Opportunistic Infection in Previously Healthy Women

Initial Manifestations of a Community-Acquired Cellular Immunodeficiency


Opportunistic infections and unusual tumors have been reported in an unprecedented outbreak of community-acquired cellular immune deficiency among homosexual and drug-abusing men. We report five women with the same syndrome. The women were residents of metropolitan New York City closely associated with drug abuse either by personal use (four patients) or close sexual contact with an abuser (one patient). One patient was bisexual. All five patients developed *Pneumocystis carinii* pneumonia as well as combinations of other opportunistic infections including oral candida, disseminated mycobacteria, and ulcerative herpes simplex infections. All patients had marked depression of cellular immune function. Three patients died. The appearance of this syndrome in women has important implications with regard to the epidemiology and etiology of this emerging syndrome.

Since 1981 a remarkable outbreak of community-acquired cellular immune dysfunction has been reported in several hundred young men (1-4). In certain urban areas in the United States, medical centers have recognized a growing population of men who come to medical attention either with opportunistic infections such as *Pneumocystis carinii* pneumonia, ulcerative herpes simplex lesions, disseminated cryptococcosis, candida esophagitis, and disseminated cytomegalovirus infection, or with unusual malignant neoplasms (4). The most frequent tumor has been an aggressive form of Kaposi's sarcoma that had previously been seen in the United States only in organ transplant recipients (4-12). Extensive evaluation including autopsies has failed to show recognizable immunosuppressive disorders, but each of the women has been closely associated with drug abuse, and one is bisexual. The extension of this outbreak to women has important implications concerning the cause, pathogenesis, and mode of transmission of this new syndrome, and should alert the medical community to consider the spread of this outbreak to new populations.

Methods

SELECTION OF PATIENTS AND CONTROLS

Between April 1981 and April 1982 the authors became aware of several cases of opportunistic infection in previously healthy women in the metropolitan New York City area. Five patients from five different hospitals were identified for this study. Histologic evidence for opportunistic infection was reviewed by the authors. A diagnosis of *P. carinii* pneumonia was accepted only if abundant *P. carinii* organisms (identified by methenamine silver, Gram-Weigert, or Giemsa stain) were present in lung tissue; if an inflammatory cellular or exudative response was present; and if no other organisms were shown by pathologic examination, cultivation (for bacteria, fungi, and mycobacteria), or by serology. Serologic studies were done as clinically indicated. Viral cultivations were attempted, but not in a systematic fashion. Pathology of any available tissue was reviewed for evidence of underlying systemic disease or infection.

The control group for in-vitro mononuclear cell studies consisted of healthy hospital personnel (matched for age, sex, and race on at least one date of testing) who were not known to be drug abusers or homosexual, and were not taking any important medications. Control subjects were excluded if they had had an acute illness the week before testing. Historic control values were used for other studies.

IMMUNOLOGIC TESTING

Patients 1 to 3 were studied in the same laboratories that did the previous studies (2) for most values. The initial lympho-
Table 1. Clinical Features of Patients with Acquired Cellular Immune Dysfunction

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Patient</th>
<th>Patient</th>
<th>Patient</th>
<th>Patient</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>31</td>
<td>25</td>
<td>26</td>
<td>37</td>
<td>27</td>
</tr>
<tr>
<td>Race</td>
<td>Black</td>
<td>Hispanic</td>
<td>Hispanic</td>
<td>Hispanic</td>
<td>White</td>
</tr>
<tr>
<td>Sexual preference</td>
<td>Bisexual</td>
<td>Heterosexual</td>
<td>Hispanic</td>
<td>Heterosexual</td>
<td>Heterosexual</td>
</tr>
<tr>
<td>Drugs used</td>
<td>Cocaine, mescaline</td>
<td>None (sexual partner is heroin addict)</td>
<td>Heroin, cocaine</td>
<td>Heroin, cocaine</td>
<td>Heroin, cocaine</td>
</tr>
<tr>
<td>Initial opportunistic infection</td>
<td>Pneumocystis carinii pneumonia</td>
<td>P. carinii pneumonia</td>
<td>P. carinii pneumonia</td>
<td>Esophageal candidiasis</td>
<td>Perianal herpes simplex</td>
</tr>
<tr>
<td>Duration of symptoms before diagnosis of opportunistic infection</td>
<td>2.5 months</td>
<td>3 weeks</td>
<td>34 months</td>
<td>2 weeks</td>
<td>3 months</td>
</tr>
<tr>
<td>Outcome of initial opportunistic infection</td>
<td>Survived</td>
<td>Survived</td>
<td>Died</td>
<td>Survived</td>
<td>Survived</td>
</tr>
<tr>
<td>Other opportunistic infections</td>
<td>Oral candidiasis</td>
<td>Oral candidiasis</td>
<td>Candida esophagitis, perirectal herpes simplex, disseminated Mycobacterium avium-intracellulare infection</td>
<td>P. carinii pneumonia</td>
<td>Disseminated M. avium-intracellulare infection, disseminated cytomegalovirus infection, P. carinii pneumonia, pulmonary aspergillosis, pseudomonas bacteremia</td>
</tr>
<tr>
<td>Follow-up after biopsy</td>
<td>6 months</td>
<td>7 months</td>
<td>9 months</td>
<td>1 month</td>
<td>7 months</td>
</tr>
<tr>
<td>Current status</td>
<td>Alive</td>
<td>Alive</td>
<td>Dead</td>
<td>Dead</td>
<td>Dead</td>
</tr>
<tr>
<td>Evaluation for underlying disease</td>
<td>Liver biopsy, bone marrow biopsy, abdominal computed tomography (CT) scan, gallium scan: no apparent disease</td>
<td>Abdominal CT scan, abdominal sonogram, gallium scan, bone scan, bone marrow biopsy, liver biopsy: no apparent disease</td>
<td>Lymph node biopsy, liver biopsy, bone marrow biopsy, splenectomy: no apparent disease</td>
<td>Autopsy: no apparent disease</td>
<td>Autopsy: no apparent disease</td>
</tr>
</tbody>
</table>

Results

PATIENT POPULATION

The clinical features of these five patients are shown in Table 1. The five women were age 25 to 37 years; one was black, one was white, and three were Hispanic. Patient 1 had regular sexual contacts with a man and a woman during the 12 months before the onset of her illness. Previously she had had multiple male sexual partners. The patient used cocaine and mescaline, but denied intrave-
nous drug abuse. Patients 2 to 5 had exclusively heterosexual relations during the previous 12 months, and denied promiscuity or prostitution. Nothing is known about the sexual preferences of their sexual partners. Patients 3 to 5 had used intravenous heroin regularly although one patient denied heroin use during the 12 months before hospitalization. Patient 2 vigorously denied narcotic abuse, but her male sexual contact was a heroin addict. All women were residents of metropolitan New York City and had no apparent contact with each other. Patient 1 worked in a hospital laundry. The others had occasional clerical jobs. Four patients had had no unusually severe or frequent infections, nor did their families, before the onset of the clinical illness.

CLINICAL ILLNESS
All five women had fever, fatigue, malaise and a weight loss of 7 to 15 kg. Cough was a prominent symptom in Patients 1 to 3, and 5, and was 2 weeks to 3 months in duration. Patient 3 had a prolonged and persistent illness (34 months) that had initially presented as weight loss and generalized lymphadenopathy.

Initial physical examinations showed that all patients had temperatures greater than 38.0 °C. One patient had oral thrush. All patients had abnormal chest examinations with diffuse bilateral rales in three patients, unilateral rales in one patient, and decreased breath sounds at one base in one patient. Two patients had generalized lymphadenopathy; two patients had hepatosplenicomegaly and one patient had hepatomegaly alone. One patient had an ulcerative perianal lesion at the time of initial examination.

ROUTINE LABORATORY EVALUATION
On initial evaluation four of five women were anemic (hemoglobin, 9.0 to 14.0 g/dL), but all had normal granulocyte counts and platelet counts. Lymphopenia was present in all patients (200 to 893 lymphocytes/mm$^3$). Three patients had abnormal liver function tests with transaminases, bilirubin, and alkaline phosphatase levels one and a half to eight times the normal values. Over the next 4 months sonograms showed extensive retroperitoneal lymph node involvement and a 10-kg weight loss since discharge. An underlying disease process has not been found (Table 1).

Patient 1, a 31-year-old black woman who worked in a hospital, developed fever, diaphoresis, lethargy, and a 7-kg weight loss over a 2½-month period in late 1981. The patient was a chronic user of mescaline and cocaine. She had had multiple male sexual partners until 12 months before presentation when she established two stable sexual relations, one with a man and one with a woman. At the time of initial presentation she was in respiratory distress and had nontender 1-cm lymphadenopathy in her anterior and posterior cervical and axillary regions. Chest radiograph showed diffuse bibasilar interstitial infiltrates. Transbronchoscopic biopsy results showed extensive P. carinii pneumonia. The patient's respiratory distress and adenopathy resolved after a 2-week course of intravenous trimethoprim-sulfamethoxazole. The patient developed neutropenia during drug therapy. Three days after termination of trimethoprim-sulfamethoxazole therapy the patient developed chills and fever that resolved within 72 hours of reinstitution of trimethoprim, 160 mg, and sulfamethoxazole, 800 mg twice daily. For 5 months since her hospital discharge the patient has been incapacitated by oral candidiasis, persistent fever, lethargy, anorexia, and an additional 10-kg weight loss, and has persistent leukopenia (leukocyte count 2000 to 4000 cells/mm$^3$). An extensive work-up (Table 1) has not shown an underlying illness or infectious process.

Patient 2, a 25-year-old Hispanic woman, developed a productive cough, weakness, and shortness of breath in October 1981. During her 3-week illness she lost 12 kg. The patient denied illicit drug use or unusual sexual practices, although her one regular male sexual contact is a chronic heroin abuser. She had shotty adenopathy and bibasilar rales. Chest radiograph showed asymmetrical interstitial infiltrates. Results of an open lung biopsy showed marked P. carinii pneumonia. She responded well to a 2-week course of trimethoprim-sulfamethoxazole, but has had oral candidiasis, fever, malaise, and an additional 10-kg weight loss since discharge. An underlying disease process has not been found (Table 1).

Patient 3, a 26-year-old Hispanic woman, was heterosexual and had a history of heroin abuse. The patient presented in November 1978 with cervical and axillary adenopathy, and a 10-kg weight loss. An extensive evaluation showed only anemia and benign follicular hyperplasia of a cervical lymph node. In April 1981, while the patient was hospitalized for bacterial pneumonia, generalized lymphadenopathy and hepatosplenicomegaly were seen, but lymph node and liver biopsy results were nondiagnostic. The patient's leukocyte count was 2860/mm$^3$ with 737 lymphocytes; sheep erythrocyte-rosetting lymphocytes, 57%; inducer/suppressor cell ratio, 0.8; surface-immunoglobulin-positive cells, 44%. Lymphocyte maximum proliferative response is shown in Table 3. In August 1981 she developed P. carinii pneumonia shown by transbronchial biopsy results and was treated with intravenous trimethoprim-sulfamethoxazole with prompt response. A severe hemolytic anemia developed that failed to respond to prednisone, 40 mg/d, and a splenectomy was done. Granulomas with acid-fast bacilli were seen in the spleen and bone marrow, and cultures of both specimens grew *Mycobacterium avium-intracellulare*. Antimycobacterial drugs were continued for only 1 week. *Candida esophagitis* shown by biopsy results developed and responded to oral nystatin. In January 1982 the patient developed fever, cachexia, right upper quadrant pain, and hepatomegaly, and had liver function tests that were six to 10 times the normal values. Over the next 4 months sonograms showed extensive retroperitoneal lymph node involvement, and *M. avium-intracellulare* grew from a liver biopsy culture and multiple sputum samples. The
patient developed progressive pulmonary infiltrates, an extensive perianal ulcer that grew herpes simplex, and profound cachexia. The patient died in April 1982; no autopsy was permitted.

Patient 4, a 37-year-old Hispanic woman with a long history of heroin abuse and methadone treatment, presented in July 1981 with fever, a 12-kg weight loss, cough, and pleuritic chest pain of 2-weeks duration. Several doses of erythromycin failed to improve her clinical status. Examination showed oropharyngeal candidiasis and a right upper lobe infiltrate. The patient was treated with erythromycin but failed to improve. Dysphagia developed and *Candida* esophagitis was shown by biopsy results. Intravenous amphotericin B was begun but the patient developed retinal lesions that were consistent clinically with *Candida* retinitis, and a sacral ulcer that was consistent with herpes simplex disease, although biopsy and culture were not done. The patient developed progressive neurologic and pulmonary dysfunction and died. The autopsy results showed *P. carinii* pneumonia but no evidence of candidiasis; the eyes were not examined.

Patient 5, a 27-year-old heterosexual white woman, had used intravenous narcotics for 3 years, and developed fever and shaking chills in January 1981. In April she developed retinal lesions that were consistent clinically with *Candida* retinitis, and a sacral ulcer that was consistent with herpes simplex disease, although biopsy and culture were not done. The patient developed progressive neurologic and pulmonary dysfunction and died. The autopsy results showed *P. carinii* pneumonia but no evidence of candidiasis; the eyes were not examined.

IMMUNOLOGIC EVALUATION

Immune function of these five patients is shown in Table 2 and 3. Two patients became neutropenic during hospitalization, apparently in response to trimethoprim-sulfamethoxazole (Patient 1) and amphotericin B (Patient 4). Levels of immunoglobulins were normal in the four patients who were tested. Antinuclear antibodies were negative and complement levels were normal in all five patients. Serum cortisol levels were normal in the three patients who were tested.

None of the patients had cutaneous reactivity to any of the antigens tested. All patients were tested against purified protein derivative (5 tuberculin units), mumps, and *Trichophyton* or *Candida*: three patients were also tested against tetanus toxoid, rubella, or purified protein derivative (250 tuberculin units). This anergy was present during the initial acute illness in all five patients, and at least once in the three patients who survived their initial illness, tested at a time when two did not appear to be acutely ill.

Lymphocyte transformation was done on the days after initial presentation shown in Table 3. Patients 1 to 5 were acutely ill at the time testing was done. Patients 1 and 2 were initially tested during their convalescence from *P. carinii* pneumonia, and when they had no identifiable infections as outpatients, although they were febrile and losing weight. Patient 3 was febrile and debilitated when tested. Patient 3 was the only patient receiving immunosuppressive therapy when tested—prednisone, 40 mg/d orally.

Lymphocyte counts showed marked lymphopenia in all five patients (Table 2). This lymphopenia did not return to normal in any patient. All four patients tested have had diminished sheep erythrocyte rosetting population on one or more determinations. The degree of impairment of a person's phytohemagglutinin response did not relate directly to the level of reduction of sheep erythrocyte rosetting lymphocytes or to the number of monoclonal phagocytic cells.

Patient 1 had a markedly depressed proliferative response to phytohemagglutinin when initially tested; this response has not changed significantly from day 81 to day 163. Response to specific antigens and mixed leuko-
Table 3. Maximum Lymphocyte Proliferative Response In Vitro to Mitogens, Antigens, and Allogeneic Cells

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration Since Initial Presentation with Opportunistic Infection</th>
<th>Phytohemagglutinin</th>
<th>Concanavalin A</th>
<th>Pokeweed Mitogen</th>
<th>Candida albicans</th>
<th>Escherichia coli</th>
<th>Staphylococcus aureus</th>
<th>Mixed Lymphocyte Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81 days</td>
<td>6878</td>
<td>ND</td>
<td>ND</td>
<td>188</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>106 days</td>
<td>7518</td>
<td>ND</td>
<td>ND</td>
<td>182</td>
<td>182</td>
<td>148</td>
<td>405</td>
</tr>
<tr>
<td>3</td>
<td>163 days</td>
<td>5356</td>
<td>756</td>
<td>ND</td>
<td>114</td>
<td>90</td>
<td>220</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>46 days</td>
<td>20,928</td>
<td>11,928</td>
<td>6,456</td>
<td>10,824</td>
<td>8,184</td>
<td>5012</td>
<td>882</td>
</tr>
<tr>
<td>5</td>
<td>92 days</td>
<td>63</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>141 days</td>
<td>5476</td>
<td>ND</td>
<td>ND</td>
<td>5348</td>
<td>108</td>
<td>ND</td>
<td>102</td>
</tr>
<tr>
<td>7</td>
<td>(250 days before opportunistic infection)</td>
<td>12,778</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Normal response</td>
<td>&gt; 20,000</td>
<td>&gt; 8600</td>
<td>&gt; 5600</td>
<td>&gt; 2800</td>
<td>&gt; 2000</td>
<td>&gt; 2000</td>
<td>&gt; 7500</td>
<td>ND</td>
</tr>
</tbody>
</table>

* Values represent ¹⁴C-thymidine incorporation after stimulation by the seven agents shown. Data are given as mean counts per minute of maximum response to any dilution of lymphocyte activator tested. Normal responses are given at the bottom of the table. Natural killer cell activity is given as percent ¹⁴Cr release at an effector target ratio of 100:1 against the K562 target cell. ND = not done.

Discussion

Before 1978, disease caused by P. carinii or by multiple opportunistic organisms was an unusual occurrence in patients who had no personal or family history of frequent or severe infection, previously documented immunosuppressive disorder, or no treatment with immunosuppressive therapy (1-3, 15, 16). Certain opportunistic infections such as cryptococcal meningitis or disseminated atypical mycobacteriosis had occasionally caused severe or fatal infection in previously healthy persons, but the patients had usually presented sporadically and had not subsequently developed additional opportunistic infections (17-19). The recent recognition of an outbreak of community-acquired immunodepression and multiple opportunistic infections among men who either abused drugs or were homosexual was an unprecedented occurrence (1-4).

The five women reported here are unique because they had been healthy all of their adult lives, yet developed P. carinii pneumonia, a disease that had been reported in only three adults before 1978 who were not known to have an immunosuppressive disorder (20-24). The five women are also unique because three had infection with multiple opportunistic organisms. It is notable that the opportunistic organisms recognized are similar to those reported in the syndrome in immunosuppressed homosexual men or narcotic abusers: P. carinii, herpes simplex, Candida, cytomegalovirus, and M. avium-intracellularis (1-4, 25). It is also remarkable that the two patients who survived have had the same type of wasting syndrome seen in the men, characterized by fever, malaise, fatigue, and profound weight loss (2). Thus, these women have been clinically shown to have the same types of unusual opportunistic infections, either singly or multiply, as the homosexual or drug-abusing men, and the same clinical course.

The women reside in a geographic area from which many of the men have been reported (4). Moreover, these women were all associated with drug abuse, a factor associated with many of the non-homosexual men (2, 4). Three of the women had been regular users of cocaine and intravenous heroin and a fourth regularly used cocaine and mescaline. One patient, however, steadfastly denied narcotics use herself, but her male sexual partner was a heroin addict. All five women denied sexual promiscuity or prostitution, and none was aware of having had sexual relations with a bisexual man or of frequenting gay gathering places. One patient did have a lesbian relationship as well as a heterosexual relationship, but the sexual and drug habits of her partners are unknown.
Thus, the association of these women with drug abuse, and perhaps with unusual sexual practice, factors related to the immunodepression-opportunistic infection syndrome in men, strongly supports the contention that these women had the same syndrome.

These women all had defects in cell-mediated immune response that were similar to the defects described in the syndrome in men (1-3). Although the women's immunoglobulin levels and complement levels were normal, these women were anergic during (five patients) and after (three patients) their acute illness. All the women except Patient 5 had markedly depressed maximum lymphocyte proliferative responses to T cell mitogens (concanavalin A and phytohemagglutinin) and to allogeneic stimulation (a T lymphocyte response), as well as to microbial stimuli (Candida albicans, Escherichia coli, and Staphylococcus aureus), which are predominantly B cell activators. When initially evaluated after their opportunistic infections, all patients were uniformly immunologically depressed. Patient 2 had normal responses to mitogens and microbial activators (but not to mixed leukocyte culture) when first tested, but her function deteriorated markedly over the next 95 days. This suggests that immunodepression may initially develop as a regional rather than a systemic phenomenon (14).

The clinical course of Patient 3 deserves particular mention because this woman may represent a larger population whose natural history is currently uncertain. We have recently begun to see, as have many urban medical centers, numerous homosexual men with generalized lymphadenopathy (26). Some of these men are asymptomatic and some have hepatosplenomegaly, low grade fever, fatigue, or weight loss. Extensive diagnostic evaluations have failed to define a recognizable immunosuppressive disorder. Patient 3 was followed clinically and immunologically during a 3½-year illness that started with histologically nonspecific lymphadenopathy, and progressed to hepatosplenomegaly, lymphopenia, reversed helper to suppressor cell ratio, and finally a host of opportunistic infections. The possibility that some homosexual men with lymphadenopathy may follow a similar course is alarming.

The development of this syndrome in women should clearly show the need for clinicians to consider the presence of community-acquired immunodepression in new patient populations. The occurrence of the syndrome in homosexual men or drug abusers as well as the potential for transmission into new groups should further the urgency to investigate this disorder so that transmission can be prevented and so a treatment can be discovered to reverse the current dismal prospects for survival that face patients who have acquired this syndrome.

References

