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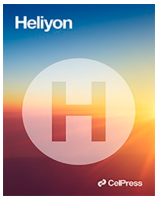

Case report

Successful rescue TNF-α blocking for *Mycobacterium genavense* – Related immune reconstitution inflammatory syndrome: A case report

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ABSTRACT

Immune reconstitution inflammatory syndrome (IRIS) has been reported in immunocompromised patients with disseminated *Mycobacterium genavense*. Management relies on high-dose corticosteroids.

We describe two cases of late-onset corticosteroid-refractory IRIS related to disseminated infection in a HIV-positive patient and a renal transplant patient who had a favorable outcome with a monoclonal TNF-α blocker.

1. Introduction

M. genavense is a slow-growing non-tuberculous mycobacterium (NTM) found in the environment and able to colonize the gastrointestinal tract of immunocompetent humans [1]. It can lead to disseminated diseases in immunocompromised patients, especially in persons living with HIV (PLWH) with CD4 counts below 50/mm^3 [2] and in solid organ transplant (SOT) recipients [3,4].

Only 30–50 % of *M. genavense* infections are diagnosed with traditional culture methods [1,2]. Definitive identification almost always requires molecular techniques, such as amplification and sequencing of the 16S ribosomal RNA (rRNA) and/or hsp65 gene [5].

Even though the immune restoration provided by ART has improved significantly the prognosis, *M. genavense* infection is still associated with five years mortality rates ranging from 39 to 50 % in PLWH [6,7].

IRIS is a clinical entity reflecting excessive reversal immune response, occurring in up to 25 % of disseminated *M. genavense* cases

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[6]. The mainstay of IRIS treatment relies on corticosteroids, but little is known about rescue therapies in this setting [8].

We thus report our experience on the management of M. *genavense* associated IRIS.

1.1. Patient 1

A 35-year-old woman was admitted in March 2020 for fever with coughing, diarrhea, skin lesions and an increased C-reactive protein (CRP) level (180 mg/L). She had undergone three kidney transplants for Denys Drash syndrome, the last in 2010. Immunosuppressive treatment included tacrolimus, mycophenolate mofetil (MMF) and steroids at a dose of 5 mg/day.

The computed tomography (CT) scan revealed ascites and celio-mesenteric and jejuno-ileal nodes that were hypermetabolic on positron emission tomography CT (PET/CT).

Acid-fast bacilli (AFB) were detected in sputum and urine samples, bone marrow aspiration (BMA), colonic, duodenal and skin biopsies. Furthermore, BMA showed hemophagocytosis but found no evidence of lymphoma or cancer. A 16S rRNA gene sequencing identified *M. genavense* on BMA. A therapy with rifampicin, clarithromycin and ethambutol was introduced in April 2020 and MMF was discontinued. Due to optic neuropathy, ethambutol was switched in July 2020 for moxifloxacin and linezolid. The worsening renal function led to a return to hemodialysis. The clinical evolution was favorable until October 2020, marked by a recurrence of fever associated with a metabolic progression of the abdominal lymph node involvement (SUV 15).

On suspicion of IRIS, steroids were increased to 1 mg/kg in October 2020 allowing a resolution of fever. Unfortunately, the patient again developed a fever a few weeks after steroids reduction in December 2020. In March 2021, repeated biopsies (BMA, ileum, colon, and duodenum) and samples (sputum, urine) failed to identify AFB. Specimen pathology performed on duodenum biopsies of March 2021 showed a macrophagic interstitial infiltration containing Ziehl + polymorphic structures while colon biopsies analysis found more non-necrotizing epithelioid focal granulomas than in the initial biopsy.

These microbiologic and pathology findings combined with the persistence of fever and the radiological progression (Fig. 1A) confirmed IRIS; increased corticosteroids to 1 mg/kg in June 2021 provided apyrexia.

In April 2021, a diagnosis of adenocarcinoma was made in a part of the colon different from the initial location of M. *genavense*. She underwent a left colectomy in May 2021. Besides, abdominal lymph nodes dissection showed no evidence of lymphatic dissemination.

In June 2021, peak drug concentrations were correctly dosed for clarithromycin. Because of the relapse of fever and persistence of cachexia with a worsening of mesenteric lymph nodes (Fig. 1B) after reduction of corticosteroids dosage to 0.5 mg/kg/day, we concluded a corticosteroid-dependent IRIS. She was treated with three injections of infliximab 5 mg/kg in September, October 2021 and January 2022. Clinical improvement was obtained three weeks after the first infliximab injection. The dose selection and schedule of administration were decided according to dosage regimen used for IRIS related to CNS TB in the literature review of Santin et al. [9]. The withdrawal of corticosteroids was hence permitted in February 2022. Given the clinical improvement and the stability of

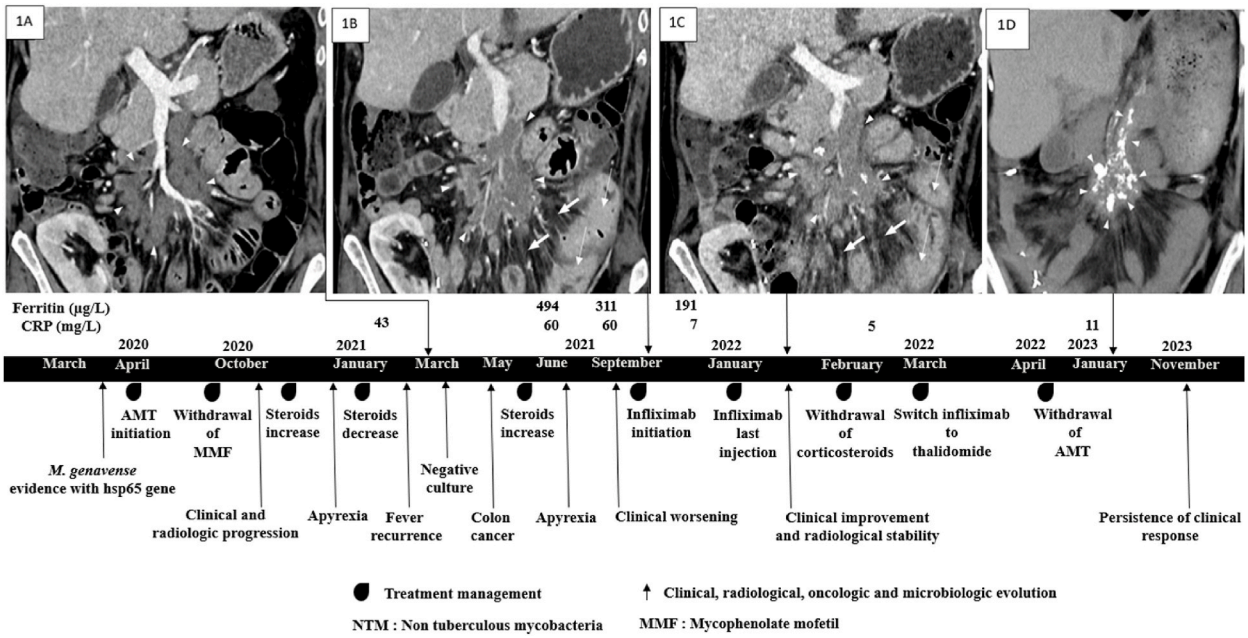

Fig. 1. Timeline and images of patient one (1A-1D). CT -scan before (1D) and after (1A-1C) contrast enhancement (Iomeron 350, Bracco Imaging France) at the portal phase. In March 2021, we found a significant increase of celio-mesenteric lymph nodes (arrowheads) (1A). In October 2021, views showed a worsening of mesenteric lymph nodes (arrowheads) with comb sign, mesenteric infiltration (thick arrows) and bowel thickened (thin arrows) (1B). In February 2022, we can notice a stability of the radiological pattern (1C). In January 2023, we observed a non-active calcifying evolution of mesenteric lymph nodes (arrowheads) (1D).

abdominal nodes involvement (Fig. 1C) with anti-TNF-α but the oncologic risk, we switched infliximab to thalidomide in February 2022 [10]. Anti-mycobacterial treatment was stopped in April 2022 and relayed by maintenance therapy with azithromycin. Otherwise, the development of renal grafts infarcts in November 2022 required transplantectomy, complicated by digestive wounds leading to recurrent digestive bacterial translocations, uncorrelated with the location of endoscopy performed in April 2021. IRIS was still controlled 12 months after thalidomide discontinuation in November 2022 with no recurrence of fever and a non-active calcifying evolution of mesenteric lymph nodes in January 2023 (Fig. 1D).

1.2. Patient 2

A 41-year-old HIV-positive man presented in April 2019 with a recent fever and pancytopenia. He was diagnosed with AIDS in 2012 and was treated with tenofovir, emtricitabine and rilpivirine, which was interrupted by the patient in October 2017. HIV load (VL) was 6.1 log and CD4 lymphocytes count was 7 per mm^3. He had hepatosplenomegaly and polyadenopathy with increased CRP level (70 mg/L). The PET/CT highlighted hypermetabolic supra and sub-diaphragmatic nodes (SUV 13). He was treated in May 2019 with clarithromycin and ethambutol for a misdiagnosis of *M. avium* disseminated infection. The patient restarted antiretroviral therapy (ART) with tenofovir, emtricitabine and raltegravir simultaneously. In September 2019, the diagnosis was corrected in *M. genavense* with hsp65 sequence on the lymph node biopsy of June and the BMA of September without positive culture. Ethambutol had been switched for rifabutin and moxifloxacin, enabling clinical improvement. HIV VL was below the limits of detection since November 2019 and ART had been changed to dolutegravir BID and doravirine in May 2020 due to significant interaction between integrase inhibitors and rifabutin. This modification of ART was not efficient to bring an immune reconstitution (CD4 117/mm^3 in August 2020). After a 15 months symptoms free period, he reported in February 2021 transitory signs of portal hypertension resulting from duodeno-jejunitis with parietal thickening, extrinsic obstruction of the superior mesenteric vein (SMV) by mesenteric infiltration composed by enlarged lymph nodes (Fig. 2A). The patient was lost to follow up from February to December 2021 when he was hospitalized for a transient abdominal pain revealing a significant increase of mesenteric lymph nodes (Fig. 2B).

The patient was admitted in April 2022 for venous mesenteric ischemia on tight stenosis of the SMV due to increased mesenteric infiltration (Fig. 2C). Anticoagulation was initiated, and endoscopic samples of the mesenteric infiltrate found fibrosis and macrophagic infiltrates with few AFBs without culture or molecular documentation and considered as residual AFBs. The diagnosis of IRIS was established considering increased CD4 (up to 180/mm^3 in June 2022 versus 98/mm3 in April 2022), the negative culture of mesenteric infiltrate samples of April 2022 and adequate blood concentrations of antimycobacterial treatments. He started taking thalidomide in June 2022, leading within the month to regression of abdominal pain, renutrition and stabilization of the mesenteric infiltration and SMV stenosis. In September 2022, despite curative heparin treatment, SMV thrombosis imposed a switch from

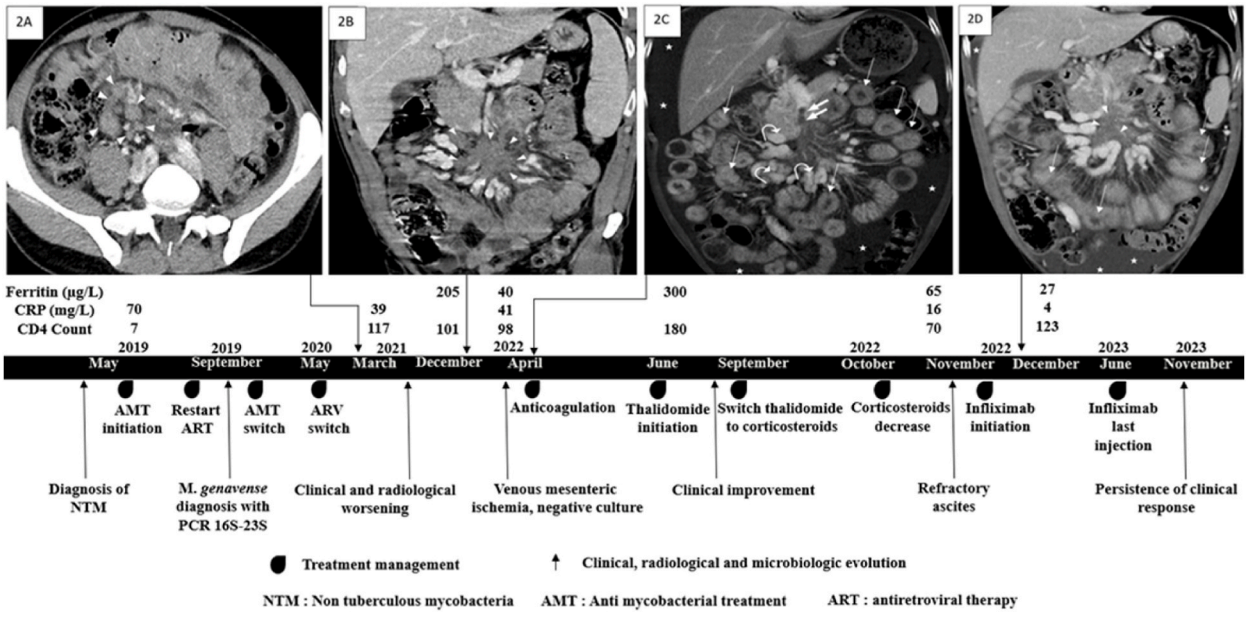

Fig. 2. Timeline and images of patient two (2A-2D). CT -scan after (2A-2D) contrast enhancement (Iomeron 350, Bracco Imaging France) at the portal phase. Enlarged mesenteric lymph nodes (arrowheads) in March 2021 (2A). In December 2021, mesenteric lymph nodes gathered in a soft tissue density mass (arrowheads) (2B). In April 2022, views showed mesenteric ischemia secondary to superior mesenteric vein thrombosis due to the enlarged mesenteric lymph nodes compression with filling defect in the superior mesenteric vein (thick arrows), varices (rounded arrows), ascites (stars), mesenteric congestion, bowel thickened (8–9 mm), target sign and hyperenhancement (thin arrows) (2C). In December 2022, these signs appear less marked after three months of infliximab, with, in particular, a decrease in the thrombosis of the superior mesenteric vein and ascites (stars) (2D).

thalidomide to corticosteroid therapy at 1.5 mg/kg/day.

From October 2022, the patient required repeated ascites punctures, parenteral nutrition and albumin supplementation due to the persistence of the compressive effect on the SMV despite 0.8 mg/kg of corticosteroids. Facing this severe corticosteroid refractory IRIS, he started treatment with infliximab 5 mg/kg every 15 days in November 2022. We noticed a dramatic clinical improvement with the complete disappearance of ascites and weight gain even after cessation of parenteral nutrition. One-month CT-scan showed almost complete regression of SMV thrombus and stability of mesenteric infiltration (Fig. 2D). The thrombus dissolution was probably in relation with the infliximab effect on the reduction of the veinous compression caused by mesenteric lymph nodes.

A maintenance treatment with infliximab 5 mg/kg was then administered every month to June 2023, without relapse after five months.

In February 2024, patient one and patient two had a persistence of clinical response.

2. Discussion

We report a clinical success of infliximab in two patients with late-onset IRIS related to disseminated *M. genavense* infection.

The patient one presented recurrence of fever associated with a metabolic progression of the abdominal lymph node involvement while patient two had signs of portal hypertension related to SMV thrombosis and a worsening of the mesenteric infiltration.

Our two patients were treated in accordance with IDSA guidelines, using macrolide, ethambutol and rifamycin for 12 months after negative culture [11].

Gastrointestinal tract involvement presented by our two patients is a classic *M. gevanense* location described by Bordes through a radiological syndrome including retractile mesenteric, duodenal wall thickening, central mesenteric mass and thrombotic events [12].

Mycobacteria-associated IRIS appears to be a consequence of increasing Th1 cells responses against mycobacterial antigens and an inhibition of Treg cells responses leading to hyperproduction of pro-inflammatory cytokines such as TNF-α, IL-6 and interferon gamma (IFN-γ) [13]. Therefore, a genetic component could also be involved in pathogenesis of mycobacterial IRIS as shown by Rocco et al. who identified an enrichment of protein-altering variants in hemophagocytic lymphohistiocytosis (HLH) -related genes in patients with mycobacterial IRIS compared to those without IRIS [14]. These genetic similarities between mycobacterial IRIS and HLH are supported by common pathophysiology features and are suggested in patient one through the hemophagocytosis found in the initial BMA [15].

Infliximab is an anti-TNF-α antibody endowed with immunomodulatory properties that notably result in a decline of $CD4^+$ T lymphocytes immediately releasing IFN-γ in response to mycobacterial antigens [16,17].

These immunological considerations have prompted some clinicians to use anti-TNF-α antibody as a rescue treatment in steroid-dependent TB IRIS involving the CNS [18,19]. More recently, Armange et al. showed an efficiency of TNF-α antagonists as salvage or corticosteroid-sparing therapeutic in 24 patients with severe IRIS related to TB [20].

The use of anti-TNF-α in NTM IRIS is less described. Two case reports have been published concerning successful treatment with infliximab in steroid-dependent IRIS due to disseminated *M. genavense* disease, with a favorable clinical and radiological outcome for both patients [21,22]. To qualify, a case recently reported by Laurent et al. described a late-onset (after seven years) fatal multi-refractory IRIS related to *M. genavense* in an HIV patient with ascites and portal thrombosis despite an increased dose of infliximab (10 mg/kg/month) and concomitant treatment with corticosteroids and colchicine [23]. Except for *M. genavense* and tuberculosis, only three cases of steroid-dependent IRIS in relation with a *M. avium* complex infection successfully treated with anti-TNF-alpha were reported, among which two received three injections and one was treated with 13 injections of infliximab [15, 24].

We acknowledge some limitations towards the anti-TNF-α use. Indeed, the increased risk of bowel perforation induced by anti-TNF-α in patients with Crohn's Disease [25] raises questions about its implementation in patients with gastrointestinal involvement, as illustrated by patient one who has experienced post-surgical intestinal wounds ten months after her last infliximab therapy. In addition, TNF-α blocker has been described as a risk factor for tuberculosis reactivation because of the key role played by TNF-α in macrophage apoptosis after bacillary infection and granuloma generation [26,27]. Given its ability to bind to both soluble and membrane TNF receptors, infliximab is one of the TNF-α blocker with the greatest impact on anti-tuberculosis immunity [28]. In his cohort of 70 patients with tuberculosis associated with infliximab, Keane et al. reported extrapulmonary diseases and mortality in respectively 34 % and 17 % of patients [29]. However, the increased risk of IRIS after anti-TNF-α withdrawal in patients with disseminated TB should encourage clinician to maintain this therapy in such situations [30]. Those considerations are in line with a case of a patient with life-threatening TB paradoxical reaction attributed to anti-TNF-α withdrawal that experimented a clinical improvement after resumption of anti-TNF-α [31].

Other therapies have been suggested in the setting of steroid-resistant IRIS such as thalidomide, an immunomodulatory therapy which also demonstrates an anti-inflammatory activity through his ability to strongly inhibit TNF-α and reduce IL6 serum level [32, 33]. For instance, those pleiotropic properties of thalidomide are used as a controversial therapeutic approach to reduce the symptoms of IRIS. In a meta-analysis including 98 children and nine adults, Panda et al. had a clinical response rate of 89 % in patients treated with thalidomide for corticosteroids refractory paradoxical reaction related to CNS-TB [34]. However, a randomized controlled trial conducted by Schoeman et al. in children with tuberculous meningitis found no difference in motor outcome between patients who received high dose of thalidomide plus standard-of-care and patients who were treated by placebo in addition to standard-of-care [35]. It should be noted that thalidomide dosage (24 mg/kg/day) used in this trial was higher than in other studies and has been associated with more adverse events such as skin rash or hepatitis [35,36].

The diagnosis of late-onset IRIS is challenging since late relapses or uncontrolled mycobacterial infections are both frequent with

M. genavense [37]. The comparison of the specimen pathology evolution performed on the consecutive biopsies can provide arguments for IRIS diagnosis by showing a reduction in AFB burden and evidence of immune reconstitution, i.e. significant increase of granulomas or organized granulomas. Moreover, Manion has highlighted the diagnostic value of the cytokine response measurement, which seems to be increased *in vitro* when CD4 T cells from HIV patients with IRIS due to *M. genavense* are exposed to the latter [22]. Early identification of severe cases of mycobacterial IRIS is also an issue. Rocco et al. has showed that patients with HLH-associated IRIS were significantly more likely to have prolonged corticosteroids and additional requirement of immunosuppressive agents such as infliximab than patients without HLH [15]. This severe disease described in patients with elevated inflammatory biomarkers such as those with HLH-associated IRIS was more particularly observed in our patient one that had a ferritin level increase up to 494 microg/l.

Moreover, we used for our patients "classic" diagnostic tools of IRIS, i.e. clinical signs worsening without evidence of progression of microbial infection, which led to a delayed diagnosis, as culture is long and often negative. Indeed, the delay between the first symptoms of IRIS and the first treatment of IRIS is, on average, nine months, and between the first symptoms of IRIS and infliximab is, on average, 22 months in the case of our patients. Thus, unlike IRIS described by Manion and Baldolli [21,22] happened within weeks of infection diagnosis, the late-onset of IRIS presented by our patients and by the case of Laurent et al. (17 months) has until now never been reported in scientific literature and should encourage clinicians to discuss this diagnosis in all patients with clinical worsening irrespective of the delay related to M. *genavense* initial diagnosis [23]. Therefore, late-onset IRIS has also been described in other opportunistic infections among HIV patients. Indeed, Vlasova-St. Louis et al. showed that patients with late cryptococcosis meningitis IRIS events had inflammatory signaling cascades characterized by upregulation of genes in adaptive immune response pathways [38].

Moreover, our work shows a different side of M. *genavense* related IRIS, with fibrosing radiological involvement, potentially less accessible to infliximab as evidenced by imaging stability.

The limitations of our case report must be taken into account. Firstly, the small number of patients and the monocentric sample are the source of numerous biases which led us to express reservations about extrapolating the results. In addition, the difference in immunosuppression between our two patients made it difficult to compare them.

To conclude, anti-TNF-α monoclonal antibodies are a promising therapeutic option for late-onset steroid-refractory IRIS due to *M. genavense*. This therapy should also be considered in steroid-dependent IRIS particularly during the first relapse after corticosteroid cessation. The absence of mycobacterial recurrence one year after infliximab initiation in our 2 patients provides first safety data potentially helpful for clinicians in the management of HIV patients or solid organ transplant who have reached a therapeutic dead end. Further assessments are needed to determine the eligible patient profile and the best timing for initiating this treatment.

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Declarations

The authors declare no conflict of interests.

Ethics statement

Informed consent was obtained for the publication of all images and data.

Data availability statement

The data that has been used is confidential.

CRediT authorship contribution statement

Hugo Bes-Berlandier: Writing – original draft, Data curation. **Margaux Garzaro:** Writing – review & editing, Conceptualization. **Claire Rouzaud:** Writing – review & editing. **Sylvain Bodard:** Writing – review & editing. **Emmanuelle Bille:** Writing – review & editing. **Maxence Ficheux:** Writing – review & editing. **Dominique Cazals-Hatem:** Writing – review & editing. **Nicolas Veziris:** Writing – review & editing. **Fanny Lanternier:** Writing – review & editing. **Olivier Lortholary:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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