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ARTICLE

A death from Langerhans cell histiocytosis and tuberculosis in 18th Century Hungary - what Paleopathology can tell us today

M. Spigelman, I. Pap and H. D. Donoghue[1]

[1]Division of Infection & Immunity, University College London

TO THE EDITOR

The discovery in 1994 of 263 bodies buried in a church crypt in Vác, Hungary (Figure1a,b) has led to some intense investigation and findings of *Mycobacterium tuberculosis* DNA.(1) These bodies were all interred in coffins which, unusually, yielded many skeletal remains of infants in a near-prefect state of preservation. One such body, of an infant, was found to have numerous bony lesions present throughout the skeleton. They appear punched out lytic lesions, with no apparent reactive changes at the edges. Under normal burial conditions such fragile bones would have been so damaged that the lesions may well have escaped notice, been regarded as *post-mortem* damage, or even been destroyed completely.

Whilst many of the people interred in the crypt had their names and ages of birth and death painted on their coffins, in the case of this infant nothing was written on the coffin. However, the likely date of the burial is approximately 1750-1770, as coffins were lowered into the crypt in sequential order. The approximate age of this child based on measurements of the long bones is 18-30 months, but if based on tooth eruption it would be 18 months. We thus put the age at between 1.5-2.5 years. The ribs contains lesions showing evidence of pure osteolytic effects with no evidence of any attempt at healing (Figure 2). The lesions appear to commence in the marrow and subsequently breach the surface. However as they breach the surface these lesions can cause a reaction in the periosteum. This can be seen in

the new bone formation noted in Figure 2. Figures 3 (petrous temporal bone) and 4 (pelvic bone) show the bone with typical destructive and multiple lytic lesions, varying in size between 3-8 mm. In fact all bones X-rayed showed such changes. One rib (Figure 5a,b) was tested for the presence of *M. tuberculosis* DNA as part of our general investigation of this population for tuberculosis. Using primers specific for the *M. tuberculosis* complex based on a 123 bp target region of the repetitive insertion sequence IS*6110*, nested PCR was performed and yielded a 92 bp product, interestingly only scrapings from the viceral surface of the rib were positive.

In a differential diagnosis of these findings we have excluded the possibility of the lesions being due to miliary tuberculosis because of the X-ray appearance, and also such diseases as chronic granulomatous disease (CGD). The latter represents a group of genetic disorders in which impaired intracellular microbial killing by phagocytes leads to granuloma formation caused by recurrent bacterial and fungal infections. In CGD bony lesions are common but whilst these are destructive they should, as do nearly all such lesions due to bacteria, show some evidence of attempted healing.(2)

Langerhans' cell histiocytosis (LCH), also referred to as Histiocytosis-X, is a spectrum of disorders characterised by over-proliferation and accumulation as lesions of 'histiocytes' ~~(Box 1)~~[6] – tissue-resident macrophages and dendritic cells, which are derived from bone-marrow stem cells in the various tissues and organs of the body.(3) The lesions can include Langerhans cells, the distinctive epidermal antigen-presenting dendritic cells, as well as other white blood cells such as monocytes or eosinophils. The second form of histiocytosis most often encountered in children is haemophagocytic lymphohistiocytosis (HLH), a disease of mononuclear phagocytes.

The etiology and pathogenesis of histiocytosis are still unknown. Early studies suggested that it was a reactive disease caused by abnormal immune regulation. A contrary view is that the histiocytes in this condition are of a clonal type, and thus this is neoplastic rather than a reactive disorder. It is now thought to be more probable that LCH is indeed a neoplasm, with a spectrum of clinical manifestations varying from benign and spontaneously

resolving, to highly malignant and fatal.(4) The condition is rare with an incidence for LCH of around 1:200,000 children.(5) The peak incidence is in children aged 1-3 years, although the disease can occur in individuals of any age and may also be congenital.(3) The annual incidence of LCH has been calculated to be between 3 and 7 cases per million people, with males being more frequently affected than females. In a retrospective study involving 32 haematology/oncology departments in France (6) 348 cases of Langerhans' cell histiocytosis, diagnosed between 1983 and 1993, were collated. The percentage of males was 56.4%. Median age at diagnosis was 30.2 months. 108 patients (31%) had isolated unifocal or bifocal bone involvement, but 67 (19%) had multifocal bone involvement. Most affected individuals have single or multiple bone lesions characterized by degenerative changes and loss of the calcium of bone (osteolysis).(7) Bone involvement is observed in 78% of cases and often includes the skull (49%), innominate bone (23%), femur (17%), orbit (11%), and ribs (8%) At times, lesions may cause a significant periosteal reaction. Langerhans' cell histiocytosis has never been identified in Paleopathology.

Histiocytosis X was recognized as potentially being present in the paleopathological literature (8) although a case of eosinophilic granuloma was suspected in a specimen from Valencia, Spain. The distinction these authors made, between Hand-Schüller-Christian Syndrome and Letterer-Siwe Disease was based on age. The former apparently affects boys between 2-5 years and the latter is said to occur from birth to 2 years and to be more proliferative.

In conclusion, our case is more within the normally accepted age group for a case of Langerhans cell histiocytosis, and this is our considered final diagnosis. In view of this diagnosis the finding of tuberculosis is not surprising. This child would have a repressed immune system, due to marrow replacement by the malignant cells, and thus be vulnerable to tuberculosis, which was widespread in this community. (1)

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Mark Spigelman[1*] Ildicó Pap[2], and Helen D.Donoghue[1]

[1] Centre for Infectious Diseases and International Health, Department of Infection, Windeyer Institute of Medical Sciences, UCL, 46, Cleveland Street, London W1T 4JF, UK

[2] Department of Anthropology, Hungarian Natural History Museum, Budapest H-1083, Hungary

Correspondence: Dr M Spigelman, Visiting Professor, Centre for Infectious Diseases and International Health, Department of Infection, Windeyer Institute of Medical Sciences, UCL, 46, Cleveland Street, London W1T 4JF, UK. E-mail: spigelman@btinternet.com

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Figure 1a Dominican Church Vác Hungary

1b Coffins now in the Memento Mori museum, Vác, Hungary

Figure 2 Rib showing lesions and raised periosteum.

Figure 3 Lesions on Petrous temporal bone.

Figure 4 Lesions on pelvis.

Figure 5a Rib showing typical lesions which was positive for DNA from the *Mycobacterium tuberculosis* complex

5b Radiograph of above rib

Box 1: What is Langerhans Cell Histiocytosis?

In the early literature symptomatic individuals were described as having one of a range of syndromes :-

9. Abt-Letterer-Siwe disease; eosinophilic granuloma;

10. Hand-Schüller-Christian syndrome;

11. Hashimoto-Pritzker syndrome;

12. Letterer-Siwe disease;

13. Pure cutaneous histiocytosis;

14. Self-healing histiocytosis.

The syndromes recognised today are:-

1 Letterer Siwe Syndrome (disseminated histiocytosis) - the acute disseminated form of histiocytosis X that occurs in infants. This is rapidly progressive and affects primarily soft tissues with no or minimal bone involvement.

2 Hand Schüller Christian Disease (multifocal histiocytosis X syndrome) - the chronic form of disseminated histiocytosis X that usually affects young children and is characterized by visceral and a variable degree of bone involvement. Radiology demonstrates that "the most common site for solitary bone lesion is skull followed by long bones, extremities, the pelvis, the ribs and the spine. Bone lesions are characterized in radiographs by round or oval lytic defects involving the medullary cavity with slightly denser and at times scalloped margins".[6]

1. Eosinophilic granuloma - the single lesion version.

Box 2

What is already known on this topic

Langerhans Cell Histiocytosis is a very rare a neoplastic disorder, with a spectrum of clinical manifestations varying from benign and spontaneously resolving, to highly malignant and fatal. More cases are found in childhood but cases may occur at any age.

What this study adds

Because of the exceptionally good preservation of the 18th century human remains from Vàc, Hungary, it has been possible to make a clinical diagnosis of Langerhans Cell Histiocytosis from the gross morphology and radiology of the bone lesions of an infant aged 1.5 to 2 years.

This is the first report of a dignosis based on palaeopathological evidence.

Molecular evidence of tuberculosis in a rib from this infant is consistent with this diagnosis, as the defective immune response would increase susceptibility to this disease, which was widesprad in this population.