.~~

5. Conclusions

~~The skeleton from Cittiglio exhibits erosive polyarticular symmetrical lesions, localized to the marginal and peripheral area of smaller joints of the hands and feet and of some larger joints, including the shoulders, elbow and hip. The cervical region of the vertebral column is also affected as attested by the fusion of two vertebrae and one lesion in the thoracic trait. Sub-periosteal new bone formations are also observed on some hand and foot tubular bones and near some affected joints. After a detailed differential diagnosis, by which the other possible inflammatory pathological conditions producing erosive features were discounted, the diagnosis of more generalized rheumatoid arthritis-like disease is hypothesized in this case, and possibly RA. Although some evidence leaves such a definitive conclusion uncertain, taking into account the difficulties of diagnosing with confidence in absence of more specific clinical tests, this diagnosis remains the most probable, in the absence of the major lesions typical of the other erosive diseases.~~

~~The mild expression of the observed lesions, together with comparisons with more advanced manifestations reported in the literature, supports a case of an early onset of the disease. Finally, the patient seems to have experienced a disease remission phase. The presence of generalized changes of joint contour, with osteophytes, marginal lipping, and eburnation, suggests a co-morbid degenerative process, most likely linked to the older age of the individual.~~

The skeleton described here adds to the evidence for the existence of forms of RA-like polyartrhopathy in the Old World before the Modern Period. On the basis of this evidence and other already published cases, these diseases seem to have been present to some extent in Europe for a greater time than previously thought. Further investigations are needed to clarify the origin and spread of erosive polyarthropathies, as well as pathological variation in them through time to investigate the differences in the signs of disease between archaeological and modern clinical cases.

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A case of erosive polyarthropathy from Medieval northern Italy (12^{th}-13^{th} centuries)

ABSTRACT

Objective: To evaluate and differentially diagnose erosive skeletal lesions located on multiple joints of an individual archaeologically recovered in 2017.

Materials: Skeletal remains of a well-preserved skeleton dating to the 12^{th}-13^{th} centuries from the Medieval church of San Biagio in Cittiglio (Varese, northern Italy).

Methods: Macroscopic and radiographic imaging.

Results: Erosive marginal symmetrical lesions are present on the metatarsophalangeal, metacarpophalangeal and interphalangeal joints of an adult male, aged 55-75 years. Osteolytic changes, in the form of pocket erosions, surface resorptions and pseudocyst formations, are also macroscopically observed on some carpal and tarsal bones and on several large peripheral joints.

Conclusions: A careful differential diagnosis of the lesions and their macroscopic and radiological appearance are suggestive of a case of rheumatoid arthritis-like polyarthropathy.

Significance: This case contributes to the debate regarding the antiquity of erosive polyarthropathies, providing additional evidence for the existence of these diseases in the Old World prior to the discovery of the Americas.

Limitations: Small sample size limits discussion of the scope of the disease in antiquity.

Suggestions for Further Research: This case highlights the need for further macroscopic, radiographic, and biomolecular studies of pre-modern European skeletal samples to investigate the hypothesized pre-existence of these pathological conditions in Europe prior to 1492.

Keywords: Erosive polyarthropathy, Rheumatoid-like arthritis, Remission phase, Osteoarthritis, Northern Italy, Middle Ages

Abbreviations: AS, ankylosing spondylitis; DIP, distal interphalangeal joint; EOA, erosive osteoarthritis; OA, osteoarthritis; PIP, proximal interphalangeal joint; PsA, psoriatic arthritis; RA, rheumatoid arthritis; ReA, reactive arthritis; SIJ, sacroiliac joint; SpAs, spondyloarthropathies

1. Introduction

In the field of paleopathology, there are many limitations associated with the diagnosis of rheumatoid arthritis (RA) in skeletal remains. This is due, in part, to the difficulty in applying clinical tests and diagnostic methods to the study of skeletal remains.

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease characterized by synovitis and destruction of joints that leads to severe disability (Aletaha et al., 2010). The etiology of RA is uncertain, but multiple genetic (Fontecchio et al., 2007; Fornaciari et al., 2012) and environmental factors have been associated with its development (Deane et al., 2017). The incidence of RA among modern populations has been reported to vary between environments and geographic areas. A recent study has investigated the epidemiology of the disease in the Italian peninsula (Rossini et al., 2014), finding a RA incidence of 35/100.000, with a peak during the eighth decade of life and a prevalence for the female sex, which tends to be similar to that of males during later life stages.

A topic under intense debate in the scientific community is the presence of RA in the Old World before 1492. Based on the first early robust description of this pathology by Landré-Beauvais in 1800, supported by the apparent absence of the disease in osteoarchaeological reports, it was suggested that rheumatoid arthritis was of recent origin (Short, 1974). Then, on the basis of the increasing number of studies conducted on archaeological samples in the USA and Europe during the 1980s (Rogers et al., 1981; Thould and Thould, 1983; Bennike, 1985; Leden et al., 1988; Kilgore, 1989), and the wider number of paleopathological cases among Pre-Columbian American populations compared to those found in Europe, researchers hypothesized that the disease had a New World origin (Rothschild et al. 1988; Woods and Rothschild, 1988; Rothschild and Woods 1990; Buchanan, 1994). However, in the last few decades, new paleopathological cases dating to the period prior to the European discovery of the Americas have multiplied in Europe and Asia (Hacking et al., 1994; Blondiaux et al., 1997; Inoue et al., 1999; Kacki, 2012; Mckinnon et al., 2013; Mays et al., 2016) Unfortunately, the majority of cases reported date to the Medieval and Post-Medieval periods, leading to the uncertainty of the antiquity of the disease in the different regions of Europe.

Here, we present a case of erosive polyarthropathy in a medieval elderly individual whose lesions are suggestive of a diagnosis of RA-like disease. This case contributes to the debate on the antiquity of this disease, as it provides additional evidence of its presence in Europe before the European discovery of the Americas.

2. Materials and methods

The medieval church of San Biagio in Cittiglio (Varese, northern Italy) has been under investigation since 2006. The excavated area revealed 71 burials and 3 ossuaries located within five successive archaeological layers dating from the 11th to 16th centuries. The skeleton under study (T.052, SU 353) was located immediately outside the church, oriented W-E and, according to the archaeological stratigraphy, dates to a time between the 12th and 13th centuries. The skeleton is well preserved and most anatomical parts are represented: the bones present and those displaying erosive

lesions are shown in Figure 1.

Sex was determined on the basis of the morphological features of the *os coxae* (Phenìce, 1969; Acsadi- Nemeskéri, 1970; Bruzek, 2002). Age at death was assessed through degenerative changes of the auricular surface and pubic symphysis (Lovejoy et al., 1985; Brooks and Suchey, 1990), sacrum (Passalacqua, 2009), and of the auricular surface and acetabulum (Rougé-Maillart et al., 2009). Stature was calculated using the formulae for white males from Trotter and Gleser (1958).

Every bone was examined under good light using a magnifying lens; furthermore, radiographic examination was conducted on the bones that displayed the more evident lesions. For X-ray and CT examinations, conventional medical radiological equipment was used (GE Healthcare Revolution-GSI 128 Layers). Imaging parameters were as follows: 100 kV, 80 mA. The slice thickness used was 2.00 mm.

For the description of the resorptive lesions, the criteria proposed by Blondiaux et al. (1997: 492) was employed to score their position, shape, size (small 1 - 3 mm, medium 3 - 5 mm and large > 5 mm in diameter), and depth (superficial 1 – 2 mm, deep 2 – 5 mm and cystic > 5 mm).

The Data Collection Codebook by Steckel et al. (2005) was employed to record the extent of osteoarthritis of the appendicular skeleton, scoring the presence of osteophytes, changes to the joint surface contours, eburnation of the articular surfaces, and degeneration of the intervertebral joints.

3. Results

Individual T.052 was a male aged 55-75 years, measuring approximately 165 cm tall. The skeleton exhibits many symmetrical and bilateral erosive lesions in the peripheral and marginal areas of the small joints of hands and feet, and also of major joints, such as the shoulder, elbow and hip (Fig. 1). Involvement of subchondral bone in the extremities is never observed, while the synovial membrane-lined bone space is most commonly affected. The erosive lesions observed are roughly circular or elliptical in shape, ranging in size from pits or small pinholes, giving the bone a “porous” appearance, to larger “scooped” pits, of greater depth (> 5 mm). The majority of lesions penetrate deeply into the bone tissue, displaying cortical destruction and undercut edges, with either sharp or rounded margins and smooth floors.

As for the macroscopic distribution of the lesions (Table 1), in the hands there is evidence of erosive arthropathy in the proximal end of the right first metacarpal (Fig. 2A), in the right and left second metacarpal heads, on the margins of the distal articular surfaces of the left third proximal phalanx (Fig. 2C), of the left third interproximal phalanx (Fig. 2B), and of the right fourth interproximal phalanx; on carpal bones, bony changes are observed in the right hamate (Fig. 2D) and triquetral. Lesions are also seen symmetrically in the feet, on the medial side of the right and left first metatarsal heads (Fig. 3A), in the margin of the distal articular surface of the left first proximal phalanx (Fig. 3B), and laterally in the proximal end of the right second metatarsal (Fig. 3C); in the tarsal bones, erosive areas are observed in the left and right cuboids.

In the major joints, polyarthritic signs are observed on the bones of the shoulder girdles: both clavicles are affected by resorptive changes on the margins of the acromial ends; the right scapula

presents many large deep lesions around the margin of the glenoid cavity (Fig. 4C). Both humeral heads are affected by many small areas of resorption (Figs. 4-5A,B), superficial erosive lesions, and some confluent lesions located around the supero-anterior and the dorso-lateral margins of the articular surfaces, and within the intertubercular grooves. Some erosive lesions are located on the lesser and greater tuberosities. On the left humerus, a deep circular lesion is present on the lateral peripheral area of the capitulum (Fig. 5C). On the right *os coxae*, one large circular cystic cavity with sharp margins and a smooth floor is observed under the posterior cornus of the articular surface of the acetabulum (Fig. 6).

In the axial skeleton, there are minor bony resorptive changes: the manubrium of the sternum is affected by small deep circular resorptive lesions on the margin of the left clavicular notch. The cervical region of the vertebral column displays bony fusion of the third and fourth cervical vertebrae, with complete filling of the intervertebral space by the deposition of irregular bone (Fig. 7A); also, the zygapophyseal joints are ankylosed (Fig. 7B), while ligamentous ossification or osteophytic bridging are not present. The sub-cervical region of the vertebral column is only marginally involved: one deep circular area of resorption is located on the margin of the right transverse costal facet of the first thoracic vertebra.

X-ray and Computed Tomographic (CT) examinations reveal evidence of reduced bone density, with radiolucent areas observed in the upper appendicular skeleton (Fig. 8). The extremities display a decrease of cancellous bone and some radiologically visible thinning with "dashed" interruptions of the cortical bone, along with points of greater radiolucency (dot-and-dash appearance). The erosive lesions observed on dry bones are recognizable on radiographic images as radiolucent shadows with slightly defined edges, or with a thin outer radiopaque border. Furthermore, CT-scans reveal the existence of periarticular internal erosive lesions that were not visible macroscopically. Two circular subcortical erosive lesions are found, respectively, at the medial and lateral margins of the base of the fourth and fifth interproximal phalanges of the right hand (Fig. 9B). Other lesions include a small circular subcortical lesion at the lateral margin of the base of the left third proximal phalanx, and an elliptical subcortical resorptive lesion along the proximal edge of the left hamate body. In the feet, particularly in the metatarsal heads, lesions are macroscopically identifiable, and include circular and irregularly-shaped subcortical lesions of variable dimensions, permitting observation of the extent and the internal development of the erosive process (Fig. 10A-F).

The radiograph of cervical vertebrae C3 and C4 shows reduction of the intervertebral joint space, while joint margins of the two individual vertebrae are still visible as well-defined radiopaque lines (Fig. 11).

Areas of calcified nodules and plaques of consolidated new bone formation are observed in several areas of the diaphysis of the tubular bones of the hands and feet (Figs. 2 and 3). These outgrowths, in the form of nodular excrescences of lighter colour, are located on the medial and lateral sides of the shafts and in marginal areas of joints, even in some of the bones affected by erosive lesions. The calcifications do not overlap the erosive lesions.

Osteoarthritis (OA) is diffusely spread throughout the entire skeleton, with marginal lipping of most articular surfaces, and osteophyte formation and eburnation in the most severe cases. The appendicular skeleton shows generalized severity changes of stages 2-3. Moderate degeneration

(stage 2) is observed in the preserved bones of hands and feet, except for the first right metacarpal, which presents more severe changes to the proximal joint contour (stage 3), including heavily polished and grooved eburnation on the carpal surface. More moderate signs are visible at both the metatarso-sesamoid joints. Extensive lipping and osteophytes are seenon both the shoulder and knee joints (stage 3), with severely flattened areas of eburnation on the medial condyles of the left femur and tibia. Moderate signs are also present in both hip joints (stage 2), with small polished areas of eburnation. A unilateral bony ankylosis of the right antero-superior sacroiliac joint is also observed: the fusion is shown to be para-articular, occurring via an anterior "bridging-osteophyte" (Resnick and Niwayama, 1988), while there is no evidence of intra-articular ankylosis.

The vertebral column exhibits generalized stage 3 degeneration, with extensive osteophyte formation and several curved projecting spicules, especially in the lower thoracic and lumbar regions of the vertebral column. The vertebrae show occasional asymmetrical changes due to the presence of slight degenerative scoliosis affecting the cervical, thoracic and lumbar regions, with at least three compensatory curves associated with a modest mid-thoracic kyphosis. Some signs of eburnation are also present on several zygapophyseal joints and vertebral bodies of the vertebral column, especially in the atlanto-odontoid joint. Schmorl's nodes are present in thoracic (n=5) and lumbar vertebrae (n= 3).

4. Discussion

The skeleton of T.052 shows evidence of symmetrical, bilateral polyarthritis, with erosive marginal lesions (affecting the so-called "bare areas" (Martel et al., 1965)), diffuse juxta-articular osteopenia and cortical thinning; bony changes predominantly involve the appendicular skeleton and extremities and the axial skeleton, to a lesser extent. To determine the specific type of polyarthropathy, a detailed differential diagnosis of inflammatory diseases of joints is essential.

For an accurate differential diagnosis of the polyarthritis present in T.052, osteoarthritis (OA), erosive osteoarthritis (EOA), gout, arthropathies belonging to the group of seronegative spondyloarthropathies (SpAs), such as ankylosing spondylitis (AS), psoriatic arthritis (PsA) and reactive arthritis (ReA), and rheumatoid arthritis (RA), must be taken into consideration.

In OA, osteopenia and marginal erosions are not present (Jacobson et al., 2008), whereas osteoarthritic cysts mainly occur in relation to weight-bearing joints (Ondrouch, 1963; Kosuge et al., 2007), and frequently develop on opposing sides of the same joint ("kissing cysts", as described in Landells, 1953). All these features are absent in the current case.

EOA presents both proliferative and erosive changes of the proximal and distal interphalangeal joints of the hands, while other joints are rarely affected (Ehrlich, 2001). In addition, this arthropathy is asymmetric and may lead to bone ankylosis (Punzi al., 2004). In our case, due to the lack of these combined proliferative and erosive lesions, and the different distribution, this possibility can be ruled out.

Gout produces arthritic erosion of the joints of the hands and feet, with large lytic lesions located both intra- and para-articularly. These erosive lesions usually appear "punched out", often show signs of remodeling, and are associated with new peri-lesion dense bone accretion, visible radiographically

(Rothschild and Heathcote, 1995). The lesions, usually monoarticular, can be polyarticular, but are asymmetric. These features are not present in the skeleton from Cittiglio, since here, the polyarticular resorptive lesions show a clear symmetrical distribution.

SpA are a group of inflammatory joint diseases that share many clinical features, especially asymmetrical peripheral joint involvement, vertebral fusion and enthesitis.

AS is the best known of the group, having symmetrical ankylosis of the sacroiliac joints, vertebral new bone formation and fusion as common features (Waldron, 2009: 57-60). The vertebral bodies begin to fuse from the lumbar region upwards, with calcification of ligaments and formation of vertebral syndesmophytes, until the ultimate appearance of "bamboo spine" is achieved, with vertebral body squaring and no skip lesions (Roberts and Manchester, 2005: 158-159). Osseous erosive lesions of the hands and feet bones are asymmetrically distributed and associated with periarticular bone proliferation, producing poorly defined and fuzzy osseous contours on X-ray (Resnick and Kransdorf, 2004). In the current case, the lesions observed show a symmetrical distribution, while bone proliferation is slight. Moreover, the skeleton shows a fusion between two cervical vertebrae, but there is no evidence of syndesmophytes or vertebral body squaring, while the thoracic and lumbar regions are not affected, permitting the rejection of a diagnosis of AS.

PsA involves the synovial joints, either monoarticularly or polyarticularly, and is generally asymmetrical, but it may also be symmetrical, thus resembling RA (Hagihara et al., 2015). The resorptive lesions are best seen in the DIP joints of the hands, proceeding from the joint margin to the centre. Hallmarks of the disease are bilateral sacro-iliitis and vertebral fusion by paravertebral bony bridges, joint ankylosis, generalized enthesitis, and proliferative new bone deposition on the shafts and around eroded joints (Waldron, 2009: 62-65) in the form of increased sub-periosteal density of the cortex that widens the diaphyses (Forresterand Kirkpatrick, 1976). Moreover, erosive lesions in PsA are often less sharply defined due to concomitant juxta-articular new bone apposition (Martel et al., 1980), sometimes producing the "ivory phalanx" sign (Sudoł-Szopińska et al., 2016). In the skeleton under study, there is no evidence of commonly occurring PsA traits. Hence, this diagnosis may be excluded.

In ReA, joint symptoms include asymmetric fusion of the sacroiliac joint (SIJ), vertebral fusion with paravertebral bridging with skip lesions (Cawley and Paine, 2015), extra-vertebral erosive changes, enthesopathy, and periosteal new bone growth on shafts and around joints, especially in the lower limbs. Indeed, in ReA the erosive lesions develop asymmetrically, the feet, ankle and knee being especially involved (Rogers et al., 1987). Vertebral bridges are formed in paravertebral locations as bony outgrowths, beginning from the lower thoracic or upper lumbar regions and proceeding upwards, with normal vertebrae being interspersed between fused ones (Waldron, 2009: 61). The absence in the present case of paravertebral bridges or intra- articular fusions of the SIJ rules out this disease.

RA is a generalized inflammatory disease of connective tissues that develops into a chronic deforming arthritis, especially of the hands and feet. The chief lesion is a synovitis, with intensive production of protoinflammatory cytokines and antibodies that stimulate osteoclastic resorption of synovial membrane-lined bone, while inhibiting bone tissue repair (Martel et al., 1965). The disease is clinically recognized as a symmetrical polyarthritis involving almost the entire appendicular

skeleton (Rothschild et al., 1990), with erosive lesions located initially in the marginal area of joints and, with the sequelae of the pathology, also involving the intra-articular space, eventually producing joint ankylosis in the most severe cases. The axial skeleton is affected to a lesser extent: the cervical spine is known to be generally involved in rheumatoid spondylitis (Rogers et al., 1987; Bywaters, 1981; Hacking et al., 1994), possibly producing fusion of the upper cervical vertebrae that, according to Jensen and Steinbach (1977), occurs in about 17% of RA patients. Juxta-articular osteopenia, resulting from erosive lesions and osteoclast activation, is another common feature of the disease (Aufderheide and Rodríguez-Martín, 1998; Roberts and Manchester, 2005; Biehler-Gomez and Cattaneo, 2018). Necessary for the diagnosis is the presence of bones of hands and feet that exhibit early manifestations of the disease (Waldron, 2009). In skeleton T.052, the pattern and distribution of erosive lesions, characterized by periarticular erosions and diffuse trabecular porosis, and the absence of distinctive features at the major sites of predilection of the other disorders considered, suggest rheumatoid arthritis as a possible candidate (Table 2). Nevertheless, some evidence found in this case leaves the diagnosis uncertain. Thus, in the absence of more confirmatory tests and diagnostic methods, a diagnosis of a more generic RA-like polyarthropathy can be suggested.

The ankylosis of the third and fourth cervical vertebrae, but with retention of the ring apophysis (Figs. 7, 11), appears not to be related to a congenital cause, as would be the case in Klippel-Feil syndrome (Fernandes and Costa, 2007), but more likely to be the clinical appearance of RA. Involvement of the cervical trait, with erosive lesions of disc space and intervertebral and facet joint ankylosis, has been reported by several authors, both in clinical (Shichikawa et al., 1978; Mallory et al., 2014; Gillick et al., 2015) and archaeological findings (Hacking et al., 1994).

One lytic lesion in the transverse process of T1, on the margin of the costovertebral facet, was also noted. This finding would be contra-indicative for a diagnosis of RA. Nevertheless, numerous clinical and archaeological findings report axial involvement with erosive lesions and fusion in sub-cervical regions (Heywood and Meyers, 1986; Hacking et al., 1994; Inoue et al., 1999; Kawaguchi et al., 2003; Lee et al., 2010; Kim et al., 2011). Therefore, the slight involvement of the thoracic region in the present skeleton does not exclude RA as a possible diagnosis.

In our case, evidences of sub-periosteal new bone apposition are observed in the form of several calcified nodules and consolidated bone formation on long bone diaphyses and around the joints displaying erosive lesions. These findings are usually considered to be contradictory to the diagnosis of RA (although this phenomenon is attested to occur in a small number of cases, as noted by Dilsen et al., 1962), and suggest, rather, the presence of PsA or AS. Nevertheless, sub-periosteal calcifications have also been found in connection with connective tissue degeneration of the periosteum due to the aging process, as reported in clinical data (Zagba-Mongalima et al., 1988). In the present individual, these bony outgrowths are located near the joint sites but do not overlap with the observed periarticular erosive lesions, and thus must not be confused with the rugosities and bony ossifications of the tendons of muscles attachments (Touraine et al., 2014). Further, these formations are milder than those one would expect in cases of SpA, since there is no evidence of substantial new layer apposition with diaphyseal widening and thickening of the cortex, or presence of the ivory phalanx sign. Therefore, a hypothesis of periosteal degeneration associated with the aging process is plausible.

Osteoporosis is evident from the trabecular thinning and rarefaction visible as radiolucent areas on radiographic images (Fig. 8). This finding has sometimes been considered diagnostic of RA (Rothschild et al., 1990; Roberts and Manchester, 2005; Waldron, 2009; Biehler-Gomez and Cattaneo, 2018), although it is probably non-specific evidence of the condition (as reported by Fletcher and Rowley, 1952).

In our case, the diagnosis is complicated by the mild manifestation of the lesions, which suggests a case of early onset pathology. The individual does not show severe destruction or ankylosis of joints, which can be diagnostic of advanced cases of RA (Inoue et al., 1999; Kim et al., 2011; Mckinnon et al., 2013). Previously published paleopathological cases of early stages of RA show similar patterns and distributions of lesions to T.052 (Bennike, 1985; Kilgore, 1989; Kacki, 2013).

The presence in this individual of some rounded borders of the lesions, visible macroscopically (Figs. 2D, 3B) and sclerosis visible radiographically (e.g. as shown by the arrow in Fig. 8), can be interpreted as a possible remission phase of the disease, which is reported to occur in 10-30% of cases (Waldron, 2009). According to Jensen and Steinbach (1977), the margins of the erosions are fuzzy and irregular during the acute phase and become smoother with the regression of the pathology. Rau (2006) reports that during inflammatory inactivity erosions go through healing, eventually developing recortication, filling and restoration. The erosions observed generally present rounded borders with sclerotic outlines visible on radiographic images, except for the lesions observed near the acetabulum (Fig. 6) and on the proximal end of the first right metacarpal (Figs. 2A, 9A), which show sharp cortical margins and no rounding of the rims. Moreover, one of the observed lesions presents apparent complete recortication at the margin of the distal articular surface of the left third interproximal phalanx and a loss of bone substance with the appearance of a circular cortical depression is observed (Fig. 2B). This lesion may be interpreted as a completely healed erosion due to the absence of exposed trabeculae and compact bone covering, while the others with rounded rims may represent a phase in the healing process (Rau, 2006). Moreover, CT-scans of the joints involved permit observation of marginal sclerosis of most the erosive lesions (Figs. 9C, 10F), that supports a quiescent phase of the polyarthropathy.

The presence of co-existing osteophytic growths, joint surface pitting, areas of eburnation and joint surface contour changes recorded from moderate to severe stages, implies a co-morbid, generalized OA, co-existence that is reported by other authors in clinical (Jacob et al., 1986; Abbott et al., 1991), autopsy (Rothschild et al., 1990) and archaeological cases (Klepinger, 1972; Kilgore, 1989; Mckinnon et al., 2013). Generalized OA is compatible with the advanced age of the individual. Furthermore, according to Ortner (2003), the superimposition of OA on pre-existing RA manifestations is common if joint mobility is maintained. With regard to the unilateral fusion of the sacroiliac joint, a degenerative interpretation is justified, since this type of ankylosis is reported in many studies of the aging process and weight transmission at the SIJ in males (Resnick, 1977; Vogler et al., 1984; Parmar et al., 2003; Dar and Hershkovitz, 2006; Imamura et al., 2014; Pialat et al. 2016).

After a detailed differential diagnosis, by which the other possible inflammatory pathological conditions producing erosive features were discounted, the diagnosis of more generalized rheumatoid arthritis-like disease is hypothesized in this case, and possibly RA.

5. Conclusions

The skeleton described here adds to the evidence for the existence of forms of RA-like polyartrhopathy in the Old World before the Modern Period. On the basis of this evidence and other already published cases, these diseases seem to have been present to some extent in Europe for a greater time than previously thought. Further investigations are needed to clarify the origin and spread of erosive polyarthropathies, as well as pathological variation in them through time to investigate the differences in the signs of disease between archaeological and modern clinical cases.

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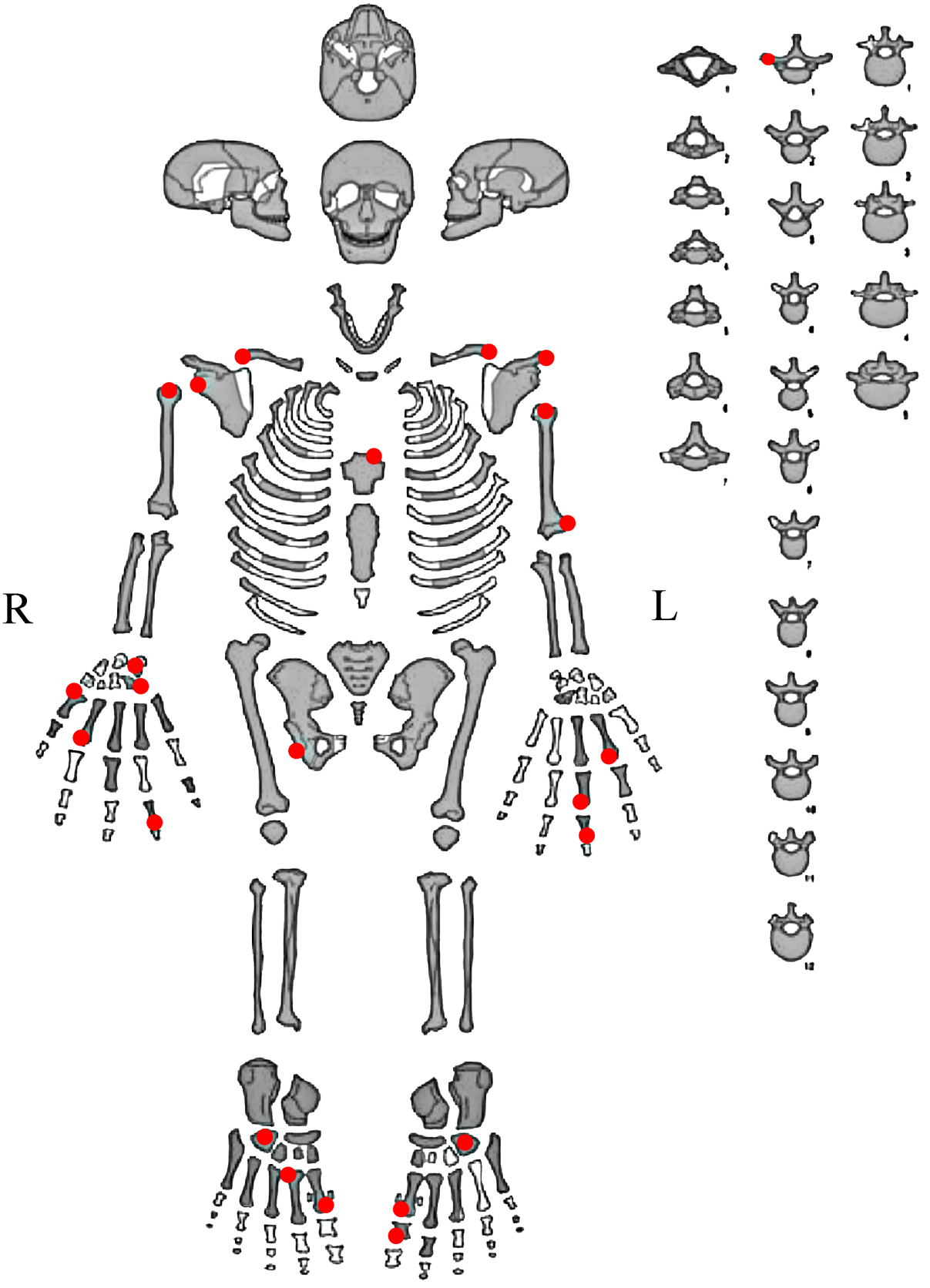
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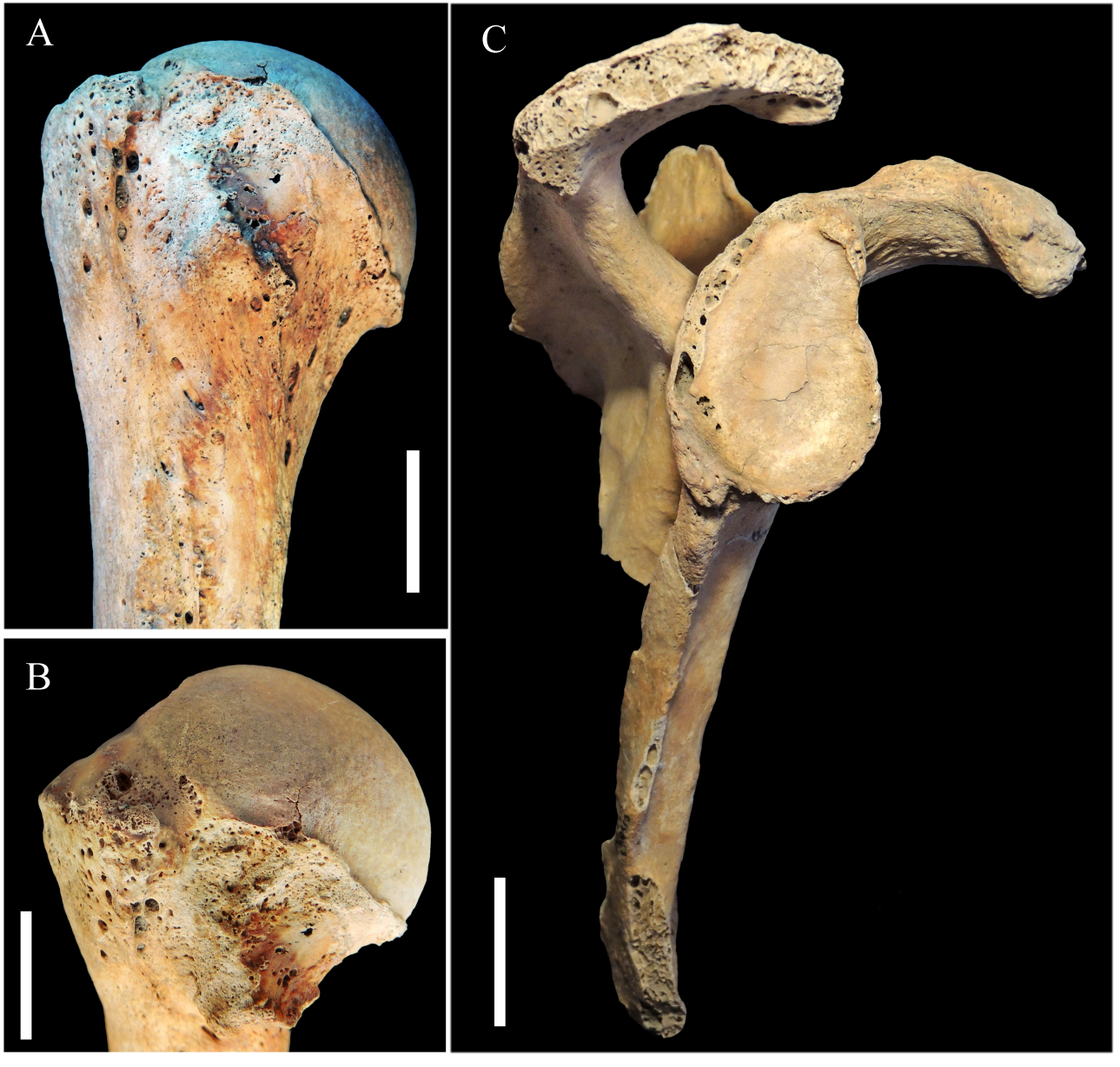
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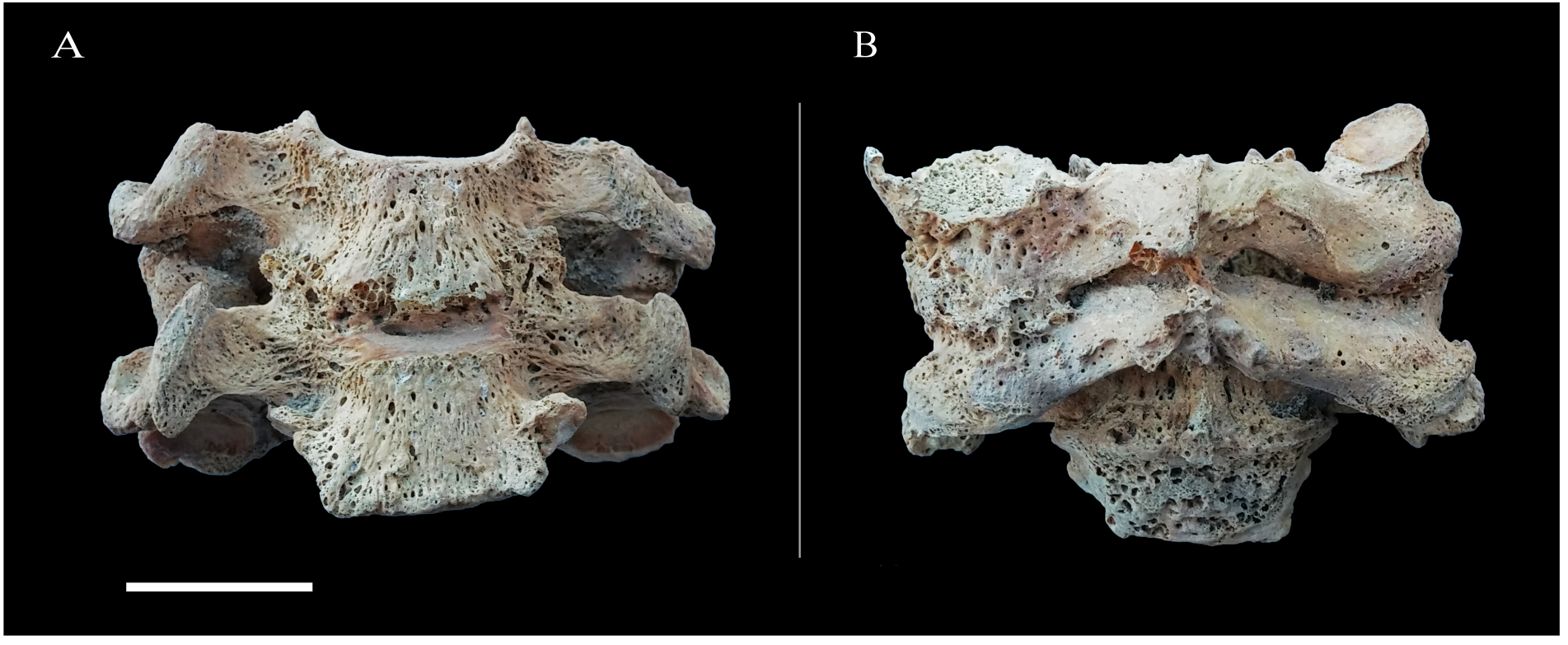
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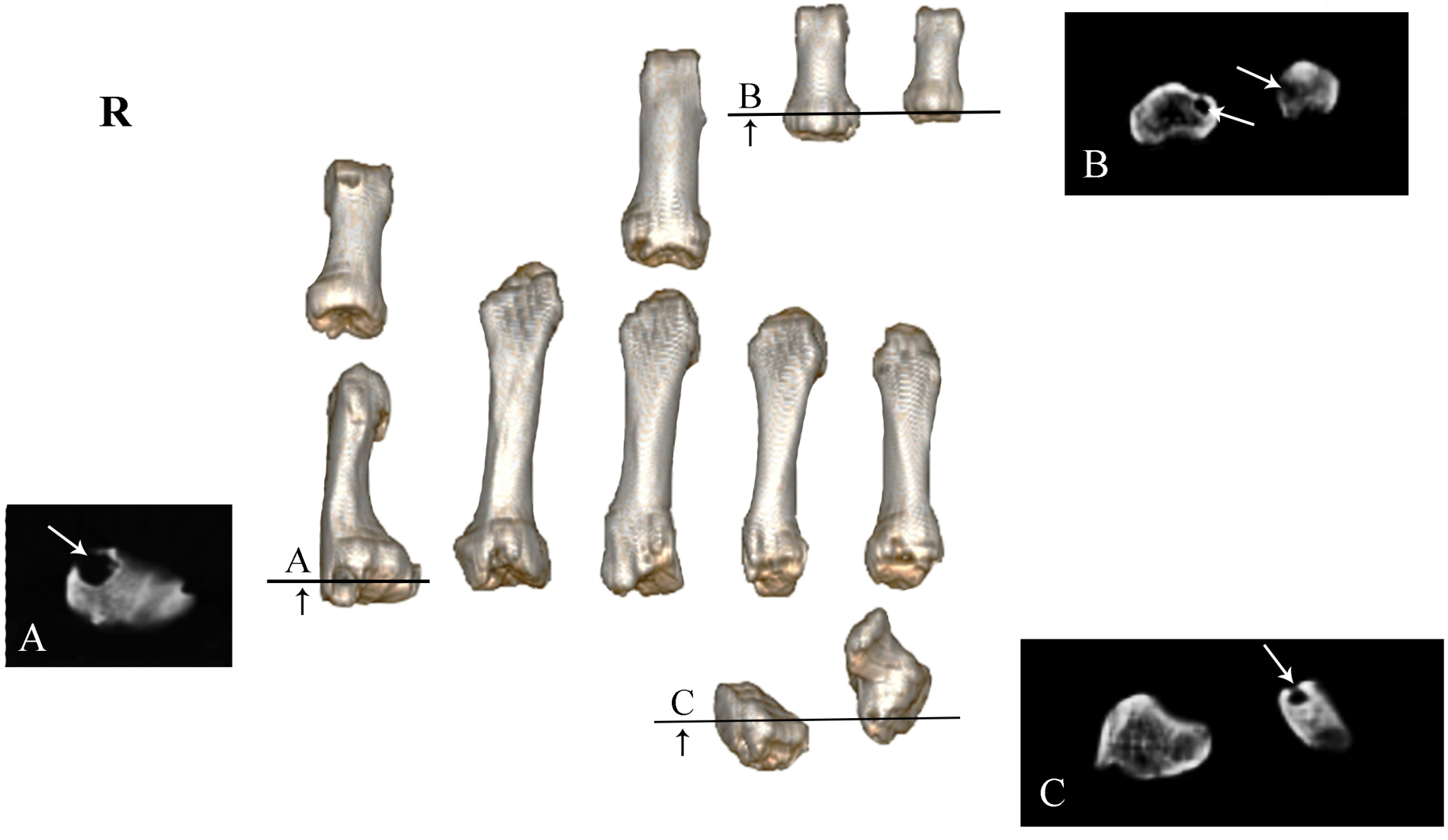
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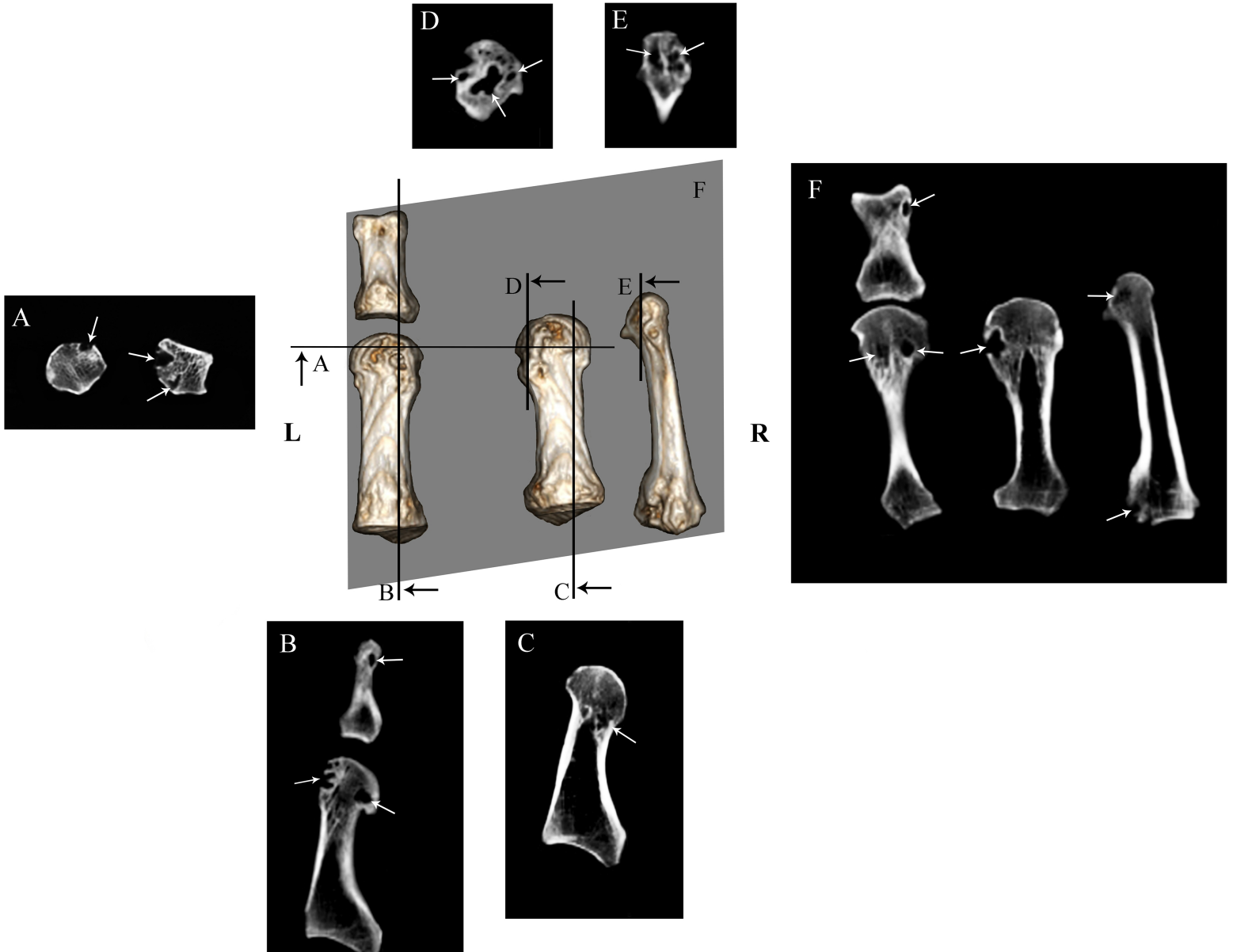
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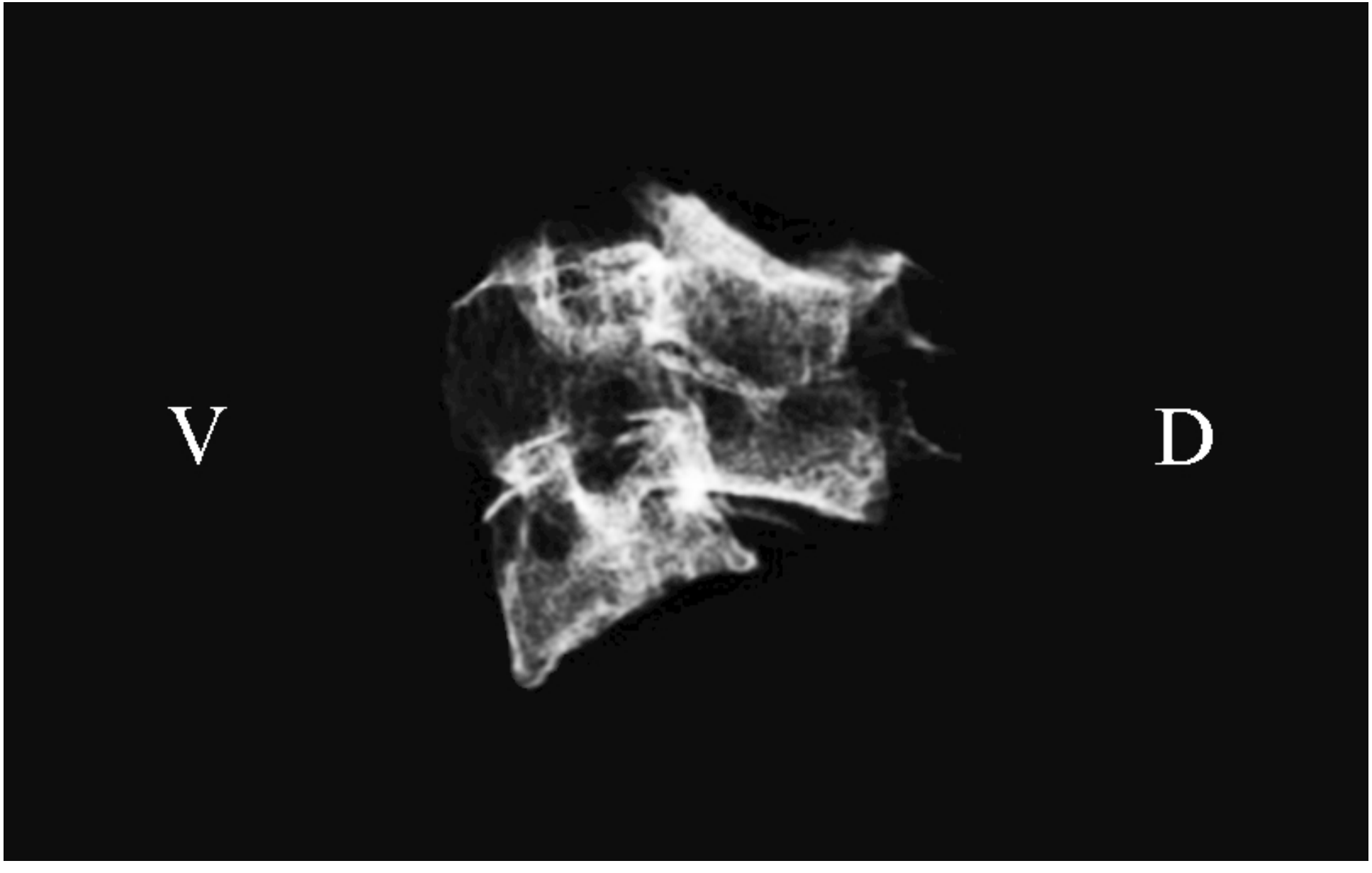
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Figure 1. Preservation of T.052 and skeletal distribution of erosive lesions: preserved bones are marked in grey and red circles indicate the pathological signs

Figure 2. Major lesions observed in the hands. (A) Proximal cystic lesion on the dorso-medial aspect of the right 1st metacarpal. (B) Distal lytic defect and cortical depression on the dorsal aspect of the left 3rd interproximal phalanx. (C) Multiple erosive lesions on the disto-radial aspect of the left 3rd proximal phalanx. (D) Palmar cyst on the body of the right hamate (All scale bars equal 2 cm)

Figure 3. Major lesions observed in the feet. (A) Multiple cystic confluent lesions on the dorsal and medial aspects of the left and right 1st metatarsals. (B) Deep elliptical erosion on the disto-medial side of the left 1st proximal phalanx. (C) Lytic resorption on the lateral aspect of the proximal end of the right 2nd metatarsal (All scale bars equal 2 cm)

Figure 4. Lesions of the right humerus and scapula. (A) Small erosive lesions on the anterior aspect of the proximal right humerus. (B) Erosive lesions on the antero-superior aspect of the lesser and greater tubercles of the proximal right humerus. (C) Lateral view of the right scapula: multiple linear erosive lesions on the margin of the glenoid cavity (All scale bars equal 2 cm)

Figure 5. Left humerus. (A) Multiple linear confluent erosive lesions on the posterior aspect of the proximal left humerus. (B) Antero-superior view of the proximal left humerus: resorptive lesions on the lesser and greater tubercles and the margins of the articular surface of the head. (C) Cystic circular lesion on the lateral margin of the distal capitulum (All scale bars equal 2 cm)

Figure 6. Lesions of the pelvic girdle. Lateral view of the acetabulum of the right os coxae: large cystic cavity on the inferior margin of the posterior cornus of the lunate articular surface (Scale bar equals 2 cm)

Figure 7. Lesions of the axial skeleton. Third and fourth cervical vertebrae, ventral (A) and dorsal (B) view of ankylosis along the bodies and the posterior zygapophyseal joints, with apposition of new bone, is observed (Scale bar equals 2 cm)

Figure 8. Radiograph of the right (R) and left (L) humeri. Radiolucent areas of trabecular thinning and rarefaction are observed at the proximal ends; the white arrow shows the focal erosion on the lateral margin of the distal capitulum

Figure 9. Three-dimensional reconstruction and Computed Tomographic images of the right (R) hand in dorsal view. (A-C) CT images of axial sections: black lines and arrows indicate the position of the section planes and the views; white arrows demonstrate the location of the erosive lesions. (A) Axial slice of the base of the 1st metacarpal demonstrating the internal appearance of the dorso-medial erosive lesion (indicated by the arrow). (B) Axial slice at the bases of the fourth and fifth interproximal phalanges showing small subcortical erosive lesions not visible upon macroscopic examination: the left arrow shows the subcortical sclerotic-lined erosion in the fourth interproximal phalanx; the right arrow indicates a radiolucent resorptive area in the fifth interproximal phalanx. (C) Axial section of the triquetral and hamate displaying the internal appearance of the lesions observed (indicated by the arrow).

Figure 10. Three-dimensional volume rendering image of the affected foot bones in dorso-medial view and

Computed Tomographic images of multiplanar slices: black lines and arrows indicate the position of the slices and the views; the grey rectangle shows the position of the transverse section plane; white arrows demonstrate the location of erosive lesions. (A) Coronal section of the 1st metatarsal heads showing the internal development of the observed major erosive lesions: the left arrow shows a portion of the erosive front on the dorsal aspect of the left 1st metatarsal head; the arrows to the right indicate the internal development of the dorso-medial erosive lesions on the head of the right 1st metatarsal and one inferior subcortical resorption (arrow below). (B) Sagittal slice through the left 1st metatarsal and proximal phalanx, demonstrating the internal appearance of the observed dorso-medial erosive lesions (the arrow in the top right shows the medial erosion of the proximal phalanx, the left arrow indicates the dorsal erosions on the metatarsal head) and one palmar subcortical lesion in the metatarsal head (right arrow below). (C-D) Multiple sagittal slices of the right 1st metatarsal showing the internal appearance of the major, circular, and irregularly-shaped lesions (the lower arrow in D indicates the development of one of the major lesion observed), and several subcortical lesions which are not visible using macroscopic examination (the arrow in C shows a subcortical star-shaped erosion; two circular subcortical lesions are displayed by the arrows in the top left and right in the slice D). (E) Sagittal slice of the right 2nd metatarsal head displaying some confluent subcortical lesions shown by the arrows. (F)Transverse section through all the affected bones of the feet showing the internal appearance of the observed lesions (the arrow in the top left and the arrow in the centre show the medial erosions of the left 1st proximal phalanx and the right metatarsal head; the left arrows indicate the development of the dorsal erosions on the left metatarsal head; the right lower arrow shows the proximal resorptive front on the medial aspect of the second metatarsal) and several subcortical lesions not visible macroscopically (the arrow in the top right shows a subcortical erosion on the 2nd metatarsal head).

Figure 11. Radiograph of the cervical ankylosis. Lateral view of the ankylosed third and fourth cervical vertebrae: joint margins of the two vertebrae are visible as well-defined radiopaque lines; interposed irregular bone is visible in the intervertebral space. (V) Ventral and (D) dorsal surfaces.

Table 1.
Detail of lesions observed on T.052

Affected bones	Side	Observation and description	Figure
C3 – C4		Synostosis	7A,B
T1		Deep circular resorption on the margin of the right transverse process costal facet	
Sacrum		Bilateral antero-superior osteophytic bridging of the sacro-iliac joint, with right-side fusion (with no intra-articular ankylosis); on the left side there is a sacral bony bridge and expansion of the auricular surface on the ilium	
Sternum		Small focal erosions around the margin of left clavicular notch	
Os coxae	R	Large circular cystic cavity, with sharp, undercut edges and scalloped floor, under the posterior cornus of the lunate articular surface of the acetabulum (some fractures on the margins of the lesion are due to post-mortem damage)	6
Clavicle	R	Small deep circular resorptive lesions on the margin of the acromial articular surface and one bigger focal erosion with a scooped floor on the same margin; pitting and osteophytic growths on the acromial articular surface	
Clavicle	L	Small circular resorptions on the margin of the acromial articular surface; pitting and small osteophytes on the sternal articular surface	
Scapula	R	Slight lipping around glenoid cavity; many small deep circular resorptive lesions on the inferior surface of the acromial process; one elliptical cystic resorptive lesion and smaller linear erosive lesions on the posterior margin of the glenoid cavity	4C
Scapula	L	Lipping of borders of the glenoid cavity; small deep circular resorptive lesions on the inferior surface of the acromial process	
Humerus	R	Lipping of margins of the articular surface of the head; pitting around the superior margin of the head; small pits on the surface of lesser tuberosity and one large circular erosive lesion surrounded by slight porosity on the surface of the greater tuberosity	4A,B
Humerus	L	Lipping of margins of the articular surface of the head; circular resorptive lesions on the antero-superior margin of the head; small marginal linear resorptive lesions on the dorso-lateral side of the head; some circular erosive lesions on the surface of the greater tuberosity; some confluent erosive lesions within the intertubercular groove; one deep circular cavity on the lateral margin of the distal capitulum	5A-C
Hamate	R	Deep circular hole on the palmar aspect of the apex of the body	2D
Triquetral	R	Small pits between the ulnar side and the articular facet for the pisiform	
1st metacarpal	R	Large cystic cavity with a scooped floor, undercut edges and sharp ridges on the dorso-medial edge of the margin of the proximal articular surface (some breaks on the margins of the lesion are due to post-mortem damage); osteophytic growths on the inferior apex of the proximal articular surface; wide furrowed eburnated surface on the inferior portion of the proximal articular facet; superficial elliptical resorption on the dorsal margin of the distal articular surface. Nodules of new bone formation on the medial and lateral side of the shaft and in proximity to the articular surface affected by the resorptive cystic lesion	2A

Table 1.
Detail of lesions (continued)

Affected bones	Side	Observation and description	Figure
2nd metacarpal	R	2 small marginal resorptions on the radial side of the head	
2nd metacarpal	L	Small peripheral pits on the radial and ulnar sides of the head	
3rd proximal phalanx (hand)	L	4 linear circular erosions on the radial margin of the distal articular facet	2C
3rd interproximal phalanx (hand)	L	Large circular resorption with smoothed floor on the dorsal margin of the distal articular facet; no trabecular bone is visible, the floor to the lesion is in continuity with the surrounding cortical bone; some plaques of consolidated new bone on the dorsal surface of the shaft	2B
4th interproximal phalanx (hand)	R	1 circular erosion on the radial margin of the distal articular facet; 3 small circular resorptions on the ulnar side of the same portion	
Cuboid	R	Area of resorption with 1 circular small erosion and diffuse small superficial pitting on the medial surface, under the articular facet for the lateral cuneiform	
Cuboid	L	Superficial areas of resorption on the plantar and medial faces	
1st metatarsal	R	3 (1 circular and cystic lesion, 1 circular deep lesion and 1 elliptical and cystic lesion, around 5 mm in diameter) peripheral erosion on the medial side of the head, with slight encroachment on the articular surface	3A
1st metatarsal	L	5 large confluent and circular cystic erosions (2-5 mm in diameter) on the dorso-medial margin of the head, with a little encroachment of the articular surface; some light-colored sub-periosteal bone outgrowths on the medial and lateral side of the shaft	3A
2nd metatarsal	R	Peripheral resorption, with groove formation due to bone loss on the lateral surface of the proximal end, between the articular facets for the third metatarsal; some light-coloured sub-periosteal bone outgrowths on the medial side of the shaft	3C
1st proximal phalanx (foot)	L	Large deep elliptical erosion on the peripheral medial portion of the distal articular surface; some new bone calcifications on the medial side of the shaft, in proximity to the distal resorptive lesion	3B

Table 1.
Distinctive features of RA, Gout, OA, EOA and SpAs (according to Resnick and Niwayama, 1983; Rogers et al., 1987; Rothschild et al., 1990; Aufderheide and Rodríguez-Martín, 2003; Ortner, 2003; Roberts and Manchester, 2005; Waldron, 2009) and their presence (+) or absence (-) in the skeleton under study

Pathological changes	Present Study	RA	Gout	OA	EOA	PsA	AS	ReA
Marginal erosive lesions	+	+	+	+	-	+	-	
Intra-articular erosions	-	+	+	+	+	+	+	
Symmetrical distribution of erosions	+	+	-	-	-	-	+ (spine)	-
Small joints of hands and feet affected	+	+	+	+	+	+	+/-	+
Multiple appendicular joints involved	+	+	-	+/-	-	+/-	+/-	-
Juxta-articular osteopenia	+	+	-	-	-	-	-	-
Joint ankylosis	-	+/-	-	-	+	+	+	-
Spinal erosion and/or fusion	+	+/-	-	-	-	+	+	+
Syndesmophytes	-	-	-	-	-	+	+	+
Joint deformities	-	+	-	+	+	+	+ (spine)	+
Entheseal changes (erosion and proliferation)	+ (few)	-	-	-	-	+	-	+
Sacroiliitis	-	-	-	+	-	+	+	+
Bridging SIJ	+	-	-	+	-	-	-	-
SIJ intra-articular ankylosis	-	-	-	-	-	-	+	+
Bone proliferation	+	-	-	+	+	+	+ (spine)	+
Periosteal reaction on shafts of long bones	-	-	-	-	-	+	-	+
New bone formation on hand and foot tubular bones	+	-	-	-	-	+	+	+

Table 1. Detail of lesions observed in T.052

Table 2. Distinctive features of RA, Gout, OA, EOA and SpAs (according to Resnick and Niwayama, 1983; Rogers et al., 1987; Rothschild et al., 1990; Aufderheide and Rodríguez-Martín, 2003; Ortner, 2003; Roberts and Manchester, 2005; Waldron, 2009) and their presence (+) or absence (-) in the skeleton under study

A case of erosive polyarthropathy from Medieval northern Italy (12th-13th centuries)

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ABSTRACT

Objective: To evaluate and differentially diagnose erosive skeletal lesions located on multiple joints of an individual archaeologically recovered in 2017.

Materials: Skeletal remains of a well-preserved skeleton dating to the 12th-13th centuries from the Medieval church of San Biagio in Cittiglio (Varese, northern Italy).
Methods: Macroscopic and radiographic imaging.
Results: Erosive marginal symmetrical lesions are present on the metatarsophalangeal, metacarpophalangeal and interphalangeal joints of an adult male, aged 55-75 years. Osteolytic changes, in the form of pocket erosions, surface resorptions and pseudocyst formations, are also macroscopically observed on some carpal and tarsal bones and on several large peripheral joints.
Conclusions: A careful differential diagnosis of the lesions and their macroscopic and radiological appearance are suggestive of a case of rheumatoid arthritis-like polyarthropathy.
Significance: This case contributes to the debate regarding the antiquity of erosive polyarthropathies, providing additional evidence for the existence of these diseases in the Old World prior to the discovery of the Americas.
Limitations: Small sample size limits discussion of the scope of the disease in antiquity.
Suggestions for Further Research: This case highlights the need for further macroscopic, radiographic, and biomolecular studies of pre-modern European skeletal samples to investigate the hypothesized pre-existence of these pathological conditions in Europe prior to 1492.

Keywords: Erosive polyarthropathy, Rheumatoid-like arthritis, Remission phase, Osteoarthritis, Northern Italy, Middle Ages

Abbreviations: AS, ankylosing spondylitis; DIP, distal interphalangeal joint; EOA, erosive osteoarthritis; OA, osteoarthritis; PIP, proximal interphalangeal joint; PsA, psoriatic arthritis; RA, rheumatoid arthritis; ReA, reactive arthritis; SIJ, sacroiliac joint; SpAs, spondyloarthropathies