Evidence of lifetime susceptibility to *Tropheryma whipplei* in patients with Whipple's disease

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Sir,
Whipple's disease (WD) is a rare chronic infection caused by *Tropheryma whipplei*, of which the main symptoms are arthralgia and diarrhoea.[1] Only this one bacterium could be responsible for the presence of asymptomatic carriage, acute disease and chronic infections with a wide spectrum of clinical symptoms.[1,2] Surprisingly, the humoral immune response of patients is lower in patients with WD compared with that in asymptomatic carriers.[2] We report the first case of a patient presenting a relapse of WD with a different genotype of *T. whipplei*.[3] The patient gave informed consent for the publication of this report.

In 1990 a 59-year-old woman was diagnosed with WD based on a positive periodic acid-Schiff (PAS) stain performed on a small bowel biopsy.[4] The patient was treated with doxycycline (200 mg/day) for 8 years and based upon a negative small bowel biopsy the treatment was then stopped. In 2000 she presented with clinical and histological relapse. She was treated with doxycycline (200 mg/day) and hydroxychloroquine (600 mg/day) with clinical effectiveness over 19 months. In 2002 she presented with new joint involvement. Relapse was confirmed by histological analysis (Figure 1a). She received oral trimethoprim/sulfamethoxazole (320 mg/1600 mg/day). After 5 days of treatment she developed a major toxidermia that contraindicated this treatment. The patient underwent successive treatments with doxycycline and hydroxychloroquine for 34 months, doxycycline alone for 8 months and, finally, with doxycycline (200 mg/day) and azithromycin (500 mg/day) for 14 months. In 2007, based upon the full disappearance of infected macrophages from a histological analysis performed on a small bowel biopsy (Figure 1b), the antibiotic treatment was stopped. Twenty months later the patient presented with arthralgia and diarrhoea. The third relapse was confirmed by positive histological analysis. Treatment with intravenous ceftriaxone for 15 days followed by oral doxycycline and hydroxychloroquine was initiated. The treatment was changed to amoxicillin after 3 months, then was stopped in November 2009. Genotyping performed in 2002, 2005 and 2007 detected type 23.[3] From 2000 onwards, all drug monitoring confirmed antibiotic compliance. In May 2010, PCR performed on saliva, stools and duodenal biopsy was positive for *T. whipplei* with a previously unknown different genotype (type 77). The fourth relapse was confirmed based on the reappearance of positive PAS staining and immunohistochemistry (Figure 1c). Several western blots of immunoglobulins were performed showing systematically a low immunological response against *T. whipplei*. Therefore, doxycycline (200 mg/day) was proposed as a lifetime treatment.

This patient was diagnosed during the initial diagnosis and the relapses using rigorous criteria with both positive PAS and immunohistochemistry performed on a small bowel biopsy.[2] Serum drug levels were regularly monitored and were always within the therapeutic range, confirming accurate patient compliance. We performed *T. whipplei* genotyping for each relapse. In addition, the serological monitoring of this patient over several years confirmed the typical and paradoxical absence of immunity, demonstrating the inability of patients to eradicate *T. whipplei*, even when infected over a long period.

This case demonstrates that it is possible for a patient with WD to present several relapses with the same genotype even though the treatment and the follow-up were adequate based on previously rigorous criteria for treatment cessation.[5] This observation supports our recommendation for the use of bactericidal combination therapy to eradicate all *T. whipplei* before ceasing treatment.[5–7] Nevertheless, our patient developed a relapse despite apparent eradication of *T. whipplei* shown by histological examination of small bowel biopsies performed before the cessation of treatment. To our knowledge, this patient is the first case of relapse after treatment with the bactericidal combination of hydroxychloroquine and doxycycline.

Moreover, we found that a patient can develop a relapse with another *T. whipplei* strain, a common and ubiquitous environmental bacterium.[2] We are confident that this is a new strain, as the type 77 genotype identified in our patient was previously unknown, excluding the possibility of sample contamination.[3] The majority of human bacterial infections are transient and do not evolve into chronic disease. Some diseases, such as chronic granulomatous disease, are due to a genetic defect and are specifically associated with repetitive bacterial infections. A recent report described the possibility of successive infections caused by genetically distinct strains of *Granulibacter bethesdensis*, a ubiquitous environmental bacterium infecting patients suffering from chronic granulomatous disease.[8] As treatment, physicians prescribe antibiotics for long periods of time, including the lifetime of their patients. Although the specific immune defects are different, an analogy between the evolution of chronic granulomatous disease and WD can be proposed.

For patients with WD, we now propose to prescribe after at least 12 months of bactericidal antibiotic therapy, lifelong antibiotic prophylaxis to prevent relapses. The occurrence of relapses with a trimethoprim/sulfamethoxazole regimen,[7] evidence from antibiotic susceptibility tests[2] and the unconfirmed (but widely held) belief that it does not cross the blood–brain barrier[5] have led us to select doxycycline.
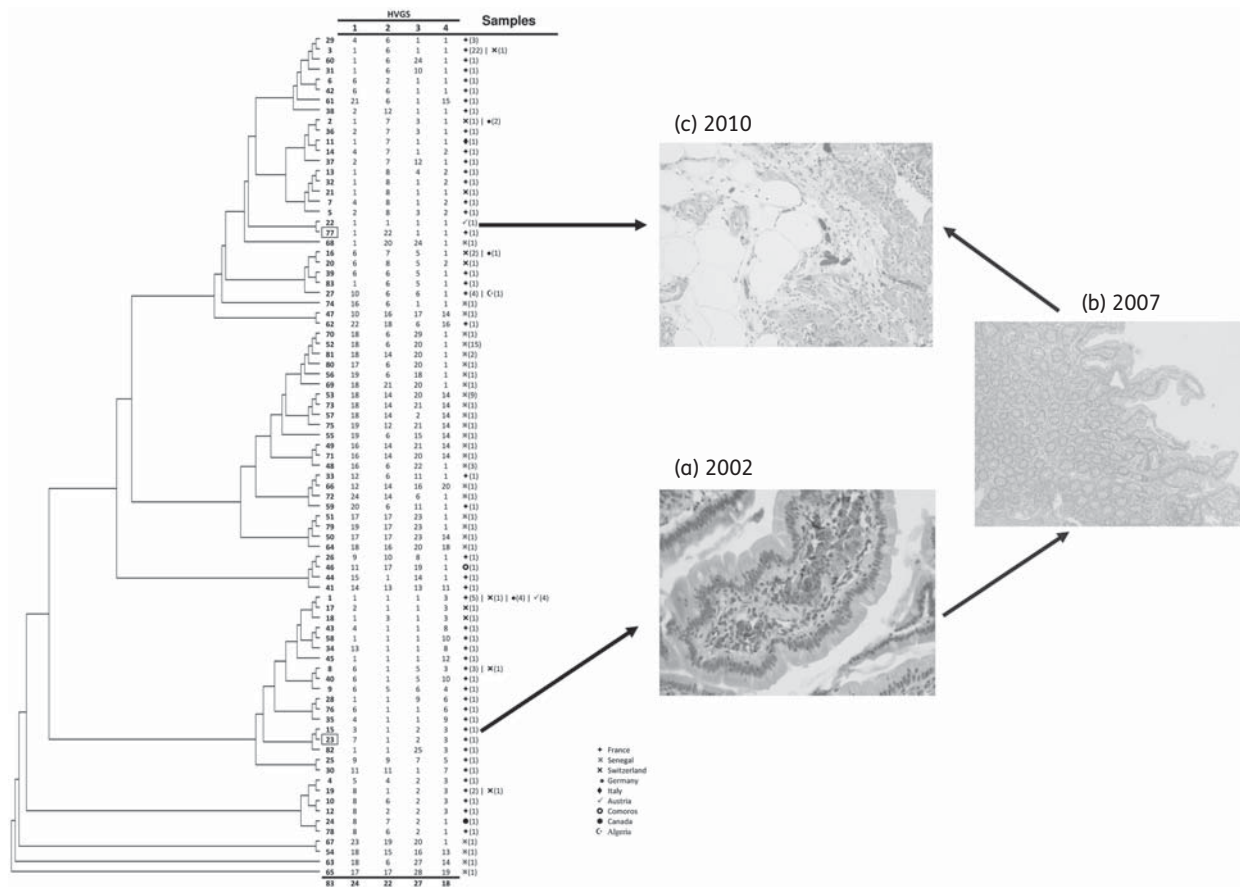
Figure 1. Dendrogram using the unweighted pair group method with arithmetic mean showing the phylogenetic organization of the different genotypes of *T. whipplei* and histological analysis of a small bowel biopsy using immunohistochemistry staining with polyclonal rabbit anti-*T. whipplei* antibody and Mayer's haemalum counterstaining. (a) *T. whipplei* in small bowel biopsy performed in 2002 (original magnification ×200). The patient was infected with genotype 23 *T. whipplei*. (b) Full disappearance of infected macrophages in 2007 (original magnification ×100). (c) Reappearance of *T. whipplei* in September 2010 at the time of the relapse with another strain (original magnification ×100). Macrophages are located in the submucosa and immunostaining is less intense, as is sometimes observed in patients previously treated with antibiotics.[4] The patient was infected with genotype 77 *T. whipplei*. HVGS, highly variable genomic sequence. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Transparency declarations

None to declare.

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