J Infect Chemother 25 (2019) 1060–1064

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Case Report

# Splenic infarction complicated with immune reconstitution inflammatory syndrome due to disseminated *Mycobacterium genavense* infection in a patient infected with human immunodeficiency virus

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ARTICLE INFO

*Article history:*
Received 8 October 2018
Received in revised form
11 April 2019
Accepted 24 May 2019
Available online 18 June 2019

*Keywords:*
Splenic infarction
Immune reconstitution inflammatory syndrome
Human immunodeficiency virus
*Mycobacterium genavense*

ABSTRACT

*Mycobacterium genavense (M. genavense)* is one of the most fastidious, difficult to culture *Mycobacterium* species. Patients infected with human immunodeficiency virus (HIV) may develop immune reconstitution inflammatory syndrome (IRIS) due to disseminated *M. genavense* infection as well as disseminated *M. avium* and *intracellulare* complex infection. Consensus regarding treatment of IRIS due to disseminated mycobacterium infection has not yet been obtained, although systemic steroid therapy has been recommended in recent guidelines. Here we report the case of a 48-year-old Japanese man diagnosed with HIV and disseminated *M. genavense* infection. His initial CD4-positive T cell count was 3/μL, and his HIV1-RNA viral load was 13,000 copies/mL. He developed IRIS due to disseminated *M. genavense* infection after two weeks of receiving antiretroviral agents. The patient's serum alkaline phosphatase level, as a barometer of disseminated *M. genavense* infection in this case, was difficult to control with several anti-mycobacterial agents, although his fever was improved by non-steroidal anti-inflammatory drugs. About five weeks after the onset of IRIS, the patient developed acute left upper quadrant pain and was diagnosed with splenic infarction by contrast-enhanced computed tomography. After the splenic infarction, the patient's serum alkaline phosphatase level decreased without systemic steroid therapy or anticoagulant agents, and his left upper quadrant pain improved naturally within a few days. This case suggests that IRIS due to disseminated *M. genavense* infection can complicate splenic infarction in patients with HIV, and splenic infarction could improve the IRIS due to disseminated *M. genavense* infection.



## 1. Introduction

*Mycobacterium genavense (M. genavense)* accounts for 4–13% of disseminated nontuberculosis mycobacterial (NTM) infections in patients infected with human immunodeficiency virus (HIV) [1]. Clinical infection has been mainly reported in Europe [1–3] and is relatively rare in Japan [4], but the specific worldwide distribution of *M. genavense* remains unknown [5]. Common clinical signs of disseminated *M. genavense* infection are weight loss, fever, abdominal pain, hepatosplenomegaly, and diarrhea [1]. These clinical signs, however, are similar to those of disseminated *Mycobacterium avium-intracellulare* complex (MAC) infection, the most common mycobacterial infection among patients infected with HIV [6]. It is difficult to distinguish between the two diseases based only on the clinical picture. Moreover, *M. genavense* is one of the most difficult *Mycobacterium* species to culture owing to its general requirement of a 6–12 month incubation period, and growth in liquid but not conventional solid media [1]. As the results of microbiological testing for this fastidious organism are often smear-positive/culture-negative [7], molecular techniques are required for identification [1]. Because of the difficulty in

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https://doi.org/10.1016/j.jiac.2019.05.023
1341-321X/

identifying *M. genavense*, in clinical practice patients with severe disseminated mycobacterium infection often receive empiric treatment with multiple anti-mycobacterial agents for several *Mycobacterium* species, including *M. tuberculosis* and MAC. Particularly in patients with HIV, however, long-term treatment with multiple anti-mycobacterial agents may induce numerous adverse effects and drug interactions with anti-retroviral agents. Therefore, the identification of *Mycobacterium* species is important for the selection of appropriate anti-mycobacterial agents. Additionally, disseminated NTM infections in patients infected with HIV often lead to the manifestation of immune reconstitution inflammatory syndrome (IRIS) following the initiation of antiretroviral therapy (ART) [8]. It is challenging, however, to distinguish IRIS due to NTM from treatment failure because the main clinical manifestations of IRIS are similar to those of disseminated NTM infection itself [8]. Therefore, initiation of systemic corticosteroid therapy for IRIS due to disseminated NTM infection is often delayed.

We present the case of a patient who developed splenic infarction associated with IRIS due to disseminated *M. genavense* infection. The patient experienced improvement of splenomegaly and decline of serum alkaline phosphatase (ALP) following splenic infarction without any specific treatment with the exception of several anti-mycobacterial agents and non-steroidal anti-inflammatory drugs (NSAIDs). To the best of our knowledge, this is the first case report of splenic infarction during IRIS resulting from disseminated *M. genavense* infection in a patient with HIV.

## 2. Case report

A 48-year-old Japanese man was admitted to an outside hospital with a 2-week history of fever, fatigue, and lymphadenopathy. The patient had a history of bipolar disorder and had lived in England over ten years earlier. He was diagnosed with HIV infection by preoperative screening tests for cervical lymph node biopsy and transferred to our hospital. The pathological results of cervical lymph node biopsy in the previous hospital showed only reactive inflammation and no evidence of malignant lymphoma, but acid-fast bacillus smear and cultures were not performed. At the time of HIV diagnosis, the patient's CD4-positive T cell count was 3 cells/μL, and his HIV1-RNA viral load was $1.3 \times 10^4$ copies/mL (Table 1). Computed tomography (CT) on admission revealed cervical and abdominal lymphadenopathy, as well as splenomegaly. The patient was diagnosed with disseminated NTM infection on the basis of a significant cell-mediated immune disorder due to HIV infection, fever, right upper quadrant pain, anemia, elevation of ALP, and CT findings. He was administered azithromycin (AZM), ethambutol (EB), and rifabutin (RBT) as empiric therapy (Fig. 1). The patient's fever and serum ALP gradually improved over the next 2 weeks, while his left cervical lymphadenopathy remained, leading to the performance of further excisional biopsy. Biopsy tissues had positive acid-fast bacilli smear results, and negative PCR results for *M. tuberculosis* and MAC. Isoniazid was added to the therapeutic regimen to cover *M. kansasii*. ART with tenofovir disoproxil fumarate/emtricitabine and dolutegravir was initiated after 5 weeks of anti-mycobacterial therapy. The patient's fever recurred with elevation of serum ALP level 2 weeks after the initiation of ART. At that time, his CD4-positive T cell count was 13 cells/μL, and his HIV1-RNA viral load decreased sharply (33 copies/mL). Abdominal CT revealed exacerbation of splenomegaly and intra-abdominal lymphadenopathy despite improvement of cervical lymphadenopathy. Fluorodeoxyglucose positron emission tomography (FDG-PET)-CT revealed increased metabolic activity of the spleen and abdominal lymph nodes (maximum standardized uptake value [SUVmax] 3.6 and 2.5, respectively). The patient's serum ALP level showed further elevation despite additional treatment for NTM with amikacin (AMK) and levofloxacin (LVFX), although his fever improved within a few days. He was diagnosed with paradoxical IRIS due to disseminated NTM infection mainly on the basis of the CT findings and the significant decline in the HIV1-RNA copy number. He received NSAIDs only, and was not administered systemic steroid therapy because of his CD4 cell counts, which were low enough to allow development of another opportunistic infection. The patient developed acute left upper quadrant pain about 5 weeks after the onset of IRIS. The pain gradually improved over the next 2 days. Abdominal contrast-enhanced CT showed a wedge-shaped splenic infarction (Fig. 2a). Negative test results were obtained for blood culture, antinuclear antibody, antineutrophilic cytoplasmic antibody, anticardiolipin antibody, and lupus anticoagulant, and no blood coagulation abnormalities were found, except for a slightly low level of activated protein C, at the time of splenic infarction (Table 1). Despite the absence of additional treatment, including anticoagulant agents and steroids, serum ALP showed significant improvement following the splenic infarction. Cervical lymph node culture results had been negative for over 8 weeks at that time. PCR and gene sequencing of the cervical lymph node tissue revealed *M. genavense* with complete homology [9]. Resolution of the patient's splenic infarction was detected on abdominal contrast-enhanced CT scan 3 weeks after discharge (Fig. 2b). On PET-CT following discharge, FDG uptake in the lymph nodes and spleen had disappeared.

## 3. Discussion

In the present case study, we elucidated two important clinical topics. First, IRIS due to disseminated *M. genavense* infection could lead to splenic infarction. The usual symptoms and laboratory findings of disseminated MAC infection in patients with HIV infection are fever, night sweats, weight loss, abdominal pain, anemia, and elevated serum ALP level [7]. Short-term systemic corticosteroid therapy is recommended for IRIS, whereas the addition of at least two anti-mycobacterial drugs not previously used is recommended for treatment failure of disseminated MAC infection [10]. In the present case, temporary improvements of fever and serum ALP level were confirmed after administration of the anti-mycobacterial drugs, and recurrence of fever and elevated serum ALP were confirmed after a significant decrease in HIV1 viral load caused by administration of ART. Despite the addition of two new anti-mycobacterial drugs, AMK and LVFX, there was no improvement in the elevated serum ALP level. For these reasons, the patient was clinically diagnosed with IRIS rather than treatment failure. We also considered the elevation of serum ALP as a barometer of disseminated NTM infection itself as well as the associated IRIS in this case. Generally, splenic infarction results from prominent splenomegaly, malignant lymphoma, infectious mononucleosis, infectious endocarditis, antiphospholipid antibody syndrome, autoimmune vasculitis, and congenital coagulation disorder, among others [11]. Two cases of splenic infarction due to mycobacterium infection have been reported [12,13]. Kyrilli et al. reported a fatal case of meningitis and splenic infarction due to disseminated *M. genavense* infection in a patient with HIV prior to the initiation of ART [12]. In the case described here, progressive splenomegaly due to disseminated *M. genavense* infection and the associated IRIS was the only cause of splenic infarction, with the exception of a slightly low level of activated protein C. It is important to note that disseminated *M. genavense* infection in patients with HIV can induce splenic infarction not only prior to the initiation of ART, but also during its IRIS. Moreover, PCR testing for the detection of *M. genavense* should be performed in patients with HIV who have suspected disseminated MAC infection and the

**Table 1**
Laboratory data on admission and onset of splenic infarction.

| On admission | | | | | | Onset of splenic infarction | |
|---|---|---|---|---|---|---|---|
| Hematology | | Biochemistry | | Infection | | Immunology | |
| WBC | 3050 /μL | TP | 6.9 g/dL | HIV1-RNA | 13000 copies/mL | MPO-ANCA | <1.0 U/mL |
| Neu | 84.3 % | Alb | 3.3 g/dL | HBcAb | (−) | PR3-ANCA | <1.0 U/mL |
| Eo | 0 % | T-Bil | 0.5 mg/dL | HCVAb | (−) | Antinuclear antibody | <40 |
| Lym | 6.2 % | AST | 57 IU/L | RPR | (−) | Coagulation | |
| CD4 | 1.7 % | ALT | 50 IU/L | TPHA | (−) | APTT | 29.3 sec |
| CD8 | 52.7 % | LDH | 351 IU/L | EBNA | (+) | PT | 95.2 % |
| RBC | 298 $\times 10^4$/μL | ALP | 732 IU/L | CMV IgG | (−) | Fib | 380 mg/dL |
| Hb | 8.4 g/dL | GGTP | 202 IU/L | Toxo IgG | (−) | D-dimer | 7.5 μg/mL |
| Ht | 25.1 % | UA | 3.3 mg/dL | BDG | 14.6 pg/mL | Anti-CL β2GPI antibody | 1.2 U/mL |
| PLT | 12.6 $\times 10^4$/μL | BUN | 16 mg/dL | IGRA | (−) | Anti-CL antibody | 8 U/mL |
| Ret | 0.58 % | Cr | 0.6 mg/dL | | | TAT | 6.5 ng/mL |
| ESR | 84 mm/h | Na | 136 mEq/L | | | PIC | 2.9 μg/mL |
| Coagulation | | K | 4.2 mEq/L | | | Cryoglobulin | (−) |
| PT-INR | 1.06 | Cl | 100 mEq/L | | | Protein C activity | 58 % |
| APTT | 24 sec | Ca | 7.7 mg/dL | | | Protein S antigen | 99 % |
| Fib | 419 mg/dL | IP | 2.9 mg/dL | | | LAC pre-neutralization | 40.9 sec |
| FDP | 18.4 μg/mL | CK | 41 IU/L | | | post-neutralization | 41.8 sec |
| | | Glu | 111 mg/dL | | | | |
| | | CRP | 5.2 mg/dL | | | | |

ESR; erythrocyte sedimentation rate, BDG; (1−3)-β-d-glucan, IGRA; interferon gamma release assay, ANCA; antineutrophil cytoplasmic antibody, Anti-CL; anti-cardiolipin, LAC; lupus anticoagulant.

associated IRIS who develop splenic infarction, but whose routine acid-fast bacillus cultures are negative.

Second, interestingly, the IRIS of disseminated *M. genavense* infection was improved after splenic infarction in the present case without administration of steroids and anticoagulant agents, if serum ALP was the barometer of IRIS, as we hypothesized. Anticoagulant therapy, heparin or warfarin, is often used to treat splenic infarction, although the actual treatment is different for each cause. Since no congenital or acquired coagulation abnormalities were found in this case, the patient did not receive any anticoagulant agents. Steroids, which are often used to treat IRIS due to MAC infection, increase the risk of further AIDS-defining opportunistic infections. Moreover, in this case, malignant lymphoma-associated HIV was also considered in the differential diagnosis based on the results of PET-CT. Additionally, most subjects in a case series of NTM-IRIS in patients infected with HIV were found to experience resolution of symptoms with no additional treatment, including systemic steroid therapy, other than anti-mycobacterial drugs [8]. The patient in the present case was not administered steroids for these reasons. It has been suggested

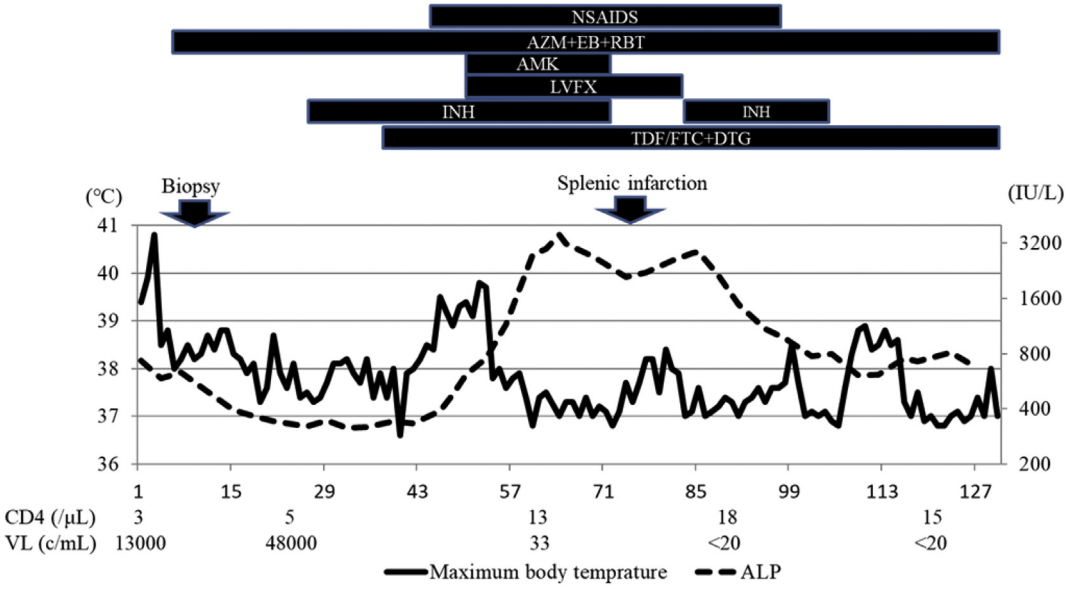


**Fig. 1.** Clinical course of the present case. NSAIDS; Non-Steroidal Anti-Inflammatory Drug, AZM; azithromycin, EB; ethambutol, RBT; rifabutin, AMK; amikacin, LVFX; levofloxacin, INH; isoniazid, TDF; tenofovir disoproxil fumarate, FTC; emtricitabine, DTG; dolutegravir, VL; HIV-1 viral load.

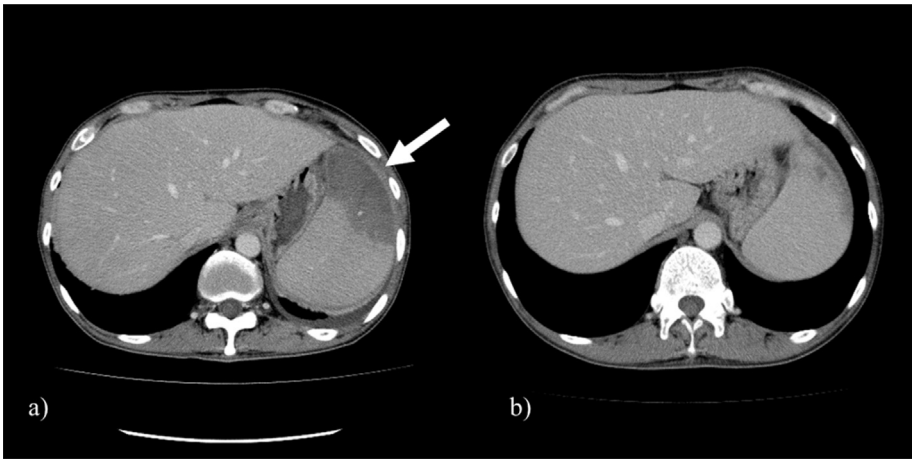


**Fig. 2.** Abdominal CT, a; Splenic infarction detected as a hypo-enhanced area in CT on 84 days after admission (*arrows*). b; Splenic infarction was improved in follow-up CT after discharge.

that MAC-IRIS in patients with HIV is induced by redistribution of activated CD45RO memory T cells in secondary lymph tissues (e.g., lymph nodes and spleen) and antigens that trigger IRIS of disseminated NTM infection may be in the form of viable organisms, dead organisms, or shed antigens [8], although the mechanism of IRIS remains to be clarified. In the case of disseminated *M. genavense* infection with spleen lesions, the pathogen is detected in the spleen [12]. Needle autopsy reports for histological and microbiological examination to clarify the cause of death have described well-formed necrotizing granulomatous inflammation, with negative Ziehl-Neelsen and GMS staining for organisms in the spleen, in patients with HIV who developed paradoxical IRIS due to disseminated *M. tuberculosis* [14]. Hammoud et al. showed association between increased metabolic activity on FDG-PET CT and IRIS in HIV patients [15]. Before ART initiation, bone marrow and spleen FDG uptake was higher in mycobacterial IRIS than those in non-IRIS, and after ART initiation, mean SUV in bone marrow and spleen remained persistently high in IRIS whereas decreased in non-IRIS. The authors explained FDG uptake reflected increased glycolysis in activated $CD4^+$ T cell and macrophages because these FDG uptake were significantly correlated with several inflammatory biomarkers. These reports suggest that *Mycobacterium* present as an infection in the spleen becomes an antigen to raise IRIS, and that strong inflammation occurs in the spleen during IRIS due to disseminated *Mycobacterium* infection. In the present case, we believe that the excessive immune reaction in the spleen decreased as a result of a reduction in the amount of viable or dead organisms and CD45Ro memory T cells due to splenic infarction.

In conclusion, IRIS due to disseminated *M. genavense* infection could lead to splenic infarction, and splenic infarction could improve the IRIS of disseminated *M. genavense* infection without the use of steroids or anticoagulant agents. Clinicians should consider *M. genavense* if a patient with HIV infection develops splenic infarction during the treatment for NTM of unknown species showing a pattern of smear-positive/culture-negative infection, including IRIS. Splenic infarction due to IRIS of *M. genavense* itself may improve the excessive immune reaction in the spleen as a result of reduction in the amount of the antigen.

## Authorship

Tomohiro Hosoda contributed to drafting the article. Mitsuo Sakamoto contributed to final approval of the version to be submitted. Kiyofumi Ohkusu contributed to acquisition of PCR and gene sequencing of *Mycobacterium genavense*. All authors meet the ICMJE authorship criteria.

## Funding

None.

## Conflicts of interest

None.

## Acknowledgments

The authors would like to thank Koushiro Miura for surgical biopsy of lymph nodes (Kawasaki Municipal Kawasaki Hospital).

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