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LETTERS TO THE EDITOR

Whipple's disease in rheumatology: insights from a Portuguese multicenter series

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Dear Editor,

Whipple's disease (WD) is a rare chronic infection caused by *Tropheryma whipplei*, typically following a biphasic course[1]. It is of particular relevance in rheumatology, as joint manifestations are often the earliest, and sometimes the only, presenting feature for years[2]. Musculoskeletal (MSK) manifestations, such as migratory arthralgia or arthritis, often precede gastrointestinal (GI) and systemic symptoms by several years, and immunosuppressive therapy may accelerate disease progression[1,3]. Due to its protean nature and ability to mimic a range of rheumatic disorders, WD remains a diagnostic challenge in rheumatology.

We conducted a national, multicenter, retrospective analysis of patients with WD initially evaluated for suspected rheumatic disease. Cases were identified through electronic health records from Portuguese Rheumatology departments. Diagnosis required confirmation by duodenal histopathology (PAS-positive macrophages) and/or polymerase chain reaction (PCR) detection of *T. whipplei*. Demographic, clinical, laboratory, and therapeutic data were analyzed descriptively. The clinical summary of cases is presented in Table I.

Seven patients were identified (71.4% male), with a mean age at MSK symptom onset of 59.9 ± 8.2 years and a median WD diagnostic delay of 4 years (IQR 1.4). MSK involvement was heterogeneous: four presented with typical migratory arthritis/arthralgia, while others mimicked polymyalgia rheumatica (n=1), asymmetric sacroiliitis (n=1), or rheumatoid arthritis (n=2). All patients tested were negative for anti-citrullinated peptide antibodies, and the majority (71.4%) was negative for rheumatoid factor. GI symptoms occurred in four patients (57.1%), mainly diarrhea (n=3), and one reported abdominal pain. Systemic features were present in six patients (85.7%), all with weight loss, and four with other constitutional symptoms. One patient had central nervous system disease with ataxia. All patients had anemia (mean hemoglobin 10.4 ± 1.2 g/dL) and elevated inflammatory markers (C reactive protein 6.1 ± 3.6 mg/dL; erythrocyte sedimentation rate 39.7 ± 26.6 mm/h). The median interval between MSK and extra-articular symptoms was 2.6 years (IQR 3). Notably, one patient presented with systemic symptoms before MSK involvement, and another developed GI/systemic features only 14 years later.

Five patients had received immunosuppressive therapy (all corticosteroids; four methotrexate; one biologics). Interestingly, the two who did not receive immunosuppression developed GI or systemic symptoms early (within one year), whereas the only patient treated with biologics did not develop such manifestations. PAS staining was negative in 3 patients (42.9%), with *T. whipplei* DNA detection by PCR proving essential for diagnosis, as expected[4]. All patients received ceftriaxone followed by trimethoprim-sulfamethoxazole for 12–24 months, achieving complete clinical remission within 1–8 weeks.

The absence of a uniform MSK presentation highlights WD as a "great imitator" in rheumatology, mimicking rheumatoid arthritis, spondyloarthritis, and polymyalgia rheumatica, contributing to diagnostic delays. A high index of suspicion is essential, particularly in patients with refractory rheumatic symptoms, along with anemia, and weight loss[1,3,5]. A longer MSK-to-systemic/GI interval contributed to delayed diagnosis, while early extra-articular features seemed to hasten recognition. This interval was shorter than in previous series[5,6] Importantly, non-MSK symptoms preceding joint complaints, as seen in one case, challenge the conventional "MSK-first" paradigm.

In this small cohort, early gastrointestinal or systemic manifestations were observed among patients not exposed to immunosuppressive therapy, whereas the patient treated with biologic agents did not develop

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TABLE I. Clinical summary of cases

Sex	Age at onset	Diagnostic delay (yrs)	MSK involvement	GI involvement	Systemic involvement	Delay MSK–GI/ systemic (yrs)	Other organ involvement	RF (IU/ mL)	ACPA (UA/ mL)	Hb (g/dL)*	CRP (mg/ dL)*	ESR (mm/h)*	Immuno-suppressive therapy	PAS stain (duodenal)	PCR (duodenal)	PCR (other samples)	Antibiotic regimen	Duration (wks)	Time to remission (wks)
M	69	4.0	Polymyalgia rheumatica	NA	Fatigue, anorexia, weight loss	3.9	NA	73.2	0	8.5	4.44	48	PDN 10 mg, MTX 20 mg	Positive	NA	NA	Ceftriaxone 2 g/2 wk + TMP-SMX 960 mg	12	2–4
M	52	4.4	Chronic seronegative polyarthritis	Diarrhea	Fever, hyperhidrosis, fatigue, anorexia, weight loss, generalized lymphadenopathy	4.0	NA	0	0	11	6.67	24	PDN 7.5 mg, MTX 12.5 mg	Positive	NA	NA	Ceftriaxone 2 g/2 wk + TMP-SMX 960 mg	18	6–8
F	47	14.7	Axial and peripheral spondyloarthritis (asymmetric sacroiliitis, migratory arthralgia in lower limbs)	Diarrhea, malabsorption	Weight loss	14.5	NA	1191	NA	9.4	2.48	9	PDN 20 mg	Positive	Positive	NA	Ceftriaxone 2 g/4 wk + TMP-SMX 960 mg	24	4
M	69	4.0	Elderly-onset RA (asymmetric involvement of hands and wrists)	Diarrhea, steatorrhea	Weight loss	–1.0	CNS – ataxia	0	0	9.8	6.12	86	PDN 5 mg, MTX 10 mg	Negative	Positive	CSF, positive	Ceftriaxone 2 g/4 wk + TMP-SMX 960 mg	12	4
F	59	2.0	Migratory polyarthralgia	Abdominal pain	Fatigue, weight loss	1.0	NA	0	NA	11.4	4.36	NA	NA	Negative	Positive	NA	Ceftriaxone 2 g/2 wk + TMP-SMX 960 mg	24	na
M	63	1.5	Migratory polyarthritis	NA	Anorexia, weight loss, lymphadenopathy, mild hepatosplenomegaly	1.2	NA	0	0	10.6	13.62	43	NA	Positive	Positive	NA	Ceftriaxone 2 g/2 wk + TMP-SMX 960 mg	12	1–2
M	60	3.7	Migratory polyarthritis and tibialis posterior tenosynovitis	NA	NA	NA	NA	0	0	11.9	5.12	28	PDN 5 mg, MTX 15 mg, LFN 20 mg, ADA, SEK, UPA	Negative	Positive	Synovial fluid, positive	Ceftriaxone 2 g/2 wk + TMP-SMX 960 mg	Ongoing	1–2

ACPA – Anti-Citrullinated Peptide Antibodies; ADA – Adalimumab; CNS – Central Nervous System; CRP – C-Reactive Protein; CSF – Cerebrospinal Fluid; ESR – Erythrocyte Sedimentation Rate; F – Female; GI – Gastrointestinal; Hb – Hemoglobin; LFN – Leflunomide; M – Male; MSK – Musculoskeletal; MTX – Methotrexate; NA – Not Applicable; na – Not Available; PAS stain – Periodic Acid–Schiff staining; PCR – Polymerase Chain Reaction; PDN – Prednisolone; RF – Rheumatoid Factor; SEK – Secukinumab; TMP-SMX – Trimethoprim-Sulfamethoxazole; UPA – Upadacitinib. *Values at diagnosis

such symptoms. Although the limited sample size and potential selection bias related to rheumatology-based recruitment preclude causal inference and limit generalizability, these observations prompt consideration of a potentially more complex relationship between immunosuppression and disease progression, possibly reflecting interindividual variability in immune responses to T. whipplei infection. Further studies in larger, more diverse cohorts are warranted.

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