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CASE REPORT

A challenging case of SARS-CoV-2- AIDS and Nocardiosis coinfection from the SMatteo COVID-19 Registry (SMACORE)

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SUMMARY

The COVID-19 pandemic is posing an unprecedented threat worldwide. One issue that has faltered, though, concerns the underestimated risk to trade all for COVID-19, misdiagnosing other potentially life-threatening diseases. Further still, the presence of respiratory symptoms in AIDS patients should stimulate more vigilant efforts to uncover other or additional infections. This case report highlights the pitfalls of diagnosing a rare pulmonary infection during the COVID-19 pandemic.

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INTRODUCTION

Pneumonia related to acquired immunodeficiency syndrome (AIDS) remains a significant cause of mortality in HIV-infected patients.

A number of pulmonary infections have to be considered when evaluating HIV+ patients with respiratory symptoms; the CD4 count can provide useful information about the type of pulmonary disease to which the patient is potentially susceptible. Besides *Pneumocystis* jirovecii pneumonia (PCP), which accounts for the majority of AIDS-defining opportunistic infection, tuberculosis (TB), bacterial, fungal and viral pneumonia should always be ruled out. Though uncommon, pulmonary infections such as *Nocardia*, *Pertussis* and *Rhodococcus* are to be considered.

Moreover, since the acute respiratory disease (COVID-19) caused by the novel coronavirus SARS-CoV-2 has emerged and spread worldwide, it must necessarily be included in the differential diagnosis pathway, even among the HIV population.

The impact of HIV infection on the natural history of COVID-19 is currently controversial, with some studies suggesting a similar outcome in patients with HIV and in the general population (Karmen-Tuohy *et al*., 2020; Vizcarra P. *et al*., 2020), and others associating HIV infection to a more severe COVID-19 course (Ho H.-E. *et al*., 2020; Gervasoni C. *et al*., 2019; Härter G. *et al*., 2020).

Notably, since cardiovascular diseases and other comorbid conditions associated with severe COVID-19 are frequent among HIV patients, this might be considered a risk factor for a worse outcome.

COVID-19 shares non-specific symptoms with many other frequent respiratory tract infectious diseases caused by bacteria and viruses, many of them that may also progress to severe conditions. Alternative diagnosis during the course of global pandemic might be underestimated and can plunge physicians into serious misconduct. This is particularly true for HIV-infected patients.

Here, we report a very challenging case of an AIDS patient presenting with fever, cough and dyspnea when Policlinico San Matteo Hospital in Pavia, Northern Italy, had been violently struck by the COVID-19 outbreak.

SMatteo COvid19 Registry (SMACORE) is the cohort of patients with a confirmed diagnosis of COVID-19 disease referred to the IRCCS Policlinico San Matteo Hospital in Pavia, Italy, from February 2020 and still ongoing. The SMACORE database includes demographic, clinical laboratory tests, treatment, and outcome data. Ethics approval for observational re-

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search using SMACORE data was obtained from the local ethics committee.

CASE REPORT

A 45-year-old woman was admitted to the Infectious Diseases department of our Hospital, IRCCS Policlinico San Matteo in Pavia, Northern Italy, with a 10-day history of fever (axillary body temperature of 40°C), cough and dyspnea.

Her past medical history revealed intravenous drug abuse and HIV/HCV coinfection 28 years before the admission. Unfortunately, since she felt healthy, the patient discontinued highly active antiretroviral therapy (HAART) around 10 years before admission.

On general inspection, she appeared fatigued. She had a temperature of 39°C, blood pressure of 140/80 mmHg and heart rate of 92 beats per minute. Her respiratory rate was 24 breaths per minute with a capillary oxygen saturation reading of 94% on room air.

Chest examination revealed bilateral basal crackles, while abdominal and hearth examinations did not yield any contributory information.

The patient also presented multiple and painful subcutaneous lumps throughout the trunk and limbs.

The initial hospital laboratory tests showed an elevation in C reactive protein (CRP), D-Dimer, Interleukin-6-10-1-8 and Lactate dehydrogenase (LDH) values. In addition, the patient had a significant neutrophilic leukocytosis (*Table 1*).

Due to the epidemiological risk and suggestive clinical and laboratory findings, a nasopharyngeal swab was performed and the transcriptase-polymerase chain reaction (RT-PCR) for acute respiratory syndrome coronavirus 2 (SARS-CoV-2) returned positive.

A chest X-ray revealed bilateral basal thickenings without pleural effusion (*Figure 1a*).

Oxygen therapy with nasal cannulae-delivering (low) flow rates of 4 L/min was then provided.

According to the T-lymphocyte subset panel, which showed a CD4 cell count of 6 cells/µl and a CD4/CD8 ratio of 0.0, the patient was diagnosed with AIDS (CDC stage 3) (Schneider E et al., 2008), and HAART with Dolutegravir and Emtricitabine/Tenofovir Alafenamide Fumarate was immediately started.

Despite the diagnosis of SARS-CoV-2 infection, it was paramount to investigate for opportunistic infections, primarily *Pneumocystis jirovecii* pneumonia (PCP) and tuberculosis.

Hence, after collecting blood cultures, sputum and urine samples, an empirical antibiotic treatment was started with Piperacillin/Tazobactam (TZP) 4.5 g four times daily and Trimetoprim (TMP) 15–20 mg/kg/day Sulfamethoxazole (SMX) 75-100 mg/kg/day.

A total body CT scan was also performed. It surprisingly showed multiple lesions with a necrotic core localized in the lungs, kidneys and soft-skin tissues; some of them had a peripheral contrast enhancement (particularly in the lungs and muscles); no brain lesions were found (*Figure 1b*).

Moreover, a luminal thrombosis of the renal vein was

Table 1 - *Laboratory findings.*

Laboratory	*Value*	*Misure*	*Reference range*
Interferon gamma (Ig γ)	0.1	pg/mL	<15,6
interleukin-1 (IL-1)	25.75	pg/ml	0-3,9
interleukin-10 (IL-10)	145.16	pg/ml	0-7,8
interleukin-2 (IL-2)	2.70	pg/ml	0-31,2
interleukin-6 (IL-6)	136.52	pg/ml	0-3,1
interleukin-8 (IL-8)	82.35	pg/ml	0-31,2
Tumor necrosis factor alpha	0.10	pg/ml	0-15,6
Leukocytes	23.28	x10^3/ul	4.00-10.00
Neutrophils	21.7	x10^3/ul	2.0-8.0
Lymphocytes	0.8	x10^3/ul	1.5-4.0
LDH	298	mU/ml	125-220
CRP	32.52	mg/dl	<0.5
PCTI	0.67	ng/ml	0.0-0.5
AST	25	U/L	<37
ALT	31	U/L	<41
Creatinine	0.55	U/L	0.80-1.20
eGFR	113.51	mL/min/1.73 m2	
BUN	24	mg/dL	10-50
Albumin	2.1	g/dL	3.5-5.0
INR	1.18		
PT	73	%	70-120

Note: PCTI = Procalcitonin, CRP = C reactive protein, LDH = Lactate dehidrogenasis, IgY = Interferon gamma, IL-1 = interleukin-1, IL-10 = interleukin-10 IL-2 = interleukin-2,IL-6 = interleukin-6, IL-8 = interleukin-8; BUN = Urea nitrogen, GGT = γ-Glutamyl transferase, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase; PT = Prothrombin time ratio; eGFR = estimated Glomerular Filtration Rate.

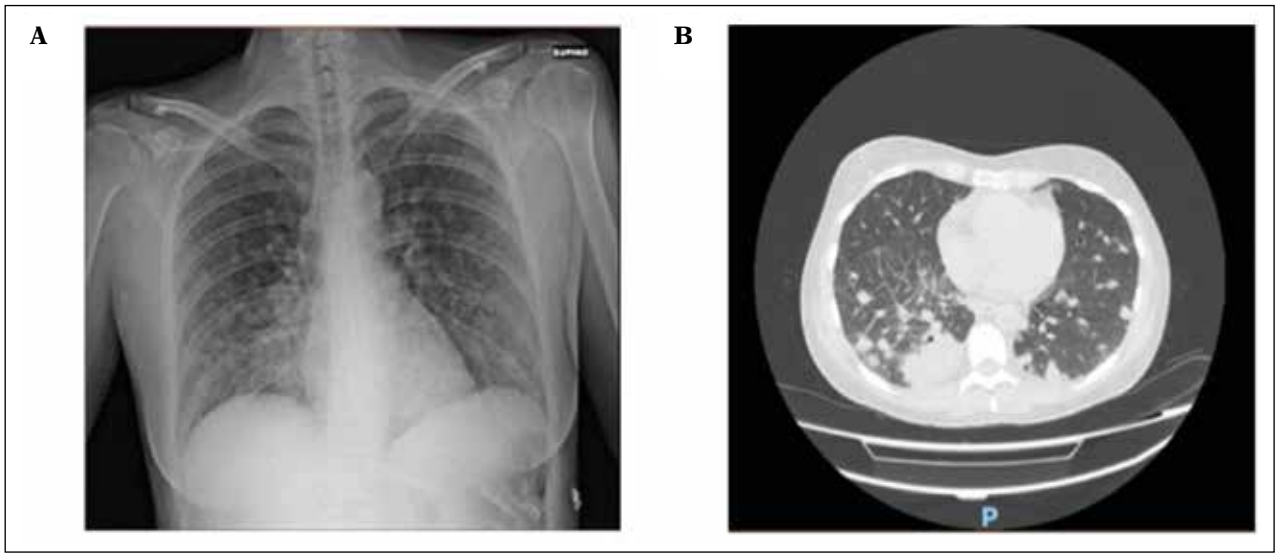

Figure 1 - *Chest radiography thickening and computed tomography images. Chest X-ray shows bilateral basal thickenings, while multiple nodular lesion were detected by CT scan.*

revealed and enoxaparin 6000 UI twice a day was promptly started.

At this point, although SARS-CoV-2 infection had been confirmed, the differential diagnosis became more intricate and a radiological suspicion of metastatic oncological disease also arose. On day 5, an excisional biopsy of one of the subcutaneous lumps was performed and profuse purulent material was drained. Simultaneously, the examination of admission sputum smears and cultures revealed the presence of numerous filamentous gram-positive bacteria (*Figure 2A*).

All these specimens were stained on blood, chocolate and Buffered Charcoal Yeast Extract (BCYE) agar plates and remarkably, they turned positive for growth of *Nocardia s*pp (*Figure 2B*). Positive samples were then identified as *Nocardia cryarcigeorgica* by staining of modified Kinyoun, morphologic evaluation and, since 2014, with Matrix-Assisted Laser Desorption Ionization Time-Of-Flight (MALDI–TOF) mass spectrometry (Microflex LT/SH Bruker Daltonik GmbH, Bremen, Germany), equipped with Bruker biotyper 3.1 software.

Prior to the availability of susceptibility results, the patient was treated with a combination therapy of three drugs: linezolid 600 mg twice daily, TMP/SMX and ceftriaxone 2 g once daily.

Sensitivity tests were performed according to Kirby

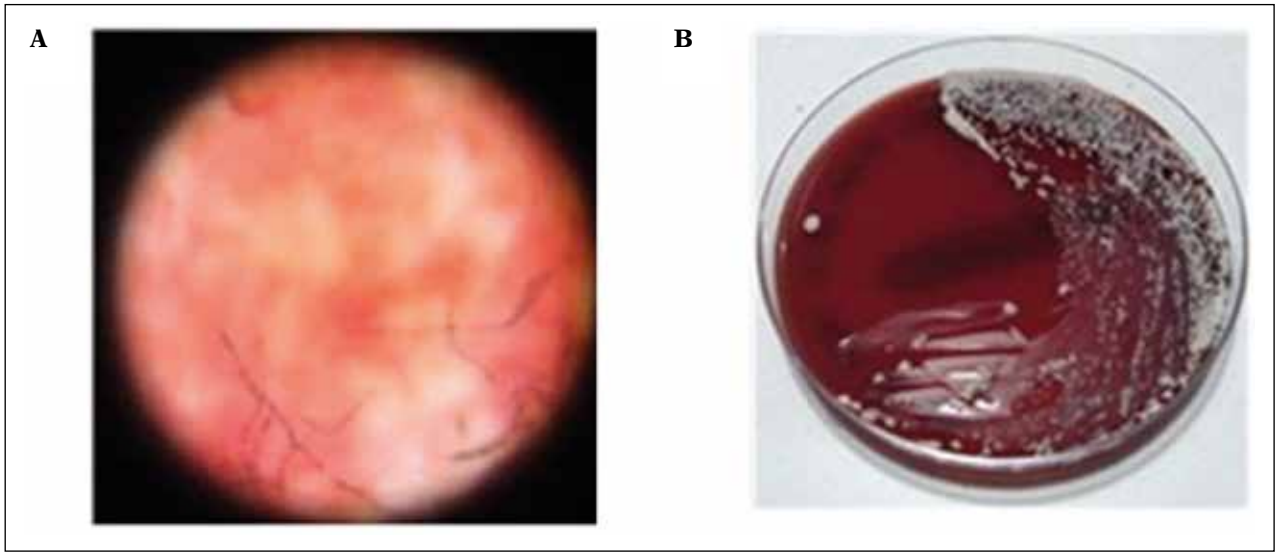

Figure 2 - *Representative images showing the presence of Gram-positive filamentous bacteria (A) and the aspect of Nocardia colonies grown on blood, chocolate and buffered charcoal yeast extract (BCYE) agar plates.*

Bauer and E-test diffusion agar and with Microdilution by the Sensititre System (TREK Diagnostic Systems Waltham, USA), and Minimum inhibitory concentration (MIC) interpretation was performed using breakpoints from Clinical and Laboratory Standards Institute (CLSI).

The susceptibility tests showed a favorable profile for TMP-SMX, amikacin and linezolid but a resistant one for amoxicillin-clavulanic acid, third-generation cephalosporins and quinolones. Therefore, ceftriaxone was replaced with amikacin 1 g daily.

Moreover, due to the persistence of a high fever which was non-responsive to non-steroid anti-inflammatory drugs (NSAIDs), we administered hydrocortisone and the fever finally broke on day 8.

To rule out the occurrence of further unexpected conditions, a bedside bronchoscopy was also performed and lower respiratory fluids turned positive for both *Nocardia cryacigeorgica* and SARS-CoV-2. *Pneumocystis* jirovecii and mycobacteria were not detected. Moreover, CMV-DNA and Cryptococcus spp. antigen was negative in the serum.

After 4 weeks of the aforementioned intravenous therapy, the overall conditions improved. Skin and soft-tissue lesions became less painful and their size slightly decreased; moreover, laboratory results and inflammatory markers improved significantly.

To further confirm this improvement, a CT scan was again performed on day 28, and showed a near-complete resolution of the lung, kidney and soft tissue lesions.

Notably, the patient was found to have a persistent positive nasal swab for SARS-CoV-2. The patient finally tested negative on day 41.

To avoid the dreaded myelotoxic effect of linezolid, the patient was dismissed with a one-week oral tedizolid. After that, the plan was to continue the antibiotic therapy for at least 1 year, during which frequent follow-up visits were scheduled. Furthermore, the patient was referred to the outpatient HIV clinic of our hospital.

DISCUSSION

It is currently uncertain if and how HIV infection impacts on the natural history of COVID-19.

Even though HIV-associated comorbid conditions have been found to hamper the severity of COVID-19, it is currently unknown whether these confounding features rather than HIV infection itself contribute to a worse COVID-19 outcome (Meyerowitz EA et al., 2020; Sigel K et al., 2020).

Several clinical trials failed to demonstrate a worse outcome in people with HIV who developed COVID-19, compared to individuals without HIV (Parks LS. *et al.*, 2020), while other cohort studies found HIV-SARS-CoV-2 coinfected patients at higher risk for ICU admission and death (Dandachi D. *et al.*, 2020). Furthermore, the demographic and clinical characteristics of patients with HIV and COVID-19 were similar to those reported in the general population (Sivaporn Gatechmpol *et al.*, 2021). Based on the available literature, Interim Guidance for COVID-19 and Persons with HIV recommend only close monitoring for this condition, especially for those patients with advanced HIV or other comorbidities (Department of Health and Human Services (HHS): Interim guidance for COVID-19 and persons with HIV, 2021). Although further studies are critically needed, in a small report CD4 cell count was not associated with severe COVID-19 among patients with HIV (Ho H.-E. *et al.*, 2020).

However, the majority of these individuals had a CD4 cell count >200 cells/μL. Hence, the real effect of host immune status on SARS-CoV-2 infection also remains uncertain and experience in AIDS patients like ours is definitively lacking.

Zhao et al. reported that their HIV patient showed an early clearance of the SARS-CoV-2 RNA, which had persistently remained undetectable on the nasal swab during hospitalization (Zhao J. *et al.*, 2019). The authors suggested that activated type I interferon (IFN) might have helped the suppression of SARS-CoV-2 (Tang X *et al.*, 2020).

In our case, type I IFN was low (*Table 1*) and the patient had very delayed clearance of SARS-CoV-2 RNA. In fact, her nasopharyngeal swab tested positive for more than 1 month after admission and eventually returned negative on day 41.

What is striking about this report, however, is that despite the long course, COVID-19 itself remained indolent and didn't require any high-flow supplement of oxygen. Moreover, no treatment for COVID-19 was administered. but instead, a low-dose hydrocortisone (100 mg twice a day), which was effective in prompt defervescence.

Currently available data from the literature seem to suggest that the clinical course of COVID-19 could be similar in HIV-infected patients with well-controlled disease and in the general population. Indeed, very few data are available for patients with advanced HIV infection and AIDS, and no firm conclusions on COVID-19 prognosis can be drawn for this subset of patients (Cooper T.J. *et al.*, 2019). In spite of the already determined SARS-CoV-2 diagnosis, our perception was that something else was behind the patient's clinical and radiological condition. Since perceptions are always to be corroborated in medical practice, we looked beyond what might have seemed obvious. Our case is paradigmatic and demonstrates that several opportunistic infections can be simultaneously observed in patients with advanced HIV infection and low CD4 count. As a consequence, a complete diagnostic workflow should be pursued in such patients in order to exclude concomitant opportunistic infections. In our case, such a workflow al-

lowed us to diagnose systemic nocardiosis.

Nocardiosis is an uncommon condition even in AIDS patients with a CD4 count below 200 cells (Pintado V. *et al.*, 2003; Uttamchandani RB et al., 1994). Probably, since a TMP-SMX prophylaxis to prevent PCP is routinely administered in such patients, they concurrently receive a prophylaxis for nocardiosis.

The genus Nocardia includes more than 80 species, 30 of which could affect humans. Specifically, the Italian scenario of nocardiosis is hardly described. In the available retrospective studies on this subject N. asteroides and N. farcinica have often been identified as the predominant species over the years (Farina C. *et al.*, 1995; Farina C. *et al.*, 2001; Mazzaferri F. *et al.*, 2018).

Differently, N. cryiacigeorgica accounted for 23.5% of 1119 Nocardia strains identified in Spain over a 10-year period (Valdezate S. *et al.*, 2017) and 13% of the 765 Nocardia strains submitted to the United States Centers for Disease Control and Prevention (CDC) (Udhe K.B. *et al.*, 2018). N. cryiacigeorgica is therefore rarely reported, at least in Italy.

Our case was considered severe nocardiosis, which usually includes all cases of disseminated disease with more than one site involved. In such a case, despite the lack of data supporting the antimicrobial treatment "of choice" and its optimal duration, a combination therapy rather than single-drug regimen for at least 12 months is generally recommended (Brown-Elliott B.A. *et al.*, 2006; Lerner P.I. *et al.*, 1996).

The outcome of Nocardia infection may be significantly influenced by the extent of the disease, but also by underlying conditions, since mortality is substantially increased in immunocompromised hosts (Lebeaux D. *et al.*, 2017; Steinbrink J. *et al.*, 2018). Nevertheless, a majority of good outcomes resides in early and effective therapy (Peleg A.Y. *et al.*, 2007).

Strikingly, the patient reacted more than well to the lengthy antibiotic treatment during hospitalization and promptly improved. No adverse drug effect was detected. Beforehand, due to the well-known myelotoxic effect of long-term linezolid and TMP/SMX combination treatment, tedizolid was off-label requested for 1 week only. Afterwards, she will continue a single-drug regimen based on TMP/SMX tablets.

Despite limited evidence on prolonged therapy, the experience of tedizolid in the treatment of pulmonary nocardiosis is promising (Giménez-Arufe V. *et al.*, 2019) due to its excellent oral bioavailability and good in-vitro activity (Brown Elliott B.A. *et al.*, 2017).

This case has been a startling surprise to all of us. On the one hand, it provided an opportunity to speculate on challenging differential diagnoses in the rough times of a global pandemic and, on the other, to review nocardiosis management.

Many questions still remain about COVID-19 and possibly even more about its impact on immunosuppressed patients like ours.

Although a close follow-up will continue for a long time, so far and against all the expectations, the course of this intricate case has been thoroughly favorable.

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