Case report

A rare case of CMV pneumonia in HIV-infection

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A B S T R A C T

Cytomegalovirus (CMV) pneumonia is a rare opportunistic infection in the setting of HIV (Human Immunodeficiency Virus)-infection. Establishing accurate diagnosis of CMV pneumonia in HIV-infection can be challenging. Co-infections by multiple opportunistic pathogens are common and a high degree of clinical vigilance to evaluate for multiple infections, including CMV pneumonia, should be maintained. As there can be a degree of overlap in clinical and radiological features amongst different opportunistic infections affecting the lungs, definitive microbiological and cytohistologic evidences are needed. Reliance on microbiological evidence of CMV in respiratory specimens alone for the diagnosis of CMV pneumonia will lead to an over-diagnosis of the condition and unnecessary treatment.

In our case report, we describe a 53-year-old man with recently diagnosed HIV-infection who presented with non-resolving pneumonia. A diagnosis of CMV pneumonia was reached through consistent clinical, radiological, microbiological and cytologic investigations. The patient made a full clinical recovery after being started on *anti*-CMV treatment.

1. Introduction

Human cytomegalovirus (CMV) is a ubiquitous double-stranded DNA virus belonging to the Herpesviridae family. Primary infection by CMV is usually asymptomatic as the intact immune system limits active viral replication effectively. Initial infection by CMV can rarely cause a self-limiting mononucleosis-like illness associated with fever, fatigue, myalgias and hepatosplenomegaly. However, CMV is capable of multiple immune evasion mechanisms [1,2] and complete eradication of the virus may not be achieved. Instead, the virus remains quiescent within endothelial cells, stem cells of the bone marrow and peripheral blood monocytes, establishing a lifelong latent infection. The seroprevalence of CMV varies greatly between races and population groups [3]. Older age, low socio-economic status, lower education levels and HIV-infection were most commonly associated with greater CMV seroprevalence [4,5].

When the immune system is suppressed, latent CMV can reactivate and replicate rapidly. This can result in high levels of CMV viremia and infection of multiple organ systems. The populations who are most at risk of CMV infection are the individuals with active haematological malignancies, HIV infection, recipients of hematopoietic stem cell transplant or solid organ transplant and individuals on significant immunosuppressive therapy for autoimmune disorders and connective tissue disease [6]. CMV infections are also increasingly recognised amongst critically ill patients in intensive care units, the majority of whom are immunocompetent prior to illness [7,8].

In the advanced stages of HIV infection, T-Helper cell function is

impaired and there is a decline of the adaptive immune response which is crucial to CMV disease control. Prior to the use of highly active antiretroviral therapy (HAART), the prevalence of CMV opportunistic infection (OI) in acquired immune deficiency syndrome (AIDS) was very high. Up to 90% of patients with AIDS were found to have evidence of disseminated CMV infection at time of autopsy [9].

The predominant manifestation of CMV in HIV-infection is CMV retinitis, affecting up to 40% of patients and accounting for 85% of all CMV related complications [10–12]. The other organs that are affected by CMV disease in AIDS include the gastrointestinal tract, peripheral and central nervous system, liver, kidneys, adrenals and lungs [12,13].

The advent of HAART in the 1990s has resulted in a substantial decrease in incidence of severe OI caused by CMV in AIDS [14]. CMV OI typically occurs in individuals presenting with AIDS-defining illness and possessing a CD4 lymphocytes count of below 100/μl. In a large epidemiological study of AIDS-defining opportunistic OI from 18,733 HIV-infected residents diagnosed from 1993 to 2008, only 0.6% had CMV infection as the initial OI and there were nil reports on CMV pneumonia [15].

Herein, we describe a very rare case of CMV pneumonia and review the literature on diagnosing this rare clinical entity in HIV-infected patients.

2. Case

A 53-year-old heterosexual man presented with fever and worsening dyspnoea over a period of 3 days. He had no history of intravenous drug

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use, tattoos or previous blood transfusions. This was his second presentation to an acute care hospital within the past month. He had initially presented to the emergency department of another hospital 3 weeks ago, with symptoms of dry cough and dyspnoea of 1-month duration. HIV serology performed then was positive and he received treatment for bacterial and presumptive *Pneumocystis jirovecii* (PJP) pneumonia. Subsequently, his respiratory symptoms improved and he was discharged with oral trimethoprim-sulfamethoxazole without corticosteroids.

At his second presentation, he was febrile at 39.2 °C and hypoxemic with pulse oximetry readings of 90% on ambient air. Initial chest radiograph [Fig. 1a] suggested bilateral middle and lower zone pneumonia. Laboratory investigations confirmed the diagnosis of AIDS and presence of a high level of CMV viremia [Table 1]. He was started on empirical treatment for bacterial and PJP pneumonia with IV piperacillin-tazobactam, trimethoprim-sulfamethoxazole and corticosteroids. Despite so, his fever and respiratory symptoms failed to improve.

The differentials for our patient's recurrent presentation and failure to response to treatment include nosocomial pneumonia, other HIV-associated opportunistic infections (OI), and immunological reaction to PJP treatment.

A computed tomography (CT) scan of the thorax revealed findings consistent with infection by a atypical pulmonary pathogen. [Fig. 1b and c].

Bronchoscopy with bronchoalveolar lavage (BAL) was performed to aid in establishment of a microbiological diagnosis for the current episode of non-resolving pneumonia.

Bacterial culture from BAL revealed the presence of *Escherichia coli* and *Klebsiella pneumoniae which were both susceptible to piperacillin-tazobactam*. Polymerase chain reaction (PCR) tests for a panel of respiratory viruses and opportunistic pathogens were positive for human coronavirus, rhinovirus, cytomegalovirus (CMV) and weakly positive for PJP. PJP microscopic examination performed on BAL was negative. This suggested a very low PJP load which was consistent with the history of recent PJP treatment. Cytologic examination of the BAL specimen revealed viral cytopathic changes consistent with CMV infection [Fig. 2].

With a CD4 cell count of 12 cells/UL and a clinical diagnosis of AIDS, our patient is a susceptible host for CMV reactivation disease. Clinically, he exhibited new symptoms of severe respiratory illness with hypoxemia while on anti-bacterial and PJP treatment. His laboratory investigations were not suggestive of an acute bacterial pneumonia process. CT thorax findings of patchy ground-glass attenuation with bilateral sub-centimetre centrilobular nodules and airspace consolidation is consistent with a pneumonitis process.

Taking into account the clinical, radiological, microbiological and cytology findings, a diagnosis of CMV pneumonia was established and our patient was started on *anti*-CMV treatment with intravenous ganciclovir. His symptoms of fever and hypoxemia resolved after 5 days of

Table 1
Pertinent laboratory investigations at presentation.

Investigations	Values	Reference range
Haemoglobin	10.8g/dL	14–18.0g/dL
White blood cell count	5.09 x 10^9/L	4.00–10.00 x 10^9/L
Absolute neutrophils	4.12 x 10^9/L	2.00–7.50 x 10^9/L
Procalcitonin	0.14 μg/L	≤0.49 μg/L
C-reactive protein	48.1mg/L	0.2–9.1 mg/L
absolute CD4 count	12 cells/UL	256–1594 cells/UL
CD4/CD8 ratio	0.11	0.7–2.5
HIV-1 RNA Load	132,410IU/ml	
CMV IgG Total Antibody	Positive	
CMV Quantitative PCR	87,857 IU/ml	

treatment. Subsequent *anti*-CMV treatment was converted to a 3 week course of oral valganciclovir. HAART was started after 2 weeks of CMV treatment to minimise the likelihood of an immune reconstitution inflammatory syndrome.

3. Discussion

Despite the decreasing incidence of CMV OI in AIDS, CMV remains a significant pathogen due to its propensity to interact with HIV and its systemic immunomodulatory effects. In the evaluation of an individual presenting with AIDS, a high level of clinical vigilance for CMV infection should be maintained.

Amongst patients with HIV, the presence of CMV is associated with an increased risk of developing neurocognitive, cardiovascular or cerebrovascular diseases. Hence, CMV may indirectly lead to greater overall mortality from non-AIDS related illnesses [16–21]. The co-infection of CMV and HIV promotes a persistent subclinical inflammatory state through the alteration of T-cell responses [22,23]. Endothelial and smooth muscle cells are stimulated to produce increased amounts of pro-angiogenic factors and inflammatory cytokines. This leads to an upregulation of atherosclerosis and vascular degeneration rate within the body [23–25].

CMV can potentiate the pathogenicity of HIV by activating HIV proviral DNA, increasing the intracellular transport of HIV transactivation proteins and effecting CD8 T cell function. With increasing levels of CMV viremia, HIV viral replication activity also increases. Increased CMV activity invariably leads to a hastened clinical progression to AIDS and an increase in AIDS-related mortality [26–31].

The pathogenicity of CMV in the lungs of HIV-infected host is also a subject of much interest. Children with HIV infection and CMV DNAemia of more than 1000 copies/ml were found to have impaired lung function. The presence of CMV in the lungs may have precipitated recurrent episodes of sub-clinical pneumonitis and bronchiolitis, leading to the loss of lung function [32]. Infants and children who had positive CMV serology were found to have a specific IFN-y T cell response that was associated with a greater risk of developing active tuberculosis [33, 34].
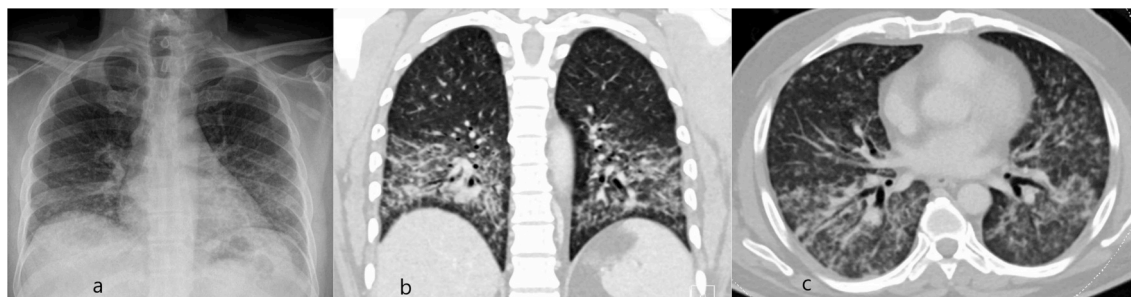

Fig. 1. Radiological images of CMV pneumonia. a: Initial chest radiograph showing bilateral diffuse airspace infiltrates over the middle and lower zones. b: CT scan of the thorax showing peri-bronchovascular consolidation predominantly affecting bilateral lower lobes of the lungs. c: CT scan of the thorax showing consolidation, scattered ground glass opacities and centrilobular pulmonary nodules.
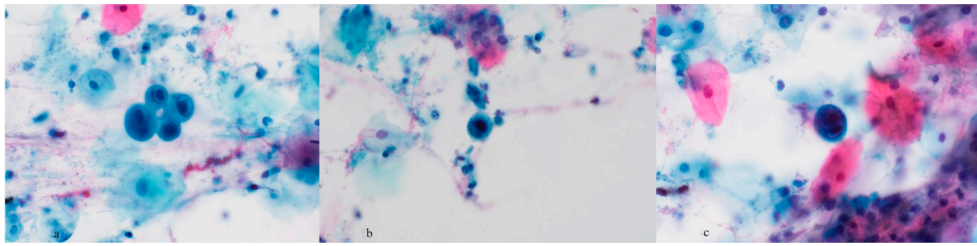
Fig. 2. Cytopathic changes of CMV infection. a: Cells with enlarged nuclei containing basophilic nuclear inclusion surrounded by a halo. b: Granular cytoplasmic inclusions seen. c: Cells with a binucleate appearance and surrounded by a clear Halo.

While bacteria, tuberculosis and PJP remain the commonest causes of pulmonary infections [35], the HIV-infected patient often harbours multiple concomitant OI and is an example where Occam's razor cannot be applied. CMV is a rare but plausible pathogen in the lungs during the advanced stages of HIV-infection. Specific work-up for the presence of CMV pneumonia should be performed if a patient with AIDS fails to respond to empirical bacterial and PJP treatment. The accurate diagnosis of CMV pneumonia during advanced HIV-infection is a challenging process and would mandate the full constellation of consistent clinical, radiological, microbiological and cytohistologic features.

Our case illustrates the continued clinical relevance and utility of BAL in aiding microbiological diagnosis of pulmonary infections during advanced HIV infections, with BAL results yielding positive microbiology for bacterial, viral and fungal microorganisms. The diagnostic yield of BAL in this setting is very high and often leads to treatment modification [36,37].

Microbiological evidence of CMV in respiratory specimens should not be used as the sole diagnostic test for CMV pneumonia during the setting of HIV-infection. The positive PCR assay for CMV from our patient BAL specimen was considered supportive but not diagnostic of CMV pneumonia. Approximately 20–50% of BAL specimens from patients with HIV-infection may test positive for CMV through PCR techniques or growth in culture mediums [38–41]. The detection of CMV in respiratory specimens via these techniques was not associated with increased hypoxemia or mortality, more likely representing asymptomatic viral shedding from airway epithelial cells than pulmonary infection.

Obtaining cytologic or histologic evidence of CMV infection within pulmonary cells and tissue is essential for the accurate diagnosis of CMV pneumonia [42]. CMV has a direct cytopathic effect on infected cells as the virus replicates intra-cellularly. CMV inclusion bodies appears within the nucleus and cytoplasm, causing the infected cells to enlarge. These changes are highly specific for CMV infection.

Demonstration of cytologic and histologic evidence of CMV infection in the lungs is very rare and reported in only 5–8% of HIV-infected patients undergoing bronchoscopy and lung biopsy [38,43,44]. This is consistent with a very low incidence of CMV pneumonia and pneumonitis in the setting of HIV infection. The innate immunity of the lungs, comprising of an intact epithelial surface layer, dendritic cells, macrophages and NK cells is relatively preserved in AIDS and remain effective at repelling CMV pulmonary infection. In addition, significant pneumonitis is unlikely to occur as progressive impairment of the adaptive immune system preclude a damaging inflammatory response to CMV antigens [3,45].

The mainstay of treatment of CMV infection involves immune reconstitution with HAART. HAART causes a rapid decline of HIV load and regeneration of the host immunity which effectively suppresses CMV viral replication and activity [24]. However, as the host immune system is restored, a paradoxical damaging inflammatory response to CMV antigens can ensue. Patients with CMV retinitis and higher CD4 counts who were initiated on HAART therapy were found to have the greatest risk of developing immune recovery vitritis and uveitis [46–48]. Specific CMV therapy may have a role in patients with high level of CMV viremia and symptomatic end organ disease as in the case of our patient.

4. Conclusion

CMV is a very rare cause of pulmonary OI in the setting of HIV-infection. CMV pneumonia should be carefully evaluated amongst patients with AIDS who are critically ill and not responding to treatment of other diagnosed pulmonary infections. The diagnosis of CMV pneumonia can only be made with consistent clinical, radiological, microbiological and cyto-histopathologic features. A high degree of clinical vigilance for this rare clinical entity must be maintained as prompt treatment with *anti*-CMV therapy is effective and can augment clinical recovery.

Declaration of competing interest

The authors of this manuscript have no conflicts of interest of funding to declare with regards to its production.

References

[1] V.C. Emery, Investigation of CMV disease in immunocompromised patients, J. Clin. Pathol. 54 (2) (2001) 84–88, https://doi.org/10.1136/jcp.54.2.84.

[2] J. Sinclair, P. Sissons, Latency and reactivation of human cytomegalovirus, J. Gen. Virol. 87 (Pt 7) (2006) 1763–1779, https://doi.org/10.1099/vir.0.81891-0.

[3] M. Zuhair, G.S.A. Smit, G. Wallis, et al., Estimation of the worldwide seroprevalence of cytomegalovirus: a systematic review and meta-analysis, Rev. Med. Virol. 29 (3) (2019) e2034, https://doi.org/10.1002/rmv.2034.

[4] A.B. Brantsaeter, M. Holberg-Petersen, S. Jeansson, A.K. Goplen, J.N. Bruun, CMV quantitative PCR in the diagnosis of CMV disease in patients with HIV-infection – a retrospective autopsy based study, BMC Infect. Dis. 7 (1) (2007), https://doi.org/10.1186/1471-2334-7-127.

[5] J.B. Jackson, A. Erice, J.A. Englund, J.R. Edson, H.H. Balfour, Prevalence of cytomegalovirus antibody in hemophiliacs and homosexuals infected with human immunodeficiency virus type 1, Transfusion 28 (2) (1988) 187–189, https://doi.org/10.1046/j.1537-2995.1988.28288179029.x.

[6] J. Styczynski, Who is the patient at risk of CMV recurrence: a review of the current scientific evidence with a focus on hematopoietic cell transplantation, Infect. Dis. Ther. 7 (1) (2017) 1–16, https://doi.org/10.1007/s40121-017-0180-z.

[7] G. Aguilar, D. Navarro, The pathogenetic role of CMV in intensive care unit patients: the uncertainity remains, J. Thorac. Dis. 9 (7) (2017) 1780–1782, https://doi.org/10.21037/jtd.2017.06.79.

[8] X. Li, Y. Huang, Z. Xu, et al., Cytomegalovirus infection and outcome in immunocompetent patients in the intensive care unit: a systematic review and meta-analysis, BMC Infect. Dis. 18 (1) (2018) 289, https://doi.org/10.1186/s12879-018-3195-5.

[9] C.M. Reichert, T.J. O'Leary, D.L. Levens, C.R. Simrell, A.M. Macher, Autopsy pathology in the acquired immune deficiency syndrome, Am. J. Pathol. 112 (3) (1983) 357–382, https://www.ncbi.nlm.nih.gov/pubmed/6311021.

[10] M.A. Jacobson, J.J. O'Donnell, D. Porteous, H.R. Brodie, D. Feigal, J. Mills, Retinal and gastrointestinal disease due to cytomegalovirus in patients with the acquired immune deficiency syndrome: prevalence, natural history, and response to ganciclovir therapy, Q. J. Med. 67 (254) (1988) 473–486.

[11] J.T. Holbrook, D.A. Jabs, D.V. Weinberg, et al., Visual loss in patients with cytomegalovirus retinitis and acquired immunodeficiency syndrome before widespread availability of highly active antiretroviral therapy, Arch. Ophthalmol. (Chicago, Ill : 1960) 121 (1) (2003) 99–107, https://doi.org/10.1001/archopht.121.1.99.

[12] K.L. Springer, A. Weinberg, Cytomegalovirus infection in the era of HAART: fewer reactivations and more immunity, J. Antimicrob. Chemother. 54 (3) (2004) 582–586, https://doi.org/10.1093/jac/dkh396.

[13] S. Gianella, S. Letendre, Cytomegalovirus and HIV: a dangerous pas de Deux, JID (J. Infect. Dis.) 214 (suppl 2) (2016) S67–S74, https://doi.org/10.1093/infdis/jiw217.

[14] B. Salzberger, P. Hartmann, F. Hanses, et al., Incidence and prognosis of CMV disease in HIV-infected patients before and after introduction of combination antiretroviral therapy, Infection 33 (5–6) (2005) 345–349, https://doi.org/10.1007/s15010-005-5050-z.

[15] J. Xiao, G. Gao, Y. Li, et al., Spectrums of opportunistic infections and malignancies in HIV-infected patients in tertiary care hospital, China, PLoS One 8 (10) (2013) e75915, https://doi.org/10.1371/journal.pone.0075915.

[16] M. Lichtner, P. Cicconi, S. Vita, et al., Cytomegalovirus coinfection is associated with an increased risk of severe non-AIDS-defining events in a large cohort of HIV-infected patients, J. Infect. Dis. 211 (2) (2015) 178–186, https://doi.org/10.1093/infdis/jiu417.

[17] P.Y. Hsue, P.W. Hunt, E. Sinclair, et al., Increased carotid intima-media thickness in HIV patients is associated with increased cytomegalovirus-specific T-cell responses, AIDS (London, England) 20 (18) (2006) 2275–2283, https://doi.org/10.1097/QAD.0b013e3280108704.

[18] A. Maniar, C. Ellis, D. Asmuth, R. Pollard, J. Rutledge, HIV infection and atherosclerosis: evaluating the drivers of inflammation, Eur. J. Prev. Cardiol. 20 (5) (2013) 720–728, https://doi.org/10.1177/2047487312447843.

[19] J.B. Muhlestein, B.D. Horne, J.F. Carlquist, et al., Cytomegalovirus seropositivity and C-reactive protein have independent and combined predictive value for mortality in patients with angiographically demonstrated coronary artery disease, Circulation 102 (16) (2000) 1917–1923, https://doi.org/10.1161/01.cir.102.16.1917.

[20] S. Letendre, A. Bharti, I. Perez-Valero, et al., Higher anti-cytomegalovirus immunoglobulin G concentrations are associated with worse neurocognitive performance during suppressive antiretroviral therapy, Clin. Infect. Dis.: An official publication of the Infectious Diseases Society of America 67 (5) (2018) 770–777, https://doi.org/10.1093/cid/ciy170.

[21] Y.-F. Yen, I. Jen, M. Chen, et al., Association of cytomegalovirus end-organ disease with stroke in people living with HIV/AIDS: a nationwide population-based cohort study, PLoS One 11 (3) (2016) e0151684, https://doi.org/10.1371/journal.pone.0151684.

[22] V. Appay, S. Fastenackels, C. Katlama, et al., Old age and anti-cytomegalovirus immunity are associated with altered T-cell reconstitution in HIV-1-infected patients, AIDS (London, England) 25 (15) (2011) 1813–1822, https://doi.org/10.1097/QAD.0b013e32834640e6.

[23] E. Merlini, K. Luzi, E. Suardi, et al., T-cell phenotypes, PLoS One, in: S. Pett (Ed.), Apoptosis and Inflammation in HIV+ Patients on Virologically Effective cART with Early Atherosclerosis, vol. 7, 2012, p. e46073, https://doi.org/10.1371/journal.pone.0046073 (9).

[24] C.E. O'Sullivan, W.L. Drew, D.J. McMullen, et al., Decrease of cytomegalovirus replication in human immunodeficiency virus infected-patients after treatment with highly active antiretroviral therapy, J. Infect. Dis. 180 (3) (1999) 847–849, https://doi.org/10.1086/314943.

[25] V.C. Emery, Restimulating interest in cytomegalovirus as a cofactor for HIV infection, JID (J. Infect. Dis.) 211 (2) (2014) 169–171, https://doi.org/10.1093/infdis/jiu419.

[26] D.A. Wohl, D. Zeng, P. Stewart, et al., Cytomegalovirus viremia, mortality, and end-organ disease among patients with AIDS receiving potent antiretroviral therapies, J. Acquir. Immune Defic. Syndr. (1999) 38 (5) (2005) 538–544, https://doi.org/10.1097/01.qai.0000155204.96973.c3.

[27] E. Adland, P. Klenerman, P. Goulder, P.C. Matthews, Ongoing burden of disease and mortality from HIV/CMV coinfection in Africa in the antiretroviral therapy era, Front. Microbiol. 6 (2015), https://doi.org/10.3389/fmicb.2015.01016.

[28] A. Kovacs, M. Schluchter, K. Easley, et al., Cytomegalovirus infection and HIV-1 disease progression in Infants born to HIV-1–Infected women, N. Engl. J. Med. 341 (2) (1999) 77–84, https://doi.org/10.1056/nejm199907083410203.

[29] S. Gianella, M. Massanella, J.O. Wertheim, D.M. Smith, The sordid affair between human herpesvirus and HIV, J. Infect. Dis. 212 (6) (2015) 845–852, https://doi.org/10.1093/infdis/jiv148.

[30] J.R. Deayton, C.A. Prof Sabin, M.A. Johnson, V.C. Emery, P. Wilson, P.D. Griffiths, Importance of cytomegalovirus viraemia in risk of disease progression and death in HIV-infected patients receiving highly active antiretroviral therapy, Lancet (London, England) 363 (9427) (2004) 2116–2121, https://doi.org/10.1016/S0140-6736(04)16500-8.

[31] J.A. Slyker, Cytomegalovirus and paediatric HIV infection, J. Virus Erad. 2 (4) (2016) 208–214. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5075347/.

[32] L.-M. Yindom, V. Simms, E.D. Majonga, et al., Unexpectedly high prevalence of cytomegalovirus DNAemia in older children and adolescents with perinatally acquired human immunodeficiency virus infection, Clin. Infect. Dis. 69 (4) (2019) 580–587, https://doi.org/10.1093/cid/ciy961.

[33] F. Cobelens, N. Nagelkerke, H. Fletcher, The convergent epidemiology of tuberculosis and human cytomegalovirus infection, F1000Research 7 (2018) 280, https://doi.org/10.12688/f1000research.14184.2.

[34] E. Whittaker, E. López-Varela, C. Broderick, J.A. Seddon, Examining the complex relationship between tuberculosis and other infectious diseases in children, Front. Pediatr. 7 (2019), https://doi.org/10.3389/fped.2019.00233.

[35] N. Benito, A. Moreno, J.M. Miro, A. Torres, Pulmonary infections in HIV-infected patients: an update in the 21st century, Eur. Respir. J. 39 (3) (2011) 730–745, https://doi.org/10.1183/09031936.00200210.

[36] R.P. Baughman, M.N. Dohn, P.T. Frame, The continuing utility of bronchoalveolar lavage to diagnose opportunistic infection in AIDS patients, Am. J. Med. 97 (6) (1994) 515–522, https://doi.org/10.1016/0002-9343(94)90346-8.

[37] R. Choo, N.S.H. Naser, N.V. Nadkarni, D. Anantham, Utility of bronchoalveolar lavage in the management of immunocompromised patients presenting with lung infiltrates, BMC Pulm. Med. 19 (1) (2019), https://doi.org/10.1186/s12890-019-0801-2.

[38] P.R. Miles, R.P. Baughman, C.C. Linnemann, Cytomegalovirus in the bronchoalveolar lavage fluid of patients with AIDS, Chest 97 (5) (1990) 1072–1076, https://doi.org/10.1378/chest.97.5.1072.

[39] S.A. Bozzette, J. Arcia, A.E. Bartok, et al., Impact of Pneumocystis carinii and cytomegalovirus on the course and outcome of atypical pneumonia in advanced human immunodeficiency virus disease, JID (J. Infect. Dis.) 165 (1) (1992) 93–98, https://doi.org/10.1093/infdis/165.1.93.

[40] M. Bower, S.E. Barton, M.R. Nelson, et al., The significance of the detection of cytomegalovirus in the bronchoalveolar lavage fluid in AIDS patients with pneumonia, AIDS 4 (4) (1990) 317–320, https://doi.org/10.1097/00002030-199004000-00005.

[41] L. Joos, P.N. Chhajed, J. Wallner, et al., Pulmonary infections diagnosed by BAL: a 12-year experience in 1066 immunocompromised patients, Respir. Med. 101 (1) (2007) 93–97, https://doi.org/10.1016/j.rmed.2006.04.006.

[42] W.L. Drew, Diagnosis of cytomegalovirus infection, Clin. Infect. Dis. 10 (Supplement_3) (1988) S468–S476, https://doi.org/10.1093/clinids/10.supplement_3.s468.

[43] A.B. Millar, G. Patou, R.F. Miller, et al., 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.

[44] M.C. Rodriguez-Barradas, E. Stool, D.M. Musher, et al., Diagnosing and treating cytomegalovirus pneumonia in patients with AIDS, Clin. Infect. Dis. 23 (1) (1996) 76–81, https://doi.org/10.1093/clinids/23.1.76.

[45] C.E. Hayner, R.P. Baughman, C.C. Linnemann, M.N. Dohn, The relationship between cytomegalovirus retrieved by bronchoalveolar lavage and mortality in patients with HIV, Chest 107 (3) (1995) 735–740, https://doi.org/10.1378/chest.107.3.735.

[46] T.H. Yeo, T.K. Yeo, E.P. Wong, R. Agrawal, S.C. Teoh, Immune recovery uveitis in HIV patients with cytomegalovirus retinitis in the era of HAART therapy-a 5-year study from Singapore, J. Ophthalmic Inflamm. Infect. 6 (1) (2016) 41, https://doi.org/10.1186/s12348-016-0110-3.

[47] M.P. Karavellas, C.Y. Lowder, C. Macdonald, C.P. Avila, W.R. Freeman, Immune recovery vitritis associated with inactive cytomegalovirus retinitis: a new syndrome, Arch. Ophthalmol. (Chicago, Ill : 1960) 116 (2) (1998) 169–175, https://doi.org/10.1001/archopht.116.2.169.

[48] R.D. Schrier, M.-K. Song, I.L. Smith, et al., Intraocular viral and immune pathogenesis of immune recovery uveitis in patients with healed cytomegalovirus retinitis, Retina 26 (2) (2006) 165–169, https://doi.org/10.1097/00006982-200602000-00007.