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Langerhans cell histiocytosis or tuberculosis on a medieval child (*Oppidum de la Granède*, *Millau*, *France* – 10th–11th centuries AD)

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S U M M A R Y

In 2008, a skeleton of a 1 – 2.5-year-old child radiocarbon dated from the 10th – 11th century AD was discovered on the oppidum of La Granède (Millau, France). It presents multiple cranial osteolytic lesions having punched-out or geographical map-like aspects associated with sequestrum and costal osteitis. A multi 3D digital approach (CT, μCT and virtual reconstruction) enabled us to refine the description and identify the diploic origin of the lytic process. Furthermore, precise observation of the extent of the lesions and associated reorganization of the skeletal micro-structure were possible. From these convergent pieces of evidence, the differential diagnosis led to three possibilities: Langerhans cell histiocytosis, tuberculosis, or Langerhans cell histiocytosis and tuberculosis.

1. Introduction

Many diseases cause osteolytic lesions of the cranial vault (Resnick, 2002). It is sometimes difficult, when considering only skeletal changes, to differentiate between these diseases. This is noticeably the case for Langerhans cell histiocytosis (LCH) and tuberculosis (TB), which can be clinically mistaken [1,2]. Interestingly, before its clinical recognition, LCH was confused with TB[3]. In paleopathology, where TB is much more commonly observed in archaeological contexts than LCH [4], this confusion is also possible. To complicate a retrospective diagnosis, an association between TB and LCH has already been reported in the clinical literature, particularly for the adults' pulmonary form [5,6]. In 2006, Spigelman and collaborators [7] have proposed this morbid association for a paleopathological case.

LCH was first described as eosinophilic granuloma by Smith [8], and later as multifocal forms by Hand [9], Schüller [10], Christian [11], Letterer [12] and Siwe [13]. Lichtenstein [14] made the link between these different expressions and named this group "histiocytosis X." LCH is a neoplastic disorder characterized by abnormal and anarchic proliferation of Langerhans cells (histiocytes presenting antigens to T lymphocytes in lymph nodes) [15]. These cells originate in the bone marrow from stem cells and are transported by blood to the epidermis. They are in charge of the immune control of the skin. Normally present only in the skin, lung and malpighian mucous membranes, Langerhans cells in LCH can infiltrate every tissue, thus characterizing the pathological condition of histiocytoses [16–19]. LCH is rare; its incidence equals 1.24/10^5/year for children aged between 0 and 2 years and 0.45/10^5/year for children up to 15 years old [3]. Its etiology remains unknown. A viral origin has never been confirmed, but a genetic disorder is suspected. Clonal proliferation of Langerhans cells could be caused by gene mutation [18], and an association of LCH with cancer is frequently mentioned [20].

Currently, three types of LCH are usually recognized. (1) The unifocal type (eosinophilic granuloma) involves only the skeletal

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system and represents 70% of cases. It can be monostotic or polyostotic and is associated with frequent pathological fractures. It affects mainly boys aged from 5 to 10 years and heals spontaneously in most cases [19,21,22]. (2) The multifocal unisystem (Händ-Schüller-Christian disease) represents 20% of cases. It is diagnosed when cranial lacunae, exophthalmia (produced by mass effect from osseous involvement of the orbit), and diabetes insipidus are observed. Boys are more affected than girls, at around 2–5 years old. While this form of LCH has a greater spread throughout the body, mortality is classically rare, occurring in up to 10% of cases (causes of death include anemia, pneumonia, *etc.*) [19,21–23]. (3) The multifocal multisystem type (Letterer-Siwe disease) affects neonates and infants up to 2 years old and presents a multi-visceral involvement (skin, liver, spleen, and lung). It represents 10% of cases and is the most aggressive form with a rather poor prognosis [19,21,22]. A consensus of researchers recognizes numerous transition forms between the three major types of LCH that can be considered different stages of the same pathological process [3,19–21,24,25]. Finally, a very rare fourth dermatological expression exists—the congenital self-healing reticulohistiocytosis (Hashimoto–Pritzker syndrome)—which only affects neonates and spontaneously heals in several weeks or months [17].

Within the paleopathological literature, only 17 cases have been reported as LCH (Table 1) concern newborn to young adults, dating from the Paleolithic to the 18th century [26–36]. Even if LCH is not frequently recognized, it is often part of a differential diagnosis [37–42]. A case presenting changes in favor of the co-occurrence of LCH and TB infection in a 2-year-old child from the 18th century has been reported by Spigelman et al. [7]. That case presents small lesions attributed to LCH, and the authors consider TB as the probable cause of death.

In the present paper, we analyzed the remains of a young individual from medieval France. This case offers an opportunity to discuss histiocytic proliferation and/or skeletal infection due to *Mycobacterium tuberculosis* to explain observed lesions. Three-dimensional methods (using CT and μCT imaging) were used to further refine the retrospective diagnosis, as there is a growing interest in paleopathology for exploring and reconstructing pathological processes using medical imaging and 3D reconstruction [43–45].

2. Material and methods

2.1. Material

The archaeological site of "*Oppidum de La Granède*" is located in southwestern France on the north edge of the Larzac plateau, dominating the city of Millau (Figure 1a). This two-component fortified site was first excavated in 1959. Since 2006, it has yielded 150 burials with over 190 individuals [46]. The first component corresponds to the habitation area, and the second to the cult. Human presence is documented as early as the Final Bronze Age, and lasted up to the 13th century AD. Funeral occupation is documented between the 5th and 10th centuries AD with two subphases (5th–7th and 7th–10th) corresponding to the evolution of the church.

In 2008, the burial of the individual named S37 was excavated in the church choir (Figure 1b). The burial, constructed of several limestone slabs, was roof-shaped ("*en bâtière*"), and contained the remains of one immature individual, which was radiocarbon dated between 973 and 1024 AD (Lyon-7496 (OxA)), and corresponded to the end of the funeral occupation. The grave has an E–W orientation with the head oriented to the west (Figure 1c). The anatomical position of the skeletal elements evidenced a primary burial. The immature bones are well preserved with a moderate representation (Figure 2a) [47]. These remains present pathological lesions identified during excavation that cannot be attributed to taphonomic processes.

2.2. Methods

All skeletal remains were macroscopically observed in detail to show pathological lesions. The skeleton was completely CT-scanned, and partly μCT-scanned (Table 2) to reveal possible inner additional pathological changes. The skull was 3D reconstructed to better visualize lesions in the space. Each bone was 3D reconstructed independently using TIVMI® 2.0. software program,[1] [48,49], and then virtually assembled using 3DSMax© software program (version 14.0.0.121, Autodesk, Inc.).

As age is frequently a key criterion for positive diagnosis among immature specimens, dental, and bone ages were both carefully estimated. Dental age estimations were performed using the maturation of 10 deciduous molars and canines [50], and 5 permanent molars and canines [51] by direct observation on isolated teeth, or by CT-scan for teeth still in place [52]. Bone age was evaluated through 11 measurements (lengths of left and right humerus, left and right radius, left tibia, left femur, right fibula, right *pars lateralis*, *pars basilaris*, right scapula, and width of right scapula) [53].

3. Results

3.1. Macroscopical description

Osteolytic lesions are only present on the axial skeleton, involving the skull (Figure 2b), and the third or fourth left rib. Cranial flat bones are the most affected with lesions present on both tables and diploïc space with variable expressions. Microporosities are observed on the surface of cranial and facial bones as well as on postcranial elements: scapula, illii, and long bone metaphyses.

Osteolytic cranial lesions do not particularly affect cranial anatomy, vary in size, and are generally surrounded by ill-defined borders. The most affected bones are the occipital (Figure 3a) and right parietal bones (Figure 3b).

The occipital bone presents a primary central osteolytic lesion and at least 7 peripheral smaller lesions. The outer table is more affected than the inner one. The central lesion shows a geographical map-like aspect; its borders are discontinuous and sinuous, blunted or abrupt. The lesion is divided in two parts by a remaining osseous bridge (Figure 3a), which is only partly affected by the osteolytic process. Isolated patches of outer table are present and evocative of *button sequestrum* (Figure 3a and d). Diploïc trabeculations have been destroyed by the osteolytic process. Borders with blunted aspect are surrounded by perpendicular striations. The smaller osteolytic lesions can be divided into two types: map-like osteolytic lesions (smaller than the central one but with a similar aspect) and punched out lesions, with well-defined and abrupt borders showing a circular 5 mm-diameter shape and perpendicular striations (Figure 3a and e).

The right parietal bone is thinned in its posterior part near the lambdoïd suture due to the abrasion of tables responsible for two map-like osteolytic areas (the medial one has an "estuary shape"). Another set of osteolytic lesions is present on a well-defined zone close to the right euryon. The outer table is most affected (Figure 3b). The left parietal bone only presents a microporotic process near the lambdoïd suture, but its anterior part is missing.

[1] http://www.pacea.u-bordeaux1.fr/TIVMI/, developed by Bruno Dutailly.