ORIGINAL PAPER

Cytomegalovirus pneumonia in HIV-infected patients: case series from Iran

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Abstract

Introduction: Cytomegalovirus (CMV) is a leading cause of morbidity and mortality among the immunosuppressed population, and it is a common cause of opportunistic infections in human immunodeficiency virus (HIV)-positive patients. In this case series study, we describe our experience with nine HIV-positive patients suffering from pneumonia who demonstrated typical cyto-pathologic evidences of CMV pneumonitis.

Material and methods: Clinical records of all HIV-infected patients with pneumonia who were admitted to National Research Institute of Tuberculosis and Lung Diseases (NRITLD), a tertiary center of tuberculosis and lung diseases in Iran, were prospectively reviewed. Results of micro-biological investigations of bronchoalveolar fluid (BAL) and trans-bronchial lung biopsy (TBLB) specimens were evaluated as well as their histological and cytological findings. All patients with cyto-pathologic evidences of CMV pneumonitis found in TBLB were extracted, characteristic of which was shown as enlarged cells with large pleomorphic nuclei, and intra-nuclear and cytoplasmic inclusions.

Results: Of these cases, seven patients were diagnosed with concomitant CMV and *Pneumocystis jiroveci* pneumonitis. Five patients had thrush, two patients tested positive for active tuberculosis, and one patient reported a history of old tuberculosis. Laboratory data analysis revealed LDH ranging from 138 to 1,140, with average amount of 653.22. CD4+ counts ranged from 12 to 156, with average of 56.22. Six patients tested positive for CMV infection with plasma polymerase chain reaction (PCR) method.

Conclusions: The differential diagnosis for CMV pneumonia in HIV-infected population is extensive and includes diseases, such as bacterial pneumonias, *Mycobacterium tuberculosis* infections, PCP, and other HIV-associated respiratory infections. Definitive diagnosis is based upon demonstration of CMV in pulmonary secretions or in lung tissue.

HIV AIDS Rev 2022; 21, 4: 327-331
DOI: https://doi.org/10.5114/hivar.2022.120159

Key words: cytomegalovirus (CMV), human immunodeficiency virus, HIV, pneumonia.

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Article history:
Received: 31.05.2020
Received in revised form: 06.04.2021
Accepted: 11.02.2022
Available online: 13.09.2022

Introduction

Cytomegalovirus (CMV) has long been recognized as an important cause of chorioretinitis, esophagitis, colitis, adrenalitis, and encephalitis in human immunodeficiency virus (HIV)-infected patients with severe immunodeficiency [1]. Although CMV is frequently isolated from pulmonary secretions of acquired immunodeficiency syndrome (AIDS) patients with pneumonia, its' contribution to morbidity and mortality of these patients is still an issue of controversy. That is because this virus is usually associated with other opportunistic pathogens, such as *Pneumocystis jiroveci*, therefore it is rarely confirmed as a sole pathogen in patients with AIDS [2, 3]. Although florid end-organ CMV diseases may no longer be a substantial problem due to increasing success of antiretroviral treatment (ART), there is growing evidence that its' impact as a co-pathogen remains highly relevant [4]. Several studies performed before the introduction of corticosteroids in the treatment of HIV-related pneumocystis pneumonia (PCP) showed that CMV co-infection does not contribute directly to pulmonary disease in these patients [5]. However, corticosteroids may impair defense mechanisms against CMV. In-vitro data in one study indicated unrestricted replication of CMV in corticosteroid-treated macrophages [6]. In another study, corticosteroid therapy was related to an increased incidence of CMV retinitis and colitis in HIV-positive patients [7].

Pneumonia caused by cytomegalovirus is among the leading causes of morbidity and mortality in immune-suppressed patients and in HIV-infected patients [8, 9]. In the evaluation of patient presenting with AIDS, a high level of clinical vigilance for detecting CMV infection should be maintained [10]. In HIV patients, the presence of CMV in bronchoalveolar lavage (BAL) specimens is not usually indicative of CMV pneumonia [11, 12], and definitive diagnosis relies on documented evidence of CMV infection in a pulmonary tissue specimen [13].

Pneumonias caused by *Pneumocystis jiroveci* are the most common opportunistic infections in the HIV-infected population [14, 15]. HIV-positive patients with CD4+ counts less than 200 cell/mm^3 are more likely to become infected with *Pneumocystis jiroveci* [16, 17].

Undoubtedly, pulmonary disease is one of the main causes of morbidity and mortality in HIV patients. In HIV-infected patients, cavitary pulmonary lesions have an extensive spectrum of diagnoses. As a result of immune insufficiency and decreased surveillance in these patients, infectious lesions are predominant, and it is very common to isolate more than one organism in their autopsies, particularly in the advanced stage of AIDS [18]. In endemic countries, tuberculosis is the most common etiology [19-21].

CMV pneumonia has a non-specific pattern in radiologic findings including reticulo-nodular infiltration bilaterally, which begins from peripheral areas and progresses to the center [22].

Before the use of chemoprophylaxis, *Pneumocystis jiroveci* was the most common cause of mortality in HIV-positive patients, and it is still the most prevalent cause of mortality in HIV-positive patients not taking chemoprophylaxis [23]. Due to the fact that PCP cannot be propagated in culture, the diagnosis of *Pneumocystis jiroveci* relies on a microscopic assessment of pulmonary tissue and examination of BAL fluid [24].

Non-productive coughs, progressive dyspnea, and fever are the most common symptoms of PCP. A normal pulmonary auscultation exam is possible in these patients [24]. The mild to moderate form of PCP can be treated as an outpatient, with oral therapy and close follow-up; however, in severe forms characterized by hypoxemia, hospitalization is more appropriate for these patients [25]. Chest radiologic findings in many cases may be normal; therefore, high resolution computed tomography (HR-CT) is more useful in revealing cystic lesions as well as a ground glass pattern [26].

For the diagnosis of *Pneumocystis jiroveci*, many techniques can be used, including immuno-fluorescence method with mono-clonal antibodies and molecular techniques, which are specific, but the specificity of this test depends on the level of *Pneumocystis jiroveci* in a sample. The best method for *Pneumocystis jiroveci* detection is BAL analysis. Sensitivity of PCR in HIV-positive patients' sputum-induced samples is high. Treatment is based on SMX-TMP, but in patients who cannot tolerate this drug, pentamidine (IV), or trimetrexate (IV) with folinic acid can be used [27].

Herein, we describe our experience with pneumonia in nine HIV-positive patients who had typical cytopathologic evidence of CMV pneumonitis in their lungs.

Material and methods

Clinical records of all HIV-infected patients with pneumonia admitted to National Research Institute of Tuberculosis and Lung Diseases (NRITLD), a tertiary center of tuberculosis and lung diseases in Iran, between December 2008 and December 2013, were prospectively reviewed. We evaluated the results of micro-biological analysis, including Gram staining, Ziehl-Neelsen staining, and culture for bacteria, myco-bacteria, viruses, and fungi performed using patients' broncho-alveolar fluid (BAL) and trans-bronchial lung biopsy (TBLB) specimens as well as histological and cytological findings. All patients with cyto-pathologic evidence of CMV pneumonitis found in TBLB were extracted, which is characterized by enlarged cells with large pleomorphic nuclei, and intra-nuclear and cytoplasmic inclusions.

Our team has recorded the following variables: age, sex, suspected mode of HIV transmission, any previous episodes of opportunistic infections, patients' signs and symptoms at the onset of disease (cough, fever, hemoptysis, and dyspnea), laboratory variables at presentation (serum lactate dehydrogenase [LDH] and CD4+ cell count), arterial oxygen saturation (SaO_2) on admission, chest radiograph on admission and discharge, BAL fluid PCR for CMV, and pharmaceutical interventions, including prescription of steroids, antivirals, and antibiotics. Ophthalmoscopic examination was performed in all patients diagnosed with CMV pneumonitis.

Moreover, we identified patients with PCP, based on performing mono-clonal staining.

Patients included in our study were followed-up as out-patients for at least 6 months. Mortality data were both obtained from their in-patient and out-patient records.

All values were expressed as mean value ± SD of the mean. Comparisons were made using Students' *t*-test. A *p*-value of < 0.05 was considered statistically significant.

Treatment policies

Trimethoprim-sulfamethoxazole (TMP-SMZ) is the drug of choice for treatment of PCP at our institution, with intravenous therapy applied for patients with moderate to severe disease, and oral therapy used for patients in milder stages. Adjunctive corticosteroids are generally recommended for patients with moderate to severe PCP infection, indicated by a PaO_2 less than 70 mmHg. All patients with PCP are treated as in-patients in our center.

ART was offered as a combination of three drugs, included two nucleoside reverse-transcriptase inhibitors and one non-nucleoside reverse-transcriptase inhibitor (zidovudine, lamivudine, and efavirenz). For patients with cyto-pathologic evidences of CMV pneumonitis found in TBLB, intravenous ganciclovir was administered at a dose of 5 mg/kg every 12 hours for three weeks, followed by a 900 mg of valganciclovir twice daily for the next three weeks, and another 900 mg of valganciclovir once daily, as a maintenance therapy.

Results

Between December 2008 and December 2014, diagnostic cyto-pathologic changes suggestive of CMV infection cytomegalic cells with typical intra-nuclear and intra-cytoplasmic inclusion bodies, were detected in the lungs of nine patients, who ultimately composed our study group. Our cases included 5 males and 4 females, with the mean age of 39.11 years (median, 37; range, 26-61). Seven patients were diagnosed with concomitant CMV and *Pneumocystis jiroveci* pneumonitis. Five patients had thrush, two patients tested positive for active tuberculosis, and one patient reported a history of old tuberculosis. All of the patients had fever, dyspnea, and cough as their chief complaints. Additionally, five patients experienced weight loss, and 2 patients suffered from hemoptysis.

One patient presented CMV retinitis in addition to *Pneumocystis jiroveci* pneumonitis and tuberculosis, and another patient had CMV colitis and thrush. In terms of laboratory data, LDH ranged from 138 to 1,140, with average LDH of 653.22. CD4+ counts ranged from 12 to 156, with average of 56.22. Six patients had positive plasma *polymerase chain reaction* (PCR) for CMV. No patient had an evidence of Kaposi's sarcoma. BAL fluid PCR for CMV was positive in all patients. Two patients died due to the extent of disease involvement. Clinical and laboratory data of the patients are shown in Table 1.

Discussion

There is a low number of recent studies focusing on opportunistic infections (OIs) and in specific pneumonias secondary to CMV infection. A descriptive case series study by Ramesh *et al.* [10] who analyzed the clinical profiles and demographics of HIV-positive patients, resembled our work the most. The mentioned paper confirmed that the respiratory system was the most common system involved in opportunistic infections, and most of these patients present-

Table 1. Clinical and laboratory data of patients

Patient No.	Sex	Age (year)	Opportunistic infections	Extra pulmonary CMV infection	SaO_2	LDH (IU/l)	CD4+	Treatment SMX-TMP/ ganciclovir/corticosteroids/ ART	Out-come
1	M	37	PCP-thrush		98	547	12	SMX-TMP/ganciclovir/ corticosteroids/HAART	Alive
2	M	39	PCP		73	875	70	SMX-TMP/ganciclovir/ART	Dead
3	F	26	PCP		91	1,140	17	SMX-TMP/ganciclovir/ corticosteroids/ART	Alive
4	F	31	TB-PCP	CMV retinitis	98	523	33	SMX-TMP/ganciclovir/ART/ anti-TB	Alive
5	M	26	Thrush-TB-PCP		86	793	156	SMX-TMP/ganciclovir/ART/ anti-TB	Alive
6	M	40	Thrush-old TB-PCP		85	784	90	SMX-TMP/ganciclovir/HAART	Alive
7	F	61	Thrush	CMV colitis	88	138	12	SMX-TMP/ganciclovir/ corticosteroids/HAART	Dead
8	F	32	PCP		67	924	44	SMX-TMP/ganciclovir/ corticosteroids/ART	Alive
9	M	60	Thrush		87	155	72	SMX-TMP/ganciclovir/ART	Alive

ed CD4+ levels lower than 200 per ml. Of their total 164 patients, an increased prevalence was recorded in the 28-37 years population, which is nearly in agreement with our age group. The most frequent opportunistic infections reported in this paper was as follows: TB (50%), candidiasis (49%), and pneumocystis (16%). The considerable prevalence of tuberculosis could be attributable to the endemic area, where the study took place. Similarly in our study, which was performed in an endemic area, two patients suffered from active TB and one reported a history of old TB. The mean CD+ cell count in patients diagnosed with CMV was 18.5/ml [10]. A study in China [28] also confirmed the greater prevalence of TB (32.5%), candidiasis (29.3%), PCP (22.4%), and CMV (21.7%). This study identified that pulmonary OIs were causing the most morbidity and mortality in the HIV-infected population. CMV was identified as the most prevalent germ (21.7%) responsible for viral pneumonitis in this population.

In our study, two cases of extra-pulmonary CMV infection were reported. A study by Bower *et al.* [29] reported that an extra-pulmonary recurrence of CMV (retinitis or colitis) occurred in 22% of patients, with the evidence of CMV in BAL as compared to 16% of those with PCP alone.

Accurate differentiation of PCP from CMV pneumonias is crucial for correct therapy selection in AIDS patients. Chest radiograph findings of CMV-infected patients vary, and include reticular or ground glass opacities, alveolar infiltration, or nodular opacities, with rare cavitary lesions [30]. The typical radiographic finding in patients who are infected with *Pneumocystis jiroveci* is bilateral perihilar interstitial infiltrations [31]. Less common features consist of multiple or solitary nodules, pneumatoceles, upper-lobe infiltrations, and pneumothorax. Thoracic lymphadenopathy and pleural effusions are rare [26]. A recent study demonstrated that the presence of consolidations, halo signs, and nodules were more frequently seen in patients with CMV pneumonias than in PCP [32].

However, a multi-cohort study by Buchacz *et al.* [33] demonstrated that the total prevalence of opportunistic infections for HIV-infected persons in care in Canada and North America is relatively low (9%), and generally declined over next episodes. Although this was not the focus of our paper, and the difference between this finding and what appears to be seen in developing countries could be attributable to a more efficient patient screening system in developed nations, more facilitated treatment access, and better socio-economic status.

Opportunistic infections are still a major cause of mortality among HIV-infected individuals. Compared to those who passed secondary to other causes, the victims of opportunistic infections were younger and more likely to be infected through hetero-sexual contact, to present with poor socio-economic conditions, to be migrants recently diagnosed with HIV infection, and to be naïve to antiretroviral therapies and OI prophylaxis [34]. A study by Bonnet *et al.* showed that of the patients who died of HIV events, 27% had died of at least one episode of OI [34]. Our recorded mortality rate (22%) confirms this finding, though it is notable that with respect to the massive case number in that study, the results are more accurate.

Conclusions

The differential diagnosis for CMV pneumonia is extensive and includes diseases, such as bacterial pneumonias, *Mycobacterium tuberculosis* infections, and other HIV-associated respiratory infections. Definitive diagnosis should be based on a demonstration of CMV in pulmonary secretions or in lung tissue.

Conflicts of interest

The authors declare no conflicts of interest.

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