




An unusual presentation of Whipple's disease: adenopathies, polyarthralgia and dermatomyositis-like symptoms

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Abstract

Whipple's disease (WD) is a rare systemic disease caused by gram-positive bacillus bacteria that invades multiple organs mainly the intestinal epithelium. Its manifestation is not only limited to the gastrointestinal tract but it also affects the joints, muscle and skin. This is a case of a 54-year-old male patient with a medical history of chronic arthritis presenting with bilateral progressive calves pain, anterior tibial hyperpigmentation, joints pain, anemia and weight loss. He was misdiagnosed as rheumatoid arthritis, for which he was treated by immunosuppressors for several years with no amelioration. After advanced investigations, he was found to have multiple retroperitoneal and mesenteric adenopathies, with an incidental finding of a mesojejunum mass during laparoscopy, from which the biopsies revealed the presence of histiocytosis and numerous intra-cytoplasmic particles with positive periodic acid–Schiff (PAS) suggesting the diagnosis of WD. Endoscopy was done and intestinal histology with polymerase chain reaction (PCR) test confirmed the diagnosis of WD. The patient was then treated with antibiotics (ceftriaxone and trimethoprim-sulfamethoxazole) with a remarkable clinical amelioration. To be aware of WD as a potential etiology behind malabsorption, musculoskeletal and skin abnormalities, is the first step in order to establish the diagnosis and provide adequate treatment, thus, improving the patient's quality of life. WD is a rare, without antibiotic treatment deadly systemic infectious disease caused by the ubiquitous Gram-positive bacterium *Tropheryma whipplei*. This article aims to report a case marked with dermatomyositis like presentation that had a missed and delayed diagnosis.

Keywords

Whipple's disease, myositis, arthralgia, melanoderma, hyperpigmentation



Introduction

Whipple's disease (WD) was called after George Hoyt Whipple who reported in 1907, the first case of lipid deposits in the intestinal mucosa. WD was named intestinal lipodystrophy. In 1949, Black-Schaffer introduced the periodic acid–Schiff (PAS) stain and demonstrated that the intracellular material was glycoprotein rather than lipid [1]. In 1961, an underlying bacterial etiology was identified [2], and it took around 40 years later to identify 16S ribosomal DNA (rDNA) sequence and establish its relationship with an intracellular organism—the actinomycetes. *Tropheryma whippelii* was then introduced [3].

This bacterium has been identified in the stool of asymptomatic individuals in Europe and Africa, and gastric aspirates in America [4], suggesting a genetic susceptibility to infection and an association between chronic infection, T-cell function impairment and certain human leukocyte antigen types [5, 6].

WD is a very rare, chronic, systemic infectious disease with an estimated annual incidence of 3 in one million, which may be fatal if not diagnosed and treated appropriately [7, 8]. In a large population-based study conducted in the US, the overall prevalence of WD was 9.8 cases per 1 million people [9].

It affects mainly middle-aged men, around fifty years old [10], and recent studies showed similar rates of affection in men and women [9]. Outdoor workers seem to be more affected by this disease [11]. The reservoir, route of transmission and natural occurrence is not identified and until now under research [12].

According to literature, the most common host of this bacterium is the mucosa of the small intestine in human [13]. The microscopic pathologic findings consist of massive infiltration of foamy macrophages containing dense PAS-positive granules [14].

Polymerase chain reaction (PCR) is increasingly used to identify bacterial 16S rDNA molecules and other targeted repeated sequences of *Tropheryma whippelii* (*T. whippelii*, formerly *Tropheryma whippelii*) [11]. The definitive diagnosis is established in PAS-positive histologic findings along with positive PCR.

WD can affect almost any organ system and is accordingly classified between classic systemic disease and localized or extraintestinal disease [15]. The clinical signs include arthralgia, weight loss, diarrhea and abdominal pain, although the clinical manifestations can vary widely.

In classic intestinal WD, bacterial and inflammatory cells infiltrate small intestinal mucosa and mesenteric lymph nodes, inducing malabsorption with resultant weight loss, diarrhea and abdominal pain and rarely gastrointestinal bleeding [10, 15, 16].

WD is frequently associated with rheumatic manifestations (60% of the cases), which precede the gastrointestinal signs in three fourths of the patients. They are often the first symptoms of the disease [16]. Joints and musculoskeletal manifestations are as following: migratory or additive non-destructive arthralgia involving large joints. Polyarthralgia including symmetric and asymmetric is often intermittent while articular attacks are acute and last for days [17]. Arthralgias and articular attacks precede intestinal symptoms several years.

The use of immunosuppressive drugs for articular treatment (the illness being sometimes misdiagnosed as seronegative rheumatic disease) may accelerate the onset of intestinal or other systemic illness [18].

Myositis is also reported to be associated with WD. Case of bilateral extraocular myositis [19] as well as a case of WD mimicking an autoinflammatory disease with myositis and soft tissue inflammation has been reported [20].

Occasionally central nervous system (CNS) and ophthalmic complications are observed [21]. CNS manifestations are myriad and usually develop in later stages of the illness [22]. Two signs are pathognomonic for CNS WD: oculomasticatory myorhythmia and oculo-facial skeletal myorhythmia, which consist of ocular nystagmus and synchronous contractions of the masticatory and proximal and distal skeletal muscles [21–23]. Even in the absence of CNS symptoms, cerebrospinal fluid *T. whippelii* PCR analysis may be positive [21], in 25% to 47% [24].

Around the malar and orbital hyperpigmentation, purpura and cheilitis are the main skin manifestations of WD. A variety of skin lesions have been described in association with WD and the most common of these is hyperpigmentation or melanoderma that develops in up to 46% of patients in the later stages of the illness.

Other characteristic skin abnormalities include subcutaneous nodules, erythema nodosum-like lesions, and inflammatory rashes that may mimic cutaneous lupus, dermatomyositis, psoriasis, or eczema [25]. Finally, fever may occur for years and is mainly low grade and intermittent. Rarely, there may be clinical manifestations of isolated central nervous system disease, endocarditis, or lung, skin, or eye disorders [26].

The most frequently used treatment included a 2-week intravenously cephalosporins followed by oral sulfonamides for 1–2 years. This therapy achieved significantly high success rate with values around 90% [27]. Response is monitored by clinical examination. Microscopic examination is not helpful for treatment follow-up specially that PAS-positive structures may persist for years despite adequate therapy [28]. Without proper antibiotic treatment, the disease invariably culminates in dissemination and is potentially fatal [29].

Herein, a case of WD was reported, with an unusual presentation: the illness was handicapping, and the diagnosis was delayed.

Case report

This is a case of a 54-year-old Lebanese man, a non-smoker, non-alcoholic, admitted to the hospital for handicapping bilateral calves swelling and pain with skin hyperpigmentation over the anterior tibial side of his legs increasing progressively. The patient was also noticed with weight loss of 10 kilograms over 3 months duration with persistent fatigue.

History goes back to 12 years prior to presentation, when the patient started to have chronic migratory peripheral polyarthritis involving the large and small joints of his upper and lower extremities, which was diagnosed as seronegative rheumatic disease treated with methotrexate and folic acid for 12 years (stopped 5 months prior to presentation). Adalimumab was then added to the regimen, taken for one year only and stopped 10 months prior to presentation due to its side effects: pleural effusion and upper respiratory infection. No beneficial effect was noted and symptoms persisted despite antirheumatic drugs. Few months prior to presentation, persistent cramping calves pain (and even pain of proximal extremity—thigh, accelerated by palpation on physical exam with anterior tibial discoloration started to develop, forcing him to ambulate only with assistance. Weight loss as mentioned above was also noted despite good appetite.

The patient is known to have diabetes mellitus type 2 on vildagliptin/metformin mixed combination and repaglinide. No other particular medical history.

He denied any other constitutional, HEENT (head, eyes, ears, nose, and throat), respiratory, cardiovascular, gastrointestinal or genitourinary symptoms, nor bipolar aphthosis. Physical examination revealed a poorly built and cachectic patient with pale skin. He had anicteric sclera with poorly injected conjunctiva. His remaining HEENT examination was unremarkable and his lungs had good bilateral air entry with no added sounds. Regular heart sounds S1 and S2 without a murmur were noted, his abdomen was soft not tender nor distended with positive bowel sounds and his joints showed no signs of arthritis. His lower limbs examination revealed bilateral thigh and calf tenderness with non-pitting swelling (right > left), with homogenous hyperpigmentation of the anterior tibial skin bilaterally. The pain was present at rest (the calves mainly) and exacerbated by active and passive movement. Neurologic exam showed normal mental status, cranial nerves, motor (strength and cerebellar), reflexes and sensations. To note that a complete cerebellar exam or gait examination wasn't done as the patient couldn't ambulate without assistance.

The patient denied undergoing any previous surgery and mentioned no family history of any specific disease.

To note that the patient is an outdoor worker. He worked in the nature and was exposed to soil.

Investigations

In addition to the laboratory blood tests in [Table 1](#), lower limbs Doppler ultrasound to rule out a deep venous thrombosis showed calves edema with muscular fascia thickening mainly at right and no evidence of thrombosis.

Table 1. Laboratory blood tests upon admission

Lab test	Result	Lab test	Result
Hemoglobin	100 g/L	Creatinine	0.76 mg/dL
Hematocrit	0.314 L/L	Calcium	8.7 mg/dL
MCV	68 fL	Magnesium	2.1 mg%
WBC	7,700/mm ³	CPK	19 U/L
Neutrophils	64% (4,928 cells/ μ L)	CRP	124 mg/L
Lymphocytes	22% (1,694 cells/mm ³)	ESR	110 mm/h
Eosinophils	6% (426 cells/mL)	TSH	3.11 mIU/L
Platelets	335 \times 10 ⁹ /L		

MCV: mean corpuscular volume; WBC: white blood cells; CPK: creatine phosphokinase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; TSH: thyroid-stimulating hormone

Lower limbs magnetic resonance imaging (MRI) to rule out myositis revealed fasciitis and myositis of the two calves of posterior predominance. A musculoskeletal MRI of the whole body was suggested for better assessment of topographic muscular involvement (Figure 1A and 1B). The latter imaging showed, in addition to the fasciitis and myositis at the level of the legs, a fissure surrounding the right semi-membranosus and the left biceps at the level of the thigh, with also a suspicion of myositis at the attachment of the right gluteus minimus. The paravertebral muscles at the level of L5 and S1 were also involved. It was also noticed the involvement of the supraspinatus and infraspinatus muscles bilaterally and symmetrically is with a very probable presence of mild myositis of the right triceps muscle.

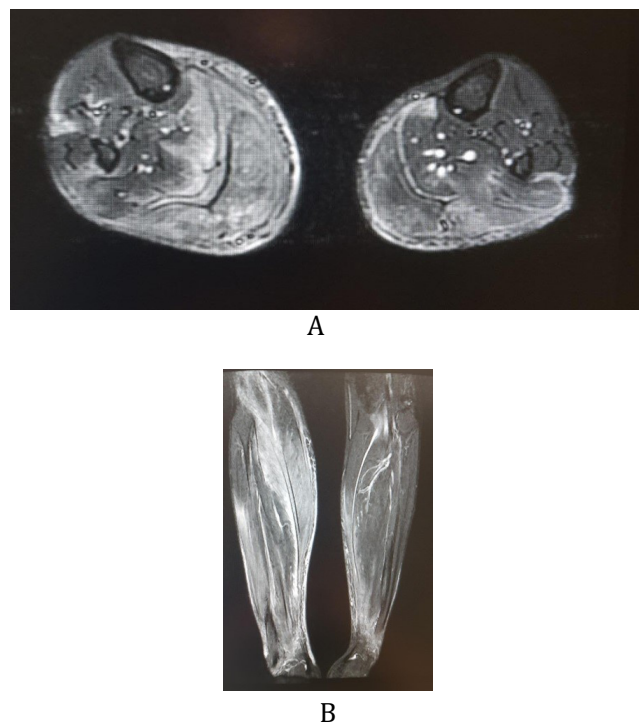


Figure 1. Muscular MRI. A: axial stir, showing myositis; B: coronal stir showing myositis

At this point, skin and muscle biopsies (biopsies of right gastrocnemius muscle and of the above skin) were done and immunofluorescence technique was performed, and it confirmed the presence of myositis and fasciitis at that same level. PAS stain was done on both muscle and skin biopsies but did not show any additional finding. Trichinellosis was ruled out.

Moreover, on MRI there was a diffuse and homogenous marrow replacement suspicious for lymphoproliferative disorder.

Therefore, a computed tomography (CT) scan for the chest, abdomen and pelvis with injection was ordered to assess the possibility of any lymphoproliferative disorder, or any other neoplasm ruling out paraneoplastic presentation (Figure 2A and 2B).

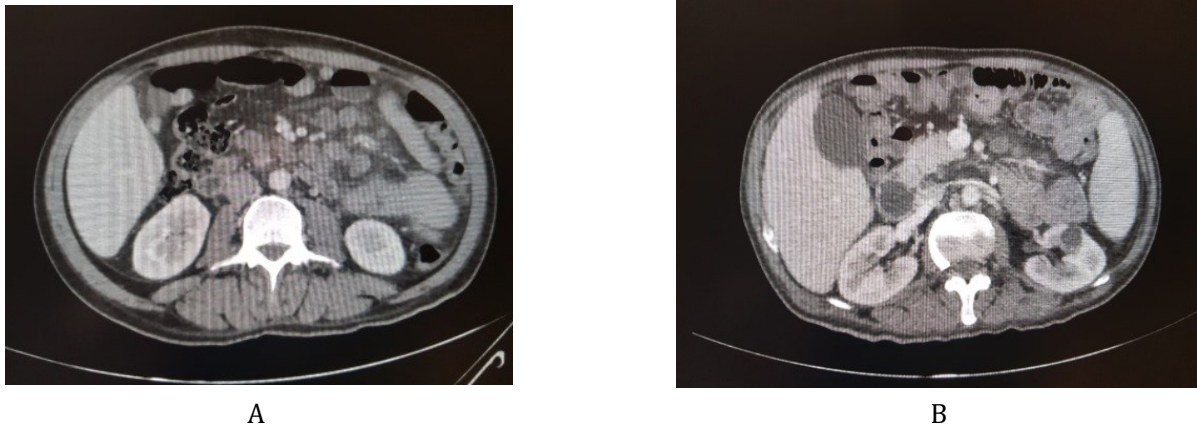


Figure 2. Enhanced CT scan of the abdomen. A: Mesenteric lymph nodes; B: jejunal thickening

The thoraco-abdomino-pelvis CT scan revealed a minimally prominent right paratracheal node measuring 10 mm, an enlarged spleen measuring 14.5 cm, mildly enlarged retroperitoneal nodes as well as moderately enlarged mesenteric nodes (the largest measures 15 mm), with diffuse increased density and haziness of the mesenteric fat, mainly in the mid abdomen and on the left side. Findings are compatible with lymphoma or metastasis, nevertheless, a benign condition such as inflammatory process cannot be ruled out.

Consequently, tuberculosis, human immunodeficiency virus (HIV) infection, autoimmune diseases, and systemic diseases were ruled out (Table 2).

Table 2. Blood tests done later in the course

Lab test	Result	Lab test	Result
ANA	Negative	c-ANCA	Negative
p-ANCA	Negative	Anti-CCP	Negative
RA test	Negative	Myositis panel	Negative
Autoimmune panel	Negative	HIV	Negative
ACE	Negative	PPD skin test	Negative

ANA: antinuclear antibodies; p-ANCA: perinuclear antineutrophil cytoplasmic antibodies; RA: rheumatoid arthritis; ACE: angiotensin converting enzyme; PPD: purified protein derivative; c-ANCA: cytoplasmic antineutrophil cytoplasmic autoantibody; CCP: cyclic citrullinated peptides

Retroperitoneal lymph nodes biopsy by laparoscopy was done to rule out lymphoma. However, during the laparoscopy, a meso-jejunal mass was identified, from which biopsies were taken and showed a lymph node structure containing multiple histiocytes with foamy cytoplasm (Figure 3A and 3B). Numerous intracytoplasmic particles positive for PAS and PAS diastase (Figure 4A and 4B) were identified. This non-Langerhans histiocytosis suggested the diagnosis of WD, but necessitated more investigations to confirm the diagnosis. In front of this finding of histiocytosis, the differential diagnosis was wide including leukemia, lymphoma, myeloma, malignant melanoma, xanthoma, Rosai-Dorman disease, Erdheim-Chester disease, storage diseases and solid tumors.

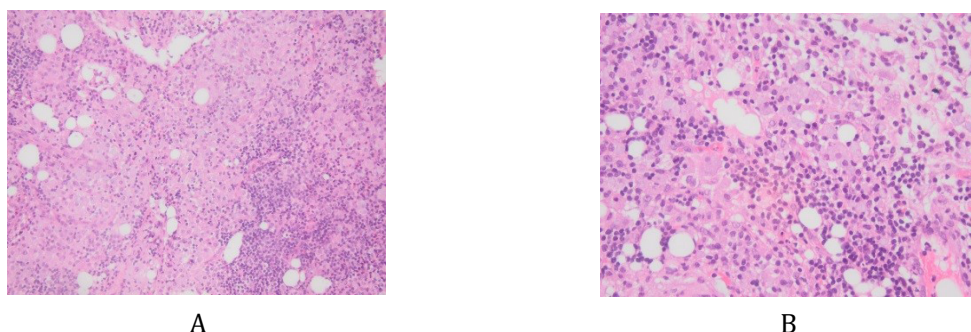


Figure 3. Histiocytes with clear foamy cytoplasm. A: hematoxylin and eosin (HE) stain, $\times 10$; B: HE, $\times 200$



Figure 4. Numerous intra-cytoplasmic particles positive for PAS stain and PAS diastase. A: PAS stain, $\times 100$; B: diastase stain, $\times 100$

The biopsy of retroperitoneal lymph nodes showed normal histological finding, ruling out malignancies.

Meanwhile, the bone marrow aspirate and biopsy were performed to rule out multiple myeloma (MM), myelodysplastic syndromes/myeloproliferative neoplasms (MDS/MPN), or myelofibrosis and showed no evidence of hematologic disease with normal cytogenetics and normal karyotype. A requested Jack2 mutation test revealed negative result.

At this point, gastroscopy and colonoscopy were done, with biopsies taken from stomach, duodenum, jejunum, ileum, and colon. The colon biopsy was normal. The duodenal, ileal and jejunal biopsies revealed WD with hyperplasia of Paneth cells (Figure 5A and 5B) with positive staining for PAS (Figure 6). Consequently, a real-time PCR performed on the biopsy to search for *T. whipplei* DNA turned positive confirming the diagnosis of WD.



Figure 5. Hematoxylin and eosin (HE) stains of the duodenal biopsy showing multiple foamy histiocytes in the axis of the villi. A: HE, $\times 100$; B: HE, $\times 200$

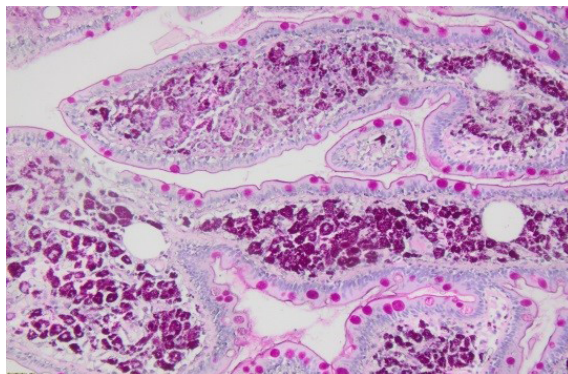


Figure 6. PAS staining of the duodenum (PAS, $\times 200$)

In view of the diagnosis, the patient was treated with a traditional ceftriaxone followed by a trimethoprim-sulfamethoxazole (TMP-SMX) regimen. He received IV Rocephin for 14 days and was discharged home on oral (per os: PO) TMP-SMX (one double-strength tablet [160 mg TMP/800 mg SMX] twice a day) for one year. He had rapid improvement of symptoms and all clinical signs within 2–3 weeks.

Discussion

The diagnosis of WD is challenging in that it allows specific treatment and difficult due to its rarity, to the diversity of clinical manifestations and to its slow progressive course that can mimic autoinflammatory, autoimmune or malignant diseases.

WD usually presents with weight loss and gastrointestinal symptoms and diagnosis is confirmed by histology duodenal biopsy [7]. More rarely WD can affect the musculoskeletal system, most often as oligo- or polyarthritis, mainly of the large joints [8] and more rarely as monoarthritis or with axial involvement [13, 21]. Exceptionally it can cause inflammation of muscles and soft tissues [16, 26].

Herein, the presentation of a WD case presenting with as a dermato-polymyositis like syndrome.

In WD, once the disease is suspected, it is important to rule out other differential diagnoses such as inflammatory bowel disease, other infectious causes, connective tissue diseases, immunosuppression and hyperthyroidism [30]. All the tests were done to our patient and were negative.

The diagnosis is usually made with endoscopic procedures and biopsies of the affected tissue. However, in 30% of cases the duodenal biopsies can be normal [31].

In this presented case, the middle-aged patient was diagnosed with seronegative polyarthritis more than twelve years ago, for which he sought multiple internists and rheumatologist. He started on multiple courses immunosuppressors (methotrexate, corticosteroids and adalimumab) without medical benefit, even worsening his medical condition. Immunosuppressive therapy may contribute to the progression of the infection and it may represent a 'second hit' in the pathogenesis of the disease [31]. It is reported in that immunosuppressants therapy may induce and accelerate the gastrointestinal symptoms in WD [27], yet it is debatable whether exposure to these agents represents an independent risk factor or is a clinical misstep before diagnosis.

Diagnosis in our case was difficult when gastrointestinal symptoms were absent. Clues for WD were lack of response to anti-inflammatory and antirheumatic disease treatment (methotrexate, adalimumab and folic acid), weight loss, signs of chronic inflammation (high CRP), signs of malabsorption (low hemoglobin) and occupational exposure.

During his hospital stay, multiple features and findings helped us to establish the diagnosis. In fact, despite extensive list of tests, the patient did not receive a clear diagnosis. What reinforced the hypothesis is that this was not only a joint disease and it could be related to a rare systemic disease mimicking polymyositis. Physical findings of skin hyperpigmentation over both lower limbs guide us toward a systemic disease. The patient had persistent elevation of inflammatory markers (ESR110, CRP124) and normocytic anemia. Muscle biopsy even was not diagnostic but it showed unspecific myositis without inclusions bodies which could be associated with WD.

Imaging was helpful to identify moderately enlarged mesenteric lymph nodes (laparoscopy has been helpful to guide biopsy) with further endoscopy showing typical duodenal changes: duodenitis and villous atrophy with subsequent biopsy revealing PAS-positive granules compatible with WD.

A similar reported case describes bilateral WD-associated extraocular muscle myositis in a 38-year-old Caucasian female who presented with acute-onset diplopia and previously had intermittent fevers, arthralgia, rash and fatigue [17]. Two cases of WD were reported, in which the manifestation was diffuse abdominal and retroperitoneal lymphadenopathies [27]. Another case in Rio de Janeiro in 2014 showed WD manifested as difficult-to-diagnose polyarthralgia in a 45-year-old male patient [17]. And another similar case has been reported in a 58-year-old female patient with a one-year history of markedly elevated inflammatory markers and progressive anemia and seronegative polyarthritis turned to have WD [17].

Screening for WD by duodenal biopsies with PAS stain plus PCR test (or immunohistochemistry) and the final diagnosis is made if it meets one of the following criteria: a positive PAS staining in duodenal tissue, two different positive tests of the same tissue or two positive tests of different tissues [32].

In this case, biopsy had a key role to achieve the diagnosis, since both soft tissue mass and digestive endoscopy duodenal biopsies were conclusive and diagnostic (two positive tests of different tissues). The

patient had a firm diagnosis of WD following PAS-positive macrophages demonstrated on mass biopsy and confirmed with positive PCR. The sensitivity of the PAS staining of small bowel biopsies ranges from 71% to 78%. In some cases, PCR is needed to confirm the diagnosis given its higher sensitivity and specificity, however PCR is not available in all centers [33]. PCR is an efficient tool for diagnosis of WD, even if PAS is negative on examination of biopsies. This was the case of a 41-year-old woman, diagnosed as WD only with PCR analysis on duodenal and mesenteric adenopathy biopsies, while PAS staining was normal [34].

The patient started on Rocephin for 14 days followed by the classical 1-year treatment with TMP-SMX. He experienced rapid improvement. The recommended gold standard treatment is with TMP-SMX 160/800 mg orally twice daily for a least 1 year. Preceded by a 2-week parenteral therapy of ceftriaxone (2 g per day).

There are different alternative treatments, depending on the toxicity and tolerance of the patients to certain antibiotics. Clinical improvement begins to be evident from days 7–21.

Relapses are largely responsible for a higher morbid-mortality, meaning the prognosis worsens with relapse and it commonly occurs after treatment. However, patients can present a relapse up to 30 years after the treatment stopped [35].

In the reported case, the patient was treated with the classical 1-year treatment and responded adequately to the pharmacological management.

WD is a rare systemic infection with *T. whipplei*, which is still a challenge to diagnose as its clinical manifestations are not specific, resembling many other systemic diseases and may manifest late during the course of the disease. Several years usually elapse between symptom onset, characteristic clinical manifestations and the diagnosis. WD should be taken into account because of its wide variety of clinical manifestations and because of its potential fatal outcome in the absence of treatment. The risk of sequelae and mortality rate are high if it's not diagnosed and treated in a timely manner.

To avoid misdiagnosis, clinicians should be aware of this unusual presentation of WD, mimicking an autoimmune disease with dermatomyositis-like presentation that should be a part of the list of the differential diagnosis, as delay in diagnosis may be life-threatening. Knowing that clinicians are able to treat this rare disease with adequate antibiotherapy once the diagnosis is established avoiding therapeutic measures that can be detrimental to the patient.

Abbreviations

CNS: central nervous system

CRP: C-reactive protein

CT: computed tomography

MRI: magnetic resonance imaging

PAS: periodic acid–Schiff

PCR: polymerase chain reaction

T. whipplei: *Tropheryma whipplei*

TMP-SMX: trimethoprim-sulfamethoxazole

WD: Whipple's disease

Declarations

Author contributions

JF, RC and NS: Writing-original draft. JN and JM: Data collection. JA: Biopsies endoscopy. CG: Interpretation of biopsy results. All authors contributed to revision of manuscript, read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

This manuscript has been approved by the Institutional Review Board of Lebanese Hospital Geitaoui.

Consent to participate

Written informed consent was obtained from the patient.

Consent to publication

Not applicable.

Availability of data and materials

All relevant data are contained within the manuscript.

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References

1. Black-Schaffer B. The tinctoral demonstration of a glycoprotein in Whipple's disease. *Proc Soc Exp Biol Med.* 1949;72:225–7.
2. Chears WC Jr, Ashworth CT. Electron microscopic study of the intestinal mucosa in Whipple's disease. Demonstration of encapsulated bacilliform bodies in the lesion. *Gastroenterology.* 1961;41:129–38.
3. Wilson KH, Blichington R, Frothingham R, Wilson JA. Phylogeny of the Whipple's-disease-associated bacterium. *Lancet.* 1991;338:474–5.
4. Keita AK, Bassene H, Tall A, Sokhna C, Ratmanov P, Trape JF, et al. *Tropheryma whipplei*: a common bacterium in rural Senegal. *PLoS Negl Trop Dis.* 2011;5:e1403.
5. Martinetti M, Biagi F, Badulli C, Feurle GE, Müller C, Moos V, et al. The HLA alleles DRB1*13 and DQB1*06 are associated to Whipple's disease. *Gastroenterology.* 2009;136:2289–94.
6. Feurle GE. Association of Whipple's disease with HLA-B27. *Lancet.* 1985;325:1336.
7. Biagi F, Balduzzi D, Delvino P, Schiepatti A, Klersy C, Corazza GR. Prevalence of Whipple's disease in north-western Italy. *Eur J Clin Microbiol Infect Dis.* 2015;34:1347–8.
8. Ojeda E, Cosme A, Lapaza J, Torrado J, Arruabarrena I, Alzate L. Whipple's disease in Spain: a clinical review of 91 patients diagnosed between 1947 and 2001. *Rev Esp Enferm Dig.* 2010;102:108–23.
9. Elchert JA, Mansoor E, Abou-Saleh M, Cooper GS. Epidemiology of Whipple's disease in the USA between 2012 and 2017: a population-based national study. *Dig Dis Sci.* 2019;64:1305–11.
10. Fleming JL, Wiesner RH, Shorter RG. Whipple's disease: clinical, biochemical, and histopathologic features and assessment of treatment in 29 patients. *Mayo Clin Proc.* 1988;63:539–51.
11. Dobbins WO 3rd. The diagnosis of Whipple's disease. *N Engl J Med.* 1995;332:390–2.
12. Keita AK, Raoult D, Fenollar F. *Tropheryma whipplei* as a commensal bacterium. *Future Microbiol.* 2013;8:57–71.
13. Ramzan NN, Loftus E Jr, Burgart LJ, Rooney M, Batts KP, Wiesner RH, et al. Diagnosis and monitoring of Whipple disease by polymerase chain reaction. *Ann Intern Med.* 1997;126:520–7.
14. Braun J, Sieper J. Rheumatologic manifestations of gastrointestinal disorders. *Curr Opin Rheumatol.* 1999;11:68–74.
15. Lagier JC, Lepidi H, Raoult D, Fenollar F. Systemic *Tropheryma whipplei*: clinical presentation of 142 patients with infections diagnosed or confirmed in a reference center. *Medicine.* 2010;89:337–45.

16. Moreno García MS, Casorrán Berges M, Del Río-Martínez PS, Bosque Peralta MT. The great unknown, Whipple's disease. *Reumatol Clin*. 2017;13:243–4.
17. Durand DV, Lecomte C, Cathébras P, Rousset H, Godeau P; the SNFMI Research Group on Whipple Disease. Whipple disease: clinical review of 52 cases. *Medicine*. 1997;76:170–84.
18. Mahnel R, Kalt A, Ring S, Stallmach A, Strober W, Marth T. Immunosuppressive therapy in Whipple's disease patients is associated with the appearance of gastrointestinal manifestations. *Am J Gastroenterol*. 2005;100:1167–73.
19. Parkash V, Mudhar HS, Wagner BE, Raoult D, Batty R, Lepidi H, et al. Bilateral ocular myositis associated with Whipple's disease. *Ocul Oncol Pathol*. 2017;3:17–21.
20. Ankli B, Khanlari B, Pegios V, Zettl A, Daikeler T. Whipple's disease mimicking an auto-inflammatory disease with myositis and soft tissue inflammation. *Joint Bone Spine*. 2018;85:645–6.
21. Louis ED, Lynch T, Kaufmann P, Fahn S, Odel J. Diagnostic guidelines in central nervous system Whipple's disease. *Ann Neurol*. 1996;40:561–8.
22. Gerard A, Sarrot-Reynauld F, Liozon E, Cathébras P, Besson G, Robin C, et al. Neurologic presentation of Whipple disease: report of 12 cases and review of the literature. *Medicine*. 2002;81:443–57.
23. Lieb K, Maiwald M, Berger M, Voderholzer U. Insomnia for 5 years. *Lancet*. 1999;354:1966.
24. Tison A, Preuss P, Leleu C, Robin F, Le Pluart A, Vix J, et al. Rheumatological features of Whipple disease. *Sci Rep*. 2021;11:12278.
25. Whipple Disease [Internet]. Musculoskeletal Key; [cited 2022 Sep 16]. Available from: <https://musculoskeletalkey.com/whipples-disease/>
26. Marth T. Whipple's disease. *Acta Clin Belg*. 2016;71:373–8.
27. Fenollar F, Puéchal X, Raoult D. Whipple's disease. *N Engl J Med*. 2007;356:55–66.
28. Lagier JC, Fenollar F, Lepidi H, Giorgi R, Million M, Raoult D. Treatment of classic Whipple's disease: from *in vitro* results to clinical outcome. *J Antimicrob Chemother*. 2014;69:219–27.
29. Guthikonda B, Rouah E, Krishnan B, Powell SZ, Goodman JC, Gopinath SP, et al. Whipple disease of the central nervous system: an unusual occurrence in association with acquired immune deficiency syndrome. *J Neurosurg*. 2010;112:983–9.
30. Dolmans RA, Boel CH, Lacle MM, Kusters JG. Clinical manifestations, treatment, and diagnosis of *Tropheryma whipplei* infections. *Clin Microbiol Rev*. 2017;30:529–55.
31. Marth T. Systematic review: Whipple's disease (*Tropheryma whipplei* infection) and its unmasking by tumour necrosis factor inhibitors. *Aliment Pharmacol Ther*. 2015;41:709–24.
32. Obst W, von Arnim U, Malfertheiner P. Whipple's disease. *Viszeralmedizin*. 2014;30:167–72.
33. Rey RM, Orozco LA, Marrugo K, López R, Pérez-Riveros ED, De la Hoz-Valle J, et al. Whipple disease diagnosed by enteroscopy: first case report in Colombia of an underdiagnosed disease and literature review. *BMC Gastroenterol*. 2020;20:197.
34. Wartique L, Lagier JC, Raoult D, Jamilloux Y, Sève P. Mesenteric lymphadenitis as a presenting feature of Whipple's disease: value of PCR analysis. *Int J Infect Dis*. 2018;75:15–7.
35. Keinath RD, Merrell DE, Vlietstra R, Dobbins WO 3rd. Antibiotic treatment and relapse in Whipple's disease. Long-term follow-up of 88 patients. *Gastroenterology*. 1985;88:1867–73.