Infezione disseminata da *Mycobacterium avium* complex con batteriemia persistente in un paziente AIDS-presenter.

Disseminated *Mycobacterium avium* complex infection with persistent bacteremia in an AIDS-presenter patient.

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Riassunto

Negli ultimi decenni, l'incidenza di casi AIDS-presenter è calata drasticamente grazie alla diffusione della terapia antiretrovirale e al suo utilizzo sempre più precoce. Fra le patologie opportunistiche associate all'AIDS, l'infezione disseminata da micobatteri non tubercolari rappresenta una grave complicanza. La presentazione clinica aspecifica, così come il difficile work-up diagnostico, possono ritardarne il riconoscimento e il successivo avvio della terapia. Ad oggi, nonostante efficaci terapie anti-micobatteriche, il fattore determinante per il successo della terapia è rappresentato dall'immuno-ricostituzione conseguente alla introduzione di una terapia antiretrovirale efficace.

Il caso qui descritto rappresenta un esempio di infezione di difficile trattamento con coinvolgimento midollare, esordito come sospetta patologica ematologica.

Abstract

In recent decades, the incidence of AIDS-presenter cases has drastically decreased thanks to the availability of highly active antiretroviral therapy (HAART) and its early use. Among the AIDS-associated opportunistic diseases, non-tuberculous mycobacteria (NTM) disseminated infection represents a serious complication. The nonspecific clinical presentation, as well as the difficult diagnostic work-up, can delay the recognition and the subsequent initiation of therapy. To date, despite effective antimycobacterial drugs, the determining factor for treatment outcome is immune reconstitution resulting from HAART introduction.

The case described here represents an example of a difficult-to-treat infection with bone marrow invasion, which began as a suspected hematological disease.

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Introduction

Non-tuberculous mycobacterial infection represents a serious complication in the clinical history of HIV-positive patients with acquired immune deficiency syndrome (AIDS) (1).

Since the introduction of highly active antiretroviral therapy (HAART), the number of patients presenting with AIDS has significantly fallen. According to the statistics from the Italian Centro Operativo AIDS (CoA), 382 new cases of AIDS were reported in Italy in 2021, compared to 5693 cases in 1995 (**Figure 1**).

In the last years, only 6.3% of patients presented with disseminated or extra-pulmonary mycobacterial infection (2).

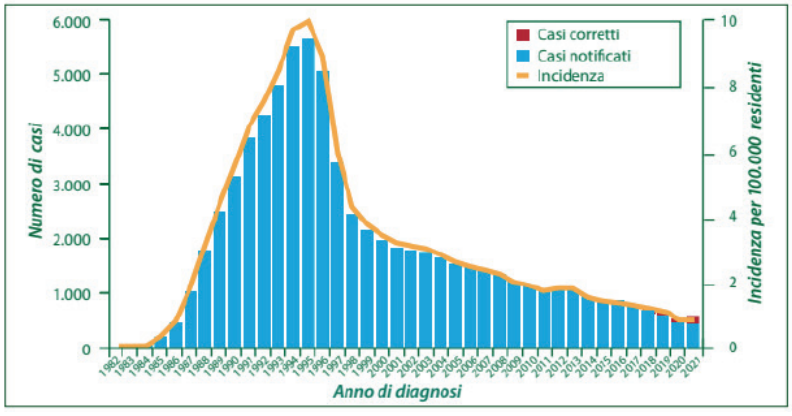
Here, we describe the case of a difficult-to-treat disseminated M. avium complex (MAC) infection in an advanced AIDS patient.

Case report

A 32-years-old Ukrainian woman, war refugee living in Italy since March 2022, presented at the emergency department of a Northern Italy hospital with fever and dry cough since several weeks in known SARS-CoV-2 infection.

Her past medical history was only significant for hemorrhoidal disease. On admission, her general conditions were poor. She was febrile and asthenic. Laboratory evaluations revealed anemia (Hb 6.7 g/dl),

Figure 1. Incidence of AIDS-cases in Italy from 1982 to 2021 (2).



elevated C-reactive protein (20.5 mg/dL) and elevate D-dimer (11.901 mcg/L).

She was initially treated with remdesivir for mild SARS-CoV-2 infection. Since her overall condition was not improving and fever persisted, HIV-test was requested, resulting positive. HIV viral load was 757,000 copies/ml and CD4+ lymphocytes count was 2/mm3: diagnosis of AIDS was made, according to the CDC classification (stage C3).

Drug resistance-test and HLA-B57 typing resulted negative. Serologies for syphilis, toxoplasmosis, hepatitis B and C were negative, as well as serum cryptococcal antigen and Quantiferon-TB test.

Anti-retroviral therapy (ART) was started with a combination of bictegravir, emtricitabine and tenofovir alafenamide (BIC/FTC/TAF).

At chest computed tomography (CT) multiple mediastinal lymphadenopathies were found.

Lymphoproliferative disease was initially suspected. She also underwent a fluorodeoxyglucose-positron emission tomography/CT (FDG-PET/CT) showing intense uptake in multiple supradiaphragmatic-subdiaphragmatic lymph nodes and diffusely increased splenic uptake. Axillary lymph node biopsy was performed. At histological examination atypical lymphoid proliferation was found in the setting of necrotizing granulomatous lymphadenitis; peripheral T-cell lymphoma (PTCL) was considered among the differential diagnoses.

Polymerase chain reaction (PCR) for M. avium complex (MAC) on the lymph node resulted positive. Specimens from sputum, blood and stool were then obtained and all cultures grew positive for MAC.

Antimycobacterial susceptibility testing was performed (results shown in **Table 1**).

A diagnosis of disseminated MAC infection was made and treatment with rifampicin (600 mg i.v., once daily), oral azithromycin (500 mg per os, twice daily) and ethambutol (1000 mg i.v., once daily) was begun. ART was switched to dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) because of drug interactions.

In order to further investigate the suspected peripheral T-cell lymphoma (PTCL), the patient was

Table 1. Antimycobacterial susceptibility test results.

1 Mycobacterium avium							
Antibiogramma	**Ceppo 1**						
	MIC						**EQUIVALENTI**
Amikacina	16	S					
Claritromicina	4	S					
Linezolid	32	R					
Moxifloxacina	4	R					

S = Sensibile Dosaggio Standard; 1 = Sensibile, aumentata esposizione (l'esportazione dipende da dose, modalità, intervallo di somministrazione dell'agente antimicrobico e distribuzione nel sito di infezione); R = resistente; SDD = Sensibile Dose-Dipendente

Table 2. CD4+ count trend.

Lymphocytes	Range	October 2022	November 2022	December 2022	January 2023
T3 (CD3+) count, n/mmc	860-2607	409	846	842	968
T4 (CD4+) count, n/mmc	493-1666	6	6	7	14
T8 (CD8+) count, n/mmc	22-1122	376	798	804	919
T3 (CD3+) %	60-87	85.14	92.43	91.41	91.6
T4 (CD4+) %	32-61	1.25	0.71	0.76	1.3
T8 (CD8+) %	14-43	78.22	87.22	87.26	86.97

transferred to our hospital as highly specialized in hematological malignancies. On admission, she was persistently febrile and complained of abdominal pain. Colonoscopy and gastroscopy were carried out, but no suspected lesions were found.

Rifampicin was switched to rifabutin (300 mg per os, once daily) due to fewer drug interactions. Suspecting PTCL and given the unclear histological finding, we performed a bone marrow biopsy: no evidence of lymphoproliferative process was found, but culture grew positive for MAC, demonstrating the extension of the opportunistic infection.

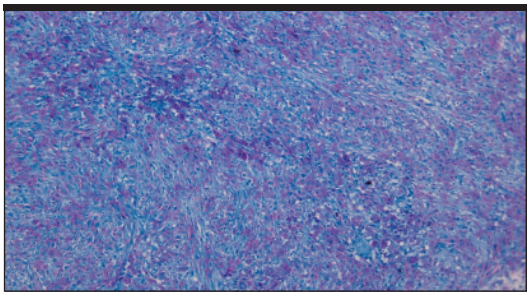
Considering the severe immunosuppression and the persisting fever, she also underwent magnetic resonance imaging (MRI) of the brain to exclude infectious foci or cerebral comorbidities, without pathological findings.

Clinically, high-grade fever persisted, and blood cultures remained positive despite treatment with active drugs, therefore amikacin (750 mg i.v., once daily) was added and continued for a total of 8 weeks.

An FDG-PET scan was repeated, confirming the multiple lymphadenopathies previously described. A new supraclavicular lymph node was extracted, showing massive presence of acid-fast bacilli (AFB) at the histological examination. (**Figure 2**)

Since lack of clinical improvement after 2 months of treatment, therapeutic drug monitoring (TDM) of her MAC therapy was requested to rule out a potential intestinal malabsorption: normal serum concentrations were observed for ethambutol, while rifabutin was underdosed (97 ng/ml; range 300-900) and therefore escalated to 450 mg per os, once daily. A new control after 1 month of adjusted dosage showed improved serum concentrations (261 ng/ml). A switch from rifabutin to clofazimine was attempted, but rapidly interrupted because of liver toxicity.

Figure 2. Histological examination of the supraclavicular lymph node, showing massive presence of acid-fast bacilli (AFB).



Also considering the possibility of drug-induced fever, all antimicrobials were stopped for 12 consecutive days. However, as no clinical improvement was observed, antimicrobial therapy has been restarted.

A new immune-virological staging was carried out at month 1, 2, 3 and 4 from ART start, showing a very slow increase in the CD4+ count (**Table 2**) despite a suppressed viral load, excluding the hypothesis of ART inefficacy or malabsorption.

Computed tomography (CT) scan of the thorax and abdomen were also repeated, describing colliquation of hilar and mediastinal lymph nodes, indicating persistence of uncontrolled disseminated infection.

Hospital stay was complicated by two relapses of SARS-CoV-2 infection, promptly and effectively treated with antiviral agents; follow-up PCR tests remained positive up to 6 months from the first episode, showing ineffective viral clearance in the setting of severe immunological alteration.

Given the persistent positivity for MAC at blood culture controls and the lack of clinical improvement with well-tolerated low-grade fever after 4 months of therapy, the patient expressed the desire to be discharged. Follow-up visits were scheduled in our out-patient clinic.

Discussion

The case here described represents a disseminated M.avium complex (dMAC) infection with blood culture persistence in a severely immunocompromised patient.

It is well known that HIV patients with low CD4 count (<50 cells/mm3) carry the highest risk for dMAC infection (3).

Despite effective treatment, dMAC remains an independent predictor of death in AIDS patients (4).

Current CDC guidelines indicate primary regimens of treatment with combination therapies including a macrolide plus ethambutol. Clarithromycin is the preferred first agent, but azithromycin is considered a valid alternative in case of drug-drug interactions or intolerance (5). Given the rapid development of macrolide resistance, their use in monotherapy is contraindicated.

A third drug should be especially used in patients with ART failure, high viral loads, or persistent bacteremia, as in our case. Options include rifabutin, a fluoroquinolone, or an injectable aminoglycoside (5).

In particular, macrolides represent the treatment cornerstone and are the only drugs, together with amikacin, for which a clinical correlation between in vitro activity and clinical response has been demonstrated (6).

It is well established that the most important factor for treatment outcome is the control of the underlying HIV infection. Our patient belongs to the so-called immunological non-responders (INRs), i.e. patients without a significant increase in CD4+ count despite a suppressed HIV load (7).

Several factors are known to influence CD4+ cell count recovery, including age, gender, transmission route, initial CD4 count, clinical stage, changes in the treatment regimen, and comorbidities (4, 8). Among the reasons for her difficult immune reconstitution, we certainly considered the low number of CD4+ cells at the start and the long-standing HIV infection.

Studies have shown how MAC infection itself worsens the clinical course of HIV patients (9, 10). Lattuada et colleagues (9) showed that MAC infection before the start of HAART, as in our patient, can affect CD4+ cell recovery. There are several factors involved: first of all, MAC bone marrow invasion impairs erythropoiesis and granulocytopoiesis (11). Secondly, the host response to mycobacteria produces immunosuppressive cytokines and releases soluble factors inhibiting erythroblastic progenitors (12).

In addition, macrophage MAC infection induces the expression of Fas ligand, which is a known activator of T lymphocytes apoptosis (13).

Since the lack of clinical response in our patient, we also performed therapeutic drug monitoring (TDM) of her MAC therapy. Data supporting PK/PD targeted dosing are insufficient and drug susceptibility is highly variable (14). As its role is still unclear, routine use of TDM is generally not recommended but should be considered in selected cases, e.g. treatment failure or HIV-coinfection (5).

Conclusion

Despite the low incidence of dMAC in the post-ART era, physicians treating AIDS patients must always be aware of this serious opportunistic infection.

Given the known effects of MAC on immune reconstitution, early and aggressive antiretroviral therapy is functional to treatment success and should therefore be started as early as possible. ■

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