

CASE REPORT

USE OF POLYMERASE CHAIN REACTION IN DIAGNOSIS OF OCCULT TUBERCULOSIS OF THE FIBULA

K. MALHAN, A. KUMAR, K. P. SHERMAN

An unusual case of tuberculosis of the lower end of the fibula in a young patient is reported. The patient presented with symptoms of pain and swelling over the outer aspect of the right ankle with full range of painless ankle movements. The plain radiographs of the ankle were normal but MRI scan showed increased signals within the lower end of the fibula on T2-weighted images. The histology of the lesion showed only a few Langhans giant cells and culture failed to grow any organism. Polymerase chain reaction analysis of the biopsy specimen, however, showed growth of *Mycobacterium tuberculosis*. The patient responded to antitubercular treatment with complete resolution of symptoms. Polymerase chain reaction analysis should be considered in atypical presentations with bone pain to rule out an occult infectious pathology.

Keywords : tuberculosis ; fibula ; polymerase chain reaction.

Mots-clés : tuberculose ; péroné ; amplification génomique.

CASE REPORT

A 28-year-old non-Caucasian male presented with pain and swelling of two months duration over the outer aspect of the right ankle. There was no history of constitutional symptoms, trauma or any recent strenuous activity. The patient did not suffer from any significant medical illness. On examination there was some swelling and deep tenderness over the lateral malleolus. The ankle had a full range of painfree movements. Plain radiographs were reported as normal. All routine blood investi-

gations including ESR and CRP were also normal. The patient failed to respond to conservative treatment. Further investigation with a bone scan revealed an increased uptake in the lower end of the fibula. The MRI images of the right ankle showed high signals in the lower end of the fibula on T2-weighted images and STIR sequences. The cortices looked intact in all sections (fig. 1).

The patient underwent open biopsy for histological examination, culture and polymerase chain reaction (PCR) analysis. Histology showed a few Langhans giant cells, but no bacilli were seen. PCR analysis showed *Mycobacterium tuberculosis*, but cultures failed to grow any organism. There was no evidence of pulmonary tuberculosis on chest radiograph. On the basis of clinical features, histology and PCR results, antitubercular treatment was started. The patient responded to the treatment with complete resolution of symptoms.

DISCUSSION

Extrapulmonary tuberculosis accounts for about 28% of all cases of tuberculosis according to a national survey in England and Wales. Lymph nodes are the commonest site involved and osteoar-

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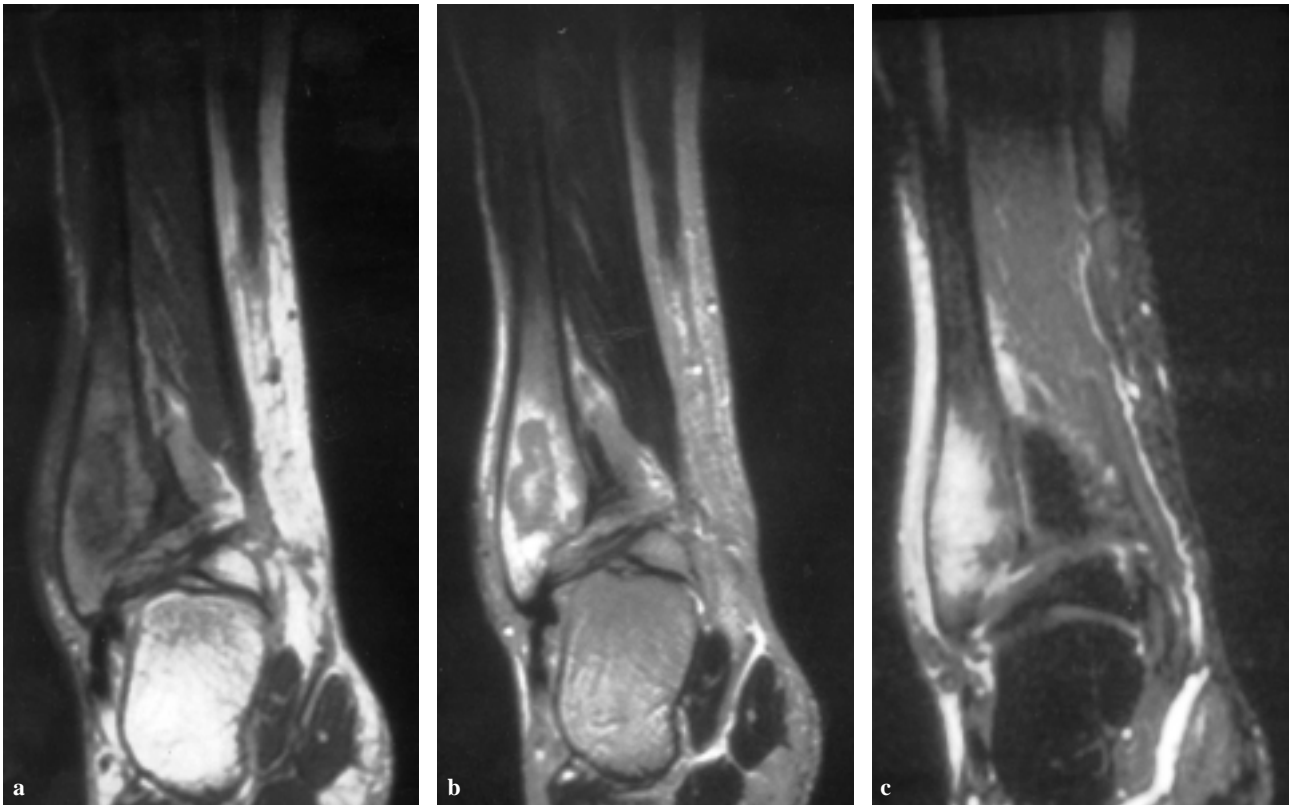


Fig 1. — MRI scan of the right ankle.

a. T1-weighted image showing an area of low intensity in the lower end of the fibula.

b. T2-weighted image showing an area of high signal surrounding an area of low intensity.

c. STIR sequence showing a homogeneous area of high signal in the lower end of the fibula with some overlying soft tissue swelling.

ticular tuberculosis constitutes about 13% of all extrapulmonary cases (6). The commonest site for skeletal tuberculosis is the spine followed by the hip, knee and ankle joints (4). Osteomyelitis without articular involvement is uncommon, though it has been reported in various locations such as ribs, scapula, fingers (4), ischium, calcaneum, proximal and distal humerus and tibia (3), and skull (7).

The diagnosis of tuberculosis is usually suspected on clinical symptoms and plain radiographs and is confirmed by demonstration of the bacilli in the infected tissues. The radiographic findings may range from soft tissue swelling without bony changes at the one end of the spectrum to osteopenia, lytic changes and destruction of the cortices with little or no periosteal reaction at the other end. In the early stages, when radiographs are normal, MRI or CT scan may help to define the extent of

the lesion. A high signal on T2-weighted images could be either fluid (edema) or a cartilaginous tumor and biopsy should be done to confirm the diagnosis. On histologic examination, the presence of Langhans giant cells is strongly suggestive of tuberculosis, but is not diagnostic, and demonstration of the bacilli is essential for a definite diagnosis. Cultures are essential, for to see one bacillus under a high-power field needs more than 10^3 organisms/mm³ of tissue (1). But cultures may take long time to grow the organism, and the sensitivity could be as low as 58% (2). Polymerase chain reaction (PCR) is a technique that amplifies a specific genome and has shown promise in identifying the DNA sequence of various slow-growing organisms including mycobacterium, viruses and fungi (2, 5, 8). Amplification techniques are particularly useful for the diagnosis of osteoarticular tuberculosis

where organisms are sparse. It has been shown to have a sensitivity of about 95 % and specificity of 83% with accuracy of 92% in the diagnosis of Pott's disease of the spine (2). However, problems of contamination, standardization and cost have prevented widespread use of this technique. False positive tests may occur in the laboratory through contamination with even a small number of organisms, which are then amplified to suggest a positive test. On the other hand, some samples may contain PCR inhibitors, which may cause false negative results in infected tissues (5, 8).

The lower end of the fibula is an uncommon site for tuberculosis. A high index of suspicion is required for an infectious or a neoplastic disease, if the bone pain does not respond to conservative treatment. Judicious use of PCR analysis coupled with clinical features and radiographic findings could help in early diagnosis and treatment of an atypical presentation of skeletal tuberculosis or any other low-grade bone infection.

REFERENCES

1. Bates J. H. Diagnosis of tuberculosis. *Chest*, 1979, 76, 757-763.
2. Berk R. H., Yazici M., Atabay N, Ozdamar O. S. *et al.* Detection of Mycobacterium tuberculosis in formaldehyde solution-fixed, paraffin-embedded tissue by polymerase chain reaction in Pott's disease. *Spine*, 1996, 21, 1991-1995.
3. Garcia S., Combalia A., Serra A., Segur J. M. *et al.* Unusual locations of osteoarticular tuberculosis. *Arch. Orthop. Trauma Surg.*, 1997, 116, 321-323.
4. Halsey J. P., Reeback J. S., Barnes C. G. A decade of skeletal tuberculosis. *Ann. Rheum. Dis.*, 1982, 41, 7-10.
5. Harrington J. T. The evolving role of direct amplification tests in diagnosing osteoarticular infections caused by mycobacterium and fungi. *Curr. Opin. Rheum.*, 1999, 11, 289-292.
6. Kumar D., Watson J. M., Charlett A., Nicholas S. *et al.* Tuberculosis in England and Wales in 1993 : Results of a national survey. *Thorax*, 1997, 52, 1060-1067.
7. LeRoux P. D., Griffin G. E., Marsh H. T., Winn H. R. Tuberculosis of the skull. A rare condition : Case report and review of the literature. *Neurosurgery*, 1990, 26, 851-856.
8. Lisby G. Application of nucleic acid amplification in clinical microbiology. *Mol. Biotech.*, 1999, 12, 75-99.

SAMENVATTING

K. MALHAN, A. KUMAR, K. P. SHERMAN. Het belang van gen-amplificatie in de diagnose van een occulte tuberculeuse aantasting van de fibula.

De schrijvers verhalen een zeldzame tuberculeuse invasie van de distale fibula bij een jeugdige patiënt. Zijn klachten bestonden in lokale zwelling en pijn op de buitenzijde van de rechter enkel, zonder stoornis van enkelfunctie en -motiliteit. Standaard RX waren negatief ; het NMR onderzoek toonde een verhoogd signaal op T2 gewogen beelden ter hoogte van het letsel. Histologisch werden enkele Langhans reuscellen gevonden ; geen groei op cultuurbodemp. Onderzoek van de biopsie bij middel van polymerase ketting reactie (PCR) bevestigde de groei van *Mycobacterium tuberculosis*. De symptomen verdwenen volledig onder antituberculeuse therapie. PCR moet worden overwogen in atypische gevallen van beenpijn om een occult infectieus proces uit te sluiten.

RÉSUMÉ

K. MALHAN, A. KUMAR, K. P. SHERMAN. Intérêt de la technique d'amplification génomique dans le diagnostic d'une atteinte tuberculeuse occulte du péroné.

Les auteurs rapportent un cas inhabituel d'atteinte tuberculeuse de l'extrémité distale du péroné chez un patient jeune. Il se plaignait de douleurs et de gonflement à la face externe de la cheville droite, avec conservation d'une amplitude de mobilité normale et indolore de la cheville. Les radiographies standard de la cheville étaient normales, mais l'IRM montrait un hypersignal au niveau de l'extrémité inférieure du péroné sur les images en T2. L'histologie de la lésion ne montrait que de rares cellules géantes de Langhans ; la culture n'a montré aucune croissance microbienne. L'analyse du tissu de biopsie par PCR (Polymerase Chain Reaction) a montré la présence de *mycobacterium tuberculosis*. Le patient a bien répondu au traitement anti-bacillaire qui a fait disparaître complètement les symptômes. Le recours à la technique d'amplification génomique (Polymerase Chain Reaction) devrait être envisagé en présence d'une douleur osseuse de présentation atypique, pour éliminer l'hypothèse d'une pathologie infectieuse.