Case In Point: Coexisting Hodgkin disease and lung cancer in a patient with AIDS

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The patient was a 41-year-old man with a history of HIV infection diagnosed 10 years before admission. He had been noncompliant with treatment, and therapy with tenofovir, efavirenz, and lamivudine had not been started until 2 months before admission, when he presented to another hospital. At the time, his CD4+ cell count was 156/µL and his viral load was 45,743 copies/mL. He also had a history of incarceration; had used injection drugs, cocaine, alcohol, and marijuana; and had a 20-pack-year tobacco history.

Highly active antiretroviral therapy has significantly decreased the morbidity and mortality associated with infectious complications of AIDS and has almost eliminated CNS lymphoma and Kaposi sarcoma. In contrast, the risks of Hodgkin disease and lung cancer have increased. We present an unusual case of concomitant Hodgkin disease and lung cancer in a patient with AIDS. To the best of our knowledge, this is the first case of 2 different primary malignancies presenting simultaneously in a patient with AIDS.

The case
The patient was a 41-year-old man with a history of HIV infection diagnosed 10 years before admission. He had been noncompliant with treatment, and therapy with tenofovir, efavirenz, and lamivudine had not been started until 2 months before admission, when he presented to another hospital. At the time, his CD4+ cell count was 156/µL and his viral load was 45,743 copies/mL. He also had a history of incarceration; had used injection drugs, cocaine, alcohol, and marijuana; and had a 20-pack-year tobacco history.

The patient had been hospitalized 8 months before admission and had been treated for a recurrent Mycobacterium avium-intracellulare infection complicated by development of deep venous thrombosis and pulmonary embolism. During that hospitalization, he was found to have mediastinal lymphadenopathy, and mediastinoscopy with a right paratracheal lymph node biopsy revealed Hodgkin disease (mixed-cellularity subtype) stage 3B (Figure 1).

He received 5 cycles of therapy with mechlorethamine, vincristine, procarbazine, and prednisone (MOPP), the last cycle occurring 3 weeks before admission. In addition, the patient was noted to have right upper lung, bilateral adrenal, and pancreatic masses, which were thought to be related to his Hodgkin disease. These masses had been stable for the past 8 months.

He now presented with a history of 3 weeks of nausea, vomiting, diarrhea, and diffuse abdominal pain, which had not responded to a course of levofloxacin, 500 mg daily, for presumed colitis, or to appropriate pain medications.

Physical examination revealed a middle-aged man in mild respiratory distress, with a respiration rate of 20 breaths per minute. He was afebrile. His heart rate was 98 beats per minute and blood pressure was 120/80 mm Hg. There was no evidence of clubbing, cyanosis, or hypertrophic osteoarthropathy.

The patient had decreased air entry in the right hemithorax. Heart sounds showed a normal S1 and S2, with a loud pulmonic component of the S2. His abdomen was soft but diffusely tender, more so on the right than on the left, with significant hepatosplenomegaly. Findings from a neurologic examination were unremarkable.

Laboratory test results revealed a white blood cell (WBC) count of 10,200/µL, with 70% polymorphonuclear neutrophils, 23% lymphocytes, 7% monocytes, and 0% eosinophils; hemoglobin level of 12.7 g/dL; and hematocrit value of 30%. Arterial blood gases on room air were pH, 7.44; PCO2, 30 mm Hg; and PO2, 78 mm Hg. Admission laboratory values were also significant for a total bilirubin level of 4.3 mg/dL (normal, 0.2 to 1.2 mg/dL); amylase, 175 U/L (normal, 25 to 125 U/L); lipase, 132 U/L (normal, 7 to 60 U/L); aspartate aminotransferase (AST), 66 U/L (normal, 10 to 40 U/L); alanine aminotransferase (ALT), 89 U/L (normal, 10 to 45 U/L); alkaline phosphatase, 1019 U/L (normal, 30 to 120 U/L); lactate dehydrogenase, 350 U/L; and cancer antigen 19-9, 51 U/mL.
Abdominal sonography, CT, and MRI revealed a dilated common bile duct of 1.2 cm, mild pancreatic duct dilatation, bilateral adrenal masses measuring 4.3 2.8 cm on the left and 5.2 3.2 cm on the right, and a mass in the pancreatic head measuring 2.3 1.4 cm (Figures 2 and 3). The pancreatic and adrenal masses had expanded since studies completed 1 month earlier. Chest CT revealed a spiculated mass in the right upper lobe measuring 3.2 3.2 cm, with an adjacent satellite lesion, and a right hilar lymph node measuring 2.3 1.5 cm (Figure 4), unchanged from previous studies. Bowel rest was prescribed for the patient, and he was given pain management and intravenous fluids. Only mild improvement was achieved: minimum liver enzyme levels reached were AST, 52 U/L; ALT, 76 U/L; alkaline phosphatase, 886 U/L; and total bilirubin, 3.2 mg/dL, with a direct bilirubin of 2.5 mg/dL. The patient’s symptoms improved, and he was able to tolerate oral intake. The workup was continued to further evaluate the lung, adrenal, and pancreatic masses.

A positron emission tomographic scan revealed increased tracer uptake in the right upper lung, right hilum and mediastinum, neck and abdomen, and left and right acetabular regions (Figure 5). Results of a CT-guided biopsy of the right upper lung mass and biopsy of the adrenal mass were consistent with non-small-cell lung carcinoma (Figure 6). The pathologic findings included large epithelial cells with nuclei that showed malignant features. The immunohistochemical staining showed uptake for keratin within the cells and abnormal nuclei, which confirmed the presence of carcinoma.

A review of the pathology sections from the previous right paratracheal lymph node biopsy demonstrated a lymphoid proliferation with several binucleated Reed-Sternberg cells and positive staining with CD-30, consistent with Hodgkin disease. This confirmed the concomitant presentation of 2 malignant processes.

The patient was deemed a poor candidate for chemotherapy because of his low performance status. Over the course of his hospital stay, he had fevers and progressively increasing levels of AST (199 U/L), ALT (108 U/L), alkaline phosphatase (1283 U/L), and total bilirubin (11.5 mg/dL, with a direct bilirubin level of 8.1 mg/dL).

The patient was given piperacillin/tazobactam, 3.375 mg IV every 6 hours, and was scheduled to undergo endoscopic retrograde cholangiopancreatography (ERCP) to relieve a presumed obstructive cholangitis. Attempts to place a stent in the common bile duct via ERCP were unsuccessful, but sufficient drainage was eventually established via percutaneous transhepatic cholangiography. Shortly after this procedure, the patient became encephalopathic and pancytopenic, with a WBC count of 1600/µL and absolute neutrophil count of 700/µL. Acute respiratory distress developed, and the patient was intubated. He required increasing respiratory support and eventually died.

Discussion

Since the advent of highly active antiretroviral therapy, the incidence of opportunistic infections has declined and survival has significantly improved in patients with AIDS. The incidence of other AIDS-defining illnesses, such as Kaposi sarcoma, primary CNS lymphoma, peripheral B-cell non-Hodgkin lymphoma of intermediate or high grade, and invasive cervical carcinoma, also has decreased. In contrast, the incidence of Hodgkin disease, squamous cell carcinoma of the skin and lip, testicular carcinoma, and lung carcinoma has increased in patients with AIDS.1

Lung cancer has been documented as the most frequently diagnosed non-AIDS-defining malignancy; the incidence is 13.6-fold higher than it is in the general population, and there is a predominance of adenocarcinoma.2 HIV-infected smokers and injection drug users are at high risk for lung cancer, and HIV-associated lung cancer occurs more commonly in younger patients—those aged 20 to 50 years.3 In general, these lung cancers are more aggressive; are associated with a poorer prognosis, with median survival of only 4 weeks to 3 months; and have a low response rate to treatment.4

There are many proposed explanations for the development of primary lung cancer in the AIDS population. The well-known impairment of the normal pulmonary defenses associated with HIV infection—natural killer cells, in particular—may allow an unchecked proliferation of spontaneously developing tumor cells and stimulate the release of aberrant growth factors, resulting in oncogenesis.1

The proliferation of growth factors is also noted in injection drug users as a result of recurrent bacterial pulmonary infections, mainly tuberculosis, and drug-induced changes in the pulmonary stroma.1 Alternatively, the diagnosis of lung cancer may often be delayed because pulmonary nodules in HIV-infected patients are often attributed to pulmonary infections.

In some studies, however, Hodgkin disease has been described as the most common non-AIDS-defining tumor, with a relative incidence of 19.8 times that in non-HIV-infected persons.2 Hodgkin disease is more likely in persons with CD4+ lymphocyte counts of less than 300/µL.5

Factors thought to play a role in the etiopathogenesis of HIV-associated Hodgkin disease involve...
mechanisms similar to those associated with lung cancer, such as a reduction in the host's cellular immunity and the direct effect of HIV on the genesis of preneoplastic lesions. Also, the intervention of viral agents, namely Epstein-Barr virus, plays a larger role than it does in the general population. The histologic features of Hodgkin disease in HIV infection are characterized by a predominance of the more aggressive and unfavorable mixed-cellularity and lymphocyte-depleted subtypes.\(^5\) The cellular background usually includes an abundance of Reed-Sternberg and fibrohistiocytoid stromal cells.

Hodgkin disease in HIV-infected patients differs from that in the general population, with a peak incidence at age 20 to 30 years, more "B" symptoms and widespread disease at presentation, and a poorer prognosis (a median survival of only 12 to 18 months).\(^{3,6}\) There is no consensus about the optimal treatment of Hodgkin disease in HIV-positive patients; thus, treatment is similar to that in HIV-negative patients. Generally, radiotherapy has been the standard treatment, although it is frequently combined with chemotherapy. For patients who have more advanced disease, chemotherapy may be used alone.

The most commonly used therapeutic protocols are MOPP; adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD); and MOPP/ABVD. Chemotherapy is usually poorly tolerated in HIV-positive patients.

In the general population, the cure rate for Hodgkin disease is quite impressive—exceeding 85% with early-stage, asymptomatic disease. The 5-year survival rates for patients with the most advanced disease are at least 50%. However, as the number of long-term survivors increases, so do the complications of treatment. Late toxic effects attributable at least in part to radiotherapy include hypothyroidism, pericarditis, and accelerated atherosclerotic heart disease.

Furthermore, patients are at increased risk for solid tumors, mainly of the thyroid, breast, and lungs, after treatment of Hodgkin disease. The incidence of these second malignancies begins to rise during the first 5 years, does not plateau, and reaches a rate of 14% to 20% after 20-year follow-up.\(^7\)

After Hodgkin disease, the second malignancies are the most common cause of death. Of these, the most common solid tumor is lung cancer, with a 3- to 13-fold increased relative incidence.\(^7\) A history of smoking, as expected, increases the risk of a second lung carcinoma, with a possible synergistic effect with radiotherapy.\(^8\)

To the best of our knowledge, this is the first case report of 2 different malignancies in the same HIV-infected patient. The diagnosis of lung cancer was delayed because the pulmonary mass was thought to be either inflammatory or related to Hodgkin disease. After the patient's condition worsened during chemotherapy, the second diagnosis was sought. In addition, this patient presented with Hodgkin disease at a CD4\(^+\) cell count below 300/µL (at 156/µL) and with the mixed-cellularity subtype.

This kind of clinical presentation was not reported in the pre-HAART era, possibly because of the significant morbidity and mortality from HIV-associated illnesses. The prolonged survival of AIDS patients in the post-HAART era has witnessed an increased incidence of certain malignancies. This underscores the importance of considering additional malignancies in HIV-infected patients who have one malignancy.

References: REFERENCES
