Transpl Int (2001) 14: 274–277

BRIEF REPORT

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Microsporidiosis in the graft of a renal transplant recipient

Received: 18 May 2000
Accepted: 28 May 2001

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Abstract Microsporidia are intracellular protozoa that are emerging as significant opportunistic infections in AIDS patients. Although there are numerous published reports of intestinal and disseminated infections in patients with AIDS, there have been only two previous reports in transplantation medicine, both on intestinal microsporidiosis. We report here the first documented case of extra-intestinal microsporidiosis in a transplant recipient. A 39-year-old renal transplant recipient presented with a pyrexia and deteriorating graft function. Light microscopic examination of a renal allograft biopsy revealed numerous microsporidian spores within the renal tubular epithelium. Transmission electron microscopy confirmed the presence of an *Encephalitozoon* infection and was highly suggestive of *Encephalitozoon intestinalis*. Therapy with albendazole was extremely effective and resulted in recovery of renal function. Although a rare cause of renal allograft dysfunction, microsporidiosis is curable. It may be underdiagnosed, and should be considered in the differential diagnosis of transplant recipients presenting with opportunistic infections.

Keywords Albendazole · Electron microscopy · *Encephalitozoon* · Graft failure · Protozoa · Microsporidia · Opportunistic infections · Renal transplantation

Abbreviations *TEM* Transmission electron microscopy

Introduction

Microsporidia are obligate intracellular parasites characterised by spores containing a unique coiled polar tubule and associated extrusion apparatus that can infect a wide variety of cells. These protozoa have grown in significance as opportunistic infections in patients with AIDS and are responsible for up to 30% of cases of diarrhoea in these patients [13]. These intestinal infections are caused by *Encephalitozoon intestinalis* and *Enterocytozoon bieneusi*. Although *E. bieneusi* is the most common cause of intestinal microsporidiosis, it never disseminates. Disseminated infections are caused by *E. intestinalis*, *Encephalitozoon cuniculi* and *Encephalitozoon hellem*. Several reports in the literature have described disseminated and renal microsporidiosis in patients with AIDS [1, 2, 3, 5, 8, 12]. This article reports the first case of extra-intestinal microsporidiosis in a renal transplant recipient.

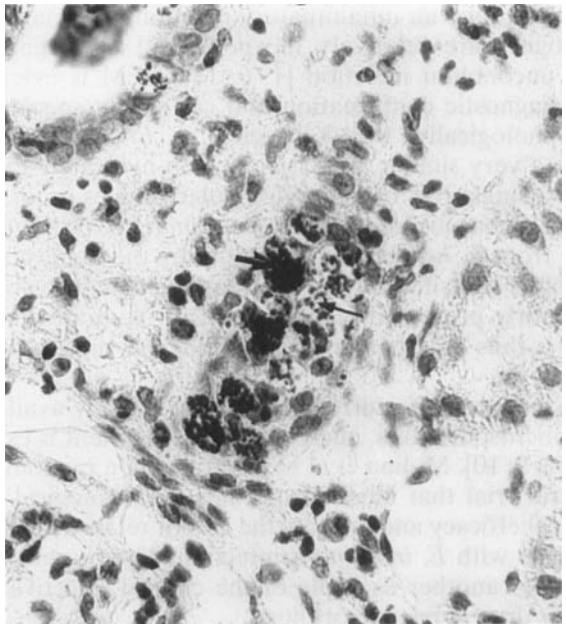

Fig. 1 Brown and Brenn stain of tubules to show spores within renal epithelial cells (*arrows*). Magnification × 160

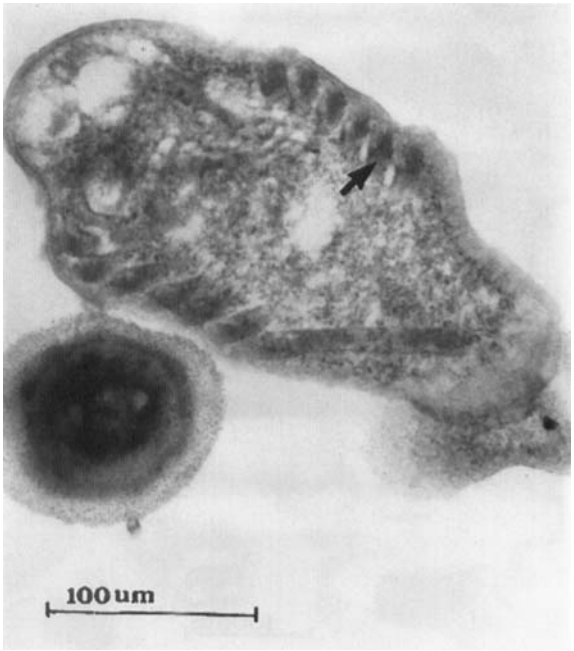

Fig. 2 TEM of spore showing the single row of coiled polar tubule (*arrow*). Magnification × 15000

Case report

A 39-year-old female presented with end-stage renal disease secondary to lupus nephritis. Chronic intermittent haemodialysis was initiated in 1988. Her first cadaveric renal transplant, performed in 1990, had failed by April 1999, and a second cadaveric renal transplant was performed in August 1999. The maintenance immunosuppression was achieved with cyclosporine, prednisone and azathioprine. In November and in December 1999, she presented with episodes of suspected acute graft rejection, which were treated with intravenous methylprednisolone. Graft function responded well, and the serum creatinine settled at 148 μmol/l. The patient was admitted 2 weeks later with a high fever, rigors, and deteriorating renal function (serum creatinine 287 μmol/l, urea 15.7 mmol/l). Although an infective cause for the pyrexia was suspected, repeated chest x-rays, sputum cultures, urine cultures, and blood cultures were negative. A CMV pp-65 antigenaemia and HIV test were also negative. A bone marrow biopsy showed no evidence of occult tuberculosis. The patient remained pyrexial and by a week after admission, the serum creatinine had risen to 476 μmol/l. A percutaneous renal biopsy was therefore performed on the 10th hospital day.

Light microscopy revealed microsporidian spores within renal tubular epithelial cells, and, to a lesser extent, within the interstitium, best seen using the modified Gram stain (Fig. 1). The interstitium showed a chronic inflammatory infiltrate, and the glomeruli appeared normal. Transmission electron microscopy (TEM) examination revealed the characteristic ultrastructural appearance of a Microsporidial infection. Spores within the renal tubular epithelial cells contained a single row of coiled polar tubules (Fig. 2) typical of the Encephalitizoa. A fibrillar matrix could be identified in places between the spores (Fig. 3), suggestive of the honeycombed parasitophorous vacuole of *Encephalitozoon intestinalis*. Accurate species-level identification was not possible due to the unavailability of specific anti-sera or PCR at our institution. Repeated urine specimens stained with a modified trichrome stain revealed numerous microsporidia, but none were found in stool- or sputum specimens.

Renal function, however, continued to deteriorate, and the serum creatinine had increased to 835 μmol/l at the time of commencing therapy with Albendazole 400 mg p.o., b.i.d. A clinical response was evident 3 days later when the pyrexia completely resolved. The renal function gradually improved, and 4 weeks after commencing therapy, the serum creatinine had decreased to 605 μmol/l. Urine specimens taken at 1 and 2 months after commencing therapy remained positive for microsporidia, and after 12 weeks of albendazole therapy the serum creatinine had decreased to 254 μmol/l. Therapy will be continued until the microsporidia has been cleared from urine specimens and then for a further 12 months to prevent relapse.

Discussion

Encephalitozoon infection with *E. intestinalis*, *E.cuniculi*, and *E. hellem* can result in intestinal and disseminated infections in immunocompromised patients. Although patients may report a preceding history of diarrhoea, and evidence for respiratory acquisition has been reported, the exact mechanisms of human transmission is poorly understood [12]. Microsporidiosis can affect virtually any organ but is predominantly found in the gastrointestinal tract, urinary tract, respiratory tract, and the eye.

Microsporidiosis involving the urinary tract is common in patients with *Encephalitozoon* infection and is frequently asymptomatic. The parasite has a predilection for renal tubular epithelium, and renal infection

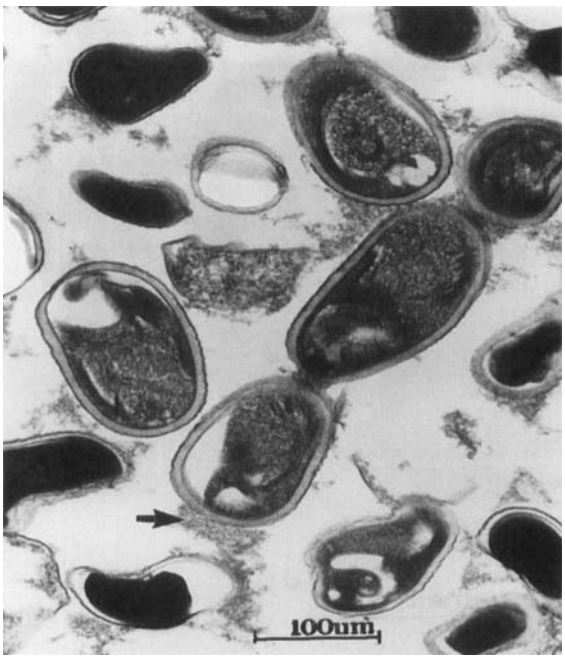

Fig. 3 TEM to show the fibrillar material (*arrow*) between spores suggesting an *E. intestinalis* infection. Magnification × 32000

can result in flank pain, proteinuria, and renal failure. Spores are carried in the urine from the kidney to the ureters and bladder, where they infect the transitional epithelium resulting in micro- or macro-haematuria.

Histological findings on renal biopsy include: a) chronic and/or granulomatous interstitial nephritis; b) microsporidian spores occurring predominantly in tubular epithelium resulting in tubular necrosis and discharging of necrotic material and spores into lumina; and c) glomeruli are spared. The organisms and spores are often missed on routine haematoxylin-eosin-stained specimens because they are extremely small in size, often only obvious with special stains (modified Gram's, Warthin-Starry, Brown & Brenn, modified trichrome), may not elicit an inflammatory reaction, and many pathologists are relatively inexperienced at diagnosing this uncommon infection [1, 6, 12]. TEM is essential for diagnostic confirmation and can aid in speciation. Morphologically, the 3 species of *Encephalitozoon* have a very similar appearance. Non-nucleated spores with a single row of 4–7 coiled polar tubules occur in a parasitophorous vacuole. *E. intestinalis* is distinguishable from *E. hellem* and *E.cuniculi* by the honeycombing of its parasitophorous vacuole, which may be absent on poorly preserved biopsy material. Accurate speciation is thus only possible with molecular biology techniques [1].

Albendazole is currently the only therapy available for microsporidiosis, and prolonged treatment is essential [3, 9, 10]. Molina et al have proven in a randomised control trial that albendazole 'has parasitological and clinical efficacy and reduces the risk of relapse in AIDS patients with *E. intestinalis* infection. The present case provides another example of the clinical effectiveness of this drug in microsporidiosis.

Disseminated and isolated renal microsporidiosis have been previously well documented in AIDS patients [3]. In contrast, the only published reports of microsporidiosis in transplantation medicine have been on patients with intestinal disease [4, 11]. To the best of our knowledge, this is the first report of extra-intestinal microsporidiosis in a transplant recipient and/or in a renal allograft. It is not clear why disseminated microsporidiosis is not found more frequently in immunocompromised transplant recipients, but this may be related to the degree of immunosuppression of most transplant recipients. Leder et al have shown that in AIDS, microsporidiosis occurs only in severely immunosuppressed patients with a median CD4 count of 20 cells/μl [7]. Although renal microsporidiosis is an extremely rare cause of renal allograft dysfunction, it is potentially curable with appropriate therapy. We suggest that this diagnosis be considered in transplant recipients presenting with a suspected opportunistic infection.

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