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CASE REPORT

Malignancy or Inflammation? A Case Report of a Young Man with Fever of Unknown Origin

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Absract A case of a young man with fever of unknown origin is presented. This diagnosis can be frustrating for both patients and physicians because the diagnostic workup often involves numerous noninvasive and invasive procedures that sometimes fail to explain the fever. In the presented case some of the imaging diagnostic findings suggested malignant hematological disorder. However, histopathological and microbiological investigation proved vertebral osteomyelitis caused by Staphylococcus haemolyticus. Diagnosis was established by positron emission tomography, magnetic resonance imaging, and culture and histopathological analysis of a spinal biopsy. 3 months of antibiotic therapy was curative. Biopsy and microbiological investigation may be necessary in patients with fever, back pain and evidence of a spinal lesion on imaging, even if neoplastic disease is suspected.

Keywords Fever of unknown origin · Chronic osteomyelitis · Vertebral biopsy · Positron emission tomography · Magnetic resonance imaging

Abbreviations

CRP	C-reactive protein
CT	computed tomography
ESR	erythrocyte sedimentation rate
FDG	fluoroxeoxyglucose
FDG-PET	fluoroxeoxyglucose positon emission tomography
FUO	fever of unknown origin
MRI	magnetic resonance imaging

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Introduction

Fever of unknown origin (FUO) in adults is defined as a temperature higher than 38.3°C (100.9°F) that lasts for more than 3 weeks with no obvious source despite appropriate investigation [1]. The differential diagnosis of FUO generally is broken into four major subgroups: infections, malignancies, autoimmune conditions, and miscellaneous. A thorough history, physical examination, and standard laboratory testing remain the basis of the initial evaluation of the patient with FUO. However, newer diagnostic modalities, including updated serology, viral cultures, computed tomography, and magnetic resonance imaging, have important roles in the assessment of these patients [2]. In FUO, there is no diagnostic gold standard against which other diagnostic tests may be measured. FUO can be frustrating for both patients and physicians because the diagnostic workup often involves numerous noninvasive and invasive procedures that sometimes fail to explain the fever [3].

Here we present a case of FUO to illustrate the difficulties of the diagnostic process, and to emphase the importance of rarely used diagnostic tools such as vertebral biopsy.

Case Report

A 30-year-old Caucasian man presented to his family doctor with persistent febrility/subfebrility, lack of appetite, weight-loss, weakness and undecided low back pain. His symptoms had appeared 6 weeks earlier and had worsened over the previous 2 weeks. There was no history of trauma or surgery. He worked as a cane-cutter. His personal and familial anamnesis was negative for malignancies, endocrine, metabolic, cardiovascular, immune and malignant diseases.

Her vital signs on admission included a blood pressure of 128/75 mmHg, a heart rate of 72 beats/min, a respiratory rate of 14 breaths/min. Physical examination revealed a low-grade fever of 37.5°C. Examination of the musculosceletal system was negative. The neurological examination was unremarkable. The clinical impression was a young man in good general condition. Routine electrocardiography, abdominal sonography, and chest X-ray were unremarkable.

Since our patient was a young person, firstly, we aimed to find the signs of infection. We could not detect any physical sign of infective process on the skin and in the oral cavity. We could not palpate pathological lymph nodes. Echocardiography did not verify the presence of endocardial vegetation. Dental, otolaryngheal and urological investigations could not find the cause of the subfebrility.

Blood investigations revealed a white cell count of 8.9×10^9, C-reactive protein (CRP) level was 118.8 mg/l, erythrocyte sedimentation rate (ESR) was 44 mm/h. Results of all the other routine laboratory tests (serum ions and glucose, renal and liver function, urine analysis and complete blood count) were in the normal range. Haemocultures were negative. Cytomegalovirus, Ebstein-Barr virus, Human immunodeficiency virus, Hepatitis virus B and C, and Leptospira serologies were negative. Tuberculin probe was negative. Before his admission, empirical amoxycillin, than ciprofloxacin, clarythromycin, and moxifloxacin therapy was indicated. After stopping the antibiotics, the persistence of febrility prompted further investigation.

Since the laboratory tests suggested infection, however, the origin was still unidentified, [^{18}F] fluoroxeoxyglucose positon emission tomography (FDG-PET) was performed to identify the supposed infection. The images demonstrated intense fluoroxeoxyglucose (FDG) uptake in the level of the fourth lumbar vertebra, with a possible extension in the spinal canal (Fig. 1).

To get more information about the nature and localization of the supposed osteal infection, a lumbar spine magnetic resonance imaging (MRI) was obtained with and without contrast in both sagittal and axial planes. Surprisingly, the MRI revealed a loss of signal through the vertebral bodies of L2, L3 and L4, which crossed the disk space. A hyperintense lesion was also identified lateral to L4 and in the paraspinal area, which was interpreted the suspicion of malignant haematological disease (Fig. 2).

Although the moderately increased erythrocyte sedimentation rate was not characteristic for hypergammaglobulinemias, and the serum calcium level was in the normal range, to exclude multiple myeloma a radiographic skeletal survey and bone marrow aspiration were performed. Samples are sent for plasma cell labeling index and cytogenetic analyses, with negative results. M protein was not detectable in the serum and urine samples. However, on the sagittal skull X ray nonspecific osteoblastic and osteolytic lesions were be found. Although the radiologist interpreted the lesions as radiological suspicion of malignant bone metastases, these types of lesions can be find in both inflammatory and malignant processes.

Because of the ambivalent results, finally, spinal biopsy was obtained and the histopathological analysis proved an aspecific chronic vertebral osteomyelitis.

Gram stain of biopsy material showed Gram-positive cocci. Direct cultures grew Stapylococcus aureus susceptible to vancomycin, ofloxacin, ciprofloxacin and amikacin.

Oral ciprofloxacin therapy was commenced and was continued for 3 months. The acute inflammatory parameters settled and there was a significant regression on MRI. To date, the patient is asymptomatic.

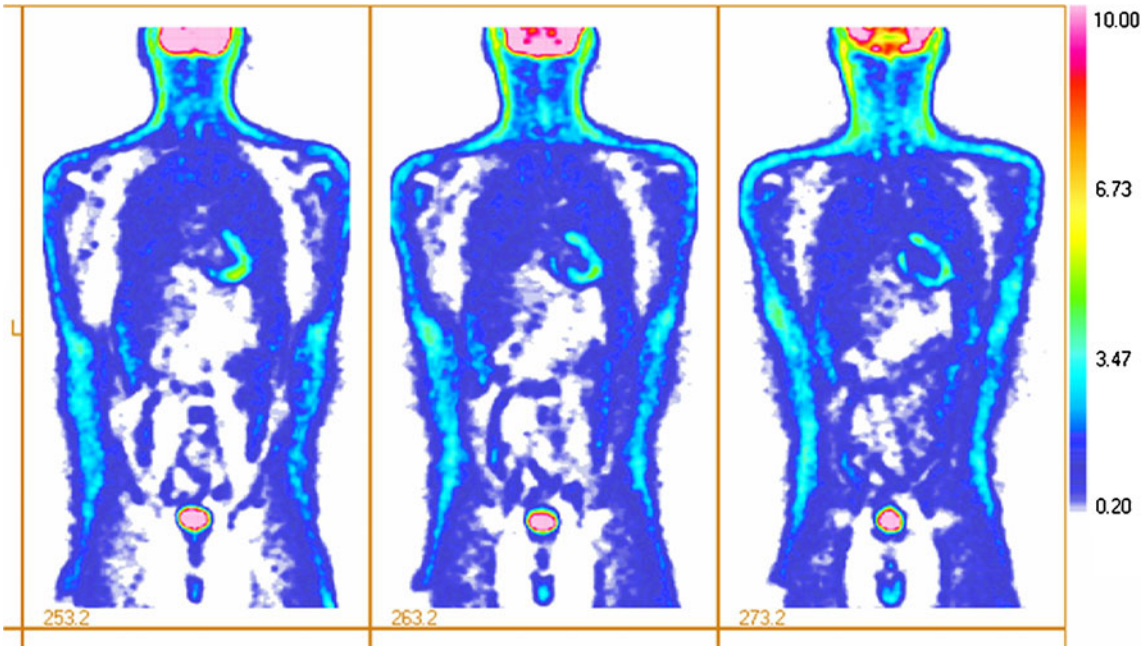

Fig. 1 Selected sagittal views from the [^{18}F] fluoroxeoxyglucose positon emission tomography (FDG-PET) demonstrating deep spinal infection in the level of the IV. lumbar vertebra

Discussion

In developed countries, pyogenic vertebral osteomyelitis is a rare cause of subfebrility, especially in young age, and the diagnosis has always been a challenge for the clinician. A typical case of spinal infection may present with tenderness, mild muscle spasm, and decreased range of motion. The patient may complain fever, anorexia and malaise [4]. In our case the physical examination did not find the local physical signs of the vertebral affection.

Pyogenic vertebral osteomyelitis usually results from haematogenous seeding of the bone. The most common source of infection is the genito-urinary system. The common causative organisms in lumbar osteomyelitis are Staphylococcus aureus, but other Gram positive bacterias such as Streptococcus equisimilis [5] and dysgalactiae [6], and Enterobacteriaceae [7] have been also implicated in human bone infections [4]. The demographics of the diseases appear to have changed, since the patients appeared to be older and in immune-suppressed status that

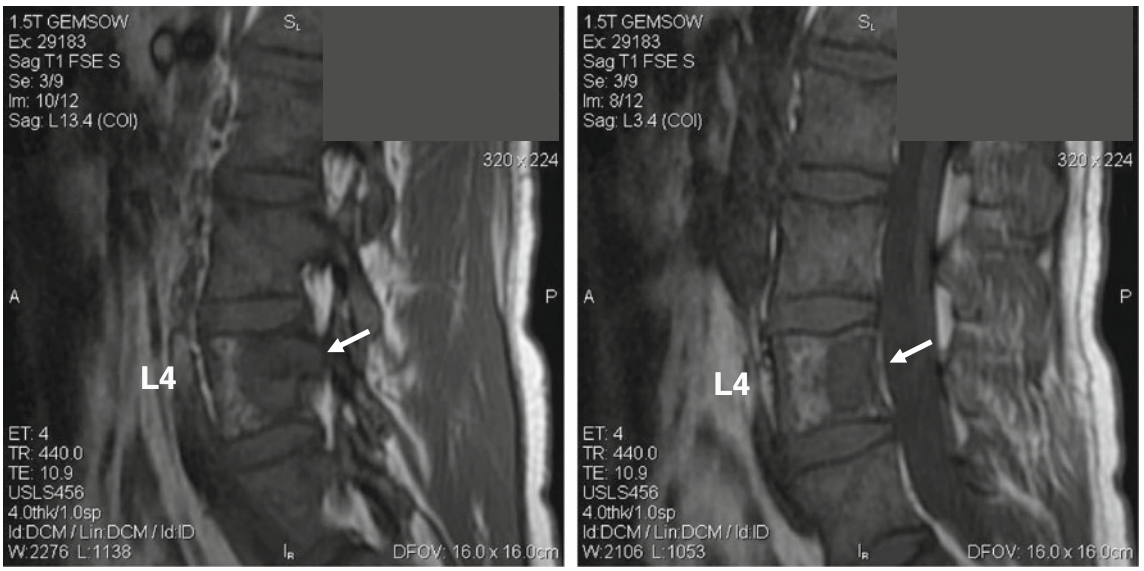

Fig. 2 Magnetic resonance imaging scans of the lumbar spine. T1-weighted image demonstrates diffuse inhomogenous destructive lesions in all of the lumbar vertebrae and a 20×10×22 mm tumor-like terime in the posterior region of the L4 vertebra (white arrows)

those previously reported. Furthermore, the infecting organisms are not the previously described S.aureus and streptococci [7]. In the presented case the source of infection was not identified, but the patient has been underwent an empiric antibiotic treatment before the hospitalization. The most likely primary causes could be the asymptomatic urinary infection and the dermal infection caused by a minor skin injury (probably during the hard physical work he made).

The early and accurate diagnosis of the infection is crucial in determining appropriate therapy and shortens the duration of the disease and the likelihood of severe sequel. Numerous imaging techniques have been used to diagnose and monitor the vertebral infections, including conventional radiography, computed tomography, magnetic resonance imaging and radionuclide imaging techniques [8].

FDG-PET has several potential advantages over other nuclear techniques. It can provide definitive results within 30–60 min of tracer administration because of the fast penetration of glucose in the lesion even in poorly perfused areas. Since normal bone marrow has only a low glucose metabolism under physiological conditions, inflammatory cellular infiltration can be easily detected. Degenerative bone alterations have only faintly increased FDG uptake, which permits the distinction of infection and other pathological processes. Finally, FDG-PET is less expensive than the combinations of radiolabelled leukocyte/bone marrow/bone scan imaging techniques [8]. Furthermore, FDG-PET combined with computed tomography (CT) may be also an excellent alternative to CT alone and conventional MRI in detecting the unknown primary tumor in patients with carcinoma of unknown primary. Compared to other diagnostic procedures that are often used in these patients FDG PET/CT is both noninvasive and a very sensitive tomographic whole-body imaging modality, allowing for the detection of a primary tumor and complete tumor staging in a single examination [9].

Magnetic resonance imaging is an effective early noninvasive diagnostic tool [10]. However, the route of hematogenous spread of microorganisms might induce osseous changes similar to those of hematogenous spread of other etiologies, such as malignant cells. Thus, vertebral osteomyelitis can have MR imaging patterns mimicking osseous metastases [11]. Early and appropriate microbiological investigation of patients with fever, back pain and inflammatory markers can reduce the possibility of diagnostic errors [4].

Initial treatment of vertebral osteomyelitis requires intravenous antibiotics, followed by oral antibiotics to complete a course of therapy. The recommended duration of antibiotic therapy vary from 4 to 6 weeks to 2 to 3 months or more [7, 12–14]. A previous review suggests a short-duration antibiotic therapy (6 weeks) without enhancing the risk of relapse. However the optimal treatment for each patient should be determined on an individualized case-by-case basis using clinical judgement [15]. A recent study found that even in patients with negative culture findings, a good outcome can be achieved by the administration of cefazolin or vancomycin for about 6 weeks. It was concluded that antibiotics selected according to the etiological setting can be initiated without the need to start empirical antibiotics. In every instance at fourth week after the initiation of antibiotic therapy, the values of CRP and ESR can provide meaningful information regarding whether clinicians need to reevaluate the effectiveness of antibiotics by performing follow-up imaging studies and monitoring the patient's clinical manifestations [16].

Although fever is present in only about one-third of cases, osteomyelitis is a common diagnosis in FUO. In the presented case imaging techniques, however, suggested malignancy. Therefore biopsy and microbiological investigation may be necessary in patients with fever and evidence of a spinal lesion on imaging [17], even if neoplastic disease is suspected.

References

1. Petersdorf RG, Beeson P (1961) Fever of unexplained origin: report on 100 cases. Medicine (Baltimore) 40:1–30
2. Roth AR, Basello GM (2003) Approach to the adult patient with fever of unknown origin. Am Fam Physician 68:2223–2228
3. Mourad O, Palda V, Detsky AS (2003) A comprehensive evidence-based approach to fever of unknown origin. Arch Intern Med 163:545–551
4. Zimmerli W (2010) Clinical practice. Vertebral osteomyelitis. N Engl J Med 362:1022–1029
5. Gomez-Rodriguez N, Ferreio-Seoane JL, Ibanez-Ruan J, Servillano-Castano J (1998) Spondylodiscitis cause by Streptococcus equisimilis. Br J Rheumatol 37:1030–1032
6. Kumar A, Sandoe J, Kumar N (2005) Three cases of vertebral osteomyelitis caused by Streptococcus dysgalactiae subsp. equisimilis. J Med Microbiol 54:1103–1105
7. Carragee EJ (1997) Pyogenic vertebral osteomyelitis. J Bone Joint Surg Am 79:874–880
8. Gemmel F, Dumarey N, Palestro CJ (2006) Radionuclide imaging of spinal infections. Eur J Nucl Med Mol Imaging 33:1226–1237
9. Kwee TC, Basu S, Cheng G, Alavi A (2010) FDG PET/CT in carcinoma of unknown primary. Eur J Nucl Med Mol Imaging 37:635–644
10. Sammak B, Abd El Bagi M, Al Shahed M et al (1999) Osteomyelitis: a review of currently used imaging techniques. Eur Radiol 9:894–900
11. Hsu CY, Yu CW, Wu MZ et al (2008) Unusual manifestations of vertebral osteomyelitis: intraosseous lesions mimicking metastases. AJNR Am J Neuroradiol 29:1104–1110
12. Gentry LO (1990) Antibiotic therapy for osteomyelitis. Infect Dis Clin North Am 4:485–499
13. Legrand E, Flipo RM, Guggenbuhl P et al (2001) Management of nontuberculous infectious discitis. treatments used in 110 patients

admitted to 12 teaching hospitals in France. Joint Bone Spine 68:504–509
14. Bhavan KP, Kirmani N (2009) Hematogenous vertebral osteomyelitis. Mol Med 106:277–282
15. Roblot F, Besnier JM, Juhel L et al (2007) Optimal duration of antibiotic therapy in vertebral osteomyelitis. Semin Arthritis Rheum 36:269–277
16. Yoon SH, Chung SK, Kim KJ et al (2010) Pyogenic vertebral osteomyelitis: identification of microorganism and laboratory markers used to predict clinical outcome. Eur Spine J 19:575–582
17. Hassoun A, Taur Y, Singer C (2006) Evaluation of thin needle aspiration biopsy in the diagnosis and management of vertebral osteomyelitis (VO). Int J Infect Dis 10:486–487