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Single Case

Fever and Increased Gastrointestinal Uptake on Positron Emission Tomography after Anti-Tumour Necrosis Factor Therapy: A Case Report of Whipple's Disease

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Keywords
Whipple's disease · Tropheryma whipplei · Arthritis · Anti-tumour necrosis factor · Case report

Abstract
Introduction: Whipple's disease is a rare condition that can present with atypical and non-specific features requiring a high index of suspicion for diagnosis. ***Case Presentation:*** We present a case of a man in his 40s with peripheral arthritis and bilateral sacro-ileitis for 4–5 years that was treated with an anti-tumour necrosis factor therapy, which led to worsening of his symptoms, elevation of the inflammatory markers, and the development of fever, night sweats, anorexia, and a significant weight loss. The patient had no abdominal pain, diarrhoea, or other gastrointestinal symptoms. An FDG-PET scan showed increased uptake in the stomach and caecum. Endoscopic examination showed inflammatory changes in the stomach and normal mucosa of the duodenum, jejunum, terminal ileum, caecum, and colon. Histopathology was inconclusive, but the diagnosis was confirmed with *Tropheryma whipplei* PCR testing. He had no neurological symptoms, but cerebrospinal fluid *Tropheryma whipplei* PCR was positive. He was treated with intravenous ceftriaxone 2 g daily for 4 weeks, followed by trimethoprim/sulfamethoxazole 160/800 mg twice daily for 1 year with close monitoring and follow-up. ***Conclusion:*** This case presents an atypical and challenging presentation of Whipple's disease and the importance of proactive testing for neurological involvement.

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Introduction

Whipple's disease is a chronic, multisystem infectious disease caused by the actinomycete *Tropheryma whipplei*; "Tropheryma" means "Nourishment Barrier" in Greek, and "Whipplei" is attributed to George Hoyt Whipple, who described the first case of Whipple's disease in 1907 [1]. *Tropheryma Whipplei* is usually found in soil; the exact transmission route and pathophysiology are poorly understood, but it is thought to involve multiple factors, including genetic, immunological, and bacterial virulence factors. Whipple's disease is rare, with a reported prevalence of 1/1,000,000 affecting men more frequently; however, a recent population-based epidemiological study of Whipple's disease in the USA showed a higher prevalence of 9.8/1,000,000 with equal prevalence in males and females [2].

Whipple's disease has diverse symptomatology, including joint pain, weight loss, abdominal pain, diarrhoea, and skin hyperpigmentation. Other less common but more severe manifestations include neuropsychiatric, cardiac, respiratory, and eye involvement.

In this case report, we present a patient diagnosed with Whipple's disease without typical gastrointestinal symptoms at the time of diagnosis. The non-rheumatological features of Whipple's disease manifested only after treatment with an anti-tumour necrosis factor (TNF) agent for bilateral sacro-ileitis.

Written informed consent was obtained from the patient to publish this case report and any accompanying images. The CARE Checklist has been completed by the authors for this case report and is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538462).

Case Report

A man in his 40s was admitted to our hospital with a history of fever, weight loss, ongoing arthralgia, and persistently high inflammatory markers. He did not have chronic medical issues or allergies and did not use any medications before this illness. He was married, never smoked, had an alcohol intake of 70–80 g weekly, and lived in an urban area. He had no family history of auto-immune, malignant, or other illnesses. He travelled to underdeveloped and tropical countries once or twice yearly for work; he had stayed in rural areas but never been unwell while overseas. He owned a dog for a long time with no other exposure to animals and never used intravenous or other illicit substances.

His symptoms started 4–5 years before the current admission, with intermittent back and migratory peripheral joint pain involving mainly the small joints of the hands and feet but also large joints, including knees and shoulders. The pain was described as a mild ache with inflammatory features, including severe pain at night and on waking up that improved with mobility; however, this was not associated with swelling, erythema, or systemic features, and he was generally feeling well. He used over-the-counter fish oil and turmeric for his arthralgia.

His arthralgia worsened 9 months before admission, with more severe lower back pain, specifically at the sacroiliac joints. He was reviewed by a rheumatologist who arranged blood tests which showed normocytic anaemia, neutrophilia, lymphopenia, elevated erythrocyte sedimentation rate, and C-reactive protein (CRP), with negative HLA-B27 test (Table 1). An MRI of the spine and sacrum showed bilateral sacro-ileitis and ankylosing spondylitis was diagnosed. He was initially treated with secukinumab for 4–5 months with no improvement in his clinical or biochemical markers. Due to the lack of response, further investigations were arranged, including an FDG-PET scan which showed a diffuse uptake throughout the stomach and mild focal uptake in the caecum and ascending colon, which was thought to be non-specific; there was an avid 21 × 16 mm enlarged para-aortic lymph node uptake and multiple

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Table 1. Blood test results on the first review 9 months before admission

Blood test	Patient's result	Reference range
Full blood count		
Haemoglobin	115 g/L	130–180
Mean corpuscular volume	81 fL	80–100
White cell count	11.9 × 10^9/L	4–11
Neutrophils	10.7 × 10^9/L	2–7.5
Lymphocytes	0.81 × 10^9/L	1–4
Platelets	407 × 10^9/L	150–450
Blood film	Unremarkable	
Inflammatory markers		
ESR	41 mm/h	0–5
CRP	102 mg/L	<5
Electrolytes	Unremarkable	
Renal function tests		
Liver function tests		
Proteins		
Total protein	62 g/L	68–85
Albumin	37 g/L	39–50
Globulin	25 g/L	23–39
Protein electrophoresis	No paraprotein	0.48–3.05
IgM level	0.33 g/L	
IgA, IgG	Within range	
Creatine kinase	20 U/L	45–250
Iron studies		
Serum iron	3 μmol/L	5–30
Transferrin	2.1 g/L	2–3.2
TIBC	48 μmol/L	46–70
Saturation	6%	10–45
Ferritin	265 μg/L	30–300
Metabolic tests		
TSH	1.39 mIU/L	0.4–3.5
Vitamin D	69 nmol	50–140
Vitamin B12	314 pmol/L	135–650
Serum folate	9.7 nmol/L	>7
Auto-immune antibodies		
CCP Abs	<1 U/mL	<5
RF	<6 IU/mL	<16
ACE level	44 U/L	8–70

(Continued on following page)

Table 1 (continued)

Blood test	Patient's result	Reference range
ANA	Not detected	0–6
ENA	Not detected	
Anti-ds DNA	<5 IU/mL	
ANCA	Negative	
HLA-B27	Not detected	
Cryoglobulins	Not detected	
Infectious		
HIV Abs	Negative	
Hepatitis B Serology	Unvaccinated	
Hepatitis C Abs	Not detected	
IGRA for TB	Negative	

It shows normocytic anaemia, neutrophilia, lymphopenia, elevated erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), with a negative HLA-B27 test.

mildly to moderately avid enlarged mesenteric nodes. Haematology review and opinion was that these lymph nodes were probably reactive. The patient used naproxen as needed to control his arthralgia, and the increased stomach uptake on FDG-PET was thought to be gastritis secondary to naproxen use.

Due to ongoing symptoms and elevated inflammatory markers, he was commenced on a second-line treatment for ankylosing spondylitis with adalimumab 2 months before admission. Paradoxically, he suffered worsening joint pain associated with new low-grade fever, night sweats, lethargy, anorexia, and worsening of his biochemical markers, necessitating admission for further investigations.

On admission, he reported a weight loss of 15 kg over 4 months, low-grade fever, and drenching night sweats for 2–4 weeks. He had recently developed a cough of 6 weeks duration, productive of a minimal amount of white-yellow sputum. He did not complain of abdominal pain, change in bowel habits, or other gastrointestinal symptoms.

On examination, he looked unwell and cachectic with generalised muscle wasting and a fever of 38°C; other vital observations were within normal limits, with no rashes or lymphadenopathy. He did not have a cardiac murmur or other stigmata of endocarditis. His abdominal examination was unremarkable, soft and non-tender to palpation, with no organomegaly and normal audible bowel sounds. He did not have joint swelling or erythema.

Blood test results showed worsening anaemia, ongoing neutrophilia, and further elevation of inflammatory markers. Extensive workup for the uncommon infectious causes of fever was arranged, which were within the normal or negative range (Table 2). The faecal calprotectin level was mildly elevated at 73 μg/g. Transthoracic echocardiography showed normal biventricular function, normal valvular structure, and function with no features of endocarditis. MRI of the spine and sacrum was repeated and showed active bilateral sacroileitis with chronic changes. Due to the undifferentiated nature of the illness, the FDG-PET scan was repeated, which showed similar results to the first FDG-PET scan with increased uptake in the stomach and caecum (Fig. 1). Endoscopic examinations of the upper and lower gastrointestinal tract were arranged; a paediatric colonoscope was used for upper examination and was inserted deeply into the jejunum; it showed severe nodular gastritis

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Table 2. Blood test results on admission

Blood test	Patient's result	Reference range
Full blood count		
Haemoglobin	93 g/L	130–180
Mean corpuscular volume	75 fL	80–100
White cell count	11.8×10^9/L	4–11
Neutrophils	9.3×10^9/L	2–7.5
Lymphocytes	2.06×10^9/L	1–4
Platelets	529×10^9/L	150–450
Blood film	Unremarkable	
Inflammatory markers		
ESR	45 mm/h	0–5
CRP	170 mg/L	<5
Procalcitonin	0.7 μg/L	<0.5
Electrolytes	Unremarkable	
Renal function tests		
Liver function tests		
Proteins		
Total protein	62 g/L	68–85
Albumin	33 g/L	39–50
Globulin	25 g/L	23–39
Infectious		
Q fever PCR	Not detected	
Q fever serology	Negative	
EBV Serology	IgG detected	
Dengue fever serology	Negative	
Lyme disease serology	Negative	
Malaria DNA	Negative	
CMV serology	Not detected	
Toxoplasma serology	Not detected	
Treponemal Abs	Non-reactive	
H. pylori serology	IgG negative	
Amoebiasis serology	Negative	
Brucella serology	Negative	
3 Sets of blood cultures	Negative	
Stool tests		
Stool microscopy	No cells, ova, cysts, parasites	
Culture	Negative	
PCR for bacteria and parasites	Negative	
Calprotectin	73 μg/g	<50

It shows worsening anaemia, ongoing neutrophilia, further elevation of inflammatory markers, and negative workup for uncommon infectious pathologies.

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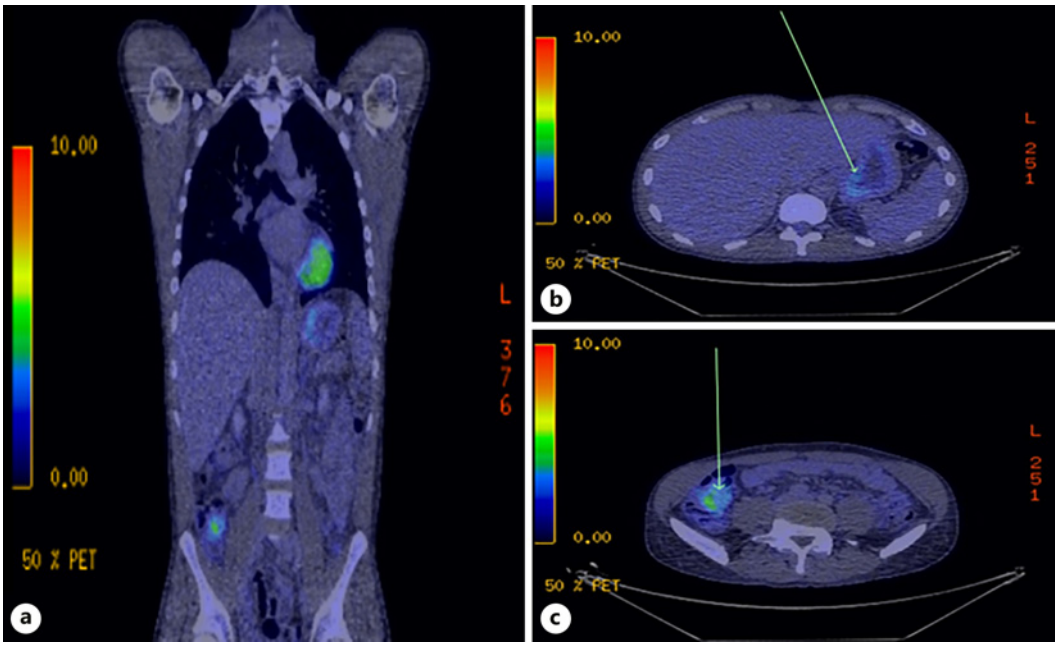

Fig. 1. FDG-PET scan on admission. **a** Coronal section showing mildly increased uptake in the stomach and caecum. **b** Axial section in the upper abdomen shows increased stomach wall uptake. **c** Axial section in the lower abdomen shows increased caecum uptake.

throughout the stomach, a medium-sized (2 cm) punched-out ulcer in the gastric body, the duodenal and jejunal mucosa appeared normal with no changes. Multiple biopsies were taken from the examined areas and sent for investigations, including *Tropheryma Whipplei* PCR; the colonoscopic examination was unremarkable, including the caecum and terminal ileum (Fig. 2).

Biopsies were reviewed and showed non-specific inflammatory changes throughout the gastrointestinal tract, with a mixed inflammatory cell infiltrate. Some villous blunting with foveolar metaplasia was noted in the small bowel mucosa. In many of the biopsies, more marked in the terminal ileum, there are scattered and focally clustered foamy histiocytes. These were demonstrated to contain granular periodic acid-Schiff (PAS) and diastase PAS-positive material (Fig. 3). PAS staining was not done on the gastric biopsies due to no inflammatory or other histological changes. The histological features were not deemed classic due to the lack of expansion of the lamina propria by foamy histiocytes and the absence of dilated lymphatic vessels. However, given the strong clinical suspicion, a diagnosis of Whipple's disease remained probable. *Tropheryma whipplei* PCR was positive in the jejunum with a strong cycle threshold value of 23; this led to the conclusion that the results were compatible with the PCR diagnosis of Whipple's disease. In retrospect, the granular material within foamy histiocytes is consistent with an atypical histological presentation of Whipple's disease. Serum *Tropheryma whipplei* PCR was tested and returned positive; serum IgM and IgG against *Tropheryma whipplei* were not detected.

Despite no neurological features, proactive testing was conducted to investigate central nervous system (CNS) involvement. The cerebrospinal fluid (CSF) *Tropheryma Whipplei* PCR was positive with a cycle threshold value of 39. MRI of the Brain showed a small hyperintense FLAIR/T2 signal foci in the subcortical white matter of the frontal lobes bilaterally; this was thought to be non-specific, and there was no cerebral atrophy, mass lesions, or contrast enhancement suggestive of advanced neurological Whipple's disease.

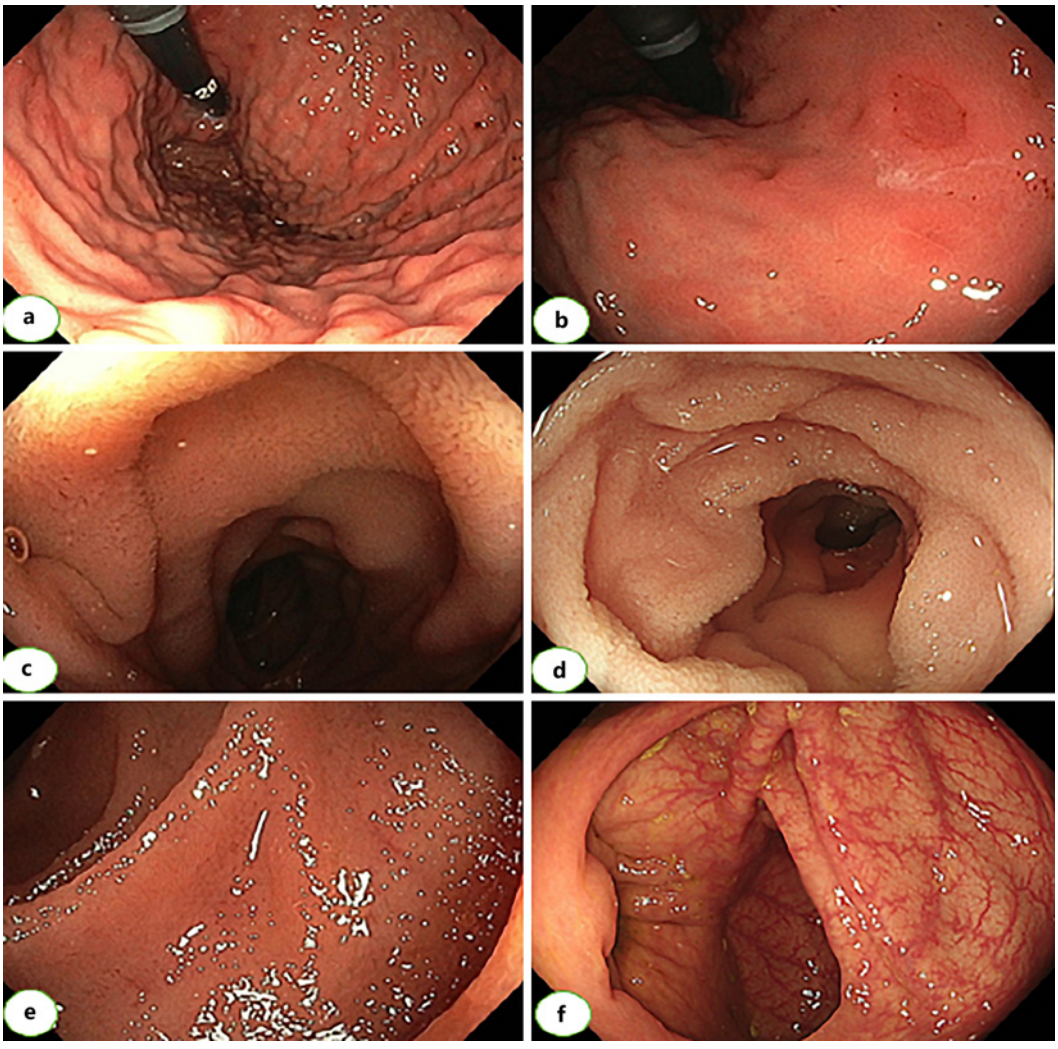

Fig. 2. Endoscopic findings. **a** Severe nodular gastritis throughout the stomach. **b** Isolated gastric ulcer. Normal endoscopic examination of the duodenum (**c**), jejunum (**d**), terminal ileum (**e**), and caecum (**f**).

The patient was treated with intravenous ceftriaxone 2 g daily for 4 weeks (rather than 2 weeks due to CNS involvement) and continued to use naproxen for arthralgia as needed, with pantoprazole 20 mg daily due to gastritis. He was followed up closely and did not develop side effects of intravenous antibiotic treatment. He was monitored closely on the commencement of intravenous antibiotics with no evidence of immune reconstitution inflammatory syndrome.

He was reviewed 4 weeks later; his back pain was resolved with a significant improvement in his lethargy, anorexia, and he started regaining weight. His follow-up blood tests showed an albumin level of 42 g/L, ESR of 9 mm/h, haemoglobin of 127 g/L, and CRP level of 6 mg/L. Trimethoprim/sulfamethoxazole 160/800 mg twice daily for 1 year was commenced.

A further follow-up plan will involve monitoring for oral antibiotic side effects and symptoms of relapse during treatment, especially neurological relapse. MRI brain, CSF PCR, and endoscopic examinations with biopsies will be repeated at the end of 12 months of antibiotic treatment to confirm negative results and resolution of the infection before ceasing the antibiotic.

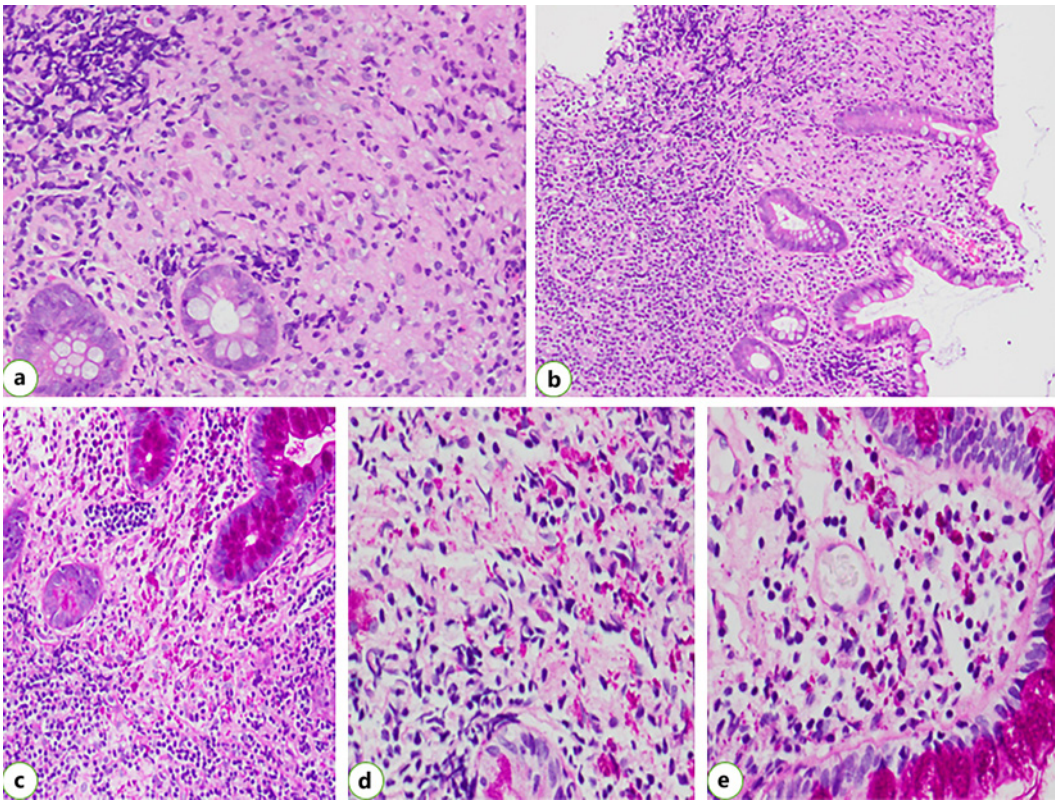

Fig. 3. Histopathology findings throughout the gastrointestinal tract. **a**, **b**, **c** Foamy histiocytes. **d**, **e** Positive periodic acid-Schiff (PAS) stain in the lamina propria.

Discussion

Whipple's disease is rare, with high morbidity and mortality if not treated [3]. Diagnosis remains challenging, especially with atypical presentations, as in this case. It requires a high index of suspicion, and PCR testing leads to a more accurate diagnosis.

A Spanish clinical review of 91 patients reported that the earliest and most common pre-diagnosis symptoms were rheumatological symptoms (57% of the patients), mainly presenting as oligoarticular arthralgias rather than arthritis, with migratory polyarthralgia being the least common. The average time between joint symptoms and the diagnosis was 3–4 years. At the time of diagnosis, weight loss was the most prevalent symptom (80%), followed by gastrointestinal symptoms, including diarrhoea in 63% and abdominal pain in 24%. Skin manifestations are prevalent and include hyperpigmentation, purpura, and nodules. Joint symptoms are less prevalent in this phase of the illness (20%) compared to the pre-diagnosis [4].

The challenge in the presented case was the absence of typical gastrointestinal symptoms of Whipple's disease. The worsening of symptoms with anti-TNF therapy raising the possibility of Whipple's disease has been reported in the literature [5]. The globulin levels in our patient were consistently normal with mildly low IgM levels; this contrasts with usually elevated serum IgM levels in patients with Whipple's disease [6].

CNS involvement in Whipple's disease can be asymptomatic. Yet, it carries a worse prognosis and a higher risk of relapse even in patients who did not have neurological symptoms on initial diagnosis. Neurological manifestations can include non-specific symptoms like headache or specific symptoms related to the areas affected, which can

involve any part of the brain or spinal cord. Investigations for neurological involvement include CSF analysis, which might show elevated protein level and pleocytosis; however, normal cytology and biochemical markers are reported in more than 50% of cases; hence, CSF *Tropheryma Whipplei* PCR and PAS staining are required. The neurological investigations also include an MRI of the whole spine and brain, which might show signs of atrophy, mass formation, enhancement, and white matter changes. Neurological involvement has significant implications on management; the initial intravenous antibiotic treatment should be extended to 4 weeks rather than 2 weeks. Oral antibiotic treatment might be extended for 2 years rather than 1 year, and all patients should have repeated MRI and CSF to confirm the resolution of abnormalities before ceasing the antibiotics [7, 8].

In conclusion, Whipple's disease can present with no gastrointestinal manifestations. Arthritis worsening with anti-TNF treatment can be a clue to an infectious process (e.g., Whipple's disease or other infectious diseases). Whipple's disease should be considered a differential diagnosis in patients with increased uptake in the gastrointestinal tract on FDG-PET. Multiple tissue, fluid, and faeces testing for PCR should be sent. A paediatric colonoscope should be used to perform a push enteroscopy, or an antegrade balloon enteroscopy should be used, aiming for deeper insertion into the jejunum to take biopsies. Proactive testing for neurological involvement should be conducted even in asymptomatic patients. Treatment involves intravenous antibiotics (usually ceftriaxone 2 g daily) for 2 weeks; meropenem is an alternative for patients with penicillin allergy [9]. Followed by oral combined antibiotics (trimethoprim/sulfamethoxazole 160/800 mg twice a day) for 1 year, cefixime is an alternative for patients with sulphur allergy or renal impairment. The duration of antibiotics should be doubled if there is CNS involvement. All patients should have confirmation of infection resolution before ceasing antibiotics [10]. Patient education and vigilant monitoring for relapse should be conducted during and after stopping antibiotics.

Acknowledgments

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Statement of Ethics

Ethical approval was obtained from the "Clinical Innovation and Audit Committee (CIAC)" at Macquarie Health on June 28, 2023, reference number: MQCIAC2023008. Written informed consent was obtained from the patient to publish the details of their medical care and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.A.: collecting the data, formatting, and writing the manuscript. B.J.: gastroenterology review, endoscopy images, and final approval. F.J.: rheumatology review and final approval. M.P.: infectious diseases review and final approval, editing the manuscript. T.L.: pathology review and providing histopathology photos. M.B.: cardiology review and final approval. R.G.: haematology review and final approval. All authors were directly involved in the clinical care of the patient.

Data Availability Statement

The data that support the findings of this study are not publicly available due to containing information that could compromise the privacy of the patient but are available from the corresponding author (A.A.) upon reasonable request.

References

1 Durand DV, Lecomte C, Cathébras P, Rousset H, Godeau P. Whipple disease: clinical review of 52 cases. Medicine. 1997;76(3):170–84. doi: 10.1097/00005792-199705000-00003.
2 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(5):1305–11. doi: 10.1007/s10620-018-5393-9.
3 Fenollar F, Puéchal X, Raoult D. Whipple's disease. N Engl J Med. 2007;356(1):55–66. doi: 10.1056/NEJMra062477.
4 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(2):108–23. doi: 10.4321/s1130-01082010000200006.
5 Mohammed F, Kurtom M, Brant A, Sampath R. Whipple's disease unmasked by TNF inhibitor therapy for treatment of seronegative rheumatoid arthritis. BMJ Case Rep. 2022;15(7):e250693. doi: 10.1136/bcr-2022-250693.
6 Geelhaar A, Moos V, Schinnerling K, Allers K, Loddenkemper C, Fenollar F, et al. Specific and nonspecific B-cell function in the small intestines of patients with Whipple's disease. Infect Immun. 2010;78(11):4589–92. doi: 10.1128/IAI.00705-10.
7 Compain C, Sacre K, Puéchal X, Klein I, Vital-Durand D, Houeto JL, et al. Central nervous system involvement in Whipple disease: clinical study of 18 patients and long-term follow-up. Medicine. 2013;92(6):324–30. doi: 10.1097/MD.0000000000000010.
8 Anderson M. Neurology of Whipple's disease. J Neurol Neurosurg Psychiatry. 2000;68(1):2–5. doi: 10.1136/jnnp.68.1.2.
9 Feurle GE, Junga NS, Marth T. Efficacy of ceftriaxone or meropenem as initial therapies in Whipple's disease. Gastroenterology. 2010;138(2):478–12. doi: 10.1053/j.gastro.2009.10.041.
10 Marth T, Moos V, Müller C, Biagi F, Schneider T. Tropheryma whipplei infection and Whipple's disease. Lancet Infect Dis. 2016;16(3):e13–22. doi: 10.1016/S1473-3099(15)00537-X.