Disseminated *Mycobacterium avium complex* disease in a patient with left ventricular assist device (Heart Mate II)

Malattia disseminata da Mycobacterium avium complex in un paziente portatore di dispositivo di assistenza ventricolare sinistra (Heart Mate II)

Maddalena Cordioli¹, Paola Del Bravo¹, Fabio Rigo¹, Anna Maria Azzini¹, Mara Merighi¹, Alberto Forni², Ercole Concia¹

¹Division of Infectious Diseases, Department of Pathology, Azienda Ospedaliera Universitaria Integrata di Verona, Policlinico “G.B. Rossi”, Verona, Italy;
²Division of Cardiothoracic Surgery, Department of Cardiovascular and Thoracic Surgery, Azienda Ospedaliera Universitaria Integrata di Verona, Ospedale Civile Maggiore, Verona, Italy

Worldwide with increasing prevalence of heart failure and limited availability of donor organs, implantable left ventricular assist devices (LVADs) are increasingly used as a bridge to heart transplantation and as a long-term myocardial surrogate. Patients with LVADs are not treated with immunosuppressive therapies and opportunistic infections related to LVADs are not described in literature.

We want to describe a case report which appears to be the first case of *Mycobacterium Avium Complex* (MAC) disease in a patient with LVAD and without other conditions associated with immune deficiency.

**CASE REPORT**

A 50-year-old Caucasian man was referred to our hospital for the evaluation of recurrent fever and generalized weakness since November 2012. The patient had received a LVAD (Heart Mate II) 2 years before and he had had a normal recover after implantation. The patient had been followed, till the admission in our Infectious Diseases ward, by the colleagues of Cardiotoracic Surgery and the exams they had performed showed mild but progressive pancytopenia and splenomegaly. The patient was admitted in our Unit for work-up of his clinical condition in May 2013. On initial presentation the patient was febrile (BT 37.7°C), he complained progressively weakness but laboratory and microbiological investigations showed only the presence of pancytopenia. The ectography confirmed the splenomegaly and chest X-ray showed numerous nodular opacities in the upper part of the right lung. Thus, we performed a bronchoscopy in order to collect a sample of broncho-alveolar lavage (BAL) fluid: both the direct examination and, later, the BAL culture showed the presence and the growth of alcohol-acid fasting bacilli which were identified, with molecular biology techniques (GenoType Mycobacterium), as *Mycobacterium intracellulare*. In the suspect of disseminated non-tuberculous mycobacteria (NTM) infection, although the patient did not show evident predisposing factors (immunosuppressive conditions and/or immunosuppressive drugs), we collected peripheral and bone marrow blood for culture. On May 22nd, following the growth of *Mycobacterium intracellulare* in all the specimens
collected and the FDG18PET-TC revealed the presence of epatosplenomegaly and diffuse bone marrow ipercaptation (FDG18PET-TC on May 7th 2013, Figures 1A-1B and Figure 2) we decided to begin the specific antiMAC-therapy with azithromycin 500 mg/die, ethambutol 1000 mg/die, rifabutin 300 mg/die, levofloxacin 500 mg/die and amikacin 750 mg iv three times a week. In the meantime we evaluated the cell mediated immunity through the CD4 T count, and a considerable deficiency in CD4 T cells (43 cells/mmc) was detected, even though both their percentage on total T cells (43%) and the CD4/CD8 ratio (1.46) were normal. Furthermore we excluded both the presence of HIV infection through HIV serological test and the possibility of a previous contact with *Mycobacterium tuberculosis complex* performing the QuantiFERON-TB test. During the next few days the clinical condition improved: the patient became afebrile and, even though the bone marrow production was still low, he was discharged from the hospital on June 6th 2013.

The anti-mycobacterial therapy continued till the end of July when, trying to reduce the anorexia and nausea complained by the patient, we reduced azitromycin to 500 mg three times a week. On September 19th 2013 we repeated a FDG18PET-TC (after 4 months of therapy) which showed an “important reduction in the bone marrow’s FDG18 captation and a reduction of the epatosplenomegaly” (Figures 3A-3B). Two weeks later we took a sample of bone marrow aspirate in order to perform a BK culture. In the same days we reduced further the antibiotic therapy taking out both the macrolide and the fluoroquinolone.

**Figures 1 - A, B - FDG18PET-TC on May 7th 2013.** The image shows epatosplenomegaly (in the circle there is the driveline of the ventricular assist device).

**Figures 2 - FDG18PET-TC on May 7th 2013.** The image shows the diffuse accumulation of the radio-labelled drug within the bone marrow.

**Figures 3 - A, B - FDG18PET-TC on September 19th 2013.** The images show both the important reduction of radio-labelled drug accumulation within the bone marrow and the decreasing of the epatosplenomegaly.
November 18th 2013, following a definitive negative result of the BK culture performed on bone marrow’s blood, amikacin was stopped and the MAC-therapy was continued with only 2 drugs (rifabutin 300 mg/die and ethambutol 800 mg/die).

After 6 months of specific therapy the patient was still pancytopenic (on average: WBC 1,300 mm³, Hb 9 g/dL, PLTs 80,000/mmc) despite the count of the medullary cells was improving.

On March 2014 the patient died before reentering in heart transplant list.

**DISCUSSION**

Since 2000, several scientific articles describe the infectious complications LVAD-related and nowadays we know that the infective global risk can vary from 22% to 72% splits up in local (36%) and bloodstream infections (64%) [1-5]. Coagulase-negative staphylococci were identified in most of these infective episodes, due to the interruption of the skin barrier, followed by Gram-negative bacilli and, far away, Candida spp [2-4].

*Mycobacterium avium complex* belongs to the family of non-tuberculous mycobacteria (NTM) ad it is mostly responsible of pulmonary diseases in patients with underlying chronic lung diseases (bronchiectasis, pneumoconiosis, prior tuberculosis) without, usually, no other risk factors. In the minority of the patients, who present impaired cellular immunity, this mycobacterium can cause disseminated infections in non contiguous organs (Disseminated-MAC-disease) [6, 7].

DMD is typically an AIDS-related disease even though, recently, had been demonstrated that other causes of immunodeficiency (drug-related deficiency, SCID, modification in the cascade of production of IFN-gamma and/or IL-12) can also increase the risk of developing DMD [8]. Furthermore, in these last years, sporadic clinical cases of DMD had been described in immunocompetent hosts [6, 9-11], although only two of this reports had deeply analyzed the patient’s cellular immunity response [7, 9]. In all the other studies, the immunological response had been deducted by the negative result of both serological HIV test and Mantoux or QuantiFERON-TB test as an indirect evidence of a normal IFNgamma and IL-12 production [6, 10].

In our clinical case, even though we have not deeply examined the cytokines production within the cellular-mediater immunological response, the IFNgamma production in the mitogenous tube during the quantiFERON-TB test was normal (1,02 UI/mL on March 22nd 2013, 1,43 UI/mL on May 22nd 2013).

We can therefore deduct that our patient could not be labelled as immunocompromised before the beginning of the infection. We still have to make clear how would be possible the dissemination of Mycobacteria long before the beginning of the bone marrow invasion by the bug and, as a consequence, the setting up of the pancytopenic status. Further studies will be needed to assess if the cellular immune impairment would be related to the presence itself of the ventricular assist devices.

**CONCLUSIONS**

The clinical story of our patient and the pathogenetic hypothesis above presented point out the possibility to include in our mental process, when we face a febrile, weakened patient with LVAD, beside the most common bacterial and fungal diseases, opportunistic infections too. Moreover this kind of stealthy infections are difficult to treat without a specific clinical suspicion and diagnostic pathway. In addition, in this kind of patients, the lack of both a correct diagnostic pathway and a specific treatment is directly related to the definitive exclusion from the transplant list, having herewith a direct impact on the patient’s quality of life and life expectancy.

**Conflicts of interests:** none

No financial support to declare

**Keywords:** Mycobacterium avium complex (MAC), Mycobacterium intracellulare, Left Ventricular Assist Device (LVAD), disseminated infection, non-HIV-infected patients.
Although disseminated *Mycobacterium avium complex* disease occurs mainly in immunocompromised hosts, especially HIV-infected patients in the last stage of the disease (AIDS), this condition is still rare in immunocompetent subjects. We report the case of a Caucasian man who received a left ventricular assist device two years before as a bridge to heart transplantation, that began to present signs and symptoms of mycobacterial infection. The diagnostic work-up we performed showed the presence of *Mycobacterium intracellulare* in lungs and both peripheral and bone marrow blood. Although evaluated, we found no abnormalities in the patient’s immune system that can be related to mycobacterial infection. The beginning of a specific therapy made the patient slowly improve and further nuclear medicine assay (PET-TC) showed a good reduction in radio-labelled drug captation.

---

**SUMMARY**

La micobatteriosi disseminata è una malattia tipica dell’ospite con grave immunodeficit a livello dell’asse cellulomediato, in primis l’infezione da HIV nella fase conclamata di malattia (AIDS). Recentemente sono stati descritti casi di disseminazione di *Mycobacterium avium complex* anche in pazienti privi di deficit immunitario. Riportiamo il caso di un uomo caucasico, portatore di dispositivo di assistenza ventricolare sinistra come soluzione-ponte al trapianto cardiaco che, a distanza di circa 2 anni dall’impianto, ha iniziato a presentare segni e sintomi compatibili con tale patologia. Le indagini eseguite hanno evidenziato la presenza di *Mycobacterium intracellulare* a livello polmonare, ematoco e midollare. Sebbene indagate, non sono state evidenziate alterazioni immunitarie che potessero spiegare l’insorgenza di micobatteriosi disseminata. L’avvio di una terapia specifica ha permesso un lento ma progressivo miglioramento della sintomatologia riportata e ad una decisiva riduzione della captazione del radiofarmaco alle indagini di medicina nucleare (PET-TC).

---

**REFERENCES**


