CASE REPORT

Case Report: Tropical sprue, diagnostic challenges of an old but unrecognized disease [version 3; peer review: 2 approved]

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Abstract

Tropical sprue (TS) is a post-infective disease of the small bowel characterized by a malabsorption syndrome affecting tropics inhabitants and visitors. Diagnosis of TS remains challenging since it can be confused with common diarrheal diseases, especially in non-endemic areas. We report a Tunisian case of latent TS.

A 58-year-old male with a history of chronic watery diarrhea, was admitted to the intensive care unit for confusion which was related to a severe metabolic acidosis. Despite the neurological improvement after hydro-electrolytic resuscitation and acid-base disorders correction, the patient continued to have three to five loose stools daily.

A nutritional assessment showed a malabsorption syndrome: iron, Vitamin B12 and folate deficiencies; normochromic normocytic anemia and hypoalbuminemia.

Gastrointestinal endoscopy showed duodenal villous atrophy and biopsy confirmed subtotal villous atrophy with increased intraepithelial lymphocytosis and a thickened hyalonalized subepithelial basal lamina. Celiac disease was evoked, however the
patient did not improve on a gluten-free diet and the celiac serology was negative.

On re-interviewing, we discovered that the patient had spent two months in India three years prior.

Given the travel history, clinico-biological and histological data TS was highly considered and a good response to a five-month antibiotic course combined to nutritional supplementation supported this diagnosis.

Clinico-biological, endoscopic and histological findings were overlapping between TS and other malabsorption diseases, explaining diagnosis difficulties. TS should be systematically discussed in tropics visitors presenting with chronic diarrhea. Improvement after micronutrient and vitamin deficiencies replacement combined to a prolonged antibiotic course supports the diagnosis of TS.

**Keywords**
Chronic diarrhea, small bowel disease, malabsorption, tropical sprue, villous atrophy.
Introduction
Tropical sprue (TS) is a very old disease. The first reported cases were described by a Yorkshireman, Dr William Hillary, among the inhabitants of the island of Barbados over 200 years ago.1 Endemic TS occurs in the tropical and subtropical regions but is underrecognized elsewhere. It is predominantly present in southern and southeast Asia and the Caribbean Islands, and rarely described in North Africa and Europe.2 Within the present era of globalization and worldwide travel, it is important for all clinicians to be aware of the possibility of TS in patients presenting with diarrhea, malabsorption, multiple nutritional deficiencies and mucosal abnormalities in the small bowel who have travelled to endemic regions.3

Diagnosis of TS remains challenging since it can be confused with common diarrheal diseases, including celiac disease, Crohn’s disease, bacterial overgrowth, and other infectious aetiologies.4

In this article, we present a Tunisian case of latent TS revealed by a confusional syndrome.

Case report
A 58-year-old North African male was admitted to the intensive care unit for confusion without fever. He was single, working as a trader and had a history of iron deficiency anemia. There were no particular family antecedents. The acute symptoms had been preceded by chronic diarrhea, worsening fatigue, and a 40 pounds weight loss over three years which were trivialized by the patient. He had neither HIV nor tuberculosis risk factors.

Physical examination revealed conjunctival pallor, diffuse abdominal pain and dehydration without fever or organomegaly. Blood glucose levels were normal, as well as the urine dipstick.

Blood tests identified metabolic acidosis (pH = 7.35, paCO₂ = 22.9 mmHg, HCO₃⁻ = 12.9 mmol/L, Base excess = -9.9, paO₂ = 88 mmHg) with normal anion gap (about 16) and which was related to gastrointestinal loss of bicarbonate. We also noted normochromic normocytic anaemia (haemoglobin = 5.7 g/dL, MCV = 81 fl, MCHC = 30 g/dL), and normal WBC (7200/μL) and platelet (174000/μL) counts. Renal and liver functions were correct (creatinine = 72 μmol/L, total bilirubin = 13.6 μmol/L, AST/ALT/ALP = 31/31/140 IU/L). The blood ionogram showed hypokalaemia (2.81 mmol/L) and hypophosphatemia (0.32 mmol/L) with normal natremia (139 mmol/L) and chloremia (110 mmol/L). Additional investigations revealed normal level of vitamin B1, normal level of IgG (13.48 g/L, normal range between 6.58 and 18.37 g/L), negative viral serologies (Hbs, HCV and HIV) and negative toxicology work-up. Brain MRI and abdominal CT scan were normals.

The most likely cause of confusion was the dehydration after ruling out cerebral causes, toxic causes, ureaemia, hepatic encephalopathy, and Gayet wernicke encephalopathy (no chronic alcoholism, no diabetes history and normal level of vitamin B1). Furthermore, we noted an improvement on the state of consciousness after hydro-electrolytic resuscitation and acid-base disorders correction. Despite the neurological improvement, the patient continued to have watery diarrhea, abdominal meteorism and weight loss. Thus, we first discussed infectious causes and the patient was treated for a possible small bowel bacterial overgrowth with an association of a third generation cephalosporin and metronidazole. The result of coproculture was negative and the parasitological stool testing wasn’t available in our laboratory. Despite antibiotherapy, he continued to have three-five loose stools daily.
A nutritional assessment was performed and showed a malabsorption syndrome: iron deficiency (ferritin = 0.84 μg/L, serum iron = 2.44 μmol/L), hypoalbuminemia (22 g/L) and hypocalcaemia (1.8 mmol/L). We also noticed slight deficiencies in Vitamin B12: 170 pg/mL (normal: 180-914 pg/mL) and folate: 3.2 μg/L (normal > 3.5 μg/L).

Upper gastrointestinal endoscopy showed partial villous atrophy (Figure 1). These changes were nonspecific but were suggestive of celiac disease. Thus, a gluten-free diet was prescribed.

Duodenal biopsy showed subtotal villous atrophy with increased intraepithelial lymphocytosis and a very thickened hyalinized sub-epithelial basal lamina: an appearance suggestive of sprue (Figure 2).

On re-interviewing, we discovered that the patient had spent two months in India (for commercial purposes) three years prior. A few months after his return, he developed chronic intermittent watery, non-bloody diarrhea. He was also experiencing asthenia and had a weight loss but he did not consult any doctor.

Celiac serologies, including endomysial antibody, tissue transglutaminase antibody, and gliadin IgA, gliadin IgG, and total IgA levels were all negative. In light of these negative serologies and lack of response to a gluten-free diet, celiac disease was unlikely.

Autoimmune enteropathy was implausible as no extra-intestinal manifestation were documented. Whipple’s disease was also unlikely as the patient didn’t have initially fever or arthralgia. The investigations carried out did not reveal any involvement of other organs (heart, lung, brain or serous cavities). Besides, the histological findings were not consistent with this pathology since no macrophage or bacillus were visualized in the duodenal biopsy.

In addition, the patient had no history of tuberculosis or contagion and the abdominal CT scan was normal. Unfortunately, PCR test for Tropheryma whippelii and Mycobacterium tuberculosis were not available in our hospital.

Beyond the digestive symptoms, we had no arguments in favor of common variable immunodeficiency enteropathy. The patient had no history of recurrent infections, the gamma globulin level was normal and the mucosal biopsy was not suggestive.

Figure 1. Gastrointestinal endoscopy showing duodenal villous atrophy.
Furthermore, medication-induced enteropathy was not discussed since the patient wasn’t under any treatment.

Given the travel history, clinico-biological, endoscopic and histological findings, TS was highly considered.

A five-month antibiotic course was prescribed (tetracycline 250 mg four times daily) combined to a nutritional supplementation (iron: 150 mg and folate: 5 mg orally daily with cyanocobalamin 1000 μg daily intramuscularly for ten days, followed by 1000 μg monthly for one year). Within one month the patient reported feeling significantly better with resolution of diarrhea, increased energy and weight gain. The biochemical parameters had normalized at the three-month check-up (haemoglobin = 9.4 g/dL, and albumin = 43 g/L). The response to treatment supported the diagnosis of TS.

On the one-year follow-up visit, the patient was continuing to improve. He gained 35 pounds of weight and the diarrhea was completely gone. We intended to check the gastrointestinal endoscopy at follow-up, but as he had progressed well, he refused to do it.

Discussion
The main strengths associated to this case report of TS were: the uncommon presentation of TS which was revealed by a confusional syndrome; and the clinico-biological, endoscopic and histological features supporting this rare and unrecognized diagnosis in non-endemic areas. Response to combined treatment confirmed the diagnosis but the lack of an endoscopic control after improvement was a limitation in our case. In fact, TS is a disease of the small intestine characterized by a malabsorption syndrome with a subtotal or partial mucosal atrophy. It occurs mainly in the tropics, particularly in most of the Greater Antilles, the northern part of South and Central America and South-East Asia. It appears to be rare in Africa, but its real frequency is unknown as small bowel biopsies are not routinely done.2,5 TS affects indigenous inhabitants and expatriates, either long-term residents or short-term visitors, in these endemic areas (the case of our patient).5,6 Patients can present with diarrhea soon after returning from the tropics, but rarely TS may be latent for months to years after leaving the endemic region, as was the case of our patient.7

The risk factors involved in the pathogenesis of this small bowel disease are immune deficiency, poor hygiene, and bacterial, viral or parasitic gastrointestinal infections.8 In fact, the most incriminated bacteria are Klebsiella pneumoniae, Escherichia coli and Enterobacter cloacae.3,8 Enterotoxin production by some strains of enterotoxigenic K. pneumonia or E. coli can lead to abnormalities of mucosal structure and function.5 Otherwise, the local action of unabsorbed bile acids might also be involved.4
The diagnosis of TS is difficult. It is based on the combination of clinico-biological, histological and evolutionary criteria.\textsuperscript{4,5,10}

- Compatible clinical presentation: diarrhea, weight loss, asthenia,
- Evidence of a malabsorption syndrome of two unrelated substances,
- Abnormal small intestinal mucosal histology,
- Exclusion of other intestinal diseases with similar presentation,
- Improvement after treatment with tetracycline and folic acid.

Therefore, TS must be considered in patients who have lived in an endemic area, presenting with chronic diarrhea and evidence of malabsorption.\textsuperscript{2} Megaloblastic anemia is common and is secondary to folate and vitamin B12 deficiencies. Although, megaloblastic anemia is the most common form of macrocytic anemia caused by vitamin B12 and/or folate deficiency, in several cases reported in the literature blood tests may reveal normocytic normochromic anemia, particularly in the early stages of macrocytic anemia or in cases of combined microcytic and macrocytic anemia.\textsuperscript{11,12} This may further explain the normochromic normocytic anemia of our patient, since he had a long history of iron deficiency responsible of a hypochromic microcytic anemia to which was added the vitamin B12 and folate deficiency. Calcium, vitamin D and magnesium-impaired absorption may also occur, with resulting osteopenia. Steatorrhea is often evident if fecal fat is measured. Furthermore, abnormal D-xylose test supports proximal small intestine malabsorption.\textsuperscript{4,5,7,10,13}

Gastrointestinal endoscopic findings are non-specific in TS. In fact, celiac disease must be considered, especially given the endoscopic abnormalities and histological similarity with TS.\textsuperscript{9,14}

Biopsy from the distal portion of the duodenum reveals villous atrophy and an increased infiltration of the lamina propria by chronic inflammatory cells (plasma cells and lymphocytes).\textsuperscript{9} Other causes of malabsorption (celiac disease, Crohn’s disease, bacterial overgrowth, autoimmune enteropathy, medication-induced enteropathy and lymphoma) must be ruled out.\textsuperscript{4,5,10,14} Although seronegative coeliac disease is rare but possible,\textsuperscript{13} our patient didn’t improve after a gluten free diet which was another argument against this diagnosis. Infectious, immune and iatrogenic causes were also unlikely in our case.

The key principles in the management of TS include rehydration, micronutrient deficiency replacement, oral folate, intramuscular vitamin B12 and antibiotics. Sulfonamides and, more recently, new quinolones, particularly ofloxacin, were tried in some previous cases reported in the literature. However, tetracycline is the antibiotic of choice, administered at a dose of 250 mg orally four times daily.\textsuperscript{4,5,10,13,15} The duration of treatment has not yet been codified, as it depends on the evolution of the disease. In general, it’s a prolonged antibiotic course over three to six months. It will be stopped after control of the restitution ad integrum of the clinico-biological and histological anomalies.\textsuperscript{5,10,16} In our case, tetracycline was prescribed for five months and the favourable response to treatment supported the diagnosis of TS, but a control by gastrointestinal endoscopy wasn’t carried out.

Complete resolution after an optimal management is standard in the returning travellers from an endemic area. However, for the tropics inhabitants, TS may relapse, requiring a prolonged follow-up given the risk of re-exposure to the infectious agent.\textsuperscript{4,7,9,16}

Conclusions
Clinico-biological, endoscopic and histological findings overlap between TS and other malabsorption diseases, explaining diagnosis difficulties. While TS is common in tropics inhabitants, it must be considered in tropics visitors presenting with chronic diarrhea after ruling out other causes. Improvement after an optimal management combining rehydration, replacement of micronutrient, folate and vitamin B12 deficiencies as well as a prolonged antibiotic course supports the diagnosis of TS.

Data availability
All data underlying the results are available as part of the article and no additional source data are required.
Consent
Written informed consent for publication of the clinical details and clinical images was obtained from the patient.

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Version 3

Reviewer Report 28 August 2024

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✓ Laisa Socorro Briongos-Figuero
Rio Hortega University Hospital, Valladolid, Spain

I think changes made a add great quality to this case and are appropriate.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious diseases; Internal Medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 24 August 2024

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✓ Wolfgang Kreisel
Department of Medicine II, Gastroenterology, Hepatology, Endocrinology and Infectious Diseases, Faculty of Medicine, University of Freiburg, Freiburg, Baden-Württemberg, Germany

The case report can be in the indexed in the revised form.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
Laisa Socorro Briongos-Figuero
Rio Hortega University Hospital, Valladolid, Spain

The study of the spectrum of malabsorption could be arduous in chronic diarrhea. I have carefully revised the manuscript and I think it's a worthy, well-structured and interesting case report but I miss some information:

- TS is a rare cause of malabsorption syndrome characterized by megaloblastic anemia due to vitamin B12 deficiency. The patient had a mild B12 deficiency and a severe iron deficiency. Could you explain your thoughts about this fact?
- Neurological disorders could be a symptom of other conditions like Whipple's disease, tuberculosis or common variable immunodeficiency enteropathy. Did a polymerase chain reaction test for Tropheryma whipplei and Mycobacterium tuberculosis underwent a on duodenal tissue or stool?
- provided imaging evidence that the mucosal lesions had resolved at follow-up would be helpful for comparison

The manuscript may be approved with reservations. Some changes are needed.

Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the case presented with sufficient detail to be useful for other practitioners?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious diseases; Internal Medicine

I confirm that I have read this submission and believe that I have an appropriate level of
expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 12 Aug 2024

Jihene Guissouma

Dear reviewer:
Thanks for the time you have devoted to review this paper and for giving us the opportunity to benefit from your expertise. Here are the answers to your comments:
- To explain the type of anemia in our case: you are absolutely right, megaloblastic anemia is the most common form of macrocytic anemia caused by vitamin B12 and/or folate deficiency. However, in some cases reported in the literature, blood tests may reveal normocytic normochromic anemia, particularly in the early stages of macrocytic anemia or in cases of combined microcytic and macrocytic anemia. This may further explain the normochromic normocytic anemia of our patient, since he had a long history of iron deficiency responsible of a hypochromic microcytic anemia to which was added the vitamin B12 and folate deficiency.

- To discuss other causes of neurological disorders and malabsorption conditions, we believe that the confusion was explained by metabolic disorders as the state of consciousness improved after hydroelectrolytic resuscitation and correction of acid-base disorders, even more so as the brain MRI was normal. Whipple's disease was unlikely as the patient didn't have initially fever or arthralgia. The investigations carried out did not reveal any involvement of other organs (heart, lung, brain or serous cavities). Besides, the Histological findings were not consistent with this disease since no macrophage or bacillus were visualized in the biopsy. In addition, the patient had no history of tuberculosis or contagion and the abdominal CT scan was normal. Unfortunately, PCR test for Tropheryma whipplei and Mycobacterium tuberculosis were not available in our hospital. Beyond the digestive symptoms, we had no arguments in favor of common variable immunodeficiency enteropathy. The patient had no history of recurrent infections, the gamma globulin level was normal and the mucosal biopsy was not suggestive. Furthermore, improvement without immunoglobulin replacement therapy was another argument against this diagnosis.

- We couldn't provide imaging evidence that the mucosal lesions had resolved at follow-up. In fact, we intended to check the gastrointestinal endoscopy at follow-up, but as the patient had progressed well, he refused to undergo it. All these points were checked in the new version. We hope that we have replied to all your queries and we are available if any other points remain unclear.

Best regards

Competing Interests: no competing interest
Wolfgang Kreisel  
Department of Medicine II, Gastroenterology, Hepatology, Endocrinology and Infectious Diseases, Faculty of Medicine, University of Freiburg, Freiburg, Baden-Württemberg, Germany

I confirm that the present version may be indexed.

Is the background of the case's history and progression described in sufficient detail?  
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?  
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?  
Yes

Is the case presented with sufficient detail to be useful for other practitioners?  
Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
Tropical sprue is a frequent cause of malassimilation syndrome in tropical countries accounting for up to 30% of affected persons. However, it is rare in Europe, North America, or Countries lining the Mediterranean Sea. The authors describe the case of a 58-years-old male patient who presented with confusion, dehydration, and watery diarrhea in a University Hospital in Tunisia. Clinical presentation, endoscopy of the duodenum, and thorough anamnestic evaluation (the patient spent 2 months in India), and response to antibiotic therapy led to the correct diagnosis of tropical sprue. The paper is very interesting, and it is well written. However, I recommend stylistic editing for English language and grammar.

Several items should be corrected or changed:
- The patients had only a mild metabolic acidosis, not a severe acidosis. The blood pH of 7.35 is at the lower limit of normal. Please indicate base excess and exact value for anion gap. Metabolic acidosis with normal anion gap proves bicarbonate loss, as the authors indicate. The confusion is rather the consequence of dehydration that the consequence of the mild (!) acidosis. The hypokalemia of 2.81 mMol/L in acidosis is a dangerous situation.
- Further blood tests clearly indicated malassimilation syndrome, as was further demonstrated by the evidence of villous atrophy. The authors use the term “hyalonalized”. Is this a generally accepted term? Should it be “hyaluronalized”? Amorphic material beneath the basal membrane resembling hyaluronic acid?
- I suggest to better discuss the differential diagnosis of villous atrophy (celiac disease, refractory celiac disease, autoimmune enteropathy, post-infectious villous atrophy etc.). Was giardiasis excluded, or other intestinal pathogens?
- Therapy and clinical course are correct described.
- As for refs., I recommend to add few newer reviews, e.g. Louis-Auguste & Kelly (2017)¹; Green et al., (2022)².

The manuscript may be approved with reservations.

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Is the background of the case’s history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Is the case presented with sufficient detail to be useful for other practitioners?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Gastroenterology. Infectious Diseases. Celiac Disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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**Author Response 31 Aug 2023**

**Jihene Guissouma**

Dear Reviewer

Thank you for accepting to review this article.

We agree that the metabolic acidosis wasn't severe in our case. The base excess and the anion gap values were -9.9 and 16 respectively.

We corrected the term hyalonalized with hyalinized.

We have better discussed the differential diagnosis. In fact, bacterial overgrowth was unlikely as the coproculture were negative and the patient didn't improve after antibiotherapy.

Unfortunately, parasitological stool testing wasn't available in our laboratory. Autoimmune enteropathy was unlikely as no extra-intestinal manifestation were documented. Furthermore, medication-induced enteropathy was not discussed since the patient wasn't under any treatment. Although seronegative celiac disease is rare but possible our patient didn't improve after gluten free diet which was another argument against this diagnosis.

We added the new reviews recommended.

**Competing Interests:** no competing interest
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