Necropsy Findings in Acquired Immunodeficiency Syndrome: A Comparison of Premortem Diagnoses with Postmortem Findings

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Necropsies were performed in 12 patients who fulfilled the Centers for Disease Control (CDC) criteria for acquired immunodeficiency syndrome (AIDS), and the postmortem findings were compared with the premortem diagnoses. All of the patients were men with a male sexual preference and histories of multiple episodes of venereal diseases. Four patients were intravenous drug abusers, while two abused amyl nitrate. All 12 of the patients had evidence of cellular immune deficiency at presentation. The causes of death were a variety of opportunistic infections and neoplasms. *Pneumocystis carinii* pneumonia was diagnosed prior to death in seven patients. Despite current therapy, all seven of those patients had persistent *Pneumocystis carinii* pneumonia at necropsy, as well as clinically undiagnosed cytomegalovirus infection. In addition, two cases of acid-fast infections, two of visceral candidiasis, one of pneumocystis pneumonia, one of central nervous system lymphoma, one of gram-negative bacterial pyelonephritis, and one of cutaneous aspergillosis were clinically unrecognized and untreated. Nine patients died with two or more infections. Thus, necropsy is a valuable tool for recognizing clinically undiagnosed infections and malignant disorders in AIDS.

MATERIALS AND METHODS

Necropsy

Twelve necropsy reports from the files of the Los Angeles County--USC Medical Center and from consultations submitted by member hospitals of the Southern California Lymphoma Study Group between January 1982 and April 1983 were available for review. All patients satisfied the CDC criteria for AIDS. The patients' medical charts, clinical histories, and postmortem tissue sections and protocols were reviewed. Histologic sections were routinely stained with hematoxylin-eosin. In all cases, special staining (methenamine silver, Fite's method, Brown-Brenn technique, methyl green-pyronine, and Giemsa) was performed in selected tissue sections in accordance with standard techniques. In the cases of lymphoma, immunoperoxidase staining for the demonstration of cytoplasmic κ and λ light chains and muramidase was performed according to procedures described previously. Selected premortem studies of lymph node biopsy specimens, peripheral blood, and malignant lymphomas are the subjects of other reports.

Blood

Peripheral blood was obtained from the patients on presentation and was submitted to the laboratory in EDTA. Peripheral blood T-cell phenotypes were measured by flow cytofluorometry with an Ortho spectrum III cytofluorograph. The fluorescein isothiocyanate-conjugated primary antibodies included helper/inducer phenotype marker (OKT-4) and suppressor/cytotoxic phenotype (OKT-8). The helper/suppressor cell ratio (H/S) was calculated as OKT-4/OKT-8. Total T cells were measured with a pan-T antibody (OKT-11) or the percentage of lymphocytes as a function of the total leucocyte count. As these studies are research tools, they were not performed in all patients.

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NECROPSY FINDINGS IN AIDS (Hu et al.)

**TABLE 1.** Clinical and Laboratory Data for Homosexual Patients with Acquired Immunodeficiency Syndrome

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr), Race</th>
<th>Work History</th>
<th>Clinical Findings*</th>
<th>Past History</th>
<th>Lymphocyte</th>
<th>Helper (H)</th>
<th>Suppressor (S)</th>
<th>H/S Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26, OC</td>
<td>Utility worker</td>
<td>Skin lesions; lymphadenopathy</td>
<td>IV drug abuse; GC; syp; candidiasis; amyl nitrate user</td>
<td>800</td>
<td>NA</td>
<td>NA</td>
<td>0.57</td>
</tr>
<tr>
<td>2</td>
<td>36, H</td>
<td>NA</td>
<td>Skin lesions; lymphadenopathy</td>
<td>Infectious hepatitis; GC; syp</td>
<td>884</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>35, H</td>
<td>Cook</td>
<td>SOB; cough; lymphadenopathy; loss of appetite</td>
<td>GC; syp; anal warts</td>
<td>528</td>
<td>121</td>
<td>280</td>
<td>0.4</td>
</tr>
<tr>
<td>4</td>
<td>31, H</td>
<td>Clerk</td>
<td>SOB; night sweats; history of coccidioidomycosis; loss of appetite</td>
<td>IV drug abuse; GC; hepatitis</td>
<td>544</td>
<td>65</td>
<td>237</td>
<td>0.3</td>
</tr>
<tr>
<td>5</td>
<td>50, H</td>
<td>Maintenance worker</td>
<td>Rectal bleeding; diarrhea; oral and anal candidiasis; loss of appetite</td>
<td>IV drug abuse; anal warts</td>
<td>710</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>31, B</td>
<td>NA</td>
<td>Dysphagia; weight loss; esophageal candidiasis</td>
<td>Herpes; GC; syp</td>
<td>700</td>
<td>35</td>
<td>462</td>
<td>0.1</td>
</tr>
<tr>
<td>7</td>
<td>32, H</td>
<td>NA</td>
<td>Weight loss; cough</td>
<td>Herpes; giardiasis; shigellosis</td>
<td>1200</td>
<td>60</td>
<td>744</td>
<td>0.08</td>
</tr>
<tr>
<td>8</td>
<td>38, B</td>
<td>Waiter</td>
<td>Cough; fever and chills</td>
<td>IV drug abuse; syp; GC; hepatitis</td>
<td>750</td>
<td>60</td>
<td>428</td>
<td>0.1</td>
</tr>
<tr>
<td>9</td>
<td>61, OC</td>
<td>NA</td>
<td>Weight loss; diarrhea; low-grade fever</td>
<td>Amyl nitrate user</td>
<td>300</td>
<td>18</td>
<td>216</td>
<td>0.1</td>
</tr>
<tr>
<td>10</td>
<td>56, H</td>
<td>Urban planner</td>
<td>SOB; fever; weight loss</td>
<td>Syp</td>
<td>987</td>
<td>69</td>
<td>464</td>
<td>0.1</td>
</tr>
<tr>
<td>11</td>
<td>30, H</td>
<td>Odd jobs</td>
<td>Weight loss; fatigue</td>
<td>NA</td>
<td>351</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>12</td>
<td>53, OC</td>
<td>NA</td>
<td>Oral candidiasis; weight loss; diarrhea; SOB</td>
<td>GC; amebiasis; history of hepatitis</td>
<td>91</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Abbreviations:** OC, occidental; H, hispanic; B, black; NA, not available; SOB, shortness of breath, GC, gonorrhea; Syp, syphilis; IV, intravenous; herpes, herpes simplex, type II.

* Include chief complaint, symptoms and physical findings at the time of presentation.

† Absolute: lymphocyte, total number of lymphocytes/mm³; helper, total number of helper phenotype as defined by OKT-4; suppressor, total number of suppressor phenotype as defined by OKT-8. H/S ratio, helper/suppressor ratio as defined by OKT-4/OKT-8.

**RESULTS**

Premortem Diagnoses and Clinical Information

The patients ranged in age from 26 to 61 years (median, 35.5 years) (table 1). All of the patients were men, and all had a male sexual preference. Racial extractions were diverse: seven patients were hispanic, three were occidental, and the remaining two were black. Occupational history was available for only seven of the 12 patients: two worked in the food service industry, two were utility workers, and one patient each worked as a clerk, an urban planner, and at odd jobs. The predominant complaints centered about the skin (two patients), respiratory tract (six patients), and the gastrointestinal system (four patients). Specifically, loss of appetite was present in three patients, weight loss in six, shortness of breath in four, low-grade fever in three, diarrhea in three, generalized lymphadenopathy in three, and discolored skin lesions in two. Three patients presented with oral and perianal lesions, which on examination and culture proved to be due to Candida species. All 12 patients had histories of at least one episode of sexually transmitted disease: syphilis in six patients, gonorrhea in seven, hepatitis in four, giardiasis in one, shigellosis in one, rectal and scrotal herpes infection in two, cytomegalovirus (CMV) in two, rectal warts in one, and colonic amebiasis in one. Four of the 12 patients had histories of intravenous drug abuse, and two related habitual amyl nitrate use.

At the time of diagnostic work-up, all patients had defects in cell immunity. The absolute lymphocyte counts ranged from 91 to 1,200 cells/mm³ (median, 705 cells/mm³). In addition, all patients tested showed anergy to common skin test antigens for tuberculosis, coccidioidomycosis, histoplasmosis, mumps, and Candida species. Peripheral blood T-cell helper/suppressor (H/S) ratios were tested in eight of the 12 patients, and, with the exception of patient 7, all showed low absolute numbers of helper and suppressor cells as well as low H/S ratios (table 1).

The hospital courses of these patients were punctuated by numerous infections, often caused by multiple organisms. Of the seven patients with tissue-proved *Pneumocystis carinii* pneumonia, four had second tissue-proved premortem infections: pulmonary CMV in one patient, disseminated *Coccidioides immitis* in one, and oral candidiasis in two. Diagnostic lung samples were obtained by transbronchial biopsy in four patients and by open biopsy in...
TABLE 2. Comparison of Premortem and Postmortem Diagnoses: Homosexual Patients with Acquired Immunodeficiency Syndrome

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical Diagnosis</th>
<th>Premortem Tissue Diagnosis</th>
<th>Postmortem Findings</th>
<th>Survival after Tissue Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R/O KS</td>
<td>KS, skin; oral candidiasis</td>
<td>KS, skin, retroperitoneal and mediastinal soft tissues, subepicardial fat, G1 tract, liver, tongue, lymph nodes, and lung; CMV, lung</td>
<td>6 mo</td>
</tr>
<tr>
<td>2</td>
<td>R/O KS</td>
<td>KS, skin, pleura</td>
<td>KS, skin, lung, tongue, G1 tract, lymph nodes, and thyroid; CMV, lung</td>
<td>6 mo</td>
</tr>
<tr>
<td>3</td>
<td>R/O TB</td>
<td>PCP, lung*; CMV, urine</td>
<td>PCP, lung; Candida, lung; DAD, lung</td>
<td>6 wk</td>
</tr>
<tr>
<td>4</td>
<td>Coccioidiomycosis</td>
<td>PCP, lung; cocci, lung</td>
<td>PCP, lung; CMV, lung; cocci, lung, hilar lymph nodes; DAD, lung; malignant lymphoma,† CNS</td>
<td>8 mo</td>
</tr>
<tr>
<td>5</td>
<td>Oral and perianal candidiasis; R/O malabsorption</td>
<td>CMV, gastric mucosa; oral and perianal candidiasis</td>
<td>Disseminated CMV; disseminated candidiasis</td>
<td>3 wk</td>
</tr>
<tr>
<td>6</td>
<td>Esophageal candida infection; R/O PCP</td>
<td>PCP, lung; oral candidiasis</td>
<td>PCP, lung; CMV, lung, adrenal glands, stomach; AFB, hilar lymph nodes</td>
<td>2 wk</td>
</tr>
<tr>
<td>7</td>
<td>R/O PCP</td>
<td>PCP, lung</td>
<td>PCP, lung; CMV, lung</td>
<td>4 wk</td>
</tr>
<tr>
<td>8</td>
<td>R/O PCP</td>
<td>PCP, lung</td>
<td>PCP, lung; chronic active hepatitis</td>
<td>2 wk</td>
</tr>
<tr>
<td>9</td>
<td>Oral candidiasis; R/O PCP; diabetes</td>
<td>Oral candidiasis; CMV, blood; malignant lymphoma‡; AAFB, sputum</td>
<td>CMV, pancreatitis; acute pneumonitis; malignant lymphoma,† lymph nodes, spleen, liver, and bone marrow; AFB, peripancreatic LN</td>
<td>8 mo</td>
</tr>
<tr>
<td>10</td>
<td>Pneumonia (pathogenesis unknown)</td>
<td>Listeria monocytogenes, blood culture</td>
<td>PCP, lung; CMV, lung, stomach,* adrenal gland</td>
<td>3 wk</td>
</tr>
<tr>
<td>11</td>
<td>R/O PCP</td>
<td>PCP, lung</td>
<td>PCP, lung; CMV, lung, cutaneous aspergillosis; disseminated AFB</td>
<td>2 wk</td>
</tr>
<tr>
<td>12</td>
<td>Oral candidiasis; R/O PCP</td>
<td>PCP, lung; oral candidiasis</td>
<td>PCP, lung; duodenal ulcer</td>
<td>3 wk</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS:** R/O, rule out; TB, tuberculosis; CNS, central nervous system; KS, Kaposi's sarcoma; PCP, Pneumocystis carinii pneumonia; CMV, cytomegalovirus infection; AAFB, atypical acid-fast bacilli; AFB, acid-fast bacilli; cocci, C. immitis; DAD, diffuse alveolar damage.

Underlining indicates diagnoses found at necropsy, unsuspected premortem.

* Recognized in review of original diagnosis; overlooked at initial diagnosis.
† B immunoblastic sarcoma (monoclonal λ).
‡ Plasmacytoid lymphocytic lymphoma (monoclonal κ).

three patients. Transbronchial biopsy was not diagnostic in only one patient (patient 9), who required a follow-up open procedure. On re-review the Pneumocystis organism was found to be present in the original transbronchial material.

Several infections occurred in unusual forms. Patients 5 and 10 presented with gastritis due to CMV; however the CMV in the latter was not recognized until he had died. In patient 10 *Listeria monocytogenes* was also cultured from the blood. In patient 9 CMV was cultured from the bloody effusion of the peripheral blood and *Mycobacterium avium—intracellulare* from the sputum. In patient 3 CMV was cultured from the urines.

**Postmortem Findings**

The time elapsed between initial premortem tissue diagnosis and the postmortem examination ranged from two weeks to eight months.

Postmortem findings are summarized in table 2. In all patients (except patient 10, in whom the blood culture grew *Listeria*) the premortem diagnosis was confirmed at necropsy. However, ten of the patients showed, in addition, a total of 15 undiagnosed infections and neoplasms. The most common unrecognized infection was widespread CMV infection (figs. 1 and 2), found in seven cases. For three additional patients CMV was recognized in premortem specimens, and all showed disseminated disease at necropsy. Eight of the patients had second diseases that were potentially treatable by current drug therapy: visceral candidiasis in two patients, disseminated acid-fast organisms in two, central nervous system lymphoma in one (fig. 3), pneumocystis pneumonia in one, gram-negative pneumonitis in one, and cutaneous aspergillosis in one. In addition, seven patients showed persistent pneumocystis pneumonia at necropsy despite accurate premortem diagnoses. The intervals between premortem diagnosis of pneumocystis pneumonia and postmortem examination ranged from nine to 35 days (average, 19 days). All patients were treated with trimethoprim and sulfamethoxazole. In addition, two patients also received pentamidine. One patient had persistent acid-fast infection despite antituberculous drug therapy.

Postmortem cultures of at least one organ were performed in eight patients. In six patients multiple cultures were performed. Blood and lung cultures in four patients were performed within 36 hours of death. The culture results correlated with histopath-
FIGURE 1 (top). Patient 9. Pancreatitis due to cytomegalovirus (CMV). The pancreatic parenchyma is disrupted by CMV infection. Both acini and islets are infected. (Hematoxylin–eosin stain, x100) Inset. CMV inclusions in the nucleus and cytoplasm of an involved islet. (Hematoxylin–eosin stain x400)

FIGURE 2 (bottom). Patient 10. Cytomegalovirus (CMV) colonization of gastric mucosa. The fundus of the stomach shows normal glandular architecture; CMV inclusions (arrows) are just perceptible at scanning magnification. (Hematoxylin–eosin stain x40) Inset. CMV inclusions in nucleus and cytoplasm of mucous cell. (Hematoxylin–eosin stain x1000)
FIGURE 3. Patient 4. Malignant lymphoma involving the meninges of the cerebellum. The leptomeninges are infiltrated by malignant lymphoma of transformed B lymphocytes. (Hematoxylin-eosin stain x 100.) Inset, immunoperoxidase (κ) light chain. (x 1,000.)

Recent studies have outlined the characteristics of patients who are at risk for the development of AIDS.1-17 The 12 men in our study seem to be similar to the subjects of previous reports in their histories of homosexual lifestyles, drug abuse, and diverse venereal and opportunistic infections.3-6,10,11,14,15 However, there were several noteworthy differences, including the findings in our study of a relatively large percentage of hispanic males, two patients with malignant lymphoma (a rarely reported complication of AIDS), and no representative of other groups at risk for AIDS, such as patients with Factor VIII deficiency or those of Haitian origin. We know of no evidence to suggest that these differences alter the types of infections, complications, or premortem and postmortem diagnoses in patients with AIDS.

The present study demonstrates the importance of assessing patients dying of AIDS by postmortem examination. Our patients, with the exception of patient 10, all underwent tissue sampling with the identification of pathogens or tumors, and AIDS was correctly diagnosed in these patients. However, ten of the patients in whom necropsy was performed had a total of 15 episodes of unrecognized disease. In half of these episodes the offending organism was CMV, involving the lungs and other organs, but in the remainder a variety of disorders were present, including visceral candidiasis, acid-fast infections, Pneumocystis carinii pneumonia, central nervous system lymphoma, gram-negative pyelonephritis, and cutaneous aspergillosis. Goldman et al.25 reviewed the problem of undiagnosed disorders recognized at necropsy in a randomly selected 1980 general population. The small number of preselected patients with AIDS precludes valid statistical comparison of the patients in our study with this and other reports.26 Our findings do support the problems of unrecognized infections.25 The patients in this series were not so often misdiagnosed as underdiagnosed.

Concerning the accuracy of pathologic diagnosis, our necropsy study demonstrates the potential pitfalls in the evaluation of tissue from patients with AIDS. Nine of our 12 patients had infections with multiple opportunistic organisms at necropsy, confirming the necessity of continued search after the identification of one agent. Furthermore, anomalous patterns of infection, such as acid-fast infection without granuloma formation (fig. 4) and CMV infection without inflammation or tissue alteration (fig. 2), may not
alert the morphologist to the possibility of infection. These findings suggest that a battery of special stains for organisms should be routinely employed in all immunocompromised patients with AIDS.

In our retrospective review of biopsy specimens with special stains, we found two diagnostic errors, both of which occurred in premortem surgical biopsies. In patient 3, Pneumocystis organisms were overlooked in the first transbronchial biopsy, necessitating open surgical biopsy, while in patient 10 CMV was missed in a gastric biopsy (fig. 2). Both patients had other untreated infections that contributed significantly to their deaths. In contrast, review of necropsy materials with special stains failed to alter the diagnoses rendered by the pathologists at necropsy. However, we must admit that the large sample of tissues available at necropsy, as well as the more leisurely review of the postmortem materials conducted by multiple pathologists, conferred advantages not available to pathologists diagnosing smaller samples of tissue, often in frozen sections and smears taken from critically ill patients.

The accuracy of tissue diagnosis in AIDS with respect to the type of biopsy is not clear. However, the efficacy of transbronchial biopsy in establishing a specific diagnosis in immunocompromised patients is low (about one third of the cases), while in patients with pneumocystis pneumonia (a relatively diffuse lesion), the accuracy is greater (60 per cent). Problems of sampling are certain to be present in diseases in which the infection is initially or remains focally distributed in tissue, e.g., CMV pneumonitis. We found no evidence of CMV in our review of premortem lung tissue, even when CMV pneumonitis was present at necropsy. However, further studies are needed to assess the significance of the sample size and the site of biopsy in AIDS.

It seems most likely that given the length of time from diagnosis to death for the patients as a group (average, three months; range, two weeks to eight months), sequential development of infections accounts for many of the discrepancies between premortem and postmortem findings. The profound immunodeficiency, multiple infectious episodes, and reported high mortality of 50 per cent at one year all suggest that such patients remain at high risk for continued infectious complications and demand constant clinical vigilance and repeated diagnostic intervention. A review of table 2 suggests that the lung is the tissue most likely to yield positive results. Therapies directed toward immune enhancement may be required. Certainly, the persistence of pneumocystis pneumonia in the face of appropriate therapy raises the question of the "curability" by drug therapy alone.

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REFERENCES