Infection in an Immunocompromised Patient, the Perfect Costume in Which to Hide

Néstor López Guerra, Pedro Castro Rebollo, and Elena Sancho Ferrando

Contents

D. Pérez-Torres et al. (eds.), *Best 2022 Clinical Cases in Intensive Care Medicine*, Lessons from the ICU,
https://doi.org/10.1007/978-3-031-36398-6_2

2

Learning Objectives

- Highlight the importance of the differential diagnosis of complications in severe immunocompromised patients.
- To learn about the antibiotic stewardship in a patient with AIDS admitted to the ICU.
- To be aware of the potential side effects of treatment and how to deal with them in a critical ill patient.
- To deal with the fragility and specific difficulties of intensive treatment of an immunocompromised patient in ICU.

2.1 Introduction

Human immunodeficiency virus (HIV) infection is a health care issue, with a global prevalence up to 37 million. There is still a high HIV-related mortality, especially in those patients with advanced-stage infections. With the development of new treatments with less adverse events, progression of patients to acquired immunodeficiency syndrome (AIDS) stage has decreased in the past decades. Nevertheless, 21.3% of patients diagnosed in 2016 in the United States (US) were already in this advanced stage [1]. Up to 10% of all HIV-infected hospitalized patients require admission to the Intensive Care Unit (ICU), mainly due to HIV-related infections, complications of antiretroviral treatment (ART), and also HIV-unrelated diseases [2].

With this case, we aim to point out the relevance of an extended differential diagnosis of the medical complications in a critically ill immunocompromised patient, such as those with AIDS-stage HIV infection.

Case Presentation

A 61 years-old male, former smoker, recently discharged from hospital after 9 days of stay due to a *Pneumocystis jirovecii* pneumonia (PCP), and consequently diagnosed of HIV in AIDS stage. He had 6 CD4+ cells/mm^3 and a viral load of 1,350,000/mm^3. Trimethoprim/sulfamethoxazole (TMP/SMX) 320/1600 mg three times a day plus steroids on tapering dose were started, as well as ART with bictegravir/emtricitabine/tenofovir alafenamide 50/25/200 mg once a day, being discharged after 9 days of admission.

Three days after finishing steroid treatment and 8 days after discharge, under correct TMP/SMX treatment, the patient developed new fever, and he consulted to the Emergency Department. On arrival, he was eupneic, with no respiratory insufficiency, mild hypotension (blood pressure of 88/56 mmHg, mean arterial pressure of 67 mmHg) without hypoperfusion signs, and afebrile. Physical examination showed preserved status, with mild rhonchi limited to the right hemithorax on pulmonary auscultation with no other relevant findings. Chest X-ray showed worsening of previous bilateral infiltrates. Main results on blood tests were C-reactive protein of 19 mg/dL (normal range (NR) less than 1 mg/dL), lactate dehydrogenase of 353 U/L (NR less than 234 U/L), and

lymphocyte count of 100/mm^3 (NR 900–4500/mm^3). Same dose of TMP/SMX, 40 mg of methylprednisolone twice a day and empiric treatment with ertapenem 1 g once a day and anidulafungin 200 mg followed by 100 mg once a day was started, and patient was readmitted to the hospital.

Once in the medical ward, high-resolution thorax computed tomography (CT) was performed showing bilateral infiltrates, with signs of organizing pneumonia (Fig. 2.1). Bronchoscopy was performed and showed a quantitative decrease in *Pneumocystis* cysts in the bronchoalveolar lavage (BAL). During the hospital stay, the microbiologist reported the isolation of *Mycobacterium avium intracelulare* (MAI) in a sputum culture from the previous admission, and treatment with azithromycin 500 mg once a day, rifampicin 600 mg once a day, ethambutol 800 mg once a day, and levofloxacin 500 mg once a day was added.

After four days, the patient developed rapid respiratory worsening. He showed an increased respiratory rate and respiratory effort, needing a non-rebreather mask. Arterial blood gas (ABG) showed pH 7.44, pCO_2 27.1 mmHg, and pO_2 98.7 mmHg; PaO_2/FiO_2 ratio was 99. He was transferred to the ICU to start high-flow nasal cannula therapy (HFNC) with 65% FiO_2 and 45 L per minute.

The initial diagnosis was acute respiratory distress syndrome due to MAI untreated infection and persistence of PCP, in context of immune reconstitution inflammatory syndrome, in a severe immunocompromised patient after recent ART initiation. Treatment with TMP/SMX, high-dose steroids, azithromycin, rifampicin, ethambutol, and levofloxacin was continued. However, the patient was persistently febrile and progressive respiratory worsening was observed, needing intubation and mechanical ventilation. The patient required a low-moderate dose of norepinephrine infusion (0.3 μcg/kg/min) mainly because of sedation. Initial mechanical ventilation settings were volume-controlled mode with protective lung ventilation: tidal volume 300 mL (5 mL/kg of predicted body weight), 28 breaths per minute, positive end-expiratory pressure (PEEP) of 14 cmH_2O, and

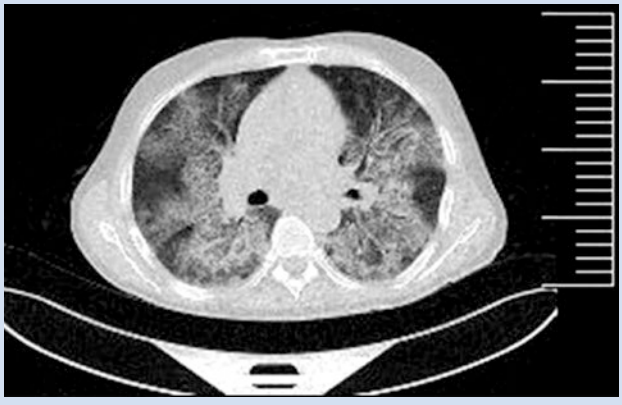

Fig. 2.1 High-resolution thorax CT showing extensive opacities in ground glass and some consolidative foci with bilateral perihilar septal thickenings with a "crazy paving" pattern

2

FiO_2 50%, with plateau pressure of 30 cmH20. ABG showed a permissive hypercapnia (pH 7.30, pCO_2 55) and pO_2 of 104 mmHg, which led to decrease in FiO_2. The clinical team decided to perform another high-resolution thorax CT that showed stable bilateral infiltrates but with a mild increase of organizing pneumonia signs. At this point, bronchoscopy was performed again, resulting in a polymerase chain reaction (PCR) test positive for cytomegalovirus (CMV) (viral load 432 UI/mL) in BAL with no macroscopic relevant findings. That results were coincident with serum CMV PCR (viral load 1500 UI/mL). It was decided to start foscarnet 4500 mg twice a day instead of ganciclovir because of persistent pancytopenia, but the patient remained feverish without any other microbiological findings. After 20 days from ICU admission, sudden anisocoria was found on the physical examination, and two tonic-clonic seizures were observed.

2.2 Investigations

Cranial CT: Hypodensities in both corona radiata, a subacute hyperdensity on right parietal lobe, and a nodular hyperdensity on left parietal lobe.

Blood cultures: 15 blood cultures repeatedly negative.

Cerebrospinal fluid (CSF) analysis: Hyperproteinorrhachia with no pleocytosis and no hypoglycorrhachia. PCR was positive for herpes virus 8 and negative for the rest of microorganisms tested (*E. coli* K1, *L. monocytogenes*, *H. influenzae*, *N. meningitis*, *S. pneumoniae*, *S. agalactiae*, CMV, herpes simplex virus 1, herpes simplex virus 2, human herpes virus 6, varicella-zoster virus, JC virus, and *Cryptococcus neoformans*). CSF culture and bacilloscopy were negatives. CSF cytology showed mild inflammatory infiltrate compound by lymphocytes and polymorphonuclear leukocytes, with no atypical cells.

Electroencephalogram: Beta activity and diffuse delta slowing, without asymmetries or epileptiform activity.

Cranial magnetic resonance imaging (MRI) (Fig. 2.2): Cortical and juxtacortical multiple lessons on cerebellum, parietal, frontal, occipital, and posterior temporal lobes, with contrast-enhancing focus and microbleeding signs, and a more extensive lesion on right parietal lobe with gyral enhancement, compatible with cerebritis.

Transesophageal echocardiography: Mitral vegetations (up to 5 × 8 mm size) and aortic vegetation, with mild mitral and aortic regurgitation. No ventricular dysfunction, no pericardial effusion.

Beta-d-glucan (BDG) assay: Positive (NR < 2.9 pg/mL): 582.8 (day 1), 330.2 (day 4), 346 (day 8), 128.2 (day 16),101.1 (day 21), 61.2 pg/mL (day 28).

Aspergillus galactomannan antigen: Negative on serum and BAL.

Positron emission tomography (PET) scan: Diffuse pulmonary hypermetabolism and focal hypermetabolism on *gluteus maximus* muscle.

***Gluteus maximus* muscle biopsy**: Negatives culture, bacterial 16S rRNA sequencing, and fungal 18S rRNA sequencing. Cytology negative for malignance.

Atypical bacteria serologies: Negative for *Chlamydia*, *Coxiella,* and *Brucella*.

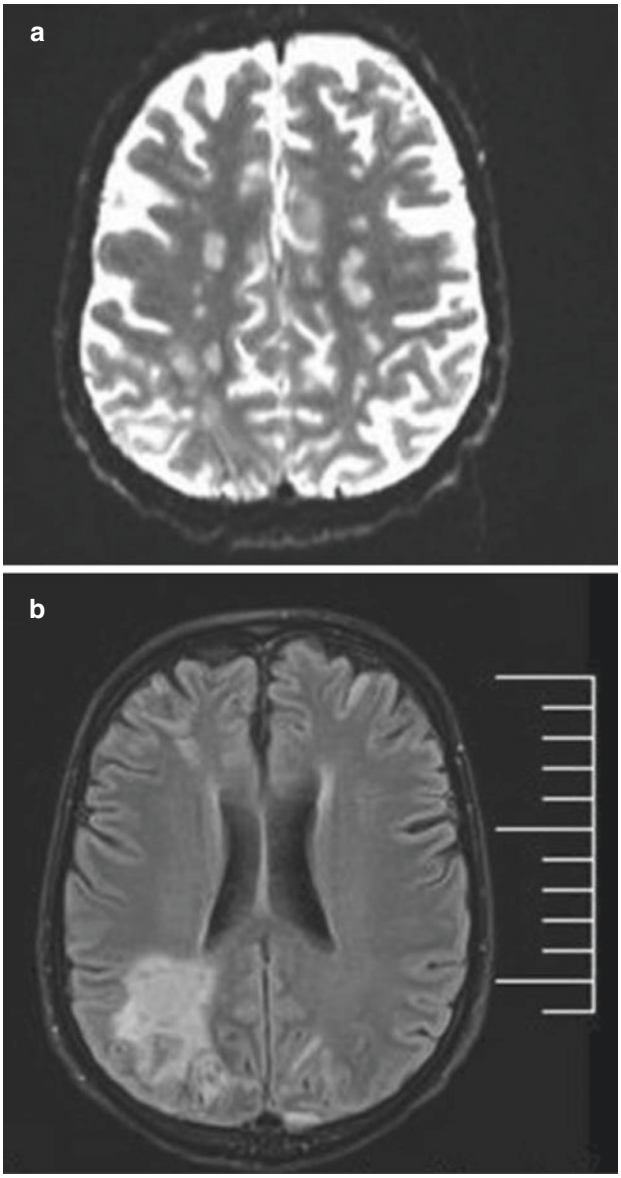

Fig. 2.2 **a** Diffusion-weighted magnetic (DWI) MRI sequence showing multiple cortical and juxtacortical ischemic lessons. **b** Fluid-attenuated inversion recovery (FLAIR) MRI sequence showing an extensive lesson on right parietal lobe with gyral enhancement

2.3 Differential Diagnosis

Fungal endocarditis.
Bacterial endocarditis (HACEK group bacteria).
MAI endocarditis.
Marantic endocarditis.

2.4 Treatment

2

2.4.1 Nonpharmacological Treatment

Mechanical ventilation on volume-controlled mode with a permissive hypercapnia strategy because of high inspiratory and plateau pressures. Maximum FiO_2 50%.

2.4.2 Pharmacological Treatment

Neurological: Sedoanalgesia with remifentanil (maximum dose 0.533 mcg/kg/min) and propofol (maximum dose 3.2 mg/kg/h). Neuromuscular blockade with cisatracurium (maximum dose 5.9 mcg/kg/h). Antiepileptic treatment with levetiracetam 1000 mg twice a day.

Cardiovascular: Low-dose norepinephrine (less than 0.1 mcg/kg/min), which was withdrawn once sedoanalgesia was tapered.

Renal: Intravenous furosemide up to 60 mg/day to reach neutral balance.

Digestive/nutritional: Full-dose enteral nutrition with protein supplementation; occasional need for prokinetic treatment because of low gastric emptying.

Infectious: Endocarditis empiric treatment with meropenem 1 g three times a day, doxycycline 100 mg twice a day, teicoplanin 400 mg 3 doses separated by 12 h followed 400 mg once a day, and anidulafungin 200 mg followed by 100 mg once a day. Antiviral treatment switch from foscarnet to ganciclovir 5 mg/kg twice a day to include herpes virus 8 coverage and ART switch from Bictegravir/emtricitabine/tenofovir alafenamide to dolutegravir/emtricitabine/tenofovir disoproxil 50/200/245 mg once a day in order to avoid pharmacological interactions. Methylprednisolone was progressively tapered to 20 mg once a day. TMP/SMX for PCP and azithromycin, rifampicin, ethambutol, and levofloxacin for MAI infection stayed without changes.

2.5 Evolution, Outcome, and Follow-up

Because of cranial CT findings and persistent fever, endocarditis was suspected and transesophageal cardiac ultrasound showed vegetations on both mitral and aortic valves with mild valvular regurgitation. Broad-spectrum antibiotic treatment was initiated including anidulafungin due to a high-titer positive BDG test. Up to 15 blood cultures were extracted with negative results, and *Chlamydia*, *Coxiella,* and *Brucella* serologies were negative. PET scan showed diffuse pulmonary hypermetabolism and focal hypermetabolism on *gluteus maximus* muscle, therefore muscle biopsy was performed. It showed a negative result on cultures, bacterial 16S rRNA sequencing, and fungal 18S rRNA sequencing, with unspecific inflammatory infiltrate on the anatomopathology study.

Because of the absence of microbiological findings in repeated blood cultures and the decrease on BDG titers on subsequent tests, AIDS-related noninfective endocarditis was diagnosed. Anidulafungin and broad-spectrum antibiotic treatment were withdrawn and therapeutic TMP/SMX was changed to prophylactic dosage (160/800 mg three times a week) when negative galactomannan test was obtained and no hyphae were found at bronchoalveolar lavage.

After two weeks, the patient developed a clinical improvement that led to the sedation withdrawal and to pass to HFNC as respiratory support. Once awaken, physical examination showed persistent anisocoria and severe symmetric myopathy without other neurological focality.

Rehabilitation was initiated, and silver tracheostomy cannula was able to get occluded. Finally, after 73 days since the admission to the ICU, the patient was discharged to the medical ward to continue the treatment. Once on medical ward, nosocomial COVID-19 infection was detected, and the patient rapidly developed clinical worsening. In consensus with his family, the medical team decided to withhold life-sustaining measures, and finally the patient died 5 months after the hospital admission because of respiratory failure.

2.6 Discussion

The incidence of infective endocarditis (IE) has risen in HIV-infected patients and is associated with a high mortality [3]. Noninfective endocarditis (NIE), also known as nonbacterial thrombotic endocarditis or marantic endocarditis, is a rare condition associated with inflammatory and hypercoagulable states such as malignancy, autoimmune diseases, and HIV infection [4]. Berlot et al. described an incidence of 1% of NIE in ICU population [5]. Systemic embolism is the main manifestation, being cerebral emboli such as those we saw in our case the least common.

Diagnostic work-up requires excluding infective endocarditis, including atypical organisms. That require serial negative blood cultures (the number of negative blood cultures rose up to 15 in our case), atypical serologies, and even molecular tests on tissue [4], such as the bacterial 16S rRNA and the fungal 18S rRNA sequencing we performed on *gluteus maximus* muscle tissue. Our patient's clinical status did not allow to perform a mitro-aortic vegetation biopsy.

As a new diagnostic technique on bloodstream infections, beta-D-glucan assay seems to be reliable as an aid to early diagnosis of candidemia and allows a prompt start of antifungal treatment. However, due to the existence of false positives, its result should be interpreted cautiously and be supported by another diagnostic test [6].

In conclusion, a structured diagnostic work-up and a prompt response against acute infections are important for the ICU clinicians, especially when dealing with severely immunocompromised patients such as AIDS-stage HIV-infected patients.

Take-Home Messages

- Taking into account of host susceptibility, a structured diagnostic work-up could help diagnose opportunistic infections in the critically ill HIV-infected patient.
- Noninfective endocarditis (NIE) is an exclusion diagnosis that requires serial negative blood cultures, negative serology for atypical microorganisms, and even molecular test on tissue to rule out unusual causes of IE.
- Indirect tests such as beta-D-glucan assay could help in the early diagnosis of invasive fungal infections, but it should not exclusively guide the treatment.

Summary

A 61-year-old male, recently diagnosed with HIV infection in AIDS stage due to a *Pneumocystis jirovecii* pneumonia (PCP), reconsulted because of fever. Worsening of previous bilateral infiltrates on chest X-ray and inflammatory signs on blood test were observed. With the suspicion of PCP relapse, steroids were restarted, as well as empiric antibiotic and antifungal treatment.

A quantitative decrease of *Pneumocystis* cysts on BAL was found, but *Mycobacterium avium intracelulare* was identified in a sputum culture from the first admission, therefore specific treatment was started. Nevertheless, the patient developed a respiratory worsening that led him to ICU admission under invasive mechanical ventilation. Positive PCR test for cytomegalovirus in BAL and serum was detected, thus foscarnet was initiated. However, he remained feverish and sudden anisocoria and seizures appeared. Cranial CT scan showed multiple ischemic injuries; therefore, with the endocarditis suspicion, transesophageal cardiac ultrasound was performed showing mitro-aortic vegetations. Antibiotherapy was initiated, as well as antifungal treatment because of positive beta-d-glucan (BDG) assay, being both stopped after repeatedly negative blood cultures and a decrease on BDG levels, with the noninfective endocarditis diagnosis.

TMP/SMX was reduced to prophylactic dosing after negative galactomannan test was obtained and hyphae presence in BAL was excluded. Rehabilitation was initiated, and silver tracheostomy cannula was successfully occluded. Finally, the patient was discharged to the medical ward to continue the treatment, where he finally died 5 months after the hospital admission due to nosocomial COVID-19 infection.

References

1. Centers for Disease Control and Prevention. Monitoring Selected National HIV Prevention and Care Objectives by Using HIV Surveillance Data, United States and 6 Dependent Areas, 2018 [cited 2020 Oct 12]. https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-25-2.pdf
2. Maphula R, Laher A, Richards G. Patterns of presentation and survival of HIV-infected patients admitted to a tertiary-level intensive care unit. HIV Med. 2020;21:334–41.
3. Giannitsioti E, Pefanis A, Gogos C, Lekkou A, Dalekos GN, Gatselis N, et al. Evolution of epidemiological characteristics of infective endocarditis in Greece. Int J Infect Dis. 2021;106:213–20.

4. Hurrell H, Roberts-Thomson R, Prendergast BD. Non-infective endocarditis. Heart. 2020;106(13):1023–9.
5. Berlot G, Calderan C, Fiorenza C, Cappelli D, Addesa S, Bussani R. Infective and non-infective endocarditis in critically ill patients: a clinical–pathological study. Intern Emerg Med. 2014;9(7):773–8.
6. Del Bono V, Delfino E, Furfaro E, Mikulska M, Nicco E, Bruzzi P, et al. Clinical performance of the (1,3)-β- D -glucan assay in early diagnosis of nosocomial candida bloodstream infections. Clin Vaccine Immunol. 2011;18(12):2113–7.