CASE REPORT

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Whipple's Disease: Case Report and Review of the Literature

Vincenzo De Francesco[1], Fabrizio Corsi[2], Antonio Pennella[2], Annamaria Bellesia[1], Giulia Fiorini[3], Dino Vaira[3], Angelo Zullo[4]

1) Section of Gastroenterology, Department of Medical Sciences, Foggia;
2) Department of Pathology, University of Foggia, Foggia;.
3) Department of Internal Medicine and Gastroenterology, University of Bologna, Bologna;
4) Gastroenterology and Digestive Endoscopy, 'Nuovo Regina Margherita' Hospital, Rome, Italy

Address for correspondence:
Vincenzo De Francesco, MD
Section of Gastroenterology, Department of Medical Sciences, University of Foggia, Ospedali Riuniti,
Viale L. Pinto,
71100 - Foggia, Italy
vdefrancesco@ospedaliriunitifoggia.it

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ABSTRACT

Whipple's disease (WD) is known as an infrequent, systemic, chronic infection caused by the actinomycete *Tropherima whipplei* (*T. whipplei*). The disease is frequently characterized by a long prodromal and protean extra-intestinal phase, which often causes misdiagnosis and inappropriate treatments. Herein, we describe the case a 62-year-old man with a histological diagnosis of WD established when oral steroid treatment was started due to rheumatic manifestations, triggering intestinal symptoms. Systematic review of the literature was performed to include studies where WD was eventually diagnosed on duodenal biopsies. Three patients' subgroups were identified according to the clinical presentation.

Key words: Whipple's disease – *Tropherima whipplei* – endoscopy – gastrointestinal tract.

Abbreviations: NSAIDs: nonsteroidal anti-inflammatory drugs; PAS: periodic acid Schiff; *T. whipplei: Tropherima whipplei*; WD: Whipple's disease.

INTRODUCTION

Firstly described on 1907 as 'intestinal lipodystrophy', Whipple's disease (WD) is known as an infrequent, systemic, chronic infection caused by the actinomycete *Tropherima whipplei* (*T. whipplei*), suspected as aetiologic agent by PCR in 1992, and isolated by culture in 2000. Currently, the diagnosis is mainly performed in demonstration of periodic acid Schiff (PAS) staining positive macrophages in the lamina propria on duodenal biopsies. Indeed, the disease typically involves the small intestinal tract, causing diarrhea, weight loss, abdominal pain and fever. However, extra-intestinal localizations may be present, including joints, muscle-skeletal system, cardiac valves, brain, eyes, lungs, and skin. Of note, symptoms suggestive of rheumatologic disorders may anticipate digestive manifestations, not infrequently leading to a misdiagnosis and detrimental immunosuppressive treatments, as previously reported [1]. Here, we reported a case of Whipple's disease discovered at endoscopy with duodenal biopsies after long-term nonsteroidal anti-inflammatory drugs (NSAIDs) treatment and we performed a systematic review of cases eventually diagnosed at upper endoscopy with biopsy.

CASE REPORT

A 62-year-old man, poultry breeder, was referred to our Gastroenterological Unit on March 2017 because of bloody diarrhea (up to 8-10 movements/daily), abdominal pain, intermittent fever, severe fatigue, and marked weight loss (18 Kg) during the last four months. He complained of hand and foot arthralgia in the last 9 months, initially treated with NSAIDs by his General Practitioner, without regression. Therefore, he was referred to a rheumatologist who diagnosed seronegative rheumatoid arthritis, and started a tapering therapy with 16 mg/daily methylprednisolone and 600 mg ibuprofen on November 2016. One month later, due to diarrhoea onset, two cycles of antibiotic therapy with rifaximin were prescribed without improvement. On the contrary, the diarrhoea became bloody so that the patient was admitted to our Unit. At entry, abdomen palpation did not reveal tenderness, and cardiac, pulmonary and neurological assessments were unrewarding. No lymphadenopathies were detected, whilst a middle hyper-pigmentation of the

light-exposed skin was noted. Laboratory tests documented a marked microcytic anaemia (Hgb: 8 gr/dl; RBC: $3.8x10^6$/dl, MCV: 72 fl, and ferritin: 21 ng/dl), hypoalbuminaemia (1.9 g/dl), and increased levels of both ESR (30 mm/h) and β2-microglobulin (11.2 mg/dl), with normal results of other routine tests. Colonoscopy was performed showing normal mucosa, but with bloody traces until the terminal ileum. Therefore, upper endoscopy was performed showing erythematosus duodenal mucosa due to diffuse haemorrhagic suffusions (Fig. 1A). Histological assessment of multiple duodenal biopsies showed large macrophage aggregates in the lamina propria, with lymphocytes and neutrophils infiltrate (Fig. 1B). PAS stain demonstrated multiple PAS-positive and diastase-resistant inclusions in foam macrophages, consistent with WD (Fig. 1C). Total body-CT scan revealed only multiple para-aortic/caval enlarged lymph nodes. Therefore, 2 g daily ceftriaxone therapy was administered intravenously for 2 weeks, and both anaemia and hypoalbuminaemia were corrected with intravenous supplementations. A prompt disappearance of both diarrhea and fatigue occurred during hospitalization. Thereafter, long-term oral therapy with 4 g daily trimethoprim-sulfamethoxazole was started, together with oral iron supplementation. On October 2017, a 9 Kg body weight gain was observed with normalization of haemoglobin levels. At repeat upper endoscopy, normal duodenal mucosa was found (Fig. 1D), whilst histological assessment showed a marked improvement, although small aggregates of foam macrophages (Fig. 1E), with rare PAS-discolored inclusions, and without neutrofils infiltrate, persisted (Fig. 1F). The patient is presently on ongoing trimethoprim-sulfamethoxazole therapy, and a further endoscopic control is planned.

LITERATURE REVIEW

A systematic review of literature was performed to include studies where WD was diagnosed at duodenal histological examination. The search was performed from January 1992 to February 2018 by using PubMed; the exploded medical subject heading terms were '*Tropherima whipplei*' or 'Whipple disease'. Boolean operators: NOT, AND, OR were also used in succession to narrow and widen the search. References of the retrieved articles were reviewed to search for potentially missed publications. Inclusion criterion was WD diagnosis performed on duodenal biopsies taken at upper endoscopy. A total of 559 studies were identified and, following evaluation of abstracts or full paper, 76 studies meeting the inclusion criteria were included in this pooled data analysis [2-77] (Fig. 2). Overall, there were 89 cases diagnosed with WD on duodenal biopsies, with a large prevalence of males (M/F: 71/18), and the mean age was 52.3 ± 11.1 years. Patients were mainly described in Germany (19 cases), USA (12 cases), Italy (10 cases), Brazil (9 cases), France (7 cases), Spain (5 cases), Japan and UK (4 cases), The Netherlands (3 cases), Portugal and Taiwan (2 cases), whilst only 1 case was reported from Austria, Australia, Balearic Isles, Belgium, Camerun, Canada, Czech Republic, Denmark, Greece, Island, Poland and Romania. Overall, intestinal symptoms were present in 60 (67.4%) patients, rheumatological symptoms in 54 (60.6%), ocular and neurological involvement in 15 (16.8%), cardiac/vascular manifestations in 14 (15.7%), dermatological lesions in 12 (13.4%), hematologic disorders in 11 (12.3%), pulmonary symptoms in 3 (8.3%) cases, and kidney involvement with amyloidosis in a single (1.1%) case. In detail, according to the

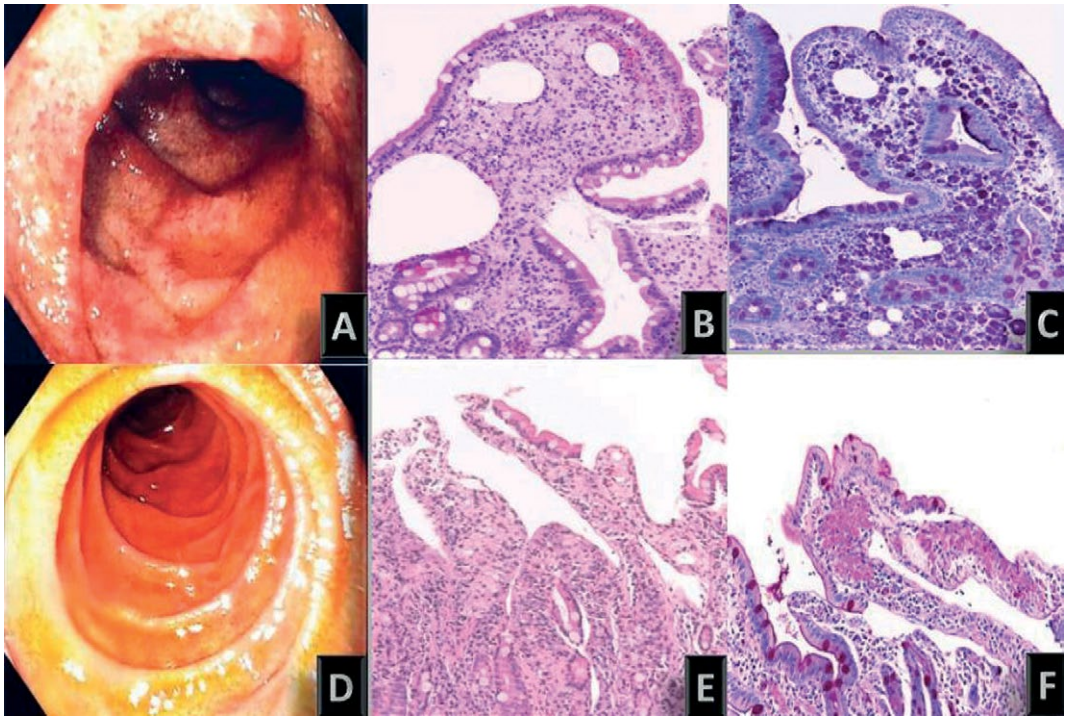

Fig. 1. Erythematosus duodenal mucosa with diffuse haemorrhagic suffusions (A). Duodenal mucosa with large macrophage aggregates in the lamina propria, with lymphocytes and neutrophils infiltrate (H&E 200x)(B). Multiple PAS-positive and diastase-resistant inclusions in foam macrophages (C). Normal duodenal mucosa at endoscopy (D). Persistence of small aggregates of foam macrophages (H&E 200x)(E), with rare PAS-discolored inclusions (PAS 200x)(F).

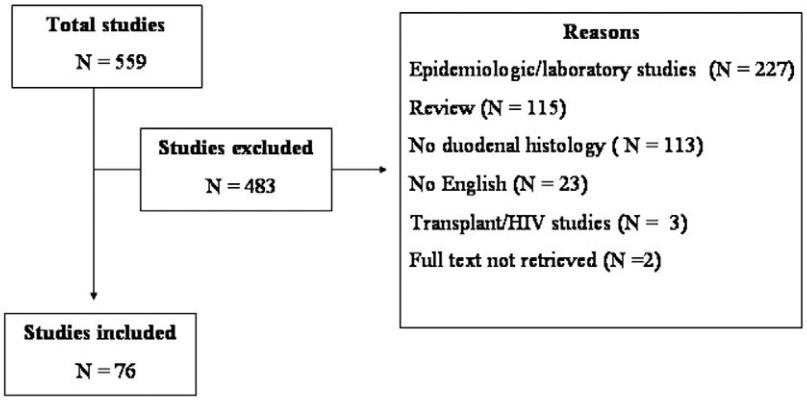

Fig. 2. Literature searching results.

clinical presentation of disease, these patients may be classified in the following three subgroups: 1) patients with early intestinal manifestations, mainly including chronic diarrhea, abdominal pain, and weight loss, suggestive of malabsorption (N = 15); 2) patients with extra-intestinal manifestations (rheumatologic, neurologic, ocular, etc.) in whom a late onset of intestinal manifestations occurred, prompting upper endoscopy (N = 45); and 3) patients with extra-intestinal manifestations, but without intestinal symptoms, in whom upper endoscopy was occasionally performed as work-up before NSAIDs or steroid therapy starting (N = 29). Of note, early appearance of intestinal symptoms significantly anticipated diagnosis (Table I).

Table I. Clinical characteristics of patients according to the initial clinical presentation.

	Early intestinal (N =15)	Extra-intestinal and late intestinal (N = 45)	Extra-intestinal only (N = 29)
Male/Female	11/4	37/8	24/5
Age (Mean±SD);years	51.1±8.3	53.5±12.5	51±10.2
Diagnosis interval; median (range); months	8 (1-48)[1]	24 (24-264)	30 (1-240)
Disease regression (%)	12 (80)	43 (96)	21 (72)
Recurrence (%)	3 (13)	2 (4)	8 (28)[2]

[1]Statistical difference ($p<0.001$) among early intestinal with the other groups (Mann-Whitney test); [2]Statistical difference ($p<0.05$) among extra-intestinal only with the other groups. (Fisher's exact test).

The most frequently used therapy was intravenous ceftriaxone for 14 days followed by long-term oral trimethoprim-sulfamethoxazole (77 cases; 86.5%; median duration: 12 months, range: 6-24), whilst different combinations with an aminoglycoside, cotrimoxazole, tetracycline were used in the remaining 12 cases. Overall, clinical remission was achieved in 76 patients, and the success rate was significantly higher for ceftriaxone followed by trimethoprim-sulfamethoxazole therapy as compared to other performed therapies (89.6% vs 58.3%, $p<0.05$; OR: 6.1, 95% CI = 1.5-24). Recurrence of disease occurred in 13 (17%) cases, during a 1-12 years follow up, and 8 (61.5%) of these patients were successfully re-treated whilst the remaining 5 cases were lost at follow-up. The recurrence rate was significantly higher in patients without intestinal symptoms (8/21, 28%) as compared to those patients with early/late intestinal symptoms (5/60, 8%) (Table I).

DISCUSSION

Whipple's disease is a chronic systemic infection caused by *T. whipplei*, generally in the presence of a defective cellular immune response [78]. A higher incidence of the infection among breeders and sewage workers has been reported, suggesting an occupational or environmental method of transmission [49, 79-81]. It is a rare disease, with protean clinical presentation, including intestinal and extra-intestinal symptoms, with consequent misdiagnosis [2]. Rheumatologic manifestations might precede intestinal symptoms, which develop when immunosuppressive therapy is introduced, as occurred in our patient and in other reports [2, 13, 82, 83]. Therefore, the onset of intestinal manifestations during immunosuppressive therapy should alert the physicians, particularly in those patients with occupational risk factors for WD. By reviewing data of literature, we found that diagnosis was performed only following several months from symptoms onset, further suggesting that this is an insidious and still neglected disease. Noteworthy, we found that WD was incidentally diagnosed at duodenal biopsies in as many as 38% of patients with extra-intestinal manifestations (arthritis, neurological symptoms, cardio-vascular, ocular disorders), but without gastrointestinal symptoms. Indeed, the presence of gastrointestinal symptoms significantly reduces the diagnostic delay from 30 to 8 months in the considered case series.

Differently from several bacterial species, culture of *T. whipplei* is very difficult and time-consuming because of the very slow bacterial grow. Therefore, diagnosis of WD is currently performed by PAS staining on duodenal biopsies. Nevertheless, the reliability of the PAS testing may be mined in a significant number of cases either by false positive results, particularly in the course of other infections (HIV, histoplasmosis, mycosis, etc.) or false negative findings during immunosuppressive treatment [84]. For these reasons, a PCR-based tool, performed on organ biopsies or different body fluids, may be necessary for diagnosing or confirming WD in some cases. Indeed, the PCR allows the detection of specific

bacterial 16S rRNA. More recently, a quantitative real-time PCR tool was found to have a higher sensitivity than a standard PCR, but this method is available only in a few centers [2, 28, 85]. Seldom, *Tropheryma* presence in biologic fluids was confirmed by the finding of the peculiar trilamellar cell wall at electron microscopy [2]. Finally, a PET-based technique was associated with a high diagnostic yield when cerebral localization was present [86].

The most frequently used treatment included a 2-week intravenously cephalosporins followed by oral sulphamides for 1-2 years. We found that this therapy achieved significantly higher success rate when compared to the others, with values approaching 90%. However, long-term therapy and follow-up are required, particularly in those patients with a longer misdiagnosis or presence of extra-intestinal involvement who are at an increased risk of treatment failure [87]. In this series, the infection recurrence rate was as high as 17%. Of note, we computed that those patients with only extra-intestinal symptoms had a recurrence more frequently than other patients.

CONCLUSIONS

Whipple's disease is a rare and ubiquitous infectious disease, presenting with different and protean manifestations. Presence of gastrointestinal symptoms significantly reduces the diagnostic delay, but they are lacking in more than one third of cases. Long-term antibiotic treatment achieves high success rates.

Conflicts of interest: None to declare.

Authors' contribution: V.d.F. and A.Z. designed and wrote the manuscript. A.B. and G.F. collected literature data. F.C. and A.P. performed histological assessment and evaluations. D.V. reviewed with constructive criticisms.

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