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TROPHERYMA WHIPPLEI INFECTION MIMICKING SARCOIDOSIS WITH AN ATYPICAL COURSE: A MOLECULARLY CONFIRMED DIAGNOSIS WITHOUT PAS-POSITIVE INTESTINAL DISEASE

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ABSTRACT

Introduction: The bacterium *Tropheryma whipplei* causes Whipple's disease, a rare chronic infection that can involve virtually any organ, especially in the late phase, and mimic inflammatory or neoplastic conditions. The interval from first symptoms to diagnosis is typically several years.

Case description: A 68-year-old man was referred for pulmonary re-evaluation 2 years after a non-caseating hilar lymph-node granuloma had led to a diagnosis of stage I (nodal) sarcoidosis. His records revealed a 3-year history of lymphadenopathy with persistently elevated C-reactive protein and a two-year history of recurrent fever and fatigue. Corticosteroid therapy for ankle synovitis caused symptomatic worsening, prompting further investigation. Extensive infectious, oncological, rheumatological and tropical-medicine workup was unrevealing. Detailed history-taking revealed a 6 kg weight loss and epigastric discomfort, and a prior short antibiotic course for incipient pneumonia had produced transient improvement, making an atypical infectious aetiology, specifically Whipple's disease, plausible. An endobronchial ultrasound–guided lymph-node aspirate and subsequently a stool sample were both positive for *T. whipplei* by quantitative polymerase chain reaction (qPCR), whereas cerebrospinal fluid PCR was negative, establishing systemic disease without central nervous system involvement. Oral doxycycline plus hydroxychloroquine produced fast and sustained clinical and biochemical remission at 1 year. Surveillance duodenal histology was periodic acid–Schiff -negative and structured clinical follow-up was arranged.

Conclusion: Whipple's disease is a great mimicker, but a treatable one, and should be considered in cases of chronic inflammation without evidence of a pathogen in primary microbiological analysis and in cases of sarcoidosis with an atypical course, particularly if symptoms do not improve or worsen while on corticosteroids.

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KEYWORDS

Whipple's disease, *Tropheryma whipplei*, sarcoidosis, fever of unknown origin, granuloma

LEARNING POINTS

- Consider Whipple's disease in any chronic, culture- and serology-negative systemic inflammatory syndrome, particularly when a diagnosis of "sarcoidosis" based on non-caseating granulomas fails to respond to, or clinically worsens under, corticosteroids, because immunosuppression can accelerate the infection.
- The diagnosis can be established by *Tropheryma whipplei*–specific quantitative polymerase chain reaction (qPCR) on tissue (here, an endobronchial ultrasound–guided lymph-node aspirate) and on non-invasive samples (typically stool, less frequently saliva), even when classic gastrointestinal symptoms and periodic acid–Schiff -positive duodenal histology are absent. Confirmation on a second specimen and cerebrospinal fluid testing to exclude central nervous system involvement should precede the prolonged antibiotic course.
- Untreated Whipple's disease is progressive and potentially fatal. Prolonged combination antibiotic therapy with structured follow-up is curative in most patients, and persistent stool-PCR positivity in an otherwise asymptomatic patient with normal duodenal histology may reflect residual deoxyribonucleic acid or colonisation rather than treatment failure.

INTRODUCTION

Whipple's disease is a rare chronic infection caused by the Gram-positive actinomycete *Tropheryma whipplei*, with an estimated incidence below one case per million per year[1]. *T. whipplei* occurs in the environment and is carried asymptomatically in the stool of about 2–4% of healthy people, yet only a minority of carriers, possibly with a subtle immune predisposition, develop chronic infection[1,2].

Although classically characterised as an intestinal lipodystrophy with diarrhoea, weight loss and malabsorption, the disease is multisystemic and often begins with migratory arthralgia or arthritis years before other manifestations. Fever, lymphadenopathy, central nervous system (CNS) and cardiac involvement also feature[1,2]. Non-specific systemic inflammation and granulomatous tissue reactions can mimic sarcoidosis, lymphoma and immune-mediated rheumatic disease, and the mean delay from symptom onset to diagnosis is 6.4 years (range 0–30)[1,3].

Classic disease is diagnosed by periodic acid–Schiff (PAS)-positive foamy macrophages in duodenal biopsies, but PAS staining lacks specificity and may be negative in extra-intestinal disease. Quantitative polymerase chain reaction (qPCR) on tissue and non-invasive samples (stool, saliva) is therefore central, with confirmation on a second specimen and cerebrospinal fluid (CSF) testing before prolonged treatment[2,4]. Granulomatous lymphadenopathy and a sarcoidosis-like presentation are recognised but underappreciated phenotypes[2,3]. Because untreated disease is progressive and potentially fatal whereas antibiotic therapy is usually curative, timely recognition is essential[2,5]. We report a case in which the diagnosis was established molecularly after a multi-year evaluation for an inflammatory syndrome initially managed as sarcoidosis.

CASE DESCRIPTION

A 68-year-old man, a lifelong non-smoker with a normal body-mass index, no regular medication and no relevant past medical history, first came to attention in the summer of 2022 *(Fig. 1)*. He was retired and reported remote leisure travel to East Africa and South Asia. Cross-sectional imaging performed for an indeterminate hyperechoic splenic lesion on ultrasound found no focal lesion but incidentally revealed mediastinal and bihilar lymphadenopathy. Screening lower endoscopy and upper endoscopy for intermittent epigastric discomfort showed only mild gastritis and a macroscopically normal duodenum, despite a persistently elevated C-reactive protein (CRP) of about 50 mg/l.

By March 2023, the lymphadenopathy had increased and extended to mesenteric stations, raising suspicion of lymphoma. Positron-emission tomography/computed tomography (PET/CT) scan showed reactive-appearing nodes without lymphoma but with pneumonic infiltration *(Fig. 2A and 2B)*. A febrile period was attributed to incipient pneumonia and resolved within days of co-amoxiclav. Coincidentally, his fatigue also improved.

Endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) of a hilar node showed scattered non-caseating epithelioid granulomas, with a bronchoalveolar-lavage (BAL) lymphocytosis (25%) and a CD4/CD8 ratio that was not elevated (0.3). A parallel mediastinal node was unremarkable. Because an atypical pathogen was not suspected, no testing for rare organisms, including T. whipplei, was requested. Routine BAL microbiology was negative. Stage I sarcoidosis was diagnosed in the spring of 2023. Apart from a moderately elevated CRP, an accelerated erythrocyte sedimentation rate (ESR) and a raised soluble interleukin-2 receptor, laboratory findings were normal *(Table 1)*.

From the summer of 2023, he developed recurrent high fevers (>40 °C) several times per week, lasting a few hours with chills, night sweats and profound fatigue, but no respiratory, gastrointestinal or urogenital symptoms.

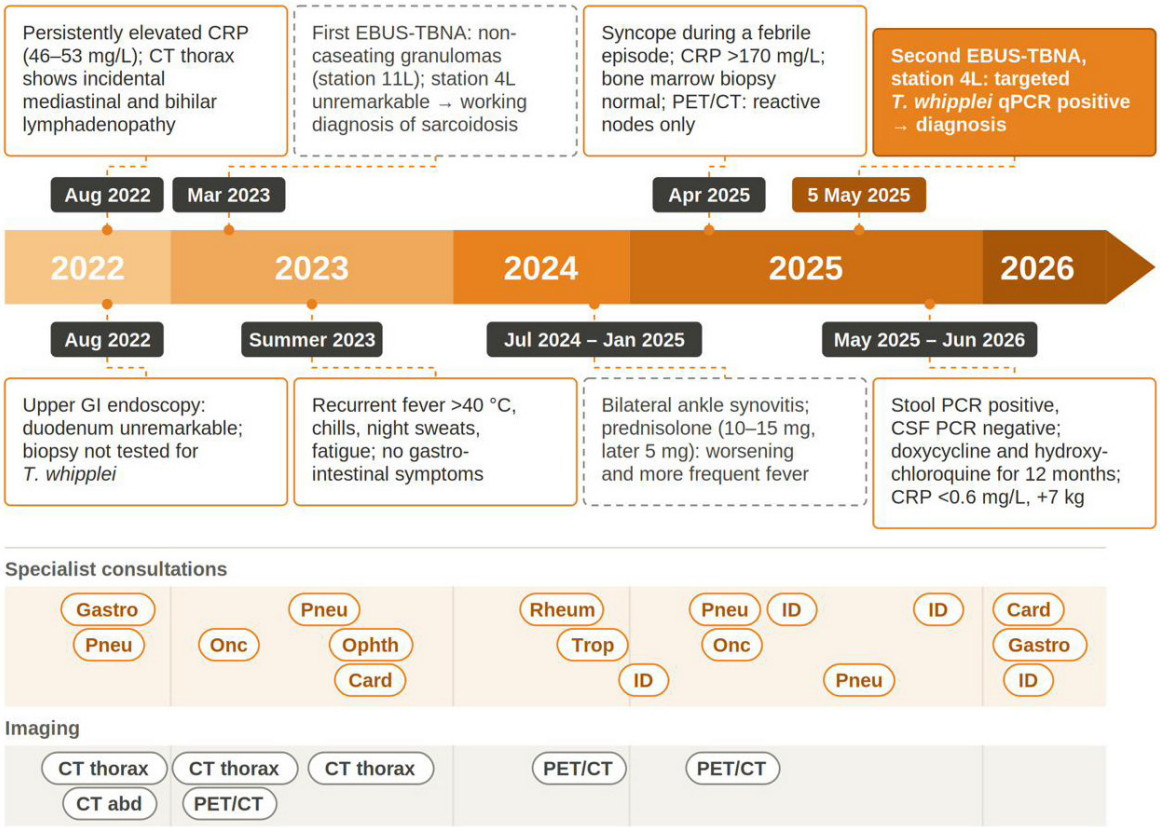


Figure 1. *Diagnostic timeline, from the first objective inflammatory findings (summer 2022) through molecular diagnosis to treatment response. Boxes above the timeline show the diagnostic investigations. Boxes below show the clinical course and treatment. Grey dashed boxes denote the period of the erroneous working diagnosis of sarcoidosis and of corticosteroid treatment. The orange box marks the diagnostic key event. The lower panels show the sequence of specialist consultations and of cross-sectional imaging.*
Abbreviations: abd, abdomen; Card, cardiology; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computed tomography; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; Gastro, gastroenterology; GI, gastrointestinal; ID, infectious diseases; Onc, oncology; Ophth, ophthalmology; PCR, polymerase chain reaction; PET/CT, positron emission tomography/computed tomography; Pneu, pneumology; qPCR, quantitative polymerase chain reaction; Rheum, rheumatology; Trop, tropical medicine.

Rheumatological review in July 2024 documented arthralgia with bilateral ankle synovitis, degenerative coxarthrosis and sacroiliac osteoarthritis. Prednisolone (initially 10–15 mg daily, later mostly 5 mg) was given for the arthritis on the background of presumed sarcoidosis until January 2025, producing no improvement but clinical worsening with more frequent fever. Because of this lack of response and the recurrent flares, a follow-up PET/CT scan was performed in September 2024. It showed no polymyalgia rheumatica, giant-cell arteritis, vasculitis, active sarcoidosis or infectious focus *(Fig. 2C and 2D)*. A tumour necrosis factor-α (TNF-α) inhibitor (infliximab) was recommended but declined by the patient. A further infectious-diseases evaluation in January 2025 was again unrevealing *(Table 1)*.

The biochemical abnormalities accrued over time: an initially isolated CRP/ESR elevation was followed from 2024 by an anaemia of chronic inflammation and culminated in April 2025 in a CRP above 170 mg/L with concurrently raised interleukin-6 and soluble interleukin-2 receptor *(Fig. 3)*. Profound fatigue severely impaired his quality of life.

In April 2025, he was admitted elsewhere with recurrent syncope during a fever flare. A transient second-degree atrioventricular block was documented and, with no recurrence and normal Holter monitoring, deemed secondary to the acute illness. Cranial imaging showed only a small incidental meningioma. Repeat PET/CT scan again showed mildly fluorodeoxyglucose (FDG)-avid, size-stable nodes interpreted as predominantly reactive *(Fig. 2E and 2F)*. Bone-marrow biopsy and peripheral-blood immunophenotyping showed no lymphoproliferative disorder.

He was again referred to pneumology for persistent culture-negative inflammation, steroid-unresponsive granulomatous lymphadenitis and, in particular, worsening fever under corticosteroids. This picture, set against the earlier transient response to antibiotics, prompted questioning of the sarcoidosis diagnosis. Renewed history-taking revealed a weight loss of about 6 kg and intermittent epigastric discomfort, and Whipple's disease was specifically considered.

In May 2025, a repeat EBUS-TBNA aspirate of the same mediastinal station (4l) that had appeared unremarkable in 2023 tested positive for *T. whipplei* by qPCR. Stool qPCR was also positive, whereas CSF qPCR was negative,

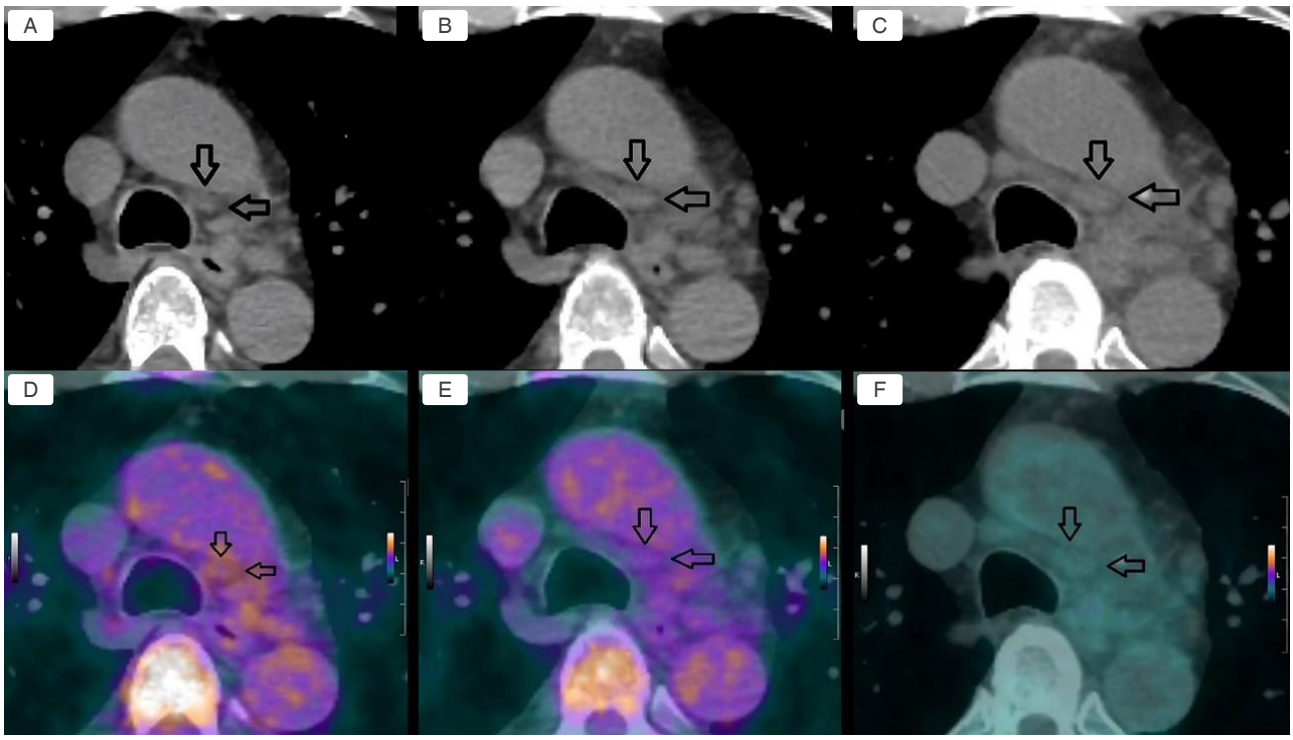


Figure 2. *Serial [18F] fluorodeoxyglucose PET/CT of the mediastinal lymph node at station 4l (arrows), the node from which the diagnosis was finally established. A, C, E) Low-dose computed tomography; B, D, F) corresponding fused PET/CT images. A, B) Baseline, March 2023: axial diameters 13.1 × 7.2 mm, SUVmax 2.34; a relatively prominent mediastinal node with FDG uptake only slightly above background activity which, together with the other mediastinal nodes, was considered compatible with a mild inflammatory, neoplastic or rheumatological process. C, D) First follow-up, September 2024, during corticosteroid treatment: 12.1 × 7.3 mm, SUVmax 2.02; the node was largely unchanged both morphologically and metabolically, in keeping with a chronic inflammatory process; in the absence of any change and of tumour-specific treatment, a neoplastic process was considered unlikely. E, F) Second follow-up, April 2025, approximately three months after prednisolone had been stopped: 16.6 × 9.0 mm, SUVmax 2.06; slight morphological progression with unchanged metabolic activity, again consistent with chronic inflammation. Abbreviations: FDG, fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography; SUVmax, maximum standardised uptake value.*

establishing systemic (classic) Whipple's disease without CNS involvement. Because the fully oral combination is not appropriate for central nervous system involvement, doxycycline penetrating the CNS poorly, treatment was deferred until the CSF result was available. With CSF qPCR negative, oral doxycycline (100 mg twice daily) plus hydroxychloroquine (200 mg three times daily) was started. Treatment produced rapid and sustained clinical and biochemical remission, with normalisation of CRP (<0.6 mg/l) and haemoglobin (145 g/l), weight gain from 69 to 76 kg and cessation of fever. Mild thrombocytopenia was attributed to hydroxychloroquine *(Fig. 4)*.

Surveillance duodenal histology at 1 year was PAS-negative, without Whipple macrophages or villous atrophy. Stool qPCR remained positive despite remission and normal duodenal histology. Because molecular assays detect bacterial deoxyribonucleic acid (DNA) irrespective of viability and correlate poorly with disease activity, this was attributed to residual DNA or colonisation rather than ongoing infection[2]. Supported by a recent randomised trial[5], the oral regimen was stopped after 12 months, with a follow-up evaluation scheduled in 6 months. He was advised to report recurrent fever, weight loss or new abdominal or cardiac symptoms promptly.

DISCUSSION

Three features make this case instructive. First, the diagnosis was reached molecularly, from a lymph-node aspirate and consequently confirmed in stool, without prominent gastrointestinal symptoms or PAS-positive duodenal histology. EBUS-TBNA is established for the evaluation of intrathoracic granulomatous lymphadenopathy including malignancy, sarcoidosis, lymphoma, and tuberculosis[6], but we are not aware of a previous report in which Whipple's disease was diagnosed from an EBUS aspirate by *T. whipplei* PCR.

Second, non-caseating granulomas and a bronchoalveolar-lavage with slight lymphocytosis were misattributed to sarcoidosis, since granulomas are not disease-specific and the CD4/CD8 ratio was not elevated (0.3), not the pattern usually seen in pulmonary sarcoidosis. This discordance was regarded, by diagnostic parsimony, as an outlier in an otherwise sarcoidosis-consistent picture. Third, the absence of response to and even worsening on corticosteroids was an important red flag, since immunosuppression can accelerate Whipple's disease[1,2]. The patient's decision to decline the TNF-α inhibitor may, in retrospect, have been protective.

A transient second-degree atrioventricular block and,

Date	Investigation	Result
Aug 2022	Upper and lower endoscopy with duodenal biopsy	Mild gastritis, macroscopically normal duodenum; specimens not tested for *T. whipplei*
Mar 2023	Bronchoalveolar lavage: routine microbiology and mycobacterial culture	Negative
Spring 2023	Routine laboratory panel	CRP 46 mg/l (reference <5), ESR 38 mm/h and raised soluble interleukin-2 receptor; haemoglobin, mean corpuscular volume, ferritin, lactate dehydrogenase and platelet count normal
Sep 2023	Ophthalmological examination	Normal
Sep 2023	Baseline echocardiography	Normal
Oct 2024	Tropical-medicine screen for parasites and tropical infections	Negative
2024	Interferon-γ release assay, HIV and hepatitis serology	Negative
Jan 2025	Repeated blood cultures, mycobacterial sputum PCR and extensive serology (*Coxiella burnetii*, HIV, hepatitis B and C, cytomegalovirus, Epstein–Barr virus, *Francisella tularensis*, *Treponema pallidum*, *Leishmania*)	Negative
Apr 2025	Bone-marrow biopsy and peripheral-blood immunophenotyping	No lymphoproliferative disorder
Apr 2025	Cranial computed tomography and magnetic resonance imaging	Small incidental meningioma only
May 2025	Cerebrospinal fluid qPCR for *T. whipplei*	Negative
Jun 2026	Surveillance duodenal histology with PAS staining	Negative; no Whipple macrophages, no villous atrophy

Table 1. *Investigations that were negative or non-diagnostic during the diagnostic work-up.*
Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PAS, periodic acid–Schiff; qPCR, quantitative polymerase chain reaction.

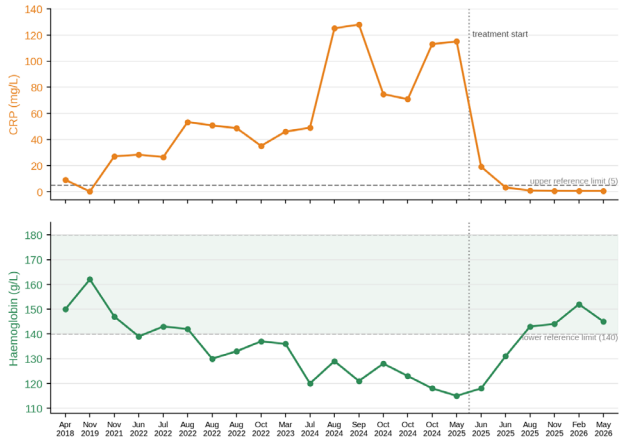


Figure 3. *Trajectory of C-reactive protein (CRP, upper panel) and haemoglobin (Hb, lower panel) from baseline through diagnosis and treatment to sustained remission; the dotted vertical line marks the start of treatment. Dashed lines indicate the reference limits (CRP, 5 mg/l; Hb, 140–180 g/l). The anaemia was normocytic and later mildly microcytic, in keeping with anaemia of chronic inflammation.*
Abbreviations: CRP, C-reactive protein; Hb, haemoglobin.

later, mild aortic regurgitation on control echocardiography were considered incidental and age-related rather than cardiac Whipple's disease: there were no vegetations, blood cultures were repeatedly negative and there was no heart failure, and the regurgitation appeared only once the patient was in remission, whereas Whipple endocarditis characteristically features vegetations and heart failure[4]. Recognising Whipple's disease matters because it is one of the few curable causes of chronic multisystem inflammation. Untreated, it steadily worsens and may prove fatal, with cardiac or CNS involvement carrying a

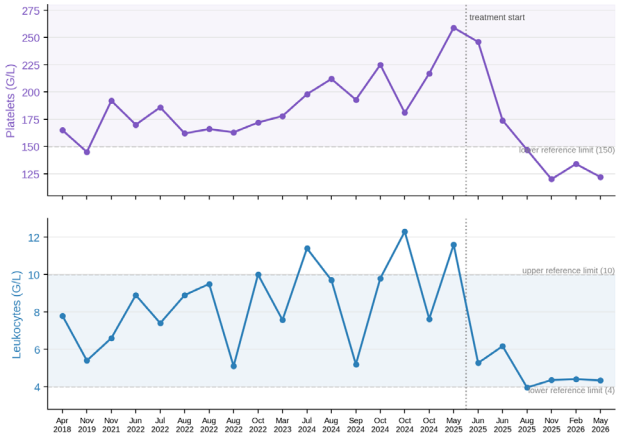


Figure 4. *Trajectory of the platelet count (upper panel) and leukocyte count (lower panel) from baseline through diagnosis and treatment to remission; the dotted vertical line marks the start of treatment. Dashed lines indicate the reference limits (platelets, 150–450 G/l; leukocytes, 4–10 G/l). The decline in platelet count during treatment was regarded as a side effect of hydroxychloroquine. The leukocyte count fluctuated around the reference range during active disease and declined to the lower normal limit during treatment.*

poorer prognosis[1]. There is, however, no single accepted regimen, and recommendations have long rested on case series and in vitro data rather than trials.

The approach most widely used in Europe is 14 days of intravenous ceftriaxone (2 g daily) or meropenem followed by 12 months of oral trimethoprim–sulfamethoxazole 160/800 mg twice daily, derived from the only randomised trial available before 2025[7]. Its weakness is pharmacological, as *T. whipplei* lacks the trimethoprim target and the combination therefore acts as sulfamethoxazole monotherapy, against which folP mutations have emerged during treatment[8,9]. The fully oral alternative (the Marseille regimen), doxycycline 100 mg twice daily plus hydroxychloroquine 200 mg three times daily for 12 to 18 months, exploits the alkalinising effect of hydroxychloroquine, which renders doxycycline bactericidal against the organism within macrophages[10].

A recent non-inferiority trial, the first direct comparison of the two, supports this regimen as first-line treatment[5], as used here, with similar rates of complete clinical remission and of relapse at 24 months. It avoids an intravenous line, permits outpatient management and sidesteps sulphonamide resistance.

CONCLUSION

Whipple's disease is a great mimicker, but a treatable one. Internists and general practitioners evaluating culture-negative inflammation or sarcoidosis with an unusual course, especially when granulomatous disease fails to respond to, or worsens under, corticosteroids, should keep this rare infection in the differential diagnosis and maintain a low threshold for targeted molecular testing, including on mediastinal lymph-node aspirates obtained for other indications.

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