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Tropical ulcer on a human tibia from 5000 years ago in Northern Italy

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Running title: Tropical ulcer, an environmental indicator?

Key words: Tropical ulcer, osteomyelitis, Italy, climate, skin, semantic confusion

Abstract

The term tropical ulcer, as applied to bone pathology, describes the specific pathologic phenomenon of the presence of a well defined osteomatous shelf formation on the anteromedial aspect of the tibia. Despite the appellation “tropical,” this pathology is not geographically limited to tropical regions, although it has not previously been reported from continental Europe. Observations of a 4583 BP burial from the Tanaro River area of Northern Italy represent the first such case. Dating of the site to the time of climate change at the end of the first Glacial suggests

that hot-warm, humid conditions may have allowed occurrence of this bone pathology, the first observed in continental Europe. A second explanation is the possible migration of an individual to Italy from an area that is more conventionally considered tropical.

Introduction

Semantics and preconceptions often confuse and prematurely limit diagnostic consideration when bone abnormalities are discovered (Rothschild and Martin, 2006). This is especially true for the isolated, well-delineated, broad-based, elevated, plaque-like excrescence on the anteromedial aspect of tibiae, a pathologic phenomenon that has been traditionally termed a tropical ulcer, or an osteomatous response to a tropical ulcer (Adamson, 1949; Brown and Middlemiss, 1956; Ennis et al., 1972; Kolawole and Bohrer, 1970; Ngu, 1967; Resnick, 2002). The plaque-like surface is typically irregular and related to the presence of an overlying skin ulcer. Despite its name, the pathology referred to as tropical ulcer is not limited geographically to tropical regions (Ngu, 1967). However, the phenomenon does not appear to have been previously reported from continental Europe. Observation of the classic pathology in Copper Age Italy stimulated this study and provides new perspective to climate change.

Materials

Human remains were recognized in a monumental prehistoric tomb in Northern Italy (Papillon, near Alba, Province of Cuneo) (Fig. 1) (Fulcheri and Micheletti Cremasco, 1998; Merlo and Micheletti Cremasco, 2004; Merlo, Micheletti Cremasco, and Fulcheri, 2003; Venturino

Gambari et al., 1999, 2011b; Zoppi et al., 2001). The site was in an alluvial plain outside the ancient course of the Tanaro River. Archaeological and pedologycal evidence suggests that the structure could be a mortuary room devised as a definitive closed space that suffered ceiling collapse (Fig. 2).

The tomb contained severely damaged skeletal and dental remains, minute copper plate fragments, and a bone awl (Venturino Gambari et al., 1999). The human remains were found in the mortuary room on the stone floor (arenaria). The pathologic tibia (AB PAP 14/36) was located in the northeast corner (Fig. 3).

The presence of remains of four adult individuals and six children suggests a kind of ancestors' house (Micheletti Cremasco et al., 2011a.b). Dating eight of these remains, sampled from secondary burials, revealed a temporal range from the end of the Neolithic to the Copper Age, from 4762 ± 53 BP calibration 2σ: 3646-3499 BC (skull fragment -OZE027) to 3679 ± 41 BP calibration 2σ: 2194-2170 BC (coxa fragment-OZF826) (Venturino Gambari et al., 2011a).

Evaluations of burial manner (secondary and synchronic burial of human remains from different earlier grave-places) allow us to identify the later Copper age as a *post quem* end date. We can date use of the monumental tomb use as a secondary burial, but not before the second half III millennium BC latest Copper age (Radiometric Dating ANSTO, Physics Division – Menai – Australia. Venturino Gambari et al., 2011a).

Methods

The antiquity of the affected tibia was assessed by radiocarbon dating (ANSTO Physics Division Menai NSW 2234 AUSTRALIA) and corrected dates determined (Venturino Gambari et al., 2011a; Zoppi et al., 2001). Non-destructive investigation methodologies were otherwise employed for the paleopathological assessment. Osteological remains were evaluated only macroscopically and by radiologic examination.

The pathologic tibial diaphysis AB_PAP 14/36 was associated with insufficient other skeletal elements to determine age or gender. It (AB PAP 36) was assigned by radiocarbon dating to the mid 5th millennium B.P.: conventional age 4583 +/- 62 B.P. (specimen OZE028 - ANSTO Physics Division Menai NSW 2234 AUSTRALIA) (Venturino Gambari et al., 2011a; Zoppi et al., 2001) (Table 1.)

Macroscopic examination of the bone surface reveals a well-delineated, broad-based elevated, 4.5 cm oval plaque-like excrescence/bony pad on the anteromedial aspect of tibiae (Fig. 4). A well-defined depressed area is present centrally (Figures 4,5). A post-mortem fracture permits recognition of thickening of the subjacent compact bone. Radiologic examination (Figures 6,7) reveals apposition of bone on the tibial surface with increased bone density in and around the lesion.

Discussion

Tropical ulcer is the term utilized to identify a specific pathologic condition of bone that has been acquired in North, Central and East Africa, South America, Northern Australia, the South Pacific and Southeast Asia, but which has never been confidently reported in continental Europe (MacDonald, 2003; Ngu, 1967). It is described as a broad-based excrescence, resembling an osteoma (region of increased bone density) on the anteromedial aspect of the tibia (Adamson, 1949; Brown and Middlemiss, 1956; Ennis et al., 1972; Kolawole and Bohrer, 1970; Ngu, 1967; Resnick, 2002). It is caused by a chronic penetrating ulcer, but is not necessarily limited to tropical regions (Ngu, 1967). It has been alternatively attributed to Vincent's type fusiform bacilli (e.g., *Fusobacterium plautivincenti* and *F. fusiformis*), spirochetes (e.g., *Borrelia vincentii, Treponema vincenti, Spirochaeta schaudinni*) and *Staphylococcal* infections complicating traumatic injuries of the skin (Adamson, 1949; Adriaans et al., 1987; Kolawole and Bohrer, 1970; MacDonald, 2003; Ngu, 1967; Resnick, 2002). Malnutrition and poor hygiene have been suggested as contributing

factors (Adamson, 1949; Ngu, 1967). A reviewer suggested an alternative pathophysiologic consideration, that the bone reaction is adaptive to a behavioural activity that puts considerable sustained pressure on the anterior tibia. It is an interesting consideration, which has not been previously associated with tropical ulcers. However, sustained pressure usually produces pressure erosions (indentations of the bone surface), not elevations (Rothschild and Martin, 2006), making such a pathophysiological contribution less likely.

There has been great confusion in application of the term tropical ulcer and distinguishing it from non-specific skin ulcer disease, which has spread to the adjacent skeleton producing a more generalized periosteal reaction (Boel and Ortner, 2011). The latter authors suggested tropical ulcers were present on skeletal elements from the American Civil War (National Museum of health and Medicine, Walter Reed Army Medical Center, Washington, D.C.), the Terry Human Anatomy and Huntington Collections (Anthropology Department, Smithsonian Institution, Washington, DC) from the early part of the 20th century, and one each from 3300 BCE Jordan, 1650 Juhle, Maryland and from Medieval Nordby, Denmark and Malmö, Sweden. These are reviewed in detail below. One of the Civil war cases, the Jordanian case, the Huntington collection case, the Maryland case, one Terry Collection case, and the Malmö, Sweden cases were reported as having components characteristic of what has been called a tropical ulcer, but their diagnosis is not confirmed (Table 2). One of the illustrated Civil War cases is excluded because it actually manifested diffuse circumferential expansion, quite different from the elevated excrescence of tropical ulcers. This tubular characterization was indistinguishable from the other cases reported by Boel and Ortner (2011) and allows their exclusion as examples of tropical ulcer. A second Civil War case had fibular involvement, characteristic of generalized osteomyelitis. The illustration of the Terry Collection case was actually that of a generalized periosteal reaction of the lower leg and the ulcer was actually excavated, not elevated. The Maryland case did have an elevated defined lesion, associated with remodeling of the entire tibia to produce a bowed appearance. The Huntington Collection case had sequestered bone (but not within the elevated area), characteristic of a bone

abscess. The Jordanian case had fibular involvement, suggestive of generalized osteomyelitis. The un-illustrated Malmö, Sweden case is difficult to assess, as Boel and Ortner (2011) noted neither smooth, eroded, undulating nor the abnormal surface bone formation, as are found in tropical ulcers. Thus, only three of the reported cases (Civil War, Maryland and Malmö, Sweden, the latter unlikely) could represent a tropical ulcer. However, the term ivory osteoma has been applied to tropical ulcers (Kolawole and Bohrer, 1970), and all reported cases had reduced, not increased density (Boel and Ortner, 2011).

None of these purported cases were from continental Europe. Roberts and Manchester (2005: 172) illustrate a tibia from 12th-16th century Chichester, Sussex, England with what they called "focal new bone formation." If that case indeed represented a tropical ulcer, could it be the tibia of a slave infected in their native Africa and therefore not European in origin? Kendall et al (2013) reported that five of 30 individuals (17%) from an East Smithfield, England cemetery were not from the local area.

Attribution of the derivation of periosteal reaction has been controversial, and is often based on speculation as to possible manifestations, rather than documented affected cases (e.g., Boel and Ortner, 2011). Venous stasis has been repeatedly cited as a cause of periosteal reaction, although documentation has proven elusive in the published record, and a shelf has not been reported (Rothschild and Martin, 2006). Generalized periosteal reaction does not produce shelves. None were seen among 300 cases of hypertrophic osteoarthropathy (Rothschild and Rothschild, 1998), nor in hundreds of cases of treponemal disease (i.e., syphilis, yaws, bejel) (Hershkovitz et al., 1995; Rothschild and Heathcote, 1993; Rothschild and Rothschild, 1994, 1995, 1996). Hypervitaminosis A has been incorrectly suggested as a cause of periosteal reaction (e.g., Boel and Ortner, 2011). It actually caused accentuated bone formation at entheses (Rothschild, Hershkovitz and Rothschild, 1995; Seawright, English and Gartner, 1970), not the shelves seen in tropical ulcer. Sickle cell disease is associated with bone infarcts and chronic osteomyelitis, but not with the raised shelf found in the tropical ulcer (Almeida and Roberts, 2005; Resnick, 2002). The Veld sore is a desert

ulcer, which usually does not affect bone (Ngu, 1967). Tumors produce a sunburst pattern not seen here (Kolawole and Bohrer, 1970; Resnick, 2002). The so-called crural ulcers reported by Nemec, Kovar and Kachnic (1965) are more extensive examples of osteomyelitis, expanding from the tibia to the fibula. Tropical ulcers differ from Buruli ulcers, caused by *Mycobacterium ulcerans*. They produce massive skin and subcutaneous tissue necrosis, but usually without bone alterations, and the shelf phenomenon has not been reported (Merritt et al., 2010).

The osteoma-like shelf of tropical ulcers appears unique to that phenomenon and is demonstrated in this tibia from the area of Alba, Italy. The specimen site is dated to shortly after the end of the first Glacial, when the temperature increased (Guidi and Piperno, 1982) and the Tanaro River location evidenced a warm humid climate. Palynological examination documents the Neolithic as a period characterized by hot-warm conditions in the Alba area, wherein the tomb was located (Arobba and Caramiello, 1998). The humidity level might have been significant, owing to the Tanaro river neighbourhood and presence of residual hygrophilous plants (Arobba and Caramiello ,1998). Does the current case represent an example of a tropical ulcer in an immigrant who migrated to Italy from a tropical area, or was it a complication of a local environmental event? Whichever explanation is accepted, this appears to be the first documentation of a tropical ulcer in continental Europe, and perhaps in Europe itself.

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Figure legends:

Fig. 1. Location map of Papillon-Alba site in northern Italy.

Fig. 2. Papillon monumental tomb (Alba-Cuneo. Northern Italy): on the left of the image you can see the violation damage (south-west corner) (From: Venturino Gambari et al., 2011a photo C.O.R.A. Soc. Coop.).

Fig. 3. Tomb plan: in the center of the structure, there is the rectangular mortuary room with human remains (grey colour) with archaeological code number. The tibia AB_PAP 14/36 is in the red circle.

Fig. 4. Alba Papillon -Right tibia (Specimen AB_PAP 14/36): Antero-medial view.

Fig. 5. Alba Papillon - Right tibia (Specimen AB_PAP 14/36): Detail of the previous view.

Fig. 6. Alba Papillon - Right tibia (Specimen AB_PAP 14/36): X-ray.

Fig. 7. Alba Papillon - Right tibia (Specimen AB_PAP 14/36): X-ray: Detail of the previous view.

Fig. 1. Location map of Papillon-Alba site in northern Italy.

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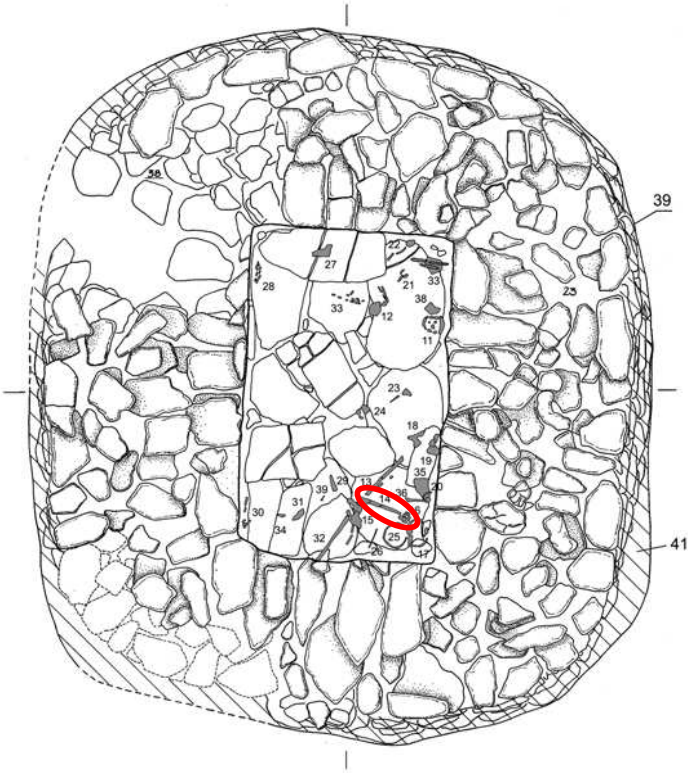

Alba Papillon -Right tibia (Specimen AB_PAP 14/36): Antero-medial view.
39x131mm (600 x 600 DPI)

Alba Papillon - Right tibia (Specimen AB_PAP 14/36): Detail of the previous view.
32x50mm (600 x 600 DPI)

Alba Papillon - Right tibia (Specimen AB_PAP 14/36): X-ray.
36x141mm (600 x 600 DPI)

Alba Papillon - Right tibia (Specimen AB_PAP 14/36): X-ray: Detail of the previous view.

6x9mm (600 x 600 DPI)

Table 1. The 1 σ and 2 σ calibrated age ranges of the bone sample collected in Alba. The table also shows the C/N and $\delta^{13}C$ values. Papillon. Radiometric Dating (ANSTO, Physics Division - Menai - Australia) Extracted from Venturino Gambari *et al.,* 2011a.

				1 σcal age ranges		2 σcal age ranges	
ANSTO code bone/site code	**C/N**	**δ13C (PDB)**	**conventional age**	**calibrate age**	**relative probability**	**calibrate age**	**relative probability**
OZE028	3.2	-21.3‰	4583 ± 62 BP	3499–3455 BC	21.2%	3517–3390 BC	25.6%
tibia				3378–3324 BC	29.6%	3389–3095 BC	74.4%
AB_PAP 14/36				3322–3314 BC	2.9%		
				3229–3172 BC	24.8%		
				3160–3116 BC	20.0%		
				3110–3104 BC	1.5%		

Table 2: Re-evaluation of Boel and Ortner's 2001 report of possible tropical ulcers.

Curation/Locale	Dating	Elevated plaque	Bone excavation	Non-focal expansion	Generalized osteomyelitis	Increased density
True tropical ulcer	not applicable	Yes	No	No	No	Yes
American Civil War*						
Case 1	1860's	No	No	Yes	No	No
Case 2	1860's	No	No	No	Yes	No
Terry Collection**	Early 20th century	No	Yes	No	Yes	No
Huntington Collection**	Early 20th century	No	Yes****	No	No	No
Jordan	3300 BCE	Yes	No	No	Yes	No
Juhle, Maryland	1650	Yes	No	Yes***	No	No
Nordby, Denmark	Medieval					
Malmö, Sweden	Medieval	?	?	?	?	No

* National Museum of health and Medicine, Walter Reed Army Medical Center, Washington, D.C., USA

** Anthropology Department, Smithsonian Institution, Washington, DC, USA

*** Remodeled and bowed.

****Sequestrated with abscess.