IDCases 13 (2018) e00437

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

Case report

Occam's razor need not apply: Advanced HIV infection presenting with five simultaneous opportunistic infections and central nervous system lymphoma

Louis-Bassett Porter[a,1], Elena Kozakewich[a,1], Ryan Clouser[b], Colleen Kershaw[c], Andrew J. Hale[b,*]

[a] The University of Vermont Medical Center, United States
[b] The University of Vermont Medical Center, Larner College of Medicine at the University of Vermont, Burlington, VT, United States
[c] Beth Israel Deaconess Medical Center, Boston, MA, United States

ARTICLE INFO

Article history:
Received 18 June 2018
Received in revised form 6 August 2018
Accepted 6 August 2018

Keywords:
Human Immunodeficiency Virus
Acquired Immunodeficiency Disorder
Opportunistic infection

ABSTRACT

Patients with Human Immunodeficiency Virus (HIV) infection and Acquired Immunodeficiency Syndrome (AIDS) are at risk for multiple infectious and oncologic complications. In such cases, Occam's razor need not apply: multiple infections and malignancies are often present concurrently upon presentation to care. A patient off anti-retroviral therapy (ART) for several years developed advanced HIV infection (CD4 count 19 cells/uL) and presented with five simultaneous opportunistic infections including *Pneumocystis jiroveci* pneumonia (PJP), cytomegalovirus (CMV) retinitis, *Mycobacterium avium* complex (MAC) bloodstream infection, chronic hepatitis B virus (HBV), and Epstein-Barr virus (EBV) viremia. Simultaneously, he was found to have primary central nervous system (CNS) B-cell lymphoma.

Treatment decisions for such patients are often complex, as ideal therapy for one disease may directly counter or interact with therapy for another. For instance, methotrexate for primary CNS lymphoma and trimethoprim/sulfamethoxazole for PJP is a strictly contraindicated medication combination. It is important to understand not just the management of any single opportunistic disease in patients with advanced HIV, but how to balance management for patients with a variety of concurrent processes. In an era when HIV care is becoming increasingly simplified, patients presenting with advanced infection highlight the lack of data on how best to manage patients with multiple concurrent disease processes. Significant further research is needed to clarify ideal comparative therapy.

Introduction

For many clinicians practicing in the United States, especially young clinicians, treatment of the manifestations of untreated HIV with progression to AIDS may be evocative of a past era of medicine that seems disconnected from the present-day. While HIV and AIDS are recognized as major issues pertaining to global health, prevalence in the United States is perceived to be much lower. However, the Centers for Disease Control and Prevention (CDC) estimate that in 2014 over 1.1 million people in the United States were living with HIV, with 15% of those patients (approximately 165,000) unaware of their HIV-positive status. Furthermore, in 2014 HIV was the eighth leading cause of death in 25–34 year-olds and ninth in 35–44 year-olds in the United States [1]. The reality is that despite significant strides in HIV prevention and antiretroviral therapy, HIV, AIDS and associated opportunistic infections remain fundamentally important topics in clinical practice in the United States.

Case description

A 56-year-old man was found by his spouse unresponsive and demonstrating generalized tonic-clonic movements with bowel and bladder incontinence. Emergency medical services were called and he was intubated for airway protection. Preceding this event, the patient had reported upper respiratory illness symptoms for several weeks with intermittent fevers, as well as altered mental status described as slowed cognition and unusual affect. He took no medications prior to admission, though did have a history of

* Corresponding author at: University of Vermont Medical Center, Infectious Disease Unit. 111 Colchester Avenue, Mailstop 115 SM2., Burlington, VT, 05401, United States.
E-mail address: Andrew.Hale@UVMhealth.org (A.J. Hale).
[1] Dr. Porter and Dr. Kozakewich contributed equally to this manuscript.

https://doi.org/10.1016/j.idcr.2018.e00437

chronic HBV and HIV acquired in the 1980s, thought to be from MSM exposure. He had previously taken HIV and HBV medications for nearly 20 years, but had discontinued all medical therapy three years prior to admission due to side effects. His CD4 T-cell count at the time of discontinuation was 250 cells/μL.

On admission the patient's temperature was 38 °C, heart rate was 127 beats per minute, respiratory rate was 12 breaths per minute, blood pressure was 122/83 mmHg, and blood oxygen saturation was 100% on FiO2 30%. He was cachectic on examination. Lungs were clear to auscultation bilaterally. Notable initial laboratory values included a serum sodium of 114 mEq/L, lactic acid of 7.5 mmol/L, creatinine kinase of 1292 U/L, hemoglobin of 12.0 gm/dl, white blood cell count of 5.8 K/μL, and platelets of 143 K/μL. Absolute CD4 T-cell count was 19 cells/uL and HIV viral load was 468,999 copies/mL. A computed tomography scan of the head revealed a right basal ganglia edematous area measuring 20 × 24 mm, with mild mass effect. A brain magnetic resonance imaging study with gadolinium showed a rim-enhancing lesion involving the right caudate and basal ganglia with mass effect indenting the right lateral ventricle (Fig. 1). Lumbar puncture revealed atypical lymphocytes with cytopathology consistent with B-cell lymphoma. The patient's respiratory status improved and he was liberated from mechanical ventilation the day following admission, though remained somnolent afterwards.

Further work-up revealed positive hepatitis B surface antigen with HBV viral load 8.23 log IU/mL, *Mycobacterium avium* complex (MAC) growth in blood cultures, positive Epstein-Barr virus (EBV) polymerase chain reaction (PCR) in cerebrospinal fluid, and serum cytomegalovirus (CMV) viral load of 2770 IU/mL with findings on funduscopic exam of creamy exudates with associated dot-blot hemorrhages, consistent with CMV retinitis. Video electroencephalogram monitoring did not record further seizure activity. Positron emission tomography (PET) showed strong fludeoxyglucose (FDG) avidity primarily within the CNS lesion, consistent with HIV-associated primary CNS B-cell lymphoma (Fig. 2). Diffuse, though weak, FDG avidity was also noted in the lungs which prompted a subsequent bronchoalveolar lavage, which demonstrated *Pneumocystis jiroveci* pneumonia (PJP) via PCR. Thus, this patient's presentation was ultimately consistent with advanced HIV infection with CD4 count of 19 cells/uL, chronic HBV, HIV and EBV-associated primary CNS B-cell lymphoma, PJP, CMV retinitis, and MAC bloodstream infection.

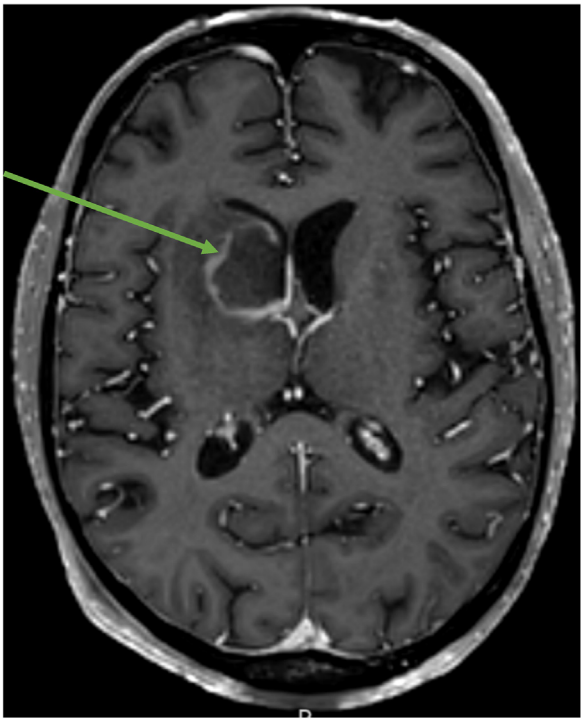

Fig. 1. Brain magnetic resonance imaging study with contrast demonstrates a single rim-enhancing lesion (green arrow) involving the right caudate and basal ganglia with mass effect indenting the right lateral ventricle. Lumbar puncture cytology demonstrated B-cell lymphoma.

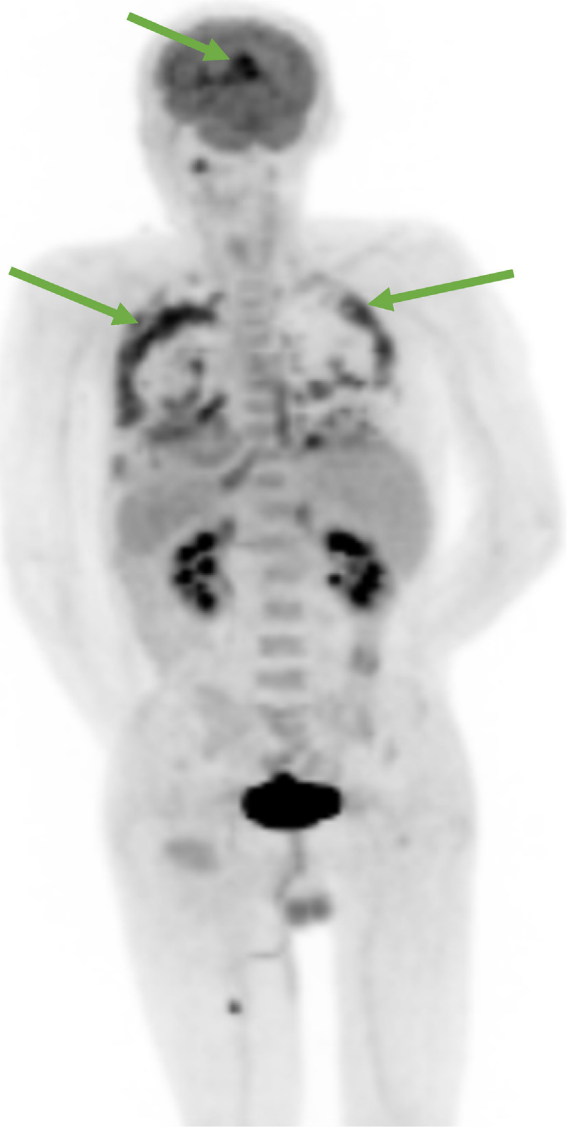

Fig. 2. Positron emission tomography study. Note the high fludeoxyglucose (FDG) avidity within the central nervous system lesion as well as uptake within lungs bilaterally (green arrows). Lumbar puncture cytology confirmed the solitary CNS lesion as HIV-associated primary CNS B-cell lymphoma, and bronchoscopy confirmed the pulmonary findings as *Pneumocystis jirovecii* pneumonia (PJP).

Initially, trimethoprim/sulfamethoxazole was started for treatment of PJP and was transitioned to atovaquone due to concern for interaction with methotrexate (planned therapy for primary B-cell lymphoma), unknown glucose-6-dehydrogenase deficiency (G6PD) status, and minimal hypoxia post-extubation. However, methotrexate was later deferred due to the patient's multiple comorbidities. CMV retinitis was initially treated with intravenous ganciclovir, though with developing marrow suppression he was transitioned to intravitreal ganciclovir injection. Anti-retroviral therapy and anti-HBV medications were initiated after seven days of CMV therapy, including tenofovir alafenamide, emtricitabine,

dolutegravir, and rilpivirine, based on prior genotype data. Clarithromycin, ethambutol, and rifabutin were recommended for MAC bloodstream infection. Dexamethasone was started for cerebral edema, after detection of primary CNS lymphoma.

The patient had ongoing encephalopathy that required the patient's family to provide direction regarding goals of care. By hospital day 36, the patient's encephalopathy had not significantly improved and the family requested that most anti-infective medications, including ART, be stopped, as this was felt to be what the patient would have wanted. At the request of the patient's spouse he was discharged home with palliative care, and passed away at home several weeks later.

Discussion

This case illuminates that despite many advances made in the fight against HIV, treatment of advanced HIV and associated opportunistic infections can be highly complex. Therapeutic conflicts present clinicians with significant treatment dilemmas. Here, numerous first-line therapies presented conflicts with the treatment of other concurrent disease processes (Fig. 3). These conflicts were two-fold: 1) First line therapies could exacerbate concurrent disease processes; 2) adverse effects of interventions including drug toxicities and drug-drug interactions.

First, treatment of certain diseases can lead to worsening of others. While initiation of ART leads to improvements in cellular immunity and overall mortality [2], this patient's multiple infections represented substantial risk of immune reconstitution inflammatory syndrome (IRIS). IRIS is defined as a paradoxical worsening of a known condition (or the new manifestation of a previously unknown condition), most commonly infection, after initiation of ART in a patient with HIV/AIDS [3]. Up to 13% of patients with HIV/AIDS may develop IRIS after initiation of ART [4]. PJP, mycobacterial infections, and CMV retinitis are commonly reported opportunistic infections associated with IRIS [5]. A recent meta-analysis reported that in patients with advanced HIV and concurrent CMV, IRIS developed in 37.7% of patients after initiation of ART [4]. IRIS occurring within a confined anatomical space, such as the eye or brain, can significantly increase morbidity and mortality [6]. In our patient there was concern that early initiation of ART carried a substantial risk of an adverse retinal outcome, potentially blindness related to ocular IRIS, and thus delay of ART would potentially be beneficial. However,compelling data exists that ART should not be delayed in HIV-infected patients presenting with PJP [7]. This presented a conflict in our patient with both CMV retinitis and PJP regarding when ART should be initiated. At present, Health and Human Services Opportunistic Infection guidelines suggest initiation of ART begin no later than two weeks after diagnosis of opportunistic infection, unless there is cryptococcal or tubercular meningitis, in which case a delay of ART initiation of several weeks is recommended [8,9]. For this patient, ART was initiated after seven days of CMV therapy. Because of his encephalopathy, it is unknown what effect this had on his vision.

The second challenge in caring for this patient's multiple infections and CNS lymphoma involved drug toxicities and drug-drug interactions. For example, with the risk for vision loss from CMV retinitis and IRIS, the use of ethambutol for MAC was problematic, as ethambutol has a well-documented toxicity of optic neuropathy [10]. For the treatment of MAC, intermittent dosing (three days a week versus every day) of ethambutol may reduce the risk of ocular toxicity [11]. Alternatively, a regimen without ethambutol can be used, though likely is inferior therapy for invasive MAC disease [12]. This patient was never initiated on MAC therapy as the direction of care moved to a comfort-focus. Furthermore, ganciclovir is the drug of choice for CMV retinitis, but its use was complicated by bone marrow suppression in a patient already with HIV-related pancytopenia [13]. This prompted the decision to use intravitreal ganciclovir for this patient, which is supported by CDC guidelines [8]. Additionally, there was concern regarding treatment of the patient's CNS lymphoma with rituximab and steroids in the setting of his chronic surface-antigen positive HBV. Although the patient presented with immune-tolerant chronic HBV, treatment with anti-CD20 or steroid therapy can precipitate acute hepatitis in up to 50% of cases [14]. Typically, HBV viral load suppressive therapy is recommended before steroid treatment is initiated [15]. Although

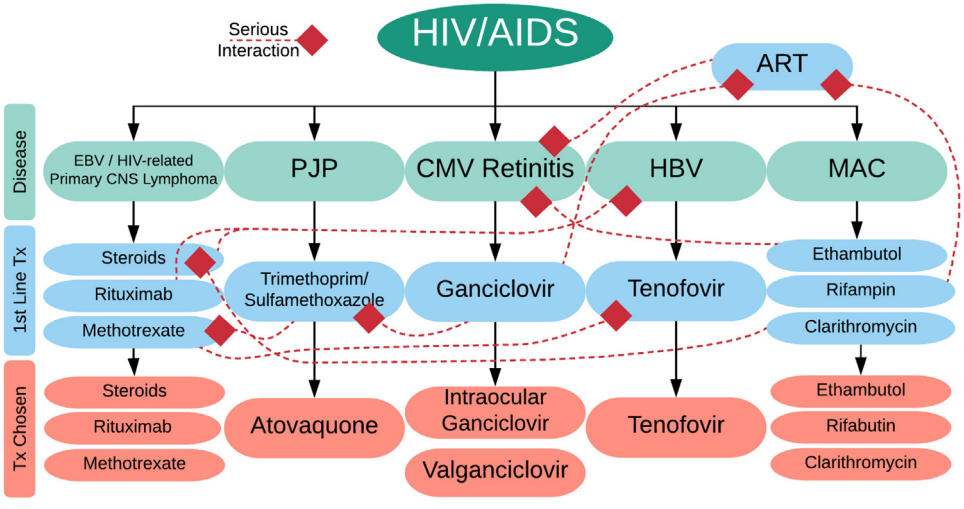

Fig. 3. Treatment algorithm and potential interactions for the case presented. Green demonstrates the disease processes that were diagnosed. Blue demonstrates first-line, guidelines-based therapy for each of these processes. Dotted red lines show potentially serious interactions of using these first-line regimens concurrently. In order from top-down and left to right: 1) ARV therapy in the setting of CMV retinitis can precipitate vision-threatening IRIS. 2) Both steroids and rituximab for CNS lymphoma can precipitate acute hepatitis from chronic HBV infection. 3) Methotrexate for CNS lymphoma and trimethroprim/sulfamethoxazole for PJP can cause critically low blood counts and are contraindicated together. 4) Ganciclovir for CMV retinitis and tenofovir for HIV and HBV, combined with trimethroprim/sulfamethoxazole, can additionally cause significant bone-marrow suppression. 5) Ethambutol for MAC can cause optic neuritis, which is concerning in a patient already with significant CMV retinitis. 6) Rifampin is a potent inducer of the cytochrome P450 CYP3A system and has many drug-drug interactions, particularly with many HIV medications. 7) Clarithromycin should be avoided with concomitant steroids as this can elevated steroid levels and cause adrenal suppression. In red at the bottom is the regimen recommended for this patient to balance these interactions.

HBV suppressive therapy was started on day seven (tenofovir alafenamide), full HBV suppression can take months, which was not an option in this case as it was vital to urgently address cerebral edema from the CNS lymphoma. Lastly, another drug-drug interaction that complicated this case was the use of trimethoprim/sulfamethoxazole (first-line therapy for PJP) in conjunction with methotrexate (first-line therapy for primary CNS lymphoma). Although the evidence is largely from case reports, trimethoprim/sulfamethoxazole may enhance the bone marrow toxicity of methotrexate and result in critical bone marrow suppression and neutropenia [16].

In an era when HIV care is generally becoming increasingly simplified, patients with advanced infection highlight the lack of data on how best to manage patients with multiple concurrent disease processes. Significant further research is needed to clarify ideal comparative therapy.

Funding

None.

Conflict of interests statement

None of the authors report any conflicts of interest.

Authorship verification

All co-authors have seen and agree with the contents of the manuscript and have contributed significantly to the work.

Consent

Informed consent was obtained for publication of this case report and accompanying images. A copy of the consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions statement

Louis-Bassett Porter, MD: conceptualization, writing original draft, review and editing.

Elena Kozakewich, MD: conceptualization, writing original draft, review and editing.

Ryan Clouser, DO: conceptualization, writing original draft, review and editing.

Colleen Kershaw, MD: conceptualization, writing original draft, review and editing.

Andrew J. Hale, MD: conceptualization, writing original draft, review and editing.

Acknowledgements

None.

References

[1] HIV/AIDS basic statistics. Centers for Disease Control and Prevention; 2018. . Available at https://www.cdc.gov/hiv/basics/statistics.html (Accessed 18 March 2018).
[2] Palella Jr FJ., Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998;338(13):853–60.
[3] Singh N, Perfect JR. Immune reconstitution syndrome associated with opportunistic mycoses. Lancet Infect Dis 2007;7(6):395–401.
[4] Müller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. Lancet Infect Dis 2010;10(4):251.
[5] Murdoch DM, Venter WD, Van Rie A, Feldman C. Immune reconstitution inflammatory syndrome (IRIS): review of common infectious manifestations and treatment options. AIDS Res Ther 2007;4:9.
[6] Franco-Paredes C, Chastain DB, Rodriguez-Morales AJ, Marcos LA. Cryptococcal meningoencephalitis in HIV/AIDS: when to start antiretroviral therapy? Ann Clin Microbiol Antimicrob 2017;16:9.
[7] Zolopa AR, Andersen J, Komarow L, Sanne I, Sanchez A, Hogg E, et al. Early antiretroviral therapy reduces AIDS Progression/Death in individuals with acute opportunistic infections: a multicenter randomized strategy trial Carr A ed.. PLoS One 2009;4(5):e5575.
[8] Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America; 2018. . Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf (Accessed 18 March 2018).
[9] Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Department of Health and Human Services; 2018. . Available at: https://aidsinfo.nih.gov/guidelines (Accessed 19 March 2018).
[10] Leibold JE. The ocular toxicity of ethambutol and its relation to dose. Ann N Y Acad Sci 1966;135(2):904.
[11] Griffith DE, Brown-Elliott BA, Shepherd S, McLarty J, Griffith L, Wallace Jr. RJ. Ethambutol ocular toxicity in treatment regimens for Mycobacterium avium complex lung disease. Am J Respir Crit Care Med 2005;172(2):250.
[12] May T, Brel F, Beuscart C, Vincent V, Perronne C, Doco-Lecompte T, et al. Comparison of combination therapy regimens for treatment of human immunodeficiency virus-infected patients with disseminated bacteremia due to Mycobacterium avium. Clin Infect Dis 1996;25(3):621–9.
[13] Feola DJ1, Thornton AC, Garvy BAD. Effects of antiretroviral therapy on immunity in patients infected with HIV. Curr Pharm Des 2006;12(9):1015–22.
[14] Tsutsumi Y, Yamamoto Y, Ito S, Ohigashi H, Shiratori S, Naruse H, et al. Hepatitis B virus reactivation with a rituximab-containing regimen. World J Hepatol 2015;7(21):2344–51.
[15] Marzano A, Angelucci E, Andreone P, Brunetto M, Bruno R, Burra P, et al. Prophylaxis and treatment of hepatitis B in immunocompromised patients. Dig Liver Dis 2007;39(5):397–408.
[16] Al-Quteimat OM, Al-Badaineh MA. Methotrexate and trimethoprim-sulphamethoxazole: extremely serious and life-threatening combination. J Clin Pharm Ther 2013;38(3):203–5.