OLGU SUNUMU / CASE REPORT

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A Multidisciplinary Approach to Opportunistic Infections in a Late-presenter Person Living with HIV

Geç Tanı Alan HIV ile Yaşayan Kişide Fırsatçı Enfeksiyonlara Multidisipliner Yaklaşım

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Abstract

Opportunistic infections remain as an important cause of morbidity and mortality in patients with human immunodeficiency virus (HIV), predominantly in patients who are not receiving antiretroviral therapy. On the other hand, the evaluation and management of patients with HIV admitted with altered mental status and abnormal neurologic examination is a challenging issue due to the non-specific nature of signs and symptoms. Cytomegalovirus (CMV) associated neurological disorders are rare in patients with HIV; however, in some cases it may lead to rapidly fatal encephalitis. Another very serious HIV-related manifestation of CMV is retinitis, which must be discerned in a clinically relevant context. We present a case of a middle age adult, presenting with a change in mental status and a wide array of neurological complaints, who was later diagnosed with HIV infection. Further clinico-radiological evaluation was conducted which revealed CMV encephalitis superimposed on a chronic ground of HIV-associated neurocognitive disorder. During the course of follow up, the patient developed AIDS-related invasive pulmonary aspergillosis and pulmonary aspergilloma, and later underwent pulmonary lobectomy in consultation with the departments of thoracic surgery and radiology. In conclusion, this case emphasizes the importance of multidisciplinary approach to patients with HIV who presents with various clinical features due to the involvement of multiple organ systems which may necessitate a tremendous amount of laboratory and radiological investigation.
Keywords: AIDS, opportunistic infections, ART

Öz

Fırsatçı enfeksiyonlar özellikle antiretroviral tedavi almayan İnsan immün yetmezlik virüsü (HIV) ile yaşayan kişilerde (HYK) hala önemli bir morbidite ve mortalite sebebidir. Öte yandan, mental durumunda değişme olan ve normal dışı nörolojik muayene bulguları ile başvuran HYK'lerin değerlendirilmesi ve yönetimi spesifik olmayan bulgu ve semptomlardan dolayı zorlayıcıdır. İnsan immün yetmezlik virüsü ile yaşayan kişilerde Sitomegalovirüs (CMV) ilişkili nörolojik bozukluklar nadir olsa da, bazı olgularda ölümcül ensefalite sebep olabilir. Sitomegalovirüs retiniti, tanının uygun klinik tablo ile konulduğu, HYK'lerde diğer ciddi bir durumdur. Bu olgu raporunda mental durumunda değişme ve yaygın nörolojik şikayetleri olan ve sonrasında HIV ile yaşayan olduğu anlaşılan orta yaşlı bir erişkin olgu sunulmuştur. İleri klinik ve radyolojik değerlendirme sonucunda HIV ilişkili nörokognitif bozukluk zemininde gelişen CMV ensefaliti gösterilmiştir. Takip sürecinde AIDS ilişkili invaziv pulmoner aspergilloz ve fungus topu geliştiren olguya, radyoloji ve göğüs cerrahi bölümleri ile konsülte edilerek pulmoner lobektomi uygulanmştır. Sonuç olarak, bu olgu çok sayıda

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Öz

organ sisteminin tutulumuna bağlı olarak değişik klinik özellikler gösteren ve çok sayıda laboratuvar ve radyolojik inceleme gerektirebilecek HYK'lere multidisipliner yaklaşımın önemini vurgulamaktadır.
Anahtar Kelimeler: AIDS, fırsatçı enfeksiyonlar, ART

Introduction

Acquired immunodeficiency syndrome (AIDS) is one of the most important global health problems of the 21st century. Untreated HIV infection increases the risk of opportunistic infectious diseases (bacteria, viruses, fungi and protozoa)[1,2]. Antiretroviral therapy prevents the development of opportunistic infectious diseases. Despite the widespread and facilitated use of HIV testing, a significant number of people living with HIV/AIDS (PLWHA) are not admitted to health institutions until the late stages of the disease[3]. Late presentation is when a person has a CD4 count of less than 350 cells/mL or presents with an AIDS-defining condition independent of CD4 count. Late presentation is one of the most important causes of morbidity, mortality, risk of disease spread and failure of antiretroviral therapy (ART)[4]. Late admission is more common in traumatic groups (minorities, drug addicts, immigrants, etc.), groups who are not sufficiently aware of the risk of HIV infection (elderly and heterosexuals), people with low socioeconomic status (low education level, etc.), and those who fear sociocultural stigma[5].

Case Report

A 58-year-old male was admitted to a university hospital under emergency conditions with complaints of weight loss, weakness, inability to walk, speech disorder, loss of balance, urinary and stool incontinence, and personality disorder. He stated that he had weakness and fatigue for a year. Two months ago, he stated that temporary inability to walk and speak developed and resolved spontaneously. It was learned that he smoked for 30 packs/year, did not drink alcohol, and had incontinence in the last few days. Vital signs were as follows: fever 37 °C, BP: 100/70 mmHg, pulse: 120/min. The general condition of the patient was evaluated as moderate, it was determined that he was aphasic, had no orientation to place and time, had orientation to person, and neck stiffness and Kernig and Brudzinski signs were negative. In laboratory examination, hemoglobin level was 8.2 g/dl and C-reactive protein (CRP) level was found to be four times higher than normal, and interstitial infiltrates were observed on direct chest X-ray. In the lung tomography performed thereupon, a cavity filled with fluid density in the left upper lobe and ground-glass opacity in the right upper lobe of the lung were observed (Figure 1). In the follow-up, when the body temperature increased to 38.5 °C, scanning for infectious focus was performed. Piperacillin/tazobactam and

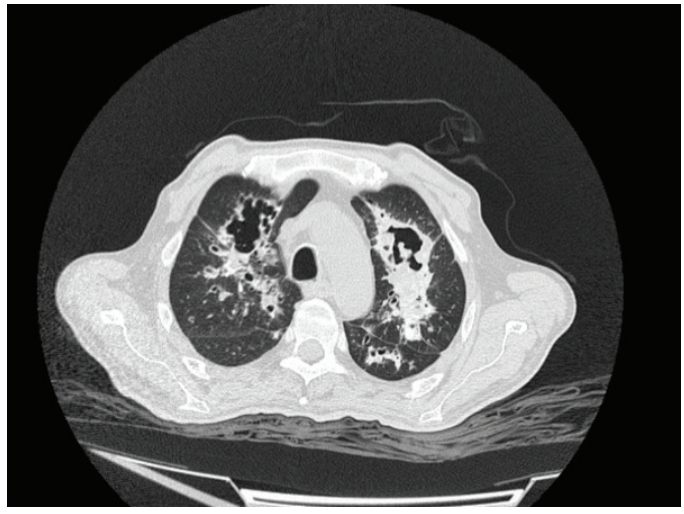

Figure 1. Cavity filled with fluid density in the upper lobe of the left lung and ground-glass opacities in the upper lobe of the right lung. 211x157 mm (72x72 DPI)

clarithromycin were started empirically with the diagnosis of pneumonia accompanied by cavitation.

Bronchoalveolar lavage (BAL) was also performed. *Candida albicans* and *Streptococcus dysgalactiae* grew in BAL culture. Acid-fast bacillus (ARB) and *Mycobacterium tuberculosis* (MTb) polymerase chain reaction (PCR) tests resulted negative in BAL and Sputum. In BAL examination, *P. jirovecii* PCR was positive and CMV PCR was 263000 copies/ml. In the preliminary diagnosis, pneumocystis pneumonia (PCP) was considered and trimethoprim-sulfamethoxazole was started at a dose of 15 mg/kg/day. Methylprednisolone at a dose of 2x40 mg/day was added as PO_2 was 61 mmHg, and caspofungin at a dose of 50 mg/day was added because candidal mucositis/esophagitis developed during the follow-up. Clarithromycin was discontinued due to hepatic toxicity developed on follow-up.

The patient's pathological findings of central nervous system (CNS) continued. Brain computed tomography (CT) was performed and the patient was consulted to the neurology clinic. In the consultation, brain magnetic resonance imaging (MRI) was planned, considering that the patient's current dementia had progressed. MR imaging revealed increased T2/FLAIR intensity consistent with encephalitis in the periventricular white matter of both cerebral hemispheres, left crus cerebri and pons. In addition, acute infarct was noted adjacent to the left part of the corpus callosum splenium (Figure 2). In the cerebrospinal fluid (CSF) examination performed for the differential diagnosis of

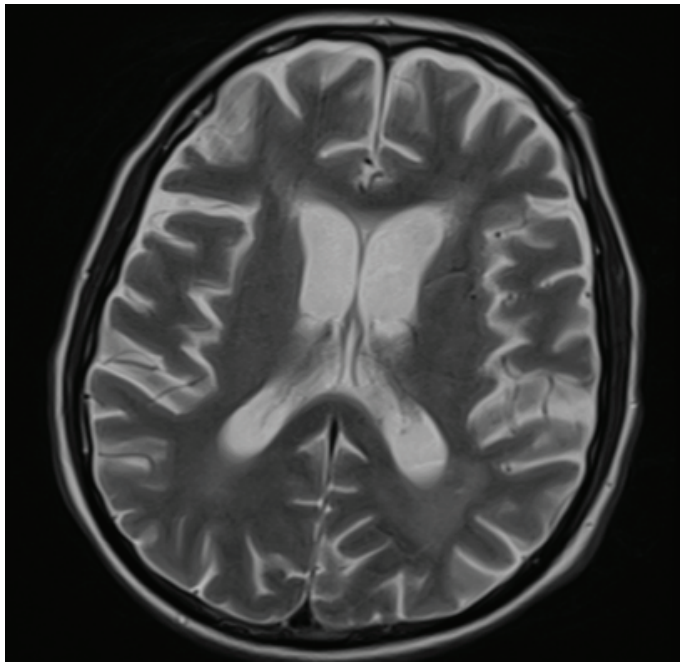

Figure 2. T2/FLAIR intensity increases consistent with encephalitis in the periventricular white matter, left crus cerebri and pons in both cerebral hemispheres. 142x138 mm (72x72 DPI)

CNS infection; opening pressure was normal, glucose level was 59 mg/dl (simultaneous blood glucose level was 100 mg/dl), and protein level was 41 mg/dl. The results of cryptococcal capsule antigen test, JC PCR, CMV PCR, HSV 1&2 PCR, MTb PCR and HHV-6 PCR in CSF were negative. No cells were observed in the direct examination of CSF, but a slightly increased number of lymphocytes and neutrophils were observed in the examination of a cytospin preparation. The anti-HIV test performed during the immunodeficiency study was positive, HIV RNA was $3.6x10^7$ copies/ml, CD4 count was 13 cells/ml, and ART consisting of tenofovir disoproxil fumarate/emtricitabine and dolutegravir was added to the patient's treatment.

In the follow-up of the patient, it was noticed that vision loss developed in the right eye and that the patient could not maintain his standing balance. The patient's current clinical and brain MRI findings were evaluated and CMV encephalitis was considered in the preliminary diagnosis, and iv ganciclovir 5 mg/kg/12 hours was added to his current treatment. At the same time, as a result of the evaluation of the ophthalmologist, an appearance compatible with CMV retinitis was determined. On the fifteenth day of his admission, the patient developed respiratory distress and fever, and air-fluid level was observed in the cavitary lesion in the left lower lobe on the chest X-ray. Considering lung abscess, the treatment was changed to meropenem 3x1 g/day. Dry cough, five-fold increase in CRP, and growth of *Aspergillus* spp. in sputum culture and new nodules in lung tomography were detected in the first month of hospitalization. With the diagnosis of invasive pulmonary aspergillosis, liposomal amphotericin B was started at a dose of 5 mg/kg.

In the patient whose serum creatinine level was previously normal, creatinine gradually increased to 1.35 mg/dl (GFR 58 ml/min). Considering renal toxicity due to amphotericin B, amphotericin B treatment was discontinued and voriconazole was switched.

The patient whose general condition was stable was discharged with TDF/FTC+DTG + ganciclovir 2x900 mg/day+ voriconazole 2x200 mg/day + TMP/SXT 2x1 tablets/day. The patient was transferred to the city where he lived to be followed up. At the first admission of the patient to the infectious diseases outpatient clinic in the city where the patient lived, CD4 count was 54 cells/ml, CD8 count 183 cells/ml, HIV virus load 97 copies/ml, CMV virus load 1847 copies/ml, blood galactomannan 0.6 ng/ml, CRP 0.662 mg/L, creatinine 1.11 mg/dl, BUN 18.3 mg/dl, albumin 4.53 g/dl, ALT 39 U/L, AST 53 U/L, ALP 174 U/L, GGT 222 U/L, CK 219 U/L, TG 272 mg/dl, and total cholesterol was 148 mg/dl. His current treatment was continued orally and the patient was followed up with monthly outpatient clinic controls. In the follow-up of CMV retinitis, the ophthalmology department continued to check the patient every three months. In this period, there were always findings of CMV retinitis sequelae in fundus examinations repeated. Subsequently, the CMV PCR remained continuously suppressed. Since he had a previous diagnosis of invasive pulmonary aspergillosis, he was followed up with lung imaging in the outpatient clinic.

During the follow-up of the patient, it was observed that the CD4 count increased, viral replication was suppressed, and the patient reached the body weight before the AIDS. At this stage, since the patient had been using oral voriconazole treatment for one year without interruption and only a fungal ball was found in the lung tomography, voriconazole treatment was discontinued and the patient was planned to be followed up closely at outpatient clinic with intervals. At approximately the twenty-first month of his illness, two months after voriconazole was discontinued, he was admitted to our outpatient clinic with complaints of chills, fever, cough, and pink/red sputum production. His general condition was good, his body temperature was 37.8 ˚C, and other vital signs were stable. On lung auscultation, widespread rales were detected on the left side. HIV RNA and CMV DNA were negative, CD4 count was 97 cells/ml. In the re-performed lung tomography, an increase in the size of the fungus ball and persistence of other findings were observed (Figure 3). Voriconazole treatment was restarted and the patient was consulted with the thoracic surgery clinic. Because a fungus ball was detected in the cavitary lesion in the upper lobe of the left lung in the thorax CT of the patient and hemoptysis was frequent, the patient underwent left upper lobectomy with a left posterolateral

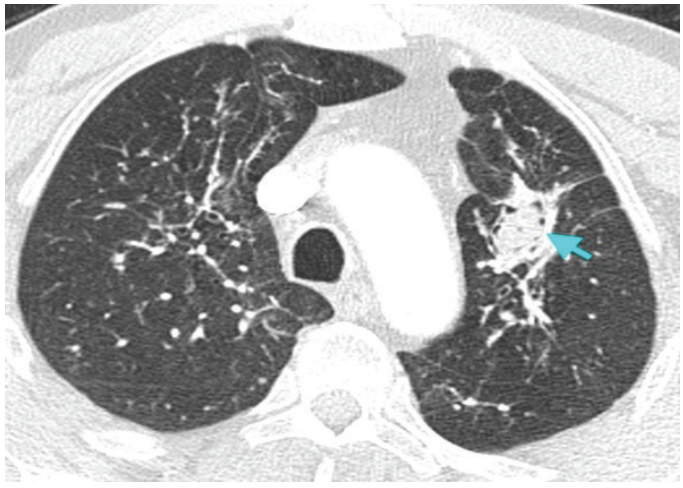

Figure 3. Increase in the size of the fungus ball. 68x48 mm (220x220 DPI)

thoracotomy. In the postoperative period, two thoracic drains were applied due to the poor lung parenchyma of the patient and the possibility of prolonged air leakage. The patient, who was able to be discharged after the seventh postoperative day surgically, was discharged on the tenth postoperative day after antibiotic treatment was completed, and the patient did not have any complaints of hemoptysis. Voriconazole treatment was continued for another three months, then voriconazole was discontinued. Despite discontinuation of voriconazole, no recurrence/reinfection of invasive pulmonary aspergillosis was observed.

Discussion

A multidisciplinary team led by an infectious disease specialist should manage patients with AIDS. It was understood that the patient was taken to the emergency room with loss of consciousness. Even if disorientation, instability, aphasia and fever are not accompanied, CNS infections are conditions that should be considered in the differential diagnosis. Apart from CNS infection, cerebrovascular accident, metastatic or primary intracranial mass, paraneoplastic syndrome, autoimmune encephalitis, and drug toxicity should be considered. Among the CNS infections, meningitis, encephalitis and brain abscess are life-threatening diseases. Patients with CNS infection may present to the emergency department with symptoms such as headache, fever, mental status changes, and behavioral and personality disorders[6]. Apart from CNS infections, the patient also had lung infection findings. Microbiological analyzes of respiratory samples should be performed quickly in the patient presenting with a picture of lung infection. Multiplex PCR technology, which has been widely used in recent years, can identify agents within hours in upper respiratory tract swab samples[7]. It is critical to identify the cause of lung infection by performing BAL in patients who are unable to obtain a sputum sample or in whom it is not possible to obtain a sample with a swab. BAL can be used in unspecified radiological infiltration or hypoxemic conditions, excluding infectious diseases. BAL can also be used to support the diagnosis of some non-infectious conditions (such as diffuse alveolar hemorrhage, pulmonary alveolar proteinosis, eosinophilic pneumonia, hypersensitivity pneumonitis, interstitial lung diseases, chronic beryllium disease, malignancies, and asbestos exposure)[8]. Evaluation of such patients in terms of immunodeficiency is also important because the spectrum of differential diagnosis is wider in immunosuppressed patients (eg, toxoplasma encephalitis, cryptococcal meningitis, CMV encephalitis). The coexistence of ground glass opacity in the lung and CNS involvement suggests that an immune deficiency may accompany. Again, a lumbar puncture will be required for the differential diagnosis of CNS infection.

Despite the advances in ART, pulmonary diseases cause serious morbidity and mortality in PLWHA[9]. Most PLWHA develop pulmonary complications at some point in the course of their illness. Bacterial pneumonia, PCP, tuberculosis (TB), cytomegalovirus pneumonia and atypical mycobacterial infections are frequently sources of pulmonary problems in PLWHAs. Respiratory syncytial virus, influenza, parainfluenza virus, *Aspergillus fumigatus* and *Cryptococcus* spp. infections can also be seen[10]. In PLWHA, developing pulmonary infections are parallel to the depletion of CD4 lymphocytes[11]. Opportunistic infections other than TB develop especially when the CD4 count is below 200 cells/mL.

Rare, life-threatening infections such as CMV infection or invasive aspergillosis are most common when the CD4 count falls below 50 cells/ml[12]. Other basic features that should be considered in the differential diagnosis are; a history of infection with a risk of recurrence (eg, TB), travel to a site predisposing to a specific opportunistic infection (eg, histoplasmosis), compliance problems with combined ART and PCP prophylaxis, and the presence of co-morbidities[12].

Today, community-acquired bacterial pneumonia is the most common infection in PLWHA and is the most common reason for hospital admission[13]. HIV infection increases the incidence of bacterial pneumonia more than 10 times[14]. For this reason, it is vital to recommend pneumococcal vaccine to PLWHA[15]. The risk of community-acquired pneumonia is increased in PLWHA, independent of CD4 count, and is much higher in people with low CD4 cell counts[16]. The causative agent of 20-40% of the patients is *Streptococcus pneumoniae*[17]. The clinical picture of community-acquired pneumonia caused by *S. pneumoniae* is similar in PLWHA and HIV-negative individuals who are demographic characteristics-matched and comorbidities-matched[18]. Haemophilus influenzae constitutes 10-15% of bacterial pneumonia[13]. This particularly affects advanced

PLWHA and a subacute clinical picture is observed in 30% of the patients.

More than half of the patients have bilateral lung infiltration. *Staphylococcus aureus* is the third most common cause of bacterial pneumonia[13]. *S. aureus* causes septic pulmonary embolism due to tricuspid valve endocarditis, especially in case of intravenous injection.

Although there is limited information about the etiology and risk factors of respiratory viral infections in PLWHA, respiratory viruses may have a role in the development of pulmonary complications in these patients[19]. ART has reduced hospitalizations due to influenza. However, influenza is an important factor of respiratory tract diseases in PLWHA[19]. PLWHA are at risk for the development of serious complications related to influenza[20]. Studies show that influenza is the most frequently reported agent in PLWHA who present to the outpatient clinic with fever and acute respiratory symptoms during the winter period. Although the disease is generally mild, pulmonary complications and death due to influenza can be seen in PLWHA. Most pulmonary complications occur with bacterial superinfection. Although influenza vaccine is indicated for all PLWHA, not all PLWHA are vaccinated or an optimal response to the vaccine cannot occur in progressively immunosuppressed PLWHA. The diagnosis of influenza is made by clinical findings or RT-PCR made from respiratory secretions during periods of high influenza frequency.

Although the incidence of PCP has decreased thanks to the widespread use of ART and prophylaxis applications targeting PCP which is the most common opportunistic infection in the AIDS period[12]. PCP in PLWHA presents with fever, dry cough, and worsening shortness of breath. The diagnosis of PCP is much easier in PLWHA than in other immunosuppressed patients. With Gomori-Grocott or Giemsa and immunofluorescent staining, *Pneumocystis jirovecii* in BAL fluid can be demonstrated with 90% sensitivity[21]. Histological staining of induced sputum, if positive, is diagnostic for PCP. Although the specificity of induced sputum analysis for PCP is 100%, its sensitivity is low (55-92%)[22]. The advantage of the PCR test is that it can diagnose patients whose clinical findings are compatible with PCP and cannot be confirmed microscopically. The disadvantage of the PCR test is that it cannot distinguish between colonization and disease due to its high sensitivity. In a meta-analysis, the sensitivity and specificity of the RT-PCR test were found 97% and 93%, respectively[23].

Pulmonary-TB (P-TB) is a common AIDS-defining infection in AIDS[24]. Globally, at least 1/3 of PLWHA are infected with MTb, and HIV infection is the biggest risk factor for TB worldwide[25]. In low- and middle-income countries, TB is one of the most common causes of death in PLWHA[13]. While P-TB presents with a typical clinical picture in individuals with high CD4 counts, it progresses with atypical radiological findings (miliary or diffuse alveolar infiltration without cavitation in the upper lobe) and extrapulmonary involvement in individuals with low CD4 count (<200 cells/ml). In people with low CD4 count, ARB may not be detected in the sputum sample. MTb PCR should be performed in at least one respiratory sample in all PLWHA suspected of having P-TB. Today, PCR is about to replace ARB staining in the diagnosis of TB. PCR can diagnose independently of sputum ARB positivity. It can also distinguish MTb from atypical mycobacteria. PCR can also predict resistance to anti-TB agents in a short time. PCR is positive in 50-80% of patients in whom ARB staining is negative but there is a growth of MTb in culture[26].

Interferon gamma release tests (IGST) are based on the in-vitro measurement of interferon gamma secreted by T cells specific for MTb antigens (ESAT-6, CFP-10). Because these antigens are specific for MTb and, more importantly, not secreted by BCG vaccine strains, IGST is more specific than tuberculin skin testing for the diagnosis of latent TB[27]. Another noteworthy point is that IGST can be negative in 30% of patients with active TB. Therefore, it should not be used as the main diagnostic tool[21]. Detection of mycobacterial lipoarabinomannan (LAM) antigen in urine has become a potential point-of-care test for the diagnosis of TB. LAM is a thermostable glycolipid found in the outer wall of mycobacterial species and is secreted from metabolically active bacilli. Since LAM is excreted by the kidneys, it can be detected in the urine. Excretion of LAM in the urine becomes more evident in advanced PLWHA and patients with disseminated TB. The urine LAM test is especially important for people with suspected TB but negative sputum smear results and for whom it is difficult to obtain a sputum sample regardless of HIV infection. While the sensitivity of the urine LAM test is between 56-85% in individuals with a CD4 count below 50 cells/ml, its specificity is more than 88%[28].

Non-MTb *Mycobacterium* spp. infections are seen with increasing frequency in PLWHA. Although the most common species is *Mycobacterium avium* complex (MAC), at least 12 different species have been described[13]. *Mycobacterium avium* complex infection predominantly develops when the CD4 cell count is below 50 cells/ml.

The most common bilateral lower lobe infiltration compatible with miliary spread, in addition to alveolar or nodular infiltrates and hilar and/or mediastinal lymphadenopathy can be seen in radiological imaging of lung. A diagnosis of pulmonary disease is made with MAC positivity in two consecutive sputum samples, a favorable clinical picture, and compatible imaging findings.

The CMV infection most commonly causes retinitis and gastrointestinal system involvement. Lung involvement is rare before the CD4 cell count is very low (<50 cells/ml)[10]. In

addition, although CMV was detected in BAL fluid together with agents such as MTb and *P. jirovecii*; the role of CMV as a causative agent of pulmonary disease was not fully understood. BAL sampling and cytology are not specific for the diagnosis of CMV pneumonia. Therefore, treatment should only be considered in the presence of symptomatic pulmonary disease after other possibilities are ruled out[29]. CMV pneumonia has no globally accepted criteria. There are diagnostic criteria used for research purposes only in organ transplant and hematopoietic cancer patients. Diagnosis is made by demonstrating CMV from blood and respiratory tract samples and proving lung involvement on tomography in individuals with appropriate clinical status[30]. The utility of BAL and CMV PCR test has not been evaluated in HIV positive patients and patients with CMV pneumonia patients[31].

The incidence of endemic fungal infections is thought to decrease after ART[21]. Although our country is located in a geography where these fungi are not endemic, it should be kept in mind that travel-related cases can be seen. Histoplasmosis is the most common endemic mycosis in PLWHA. Diffuse histoplasmosis and coccidioidomycosis mostly develop when the CD4 cell count is below 100 cells/ml[10].

Cryptococcosis is most commonly seen as a diffuse disease. Lung is the second most common site of involvement after CNS. Pulmonary cryptococcosis is more acute in PLWHA than in HIV-negative individuals[10].

Although neurological diseases caused by CMV are rare, they can be life-threatening and fatal. CMV can cause encephalitis, polyradiculitis, retinitis and rarely myelitis[32]. CMV encephalitis occurs with reactivation as a result of CD4 cell count less than 50 cells/ml and usually progresses with delirium, confusion and focal neurological disorders. The diagnosis of CMV encephalitis is made by showing CMV PCR positivity in the CSF in the presence of a clinical course with neurological involvement compatible with CMV infection[33]. CMV encephalitis can be seen on MRI as diffuse micronodular encephalitis or ventriculoencephalitis. Micronodular encephalitis is characterized by multifocal, widely distributed micronodules in the cortex, basal ganglia, brainstem, and cerebellum, while ventriculoencephalitis is characterized by progressive ventricular enlargement, periventricular involvement, and increased periventricular signal on T2-weighted imaging. The sensitivity of PCR is 95% and the specificity is 85%. Serum CMV PCR may also be positive in individuals with low CD4 cell counts but without CMV-related neurological disease. Because this test has low positive predictive values, it cannot be used as a screening test for CMV-related diseases[21].

Although the incidence rate of progressive multifocal leukoencephalopathy (PML) has decreased markedly with the widespread use of ARTs, PML remains an important CNS complication of HIV[34]. Progressive multifocal leukoencephalopathy is a demyelinating disease that occurs with the reactivation of JC virus in severely immunosuppressed patients. Although JCV reactivation typically occurs when the CD4 cell count is 100 cells/ml, JCV infection can also be observed in conditions with high CD4 cell counts[34,35]. PML presents with rapidly progressive focal neurological deficit, hemiparesis, visual field loss, ataxia, aphasia, and cognitive impairment. The definitive diagnosis of PML is made by showing JCV PCR positivity in CSF in addition to imaging and clinical features. Although the specificity of the JC virus PCR test used in PML is 98%, its sensitivity may be as low as 76%[32].

With the development and widespread use of ARTs, there has been a significant decrease in the severity of HIV encephalitis over the years, but it has been shown that even in the presence of ARTs, almost half of PLWHA develop mild to moderate neurocognitive impairment during their illness[36,37]. The clinical presentation of HIV encephalitis or HIV-related neurocognitive disorder ranges from asymptomatic or mild neurocognitive impairment to severe dementia[38]. HIV encephalitis typically presents with signs of subcortical dementia (slowing memory and psychomotor speed, depressive symptoms, and movement disorders). The diagnosis of HIV encephalitis is based on a combination of neuropsychiatric evaluations and radiological imaging.

In HIV encephalitis, focal areas with high signal intensity can be seen in both cerebral hemispheres, which usually begin unilaterally on T2-weighted images on MRI. In later phases, bilateral T2 hyperintense areas characterized by deep white matter involvement may be seen on MRI. These involvement areas do not create a mass effect[39]. In the brain MRI of the patient, T2 hyperintense lesions are observed in the bilateral frontoparietal subcortical deep white matter and periventricular white matter, and the findings are compatible with HIV encephalitis (Figure 4). Epidemiological studies have shown that ART combinations significantly reduce morbidity and mortality in PLWHA[40]. The life expectancy of patients who are treated before severe immunosuppression and do not have significant co-morbidities approaches that of the general population. In addition, ARTs used prevent the transmission of HIV. For these reasons, ART should be started as soon as possible in all PLWHA, regardless of CD4 count [41].

The radiological findings of the involvement of *Aspergillus* in the lung parenchyma vary depending on the immune status of the patient and the phase of the disease. In allergic bronchopulmonary aspergillosis, tubular-shaped density increases are observed mostly in the upper lobes of the lung, representing bronchiectasis impacted by mucus, on CT. Atelectatic changes can be observed. In aspergilloma, mycetoma is observed in the form of soft tissue density in the cavity. CT

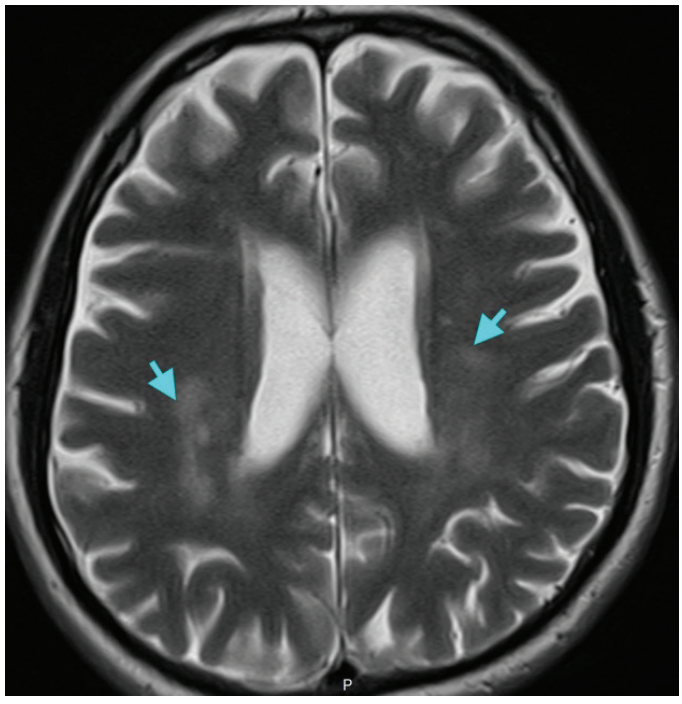

Figure 4. T2 hyperintense lesions in bilateral frontoparietal subcortical deep white matter and periventricular white matter. 72x74 mm (220x220 DPI)

images obtained in different positions (supine, prone) of the patient show that the mycetoma has moved within the cavity. There is a crescent-shaped air density between the mycetoma and the cavitary lesion wall. In semiinvasive aspergillosis, consolidations leading to necrosis and forming cavities are often seen. Pulmonary nodules, pleural thickening, bronchial wall thickening and endobronchial nodules can be observed as accompanying imaging findings in these patients. In invasive aspergillosis, on the other hand, on CT, thickening of the airway wall, peribronchial consolidation, an increase in density in the form of a budded tree view, and the classical finding, the 'halo sign', which is observed as an increase in the nodular consolidation area and its surrounding ground glass density are seen[42].

In the thorax CT of the tenth month of the first presentation of this patient, tubular bronchiectasis with fibrotic changes in the upper lobes of both lungs and a fungal ball (mycetoma) in the cavitary lesion in the left lung upper lobe are observed (Figure 5).

Three main classes of drugs can be used in the treatment of invasive pulmonary aspergillosis: polyenes, azoles, and echinocandins. Most patients are given voriconazole or isavuconazole as initial therapy in line with current guideline recommendations[43]. A combination of voriconazole and an echinocandin is recommended in patients with severely invasive aspergillosis. Voriconazole has oral and intravenous forms. Voriconazole is used as 6 mg/kg every 12 hours on the first

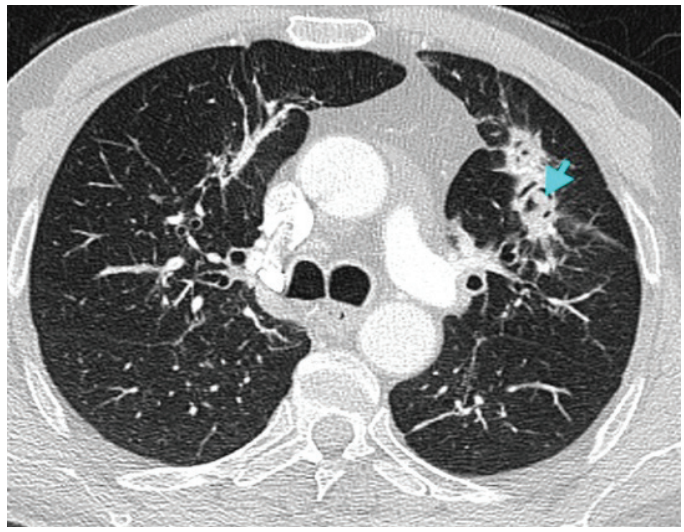

Figure 5. Tubular bronchiectasis with fibrotic changes in the upper lobes of both lungs and a fungus ball (mycetoma) in the cavitary lesion in the upper lobe of the left lung. 62x48 mm (220x220 DPI)

day of treatment, and then 4 mg/kg IV every 12 hours. When the patient is able to tolerate oral therapy, oral therapy can be started at 200 mg every 12 hours.

The minimum duration of treatment in invasive aspergillosis is between 6-12 weeks; however, this process may take months or even years in patients whose immune system does not recover[44,45].

Although there are many causes (bronchiectasis, tumor, foreign body, pulmonary embolism, etc.) in the differential diagnosis of hemoptysis in the patient with hemoptysis complaints, lung infections come to mind primarily in PLWHA. Tuberculosis, bacterial lung abscess and lung fungal infections, which are the reality of our country, are the first differential diagnoses that come to mind[46]. Hemoptysis is a serious, life-threatening complication of invasive aspergillosis. Erosion of the bronchial arteries is one of the causes of this bleeding.

Even if patients are stabilized by bronchial artery embolization, recurrent bleeding is common. Surgical resection is the most preferred treatment method, since medical treatment is also limited and hemoptysis is a life-threatening complication. However, surgery cannot be applied to all patients, since patients with aspergilloma generally have limited respiratory reserves due to underlying lung diseases, and conservative treatment is preferred[47,48]. Limited resections such as "wedge" resection can be applied, as well as wider resections such as lobectomy and pneumonectomy. Various surgical options are available, from cavernostomy or cavernomyoplasty to thoracomioplasty. The surgical method is determined according to the patient's condition. The main point in surgery is not to leave any infected tissue behind in order to prevent recurrence. Mortality in aspergilloma surgery is up to 44%[49]. The cause of

mortality is bleeding that may occur during surgery, as well as bronchopleural fistula and empyema that may develop in the postoperative period[47,49]. The surgery was performed electively because our patient had sufficient respiratory reserve and effort capacity, did not have any additional disease, had an aspergilloma cavity as wide as 8.5 cm, and had recurrent hemoptysis that did not regress despite antifungal treatment.

In the surgery performed with thoracotomy, it was observed that the lung was widely adhered to the thoracic wall and diaphragmatic surface. The possible cause of adhesions was past infections.

In the macroscopic examination of the cross-sectional surface of the lung upper lobectomy material, it was observed that some bronchial branches were enlarged and their walls were thickened, and a soft, necrotic material was found in their lumens. In the microscopic examination of the prepared sections, dilatation of medium-sized bronchial branches, thickening with a fibroinflammatory reaction in the wall, as well as necrosis in the mucosa and hyphal structures and necrotic debris in the lumen were observed. The inflammatory reaction was accompanied by diffuse dystrophic calcification. In addition, similar necrotic calcified foci containing fungal structures were observed in the alveolar parenchyma. The structures observed were hyphae structures with wide and frequent septations, with smooth contours and 45 degrees angle to each other. These features defined for the hyphae seen (septate, smooth contoured and branching at 45 degrees) are compatible with the morphological features of other mold fungi (*Fusarium, Scedosporium, Acremonium*) that cause hyalohifomycosis as well as *Aspergillus*.

Fungal structures became evident histopathologically when Gomori methenamine silvering (GMS) and hematoxylin-eosin stains were applied (Figures 6, 7).

In our case, although fungal elements were not observed in the mycology laboratory during the microscopic examination of the tissue samples, mold growth in the culture and hyphae were observed in the histopathological examinations. The sensitivity of direct microscopy in the diagnosis of invasive mycoses is highly variable. It is known that the sensitivity increases with the use of fungi-specific dyes such as calcofluor white, GMS and Whey[50,51]. However; in some cases, the amount and nature of the incoming sample may limit the applicability of different processes. This patient was diagnosed as having a fungus ball radiologically and then lobectomy was performed. Since the tissue taken was very large, it might not be possible for the materials sent for different procedures to be homogeneous in terms of microorganism load. The fact that the growth was observed in the fungus culture after 10 days suggested that the amount of fungus in the sample reaching the mycology laboratory was low. This may also explain the false negatives in microscopy in the mycology laboratory. During the follow-up of the patient, no fungal element was found in the Gram stained smear made from the tissue sample; however, mold growth was observed on Sabouraud dextrose agar. Growing mold was defined morphologically as *Aspergillus niger* complex[50]. Antifungal susceptibility testing was performed according to the recommendations of the European Committee on

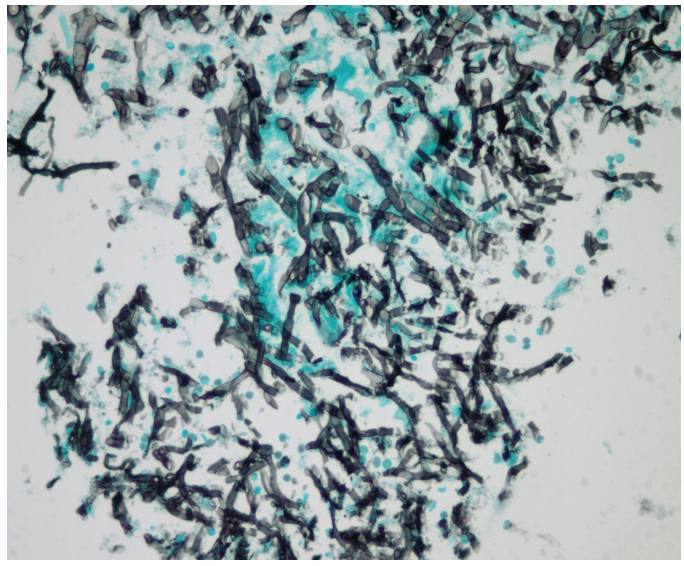

Figure 6. Hyphae structures with regular contours and 45 degrees angle to each other showing wide and frequent septations in Gomori methenamine silvering 629x517 mm (72x72 DPI)

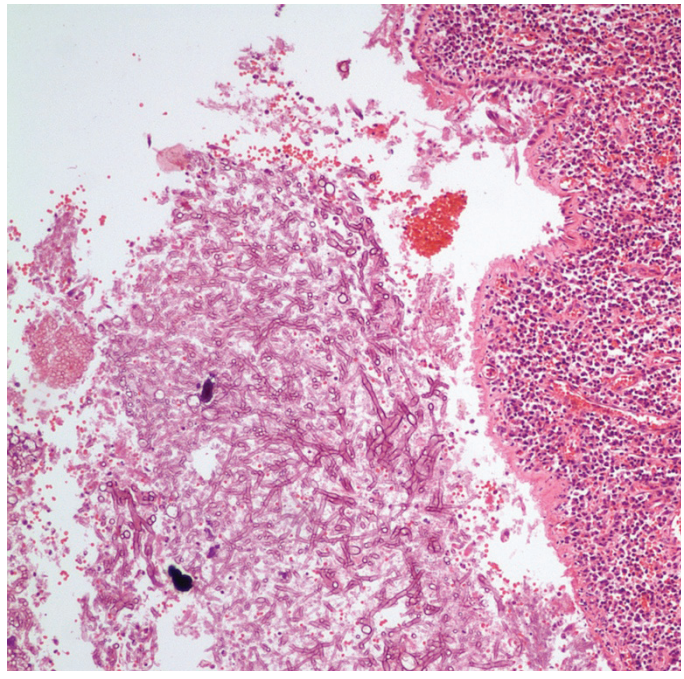

Figure 7. Hyphae structures with regular contours and 45 degrees angle to each other, showing wide and frequent septations in hematoxylin-eosin 722x722 mm (72x72 DPI)

Antimicrobial Susceptibility Testing and the minimum inhibitory concentration values obtained were as follows: amphotericin B 0.125 mg/L (sensitive), voriconazole 1 mg/L, posaconazole 0.125 mg/L, and itraconazole 0.25 mg/L[52].

Conclusion

Thanks to modern ART and effective treatment of opportunistic infections, PLWHA have achieved life expectancy comparable to HIV-negative people. In this article, a patient that was followed up with a multidisciplinary approach and resulted in a satisfactory manner was discussed. Early diagnosis of HIV infection is vital. Delays in diagnosis cause delays in treatment and patients present with a life-threatening condition. Our patient received appropriate treatment following the necessary investigations in the health institution where he was admitted with more than one opportunistic infection and was transferred to another center for follow-up of his treatment. The referral process is an important step that can lead to the disappearance of patients and their withdrawal from treatment. Here, the patient's referral and connection to the next follow-up center took place under ideal conditions, and it was possible to continue the follow-up of the patient. Multidisciplinary teamwork was the main factor contributing to the success in the follow-up of this patient.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.R.B., Y.B., S.U., M.Ç.S., D.G., S.Ç.Ö., M.R.O., S.A.A., A.Ç.İ., D.İ., S.Ü., Concept: A.R.B., Y.B., A.Ç.İ., Design: A.R.B., Y.B., D.G., A.Ç.İ., Data Collection or Processing: A.R.B., Y.B., D.G., M.R.O., A.Ç.İ., Analysis or Interpretation: A.R.B., Y.B., D.G., A.Ç.İ., Literature Search: A.R.B., Y.B., D.G., A.Ç.İ., Writing: A.R.B., Y.B., S.U., M.Ç.S., D.G., S.Ç.Ö., M.R.O., A.Ç.İ., D.İ., S.Ü.

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