Case reports

HIDDEN TUBERCULOSIS REVEALED BY BONE MARROW BIOPSY AS CAUSE OF FEVER OF UNKNOWN ORIGIN

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ABSTRACT

Fever of unknown origin is a frequent clinical problem, especially in the elderly, giving cause to hospital admission and multiple investigations. Starting with a case report of an 84-year-old male patient with fever of unknown origin with presence of bone marrow granuloma attributed to infection by *Mycobacterium tuberculosis*, incidence, risk factors, clinical and biochemical findings of extrapulmonary tuberculosis will be highlighted. This underlines the need of elaborate investigation including bone marrow biopsy when confronted with fever of unknown origin.

INTRODUCTION

Fever of unknown origin is a frequent clinical problem giving cause to hospital admission and multiple investigations. Tuberculosis is still one of the major deadly infectious causes, mainly in less-developed countries. Bone marrow tuberculosis is one of the rare forms of extrapulmonary infection due to *Mycobacterium tuberculosis*. Starting with a case report, characteristics will be highlighted.

CASE REPORT

An 84-year-old male patient was admitted because of fever of unknown origin and progressive decline of his clinical condition. He became unwell 6 weeks prior to admission and had deteriorated since. He described febrile episodes (maximum 40° Celsius) appearing mostly during the night and accompanied by cold chills and excessive sweating. During that period, the patient lost about 6 kilograms. There was no anamnestic focus of infection.

He had a previous history of intermediately differentiated prostate cancer (Gleason score 5) 11 years prior to admission. This was treated surgically with adjuvant hormonal therapy. Furthermore, the patient was being treated for arterial hypertension, heartburn and asthma. During World War II the patient was deported to a German concentration camp in Flossenbürg, where he suffered from lung tuberculosis. This was treated with a right-sided therapeutic pneumothorax as was customary in those days. The patient used to work as a janitor in Belgium and had never stayed

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outside Europe. His current medicines at admission were paracetamol, phenoterol-ipratropium (Atrivent), salmeterol (Serevent), leuprorelin (Lucrin depot) monthly, citalopram (Cipramil), zafirlukast (Accolate) and allopurinol. These were all stopped a couple days after admission.

Clinically we found a well-nourished patient without acute distress (temperature 37° Celsius, blood pressure 150/80 mmHg, pulse 80/min) with some facial and truncal teleangiectasia. Auscultation of the thorax revealed a pansystolic murmur and some coarse ronchi. No further abnormalities were obtained on clinical examination.

Blood results at admission showed minor normochromic normocytic anaemia (Hb 11,5 g/dl), elevated erythrocyte sedimentation rate (95 mm/h) and C-reactive protein (CRP 13,3 mg/dl), and normal white cell count with slight neutrophilia (total $6,4 \cdot 10^{12}/l$, 81% neutrophils). Electrolytes, renal and liver function tests were within normal limits, with the exception of mild hyponatraemia.

Chest radiography demonstrated a right-sided pleural calcification with little mediastinal shift to the right. A compression fracture of the first lumbar vertebra were visualised on radiography of the abdomen. CT scan of the thorax and abdomen revealed the previously noticed pleural calcification, calcifications of the abdominal aorta and some nephrolithiasis. Tuberculin skin test was performed but did not give rise to dermal induration.

During hospitalisation the patient remained febrile with spikes of fever accompanied by further decline of his clinical condition. He became completely dependent on the nursing staff for transfers and personal hygiene. Bone scintigraphy and total body leukocyte scanning showed a hot spot at D₁₂-L₁. Specific magnetic resonance imaging of the spine showed posttraumatic oedema due to an osteoporotic compression fracture.

Bone marrow biopsy showed normocellular bone marrow with 10 to 15% polyclonal plasmacytes but with elevated κ/λ ratio suggestive of monoclonal gammopathy of unknown significance (MGUS). B-

Figure 1: Presence of Langhans Type Granuloma in Bone Marrow (arrow heads)

cell lymphoma was excluded by the negative staining for CD79A. Microscopic examination demonstrated 2 granulomas, of which 1 Langhans type (Figure 1). Multiple Ziehl-Neelsen staining of bone marrow, urine samples and gastric secretions were all negative. Bone marrow PCR for *Mycobacterium tuberculosis* was also negative.

There was no proven evidence of tuberculosis but the presence of 1 Langhans granuloma in the bone marrow in addition to the unexplained febrile episodes and the patients' previous history of tuberculosis led to the tentative diagnosis of bone marrow tuberculosis. Standard anti-tuberculosis therapy was initiated. One week after commencing treatment the patient had recovered with a clear defervescence and reduction in C-reactive protein. At the end of treatment (nine months after discharge) the patient was in good health without febrile episodes.

REVIEW OF THE LITERATURE AND DISCUSSION

Fever of unknown origin (FUO) is a diagnostic challenge giving cause to hospital admission and multiple, sometimes invasive, investigations. Infections are frequently found causes of fever of unknown origin, followed by multisystemic diseases, various neoplasms and multiple drugs (1). In the elderly, FUO is most frequently caused by multisystemic diseases with temporal arteritis as most frequent specific diagnosis (2, 3).

Infection by *Mycobacterium tuberculosis* is still common in Europe (incidence range 3 – 138 per 100.000 persons per year in 2004) (4), especially among the elderly and patients with suppressed immunity (5). Recurrence of tuberculosis is assumed to be associated with male sex and advanced age (6). Extrapulmonary, military or occult tuberculosis occurs in about 15 to 20% of disease in HIV-seronegative patients and mostly gives rise to rather aspecific manifestations such as fever, weakness, night sweats, anorexia and weight loss, so-called B-symptoms. Other clinical findings can be hepatomegaly, splenomegaly, lymphadenopathies, haemoptysis, neck stiffness and change in mental status (7, 8). However, with increasing age there's a lower prevalence of night sweats, haemoptysis and fever (9). Biochemical analysis often shows a typical triad of mild thrombocytopenia, neutrophilia and hyponatraemia (10).

If no sufficient explanation for fever of unknown origin, bone marrow biopsy needs to be considered, especially in case of suppressed level of immunity such

as HIV infection, intake of steroids, elderly patients and associated haematological malignancies. Microscopic examination of infected bone marrow occasionally shows granulomas (range 13 to 56%) of the Langhans type, with often negative Ziehl-Neelsen staining for acid-fast bacilli (range 0 to 19%) (11). More recently, diagnosis of tuberculosis can be confirmed by using highly sensitive polymerase chain reaction (PCR) with positive results up to 70% (12).

Tuberculin skin test is still frequently performed in the investigation of fever of unknown origin and is usually positive when previous history of mycobacterial infection, although 15% can be negative with proven tuberculosis, especially in the elderly since tuberculin skin test sensitivity declines with age (13).

Actually treatment with isoniazid, rifampicin and pyrazinamide is considered to be the golden standard for extrapulmonary tuberculosis, and a fourth drug is generally recommended for the first 2 months (14). The mortality depends usually on the co-morbidity of the patient, especially cancer in the elderly population (15).

In our case, diagnosis was made on the clinical presentation and the presence of Langhans type granuloma in the bone marrow. The patient was started on anti-tuberculosis treatment because of the risk for recurrence of tuberculosis (elderly male patient and previous pulmonary tuberculosis only treated by pneumothorax). Although bone marrow culture and PCR were negative, there was a clear response on treatment, strengthening the diagnosis of isolated bone marrow tuberculosis and underlining the value of diagnostic bone marrow biopsy in the investigation of fever of unknown origin.

CONCLUSION

Tuberculosis is still a common infectious cause of fever of unknown origin, but extrapulmonary tuberculosis is difficult to diagnose because of its aspecific characteristics. All non-essential drugs should be stopped as a first diagnostic step. If no sufficient explanation for fever of unknown origin can be found, bone marrow biopsy should be performed, especially in case of suppressed level of immunity. Infection by *Mycobacterium tuberculosis* should always be part of differential diagnosis when confronted with a patient with fever of unknown origin, especially with previous medical history of tuberculosis, HIV seropositivity or advanced age. Treatment should be commenced as soon as the clinical status of an at-risk patient declines.

ABSTRACT

Koorts van ongekende oorsprong is een frequent klinisch probleem, vooral in de oudere populatie, en vereist dikwijls opname en verschillende onderzoeken. Aan de hand van een casus van een 84-jarige man met koorts van ongekende oorsprong met beenmerggranulomen toegeschreven aan een infectie met *Mycobacterium tuberculosis* worden de incidentie, risicofactoren, klinische en biochemische bevindingen van extrapulmonaire tuberculose belicht. Dit bewijst de noodzaak van diepgaande onderzoeken, inclusief beenmergbiopsie, bij koorts van ongekende oorsprong.

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