CASE REPORT

Mesenterial involvement of *Mycobacterium genavense* infection: hard to find, hard to treat

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SUMMARY

Mycobacterium genavense is a rare pathogen affecting severely immunosuppressed patients. We report the case of persistent relapsing *M. genavense* infection in a 48-year-old African man with a positive diagnosis of HIV infection. Despite being under effective antiretroviral therapy with partial immune reconstitution, he developed irreversible long-term abdominal complications, possibly due to persistent *M. genavense* infection and sustained inflammation. Case management consists of individual risk assessment, close follow-up and personalised treatment strategies concerning the duration of antimycobacterial therapy and early application of steroids. Patients with profound immunosuppression, a high viral load at HIV diagnosis and a high burden of *M. genavense*, appear to be at higher risk. The pathogenicity of this complication is not well known and its optimal management has still to be determined.

BACKGROUND

Mycobacterium genavense (MG) is a non-tuberculous mycobacterium (NTM) first described in 1990 by Hirschel *et al*¹ in a patient with AIDS and identified 2 years later by PCR.² Severely immunosuppressed, HIV-infected patients with less than 50 CD4 cells/ μ L are mainly affected.^{3–5} *M. genavense* is a slow-growing *Mycobacterium* that requires special media for culture. Identification relies on molecular techniques,⁶ and the pathogenic mechanisms of *M. genavense* remain unknown. *M. genavense* has been isolated mainly from pet birds,⁷ but it was also found in the gastrointestinal tracts of healthy individuals,⁸ leading to the assumption that the first step of infection may be colonisation of the gastrointestinal tract. Prognosis in HIV-positive patients was very poor before the advent of combined antiretroviral therapy (cART).⁵ However, the previous median survival rate of 6–10 months has improved significantly and more than 50% of patients now survive 5 years.³ If the incidence of NTM infections in HIV-infected patients is decreasing in developed countries due to the earlier start of cART, it may remain a considerable problem in developing countries where HIV remains highly underdiagnosed, and diagnostic and treatment options for NTM are lacking. In addition, NTM infections are now observed in immunosuppressed non-HIV-infected patients, for example, transplant recipients, or in other immunosuppression contexts,^{4,9} thus creating a new diagnostic and management challenge for clinicians. In this case report, we describe persistent relapsing *M. genavense* infection in an HIV-infected patient

who developed long-term complications with bulky lymph node enlargement, fibrosis and chylous ascites.

CASE PRESENTATION

A 48-year-old African man was diagnosed HIV positive in 2010 (CD4 31 cells/ μ L; 3%) when presenting to our emergency unit for an episode of motor-sensitive myelopathy and biopsy-confirmed cytomegalovirus colitis. cART (tenofovir/emtricitabine/efavirenz) was immediately started. Three months later, he presented with wasting and raised inflammation markers. A CT-scan revealed mesenteric and retroperitoneal lymph node enlargement. Acid-fast bacilli were found in his duodenal mucosa and *M. genavense* was identified by 16S rRNA sequence analysis of positive liquid cultures of a mesenteric lymph node biopsy. The sequence of the 16S rRNA gene was determined on a capillary sequence analyser (ABI 3130XL DNA analyser; Applied Biosystems, Foster City, California, USA) and identified according to protocols published by the Clinical and Laboratory Standards Institute.¹⁰

Antimycobacterial treatment (clarithromycin, ethambutol, rifabutin,) was initiated, but stopped after 2 months due to serious hepatotoxicity. Whether this was due to drug toxicity or NTM infection remains open. The liver recovered fully after the patient stopped the antimycobacterial drugs. Because of ongoing immune reconstitution after having stopped the antimycobacterial drugs, (CD4 108 cells/ μ L, HIV-RNA 61 copies/mL) and the absence of any clinical symptoms indicating active mycobacterial disease, it was decided not to reintroduce antimycobacterial therapy at this time.

Ten months later, the patient developed clinically apparent bulky abdominal lymph nodes. As the HIV virus had been effectively suppressed for 12 months and the CD4 count was stable at $\approx$ 230 cells/ μ L, it was decided not to perform a biopsy immediately, but to instead follow the patient with close biological and radiological surveillance, in the assumption it might be immune reconstitution syndrome (IRS). No evidence for lymphoma or other opportunistic infections was found at this time.

After 1 year of close observation, the patient suddenly presented with weight loss, abdominal pain and diarrhoea. The abdominal CT-scan showed stability of the bulky lymph nodes, but also showed the development of superior mesenteric vein compression with portal hypertension and jejunal wall thickening. HIV-RNA was less than 20 copies/mL and the CD4 count was 286 cells/ μ L (14%). Acid-fast bacilli were found in a cervical lymph

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node and one blood culture returned positive, revealing *M. genavense* by sequencing using the same method as mentioned above. Liver and lymph node biopsies showed granulomas. We diagnosed persistent *M. genavense* infection with underlying IRS 23 months after having revealed *M. genavense* disseminated disease for the first time in this patient, and introduced a combination treatment of azithromycin, ethambutol and rifabutin, together with prednisone (0.5 mg/kg body weight). The patient gained weight and his abdominal discomfort resolved.

After tapering and cessation of prednisone over a 2-month period, the patient again felt worse. The bulky abdominal lymph nodes persisted and he developed chylous ascites, anaemia, lymphopenia and cholestasis, despite ongoing suppressive antiretroviral treatment and antimycobacterial treatment. The ascites was tested negative for *M. genavense* by microscopy and culture. A further biopsy performed by laparotomy revealed lymph node fibrosis with no signs of ongoing mycobacterial infection or activated immune reactions (absence of acid-fast bacilli or granuloma). Unfortunately, culture and PCR of lymph node tissue could not be performed this time for technical reasons. Blood cultures were repeatedly negative. None of the biopsies suggested lymphoma, other malignancies or concomitant infections. Antimycobacterial therapy was changed to ethambutol, clarithromycin and rifampicin, and prednisone was reintroduced at 0.5 mg/kg body weight and tapered progressively. An antibiogramme performed on the former positive cultures confirmed sensitivity for rifampicin and clarithromycin. Symptomatic treatment was started with diuretic therapy and a low fat diet for chylous ascites.

The patient showed clinical and biological improvement during the following 6 months with weight gain, normalisation of laboratory parameters and resolution of the chylous ascites. Prednisone was entirely stopped 10 months after the first introduction. A CT-scan 17 (figure 1) and 24 months after the diagnosis of relapsed *M. genavense* infection and reinitiation of antimycobacterial treatment showed slowly regressive, retroperitoneal and mesenteric lymph nodes. The patient is still on antimycobacterial treatment, 25 months after the diagnosis of *M. genavense* relapse.

DISCUSSION

We report a case of a persistent relapsing *M. genavense* infection complicated by abdominal lymph node fibrosis, resulting in mesenteric vein compression, jejunal wall thickening and chylous ascitis. To the best of our knowledge, this is the first report of a persistent *M. genavense* infection with secondary

Figure 1 Abdominal CT scan, April 2013: hypodense, intra-abdominal and retroperitoneal mass infiltrating the coeliac trunk and its collaterals, the mesenteric superior artery, the renal peduncle and the third part of the duodenum, without any thrombosis.

dissemination, despite a sustained CD4 cell count of >200 cells/mm³. Some explanations for this condition might be the short duration of antimycobacterial therapy received by our patient. Despite successful antiretroviral treatment with a suppressed viraemia, immune reconstitution, however, remained hampered by the chronic relapsing *M. genavense* infection, with CD4 cell count percentage remaining between 10% and 14% at best. Relapsing and chronic *M. genavense* infections have been reported in a case series by Charles *et al*,³ but not described in detail. By contrast, relapse of *Mycobacterium avium* complex (MAC) infection has been reported in the literature, usually presenting as a more localised disease in patients with a CD4 count of >100 cells/ μ L. In general, these cases presented inadequate CD4 cell recovery of <200 cells/mm³.^{11 12} Only one case had a relapse with a localised MAC infection, despite adequate CD4 cell recovery (>600 cells/mm³, 31%).¹³ A reinfection by another *M. genavense* strain has not been formally excluded in our case (eg, by full sequence of the mycobacteria), but seems less probable in the setting of these rarely pathogenic bacteria and with regards to the very short initial treatment.

The clinical presentation of *M. genavense* infection is very similar to that of MAC.¹⁴ They both affect patients with profound immunosuppression (<50 CD4 cells/mm³) and often present a high affinity with the abdominal tract,^{3 4 14–17} resulting in abdominal pain, hepatosplenomegaly, diarrhoea and lymph node enlargement, sometimes associated with ascites.^{2–4}

In the case of IRS in *M. genavense* or MAC infection, abdominal symptoms may worsen and lead to severe complications. NTM-associated IRS is well described in HIV-infected patients receiving cART, and clinical features are often atypical.^{11 18 19} Histological examination of the associated lesions show intense granulomas and few or no surrounding organisms, sometimes associated with central necrosis, thus reflecting the immunopathological response to the antigen.^{19 20} Phillips *et al*²¹ characterised three major presentations of NTM-associated IRS in a series of 51 patients (2 *M. genavense*, 42 MAC and 6 non-identified mycobacterial cases) consisting of peripheral lymphadenitis, pulmonary-thoracic disease and intra-abdominal disease. They observed that patients with abdominal localisations were more likely to have previous disseminated MAC infection, lower CD4+ cell counts and positive blood culture results at the time of NTM-IRS diagnosis. They also had higher rates of relapse. Another risk factor might be a greater burden of mycobacteria before the initiation of cART.

Long-term complications of *M. genavense* have not been extensively described in the literature. Borde *et al*²² recently suggested a pathogen-specific syndrome for *M. genavense* infection similar to retractile mesenteritis, a very poorly understood disease affecting the small bowel mesentery with chronic fibrosing inflammation.²³ There are few data on the natural history and therapeutic options for this condition. The development of chylous ascites, a very rare complication, has been described in the context of retractile mesenteritis,^{23 24} as well as in MAC infection.^{25 26} It is believed that direct mechanical compression by a mesenteric mass encasing the bowel, blood vessels and lymphatics result in abdominal pain, bowel obstruction, ischaemia and chylous ascites, caused by infiltration and erosion. Cases of MAC infection and the development of massive abdominal lymph nodes and chylous ascites are mentioned in retrospective case series, but without data concerning the histology and clinical course.^{25 26} The last histological examination of our patient's abdominal lymph node revealed extensive fibrosis, but no signs of active inflammation or infection. We hypothesise, therefore, that our patient had a persistent (22-month) *M. genavense* infection

localised in the abdominal lymph nodes, which provoked a sustained inflammatory response leading to lymph node enlargement and dominating gastrointestinal symptoms, similar to the clinical picture of chronic retractile mesenteritis.

Indications, type and duration of treatment for NTM infections have yet to be established. A prolonged duration of antimycobacterial treatment for several months could be reasonable in some cases, but the exact duration and patient profile have yet to be determined.²¹ Some cases reported in the literature developed IRS or infection-related complications, despite long-term antimycobacterial treatment (12–18 months).^{12–21} In a similar manner, the indications, optimal dose and duration of treatment with prednisone are not yet established in the setting of NTM-associated IRS, and should be evaluated individually.²¹

In summary, there is a risk of persistent relapsing *M. genavense* infection in individuals with seemingly adequate immune reconstitution, mainly affecting patients with profound immunosuppression and a high viral load at the time of HIV diagnosis, including a high burden of *M. genavense*. Ongoing subclinical immune reaction carries the risk of being unable to control *M. genavense* infection and may lead to chronic irreversible complications, such as retractile mesenteritis, in those with predominant abdominal localisation. We strongly recommend that patients with *M. genavense* infection undergo an individual risk assessment, close follow-up and treatment strategies tailored to their specific needs. The early use of steroids with slow tapering should be considered if sustained IRS is suspected.

Learning points

- ▶ *Mycobacterium genavense* infection still remains a potential live-threatening opportunistic infection for HIV-infected patients in the era of combined antiretroviral therapy.
- ▶ Chronic and irreversible complications are described, such as retractile mesenteritis.
- ▶ Prolonged antimycobacterial therapy and the early application of steroids should be considered in high-risk patients with a suspicion of sustained inflammatory response.

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