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Two pandemics intertwined around one patient: Interstitial pneumonia as the first presentation of HIV/AIDS, be it *Pneumocystis jirovecii*, cytomegalovirus, SARS-CoV2 or all?-A case report

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ABSTRACT

Concerns have been mounting regarding the underdiagnosis of HIV among respiratory co-infections associated with the COVID-19 pandemic. The delay in recognizing HIV/AIDS may be attributed to the similarities in clinical, laboratory (lymphopenia) and imaging presentations, which are typical for advanced AIDS but could also be indicative of a COVID-19 infection.

Herein, we present a case of a 38-year-old ultraorthodox Jew with a late diagnosis of AIDS in the context of COVID-19 infection. This occurred after several months of recurrent respiratory infections compounded by SARS-COV 2 infection, during which no HIV testing was conducted. As a result, a cascade of various opportunistic infections ensued, leading to an extended hospitalization period, ultimately culminating in the patient's demise despite receiving optimal treatment.

1. Introduction

While HIV diagnosis is widely availed worldwide, there is still a deferment of diagnosis in individuals who do not belong to classical risk groups, particularly in conservative communities where awareness is limited due to a lack of sexual education and scarce information.

As 30% [1] of AIDS cases presenting with respiratory manifestations, concerns have arisen regarding delays in diagnosing HIV and respiratory coinfections during the COVID-19 pandemic. The delay may arise from the resemblance of clinical and imaging presentations, as well as from lymphopenia, which is typical for advanced AIDS but could also be indicative of COVID-19 infection.

Here, we present a case of a 38-year-old ultraorthodox Jew with a late HIV diagnosis after experiencing several months of recurrent respiratory infections. No HIV test was performed during this time, and the patient presented with co-infections of SARS-CoVs, *and Pneumocystis jirovecii*, leading to an extended hospitalization course that, unfortunately, resulted in death.

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2. Case presentation

A 38-year-old ultra-orthodox Jewish male was initially diagnosed as suffering from an asymptomatic COVID-19 infection, given contact with a patient and confirmation by a PCR test (Fig. 1A). After four months, he presented with atypical community-acquired-pneumonia (CAP) and received oral treatment comprising cefuroxime and azithromycin. Following this treatment and a seemingly uneventful recovery, he experienced another episode of CAP three months later, for which he was retreated with antibiotics. As he did not improve clinically, he was evaluated by a pulmonologist who referred him to preform chest computed tomography and hematological consultation due to neutropenia and lymphopenia. One week later, due to persistent clinical symptoms with a fever spike of 39.0°c, he was reassessed in the emergency room and diagnosed with a recurrent COVID-19 infection (Cycle threshold (CT) value of 20). Since his oxygen saturation was within normal limits, and pulmonary embolism was ruled out by computed tomography pulmonary angiography, he was advised to continue home quarantine for 10 days. Regrettably, two weeks later, his clinical symptoms have worsened, leading to his admission to the COVID unit.

Upon his admission (Fig. 1B) the patient was afebrile, featured a normal blood pressure (105/69 mmHg), but presented with tachypnea at a rate of 32 breaths per minute, and was desaturated (85%0_2 at room air) necessitating oxygen support, first through a nasal cannula and then via a facial mask. The physical examination revealed diffuse bilateral crepitation. Laboratory tests indicated a mild leukopenia (white blood cell count of 3.1K with a low lymphocyte count (300) and a normal neutrophil count (2500), normocytic anemia with a hemoglobin level of 11.8 GR%, and elevated C-reactive protein (14.75 mg/dL, normal <0.5), ferritin (1353 ng/mL, normal range 22–322), and d-dimers (1.52 mg/L, normal 0–0.44). A second PCR test for COVID-19 was positive, (CT value 27.2) while chest radiography revealed diffuse bilateral infiltrates, most pronounced in the lower lobes (Fig. 2A).

The patient's condition was classified as severe COVID-19. He received dexamethasone as treatment and did not receive Remdesivir due to his long-standing illness. Given the atypical clinical course and severity of his second COVID-19 episode, he was evaluated for immune deficiency, with HIV coming back positive. Further evaluation noted no CD4 cells at peripheral blood, coupled with a HIV viral load (VL) of 255,000 copies/ml. Despite convalescent plasma not being proven beneficial in immunocompetent COVID-19 patients, the patient was administered two units of convalescent plasma due to his severe immune suppression and very low anti-S titer (119.8 AU/ml, positive >50 AU/ml). Chest computed tomography scan initially indicated infiltrates related to COVID-19 (Fig. 2B–D), but later reevaluated to feature specific radiological findings (peri-hilar predominance and basal sparing) suspicious of atypical pathogens such as *Pneumocystis jirovecii* (PJ). Bronchoscopy confirmed the presence of multiple silver-stained cysts of PJ in the bronchoalveolar lavage (BAL) fluid (Fig. 3A–B). Galactomannan in the lavage fluid was negative, and CMV viral load was 8700 copies/ml but was negative in peripheral blood. Following bronchoscopy, the patient's condition deteriorated, and he became hemodynamically unstable, confused, and increasingly desaturated, requiring higher respiratory support through high-flow nasal cannula (HFNC) with 65% oxygen. He was transferred to the COVID-ICU and treated with a high dose of trimethoprim-sulfamethoxazole, fluconazole, vancomycin and meropenem. Two days later, as cultures did not indicate any another pathogenic growth and his condition stabilized, all treatments were discontinued, except for trimethoprim–sulfamethoxazole and steroids. A week later, antiretroviral therapy-bictegravir/emtricitabine/tenofovir/alafenamide (Biktarvy) was initiated, resulting in transient clinical improvement followed, 5 days later, with progressing respiratory distress (necessitating a maximal HFNC support with a PaO2 of 75 mm), agitation, reemerging fever and further elevation of CRP. SARS-CoV2 viral load (VL) did not improve (CT value 21.5), leading to the administration of two additional units of convalescent plasma and a 10-day course of remdesivir, which did not favorably impact the SARS-

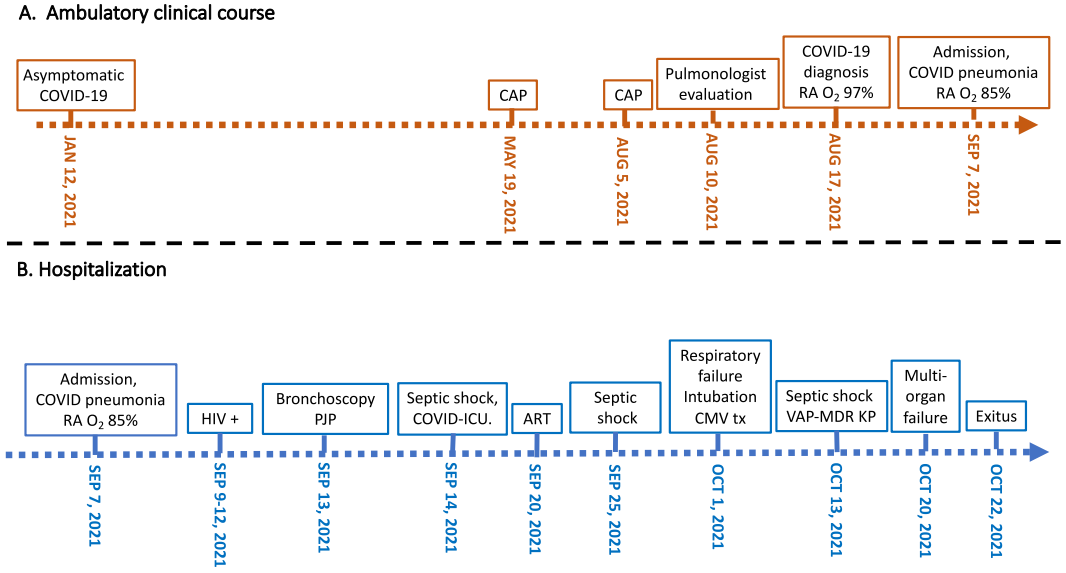

Fig. 1. Time line of the clinical course. (A) Course before admission, (B) course from admission to death.

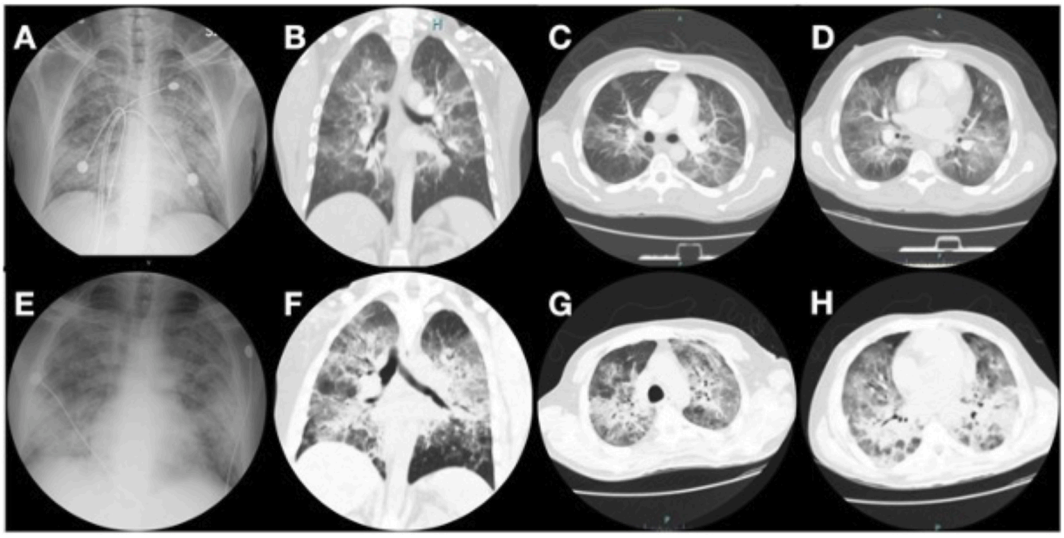

Fig. 2. Imaging-Chest X-ray and CT scan of the lung upon patient admission (A to D), indicating bilateral consolidations which worsened two weeks later (E to H).

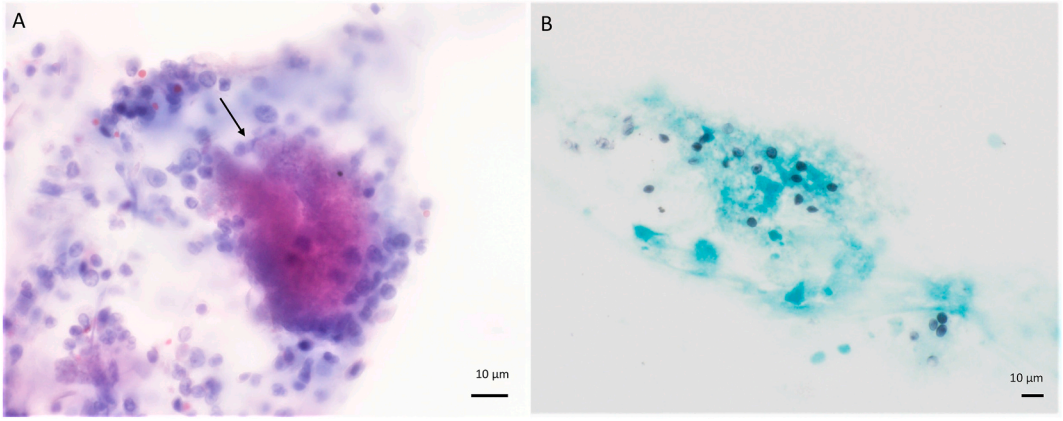

Fig. 3. Pathology-Bronchial lavage specimen was examined using Papanicolaou and Grocott methenamine silver stains. (A) Papanicolaou stain shows distinctive casts of frothy proteinaceous debris containing collections of encysted sporozoites. Scale bar = 10 μm. (B) Grocott methenamine silver highlights numerous crescent-shaped cysts containing a nucleolus, diagnostic of pneumocystis carinii pneumonia. Scale bar = 10 μm.

CoV2 viral load. Respiratory failure ensued, requiring mechanical support, and chest radiography was notable for a worsening lung consolidations (Fig. 2D–H). The patient was empirically treated for CMV with Ganciclovir, coupled with high-dose solumedrol for suspected immune reconstitution inflammatory syndrome (IRIS), or SARS-CoV2 related inflammation. A day later, he was found to be viremic with 200,000 copies of CMV per ml, treated by nitric oxide and proning to improve oxygenation and ventilation, but did not improve. A ventilator associated pneumonia resulted in multidrug-resistant *Klebsiella pneumonia* sepsis, which was treated with broad-spectrum antibiotics (meropenem & colistin) for 10 days. Despite some clinical and laboratory improvement, the patient continued to experience severe respiratory failure, partly due to progression into fibrotic stage COVID-19, and gradually developed multi-organ failure including renal, gastrointestinal tract, and bone marrow dysfunction, leading to the patient's demise 53 days after admission.

3. Discussion

3.1. HIV and COVID 19

Interaction between COVID-19 and HIV infections has been the subject of intense investigation over the past 2.5 years, aiming to determine whether HIV is a risk factor for increased mortality from COVID-19, and identifying risk factors in HIV patients for the development of severe COVID pneumonia. Sigel et al. [2] assessed 88 people living with HIV (PLWH) who were hospitalized due to COVID-19 during a 5-week period in 2020 in New York. No differences in outcome were noted between admitted PLWH and the

case-control group, suggesting that the outcome for HIV patients infected with SARS-CoV2 may not be different from that of the general population.

A year later, Geretti et al. [3] reviewed the medical records of 122 PLWH in the UK who were admitted to the hospital with COVID pneumonia. Demographics and outcomes wee compared to a control group of 47,400 HIV negative individuals admitted with COVID pneumonia. Analysis revealed that COVID-19-admiteed PLWH were significantly younger, had fewer co-morbidities, and presented with more systemic symptoms as compared to infected HIV-negative controls. After adjusting for age, the risk of mortality was found to be 47% higher in the HIV group.

3.2. Similarity of PJP and SARS-CoV2

Pneumocystis jirovecii (PJP) is a well-known pathogen causing opportunistic infections in HIV patients and is considered the most common life-threatening pulmonary infection in AIDS. PJP and COVID-19 often have similar presentations and may overlap in imaging studies [4] (Fig. 4A–C and D–F respectively). Additionally, both infections are associated with lymphopenia (80% in COVID-19 [5] and 49.1% of HIV [6]). As a result, PJP infection may be masked, especially in immunosuppressed patients, upon co-infection with SARS-CoV-2.

Mang [7], Baht [8], Broadhurst [9], Anggraeni [10], Rubiano [11] and Blanco [12] reported cases similar to ours, stressing the possibility of a delayed HIV and PJP diagnosis, masked by SARS-COV-2 infection. Coleman et al. [4] described a case of a well-controlled HIV patient who was initially diagnosed with PJP, thereby missing the COVID-19 co-infection diagnosis, which was later made using a multiplex PCR. Cases of COVID-19 and PJP coinfection in non-immune suppressed patients (not treated with steroids due to COVID-19) [13], indicate that immune suppression and dysregulation induced by SARS-CoV-2 [5] may play a contributing role in the pathogenesis of PJP. Additionally, the British guidelines by the National Institute for Health and Care Excellence (NICE) recommend HIV testing in all hospital admissions for suspected CAP and in anyone with suspected PJP. As these admitted patients are likely to be also suspected to be suffering of COVID-19, the British HIV Association (BHIVA) has called for HIV testing of all suspected COVID-19 cases requiring hospitalization [14].

3.3. CMV and AIDS

The role of CMV as a primary pulmonary pathogen in AIDS patients is controversial [15]. Paradoxically, CMV virions are found in respiratory secretions of 19%–43% of HIV patients, and in 37%–53% of patients suffering of PJP. As lung tissue damage is not proportionally associated with CMV titers [16], CMV identified in respiratory secretions is considered a bystander in AIDS patients, thus

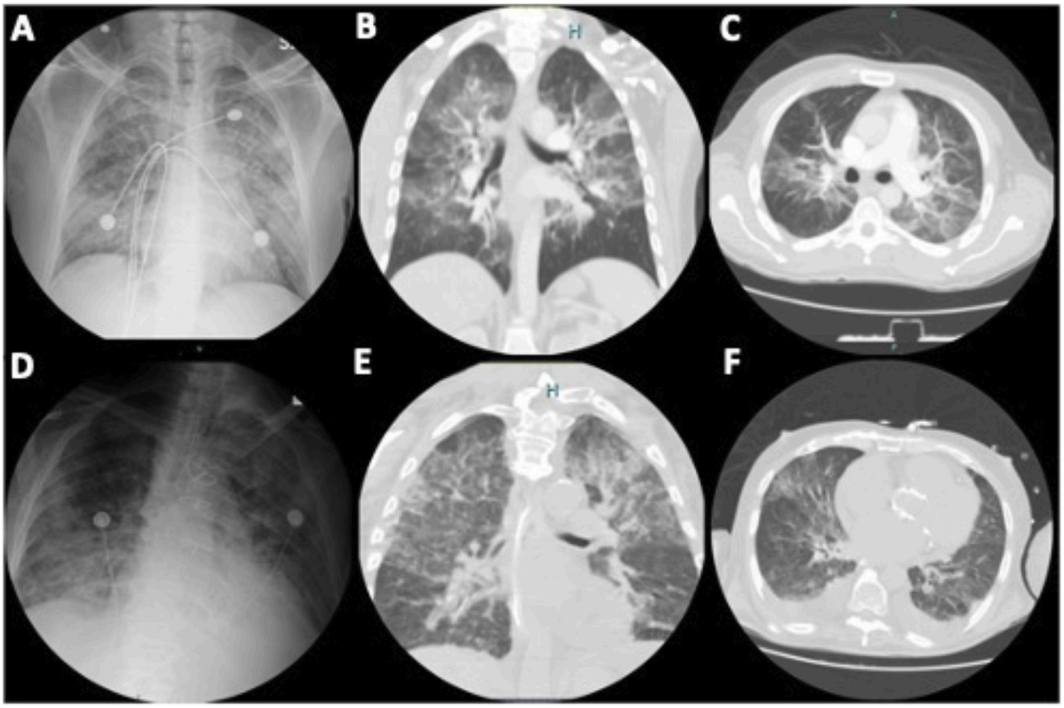

Fig. 4. COVID19 vs PJP imaging. A comparison of chest imaging of the index patient (A–C) and a different COVID 19 patient (D–F) illustrating the central predominance of PJP infiltrates and the peripheral predominance of SARS-CoV-2 infiltrates. A + D-AP chest X rays, B + E chest CT (coronal), C + F (sagittal).

the American guidelines recommend searching for a more likely causative pathogen in this context [17]. In contrast of other immunosuppressed patients, such as solid organ and hematological stem cell transplant recipients, targeted anti CMV treatment remains debated in HIV patients.

3.4. HIV late presenters

Means of making an earlier diagnosis in this case included testing of the patient's wife (diagnosed as HIV+ in parallel to the patient) during her previous pregnancies, 10 and 5 years earlier. Only recently has the Israeli Ministry of health recommendations been adapted to the global WHO recommendation of screening every pregnant woman for HIV infection, regardless of risk factors. Levy et al. [18] reported in a retrospective observational Israeli cohort study, that 33·4% of newly diagnosed HIV between 2010 and 2015 were late presenters (LP-CD4 less than 350 cells/μL) and 16% featured an advanced HIV-related disease. Age above 50 and heterosexuality were risk factors for a delay in diagnosis. For 47 patients who were diagnosed with AIDS, there were overall 65 episodes of missed opportunities of diagnosing HIV in the 5 years preceding diagnosis. Similar observation were made by Powell et al. Much higher rates of HIV late presenters were reported during 2011–2020 by the European Centre for Disease Prevention and Control in Albania (69%) Armenia (62%) Denmark (61%) and Italy (60%) [19]. The late presentation resulted in a higher adjusted mortality rate ration of 1·71 and a 9-fold higher incidence of AIDS-events/deaths within 1 year of HIV-diagnosis [20]. Israel constitutes of a mosaic of religions and cultures, characterized by two large conservative communities-religious Jews (composed of ultra-orthodox, religious, or traditional communities) and local Arabs. In these communities, HIV awareness is limited owing to a lack of sexual education and deterred information, attributing two additional risk factors for late HIV diagnosis. As universal screening is not cost effective in these communities due to low endemicity,improving physician awareness to HIV, while accounting for cultural sensitivities, may optimize HIV eradication efforts.

Informed consent was obtained from the wife of the patient, as the patient had passed away.

4. Conclusion

Underdiagnosis of HIV in the context of co-occurring respiratory infections pose a substantial challenge during the COVID-19 pandemic, due to similarities in clinical, laboratory, and imaging presentations, resulting in a delayed diagnosis, prevention, and treatment of HIV [14]. More vigorously HIV screening of every atypical pneumonia or admitted case of COVID19 as suggested NICE and BHIVA is needed [14]. HIV underdiagnosis is especially prevalent among individuals who do not fit into the typical HIV risk groups, and those belonging to conservative communities whose awareness of HIV remains limited. Improving physicians' awareness of subtle and early manifestations of HIV may enable earlier diagnosis and treatment, thus preventing further transmission and clinical complications.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] M.R. Gingo, G.K. Balasubramani, T.B. Rice, L. Kingsley, E.C. Kleerup, R. Detels, E.C. Seaberg, R.M. Greenblatt, S. Holman, L. Huang, et al., Pulmonary symptoms and diagnoses are associated with HIV in the MACS and WIHS cohorts, BMC Pulm. Med. 14 (2014) 75, https://doi.org/10.1186/s12879-020-05261-7.

[2] K. Sigel, T. Swartz, E. Golden, I. Paranjpe, S. Somani, F. Richter, J.K. De Freitas, R. Miotto, S. Zhao, P. Polak, et al., Coronavirus 2019 and people living with human immunodeficiency virus: outcomes for hospitalized patients in New York city, Clin. Infect. Dis. 71 (11) (2020) 2933–2938, https://doi.org/10.1093/cid/ciaa880.

[3] A.M. Geretti, A.J. Stockdale, S.H. Kelly, M. Cevik, S. Collins, L. Waters, G. Villa, A. Docherty, E.M. Harrison, L. Turtle, et al., Outcomes of coronavirus disease 2019 (COVID-19) related hospitalization among people with human immunodeficiency virus (HIV) in the ISARIC World health Organization (WHO) clinical characterization protocol (UK): a prospective observational study, Clin. Infect. Dis. 73 (7) (2021) e2095–e2106, https://doi.org/10.1093/cid/ciaa1605.

[4] H. Coleman, L.B. Snell, R. Simons, S.T. Douthwaite, M.J. Lee, Coronavirus disease 2019 and Pneumocystis jirovecii pneumonia: a diagnostic dilemma in HIV, AIDS 34 (8) (2020) 1258–1260, https://doi.org/10.1097/QAD.0000000000002571.

[5] B. Xu, C.Y. Fan, A.L. Wang, Y.L. Zou, Y.H. Yu, C. He, W.G. Xia, J.X. Zhang, Q. Miao, Suppressed T cell-mediated immunity in patients with COVID-19: a clinical retrospective study in Wuhan, China, J. Infect. 81 (1) (2020) e51–e60, https://doi.org/10.1016/j.jinf.2020.04.012.

[6] S. Parinitha, M. Kulkarni, Haematological changes in HIV infection with correlation to CD4 cell count, Australas. Med. J. 5 (3) (2012) 157–162, https://doi.org/10.4066/AMJ.20121008.

[7] S. Mang, D. Kaddu-Mulindwa, C. Metz, A. Becker, F. Seiler, S. Smola, A. Massmann, S.L. Becker, C. Papan, R. Bals, et al., Pneumocystis jirovecii pneumonia and severe acute respiratory syndrome coronavirus 2 coinfection in a patient with newly diagnosed HIV-1 infection, Clin. Infect. Dis. 72 (8) (2021) 1487–1489, https://doi.org/10.1093/cid/ciaa906.

[8] P. Bhat, M. Noval, J.B. Doub, E. Heil, Concurrent COVID-19 and Pneumocystis jirovecii pneumonia in a severely immunocompromised 25-year-old patient, Int. J. Infect. Dis. 99 (2020) 119–121, https://doi.org/10.1016/j.ijid.2020.07.061.
[9] A.G.B. Broadhurst, U. Lalla, J.J. Taljaard, E.H. Louw, C.F.N. Koegelenberg, B.W. Allwood, The diagnostic challenge of pneumocystis pneumonia and COVID-19 co-infection in HIV, Respirol. Case Rep. 9 (4) (2021), e00725, https://doi.org/10.1002/rcr2.725.
[10] A.T. Anggraeni, S. Soedarsono, B. Soeprijanto, Concurrent COVID-19 and Pneumocystis jirovecii pneumonia: the importance of radiological diagnostic and HIV testing, Radiol. Case Rep. 16 (12) (2021) 3685–3689, https://doi.org/10.1016/j.radcr.2021.09.002.
[11] C. Rubiano, K. Tompkins, S.A. Sellers, B. Bramson, J. Eron, J.B. Parr, A.J. Schranz, Pneumocystis and severe acute respiratory syndrome coronavirus 2 coinfection: a case report and review of an emerging diagnostic dilemma, Open Forum Infect. Dis. 8 (1) (2021) ofaa633, https://doi.org/10.1093/ofid/ofaa633.
[12] J.L. Blanco, J. Ambrosioni, F. Garcia, E. Martinez, A. Soriano, J. Mallolas, J.M. Miro, C-iH. Investigators, COVID-19 in patients with HIV: clinical case series, Lancet HIV 7 (5) (2020) e314–e316, https://doi.org/10.1016/S2352-3018(20)30111-9.
[13] A.A. Menon, D.D. Berg, E.J. Brea, A.J. Deutsch, K.K. Kidia, E.G. Thurber, S.B. Polsky, T. Yeh, J.A. Duskin, A.M. Holliday, et al., A case of COVID-19 and pneumocystis jirovecii coinfection, Am. J. Respir. Crit. Care Med. 202 (1) (2020) 136–138, https://doi.org/10.1164/rccm.202003-0766LE.
[14] S. Kelly, L. Waters, M. Cevik, S. Collins, J. Lewis, M.S. Wu, T.J. Blanchard, A.M. Geretti, Pneumocystis pneumonia, a COVID-19 mimic, reminds us of the importance of HIV testing in COVID-19, Clin. Med. 20 (6) (2020) 590–592, https://doi.org/10.7861/clinmed.2020-0565.
[15] A.B. Millar, G. Patou, R.F. Miller, J.E. Grundy, D.R. Katz, I.V. Weller, S.J. Semple, Cytomegalovirus in the lungs of patients with AIDS. Respiratory pathogen or passenger? Am. Rev. Respir. Dis. 141 (6) (1990) 1474–1477, https://doi.org/10.1164/ajrccm/141.6.1474.
[16] C. Uberti-Foppa, F. Lillo, M.R. Terreni, A. Puglisi, M. Guffanti, N. Gianotti, A. Lazzarin, Cytomegalovirus pneumonia in AIDS patients: value of cytomegalovirus culture from BAL fluid and correlation with lung disease, Chest 113 (4) (1998) 919–923, https://doi.org/10.1378/chest.113.4.919.
[17] Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new.Acceseed 27.7.23.
[18] I. Levy, Y. Maor, N. Mahroum, L. Olmer, A. Wieder, V. Litchevski, O. Mor, G. Rahav, Missed opportunities for earlier diagnosis of HIV in patients who presented with advanced HIV disease: a retrospective cohort study, BMJ Open 6 (11) (2016), e012721, 10.1136/bmjopen-2016- 012721.
[19] HIV/AIDS surveillance in Europe. https://www.ecdc.europa.eu/en/publications-data/hiv-aids-surveillance-europe-2021-2020-data, 2021. Accessed 27.7.23.
[20] Late presentation working groups in Euro S, cohere: Estimating the burden of HIV late presentation and its attributable morbidity and mortality across Europe 2010-2016, BMC Infect. Dis. 20 (1) (2020) 728, https://doi.org/10.1186/s12879-020-05261-7.