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CASE REPORT

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Spondylodiscitis as the first manifestation of Whipple's disease–a removal worker with chronic low back pain

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Abstract Whipple's disease is a rare systemic infectious disease caused by the actinobacterium *Tropheryma whipplei*. Spondylodiscitis is an extremely rare manifestation of the infection and has previously been described in only three case reports. We present a 55-year-old man with persistent lumbago and signs of systemic illness, but without any gastrointestinal symptoms or arthralgia. The signal response in the lumbar spine in magnetic resonance tomography, both native and after intravenous gadolinium administration, was compatible with spondylodiscitis at the L4/L5 level. Culture of a specimen obtained by radiographically guided disc puncture and repeated blood cultures remained sterile. *Tropheryma whipplei* was detected by PCR amplification in material obtained from the disc specimen, from a biopsy of the terminal ileum and from the stool. The histology of duodenum, terminal ileum, colon and disc material was normal and, in particular, showed no PAS-positive inclusions in macrophages. Long-term antibiotic treatment with sulphamethoxazole and trimethoprim was successful, with marked improvement of the low back pain and normalisation of the systemic inflammatory signs. The possibility of Whipple's disease must be suspected in the case of a 'culture-negative' spondylodiscitis even if there are no gastrointestinal symptoms and no arthralgia present.

Keywords Low back pain · Spondylodiscitis · Whipple's disease

Abbreviations *PAS* Periodic acid–Schiff · *PCR* Polymerase chain reaction · *PSA* Prostate-specific antigen · EDTA Ethylene diamine tetra-acetic acid

Introduction

Whipple's disease, first described in 1907, is a systemic infectious disease caused by *Tropheryma whipplei*. The main clinical symptoms are diarrhoea, weight loss and arthralgia, with cardiac or central nervous manifestations being indicative of a poor prognosis [1, 2, 3]. The clinical suspicion is usually confirmed by the detection of diastase-resistant, non-acid fast PAS (periodic acid–Schiff stain)-positive inclusions in macrophages of the small intestinal mucosa, or the electron microscopic imaging of the typical trilamellar cell membrane of the pathogen. Culture of the organism has recently been described but is not available for routine diagnosis [4, 5]. Molecular genetic detection by means of broad-spectrum PCR (polymerase chain reaction) amplification of the bacterial 16S ribosomal RNA gene and subsequent identification by sequencing of the amplicon or by species-specific PCR is gaining increasing diagnostic relevance [2, 6, 7, 8, 9].

We report a case of 'culture-negative' spondylodiscitis as the first manifestation of Whipple's disease in which the pathogen was finally detected by broad-spectrum PCR with DNA isolated from disc puncture biopsy material.

Case report

A 55-year-old removal worker was hospitalised for lumbago that had been refractory to physiotherapy and analgesic medication for a year, with the appearance of

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lower lumbar pain at night over the past 4 months. Systemic manifestations included loss of appetite, an unintentional loss of 4 kg in weight over 4 months, and occasional night sweats. Arthralgia and gastrointestinal symptoms such as diarrhoea or increased stool frequency were completely absent. The most prominent clinical features were lower lumbar percussion pain and the reduction of lumbar spinal mobility by two-thirds. The neurological findings and peripheral joint status were normal. The patient was afebrile.

The initial laboratory tests gave the following results: ESR 52 mm/h, CRP 50 mg/l (reference range up to 10 mg/l), leucocytes 8.5×10^9/l with 48.5% stabnuclear; haemoglobin 14.9 g/dl, platelets 506×10^9/l; four blood cultures without microbial growth; immune fixation of serum and urine as well as PSA normal; HIV serology negative.

Magnetic resonance tomography of the lumbar spine revealed a sacralisation of the fifth lumbar vertebra as well as a considerable reduction in the height of the L4/L5 intervertebral space, with erosive alterations of the adjacent vertebral end plates (as previously documented by plain radiographs). With T_2 weighting the signal was increased centrally in the L4/L5 disc and there was L4 and L5 vertebral body oedema, with marked enhancement after gadolinium administration. Streaky enhancement, more marked on the left, was also found in the paravertebral space, but without evidence of a paravertebral or epidural abscess (Figs 1a–1c and 2a and b). A conventional chest X-ray and an abdominal CT scan were normal.

We performed an invasive exploration by radiographically guided disc puncture biopsy because of persistent low back pain over 1 year with signs of systemic disease and the development of lumbar pain also at night and on percussion, together with elevated inflammatory parameters and a marked left shift in the differential blood count, as well as a magnetic resonance tomography scan suggesting L4/L5 spondylodiscitis with an absence of microbial growth in four blood cultures.

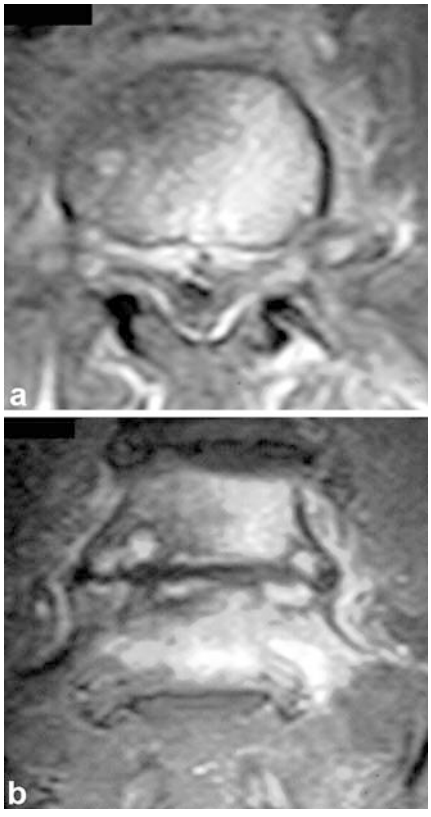

Fig. 2 **a** MRI of L4 lumbar vertebra, horizontal, fat-suppressed and after i.v. gadolinium; **b** MRI of lumbosacral transition, frontal, fat-suppressed and after i.v. gadolinium. Left-accentuated enhancement of L4 and L5 vertebral bodies with streaky paravertebral enhancement, more marked on the left. No abscess formation. Erosive alterations of the L4/L5 end plates with enhancement, central enhancement in the height-reduced disc. Degenerative spinal canal stenosis

Culture of the disc puncture biopsy material, including cultivation for *Mycobacterium tuberculosis,* revealed no microbial growth. Oesophageogastroduodenoscopy was normal, as was coloileoscopy, apart from a small ulcer on the ileocaecal valve. Histologically, the disc puncture biopsy material showed partially necrotic, partially degeneratively altered fibrous cartilage in pla-

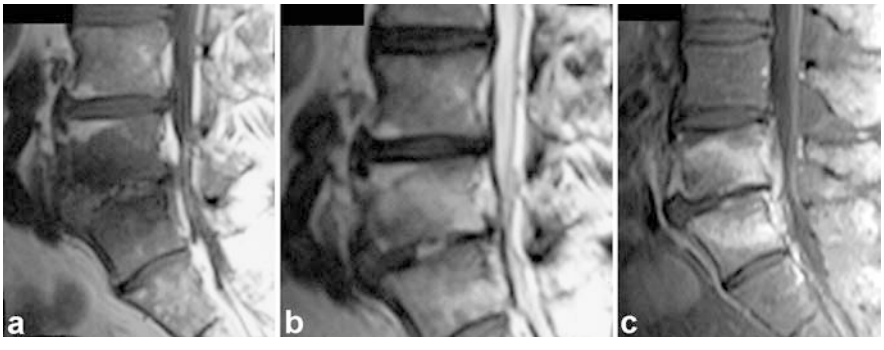

Fig. 1 Magnetic resonance tomography of the lumbar spine, both native and after intravenous gadolinium. **a** MRI of lumbar spine, sagittal, T_1 weighting; **b** MRI of lumbar spine, sagittal, T_2 weighting; **c** MRI of lumbar spine, sagittal, fat-suppressed and after i.v. gadolinium. Lumbar L4/L5 disc reduced in height, with central T_2 hyperintense signal. Erosive alterations of L4 bottom plate and L5 top plate, as well as bone marrow oedema of both vertebral bodies (more marked on the left) with enhancement after intravenous gadolinium. No epidural or paravertebral abscess

ces. The histology of the biopsy material from duodenum, terminal ileum and colon was normal, apart from regenerative epithelial fragments and granulation tissue in the area of the small ileocaecal valve ulcer. In particular, no PAS-positive inclusions in macrophages were detected.

In contrast, broad-spectrum PCR [9] revealed *T. whipplei* DNA in material from the L4/L5 disc puncture biopsy. This result was confirmed by two different species-specific real-time PCR assays targeting the 16S rDNA and an open reading frame of unknown function, respectively [10]. Biopsies from terminal ileum and colon, as well as a stool sample, were also positive using the specific assay targeting the 16S rDNA, but no *T. whipplei* DNA was found in an EDTA blood sample.

Antibiotic therapy with sulphamethoxazole and trimethoprim (800 mg plus 160 mg twice daily; additional folic acid substitution) led to normalisation of the inflammatory parameters within 1 month, and the patient was asymptomatic and fully able to work 5 months after starting therapy.

Discussion

To our knowledge, only three cases of Whipple's disease with spondylodiscitis as the main manifestation have been reported [9, 11, 12]. There seems to be an accumulation of cases of Whipple's disease with unusual presentation in the Zurich area and eastern Switzerland, as 3 of the 4 spondylitis cases as well as at least 7 other cases have been observed in this geographical area within a short time (four cases of endocarditis, one each with involvement of the CNS, the bone marrow and the joints, respectively) [11, 13, 14, 15]. In one of these 7 patients, PAS-positive bacteria were detected in bone marrow biopsy material [15]. We assume that the high incidence of Whipple's disease found in the Zurich area is not related to a peculiar epidemiologic situation but rather to the increased use of molecular methods for the analysis of unclear infections, especially the broad-spectrum PCR on usually sterile specimens.

A notable feature of our case is the absence of gastrointestinal symptoms and arthralgia. In recent years there has been an increasing number of reports of various organ manifestations of Whipple's disease without clinical or histological evidence for an involvement of the gastrointestinal tract [9, 11, 13].

The indication for invasive exploration was based on several 'red flags' for a secondary form of low back pain that had been refractory to treatment for 1 year. Apart from lower lumbar pain at night and on percussion, signs of systemic disease developed, with loss of appetite, weight loss and night sweats combined with elevated inflammatory parameters and a left shift in the differential blood count. The signal alteration in a magnetic resonance tomography scan of the lumbar spine was compatible with spondylodiscitis. Repeated blood cultures failed to show microbial growth and there was no evidence of any underlying neoplastic disease.

After we failed to detect any pathogen in the L4/L5 disc puncture biopsy material by histological examination and conventional culture, the specimen was examined by broad-spectrum PCR. Sequencing of the amplicon revealed *T. whipplei* in the material from the disc puncture biopsy. We did not attempt to culture *T. whipplei* using cell cultures because at the time the specimens were taken, Whipple's disease was not suspected clinically. This illustrates the usefulness of broad-spectrum PCR, which detects any bacterium if present in sufficient numbers. The presence of *T. whipplei* was subsequently confirmed with two independent species-specific PCR assays with DNA from the disc puncture biopsy, as well as by a positive PCR from duodenum and colon biopsies, respectively. Despite positive PCR results, the histological findings in material from the duodenum, terminal ileum, colon and disc puncture biopsy were normal, and in particular there were no PAS-positive inclusions in macrophages.

T. whipplei seems to be a rather common environmental organism and is detectable in the gastrointestinal tract of a significant proportion of asymptomatic carriers. In a prospective study with elective gastroscopy in 105 patients without signs of Whipple's disease, positive results were obtained by PCR amplification in 11.4% of gastric juice aspirates and 4.8% of duodenal biopsies [16]. These results were confirmed in a follow-up study, with 6 of 14 initially positive subjects being also positive in saliva [17]. Similarly, *T. whipplei* DNA was detected by PCR in the saliva of 35% of 40 healthy persons [18], with results remaining positive in a repeat test. In contrast, *T. whipplei* DNA has not so far been reported from usually sterile locations (joints, cerebrospinal fluid) from persons without Whipple's disease. Gene sequences specific for *T. whipplei* were also found in 25 of 38 effluent water samples from five different sewage plants in southern Germany [19]. Whether these findings indeed indicate environmental occurrence of the organism is debatable, as it may as well simply reflect fecal excretion. *T. whipplei* may be a commensal bacterium that leads to systemic infection only under special, as yet undefined circumstances, such as macrophage dysfunction. Despite this possible widespread environmental occurrence, a positive finding of specific DNA by PCR in the context of an infection of a normally sterile body site can be considered diagnostic.

The recent sequencing of the complete *T. whipplei* genome provides new insights into the biology of this pathogen, with the possible perspective of new diagnostic strategies [20].

In summary, the possibility of Whipple's disease must be suspected in the case of a 'culture negative' spondylodiscitis, even if there are no gastrointestinal symptoms and no arthralgia present. Compared to histological detection of non-acid-fast PAS-positive macrophage inclusions, PCR amplification of the specific 16S rRNA gene sequences of *T. whipplei* is more sensitive and

allows early diagnosis and the introduction of long-term antibiotic therapy.

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