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Original Article

Opportunistic infections in adults with acquired immunodeficiency syndrome: a comparison of clinical and autopsy findings

Hung-Jen Tang[1], Yung-Ching Liu[2], Muh-Young Yen[2], Yao-Shen Chen[2], Shue-Ren Wann[2], Hsi-Hsun Lin[2], Susan Shin-Jung Lee[2], Wei-Ru Lin[2], Chun-Kai Huang[2], Bo-An Su[1], Ping-Chin Chang[1], Chien-Ming Li[1], Hui-Hua Tseng[3]

[1]Section of Infectious Diseases, Department of Internal Medicine, Chi-Mei Medical Center, Tainan; and [2]Section of Infectious Diseases and Microbiology and [3]Department of Pathology and Laboratory Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

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Background and Purpose: Many opportunistic infections causing death in acquired immunodeficiency syndrome (AIDS) patients are often not diagnosed prior to death. The objective of this study was to compare the premortem and postmortem diagnoses of opportunistic infections and tumors among 15 AIDS patients treated in a hospital in southern Taiwan.

Methods: Total autopsy (brain, chest and abdominal cavity) was performed in 2 patients, and partial autopsy in 13.

Results: *Pneumocystis carinii* pneumonia, candidiasis, lymphoma, Kaposi's sarcoma, toxoplasmosis and salmonellosis were more commonly diagnosed before death than at autopsy. By contrast, cytomegalovirus (CMV) infections and herpes simplex virus or varicella-zoster virus infections were more frequently diagnosed at postmortem examinations than prior to death.

Conclusions: In conclusion, this study found substantial discrepancies between autopsy findings and premortem clinical diagnoses in AIDS patients, especially for CMV infection.

Key words: Acquired immunodeficiency syndrome, autopsy, opportunistic infections

Introduction

The clinical manifestations of acquired immunodeficiency syndrome (AIDS) are characterized by opportunistic infections or tumors (lymphoma or Kaposi's sarcoma) secondary to impaired function of T-lymphocytes that increase the host's susceptibility to opportunistic infections [1]. The opportunistic infections or tumors related to AIDS have the following characteristics: atypical, asymptomatic or subclinical presentations; coexisting infection with multiple organisms; multi-organ involvement; frequent dissemination and rarely curable before the introduction of highly active anti-retroviral therapy (HAART). The prevalence of various opportunistic infections in AIDS patients in different populations has changed over time, because of the introduction of antimicrobial prophylaxis against *Pneumocystis carinii* pneumonia (PCP) and *Mycobacterium avium* complex infection, and HAART. Nearly all of the opportunistic infections are declining in incidence with the introduction of HAART [2].

Opportunistic infections or malignancies continue to occur in human immunodeficiency virus type-1 (HIV-1)-infected patients who have limited access to medical care, and who develop virologic and immunologic failure to HAART. Opportunistic infections causing death in AIDS patients are often not diagnosed prior to death. For this reason, the performance of autopsy on patients who have died of AIDS can be of great value to physicians caring for these patients. Autopsy may identify diseases that were not clinically suspected or diagnosed and permits additional assessment of the

Corresponding author: Dr. Yung-Ching Liu, Section of Infectious Diseases, Department of Internal Medicine, Kaohsiung Veterans General Hospital, 386, Ta-Chung 1st Road, Kaohsiung, Taiwan. E-mail: 8409d1@mail.chimei.org.tw

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effectiveness of treatment modalities and diagnostic tests. By providing this type of information, autopsy serves as an important quality control measure in the delivery of medical care to AIDS patients [3-5]. The purpose of this study was to examine the differences between premortem diagnosis of opportunistic infections and postmortem findings among AIDS patients.

Methods

From May 1991 to July 1999, HIV-1 infection was confirmed in 159 patients at Kaohsiung Veterans General Hospital (KH-VGH), a 1000-bed teaching hospital serving as a center for the care of AIDS patients in southern Taiwan. Review of the medical records of autopsy cases examined during this study period identified 16 HIV-1-infected patients, among whom 15 had complete data available. The diagnoses of opportunistic infections were made by radiologists and infectious diseases specialists based on serology, microbiology and image studies. The demographic data, premortem clinical findings, laboratory data and autopsy findings of these patients were collected and analyzed.

All autopsies were performed at the Department of Pathology of KH-VGH. Sections for histology were taken from all parenchymal organs. All sections were stained with hematoxylin and eosin, periodic acid-Schiff, methenamine silver, Ziehl-Neelsen stain, or other stains as necessary. Cytomegalovirus (CMV) infection was diagnosed by observing typical inclusion bodies on hematoxylin and eosin stain. Mycobacterial infection was diagnosed by the finding of caseous necrosis, granuloma with multinucleated giant cells, or foamy histiocytes with intracellular acid-fast bacilli. Immunoperoxidase staining for CMV was not available at our hospital during the study period.

Results

Of the 15 AIDS patients with autopsy study, 12 had received prior trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis or therapy, and 13 patients had received antiretroviral therapy for an average of 12 months (range, 3-48 months). Total autopsy (brain, chest and abdominal cavity) was performed in 2 patients, and partial autopsy (only chest and abdominal cavity) in the remaining 13. There were 14 men and 1 woman. Their mean age was 45 years (range, 22-71 years). The mean duration between diagnosis of AIDS and death was 19 months (range, 3-36 months). The mean CD4 count was 0.131×10^9 cells/L (range, $0.005\text{-}0.450 \times 10^9$ cells/L). Eight patients were heterosexual, 3 bisexual, 2 homosexual, and 1 was an intravenous drug user. One

Table 1. Clinical diagnoses and pathological postmortem diagnoses in 15 patients with human immunodeficiency virus (HIV) type-1 infection

Case no.	Clinical diagnosis	Postmortem diagnosis
1	Cerebral toxoplasmosis	CMV enteritis and adrenalitis, gastric Kaposi's sarcoma
2	PCP	CMV pneumonitis, herpes esophagitis
3	Salmonellosis, Kaposi's sarcoma	Disseminated CMV infection, amebic liver abscess
4	Salmonellosis, pyogenic pericarditis	CMV pericarditis and pneumonitis, pulmonary mycobacterial infection
5	PCP, Pulmonary TB, CMV retinitis, splenic abscess	Disseminated mycobacterial and CMV infection, pulmonary mucormycosis
6	Pulmonary TB	Disseminated mycobacterial and CMV infection, leiomyoma
7	PCP, Kaposi's sarcoma	PCP, disseminated CMV infection
8	Pulmonary TB, PCP, CMV retinitis, lymphoma, Kaposi's sarcoma	Disseminated mycobacterial and CMV infection
9[a]	CNS lymphoma, cryptococcal meningitis, cerebral toxoplasmosis	Cryptococcal meningitis, malignant lymphoma of the brain
10	Myelodysplastic syndrome	HIV myelopathy
11	Burkitt's lymphoma	Malignant lymphoma
12	Pulmonary TB	Pulmonary mycobacterial infection
13	Syphilis	Bronchopneumonia
14[a]	Cryptococcal meningitis, PCP	Pulmonary cryptococcosis, cryptococcal meningitis
15	Pulmonary TB, PCP, gonococcal vulvar abscess	Pulmonary mycobacterial infection

Abbreviations: PCP = *Pneumocystis carinii* pneumonia; TB = tuberculosis; CMV = cytomegalovirus; CNS = central nervous system
[a]Total autopsy.

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Table 2. Clinical features and pre- and postmortem diagnoses in human immunodeficiency virus type-1 infected patients with cytomegalovirus (CMV) involvement at autopsy

Case no.	Symptoms/ signs	Premortem diagnoses	Postmortem diagnoses	CD4 count (x 10^9 cells/L)	TMP-SMX therapy	CMV involvement at autopsy
1	–	Cerebral toxoplasmosis	–	0.176	-	Cecum, adrenal gland
2	Fever, cough, dyspnea	PCP	Herpes esophagitis	0.005	+	Lung
3	Fever, diarrhea, abdominal pain	Salmonellosis, Kaposi's sarcoma	Liver abscess	0.12	+	Liver, spleen, ileum, rectum, adrenal gland, lymph node, seminal vesicle
4	Fever, dyspnea, diarrhea	Salmonellosis, pyogenic pericarditis	Mycobacterial infection	0.032	+	Lung, pericardium
5	Fever, cough, general malaise	PCP, CMV retinitis, pulmonary TB, splenic abscess	Disseminated mycobacterial infection, pulmonary mucormycosis	0.006	+	Lung, colon, adrenal gland
6	Fever, diarrhea, general malaise	Pulmonary TB	Disseminated mycobacterial infection	0.05	+	Lung, colon, adrenal gland
7	Fever, cough, iarrhea	PCP, Kaposi's sarcoma	PCP	0.028	+	Lung, stomach, adrenal gland
8	Fever, cough, visual field defect	PCP, CMV retinitis, pulmonary TB	Disseminated mycobacterial infection	0.033	+	Mesenteric lymph node, adrenal gland

Abbreviations: PCP = *Pneumocystis carinii* pneumonia; TB = tuberculosis; TMP-SMX = trimethoprim-sulfamethoxazole

patient was infected after receipt of HIV-1-contaminated blood product during a subtotal gastrectomy in 1996.

The premortem clinical diagnoses made at the last admission included PCP (6 patients), mycobacterial infection (5), candidiasis (4), lymphoma (4), Kaposi's sarcoma (3), toxoplasmosis (2), CMV infection (2), cryptococcosis (2), salmonellosis (2), and herpes simplex virus infection (1) [Table 1]. Thus, the premortem diagnostic rate of CMV infection was 25% (2/8), and that of mycobacterial infection was 83% (5/6). The opportunistic infections or tumors found at autopsy were CMV infection (8 patients), mycobacterial infection (6), herpes simplex or varicella-zoster virus (3), PCP (2), cryptococcosis (2), lymphoma (2), Kaposi's sarcoma (1), candidiasis (1) and mucormycosis (1).

Of the 8 patients with a diagnosis of CMV infection at postmortem examination, only 2 had a premortem diagnosis of CMV, presenting as retinitis in both cases. The CD4 counts of the patients with CMV infection were uniformly below 0.05×10^9 cells/L, except for 1 patient who had a CD4 count of 0.12×10^9 cells /L. Autopsy pathology reports showed CMV involvement of adrenal glands in 6 patients, lung in 5, intestine in 4, lymph nodes in 2, retina in 2, liver in 1, spleen in 1, stomach in 1, pericardium in 1, and seminal vesicles in 1 (Table 2). Of the 5 patients with CMV pneumonitis (Fig. 1), 4 had coexisting pulmonary diseases, including mycobacterial infection (3 patients) [Fig. 2] and PCP (1). None of these patients had a premortem diagnosis of CMV pneumonitis, and thus none received ganciclovir therapy. All 5 patients with CMV pneumonitis had severe lung damage on pathology, which resulted in respiratory failure and subsequent death. Postmortem evidence of CMV infection was found in the gastrointestinal tract in 5 patients. Only 3 of the 5 patients had clinical symptoms of diarrhea, fever or abdominal pain without an established premortem etiology. CMV infection most often involved the colon, followed by rectum, cecum, ileum or stomach.

Pulmonary mycobacterial infection had been suspected clinically in 5 of the 6 patients with an autopsy diagnosis of mycobacteriosis. Premortem CD4 count was less than 0.05×10^9 cells/L in 4 of these patients, while 1 patient had a CD4 count of 0.105×10^9 cells/L. Typical radiological patterns of pulmonary tuberculosis, i.e., alveolar and interstitial infiltration at the upper lung fields, were noted on chest radiography in 2 patients (cases 6 and 12), and nonspecific patterns were noted in the others. Extrapulmonary or disseminated mycobacterial infection was found in 3 patients, involving the liver, spleen, and mesenteric or retroperitoneal lymph nodes. However, none of these patients had a premortem diagnosis of disseminated mycobacterial infection.

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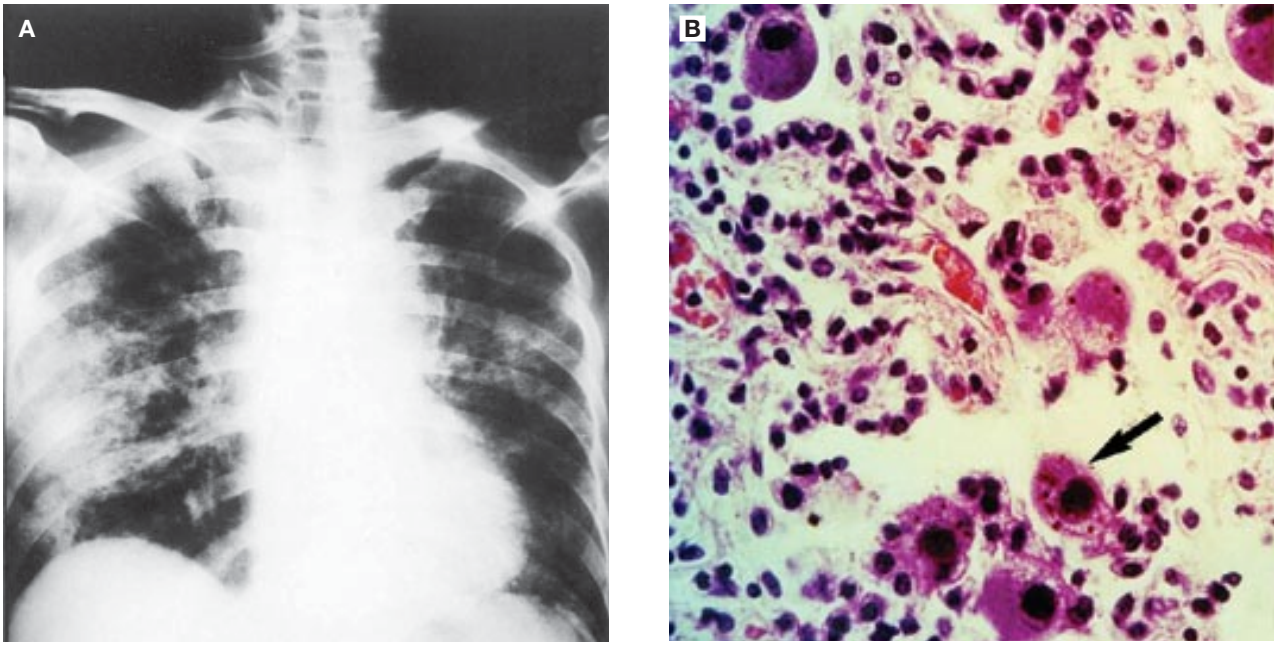

Fig. 1. A) Chest film discloses alveolar infiltration at the right lung field (right) in a 46-year-old heterosexual man (case 2) with fever, chills and dyspnea and a clinical diagnosis of *Pneumocystis carinii* pneumonia. Cytomegalovirus pneumonitis was diagnosed postmortem. B) Intranuclear inclusion bodies (arrow) can be seen with alveolar cells in lung tissue (left) [hematoxylin and eosin stain, × 400].

A premortem diagnosis of PCP was made in 6 of 15 patients, all of whom received TMP-SMX as empirical therapy or prophylaxis prior to death. The diagnosis of PCP was made by postmortem pathological findings in only 1 patient (case 7).

Cryptococcus was diagnosed premortem in 2 patients (cases 9 and 14). One patient with a premortem diagnosis of cryptococcal meningitis had concomitant lymphoma of the central nervous system which was only diagnosed at autopsy. The other patient with

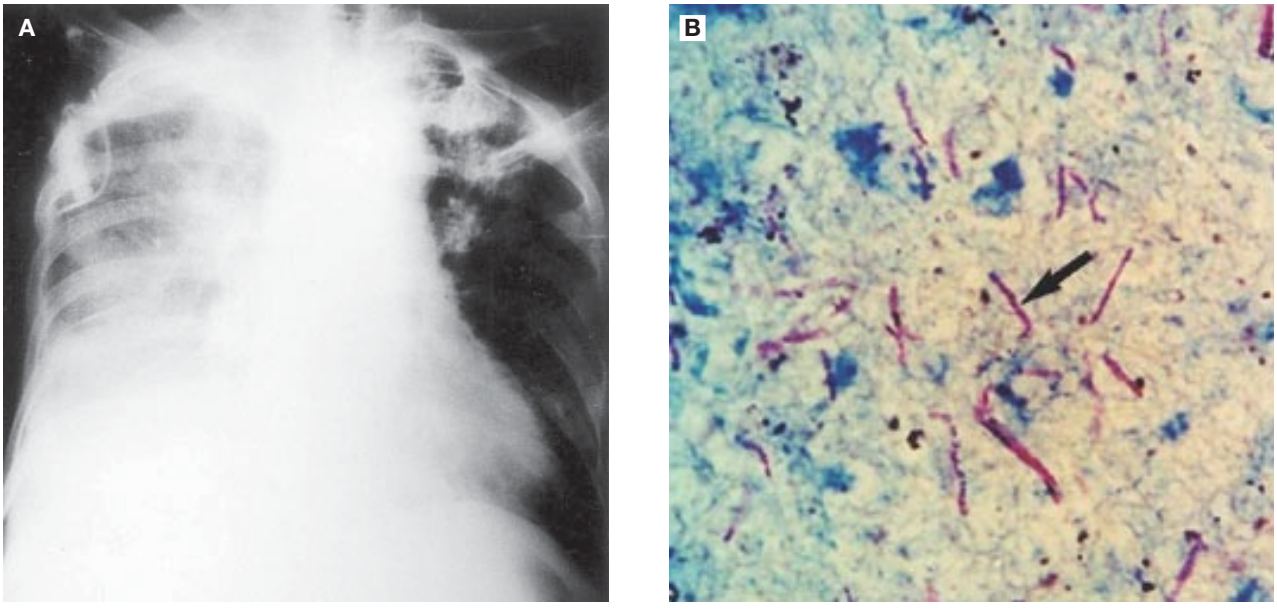

Fig. 2. A) Chest film reveals infiltration at right and left upper lung fields, and right-sided pleural effusion in a 29-year-old man (case 8) with a history of prostitution who presented with fever and cough. *Pneumocystis carinii* pneumonia and tuberculosis were clinically suspected. Postmortem study, however, led to the diagnosis of disseminated cytomegalovirus and mycobacterial infection. B) A large number of acid-fast bacilli (arrow) are seen on the histopathological section of lung tissue (Kinyoun's stain, × 1000).

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cryptococcal meningitis had pulmonary cryptococcoma which was not diagnosed until autopsy.

Kaposi's sarcoma of the stomach was found incidentally at autopsy in 1 patient (case 1), and 2 patients (cases 9 and 11) had postmortem diagnosis of malignant lymphoma.

Discussion

This study revealed many discrepancies between the pre- and postmortem diagnoses in patients with AIDS. Dore et al [6] found that CMV infection was commonly identified postmortem and there was a low concordance between clinical diagnosis and autopsy findings in HIV-infected patients. Our results support this finding. In this series, CMV infection was underdiagnosed in patients with HIV-related respiratory diseases. However, the extent to which CMV should be considered a true pulmonary pathogen, as opposed to a colonizing agent, remains controversial.

CMV is a common cause of morbidity in HIV-infected patients, especially in those with severe immunosuppression [6-8]. Previous autopsy studies of AIDS patients found that CMV was the most common and widespread opportunistic pathogen [9,10]. In this study, CMV infection was found in about a half of the patients (53%, 8 of 15 patients). Although the high prevalence of CMV infection of the retina and gastrointestinal tract is well recognized and known to cause substantial morbidity, the prevalence and clinical significance of CMV infection at other sites, particularly the lung and adrenal glands, remains unclear. Dore et al's clinicopathological study of AIDS autopsies [6] also found that CMV pneumonitis and CMV adrenalitis were vastly under-recognized.

Similar to the results of Afessa et al [11], mycobacterial infection was also a common autopsy finding in this study. Pulmonary tuberculosis had been suspected clinically in 5 of 6 patients with autopsy diagnosis of pulmonary mycobacterial infections. Afessa et al [11] also reported that bacterial bronchopneumonia, PCP, pulmonary tuberculosis or mycobacteria other than tuberculosis and CMV were the 4 most common pathogens in the lung of HIV-infected patients. HIV-infected patients with pulmonary mycobacterial infection often present with atypical radiological patterns, including interstitial infiltrations, hilar lymphadenopathy or pleural effusions, and with frequent dissemination.

Before the advent of prophylactic usage of TMP-SMX or pentamidine, PCP had been a common opportunistic infection in AIDS patients [12]. In this study, PCP was initially diagnosed in 75% of patients with fever, cough or dyspnea, and these patients all received empirical TMP-SMX therapy, which may explain the low postmortem diagnostic rate for PCP.

Cryptococcosis is another common opportunistic infection in AIDS patients. Chuck and Sande [13] reviewed 106 AIDS patients with cryptococcal infection, and found that meningitis was the most common manifestation. Other manifestations of cryptococcal infection included cryptococcemia, pneumonia and urinary tract infection. Cryptococcal meningitis was easily diagnosed before autopsy because of the high yield rate of India ink staining of CSF specimens and the high sensitivity rate of cryptococcal antigen testing of CSF or blood specimens. In the present study, cryptococcal meningitis was clinically diagnosed in 2 patients based on positive findings of India ink preparation and cryptococcal antigen in CSF.

In conclusion, this study of 15 autopsy cases of AIDS found substantial discrepancies between autopsy findings and premortem clinical diagnoses, especially CMV infection.

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