JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Case Report

A rare case of Whipple disease presenting as a hydrosalpinx and granulomatous peritonitis

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Abstract

Introduction: Whipple disease is a rare infectious disease caused by the bacterium *Tropheryma whipplei*. The classic form affects gastrointestinal and musculoskeletal systems; but other forms may damage the heart, brain, or lungs. Due to non-specific and diverse clinical symptoms, diagnosis of Whipple disease is challenging and often late. Adequate and timely antibiotic treatment is essential for favorable outcome.

Case presentation: Here we present a case of a young woman admitted to the gynecological clinic for diagnostic laparoscopy for suspected haemato-/hydro- salpinx and peritoneal endometriosis. Macroscopic findings during laparoscopy revealed miliary whitish lesions in the pelvis and histopathology reported granulomatous salpingitis and peritonitis. She was complaining of intermittent abdominal pain, bloating and weight loss. Subsequently, the laparoscopy symptoms worsened and her general condition deteriorated. Differential diagnosis included infective agents such as *Mycobacterium tuberculosis*; in addition to sarcoidosis, granulomatosis with polyangiitis, and malignancies; all of which were excluded. Finally, *Tropheryma whipplei* was suspected, and after esophagogastroduodenoscopy with duodenal biopsy, long-term antibiotic treatment was initiated and the patient fully recovered.

Conclusions: Although Whipple disease is rare, it is important to have a high level of awareness for *Tropheryma whipplei* infection. The localization and course of Whipple's disease may be unpredictable, but a favorable outcome is expected with adequate antibiotic treatment.

Key words: Whipple disease; granulomatous salpingitis; antibiotics.

J Infect Dev Ctries 2024; 18(8):1308-1312. doi:10.3855/jidc.17984

(Received 24 January 2023 – Accepted 04 July 2023)

Introduction

Whipple's disease (WD) is a rare, multi-systemic infectious disease [1]. Although the first case of WD was described by George Hoyt Whipple more than a century ago, it still remains a diagnostic challenge due to diverse clinical manifestations [2]. It mainly affects middle-aged Caucasian men and the incidence ranges from 1 to 6 new cases per 10,000,000 persons per year worldwide [2]. It is believed that 20% of people are asymptomatic carriers and represent a large reservoir for oro-fecal and oro-oral transmission [2,3]. The classic form affects gastrointestinal and musculoskeletal systems, but other tissues and organs (such as lymph nodes, heart, brain, lungs) can be affected [2,4]. Arthralgia, accompanied by diarrhea, malabsorption, and weight loss are classic symptoms of WD [3]. Diagnosis is often difficult because *Tropheryma whipplei*, the causal organism, is a great mimicker with a wide variety of symptoms and non-specific laboratory findings [5].

Here, we present a rare case of WD with the involvement of peritoneal and pelvic structures.

Case presentation

A 27-year-old woman was admitted to the Clinic for Obstetrics and Gynecology, University Clinical Center of Serbia, for suspected left haemato-/hydro- salpinx and peritoneal endometriosis.

The patient's chief complaint was abdominal pain, localized in both supra- and infra- umbilical portions, that was intermittently present for the last two years. The pain was exacerbated after the second cesarean section, and was accompanied by bloating, hair loss, and subfebrile episodes. She also noticed looser stools, without significant change in their frequency or color. No other gastrointestinal symptoms were reported. Over the period of six months prior to admission, she

had lost 12 Kg of weight. An abdominal computed tomography (CT) scan reported a small amount of ascites, hepatosplenomegaly, and liver hemangiomas, without other significant findings. Pelvic magnetic resonance imaging (MRI) revealed peritoneal thickening in the Douglas pouch, suggestive of endometriosis; and the tubular structure between the uterus and the left ovary, measuring 40 × 15 mm, suggesting dilated left uterine tube and enlarged external iliac lymph nodes. Uterine and ovarian morphology appeared normal.

The patient had no chronic illnesses and no surgical interventions apart from the two cesarean sections done two years and seven months prior. She did not report regular usage of any medication. She also reported that her brother had tuberculosis four years ago.

Both physical and bimanual gynecological examination upon admission, and the chest radiography were unremarkable. Initial laboratory findings (including thyroid hormone levels) were within normal range, except for the elevated values of cancer antigen (CA 125) –159.0 U/mL (normal range 0–35 U/mL), which is often seen in patients with ascites.

Diagnostic laparoscopy was performed. Intraoperative findings revealed miliary whitish lesions, measuring 1–3 mm, dispersed all over the pelvic organs and pelvic wall. There were adhesions between the uterus, bladder, and adnexa. Left uterine tube was dilated and appeared inflamed. Two hundred milliliters of serous fluid was discovered in the Douglas pouch (Figures 1–3).

Left salpingectomy and peritoneal and omental biopsies were performed, as well as the biopsy of the broad uterine ligament beneath the right ovary. The histopathological report showed granulomatous salpingitis and peritonitis with negative Ziehl-Nissen stain. Cytology of the aspirated fluid excluded malignancy; microbiological cultures remained sterile, and protein concentration corresponded to the exudate. Loewenstein culture and polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* were negative.

The patient was discharged from the clinic in good condition, and was prescribed a five-day course of the first generation cephalosporin due to the findings of the exudate.

However, over the course of a few weeks, previous symptoms reappeared and the patient's general condition deteriorated. Abdominal pain worsened and nausea appeared. She reported febrile episodes and general weakness. Additionally, the patient developed pleural effusions, ascites, and peripheral edema; and was admitted to the Military Medical Academy. Laboratory findings showed elevated inflammation markers with C-reactive protein (CRP) measuring 284 mg/L (normal range < 10 mg/L). CA 125 levels were also elevated (299.2 U/mL; normal range 0–35 U/mL). Upon admission dual empirical antibiotic therapy with ceftriaxone and metronidazole was started.

Figure 1. Laparoscopy findings: milliary whitish lesions over the serosa of the right fallopian tube and mesosalpinx.

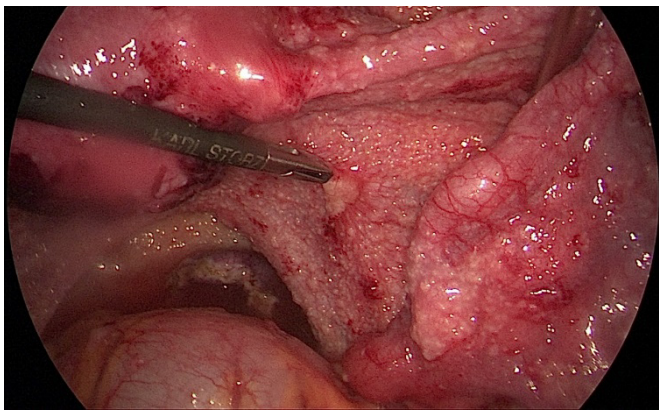


Figure 2. Laparoscopy findings: edematous left fallopian tube and left ovary.

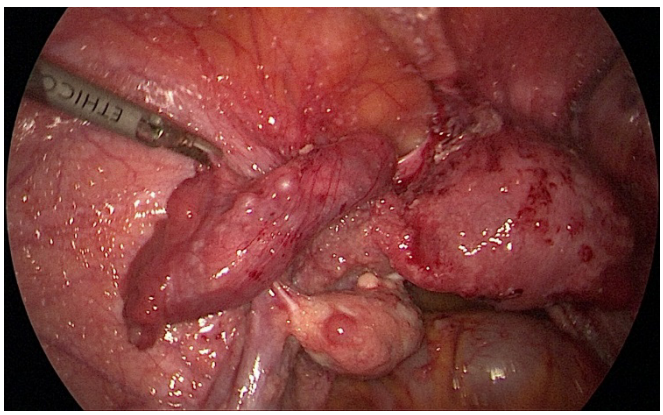
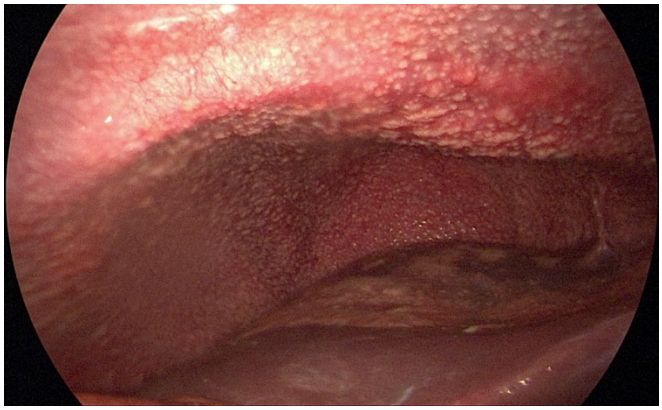


Figure 3. Laparoscopy findings: milliary whitish lesions on the parietal peritoneum.



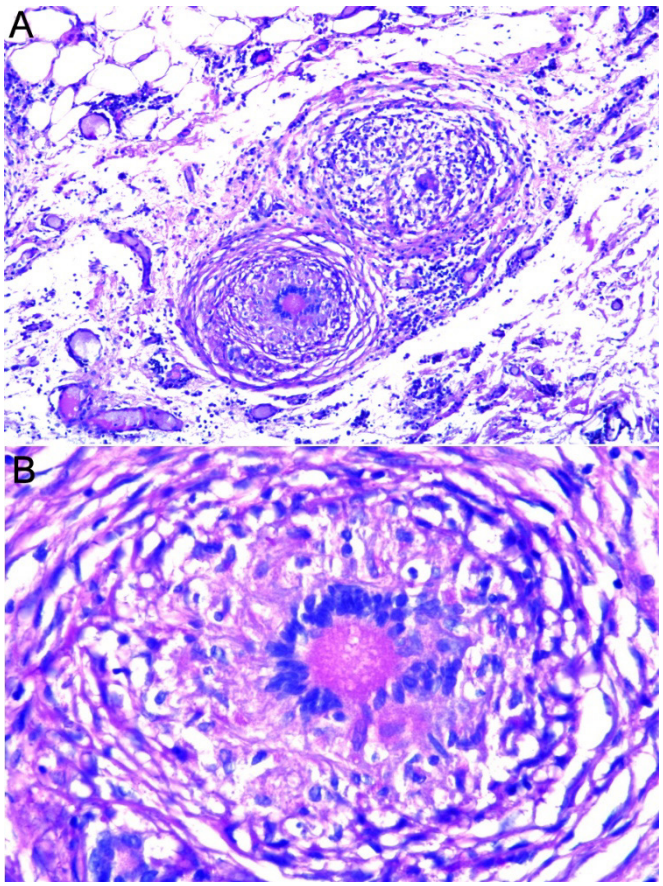
Detailed medical history evaluation and directed questions revealed that the patient had had migratory arthralgia a couple of years before the current symptoms started, but had never sought medical help, nor received any treatment. At this point, multi-slice computed tomography (MSCT) of thorax, abdomen and pelvis showed enlarged mediastinal and abdominal lymph nodes, ascites and right pleural effusion. Thoracocentesis of the right pleural effusion was done and 600 mL of serous liquid was evacuated. There was no evidence of malignant cells and acid-fast-resistant bacilli in the aspirated fluid. Bronchoscopy examination and the bronchial fluid cytological examination were within normal limits. PCR for the *Mycobacterium tuberculosis* was negative, and the microbiological cultures remained sterile for both the pleural effusion and the bronchoscopy aspirate.

Differential diagnosis workup excluded tuberculosis, sarcoidosis, and granulomatosis with polyangiitis. Finally, WD was suspected, and esophagogastroduodenoscopy with duodenal biopsy was performed. Macroscopically, duodenal mucosa was unremarkable except for the localized mucosal hyperemia. Histopathological result of the duodenal biopsy revealed edema, congestion and scarce diffuse inflammatory infiltrate composed of lymphocytes and plasmocytes, which were inconclusive for Whipple's disease. Periodic acid Schiff (PAS) and Ziehl-Neelsen staining were both negative.

Since the patient had already received intravenous ceftriaxone, antibiotic therapy with trimethoprim-sulphometoxasol (960 mg PO) was started. The therapy led to prompt clinical improvement, with the resolution of pleural effusion, ascites, and marked drop in inflammatory parameters. Revision of the pathohistological finding of the biopsy specimen retrieved during laparoscopy — omentum and fallopian tube — showed PAS positive staining, thus confirming WD (Figures 4–5).

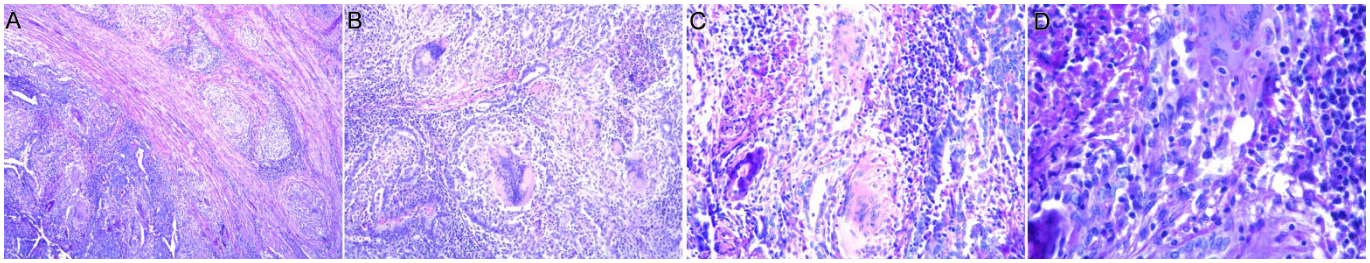
The patient was discharged from the hospital after twelve days in a good condition. During follow up the patient remained stable, gained weight, and reported resolution of all the symptoms. She had completed a one-year antibiotic course, and was without signs of the disease.

Figure 5. Pathology specimen showing granulomatous reaction in omentum caused by *Tropheryma whipplei*.



A. Magnification x100; B. Magnification x400.

Figure 4. Pathology specimen showing granulomatous reaction in the fallopian tube. Granuloma can be seen infiltrating the fallopian tube transmurally, and affecting both the fibrous layer and mucosa. Prominent chronic mononuclear inflammatory reaction is also visible. Greater magnification revealed giant, multinuclear cells containing PAS positive bacilli in the cytoplasm.



A. Magnification x50; B. Magnification x100; C. Magnification x200; D. Magnification x400.

Discussion

This paper describes the case of a young woman with WD that presented with granulomatous peritonitis at laparoscopy. To the best of the authors' knowledge, this is the first case that describes PAS positive lesions corresponding to *Tropheryma whipplei* infection in the muscular layer of the uterine tube.

The classic form of WD develops through three stages. Fever, arthritis, and arthralgia correspond with early stage symptoms and often precede years before gastrointestinal symptoms occur (middle stage) [2]. Our patient had also experienced arthralgia in the past which was left unexamined. Furthermore, since it is a rather common complaint, the patient did not report it at the first admission. In the late stage, the disease affects eyes, heart and central nervous system [2]. In the case presented here, the treatment was started before the late phase began.

There are several reasons why WD remains underdiagnosed. Firstly, *Tropheryma whipplei* is a common pathogen in the human intestine and respiratory tract; thus, most people are asymptomatic carriers [2,4]. The possible explanation lies in the functional immune response of those people, which is responsible for the effective clearance of the microorganism. On the other hand, it has been suggested that developing WD is associated with host immune deficiency such as low CD4/CD8 T-cell ratio and low activity of type 1 T-helper cells [6-8].

In our patient, the symptoms of the disease commenced within a short time interval after the second pregnancy, thus raising the question whether the pregnancy could have affected the disease course. It is a well-known fact that pregnancy induces physiological immune system changes. Recent studies indicate that during pregnancy, the number of T-helper cells type 1 is lower, although CD4/CD8 T-cell ratio remains the same [9]. However, there are many more immunological adaptations during pregnancy that could modulate the response to infection, and the possible link between pregnancy induced immunological changes and the *Tropheryma whipplei* infection warrants further investigation.

Secondly, symptoms of the WD—arthralgia and gastroenteritis—are common, non-specific, usually self-limiting, and withdraw after symptomatic treatment. Therefore, patients rarely seek medical help. Also, there is a latency period between the first phase of the migratory large joint arthritis and consumptive state with marked gastrointestinal symptoms and the symptoms related to wastage that could last for up to 30 years [10]. Our patient was never examined or treated for the migratory arthralgia, which occurred years before diarrhea and abdominal pain started.

WD should be taken into consideration in all patients with the typical tetrad of symptoms—arthralgias, diarrhea, abdominal pain, and weight loss [11–12]. Differential diagnosis of WD includes a wide range of infectious diseases (caused by *Mycobacterium avium* complex, *Bacillus cereus*, *Corynebacterium*, histoplasmosis, and some fungi), but also sarcoidosis, granulomatosis with polyangiitis, lymphoma, and other malignancies need to be excluded [1,3,13].

Unusual forms of WD have been reported in the literature. The tumoral form mimicking carcinomatosis with retroperitoneal pseudotumor formation has been described [5]. Taiwanese authors reported a case of WD with generalized lymphadenopathy and peritoneal adhesions, ascites, and peritoneal miliary plaques; findings that were consistent with chronic tuberculous peritonitis, similar to those in the case presented [14].

Our patient's thoracal and abdominal MSCT scan also showed enlarged mediastinal and abdominal lymph nodes. Similarly, intraoperative finding of whitish miliary peritoneal lesions, and positive family history initially misled us to suspect tuberculosis. However, Loewenstein cultures and PCR for *Mycobacterium tuberculosis* were negative. Persisting abdominal pain with the onset of low-grade fever and deterioration of the overall condition, eventually led to esophagogastroduodenoscopy with duodenal biopsy which is the typical diagnostic method. Diagnosis of WD is made using histopathology with PAS staining, PCR, and/or immunohistochemistry [2]. Apart from the duodenal biopsy specimen, *Tropheryma whipplei* may be found in other tissue and fluid specimens such as cerebrospinal fluid, brain biopsy, myocardial/heart valve biopsy, synovial fluid and tissue, and lymphatic tissue [3,4,15]. In the case presented here, PAS staining was negative on duodenal biopsy specimen. The possible explanation lies in the fact that PAS positivity disappears soon after the initiation of the antibiotic treatment, and the patient had received antibiotic therapy prior to esophagogastrodudenoscopy (EGDS) [4]. However, PAS staining of the material from the laparoscopic surgery—omental, peritoneum and uterine tube specimens—were positive in all the cases. To the best of the authors' knowledge, this is the first case of WD with the PAS positive inclusions in the uterine tube.

Long term antibiotic treatment is the cornerstone of therapy. It requires a combination of initial intravenous

use of penicillin or ceftriaxone, followed by maintenance oral therapy with trimethoprim-sulfamethoxazole [2,16,17]. Doxycycline and hydroxychloroquine are second-line therapy [18]. Duration of therapy depends on clinical presentation and presence of extraintestinal manifestations. Our patient's response to therapy and recovery was quick and efficient, and stayed stable after one year of trimethoprim-sulfamethoxazole therapy.

Conclusions

WD is a relatively rare infectious disease with potentially lethal outcome. Due to the non-specific symptoms and possible diverse clinical manifestations, diagnosis is often established late in the course of the disease. It is therefore necessary to maintain a high level of suspicion and take infection with *Tropheryma whipplei* into consideration as differential diagnosis in patients with migratory asymmetric arthritis and gastrointestinal symptoms, once the more common causes have been ruled out. With a timely diagnosis and adequate antibiotic treatment, the course of WD is favorable, as was in the case described.

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Conflict of interests: No conflict of interests is declared.