Le Infezioni in Medicina, n. 1, 139-142, 2022
doi: 10.53854/liim-3001-18

Whipple's disease: a case report in Santa Catarina, Brazil

Camila Kleber Stroher, Arthur Lichs Marçal Santos, Leandra Ceron, Liandra Luisa Fabrin
Hospital Universitário Santa Terezinha (HUST) da Universidade do Oeste de Santa Catarina (UNOESC), Joaçaba, Brazil

Article received 5 November, 2021; accepted 9 January, 2022

SUMMARY

Whipple's disease is a rare systemic infection caused by a diastase-resistant and Gram-positive bacillus called *Tropheryma whipplei*. The diagnosis of the disease is difficult and often late due to the variety of the symptoms. The objective of this study was to report a rare case of Whipple's disease treated at the Internal Medicine service of a hospital in the Midwest of Santa Catarina, Brazil. The patient was invited for an interview to describe the history of symptoms and previous treatments. Additionally, test results and treatments performed during hospitalization were assessed through the medical records. The case report describes a 39-year-old white male who presented, at the time of diagnosis, severe diarrhea, hematochezia, weight loss, fever, and inguinal adenomegaly, in addition to preceding migratory polyarthritis. After investigation, the diagnosis of Whipple's disease was achieved in conjunction with antibiotic treatment, with improvement of clinical and laboratory symptoms after 15 days. This case highlights the broad array of symptoms and the non-specific features of the Whipple's disease. Establishing an early diagnosis is essential for the success of the treatment, avoiding a long-lasting escalation of symptoms, which lead to cachexia and a devastating loss of the patient's quality of life.

Keywords: Whipple disease, *Tropheryma whipplei,* diagnosis.

INTRODUCTION

Whipple's disease is a rare multisystemic infection with incidence of 12 new cases per year worldwide, caused by *Tropheryma whipplei* (formerly *Tropheryma whipplelii*), a diastase resistant and Gram-positive bacillus [1]. The disease was named after George Hoyt Whipple, the physician who first reported it by describing the case of a 36-year-old man who presented diarrhea, weight loss, fever, and preceding migratory polyarthritis [1]. After the death of the patient, Dr. Whipple studied, in 1907, the intestinal tissue and the lymphatic ganglia of the mesentery of the deceased, aiming to better understand the pathology [2]. Following the anatomopathological analysis, the study of the disease continued. The intent was to discover the etiological agent, that could affect almost all organs of the human body, as the heart and the central nervous system (CNS) were involved in some patients [2]. In 1952, the first case was successfully treated with the use of antibacterial therapy with chloramphenicol, but only in 1992 the bacterium was identified in the submucous tissue, in the interior of macrophages [3]. The population most affected by the Whipple's disease are men, white-skinned, middle-aged, with an average of 49 years of age, and from rural areas [2]. The pathogenesis of the Whipple's disease is still uncertain, but it is believed that *Tropheryma whipplei* is a commensal bacterium in humans, that systemically spreads through the lymphatic pathway, in mesenteric and mediastinal lymph nodes [4]. The disease frequently has a late diagnosis, due to its broad clinical presentation and rarity. The precise diagnosis involves the biopsy of tissues from the small intestine, lymphatic ganglia, liver, brain, meninges, pericardium, endocardium, among others, evincing the

Corresponding author
Arthur Lichs Marçal Santos
E-mail: alms_arthur@hotmail.com

systemic nature of the pathology. In most cases, antibiotic treatment and nutritional recovery lead to the normalization of these alterations. However, relapses are recurrent after the withdrawal of antibiotics and even during treatment [2].

CASE REPORT

The case report consisted of a patient diagnosed with Whipple's disease at Santa Terezinha University Hospital (Hospital Universitário Santa Terezinha, HUST), a hospital in the Midwest of Santa Catarina, Brazil. The patient was under the care of the authors during his hospital admission, from December of 2020 to January of 2021. This study was approved by the local Ethics Committee in Research under the protocol number 45078021.0.0000.5367. Patient data were obtained in two stages. The first stage consisted of a direct interview with the patient to collect the chronology of the symptoms and therapeutic approaches attempted before the identification of the etiologic agent. The second stage consisted in the assessment of test results in the medical records and the hospital's digital system. The interview was performed in the patient room, after proper clarification about the research and signing the free and informed consent form. The second stage data were collected in the hospital. The information collected from the medical records and digital system were laboratory and imaging test results and anatomopathological reports. This study describes the case of a 39 years old white male. The patient was referred to the HUST Oncology Department in December of 2020, due to the identification of bilateral inguinal lymphadenomegaly that manifested approximately two months earlier. By the moment of the medical consultation, the patient had liquid, voluminous, and explosive diarrhea, with an average of eight daily episodes, associated with abdominal distension, hematochezia, and loss of 22 kg over the previous six months. Concerning the patient's medical history, he reported that in 2016 he started to experience arthralgia, stiffness, and edema in the knee, ankle, wrist, and proximal interphalangeal joints, all of which were declining in frequency and intensity since admission to the hospital. In 2017, the patient started to suffer from daily dry cough, similar to an allergic symptom, high fever at night (38.5°C - 40°C) and muscle weakness, mainly at night. He was treated with benzathine benzylpenicillin (trade name Benzetacil) in intervals of 20 days for two months, prescribed by an infectious disease specialist, due to a suspicion of rheumatic fever. After temporary improvement, in April 2020 the patient started to experience with explosive diarrhea associated with asthenia. These events happened, on average, eight to ten times a day, accompanied by hematochezia and anorexia. He was admitted to the hospital for hydration and transfusion of erythrocyte concentrate. In October of the same year the patient had already lost 20 kg, alongside the development of bilateral adenomegaly in the inguinal fossae. In December 14, 2020, the patient was admitted to HUST. In the occasion, he was examined by computed tomography (CT) scan of the abdomen followed by the surgical excision of lymph node samples for biopsy and anatomopathological examination. After that, the patient was discharged home. CT examination identified enlarged and clustered lymph nodes in the region of the vena cava and portal vein, in the retroperitoneal area, and close to mesenteric vessels and peritoneum. The excisional biopsy of two right inguinal and two retroperitoneal lymph nodes was performed by an experienced surgeon, and the samples were analyzed by a pathologist using the frozen section method. Slide analysis of all four lymph nodes was negative for malignancies, with a large quantity of foamy macrophages. Anatomo-pathological analysis of the excised lymph nodes was performed by the same pathologist. This analysis included two lymph nodes from the right inguinal region (the largest one measuring 1,2x1.0x1.0 cm) and seven lymph nodes of the retroperitoneal region (the largest one measuring 1.5x1.0x1.0). All presented cystic spaces and a high quantity of foamy macrophages containing cytoplasmatic granules positive for periodic acid-Schiff (PAS) and negative for Ziehl-Neelsen staining, which is consistent with Whipple's disease [5]. Cuts were also examined for fungi and acid-alcohol-fast bacilli (AAFB), returning negative results. When the diagnosis was achieved, the patient was cachectic, jaundiced, with hyperpigmentation of the facial skin, and purpura in the lower limbs. In December 28, 2020 the patient was hospitalized at HUST, with care provided by the gastroenterology team. Two hemoculture samples and one uroculture sample were collected, with negative results for *Tropheryma whipplei*.

In order to investigate whether the cerebrospinal fluid or the CNS were infected, lumbar puncture was performed and the material was subjected to specific investigation for *Tropheryma whipplei*, returning negative results. In the same period, no alterations were identified by transthoracic echocardiogram. The patient remained in the HUST Medical Clinic sector, treated with 2 g/day of intravenous ceftriaxone for two weeks. During the hospitalization period the patient suffered from diarrhea with hematochezia in the first seven days, which reversed after treatment. The patient was discharged to ambulatory care as he showed improvements with this first treatment. Oral sulfamethoxazole/trimethoprim 800/160 mg twice a day was prescribed for the maintenance phase, with orientation to maintain this treatment for 12 months. The patient is currently receiving follow-up care. With the pharmacological treatment, he had no relapses and remains asymptomatic.

DISCUSSION

Whipple's disease is a rare systemic disorder caused by a Gram-positive bacterium named *Tropheryma whipplei* [6]. The bacteria are found in soil and sewers, and also in the gastric acid, saliva, and small intestine of infected individuals, where they can persist commensally without causing the disease, as some infected patients may develop enough immune response to avoid it [4, 6]. The global incidence is estimated to be around 12 new cases per year [1]. Despite the scarce evidence, male individuals are more susceptible to the disease, which can be related to a predisposition associated with the X gene in addition to the greater proportion of men working in rural areas. People with white skin color are also more susceptible, and the average age of onset is 49 years old. Start of symptoms and diagnosis usually happen around 7.5 years after infection [7]. Clinical manifestations are diverse, as the bacteria can infect different tissues. In the classic symptomatology, the Whipple's disease starts with arthralgia, arthritis, fever, and asthenia. In the intermediate phase, it might include diarrhea, weight loss, and, in the final stage, impairment of the nervous system, eyes, and heart [4]. Comparing the stages of the disease with the case in discussion, at the age of 34 the patient started to show symptoms similar to rheumatoid arthritis, especially with arthralgia, morning stiffness, and edema in the articulations, making he seek treatment with a rheumatologist. In 90% of the cases, the first symptom of the Whipple's disease is arthritis in the knees, ankles, and wrists [4]. The patients are generally diagnosed with a rheumatic disease and treated with immunosuppressants, which may favor the spread of the disease. After six months, non-specific symptoms such as daily dry cough similar to an allergy, high fever at night (38.5°C - 40°C), and muscle weakness mainly at night made the patient seek medical assistance one more time. These symptoms were controlled with benzathine benzylpenicillin, even though diagnosis for Whipple's disease was still absent. Four years after the onset of the symptoms, the patient started to suffer from diarrhea of medium intensity, with 8-10 evacuations per day, alongside hematochezia, anorexia, and asthenia. It is known that the most prominent symptoms are gastrointestinal, such as diarrhea, abdominal pain, and steatorrhea, accompanied with anorexia, hepatosplenomegaly, and poor absorption, evolving to severe weight loss [1]. The malabsorption syndrome is a consequence of the small intestine being the main target of the bacteria. In the case being discussed, the malabsorption syndrome lasted for more than six months, leading to a significant weight loss, of nearly 20 kg. As *Tropheryma whipplei* has affinity with the lymph node tissue, the patient showed bilateral inguinal adenomegaly by the end of the second semester of 2020. Because of that, the patient was referred to the HUST Oncology Department, where a biopsy was performed and the diagnosis for bacterial infection was confirmed.

The protocol for the identification CNS infections was applied during hospitalization, because in 45% of the cases the third most frequent manifestation of the disease are cognitive disorders, impairment of ocular movements, myoclonia, hypothalamic alterations, seizures, and focal neurological impairments [4]. No CNS alterations were reported in this clinical case.

In the moment of hospitalization, the patient showed facial hyperpigmentation. It is known that skin injuries, lymphadenopathy, anemia, pancytopenia, skin hyperpigmentation, uveitis, vitritis, papilledema, endocarditis, among others, are observed in late stages [6].

Some non-specific laboratory findings might

point towards the pathology, including anemia, eosinophilia, lymphocytopenia, thrombocytosis, and alterations that are indicative of malabsorption, such as decrease in xylose, carotenes, and cholesterol [4].

Treatment is performed with antibiotics. When this is not the case, the disease might be lethal. Clinical improvement of the patient under treatment is observed in the first weeks [8]. There is a greater risk of relapse when the CNS is affected or when the antibiotic is unable to cross the blood-brain barrier. Treatment includes penicillins associated with third generation cephalosporines, macrolides, tetracyclines, streptomycin, among others [4].

CONCLUSIONS

The case reported highlights the Whipple's disease varied and non-specific symptomatology. The late identification of the disease exposes the patients to numerous possible inefficient treatment strategies depending on the main symptoms shown in the current stage of the disease. While the correct diagnosis and treatment are not determined, the patients experience a significant clinical decline with life-threatening risk. The challenge posed by the Whipple's disease is to establish an early diagnosis to avoid a long-lasting escalation of symptoms that lead to cachexia and devastating loss in quality of life.

Conflicts of interest
The authors have no conflicts of interest to disclose.

Funding
None.

REFERENCES

[1] Oliveira L, Gorjão R, de Deus JR. Whipple's disease. *J Port Gastroenterol*. 2010; 17 (2), 69-77.
[2] Silva M, Bragança I, Parreira M, Pedroso E, Miranda C. Whipple's disease - a clinical case. *Med Interna*. 2002; 9 (2), 87-91.
[3] Oliveira J, Araújo E, Crespo J, Almiro E, Porto A. Longstanding polyarthritis and Whipple's Disease - a clinical case. *Med Interna*. 2004; 11 (2), 82-6.
[4] Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. Clinical manifestations, treatment, and diagnosis of *Tropheryma whipplei* infections. *Clin Microbiol Rev*. 2017; 30 (2), 529-55.
[5] Bai J, Mazure R, Vazquez H, et al. Whipple's disease. *Clin Gastroenterol Hepatol*. 2004; 2 (10), 849-60.
[6] Marth T, Moos V, Müller C, Biagi F, Schneider T. Tropheryma whipplei infection and Whipple's disease. *Lancet Infect Dis*. 2016; 16 (3), e13-22.
[7] Günther U, Moos V, Offenmüller G, et al. Gastrointestinal diagnosis of classical Whipple disease: clinical, endoscopic, and histopathologic features in 191 patients. *Medicine (Baltimore)*. 2015; 94 (15), e714.
[8] Lagier J-C, Raoult D. Whipple's disease and *Tropheryma whipplei* infections: when to suspect them and how to diagnose and treat them. *Curr Opin Infect Dis*. 2018; 31 (6), 463-70.