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Opportunistic Infections in a Patient with Newly Diagnosed HIV

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Abstract

Introduction: Human immunodeficiency virus is a virus that attacks the body's immune system. Current antiretroviral therapy allows patients living with human immunodeficiency virus to maintain a normal CD4 count and achieve undetectable viral loads. The advancement of medications and improved accessibility over the last two decades has significantly decreased the vulnerability to opportunistic infections. Immune reconstitution inflammatory syndrome is a collection of inflammatory disorders that can occur in patients who start antiretroviral therapy due to pre-existing infectious processes. **Case Report:** A 26-year-old Peruvian male, with no prior medical history, presented multiple times to the emergency department with generalized fever, chills, and fatigue. He reported unprotected sexual activity and was diagnosed with human immunodeficiency virus. Upon discharge, he was initiated on antiretroviral therapy. In the following months, the patient presented with the rare finding of eight complications, including seven infections likely due to immune reconstitution inflammatory syndrome. We provide a comprehensive review of treatments to treat concurrent illnesses. **Conclusion:** This patient's eight complications highlight the severity of opportunistic infections that may arise due to immune reconstitution inflammatory syndrome. The high number of co-infections presented within the initial three weeks of therapy, and the subsequent complications present the need to monitor patients closely when starting antiretroviral therapy. Multiple concomitant therapies increase the risk of interactions and complications; hence, staying up to date on the management of opportunistic infections is vital to avoid the increased mortality risk in patients. This case provides a comprehensive review of treatments for a complicated and rare human immunodeficiency virus case.

Keywords: Human Immunodeficiency Virus (HIV); Opportunistic Infections; Immune reconstitution inflammatory syndrome (IRIS); Antiretroviral therapy (ART); Human Herpes Simplex Virus - 8 (HHV8).

Abbreviations: AIDS: acquired immunodeficiency syndrome; ART: antiretroviral therapy; BAL: Broncho alveolar lavage; CMV: cytomegalovirus; CRP: C-reactive protein; CT: computed tomography; CTLs: cytotoxic T lymphocytes; EBER: Epstein-Barr encoding region; EBV: Epstein-Barr virus; ELISA: enzyme-linked immunosorbent assay; ESR: erythrocyte sedimentation rate; HHV-8: human herpesvirus-8; HIV: human immunodeficiency virus; HLH: hemophagocytic lymphohistiocytosis; HSV: herpes simplex virus; IRIS: immune reconstitution inflammatory syndrome; LANA: latency-associated nuclear antigen; MAC: Mycobacterium avium complex; MSSA: methicillin-sensitive Staphylococcus aureus; NK: natural killer; PCP: Pneumocystis jirovecii; PCR: Polymerase Chain Reaction; RBC: red blood cell; TMP/SMX: sulfamethoxazole-trimethoprim; WBC: white blood cell.

Introduction

Here, we present a patient who was newly diagnosed with human immunodeficiency virus (HIV) and later presented with several complications, including seven infections, all likely a result of immune reconstitution inflammatory syndrome (IRIS) in the setting of antiretroviral therapy (ART). HIV is an enveloped single-stranded RNA retrovirus that invades CD4 cells of the immune system and replicates using reverse transcription [1]. This attack leads to an immunocompromised state, complicating the body's ability to fight off infections [2]. Without antiretroviral therapy (ART), life-threatening opportunistic infections can arise, HIV can eventually progress into acquired immunodeficiency syndrome (AIDS), and the overall mortality rate increases to over 90% [3]. Initiating ART allows the immune system to recover by not only increasing the CD4 count over time but also reducing the viral load to undetectable levels [1]. Opportunistic infections are broadly defined as infections that occur more frequently and are more severe in immunocompromised individuals, such as those living with HIV, a risk that increases in those with a CD4 count of <200 cells/microliter [4]. IRIS can worsen or unmask these opportunistic infections and is caused by a dysregulated hyper-inflammatory immune response against co-infecting pathogens [5,6]. It occurs in 16% of patients with HIV when starting ART, typically occurring within four to eight weeks of initiation [7,8]. This response can present as either "paradoxical," defined as a known infection worsening while the patient is receiving ART, or an "unmasking," where a previously undiagnosed infection is discovered [9,10]. The most common infections associated with IRIS include Mycobacterium tuberculosis, Cryptococcus spp., Mycobacterium avium complex (MAC), Human Herpesvirus-8 (HHV-8), and cytomegalovirus (CMV) [6,11]. Management of IRIS includes treatment of the underlying conditions and continuation of ART [12]. Steroids should be given to select patients for certain opportunistic infections, such as CMV retinitis and tuberculosis [13]. Throughout the case report, we will discuss the treatment of conditions associated with IRIS in a male with newly diagnosed HIV.

Case Report

A 26-year-old Peruvian man from Ecuador, with no prior medical history, presented on the first day of admission to the emergency department with ongoing fevers, unintentional weight loss, and fatigue. He reported unprotected sexual activity with males, including a sexual encounter with a known HIV-positive individual five years prior. He was found to be HIV-positive, with a viral load of 1,590,000 copies/mL and a CD4 count of 47 cells/microliter. Due to concerns of pneumonia based on imaging findings, he was started on broad-spectrum antibiotics along with prophylactic therapy for MAC. He was also initiated on the treatment dose of sulfamethoxazole-trimethoprim (TMP/SMX) due to clinical suspicion for *Pneumocystis jirovecii* (PCP) and prophylaxis for *Toxoplasmosis gondii*. He was found to have oral ulcers due to herpes simplex virus (HSV) for which he was prescribed valacyclovir. Further pulmonary workup revealed *Streptococcus agalactiae* and methicillin-sensitive *Staphylococcus aureus* (MSSA) pneumonia, for which cefazolin was initiated and continued until his discharge. After clearance, he was seen in the outpatient HIV clinic where bictegravir/emtricitabine/tenofovir alafenamide was initiated. Approximately three weeks after starting TMP/SMX, the patient was readmitted with a persistent fever, cough, transaminitis, and left lower quadrant pain. Cefepime and metronidazole were initiated to cover for suspected pneumonia and intra-abdominal infection. Due to his transaminitis, his antiretroviral therapy was held. Further, due to frequent vomiting when taking TMP-SMX, the treatment was switched to atovaquone. Upon further workup, he was diagnosed with suspected IRIS due to elevated ferritin, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), and he was initiated on steroid therapy. On day 10 of this admission, his Epstein-Barr Virus (EBV) and CMV PCR returned elevated at 130 copies/mL and 22,000 copies/mL, respectively. The (1,3)-β-D-Glucan test returned elevated at 500 pg/mL; however, due to no identifiable source of fungal infection, therapy was not initiated and he was discharged. The patient was readmitted two days after the previous admission with fevers and upper respiratory infection symptoms, for which he received approximately a week of antibiotics before discharge. Three days after the previous discharge, the patient was readmitted with fevers, cough, tachycardia, and hypotension requiring vasopressor support, skin lesions, and pancytopenia. A computed tomography (CT) scan showed splenomegaly and retroperitoneal lymphadenopathy with concern for hemophagocytic lymphohistiocytosis (HLH) for which he received corticosteroids and intravenous immunoglobulin. Due to concern for MAC, he was started on clarithromycin and ethambutol. A lymph node biopsy confirmed EBV and CMV infection, and a repeat CMV PCR and EBV PCR showed a significant rise in viral load to 95,900 copies/mL and 90,100 copies/mL, respectively; post-diagnosis, ethambutol and clarithromycin were discontinued. He was initiated on intravenous ganciclovir therapy for fifteen days but was switched to intravenous foscarnet due to profound thrombocytopenia, a known adverse drug effect of ganciclovir. A bone biopsy was ordered to rule out other infections. On the fifth day of this admission, he was restarted on bictegravir/emtricitabine/tenofovir alafenamide and dexamethasone for AIDS and IRIS, respectively. A peripheral blood smear showed fungi-like structures in the neutrophils, leading to concern for histoplasmosis. Although his histoplasmin antibodies were negative on a previous admission, there was a concern that it was a false negative due to his inability to mount an immune response in a severely immunocompromised state. Itraconazole was initiated

while the results of the bone biopsy were pending. Nine days later, the bone biopsy results confirmed trilineage hematopoietic bone marrow with diffuse involvement by H. *capsulatum*, which led to the change of therapy from itraconazole to liposomal amphotericin B for fourteen days for disseminated histoplasmosis. A lymph node biopsy on the nineteenth day of admission was consistent with histoplasmosis. After completing fourteen days of therapy, he transitioned to itraconazole maintenance therapy with a therapeutic level (1.2 mcg/mL) achieved following dose modification and discontinuation of his interacting medications. Histoplasma antigen trended down from 0.7 ng/mL to 0.37 ng/mL, indicating a response to therapy. Thirteen days into this admission, the patient developed diarrhea which prompted the ordering of a C. *difficile* toxin and antigen test and a gastrointestinal panel; the C. *difficile* tests were positive and *Cryptosporidium* was detected in the panel, for which oral vancomycin for ten days and oral nitazoxanide for sixteen days were initiated, respectively. Due to risk factors for recurrent C. *difficile* infection, the patient remained on an oral vancomycin taper. The patient continued to endorse diarrhea, with a repeat stool PCR continuing to remain positive for *Cryptosporidium*. Thus, nitazoxanide was continued for an additional fourteen days after which the patient's diarrhea resolved to complete thirty days of therapy. Eighteen days into the current admission, the CMV PCR and EBV PCR detected 3500 copies/mL and 369 copies/mL, respectively; eleven days later, repeat tests were done which showed undetectable levels of both, indicating a response to therapy. He was restarted on valacyclovir 1000 mg twice daily for a sacral ulcer secondary to HSV-2, confirmed via nucleic acid amplification for an additional ten days. Due to recurrent infection, he was continued on valacyclovir prophylaxis. Throughout his prolonged stay, his pancytopenia worsened, with white blood cell counts (WBCs) as low as 1.7 x 10^3/mm^3, red blood cell count (RBC) at 2.79 x 106/mm^3, and platelets at 63,000/mm^3, which prompted HHV-8 testing. On day 64, the HHV-8 PCR was positive with 7.6 log copies/mL and a HHV-8 viral load of 36,800,000 copies/mL. As a result, the patient remained on his antiretroviral treatment to treat the underlying cause of the HHV-8. Upon review for discharge, his HIV viral load decreased to 60 copies/mL and CD4 increased to 26 cells/mm^3 after three months of ART. He was discharged on atovaquone, itraconazole, valacyclovir, and vancomycin taper doses with a plan to follow up in the outpatient HIV clinic.

Discussion

We have presented a patient case with multiple concomitant infections due to uncontrolled HIV of unknown duration. The patient was promptly started on ART after his first admission. His subsequent rehospitalizations for flu-like symptoms, multiple co-infections, and rapid increases in EBV and CMV viral load prompted speculation of IRIS. Immune reconstitution inflammatory syndrome must be considered in patients with severely immunocompromised states, as seen by our patient's CD4 count of 41 cells/mm^3 and high viral loads. Moreover, IRIS has a higher predisposition to occur in the first few weeks following ART initiation and this highlights the need for close monitoring of patients starting ART to prevent the high IRIS mortality rate and associated complications. Proper prophylaxis agents should also be initiated to avoid complications, and alternative agents should be used when first-line agents fail or are contraindicated. This patient developed PCP, CMV, HHV-8 and less common infections associated with IRIS, such as Cryptosporidium, EBV, HSV, and Histoplasmosis spp. One of the most common opportunistic infections in patients with HIV is PCP, which is a unicellular fungus that manifests in patients as progressive dyspnea, nonproductive cough, chest discomfort, and fever. The organism can be detected by microscopic identification in induced sputum or bronchoalveolar lavage (BAL) or PCR testing [12,14]. Moreover, mortality can reach 10-12% if patients have hypoxemia, significantly low CD4 counts, or severe comorbidities. The prognosis is nearly always fatal without treatment [15]. Therefore, if suspecting PCP, empiric therapy should be initiated with TMP/SMX, with alternatives including atovaquone, pentamidine, or primaquine [16-18].As presented here, the patient became intolerant to TMP/SMX after three weeks with vomiting and skin rashes; thus, he was switched to atovaquone for PCP prophylaxis. Some viral opportunistic infections include HSV, CMV, and EBV. Herpes simplex virus can be classified into two types, HSV-1 and HSV-2. This virus normally remains dormant but can become activated due to periods of stress or immunocompromised states [19]. Symptoms manifest as painful oral or genital blisters, or ulcers that may recur over time. Fever, body aches, and swollen lymph nodes can also be present upon review of systems. All patients with herpes should be tested using HSV-specific testing, such as HSV serology or viral PCR. The recommended treatment options by the Centers for Disease Control and Prevention (CDC) for the first clinical episode, daily suppressive therapy, and episodic therapy include oral acyclovir, famciclovir, and valacyclovir [20-23]. General side effects include headache, nausea, vomiting, dizziness, and acute kidney injury [24]. Pancytopenia is a rare adverse reaction of those agents; therefore, the team had initially attributed the patient's pancytopenia to the antivirals as the origin until EBV and CMV were confirmed. One of the complications during the patient's hospital course was HLH. Hemophagocytic lymphohistiocytosis is a life-threatening immune dysregulation of natural killer (NK) cells with or without cytotoxic T lymphocytes (CTLs). This pathogenesis leads to hypercytokinemia and an accumulation of activated lymphocytes and macrophages (termed histiocytes) in organs and tissues. The clinical presentation is consistent with our patient as characterized by fever, cytopenias, hepatosplenomegaly, and hyperferritinemia [25-28]. HIV-

associated HLH is treated with short-term corticosteroid therapy with or without intravenous immunoglobulin (IVIG). However, this patient also had EBV, causing suspicion of possible EBV-associated HLH. Therapy for EBV can be used or the HLH-94 protocol can be considered depending on clinical severity [29]. Another underlying infection that may arise due to IRIS is cytomegalovirus, which is a double-stranded DNA virus of the Herpesviridae family. Patients most commonly present with retinitis or other symptoms such as colitis, other gastrointestinal manifestations, pneumonia, disease of the central nervous system, or IRIS. Our patient reported no symptoms of vision changes but did demonstrate pneumonia-like symptoms and IRIS. Furthermore, PCR tests, histopathology/cytology, virus culture, antigenemia, retinal changes, or endoscopy can detect CMV in blood. Treatment options include anti-CMV therapy and ART. The preferred therapy is intravenous ganciclovir for 14-21 days, then maintenance therapy with either intravenous ganciclovir daily or oral valganciclovir daily. For patients not responding to single-drug therapy or continued disease progression, alternative agents can be considered. These agents include combination therapy with ganciclovir and foscarnet or monotherapy such as foscarnet or cidofovir [30-32]. Moreover, EBV is another complication in severely immunocompromised individuals, notably those with HIV. This virus is a double-stranded DNA herpesvirus in the human B cell. Patients present with asymptomatic or non-specific symptoms such as fatigue, splenomegaly, lymphadenopathy, headache, malaise, fever, and sore throat. Lab abnormalities consist of lymphocytosis and elevations in liver function tests. EBV can be detected through heterophile antibody testing, serologies, viral load testing via PCR, and Epstein-Barr encoding region (EBER) in situ hybridization. For treatment, there are currently no approved antiviral medications. Intravenous or oral acyclovir and ganciclovir have demonstrated in vitro activity against the lytic phase infection by reducing viral shedding [33,34]. However, there is a lack of evidence for reducing relevant clinical outcomes in severity and duration of symptoms. Thus, the mainstay of treatment is supportive care such as fever and pain reduction [35]. Histoplasmosis is an infection caused by a dimorphic fungus called Histoplasma capsulatum [4]. It primarily lives in soil containing large bird droppings and is predominantly found east of the Ohio and Mississippi River valleys, an area commonly referred to as the “Histo Belt” [6,9]. In immunocompromised individuals, fungal pathogens such as Histoplasma can invade the host organism and cause common symptoms such as fever, fatigue, weight loss, cough, chest pain and dyspnea [15]. Histoplasma can be detected via antigen tests in blood or urine and peripheral blood smears. Bone marrow, blood, respiratory secretion cultures and histopathology of mucocutaneous lesions, skin, liver, and bone marrow samples can also be used as verification tools [36]. Histoplasmosis is commonly treated with antifungal agents such as itraconazole [9]. For disseminated histoplasmosis, more aggressive therapy is initiated with intravenous liposomal amphotericin B for 1-2 weeks, followed by oral itraconazole three times daily for three days, followed by twice daily for at least twelve months [32]. Cryptosporidium is an intracellular, enteric protozoan that causes a diarrheal disease known as cryptosporidiosis and should be monitored for in high-risk patients [21]. Similarly to histoplasmosis, this parasite grows in the presence of a compromised immune system.Patients present with concomitant watery diarrhea, abdominal pain, nausea, and vomiting. Cryptosporidium can be microscopically detected by identifying oocytes in stool or tissue, PCR tests, or utilizing enzyme-linked immunosorbent assay (ELISA). Common treatments include nitazoxanide and support care with rehydration and electrolyte repletion [14,37]. Finally, HHV-8 is a double-stranded DNA virus, part of the herpesvirus family, and should be monitored in HIV patients. This virus can cause diseases including Kaposi sarcoma-associated herpesvirus, a cancer in which metastatic cells are found in the skin or mucous membranes that line the gastrointestinal tract and can be triggered by a weakened immune system, especially if invaded/occupied by Herpes virus [25,38,39,40]. Patients can present with purple to brown lesions, multiple sites of lymphadenopathy, hepatosplenomegaly, elevated IL-6, thrombocytopenia, or organ failure if severe. HHV-8 can be detected by immunohistochemical staining with antibodies targeting latency-associated nuclear antigen (LANA), PCR, or nucleic acid testing in plasma and peripheral blood mononuclear cells. Before the availability of effective treatment options, Kaposi sarcoma was diagnosed at a high rate due to uncontrolled HIV infections during the AIDS epidemic. Current management of HHV-8 and associated diseases includes ART, antiviral therapy such as ganciclovir, foscarnet, cidofovir, adefovir, and cytotoxic chemotherapy [29]. Complications not only arise from opportunistic infections but can also originate from the different antimicrobials that are used to treat these infections; antibiotics, antifungals, and antivirals all contain adverse side effects and if initiated simultaneously, there is an increased risk of complications. This risk was demonstrated when the patient developed a C. difficile infection due to the use of multiple antibiotics for a prolonged duration and his immunocompromised state. C. difficile is a gram-positive, toxin-producing, anaerobic bacteria that infects the colon to cause antibiotic-associated diarrhea [30,31]. Common first-line treatment options include fidaxomicin and oral vancomycin. The significance of this case describes a patient with uncontrolled HIV who presented with complex complications. Early HIV identification and appropriate intervention from both the patient and providers are integral in achieving optimal patient outcomes. The patient presented with lymphadenopathy, neutropenia, and splenomegaly within three weeks of initiating ART. This rapid turnaround time and the patient’s eight

complications, including seven infections, highlight the severity of opportunistic infections that may arise due to IRIS when ART is initiated. The highly fatal outcomes in patients with IRIS present the need for timely identification of multiple, simultaneous infections that may be viral, bacterial, or fungal, and require extensive knowledge of current treatment guidelines.Multiple therapies increase the risk of interactions and complications; hence, understanding adverse effects and alternative therapies is crucial for improved patient care and demonstrates the impact of interdisciplinary teams.

Conclusion

In conclusion, we have described the clinical and treatment course of a 26-year-old man with multiple readmissions due to underlying HIV and IRIS-induced opportunistic infections. Despite the rapid development and expansion of HIV treatment, IRIS is a potential risk throughout management, especially at the onset of therapy initiation, and patients need to be consistently monitored for opportunistic infections. This case provided a comprehensive review of treatments for a patient diagnosed with HIV with multiple co-infections while maintaining ART in order to build up a competent immune system.

Declarations

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Consent for publication: Informed consent was obtained from the patient, consent form available upon request

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