Central Nervous System Pneumocystosis in a Patient with AIDS

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Extrapulmonary involvement with *Pneumocystis carinii* has been described in 0.5%–2.5% of persons with AIDS. One hundred nine patients with AIDS and confirmed extrapulmonary pneumocystosis were identified, and seven of these patients (including our patient) had central nervous system (CNS) pneumocystosis. Of these seven patients, six had prior AIDS-related complications, and three had previous *P. carinii* pneumonia. Six patients had CNS symptoms, one of whom underwent a focal neurological examination. No cases were diagnosed before death. The involved sites were the cerebral cortex (2 patients), meninges (2), pituitary gland (1), putamen (1), and nonspecified locations (3). In two patients, organisms were seen around blood vessels, and in five patients there was concurrent neuropathology. In summary, CNS involvement with *P. carinii* usually occurs as a late complication of AIDS and probably represents hemogenous dissemination.

Infection with *Pneumocystis carinii* remains a common complication in patients with AIDS. *P. carinii* pneumonia (PCP) continues to be the initial AIDS-related manifestation in 25% of patients and occurs in >50% of patients before they die [1]. *P. carinii* infections may extend beyond the lungs, and extrapulmonary pneumocystosis has been described in 0.5%–2.5% of persons with AIDS [2, 3].

We recently cared for a woman with AIDS in whom clinically unsuspected CNS pneumocystosis was discovered at autopsy. We report her case and review the literature on extrapulmonary pneumocystosis with an emphasis on CNS involvement.

Case Report

In March 1991, a 41-year-old woman was admitted to Duke University Medical Center (Durham, NC) because of profound headache and cough. Culture of her CSF yielded *Cryptococcus neoformans*, and she was then discovered to be HIV-seropositive (initial absolute CD4+ lymphocyte count, 51/mm^3^). An MRI revealed an increased signal in the region of her left basal ganglia and in her white matter, which was believed to be due to HIV encephalitis or cryptococcal infection.

She was treated with amphotericin B and flucytosine followed by oral fluconazole; she also received trimethoprim-sulfamethoxazole (TMP-SMZ) as prophylaxis for PCP. She soon developed a diffuse erythematous rash that resolved after discontinuation of TMP-SMZ therapy; she began monthly treatment with aerosolized pentamidine (300 mg). In May 1992, she received a 3-week course of treatment with dapsone and trimethoprim. She resumed monthly therapy with aerosolized pentamidine. In August 1993, she developed disseminated *Mycobacterium avium* complex infection, and in March 1994, she developed cytomegalovirus retinitis. In April 1994, she complained of cough, and a chest roentgenogram revealed a right-upper-lobe infiltrate. She was treated empirically for recurrent PCP with oral atovaquone for 6 weeks, and her clinical condition improved. During the summer of 1994, her clinical condition deteriorated, and she received palliative care. She died on 23 September 1994, and an autopsy was performed.

Autopsy results. The general autopsy revealed severe necrotizing pneumonia with multiple abscesses and extensive vascular invasion by *Aspergillus* species. There were multiple septic infarcts containing *Aspergillus* in both kidneys. Examination of the eyes showed cytomegalovirus retinitis bilaterally with retinal degeneration. No *Pneumocystis* organisms were identified outside of the CNS, despite Grocott-Gomori methenamine–silver nitrate staining of samples from all major organs.

The fresh brain weighed 918 g. The meninges over the superior parietal lobe were cloudy. The brain was sectioned in 1-cm slices in a coronal fashion. There was a 0.9-cm cystic defect in the anterior limb of the left internal capsule, and no other gross lesions were found. Examination of the cyst showed subacute infarction characterized by a macrophage infiltrate with adjacent severe gliosis and edema.

Grocott-Gomori methenamine–silver nitrate staining of the perivascular space of a juxtaposed blood vessel demonstrated *Pneumocystis* organisms. In the adjacent putamen, areas of vacuolation with a bubbly appearing neuropil that was most pronounced around blood vessels were seen in virtually every
Figure 1. Photomicrograph revealing focal edema and vacuolation (arrows) of the neuropil in the basal ganglia of a patient with AIDS and CNS pneumocystosis. Note the small cystlike spaces in the vicinity (hematoxylin-eosin/luxol fast blue stain; original magnification × 130).

Photomicrograph of the same area in figure 1 at a higher magnification; characteristic boat-shaped Pneumocystis organisms are demonstrated (arrow) (Grocott-Gomori methenamine–silver nitrate stain; original magnification, × 680).

section (figure 1). Grocott-Gomori methenamine–silver nitrate staining of the vacuolated space demonstrated many Pneumocystis organisms (figure 2). Pneumocystis organisms were also seen in the meninges and adjacent to an area of acute hemorrhage in the caudate nucleus. Multiple areas of ischemic damage characterized by tissue edema, reactive astrocytosis, and a scanty macrophage infiltrate were associated with perivascular accumulations of Pneumocystis organisms. In addition, pallor of cerebral myelin and severe myelopathy of the posterior white columns (findings consistent with HIV encephalopathy and myelopathy) were found. Pneumocystis organisms were not seen in the cerebral myelin or the posterior white columns.

Literature Review

A search of the English-language literature from 1981 to 1995 was performed to identify reports or reviews of cases of histologically confirmed extrapulmonary pneumocystosis. These cases were reviewed for the sites of P. carinii infection, and the cases of patients with CNS pneumocystosis were reviewed in greater detail.

Results

One hundred eight cases of extrapulmonary pneumocystosis were reported in the literature. The sites of documented extrapulmonary pneumocystosis included the liver (41% of cases), spleen (34%), lymph nodes (28%), thyroid gland (23%), kidneys (19%), bone marrow (18%), adrenal glands (15%), eyes (11%), and others.

Nervous system localization was documented in seven cases (6%), including CNS pneumocystosis in six cases and involvement of ganglia in the sympathetic nervous system in one case. The six patients with CNS involvement [3–8] and our patient are described in table 1. Of these seven patients, six had a history of at least one AIDS-related clinical complication, and five had at least two prior AIDS-related clinical complications. Three patients had a history of PCP. Five patients (71%) were receiving aerosolized pentamidine prophylaxis, and two (29%) were not receiving any prophylaxis.
Table 1. Summary of data on CNS pneumocystosis in seven patients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (y)/sex</th>
<th>Risk behavior</th>
<th>Complication(s)</th>
<th>Symptoms</th>
<th>Clinical course</th>
<th>Extra-CNS Isolation of Pneumocystis</th>
<th>CNS Localization of Pneumocystis</th>
<th>Concurrent neuropathology</th>
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<tbody>
<tr>
<td>[4], 40/M</td>
<td>Homosexual</td>
<td>KS, cryptococcosis, CMV retinitis, Staphylococcus aureus sepsis, recurrent bacterial respiratory tract infections</td>
<td>Progressive confusion and withdrawal, severe dyspnea, decreased urinary output</td>
<td>Cerebral atrophy by head CT, no aggressive measures, death</td>
<td>Lungs, widely disseminated</td>
<td>Virchow-Robin spaces, surrounding rare cortical arterioles</td>
<td>HIV encephalopathy</td>
<td></td>
</tr>
<tr>
<td>[5], 26/M</td>
<td>Transfusion</td>
<td>Four prior episodes of PCP</td>
<td>Dry gangrene of toes, no neurological symptoms</td>
<td>Sudden death</td>
<td>Lungs, widely disseminated</td>
<td>Not specified</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>[3], 33/M</td>
<td>Homosexual</td>
<td>KS, candidal esophagitis, CMV retinitis, MAC infection, three prior episodes of PCP</td>
<td>Lethargy, substernal chest pain</td>
<td>Respiratory insufficiency, DIC, hypotension, death</td>
<td>Lungs, widely disseminated</td>
<td>Pituitary gland</td>
<td>None</td>
<td></td>
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<tr>
<td>[6], 41/M</td>
<td>Homosexual</td>
<td>Cryptococcosis</td>
<td>Headache, nausea, fever, cough</td>
<td>Sudden death</td>
<td>None</td>
<td>Cerebral cortex and meninges</td>
<td>Cryptococcosis</td>
<td></td>
</tr>
<tr>
<td>[7], 30/M</td>
<td>IDU</td>
<td>None</td>
<td>Headache, somnolence, disorientation, fever, left-leg paresis</td>
<td>Initial improvement then bronchopneumonia, death</td>
<td>Lungs</td>
<td>Four abscesses</td>
<td>Toxoplasma gondii infection</td>
<td></td>
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<tr>
<td>[8], 32/M</td>
<td>Homosexual</td>
<td>Cryptococcosis, CMV retinitis</td>
<td>Declining mental status, fever</td>
<td>Progressive respiratory insufficiency, death</td>
<td>Lungs, widely disseminated</td>
<td>Not specified</td>
<td>Cryptococcosis</td>
<td></td>
</tr>
<tr>
<td>[PR], 45/F</td>
<td>HSP</td>
<td>Cryptococcosis, Mycobacterium kansasii and MAC infections, CMV retinitis, aspergillus pneumonia, two prior episodes of PCP</td>
<td>Declining mental status, generalized weakness</td>
<td>Progressive clinical deterioration, death</td>
<td>None</td>
<td>Putamen around blood vessels, meninges over right parietal lobe</td>
<td>HIV encephalopathy, meningeal fibrosis</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. CMV = cytomegalovirus; DIC = disseminated intravascular coagulation; HSP = heterosexual partner of HIV-infected person; IDU = injecting drug user; KS = Kaposi’s sarcoma; MAC = Mycobacterium avium complex; PR = present report

Six patients had potential CNS symptoms, including confusion, disorientation, headache, somnolence, and nausea. Three patients had fever. One patient had a left-leg paresis at the time of neurological examination. Two patients underwent CT of the head; it revealed cerebral atrophy in one patient and abnormalities in one 2 years before Pneumocystis was discovered at the corresponding sites. No patients underwent lumbar puncture.

CNS pneumocystosis was not suspected in any of the patients before death. At autopsy, five patients (71%) had concurrent PCP, and four (57%) had widely disseminated pneumocystosis. The involved neuroanatomic locations included the cerebral cortex (2 patients), meninges (2), pituitary gland (1), putamen (1), and nonspecified locations (3). In two patients, organisms were seen around blood vessels. In five patients (71%), there was concurrent neuropathology: HIV encephalopathy (2 patients), cryptococcosis (2), toxoplasma abscesses (1), and meningeal fibrosis from treated cryptococcal meningitis (1).

Discussion

Dissemination of Pneumocystis beyond the lungs may involve local areas such as the chest and distant sites, a pattern suggesting both lymphatic and hematogenous spread. Numerous reports have documented the predilection of P. carinii for vascular involvement [2, 5, 8–24]. Pneumocystis organisms have been found to cause vasculitis within the vasa vasmorum of the aorta and within the lumina of small arterioles. In addition, cocultivation of peripheral blood lymphocytes and PCR amplification of organism-specific nucleic acid have suggested that P. carinii is present in the bloodstream of patients with PCP and disseminated disease [25–27].

CNS pneumocystosis has now been described in seven patients. Six patients had a history of previous opportunistic infections, including three with a history of PCP. Potential neurological symptoms were present in six patients, but only one had focal abnormalities at the time of neurological examination. A head CT of one patient revealed cerebral atrophy, and a head CT of our patient showed focal abnormalities 2 years before P. carinii was discovered at the corresponding sites during autopsy. It is possible that our patient had chronic CNS infection with Pneumocystis that was partially controlled but not cured by treatment with dapsone and trimethoprim and with atovaquone.

In two patients with CNS pneumocystosis, organisms were identified in perivascular spaces. These observations further support the role of hematogenous dissemination in extraplu-
nary pneumocystosis. CNS pneumocystosis was associated with other active neurological infections in five patients and with healed cryptococcal meningitis in one patient. It is possible that these infections may cause alterations in the local vascular architecture and flow, with the subsequent localization of *P. carinii* in the CNS during the hematogenous phase.

Two patients died suddenly, and five patients’ clinical conditions progressively deteriorated before their deaths. CNS pneumo-
cystosis was clinically unsuspected in all patients, and it was discovered only at autopsy. In most patients (four of seven), *P. carinii* had widely disseminated. The contribution of CNS pneumocystosis to their deaths is uncertain given their comorbid illnesses, and the clinical significance of CNS pneumocystosis remains to be determined.

References