CASE REPORT

Whipple's disease: a rare case of malabsorption

Ana Lopes,¹ Ana Filipa Santos,² Maria Joana Alvarenga,¹ Alberto Mello e Silva¹¹Department of Medicina Interna, Hospital Egas Moniz, Lisbon, Portugal²Department of Pneumologia, Hospital Egas Moniz, CHLO, Lisboa, Portugal

Correspondence to

Dr Ana Lopes, acferrazlopes@gmail.com

Accepted 14 February 2018

SUMMARY

Whipple's disease is a chronic, rare, multisystemic, infectious entity, described for the first time in 1907. Its aetiological agent is the Gram-negative rod, *Tropheryma whippelii*, which was isolated for the first time in 2001 from a cardiac valve of a patient with endocarditis. We present the case of a 71-year-old man, who came into the emergency room complaining of anorexia, weakness, abdominal pain and diarrhoea with haematochezia and presented disseminated palpable purpuric lesions, predominantly in the lower limbs. The upper endoscopy showed a duodenal vasculitis and the biopsy of that location revealed aspects suggestive of Whipple's disease. We started him on antibiotics according to the recent orientations with progressive clinical and analytical improvement, although he developed an immune reconstitution syndrome, which lasted for 2 weeks.

BACKGROUND

Whipple's disease is a rare nosological entity, with a tetrad of characteristic but unspecific manifestations (arthralgia, anorexia, abdominal pain and diarrhoea). It may present atypically and out of its usual age range, leading to subdiagnosing and chronic evolution. Insidious manifestations of gastrointestinal symptoms associated to consumptive states arising from malabsorption should raise clinical suspicion for Whipple's disease. Besides the common manifestations, less frequently there may be neurological, renal, cardiovascular or cutaneous alterations, usually related to the malabsorption, as it was in this patient's case. Since there is a small number of cases described and given the atypical presentation in this patient, we consider this discussion as useful to alert to the consequences of subdiagnosis of Whipple's disease.

CASE PRESENTATION

A 71-year-old man presented to the emergency room complaining of anorexia, asthenia and abdominal pain located in the hypochondrium and right flank for more than 3 months. He also referred abundant liquid diarrhoea with pinkish faeces and weight loss of 5 kg in the last 15 days, for which he had done unknown antibiotic therapy. He had brought blood tests dated a month before that showed normocytic/normochromic anaemia (Hb 11.8 g/dL), abdominal ultrasound and CT that only revealed gallstones without evidence of cholecystitis. He lived in a rural environment until he was 19 years old and

then migrated to the city to work as an electrician, and later he worked in car washing for about 30 years. As for the pathological history, he had a vertiginous syndrome of unclear aetiology, essential arterial hypertension, bilateral cataracts and unspecified osteoarticular pathology, to which he was medicated with non-steroidal anti-inflammatory drugs (diclofenac and acetaminophen). There was no history of food or drug allergy. His father had died of pulmonary tuberculosis, his mother died of bowel cancer and he had a brother who also died of bowel cancer at the age of 59. The physical examination showed prostration, mucocutaneous pallor and palpable purpuric lesions on the abdomen, thorax and predominantly lower limbs. He had pain in the upper abdominal quadrants with deep palpation, without peritoneal irritation and there was no evidence of abdominal masses or organomegaly. The neurological observation did not show signs or symptoms suggestive of central nervous system affection.

INVESTIGATIONS

From the work-up, we emphasise: normocytic normochromic anaemia (haemoglobin (Hb) 9.4 g/dL, mean globular volume (MGV) 82.2 fL, mean corpuscular haemoglobin (MCH) 26.2 pg/mL), hypocoagulability (prothrombin time (PT) 16s, international normalised ratio (INR) 1.5, activated partial thromboplastin time (aPTT) 29.7s) without thrombocytopenia, elevation of reactive C protein (RCP) (7 mg/dL), acute renal injury (creatinine 1.44 mg/dL), hepatic dysfunction (PT 16s, albumin 2.2 g/dL) without elevation of hepatic cytolysis enzymes and proteic malnutrition (total protein 4.4 g/dL). The search for A and B toxin for *Clostridium difficile* was negative, as were the serologies for HIV 1/2, hepatitis B virus, hepatitis C virus, cytomegalovirus and Epstein-Barr virus. The biochemical analysis of urine showed no alterations. A cutaneous biopsy was performed due to suspicion of a systemic vasculitis with involvement of the digestive tract, which revealed alterations compatible with scurvy. The autoimmunity study was negative for rheumatoid factor, antineutrophil cytoplasmic antibodies, antiextractable nuclear antigen s and antidouble-stranded DNA and antinuclear antibodies were positive with a titre of 1/160 and a mottled pattern. An endoscopic study (upper and lower) was conducted and revealed duodenal vasculitis. The duodenal biopsy revealed 'important expansion of the lamina propria due to numerous macrophages with cytoplasm filled with periodic acid-Schiff (PAS)-positive granules' and 'negative

To cite: Lopes A, Santos AF, Alvarenga MJ, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-222955

result for research of acid–alcohol-resistant bacilli by Ziehl–Neelsen colouring technique’.

DIFFERENTIAL DIAGNOSIS

Iatrogenic upper gastrointestinal haemorrhage secondary to non-steroidal anti-inflammatory drugs.

Digestive tract cancer.

Systemic vasculitis with affection of gastrointestinal tract.

TREATMENT

We started the patient on antibiotics with ceftriaxone 2 g a day for 2 weeks and then cotrimoxazole 960 mg twice a day, during 1 year.

OUTCOME AND FOLLOW-UP

At the second day of treatment with ceftriaxone, he presented fever (maximum tympanic temperature of 38.2°C) that lasted 2 days. Although there was an improvement in his clinical status, with regression of the cutaneous lesions and resolution of the abdominal pain, he started having a nocturnal fever spike that started at the sixth day of antibiotics, with poor response to the antipyretics. As the fever persisted and to exclude the possibility of a nosocomial infection, blood and urine were collected for bacterial examinations, and the results came out negative. Afterwards he became afebrile, gained weight (59 kg at discharge) and was discharged asymptomatic and with reference to an internal medicine consultation. After discharge, he remained asymptomatic, kept gaining weight and had no other complications. At the follow-up consultation, 1 year later, there was clinical (79.2 kg) and analytical improvement of the absorptive deficits (Hb 14.6 g/dL, VGM 89.4 fL, PT 11.3 s, INR 1.1, aPTT 24.1 s, total protein 6.5 g/dL, albumin 3.5 g/dL, aspartate transaminase 21 UI/L, alanine transaminase 17 UI/L, alkaline phosphatase 85 UI/L, gamma glutamyl transferase 28 UI/L, vitamin C 1.7 mg/dL, normal upper gastrointestinal endoscopy and small bowel biopsy with evidence of chronic duodenitis and rare PAS-positive macrophages).

DISCUSSION

Tropheryma whippiei is a ubiquitous bacteria, highly prevalent in stool cultures of individuals who contact frequently with residual water or sewers, as was the case of the referred patient, who lived in a rural environment until he was 19 years old and worked in contact with residual and stagnant water.^{1–5} Data on the incidence of Whipple’s disease still lack scientific evidence. Given its rareness, the fact that *T. whippiei* has been isolated in stool and saliva samples of healthy individuals and that Whipple’s disease has an insidious course, its prevalence is difficult to predict with accuracy.^{6,7} In a small study concerning the north-western part of Italy, it was possible to estimate the prevalence of Whipple’s disease in 3 per 1 million.⁶ It affects mainly men, with a higher incidence between the age of 40 and 50 and particularly Caucasian individuals of European ascendance.^{1–5} There is not a confirmed familial association.⁸ In this particular case, the disease presents out of the usual age range, allowing us to speculate about the real duration of symptoms and the results of a more premature investigation. The most consensual hypothesis is that inoculation occurs by the faecal–oral route and the infection depends on the host susceptibility in relation to a certain degree of immunodeficiency.^{5,9} The macrophages of the intestinal lamina propria are the main target of the bacillus and allow some immune tolerance.⁹ *T. whippiei* was also identified in tissues such as the

capillary and lymphatic endothelium, colon, liver, brain, heart, lung, synovial membrane, kidney, bone marrow and skin and in all of these was evidenced a marked reduction in the local inflammatory response to its presence. Host-related factors, like immune response deficits and properties of the aetiological agent, seem to concur to the development of infection. The classic picture of the disease is characterised by four cardinal manifestations: arthralgia, weight loss, diarrhoea and abdominal pain. It has two distinct phases, with a time gap that can go from 4 months to 6 years.^{1,3,4} The first phase is characterised by migratory arthritis or arthralgia of the large joints (usually knees, ankles, fingers, wrists and elbows) that, in some cases, may present with synovial effusion.^{1,10} The second phase leads to a consumptive state and includes the gastrointestinal symptoms such as chronic diarrhoea, weight loss, abdominal pain and distension; the latter secondary to ascites or adenomegaly, rectal bleeding and manifestations that arise from absorptive deficits, namely prothrombin time prolongation (vitamin K deficit), ascites or oedema (hypoalbuminaemia), carotene deficit or ferropenic anaemia.^{1,3–5} In this patient’s case, it was not possible to figure out if the articular complaints could correspond to migratory arthralgia or if those preceded the other complaints. Nevertheless, he presented three of the four main manifestations when he came into the emergency room. Through the initial blood evaluation and cutaneous biopsy, we were also able to identify the signs of absorptive deficit. In advanced phases of the disease that correlate directly with the duration of the non-treated infection, manifestations of invasion of the central nervous system may arise, usually as a part of state of multiple organ affection that manifest mainly by cognitive dysfunction.⁴ There are two pathognomonic signs, and at least one of them is present in about 20% of the patients, which are oculomasticatory myorhythmia (repetitive ocular convergence movements associated with synchronous contractions of the masticatory muscles)^{1,4,5,10} and oculofacial-skeletal myorhythmia. Usually, they occur in association with supranuclear ophthalmoplegia. In case of clinical suspicion, it is recommended to perform a CT or MRI, which may reveal unspecific focal lesions.⁵ Besides the classic manifestations, cardiac disease may also occur, affecting at least one of the structures of the cardiac wall, usually the endocardium. The cardiac involvement is more common in men over 60 years old and is not always accompanied by manifestations of systemic infection.^{3,4} Valve compromise is frequent, particularly of the mitral and aortic valves. Prosthetic valves, mainly the biological ones, may also be colonised. In the case presented here, the patient did not show symptoms or signs suggestive of cardiac or neurological involvement, nevertheless, the absence of involvement of such organs was confirmed by a thorough neurological evaluation and transthoracic echocardiogram with Doppler. Even less common presentations include manifestations of pleuropulmonary, renal, endocrinological or mucocutaneous affection, non-thrombocytopenic purpura and infection of articular prosthetics. Recently, there was also described pneumonia associated to *T. whippiei*.^{5,11} When cutaneous manifestations occur, they are usually associated to the malabsorptive deficits arising from the intestinal disease, as it was the case of this patient in which those (non-thrombocytopenic disseminated palpable purpura) came out to be a consequence of the absorptive deficit—compatible with vitamin C deficit. About 15% of the patients do not present the classic symptoms or presented only with extraintestinal manifestations.^{2,4} The definitive diagnosis is based on histological findings, as the clinical manifestation can be multiple and are

Learning points

- ▶ *Tropheryma whippelii* is frequently identified in coprocultures, mostly in individuals who live in rural environments or are in contact with residual water.
- ▶ The inoculation occurs by the oral–faecal route, but the infection depends on an immune deficit, mainly of the cellular immunity and on the bacterial burden.
- ▶ There are four cardinal manifestations: arthralgia, abdominal pain, diarrhoea and weight loss. However, other manifestations may occur, such as neurological or cardiovascular and, less commonly, pleuropulmonary, haematological, renal or endocrinological ones.
- ▶ The definite diagnosis is histological and is characterised by the identification of periodic acid–Schiff-positive macrophages in the lamina propria of the small bowel.
- ▶ Treatment consists in intravenous ceftriaxone 2 g daily during 2 weeks, followed by oral cotrimoxazole 960 mg twice a day for at least 1 year. It may precipitate high fever in the first 2 hours (Jarisch–Herxheimer reaction) or in the first 2 weeks (immune reconstitution syndrome).

non-specific,^{4 5} and that is why the upper endoscopy with biopsy of the duodenal mucosa is one of the first steps in the investigation. The macroscopic characteristics consist in villi atrophy and dilation, thickening and fibrinous exudation in the peritoneal surface, associated to a growth of the mesenteric lymphatic ganglia. Microscopically, it is characterised by dilation of the villi secondary to the infiltration of the lamina propria by PAS-positive macrophages that can also be identified in other tissues.^{1–5 9 10 12 13} When in doubt, the diagnosis may be confirmed by identification of *T. whippelii* by electronic microscopy or by PCR of its genetic material.⁵ Cases of positive PCR in the absence of histological features may correspond to low local bacterial burden, irregular affection of the mucosa or submucosal infections.^{1 3 4} In the case presented, the diagnosis was made by the identification of PAS-positive macrophages in the duodenal lamina propria. First line of treatment consists in intravenous ceftriaxone 2 g per day, in a single daily administration for 2 weeks, followed by at least 1 year of doxycycline 100 mg twice a day or cotrimoxazole 960 mg twice a day,^{3–5 10} with the purpose of eliminating the bacteria and reducing the occurrence of relapse. Central nervous system infection requires therapy with penicillin G 4 MIU every 4 hours or a third-generation cephalosporin (ceftriaxone 2 g twice a day for 4 weeks, followed by at least a year of cotrimoxazole 960 mg twice a day or chloramphenicol in case of allergy to cotrimoxazole). Recent prospective studies have demonstrated similar results with meropenem compared with ceftriaxone, although the reduced size of the sample did not permit the extrapolation of the results.^{4 5} Relapse is described to occur in 17%–35% of the patients, and it is related to the inability to eliminate the bacteria with the initial course of antibiotics. Neurological manifestations may relapse in about 10%–40% of the cases.^{1 5} Clinical improvement is usually seen between the 7th and the 21st day. The response to the treatment may be evaluated by monitoring the haematocrit, weight and symptomatic evolution of the patient.^{4 5} Several cases of Jarisch–Herxheimer reaction are described, usually about 1 to 2 hours after the initiation of antibiotics,

mainly penicillin. Its main features are fever, chills, headache, hypotension and severe abdominal or pleuritic chest pain. An immune reconstitution syndrome may develop during the first weeks of antibiotic treatment. It is characterised by high fever but may develop with arthritis, pleurisy, erythema nodosum and bowel perforation, which may be mistaken for a relapse. The main risk factors for immune reconstitution syndrome are prolonged immunosuppressant therapy prior to the diagnosis and involvement of the central nervous system. The fever experienced by our patient after the second day of antibiotic therapy, associated to an improvement of the other clinical symptoms, without evidence of other infections, may be interpreted as an immune reconstitution syndrome. After the patient's discharge, it is recommended to have a follow-up consultation every 6 months during the first year and then annually.¹⁴ Endoscopic study and duodenal biopsy may be indicated in case of relevant gastrointestinal manifestations.^{4 5} The presence of PAS-positive macrophages in advanced phases of the treatment is an indicator of inadequate response.⁴

Contributors AL: conception and design, acquisition of data or analysis and interpretation of data. AFS: acquisition of data. MJA: drafting the article or revising it critically for important intellectual content. AMS: final approval of the version published. MJA and AMS: agreement to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- Schneider T, Moos V, Loddenkemper C, et al. Whipple's disease: new aspects of pathogenesis and treatment. *Lancet Infect Dis* 2008;8:179–90.
- Knaapen HK, Barrera P. Therapy for Whipple's disease. *J Antimicrob Chemother* 2007;60:457–8.
- Boulos A, Rolain JM, Raoult D. Antibiotic susceptibility of *Tropheryma whippelii* in MRC5 cells. *Antimicrob Agents Chemother* 2004;48:747–52.
- Lagier JC, Lepidi H, Raoult D, et al. Systemic *Tropheryma whippelii*: clinical presentation of 142 patients with infections diagnosed or confirmed in a reference center. *Medicine* 2010;89:337–45.
- Desnues B, Al Moussawi K, Fenollar F. New insights into Whipple's disease and *Tropheryma whippelii* infections. *Microbes Infect* 2010;12:1102–10.
- Biagi F, Balduzzi D, Delvino P, et al. Prevalence of Whipple's disease in north-western Italy. *Eur J Clin Microbiol Infect Dis* 2015;34:1347–8.
- Marth T, Moos V, Müller C, et al. *Tropheryma whippelii* infection and Whipple's disease. *Lancet Infect Dis* 2016;16:e13–22.
- Fenollar F, Laouira S, Lepidi H, et al. Value of *Tropheryma whippelii* quantitative polymerase chain reaction assay for the diagnosis of Whipple disease: usefulness of saliva and stool specimens for first-line screening. *Clin Infect Dis* 2008;47:659–67.
- Bonhomme CJ, Renesto P, Desnues B, et al. *Tropheryma whippelii* glycosylation in the pathophysiologic profile of Whipple's disease. *J Infect Dis* 2009;199:1043–52.
- Lagier JC, Fenollar F, Lepidi H, et al. Failure and relapse after treatment with trimethoprim/sulfamethoxazole in classic Whipple's disease. *J Antimicrob Chemother* 2010;65:2005–12.
- Jackuliak P, Koller T, Baqi L, et al. Whipple's disease-generalized stage. *Dig Dis Sci* 2008;53:3250–8.
- Feurle GE, Jung NS, Marth T. Efficacy of ceftriaxone or meropenem as initial therapies in Whipple's disease. *Gastroenterology* 2010;138:478–86.
- Gorvel L, Al Moussawi K, Ghigo E, et al. *Tropheryma whippelii*, the Whipple's disease bacillus, induces macrophage apoptosis through the extrinsic pathway. *Cell Death Dis* 2010;1:e34.
- Apstein MD, Schneider T. *Whipple's disease*. Up To Date, 2016.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow