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An Okhotsk adult female human skeleton (11th/12th century AD) with possible SAPHO syndrome from Hamanaka 2 site, Rebun Island, northern Japan

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Abstract We present the oldest human skeletal case yet identified with possible SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis), a chronic disease involving the skin, bone, and joints. A human skeleton with a severe pathological condition was recovered from a shell mound of the prehistoric Okhotsk culture at the Hamanaka 2 site, Rebun Island, Hokkaido, Japan in 2013. Morphological and *Amelogenin* gene analyses determined the sex as female, and the age at time of death was estimated to be in the forties using analysis of the auricular surface of the ilium. The stable isotope ratios of this individual (NAT002) and other Hamanaka 2 samples indicated a heavy dependence on marine mammals and fish for dietary protein intake. Radiocarbon age on collagen from the bone of NAT002 was 1689 ± 20 BP, or 1060–1155 (68.2%) calAD. Macroscopic and computed tomography (CT) findings indicated diffuse hyperostosis in the axial and appendicular skeleton, including the mandible, vertebrae, clavicles, sternum, scapulae, humeri, radii, ulnae, and ilium, caused by osteitis and synovitis. The bilateral clavicles were most affected, in which CT imaging revealed irregular cortical thickening, termed 'grotesque periostitis.' The case was diagnosed as most likely having SAPHO syndrome, although dermatological findings could not be detected. Although SAPHO syndrome is a fairly new concept in autoimmune diseases, this case suggests the syndrome originated much earlier in human history.

Key words: SAPHO syndrome, Japanese archipelago, Okhotsk culture, human skeleton, hyperostosis

Introduction

Archaeologists have revealed that the prehistoric Okhotsk culture was distributed around southern Sakhalin, the Okhotsk Sea coast of Hokkaido, and the Kurile Islands from the 5th to the 13th centuries A.D. (Figure 1), and that the Okhotsk people had developed a considerable maritime adaptation (e.g. Befu and Chard, 1964; Vasiliefsky, 1978; Kikuchi, 1999). To obtain food, the Okhotsk people concentrated primarily on fishing and hunting for sea mammals such as fur seals, whales, and sea lions (Yamaura, 1998; Yamaura and Ushiro, 1999), as confirmed by zooarchaeological and isotopic studies (Hudson, 2004; Naito et al., 2010). Bone-derived tools, including hooks and harpoons for hunting and fishing, have been found at Okhotsk archaeological sites (Hudson, 2004). In addition, the Okhotsk people used watercraft and probably fished with nets, given that stone net weights have also been discovered. These cultural characteristics considerably differ from those of the native an-

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cient Hokkaido peoples, or the Ainu ancestors. At Wakkanai City, the northernmost city on Hokkaido, the current average annual temperature is approximately 7°C, with temperatures of –5°C recorded in January. Ice floes are prevalent along the coast of the Okhotsk Sea from February to March.

Many human skeletal remains have been excavated from the area between 1924 and the present day, and classical morphological studies, based on cranial and postcranial skeletons, suggested their similarity to current Amur basin or northern Sakhalin peoples (Kiyono, 1925; Kodama, 1947; Yamaguchi, 1981; Ishida, 1988, 1996; Kozintsev, 1990, 1992; Shigematsu et al., 2004; Komesu et al., 2008). This relationship is also supported by the results of recent mitochondrial DNA analyses (Sato et al., 2007, 2009). Severe degenerative changes and compression fractures were found in the spines and limb bones of these remains, probably due to the heavy loads associated with marine mammal hunting and fishing (Ishida et al., 1994; Shimoda et al., 2012; Suzuki et al., 2016).

Several archaeological sites of the Okhotsk culture are located in the Hamanaka area, on the northern coast of Rebun Island, Hokkaido (Figure 1). Many human skeletal remains of the Okhotsk culture have been recovered from these sites. For example, Sakuzaemon Kodama of Hokkaido University unearthed remains of about 20 human skeletons at the Funadomari site in 1949 (Ito and Kodama, 1963), and Tadahiko Matsuno of Hokkaido University recovered four human interments at the Kanazaki site in 1967 (Matsuno et al., 1968).

The Hamanaka-2 site was excavated by Ushio Maeda of the University of Tsukuba and Kiyoshi Yamaura of Rikkyo University in 1990; they found the remains of eight infants and children in a shell mound (Maeda and Yamaura, 1992). The physical characteristics of those skeletons were reported by their colleagues (Ishida and Hanihara, 1992). Several researchers continued excavations at the Hamanaka-2 site from 1991 to 1995 in the hope of elucidating the origin, affinity, and lifestyle of the Okhotsk culture (Yamaura and Maeda, 1994; Nishimoto, 2000).

Figure 1. Locations of the Hamanaka 2 site and main sites of the Okhotsk culture (5th–13th centuries AD).

An international and multidisciplinary team, including Japanese and Canadian scientists, began to excavate the Nakatani section of the Hamanaka-2 site in 2011 in order to investigate hunter-gatherer cultural dynamics during the

Figure 2. NAT002 skeleton in situ in the burial site, recovered from the upper surface of a shell mound of the Okhotsk culture.

Middle Holocene in Hokkaido (Kato et al., 2012, 2015). From 2011 to 2013, the remains of three human skeletons of the Okhotsk culture were recovered in the area, one of which (NAT002) was affected by severe hyperostotic changes, or abnormal excessive growth of bone, suggesting SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis) or sternoclavicular hyperostosis (Colina et al., 2009). This is the first case of such pathological changes among the Hamanaka-2 remains, although severe dental calculus deposits or vertebral compression fracture were found in other skeletons (Hanihara et al., 1994; Ishida et al., 1994). In the current study, we present this pathological finding and consider its cause.

Presentation of Case

NAT002 was recovered from the upper surface of a shell mound of the Okhotsk culture at the Nakatani section of the Hamanaka-2 site in 2013 (Figure 2). An iron bracelet, knife, and fishhook were found in association with the burial site (Figure 3). The skeleton was laying on its right side with flexed right arm and extended left arm. The cranium, trunk, and upper limb bones were well preserved, but the lower limb bones were missing except for the left hip bone, right talus, and left cuboid (Figure 4).

The sex was determined to be female based on the morphology of the greater sciatic notch as well as the characteristics of the cranium and long bones and *Amelogenin* gene analyses. Genetic sex determination using the AmpFLSTR® MiniFiler™ PCR Amplification Kit and AmpFLSTR® Iden-

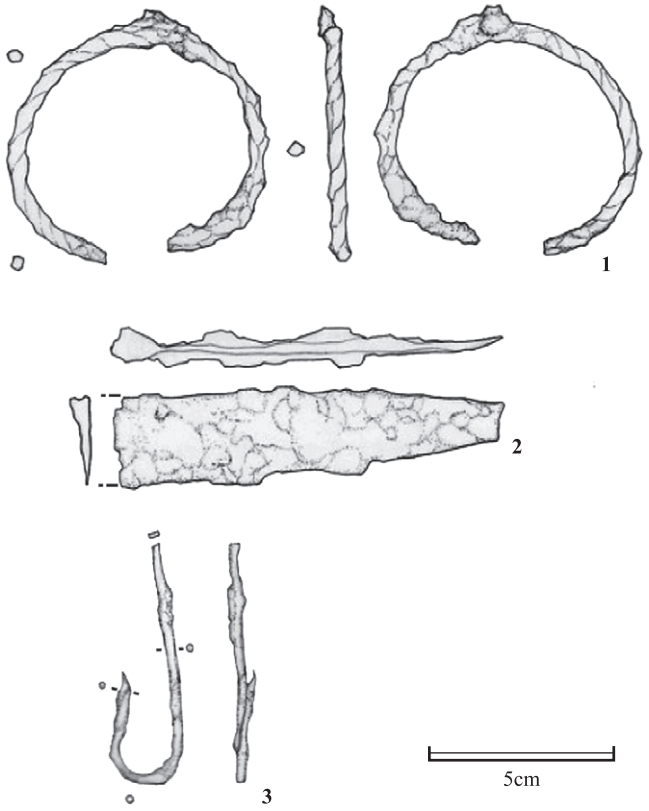


Figure 3. Drawing of an iron-made bracelet (1), knife (2), and fishhook (3) accompanying the NAT002 skeleton.

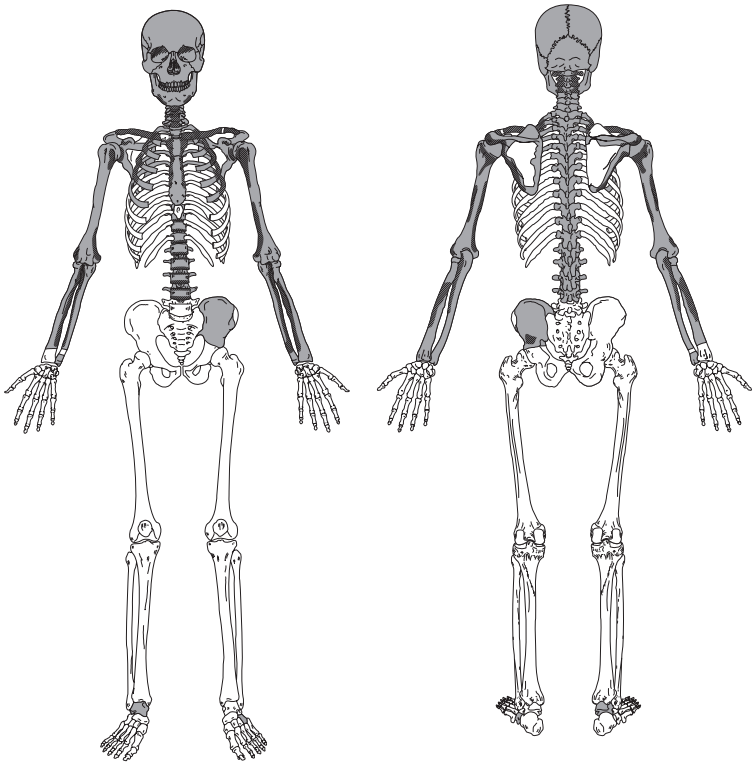
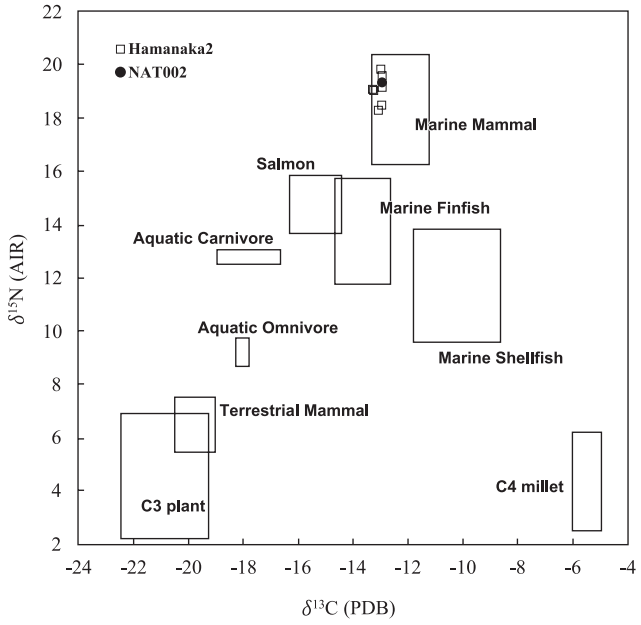


Figure 4. Schematic representation of skeletal preservation (gray area) and lesion distribution (shaded area).



tifiler® PCR Amplification Kit (Life Technologies) was performed in the laboratories of the University of the Ryukyus and University of Yamanashi, respectively. The age at time of death was estimated to be in the forties based on the auricular surfaces of the ilium (Nagaoka et al., 2006, 2012). Stature was estimated at 152.8 cm using the maximum humeral and radial lengths based on the formula of Sasou and Hanihara (1998).

Figure 5 shows carbon and nitrogen isotope ratios in human collagen compared with nutritional resources, with an enrichment correction of 3.5 for nitrogen and 4.5 for carbon, using adult human bones of both sexes from the Hamanaka 2 samples excavated in 1990 and 1994 (Tsutaya et al., 2015). The stable isotope ratios of the Hamanaka 2 samples ranged

Figure 5. Carbon and nitrogen isotope ratios in human collagen compared with nutritional resources with an enrichment correction of 3.5 for nitrogen and 4.5 for carbon. Isotope ratios are shown as delta values compared with international standards (VPDB and AIR for carbon and nitrogen, respectively). The ratios of the NAT002 and other Hamanaka 2 samples were distributed in the same ranges.

Figure 6. Diffuse hyperostoses and osteitis found in the mandible (a), vertebrae (b), ribs (c), and left hip bone (d). Severe hyperostosis around the ligament and joint capsule attachment of the atlas and axis (e). Cortical thickening at the external surface of the rib (f).

from –14‰ to –12‰ for $\delta^{13}C$ and from 18‰ to 20‰ for $\delta^{15}N$, indicating a heavy dependence on marine mammals and fishes for dietary protein intake, as shown in Figure 5 (Naito et al., 2010; Tsutaya et al., 2014, 2015). The ratios of NAT002 are within this range, indicating that this female had consumed a roughly similar diet. The radiocarbon age of collagen from a bone sample of NAT002 was 1689 ± 20 BP (ID: TKa-16063), or 1060–1155 (68.2%) calAD, corresponding to the final stage of the Okhotsk culture. Radiocarbon dating and stable isotope tests were performed in the laboratory of the University Museum of the University of Tokyo by Minoru Yoneda.

The shaded area in Figure 4 shows the distribution of pathological changes in the NAT002 individual, which includes the mandible, sternum, vertebrae, ribs, clavicles, scapulae, humeri, radii, ulnae, and left ilium. Macroscopic and computed tomography (CT) imaging findings are as follows (Figure 6, Figure 7, Figure 8, Figure 9):

- Mandible (Figure 6a): hyperostosis at the insertion point of the masseter muscle.
- Vertebrae (Figure 6b): hyperostosis at the tendon, ligament, and joint capsule attachments, especially in the atlas and axis. The atlas affected hyperostosis at the attachments of ligaments of the median atlantoaxial joint (Figure 6e). Hyperostosis at the transverse ligament of atlas of the axis (Figure 6e).
- Ribs (Figure 6c): hyperostosis around the attachment points of muscles, including the serratus anterior, erector spinae, and serratus posterior muscles. Macroscopic findings included cortical thickening at the external surface of the rib (Figure 6f).
- Left ilium (Figure 6d): hyperostosis at the supra-acetabular margin. The auricular surface was intact.
- Clavicles (Figure 7a–d): severe hyperostosis around the sternal and acromial ends and the attachments of the trapezius and sternocleidomastoid muscles and the coraco-clavicular and acromioclavicular ligaments (Figure 8). CT imaging revealed bilateral irregular cortical thicken-

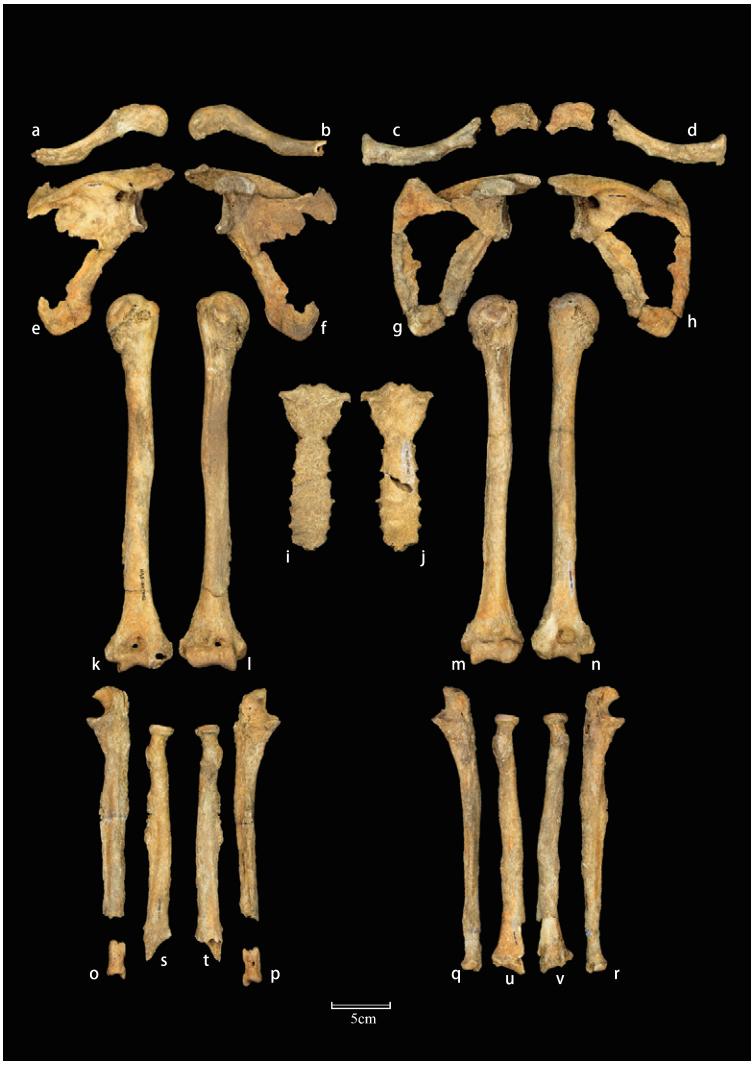


Figure 7. Diffuse hyperostoses and osteitis found in the clavicles (a, b, c, d), scapulae (e, f, g, h), sternum (i, j), humeri (k, l, m, n), ulnae (o, p, q, r), and radii (s, t, u, v).

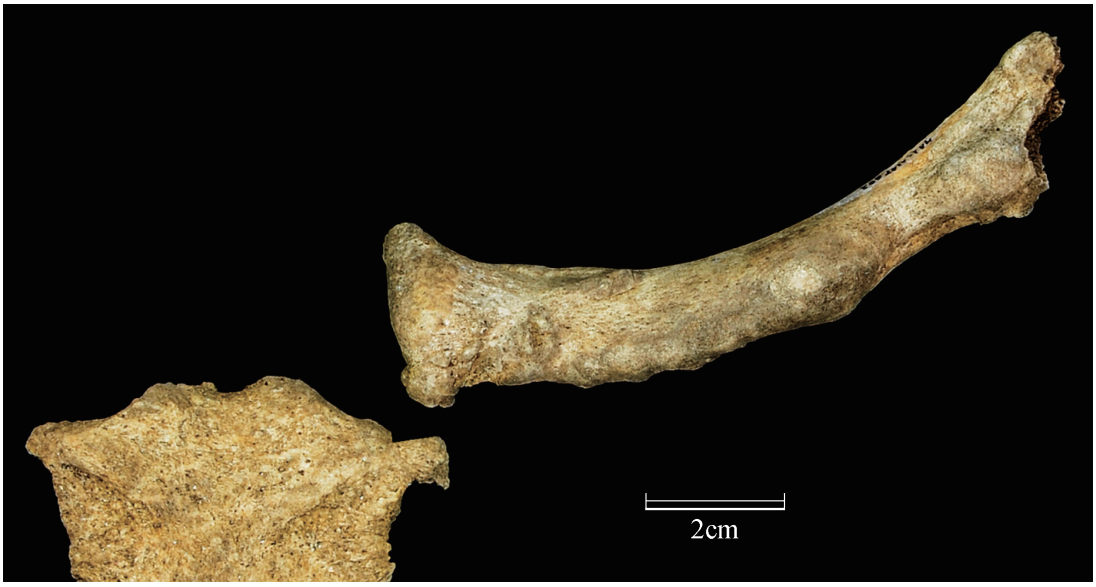


Figure 8. Severe hyperostosis around the sternal end and the sternocleidomastoid muscle attachment of the left clavicle (superior view). Hyperostosis found in the attachment site for left first costal cartilage of the manubrium of the sternum (anterior view).

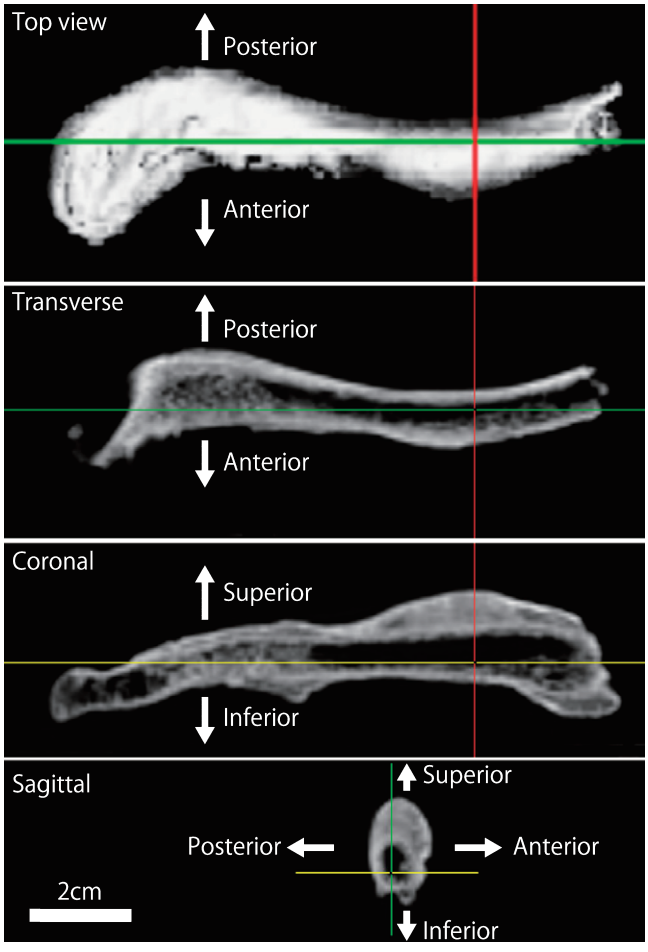


Figure 9. CT images of the right clavicle showed irregular cortical thickening, termed 'grotesque periostitis.'

ing, termed 'grotesque periostitis' (Figure 9).

- Scapulae (Figure 7e–h): hyperostosis around the margin of the glenoid cavity, coracoid process, and lateral and medial borders, caused by osteitis and synovitis.
- Sternum (Figure 7i and j): slight thickening and hyperostosis.
- Humeri (Figure 7k–n): hyperostosis, caused by osteitis and synovitis, around the articular margins of the humeral head and condyles.
- Radii and ulnae (Figures 7o–v): hyperostosis at the attachment of the supinator and pronator teres muscles and at the interosseous borders, probably resulting in limitation of pronation and supination movement.

In addition, the female had chronic apical periodontitis at the right upper canine and antemortem tooth loss of the first premolar. Excessive amounts of secondary cementum were deposited on the root surface of the right upper canine. Around the tooth socket, sclerotic bone tissue was diagnosed as condensing osteitis.

Differential Diagnosis

Widespread hyperostosis, or cortical thickening, was recognized in both the axial and appendicular skeleton except for the cranial vault. Within the skeleton, the clavicles were most severely affected. No ankylosis of the adjacent bones was observed.

These conditions may be caused by several diseases, including bone tumors (benign, primary, and metastatic malignancies), infectious osteomyelitis, degenerative joint disease, ankylosing spondylitis, psoriatic arthritis, diffuse idiopathic skeletal hyperostosis (DISH), primary hypertrophic osteoarthropathy, sternocostoclavicular hyperostosis, Paget's disease, chronic recurrent multifocal osteomyelitis (CRMO), some anemic conditions, and others (Resnick,

2002). However, SAPHO syndrome is the most likely diagnosis for this pathological status, although dermatological findings could not be detected (Depasquale et al., 2012).

Diffuse diaphyseal hyperostosis can eliminate the possibility of bone tumors, Paget's disease, and degenerative joint disease. Primary bone tumors, such as Ewing's sarcoma, are mainly solitary (Kahn and Khan, 1994). Skeletal metastases are typically multiple, but well defined (Resnick, 2002). Paget's disease with bone deformity can affect the cranial vault, coxal bone, and lumbar vertebrae, often with an asymmetric distribution (Galson and Roodman, 2014). However, neither the cranial vault nor the coxal bone was affected in this case. Degenerative joint disease does not affect the diaphysis.

Hematogenous osteomyelitis in adults is usually localized to the epiphysis with joint involvement. However, infection may spread to the diaphysis of long bones, spine, and pelvis, resulting in chronic osteomyelitis with sinus tracts (Resnick, 2002). Because cortical lucency, radiolucent cortical or medullary lesions, and sinus tracts were not seen, infectious osteomyelitis could be excluded in this case. Both the intact auricular surface of the ilium and absence of ankylosis in other vertebrae also eliminated the diagnosis of ankylosing spondylitis (Jang et al., 2011; Louie and Ward, 2014). Psoriatic arthritis seldom shows signs of osteitis with hyperostosis, as seen in osteoarthritis (Assmann, 2012; McGonagle et al., 2015). The absence of anterolateral flowing ossification of the vertebrae differentiated this case from DISH (Mazières, 2013). The predominant features of primary hypertrophic osteoarthropathy are periostitis of distal extremities, pelvis, and cranial vault (Resnick, 2002), with the vertebrae, ribs, and clavicles rarely affected. This presentation differs from the features of the present case. Anemic conditions, such as iron-deficiency anemia, may result in marrow hyperostosis mainly in the cranial vault, however, which usually affects infants and children (Resnick, 2002; Walker et al., 2009).

Sternocostoclavicular hyperostosis was originally reported as a syndrome characterized by hyperostosis of the anterior thoracic bones, including the clavicle, rib, and sternum, and by pustulosis of the palms and soles (Sasaki, 1967; Resnick, 1980; Kalke et al., 2001). Because this syndrome can also involve the spine, pelvis, and appendicular skeleton (Kalke et al., 2001), the term SAPHO syndrome was recently established and includes cases with sternocostoclavicular hyperostosis (van der Kloot et al., 2010). CRMO primarily affects children and adolescents, although it is often believed to lie along the same clinical spectrum of SAPHO (Tlougan et al., 2009; Costa-Reis and Sullivan, 2013).

Diagnosis

As described above, diffuse hyperostosis was seen in the adult female axial and appendicular skeleton, and the bilateral clavicles were most affected. Diagnostic criteria for SAPHO syndrome have been proposed by several clinicians (Kahn and Khan, 1994; Colina et al., 2009). Sternocostoclavicular hyperostosis and/or hyperostoses of the anterior chest wall, limb, and spine with or without dermatoses are among the diagnostic features of SAPHO syndrome (Colina et al., 2009). Thus, although soft tissue pathological findings could not be detected, we can diagnose this case as most likely reflecting SAPHO syndrome through differential diagnosis.

SAPHO Syndrome

French researchers first proposed a specific dermatological and skeletal combination of synovitis, acne, pustulosis, hyperostosis, and osteitis as 'SAPHO syndrome' based on a national survey in 1987 and 1988 (Benhamou et al., 1988). Historically, Japanese orthopedic surgeons had already reported a case of bilateral clavicular osteomyelitis with palmoplantar pustulosis and identified patients with similar conditions (Sasaki, 1967; Sonozaki et al., 1981).

Many survey and systematic review studies have revealed the features of SAPHO syndrome, a chronic disease that involves the skin, bone, and joints (Sonozaki et al., 1981; Kahn and Khan, 1994; Cotten et al., 1995; Hayem et al., 1999; Colina et al., 2009; Govoni et al., 2009; Magrey and Khan, 2009; Sallés et al., 2011; Naves et al., 2013; Witt et al., 2014; Leone et al., 2015). More than half of patients are female, and ages of onset and diagnosis range from young to middle adulthood. The geographical distribution of SAPHO is concentrated in northern Europe and Japan, where the prevalence is about 1 in 10000.

Based on the literature, hyperostosis and osteitis/osteomyelitis are mainly involved in the anterior chest wall and axial skeleton, associated with palmoplantar pustulosis and severe acne. The long bones of the tibia, femur, humerus, ulna, and radius and the mandible can be involved. Hyperostosis is highly characteristic, with osteosclerosis, periosteal new bone formation, and enlargement of the bone. Synovitis and arthritis are usually associated.

SAPHO syndrome is sometimes complicated with inflammatory bowel diseases (Crohn's disease and ulcerative colitis) and clinical or subclinical autoimmune thyroiditis. Its pathogenesis still remains unclear. However, *Propionibacterium acnes* has been frequently identified in patients (Cogen et al., 2008). In addition, HLA-B27 antigen may increase the risk for SAPHO syndrome in the European population. Therefore, it is likely that an autoimmune reaction combined with some genetic predisposition and infectious agents leads to the onset of SAPHO syndrome (Rukavina, 2015).

Prehistoric Okhotsk Female with SAPHO Syndrome

The prehistoric Okhotsk female examined in this study appears to have been affected with SAPHO syndrome. However, as described above, this syndrome has only recently been recognized. Its cause is believed to be an autoimmune reaction, although *P. acne* infection has been associated with it occasionally (Cogen et al., 2008). According to the 'hygiene hypothesis' of a causal relationship between the recent decrease of infections and the increase in immunological disease, this new syndrome is thought to have developed only quite recently in the human past (Okada et al., 2010). However, it is not surprising that this prehistoric Okhotsk female was affected with the SAPHO syndrome, in light of the origin of related autoimmune disorders, e.g. rheumatoid

arthritis, which possibly dates back 1000 years (Rothschild et al., 1988; Entezami et al., 2011). The cause of death still remains unknown. However, this individual must have suffered from pain, fever, and skin inflammation for a long time.

In conclusion, we present the oldest known human skeletal case with likely SAPHO syndrome. Genome analysis of this individual will reveal more detailed information and insight on the SAPHO syndrome to contribute to modern clinical science.

Conflict of interest

All authors declare no conflict of interest.

Acknowledgments

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