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Atypical response of spondyloarthritis to biologics revealing Whipple's disease: a case-report*

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*This observation is registered in the French pharmacovigilance database under the reference NY 2017 2387 (30 November 2017).

KEYWORDS
Whipple's disease; biologics; paradoxical aggravation

Abbreviations
Anti-TNF: anti tumor necrosis factor
CT-PET: positron emission tomography-computed tomography
DOX: doxycycline
HCQ: hydroxychloroquine
HLAB27: human leucocyte antigen B27
MRI: magnetic resonance imaging
NSAID: non steroidal anti-inflammatory drug
PAS: periodic-acid-Shiff
PCR: polymerase chain reactions
SPA: spondyloarthritis
WHO: World health organisation

Whipple's disease (WD) mimicking a chronic inflammatory rheumatism with a severe weight loss and diarrhea is often undiagnosed. WD revelation during biologics for arthritides seems to be increasingly observed.
A 52-year-old woman was diagnosed human leucocyte antigen B27 (HLA B27)-negative spondyloarthritis (SPA) for 4 years, with a left sacroiliitis on magnetic resonance imaging (MRI). Due to nonsteroidal anti-inflammatory drug (NSAIDs) plus methotrexate inefficiency and high disease activity, she was treated with a rotation of anti-tumor necrosis factor (anti-TNF) for 14

months without any efficacy (etanercept, adalimumab and golimumab). Ultimately, her general state deteriorated suddenly and major biological inflammation led to anti-TNF discontinuation. Transient paresthesia of one arm and transient diplopia occurred. Nonetheless, cerebral MRI and positron emission tomography scans (PET scans) were normal. Six months later, given the clinical and biological worsening, a new positron emission tomography–computed tomography (CT-PET) scan revealed diffuse active mesenteric polyadenopathies (Fig 1). In addition, *Trophyrema whipplei* polymerase chain reactions (PCRs) on blood, saliva and stools were highly positive. Moreover, duodenitis and lymph node biopsies revealed a macrophagic periodic-acid-Shiff (PAS) positive infiltrate thereby confirming WD. Combined doxycycline (DOX) and hydroxychloroquine (HCQ) allowed the normalization of inflammatory parameters and a dramatic clinical improvement. An immune reconstitution syndrome was prevented by co-prescribing thalidomide.

Therefore, the articular expression of WD can mimic SPA [1]. Despite a classical pre-biologics assessment, features of WD may be revealed at a late stage of the disease, once severe criteria manifest (neurological impairment, polyadenopathy [2], highly infectious load). The deterioration of the clinical status after initiating biologics appears a growing mode of WD revelation especially during seronegative rheumatoid arthritis in a recent case-series of 5 patients [3]. Other punctual case-series have been published after the largest work (16 cases between 2000 and 2010) of the French reference center [4]: two patients in Spain [5], seven patients in France [6, 7], one in the USA [8] and Germany [9]. In addition, fifteen reports of WD during biologics have been documented worldwide in the World health organisation (WHO) global pharmacovigilance database up to March 2017: six with infliximab, five with adalimumab, four with etanercept, three with golimumab and one with tocilizumab.

When WD is suspected, qPCR (salivary and fecal) has to be carried out quickly. If positive, duodenal biopsies must be performed to find a villous atrophy with infiltration of the lamina propria by lipid deposits and foamy macrophages, positive for PAS staining. The current treatment combines DOX and HCQ for 12 months, followed by lifelong DOX.

Finally, lack of a response or paradoxical aggravation of SPA, or seronegative polyarthritides, during biologics should evoke WD. Causality (C2S2) has been assessed by using the French method [10].

Disclosure of interest

The authors declare that they have no competing interest.

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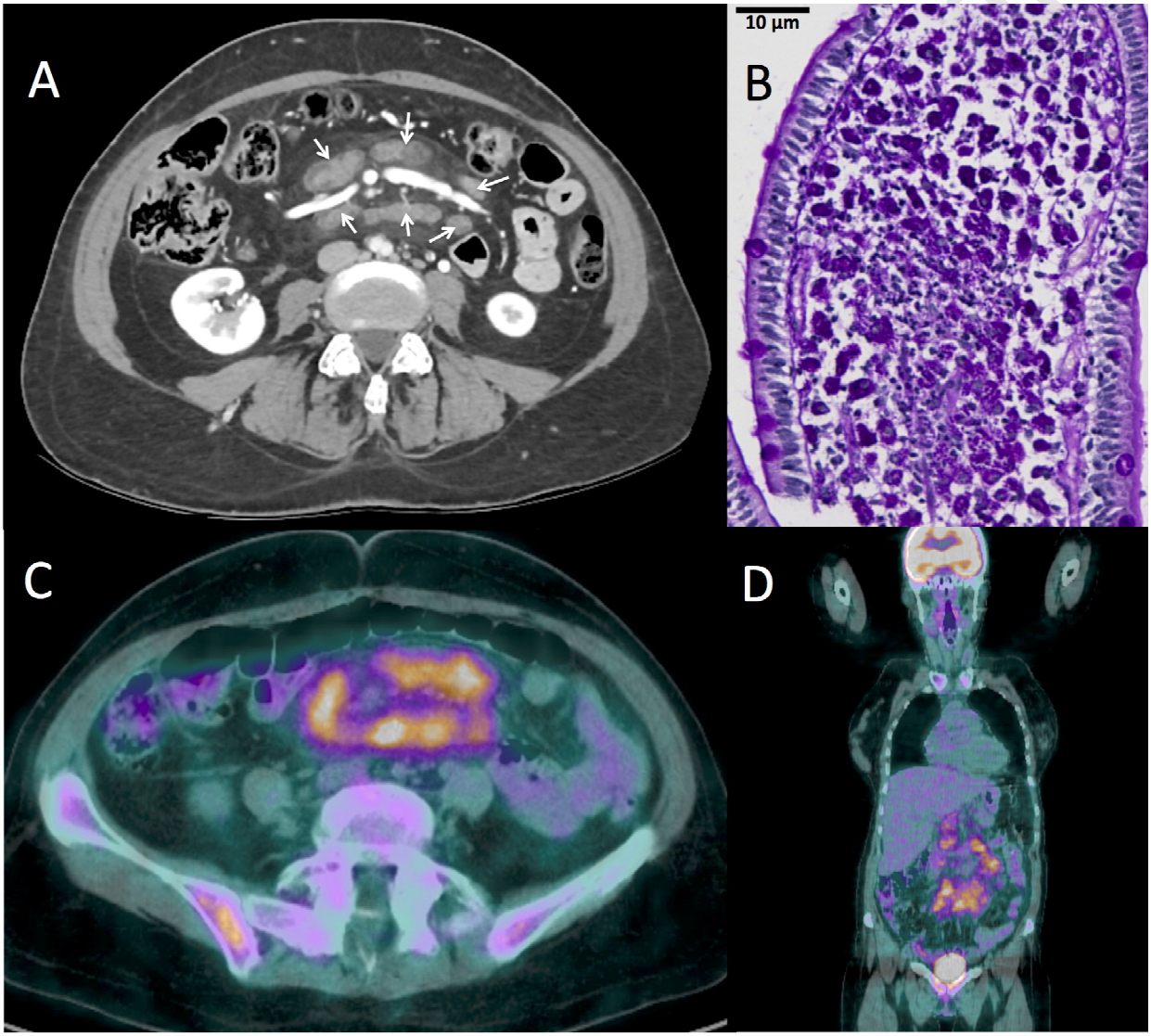

Figure 1.
A: Abdominal axial CT-scan revealing multiple mesenteric lymph nodes (→) with pathognomonic aspect of WD lymphadenopathy with central low attenuation due to a high fat content secondary to the infiltration of the sinus. *NB: This gave the initial name to the disease: "mesenteric lipodystrophy"*.
B: Histological detection of WD in a duodenal villus: intense periodic acid–Schiff staining of bacilli demonstrated within the macrophages of the lamina propria (scale bar = 10 µm).

C & D: Axial and coronal PET scans: Fluorodeoxyglucose hyperactivity (red) of mesenteric lymph nodes. Please note that iliac crest hyperactivity is secondary to systemic inflammatory syndrome.