Case Report from the New York-New Jersey Intercity Infectious Disease Rounds
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Fatal Unrecognized Cutaneous and Systemic Kaposi's Sarcoma in an AIDS Patient with Acute Cryptococcal Meningoencephalitis

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CASE DESCRIPTION

A 45-year-old African-American male was admitted to the hospital complaining of back and chest discomfort and general malaise of 4 days’ duration. He also reported unquantified weight loss, occasional low-grade fever, drenching night sweats, productive cough, whitish expectoration, and pleuritic chest pain. He denied headache, vomiting, diarrhea, dysuria, and abdominal pain.

The married father of six children, he was a former crack user, moderate smoker, nonalcoholic known to have acquired immunodeficiency syndrome (AIDS), on the basis of CD4 cell count of 5/μL, done 3 months before admission. His tuberculin test (PPD) result had been anergic 2 weeks previously. He denied any history of heart disease, diabetes, hypertension, or drug allergies. He was born and raised in New York and had no travel history.

When the paramedics arrived at his house, they found him lying on his bed, and saying, “I might as well go to the hospital.” He told them he was out of his medications, and he did not know their names. Vital signs were recorded as follows: blood pressure (BP) 116/72; pulse rate (PR) 80, regular; respiration rate (RR) 16; and Glasgow Coma scale, 15.

In the emergency department, the patient’s temperature was 96°F (35.8°C); PR 78; RR 16; and BP 110/70. He was noted to have poor oral hygiene, and tender lumbar vertebral 1-5. No gross abnormality was found on examination of respiratory, cardiovascular, and gastrointestinal systems.

Preliminary laboratory results showed:

- White blood cell count (WBC): 5.7 × 10⁹/L
- Neutrophils: 31%
- Lymphocytes: 58%
- Bands: 1%
- Eosinophils: 7%
- Monocytes: 3%
- Hematocrit: 0.28
- Platelet count: 427 × 10⁹/L
- Mean corpuscular volume (MCV): 85.2 fl
- Glucose: 9.38 mmol/L
- Blood urea nitrogen (BUN): 7.49 mmol/L
- Creatinine serum: 137.2 μmol/dL
- Sodium (Na+): 138.9 mmol/L
- Potassium (K+): 4.02 mmol/L
- Carbon dioxide (CO₂): 21.3 mmol/L
- Aspartate aminotransferase (AST): 23 IU/L
- Alanine aminotransferase (ALT): 18 IU/L
- Thyroid panel (TP): 67 μg/L
- Calcium (Ca++): 2.02 mmol/L
- Magnesium (Mg++): 0.61 mmol/L
- Total bilirubin: 8.55 μmol/L
- Arterial blood gases (ABG) on room oxygen (O₂): pH 7.40; PO₂ = 6.43 kPa; PCO₂ = 4.25 kPa; oxygen saturation = 84.3%
- Lumbar spine radiograph: normal

Chest radiograph: cardiomegaly, no parenchymal infiltration nor consolidation; the left costophrenic recess was slightly blunted; the hemidiaphragms were sharp; perivascular cuffing was evident with prominent pulmonary vascular shadows; the cardiac silhouette was enlarged in size, shape, and configuration, consistent with cardiomegaly; radiographic signs suggestive of congestive heart failure were noted; the tracheobronchial tree was midline and patent (Figure 1).

Electrocardiogram: normal sinus rhythm (NSR) = 98/min, normal electrical axis, normal intervals, and no acute sinus tachycardia (ST) changes.

The patient was admitted to the medical ward where physical examination revealed:

- Vital signs: temp 96°F (35.5°C); PR 78, regular; RR 16; BP 110/70
- Ill-looking middle-aged man, in no acute distress; pupils 3 mm in size, equally reactive
- Bilateral bronchial breath sounds, fine basal rales

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Point of maximal impulse (PMI) in fifth costal interspace
Heart sound: only S1 and S2 were heard, regular, without murmur, rub or gallop
Old abdominal scar of childhood injury
Abdomen was flat, soft, nontender without hepatosplenomegaly or palpable masses
Swollen glans penis, ulcerative lesion of 3 cm in diameter at the base of the phallus
As per the patient, "It started as little itchy pimple," then it became an ulcer
The prostate was enlarged (1+)
Stools guaiac, negative
The patient was alert, fully oriented, with no meningismus or focal neurologic deficit

**DIAGNOSIS**

What is the differential diagnosis?
1. Tuberculosis (TB)
2. Syphilis
3. Herpes simplex infection
4. Aspergillosis
5. Pneumocystis carinii pneumonia (PCP)

**Tuberculosis**

Incorrect. However, this is a reasonable suggestion in this chronically ill New York City resident with AIDS and a history of weight loss, low-grade fever, drenching night sweats, productive cough. As published by Pitchenick and others, the chest radiograph may be atypical or even normal in such profoundly immunosuppressed individuals with pulmonary TB. Instead, the radiographic pattern of this patient is consistent with congestive changes. Nonetheless, it is reasonable to place such a high-risk patient on acid-fast bacilli (AFB) isolation while pursuing appropriate investigations. Empirical antituberculous therapy is recommended as soon as sputum collection is complete.

**Syphilis**

Correct. Syphilis has been called "the great mimicker." The chancre of primary syphilis is usually indurated, a finding not seen here. A darkfield test would have been appropriate, but it is not routinely available. The rapid plasma reagin (RPR) test was reactive at 1:4 and confirmed by a positive fluorescent treponemal antibody absorption (FTA-ABS) test. The patient was treated with penicillin, but syphilis alone cannot explain the entire clinical presentation. As in many similar cases, this patient probably had more than one disease simultaneously; therefore, further investigations were warranted.

**Herpes Simplex**

Incorrect. Indeed, the penile lesion is compatible with herpes simplex virus (HSV) genitalis. The patient was started empirically on acyclovir. Again, this constellation of symptoms cannot be attributed to HSV alone, unless it is disseminated.

**Aspergillosis**

Incorrect. Invasive pulmonary aspergillosis is usually a late manifestation of AIDS in patients with CD4 cell count less than 50/µL. It can present with cough, fever, and weight loss. A prominent feature is chest pain, which can be refractory, troublesome, and associated with hemoptysis. Pulmonary aspergillosis can present as invasive parenchymal, endobronchial, or intracavitary disease. In patients with AIDS, more than one pathologic type can be recovered on autopsy. Generally, lifelong suppressive therapy is indicated.

**Pneumocystis carinii Pneumonia**

Incorrect. The clinical presentation and the arterial blood gas support the diagnosis of severe PCP and justify empirical treatment. However, PCP by itself would rarely cause drenching night sweats and pleuritic chest pain. Cardiomegaly is not a feature of PCP.

**CLINICAL COURSE**

The patient was treated empirically with intravenous trimethoprim-sulfamethoxazole, penicillin, and acyclovir. However, he spiked fever to 100°F, 102°F and 104°F on day 2, 3, and 4, respectively. On day 4, he became lethargic, confused, and disoriented. An emergent lumbar puncture was done. Cerebrospinal fluid (CSF) was cloudy, colorless, with opening pressure of 15 cm H₂O, WBC 50 × 10⁶/L, neutrophils 51%, lymphocytes 48%, eosinophils 1%, red blood cell count (RBC) 10,450 × 10⁶/L, protein 0.46 g/L, glucose 5.77 mmol/L. Venereal Disease Research Laboratory (VDRL) test and AFB smear were negative. India ink was positive; CSF cryptococcal antigen (Ag) reactive, 1:512.

Laboratory tests included culture: Cryptococcus neoformans; and Gram stain: few neutrophils, no organisms.

Head computed tomography (CT) without contrast (creatinine 205.87 µmol/dL): mild to moderate atrophy, no focal intracranial lesion.

Four sputum samples were AFB-negative. Amphotericin B andisoniazid (INH), rifampin, pyrazinamide (PZA), and ethambutol were initiated, oral acyclovir and intramuscular weekly penicillin continued.

On the ninth hospital day, a noncontrast chest CT revealed massive pericardial effusion (Figure 2A and B); at that time, the patient was asymptomatic; EKG was not consistent with tamponade.

Two weeks after admission, the patient went into acute respiratory distress and was intubated and transferred to the intensive care unit (ICU) (Figure 3). Broad-spectrum antimicrobials were added. Echocardiogram
confirmed massive pericardial effusion without tamponade. But 5 days later, the patient developed tamponade and underwent emergent pericardiocentesis, which yielded 1000 cc of serosanguinous fluid, few WBCs, and no organisms; culture and cytology were negative. A pericardial window was performed after 24 hours. Histopathology demonstrated acute and chronic pericarditis, absence of granuloma, and negative AFB and silver stains. After 10 days in the ICU, the patient was extubated and transferred to the medical service. One week later, the patient again went into acute respiratory distress, and he was reintubated. Chest radiograph revealed diffuse pulmonary densities from hilum toward the periphery (Figure 5). Arterial blood gases on 2 L O2: pH 7.31; PO₂ = 8.26 kPa; PCO₂ = 3.59 kPa; oxygen saturation = 88.8%, CO₂ = 15.5 mmol/L.

Spinal tap was repeated and showed CSF was clear, colorless, with opening pressure of 12 cm H₂O, WBC 1 × 10⁶/L, RBC 17 × 10⁶/L, protein 0.26 g/L, glucose 3.21 mmol/L, India ink and cultures negative. The patient’s clinical condition continued to deteriorate, and he died 1 week later. Acyclovir was continued during the entire hospitalization. After 1 week of treatment, the penile ulcer regressed by about 5 to 10%, then it remained unchanged.

**MAJOR AUTOPSY FINDINGS**

Findings on autopsy included the following:

- Systemic Kaposi’s sarcoma (KS), involving heart (Figure 4), lungs (Figure 5), liver, small intestine (Figure 6), and skin.
Kaposi's sarcoma is an angioproliferative disease characterized by interweaving bands of spindle cells, with irregular slit-like vascular channels, within a network of reticular and collagen fibers. Similar histologic features are encountered in the different forms of KS (i.e., classic, endemic, and epidemic KS). Moritz Kaposi originally described classic Kaposi's sarcoma in 1872. This is usually a mild disease affecting predominantly elderly men of Ashkenazi Jewish descent or from Mediterranean areas. It usually involves the lower extremities. Endemic KS affects men and women equally and also children in equatorial Africa. Kaposi's sarcoma has also been recognized in HIV seronegative immunosuppressed individuals. Once the immunosuppressive therapy is removed, spontaneous resolution has been observed in 50% of cases. Kaposi's sarcoma can appear at any stage of HIV infection. In the presence of an acute opportunistic infection, lower CD4 cell count, and B symptoms, it follows a more rapid course. The role of several cytokines in the pathogenesis of KS has been elucidated; IL-6 seems to be predominant, for providing the pathway for tumor necrosis factor (TNF) and IL-1 to exert their activity. Researchers at the National Cancer Institute have established that HIV-1 Tat protein enhances endothelial cell growth and type IV collagenase expression in response to basic fibroblast growth factor, mimicking extracellular matrix protein. But a subsequent report of KS in HIV-seronegative homosexual men casts a shadow on this assertion and reinforces the notion of sexual transmission of KS by an infectious agent other than HIV.

The etiology of KS has eluded scientists for many years. However, since the dawn of the AIDS epidemics, questions have been raised concerning the possibility of a sexually transmitted agent, because

1. Among HIV-infected individuals, KS is much more prevalent in homosexual and bisexual men than in hemophiliacs, injecting drug users, and women.
2. Among homosexual men, the prevalence of KS increases with the frequency of multiple sexual part-
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ners, and of anal-oral contact; KS is also associated with receptive anal intercourse.9

3. Women with KS tend to have a higher proportion of bisexual partners who also have KS.10

In December of 1994, Chang and colleagues shed light on the mysteries of KS.11 Using representational difference analysis, they discovered the unique DNA sequences of a novel herpesvirus (Kaposi’s sarcoma-associated herpesvirus [KSHV]), closely related to the Gamma-herpesvirinae, herpesvirus saimiri, and Epstein-Barr virus, in more than 90% of KS tissues collected from patients with AIDS.11 In less than a year, they and others identified DNA sequences of KSHV in classic and endemic KS and also in KS that occurs in HIV-negative homosexual men.12,13 A study by Whitby and co-workers supports the causative role of KSHV in KS.14 Their theory was supported by the isolation of KSHV in spindle and endothelial cells, cell types thought to be neoplastic in these lesions.13 A system for the lytic growth of the virus in a latently infected B-cell line was developed by scientists at the University of California at San Francisco which allowed them to first visualize the ultrastructure of the virus.16

Despite their variation in pigmentation, size, shape, and distribution, the mucocutaneous lesions of KS are usually not difficult to recognize. They can be brownish or black in dark-skinned individuals and pink to purplish, or brown, in light-skinned individuals. They may be flat, raised, nodular, exophytic, and rarely, subcutaneous.17 They arise predominantly in the oral cavity, the periauricular and periorbital areas, the ears, the lower extremities, the genitals, and the chest. Almost any part of the body has been involved, including many organs (e.g., bronchopulmonary tree, the gastrointestinal tract, the heart, and the bone marrow). Genital KS lesions are rarely ulcerated, except in the presence of edema after radiotherapy of lower extremities or secondary infection. Most visceral KS lesions remain asymptomatic. The clinical manifestations are nonspecific. Pulmonary KS can present as a chronic insidious illness characterized by frequent bouts of respiratory ailments. Symptoms including dry cough, chest pain, hemoptysis, and fever have been reported. Wheezing can ensue when endobronchial lesions are significant. Pleuritic chest pain may be caused by pleural effusion, which may not be apparent on chest radiograph. In fact, chest radiograph may be normal in 5 to 20% of the cases, but typical findings are perihilar infiltrates following the septal lines, and nodular opacities that may coalesce and progress rapidly in the setting of an acute opportunistic infection.18 The final diagnosis relies on histopathologic examination of biopsy samples. Recently, a less invasive approach using a nested polymerase chain reaction (PCR) has been reported by Cathomas and colleagues.19 They isolated human herpesvirus (HHV)-8 DNA in the bronchoalveolar lavage fluid of patients with pulmonary KS. If further studies confirm the diagnostic value of this technique, it may obviate the need for a transbronchial biopsy. A screening test, which detects antibody to a latency-associated nuclear antigen (LANA), has been developed. Published results have shown a strong correlation between anti-LANA reactivity and the risk of KS.20 Cardiomegaly due to heart involvement by KS is sometimes apparent on chest radiograph, especially when it is associated with pericardial effusion, which may lead to cardiac tamponade. In other patients seen at Harlem Hospital Center an epicardial surface studded with purple or red nodules of KS has been revealed during pericardial window (Unpublished data).

Chemotherapy may be effective in improving symptoms, inducing tumor regression, and reducing edema. Monotherapy and various combination regimens as well as radiotherapy have been used.22 Newer modalities of therapy undergoing clinical trials include liposomal anthracyclines, camptothecins, a novel class of drugs that are both antineoplastic and antiviral, and IL-4, an antagonist of IL-6. In particular, a large phase III trial has shown similar efficacy between liposomal daunorubicin and Adriamycin (doxorubicin), bleomycin, and vinblastine (ABV). Response rates, time to treatment failure, and overall survival were
not significantly different. \(^23\) Whatever the therapeutic agents chosen, antiretroviral therapy, prophylaxis for opportunistic infections, and the use of hematopoietic growth factors should be routinely included in the management of these patients. There have been anecdotal reports of regression of AIDS-related KS lesions and clearance of HHV-8 from peripheral blood mononuclear cells following treatment with an HIV-1 protease inhibitor. \(^24,25\) However, at present, the impact of protease inhibitors on the incidence and treatment of KS is undetermined. Researchers at Lee Moffitt Cancer Center in Florida developed an antiviral drug assay using lytic KSHV DNA synthesis induction by the phorbol ester 12-O-tetradecanoyl phorbol-13-acetate (TPA) in BCBL-1 cells. This assay was useful to obtain accurate 50% inhibitory concentration (IC\(_{50}\)) values. It was determined that KSHV is sensitive to cidovir, moderately sensitive to phosphonoformic acid, and ganciclovir, and weakly sensitive to acyclovir. \(^26\) Neyts and De Clercq examined the concentrations required to reduce HHV-8 DNA synthesis in TPA-stimulated BCBL-1 cells 8. S2242, a novel nucleoside analogue, with broad-spectrum activity against all herpesviruses, including thymidine kinase (TK)-deficient strains, exerted the most potent inhibition. It was followed by adcfovir, a compound with anti-HIV-1 activity (90% effective concentration \(\text{EC}_{50}\), 0.6 ± 0.5 \(\mu\)M) and cidovir (\(\text{EC}_{50}\), 18 ± 9 \(\mu\)M), which has long-lasting inhibition of KSHV replication. The 50% effective concentration (\(\text{EC}_{50}\)) of foscarnet was fourfold higher than that of adcfovir (177 \(\mu\)M and 39 \(\mu\)M, respectively). \(^27\) These experiments may open the door of antiviral trials for KSHV.

REFERENCES