Whipple's disease as a systemic infectious disease – a case presentation

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ABSTRACT

Introduction: Whipple's disease is a chronic systemic infectious disorder with *Tropheryma whipplei* as an etiologic agent, occurring rarely and affecting numerous organs and systems. The variety of symptoms and a non-typical course make it difficult to establish a proper diagnosis.
Purpose: In this study, etiopathogenesis, diagnostics and treatment of Whipple's disease were presented based on the case report of 60-year-old man diagnosed with Whipple's disease.
Case presentation: Persistent diarrhoea with weight loss, lymphadenopathy in the abdominal cavity and moderate microcytic anemia predominated in the clinical picture. Diagnosis was put based on the clinical picture and macroscopic assessment of the small intestine and the presence of macrophages filled with a PAS-positive substance in the lamina propria. To deepen diagnostics, samples collected were assessed showing macrophages with the damaged mucosa, containing numerous elongated micro-organisms whose ultrastructure corresponded to *Tropheryma whipplei*. The patient's clinical conditions improved after antibiotic therapy.
Conclusions: It is vital to remember about Whipple's disease in patients with chronic diseases due to a non-specific clinical picture and difficulties in establishing a proper diagnosis. When the disease is diagnosed unequivocally, proper and effective antibiotic therapy should be instituted immediately.
Keywords: infectious disease, systemic disease, *Tropheryma whipplei,* Whipple's disease

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INTRODUCTION

Whipple's disease is a systemic, infectious disease affecting numerous organs. It most frequently affects the digestive, cardiovascular, nervous, respiratory and osteoarticular system. *Tropheryma whipplei* is its aetiological agent. Whipple's disease is a rare disorder occurring in about 0.01% of the population, mainly Caucasians, males from 40 to 50 years old.

In 1907 year, George Hoyta Whipple described the disease for the first time, enumerating irregular bowel movements with steatorrhea, a significant body massloss, polyarthritis and abdominal pains with characteristic histopathological lesions [1]. The syndrome with symptoms listed above was described as intestinal lipodystrophy. After 42 years, the present name - Whipple's disease was introduced, when macrophages containing PAS – positive intracellular material were detected in autopsy or laparotomy (Periodic Acid Schiff staining). In this period, no data on effective treatment of this disease with antibiotics were available [2].

In the 1960's, the bacterium believed to be similar to microorganisms causing tuberculosis was discovered and found responsible for Whipple's disease.

The basis of diagnosis was detection of PAS-positive macrophages and identification of *Tropheryma whipplei* in electron microscopy [3]. A pathogenic microorganism *Tropheryma whipplei* belongs to Gram-positive rods included in the family of Cellulomonadaceaea [4]. In 2000 year, after collecting the samples from the material found in the patient's cardiac valves, a pathogen was successfully cultured, using human fibroblasts. Further studies carried out in 2003 year resulted in the discovery of a complete genome of the bacterium, facilitating its detection by means if a specific polymerase chain reaction - PCR [5,6].

Whipple's disease is a very rare disorder accounting for 30 cases a year in the world. It more frequently occurs in Caucasian males, from 50 to 60 years old than in women, mainly after the age of 70. The aetiological route has not been explained. The more frequent incidence of Whipple's disease in farmers may suggest that bacteria are transmitted via water. Additionally, there are data indicating hereditary predispositions to this disorder. In Dobbins's study [7], 25% of patients had HLA B27antigen probably increasing a risk of developing this disease. Furthermore, it has been speculated that people with *Tropheryma whipplei* infection have the impaired immune system characterised by a low cofactor of CD4/CD8 T cells, enhanced activity of Th_2 and decreased activity of Th_1, which is associated with overproduction of interleukin 4 (IL-4) and lower production of IL-12 and interferon-gamma, contributing to the development of this disease [8-11].

Clinical symptoms of the disease are non-specific and no characteristic pathognomonic symptoms can be observed, either. Its clinical course frequently suggests disorders of the digestive system with primary general symptoms like: diarrhoea, chills, fever, enlarged lymph nodes, abdominal pains and weight loss. Additionally, symptoms of the circulatory system, nervous system and osteoarticular system can be observed in patients [12-15].

In Whipple' disease diagnostics, a great diagnostic value is attributed to the atrophy of intestinal villi in a bioptate of the small intestine mucosa, and the basic diagnosis is made on the presence of PAS-positive macrophages [16]. Whipple's disease is confirmed based on the bacterial RNA identification with PCR technique as well as the presence of this microorganism in electron microscopy [17]. In the laboratory tests, an increase in inflammatory parameters, hypalbuminaemia, hypokalaemia, hypocalcaemia, and microcytic anaemia associated with iron deficiency are determined. In this study, a clinical picture, diagnostics and treatment of a patient with Whipple's disease were presented. It should be emphasised that a course of disorder is long-lasting, without significant symptoms, a lot of test results are non-specific and treatment is not effective enough to be considered satisfying.

CASE REPORT

A 60-year-old man was admitted to the Department of Internal Medicine and Gastroenterology of Jędrzej Śniadecki Provincial Polyclinical Hospital of Białystok due to pain in the middle epigastrium, chronic diarrhoea with loose bowels up to 8 in 24 hours, occasionally containing blood, a subfebrile state up to 37.4°C and significant weight loss (about 20 kg during last 4 months).

The patient reported malaise and pains in the lumbar region, the knee and hip joints. The patient's history revealed 13-year seronegative arthritis, microcytic anaemia diagnosed 10 years ago and general lymphadenopathy. The man had pulmonary embolism in the past. No atherosclerotic lesions (in the coronary vessels) were found in the coronary angiography. The available medical documents didn't contain any information about the length of lymphadenopathy, lymphnodes biopsy, synovial fluid analysis during 13-years of arthritis, cause of pulmonary embolism and information about the reason for coronary angiography.

Subjective examination revealed the features of malnutrition, pale skin and mucosal membranes, hemorrhagic rash on the skin in the sacral vertebrae region and lower extremities,

enlarged painless cervical supraclavicular, axillar and inguinal lymph nodes, systolic murmur and pain in the middle epigastrium at palpation.

Patient in connection with symptoms such as chronic diarrhoea, fever and weight loss had diagnosed on the Department on Gastroenterology. The laboratory tests performed at admission showed severe macrocytic anaemia (HGB 6.9 g/dl), increased level of D-dimers (597) and INR – 9.27 and prolonged time of PT up to 81.2 sec and slightly enhanced inflammatory parameters (CRP-17.1mg/l; OB- 21mm/h). Cancer markers (CEA and AFP) were within the norm. No pathogens were cultured in the stool.

Available ultrasonography of the abdominal cavity was normal without limphodenopathy. During the treatment the CT scan was perform and showed lymphadenopathy around the mesentery of the small intestine. Gastroscopy demonstrated mosaic gastric mucosa, non-uniform hyperaemic mucosa in the duodenal bulb and some blenching with hypertrophic folds and thickened villi in the outside bulbar region (Figure 1).

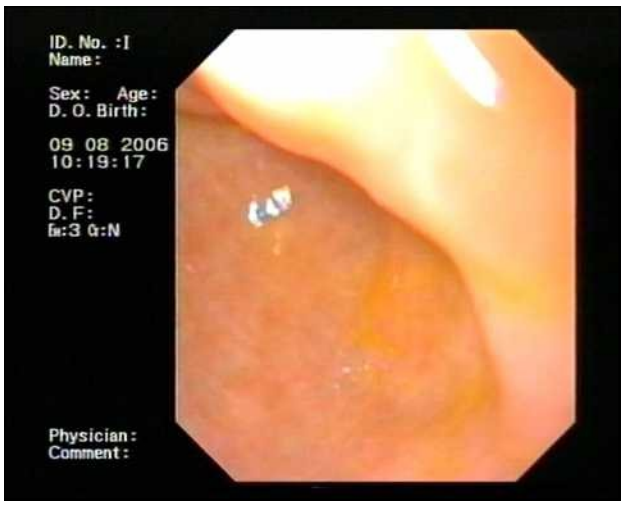

Figure 1. Endoscopic picture of gastroscopy

Colonoscopy showed numerous foci of hyperaemic mucosa (5-10 mm). Similar less intensive lesions were found in the small intestine. Microscopy revealed chronic inflammation of the small intestine and shortened intestinal villi (Figure 2). Macrophages with PAS –positive substance were seen in lamina propria (Figure 3).

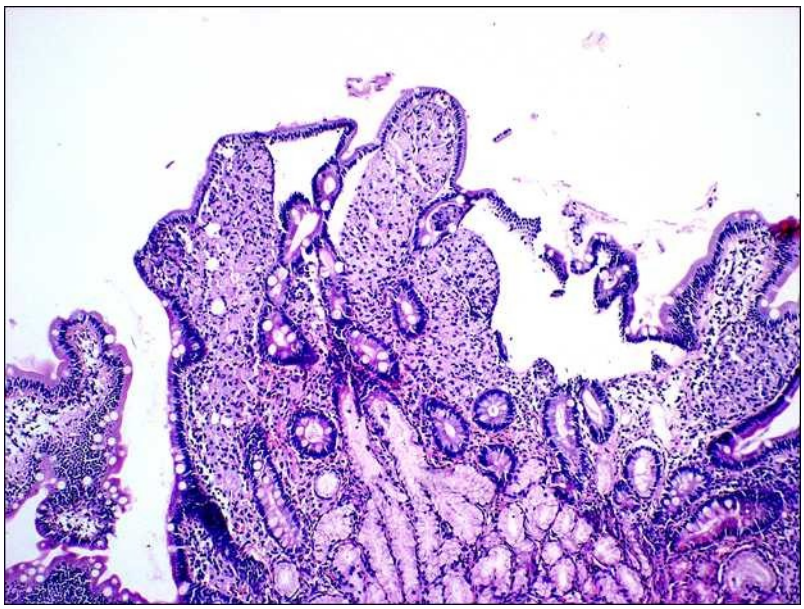

Figure 2. Small intestine - mucosa in chronic inflammation, shortened intestinal villi. Hematoxylin and eosin staining, magnification x100

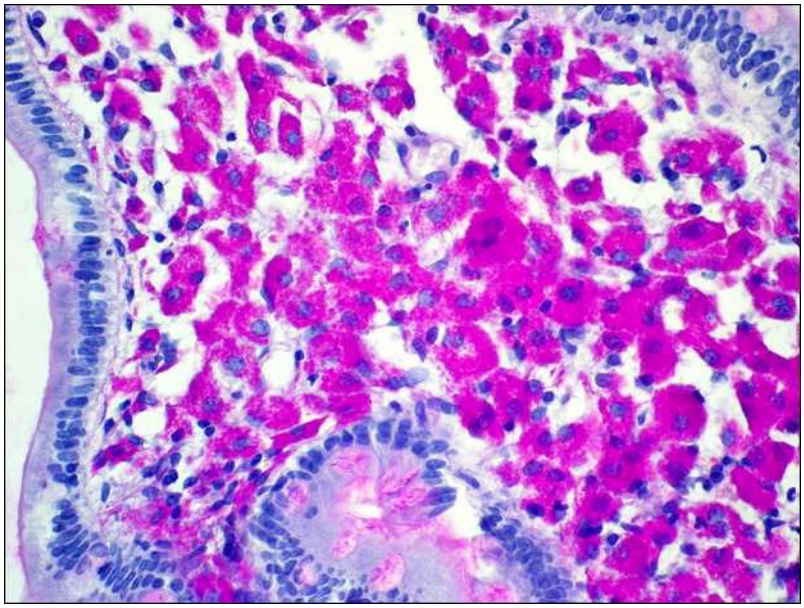

Figure 3. Small intestine – PAS-positive macrophages in mucosal lamina propria PAS staining (Periodic Acid Schiff staining), magnification x 200

Microscopy of the small intestine suggested Whipple's disease. To deepen diagnostics, mucosal samples of the small intestine were examined in the electron microscope, showing macrophages with the damaged mucosal membrane containing numerous elongated microorganisms corresponding structurally to *Tropheryma whipplei* (Figure 4). Due to presence of this microorganism in electron microscopy, PCR technique was not carried out because this test was not available in the department.

a b

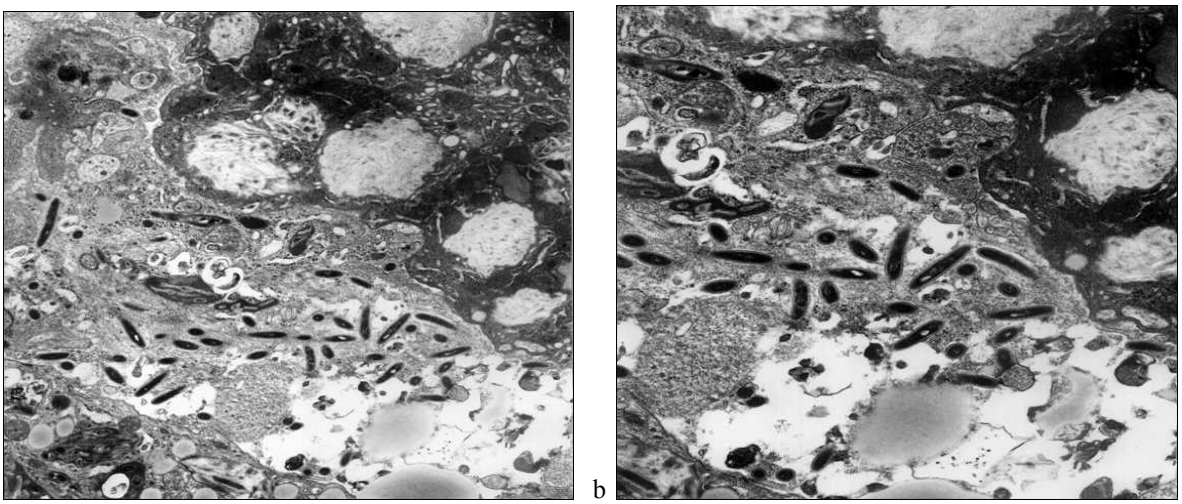

Figure 4. Macrophages with damaged mucosa containing numerous elongated microorganisms corresponding structurally to *Tropheryma whipplei*. Electron microscopy: A- magnification x 4400, B- magnification x 7000

In treatment, ceftriaxone 2g/24 hours i.v. per 2 weeks and then cotrimoxazol was administered twice daily 960 mg/24 hours per one year. Due to pulmonary embolism in the past, the patient was treated with acenocoumarol. Additionally, diltiazem, fraxiparine, iron preparations i.v. and transfusion of 3units of erythrocyte concentrate of A Rh/+/group were applied in the therapy. The patient's health status improved gradually, abdominal pains subdued and the results of check-up tests improved after 3-month-treatment (CRP 5mg/l, HGB-13.1g/dl, MCV-88.4, PLT-238x10^3/ml). Time PT-23.5 sec., INR-2.14, D-Dimery-188, iron-66 ug/dl. The level of INR was elevated (INR-2.14) due to the patient receiving acenocoumarol. The available medical documentation didn't reveal an improvement in lymphadenopathy.

Check-up gastroscopy demonstrated mosaic gastric mucosa with single patechiae and slightly hyperaemic mucosa in the duodenal bulb.

Smooth mucosa and shortened villi were observed in the outer bulbar region (Figure 5).

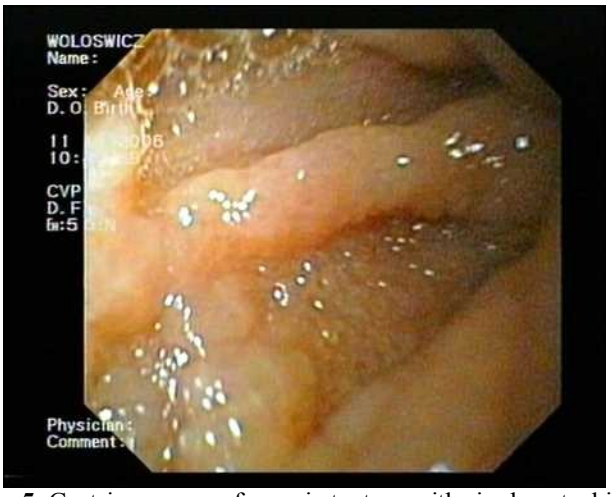

Fig. 5. Gastric mucosa of mosaic texture with single petechiae

DISCUSSION

Due to the low incidence of Whipple's disease and its difficult diagnosis, a patient's very detailed medical history, clinical examination, laboratory tests, endoscopic evaluation of the gastrointestinal tract and histopathological examination of mucosal bioptates should be regarded as basic in recognising this disease.

In most cases, untreated Whipple's disease has three stages of development. In the first stage, symptoms are non-specific including inflammation and pains of the hip, knee or elbow joints (reported in 85% of cases), accompanied by abdominal pain, decreased appetite and subfebrile states. In the next stage, watery diarrhea and general weakness with body mass loss are observed. The latter is the most common symptom revealed in Whipple's disease reported in 90% of patients. In the last stage, cachexia and lymphadenopathy occur [18,19]. Additionally, pneumonia, pericarditis lesions in the coronary vessels increasing a risk of heart infarct, iron deficiency anaemia, general symptoms, such as hypovolemic shock are described [12-14,20]. In 5% of cases, symptoms of the central nervous system e.g., ptosis, depression, dementia, atactic gait, insomnia, personality changes and meningitis are reported [15]. The patient described in our case report belonged to the group of individuals with significant clinical symptoms of the gastrointestinal tract.

However, the cases of isolated clinical symptoms coming from only the nervous system have been reported [21,22]. In 2015, Peregrin et al. [23] described the case of 33year-old-woman with primary Whipple's disease of the nervous system without neurological symptoms. The patient had migratory arthralgia of the large joints and other non-specific symptoms including back pain and a subfebrile state. Interesting is patient's history: 13-year seronegative arthritis, microcytic anaemia diagnosed 10 years ago and general lymphadenopathy. The question is whether these symptoms could be caused by an infection of *Tropheryma whipplei* during this entire time. The patient underwent numerous diagnostic investigations e.g., computer tomography and magnetic resonance despite lack of neurological symptoms. The investigations showed mass-like changes within the brain tissue, while histological examination revealed PAS-positive macrophages. To confirm Whipple's disease, biopsy of the duodenum was performed. The bioptates from the small intestine were PAS-negative [23]. Another interesting case described by Gubler et al. [24] referred to the patient with endocarditis in the course of Whipple's disease without symptoms of the digestive system.

In case of Whipple's disease, diagnosis should be differentiated from other diseases such as AIDS (similar macrophages with Mycobacterium avium infection), histoplasmosis, macroglo-bulineamia and many others. Lymphadenopathy revealed in the patient circumstantiated histopathological examinations of the lymph nodes to recognise Hodgkin lymphoma. *Tropheryma whipplei* bacteria are suspected to contribute to the development lymphomas [25].

At present endoscopy with biopsy of the duodenum is the most important diagnostic examination in Whipple's disease. Gunther et al. [26] proposed the three-stage diagnostic scheme based on their experience of 191 cases of Whipple's disease. At first, in patients suspected of Whipple's disease (even if no symptoms of the digestive system are reported) gastroscopy with biopsy of at

least 5 samples from the duodenum and two examinations: histological with PAS staining and PCR or *Tropheryma whipplei* specific immuno-histochemical staining should be performed. In case of doubtful results of the first stage, samples of tissues or fluid (cerebrospinal, synovial or pleural fluid, lymph node) changed pathologically should be collected and examined in the second stage. The third stage includes lumbar puncture in patients with Whipple's disease with determination of microorganisms in the cerebrospinal fluid by PCR method to confirm infection of the nervous system.

In our case report, diagnostics of Whipple's disease was based on the patient's medical history, the results of histopathological examinations of mucosal samples of the mucosa from the gastrointestinal tract and the microorganisms corresponding structurally to *Tropheryma whipplei* present within macrophages in electron microscopy. Besides numerous complaints reported by the patient, the results of laboratory tests and bioptates of gastric, duodenal and colonic mucosa collected in gastroscopy and colonoscopy proved lesions characteristic of Whipple's disease described in the literature. Shortened villi and macrophages with PAS-positive substance were the most important features observed in the microscopic examination of the gastrointestinal tract mucosa. In the literature there are cases describing PAS-positive macrophages not only in the small intestine, colon and stomach but in the pancreas, spleen, kidneys and urinary bladder, as well. This may be explained by a very different clinical picture of Whipple's disease [27].

Patients suspected of Whipple's disease should be treated very carefully in diagnostics and treatment due to a non-specific, multiorganic, chronic and very differentiated clinical picture. This disease is frequently mistaken for rheumatoid arthritis and mistreated with steroids and immunosuppressive medications for many months. Whipple's disease untreated for a long period may lead to cachexia and death. Current recommendations regarding treatment are established based on clinical cases. Long-termed antibiotic therapy including oral administration of cotrimoxazole or intravenous administration of ceftriaxone severe cases is the way to prevent Whipple's disease development [28]. The therapy is long and frequently ineffective, depending on severity of symptoms and their duration. Additionally, antibiotic therapy should be supplemented with microelements, macroelements and vitamins [28-30]. In about 10% of patients, Immune Reconstitution Inflammatory Syndrome (IRIS) associated with overproduction of CD4+ lymphocytes caused by the impaired regulating function of T cells can occur during treatment. The main symptoms of IRIS are frequently fever and arthralgia, which intensifies during subsequent months of therapy [11,31].

CONCLUSIONS

Proper treatment is effective but for a short period. Unfortunately, relapses of the disease may lead to cachexia and death. Thus it is vital to remember about Whipple's disease in patients with chronic diseases due to a non-specific clinical picture and difficulties in establishing a proper diagnosis. When the disease is diagnosed unequivocally, proper and effective antibiotic therapy should be instituted immediately.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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