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Case 18-2009: A 24-Year-Old Woman with AIDS and Tuberculosis with Progressive Cough, Dyspnea, and Wasting

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PRESENTATION OF CASE

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Dr. Anne Griffin (Medicine and Pediatrics): A 24-year-old woman with the acquired immunodeficiency syndrome (AIDS) and pulmonary tuberculosis was admitted to a hospital in South Africa that is affiliated with this hospital, because of progressive cough, dyspnea, and wasting.

A diagnosis of pulmonary tuberculosis was made 7 months earlier, when she presented at another facility with a productive cough, and a sputum specimen was positive for acid-fast bacilli on sputum-smear microscopy. No chest radiograph was obtained. She had no known history of active tuberculosis. The patient was enrolled in a local Directly Observed Treatment (DOTS) program, and antimycobacterial therapy (isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months, followed by isoniazid and rifampin for 4 months) was administered according to the South African National Tuberculosis Control Programme guidelines. The next month, a test for human immunodeficiency virus (HIV) infection was positive; the CD4+ T-lymphocyte count was 102 cells per cubic millimeter.

After 6 months of therapy, the productive cough persisted and stained specimens of sputum remained positive for acid-fast bacilli. Isoniazid and rifampin were continued. Approximately 6 weeks before admission, the patient's cough worsened and dyspnea developed and worsened, with fevers, night sweats, and weight loss. She became progressively debilitated and was admitted to the hospital.

She reported having been hospitalized elsewhere for 4 months during the previous year; no further information was available. She had no known allergies. She had not received antiretroviral medications or prophylaxis for *Pneumocystis jirovecii*. Her only medications were rifampin and isoniazid. She was single, with no children. She lived in a poor community in the province of KwaZulu-Natal, South Africa, and was unemployed. She did not smoke, drink alcohol, or use recreational drugs, and she had never worked in a health care facility or been incarcerated. She was a member of the Zulu ethnic group. No other family members were known to have tuberculosis.

On examination, the patient was alert and oriented but emaciated and in respiratory distress. The weight was 51 kg, the temperature 40°C, the blood pressure 97/54 mm Hg, and the pulse 132 beats per minute; the respirations were 30 to 36 breaths per minute, with an oxygen saturation of 93% while the patient was receiving supplemental oxygen (40%) by face mask. The mucous membranes and conjunctivae were pale. There were coarse rales bilaterally, bronchial breath sounds in the left upper lung fields, and wheezing in the right lung fields on inspiration and expiration. The heart sounds were normal. There was bilateral pedal edema (1+). The remainder of the examination was normal. A chest radiograph showed multiple cavities and air-space opacities in the left lung, with loss of volume and a slight shift of the mediastinum to the left. Focal consolidation in the right upper lobe and left pleural thickening or a small pleural effusion were present. She was admitted to the hospital.

Amoxicillin–clavulanate intravenously and high-dose trimethoprim–sulfamethoxazole orally were begun, along with intravenous crystalloid solution; isoniazid and rifampin were continued, and pyridoxine was added. The patient was able to eat and bathe independently but remained in bed most of the time. Fevers and cough persisted, and smears of sputum specimens showed acid-fast bacilli. On the eighth day, she was transferred from an open ward to a respiratory-isolation ward; amoxicillin–clavulanate was discontinued, and ceftriaxone and gentamicin were begun intravenously. During the next 2 weeks, her condition gradually worsened, with chest pain that radiated to the right shoulder and neck, a fluctuating temperature (up to 40°C), increasing dyspnea, and weakness. Laboratory-test results are shown in Table 1. Oral candidiasis developed; ceftriaxone was discontinued, and oral fluconazole was begun. On the 19th day, the left leg was swollen and edematous; enoxaparin and intravenous fluids were administered. Noninvasive venous studies of the legs were scheduled. The next morning, she appeared confused. Later that day, dyspnea worsened, and she died.

Three months later, results of a diagnostic test were received.

Table 1. Results of Laboratory Tests.*

Variable	Reference Range†	15th Hospital Day
Hematocrit (%)	37–52	20.8
Hemoglobin (g/dl)	12–18	7.2
White cells (per mm ³)	5200–12,400	7150
Differential count (%)		
Neutrophils	40–74	77
Lymphocytes	19–48	19
Monocytes	3–9	2
Eosinophils	0–7	1
Basophils	0–2	1
Platelets (per mm ³)	130,000–400,000	99,000
Mean corpuscular volume (μm ³)	80–99	84.7
Sodium (mmol/liter)	135–148	130
Potassium (mmol/liter)	3.6–5.3	3.5
Chloride (mmol/liter)	95–105	108
Carbon dioxide (mmol/liter)	23.0–31.9	17
Urea nitrogen (mg/dl)	8.4–18.2	43.1
Creatinine (mg/dl)	0.68–1.36	1.71
Total bilirubin (mg/dl)	0.18–1.00	0.6
Protein (g/dl)		
Total	6.0–8.0	7.2
Albumin	3.2–5.0	1.4
γ-Glutamyltransferase (IU/liter)	10–60	71
Alkaline phosphatase (IU/liter)	42–121	125
Aspartate aminotransferase (IU/liter)	10–40	59
Alanine aminotransferase (IU/liter)	10–45	16
Lactate dehydrogenase (IU/liter)	266–500	1101
C-reactive protein (mg/liter)	<8	125

* To convert the value for urea nitrogen to millimoles per liter, multiply by 0.357.

To convert the value for creatinine to micromoles per liter, multiply by 88.4.

To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

† Reference values and results are for tests performed at the hospital in South Africa. Reference values are affected by many variables, including the patient population and the laboratory methods used. They may therefore not be appropriate for all patients.

DIFFERENTIAL DIAGNOSIS

Dr. Douglas Wilson: Edendale Hospital is a district and regional facility in Pietermaritzburg, in the KwaZulu–Natal province of South Africa. Resi-

dents in internal medicine from Massachusetts General Hospital participate in clinical and educational services as part of a Global Health elective. The hospital serves about 1 million people from communities that have prevalence rates of HIV infection and tuberculosis that are among the highest in the world. This patient, who was infected with both HIV and tuberculosis, was referred to our hospital because of evidence of progressive tuberculosis, despite appropriate treatment.

May we review the radiology studies?

Dr. Subba Digumarthy: There are multiple cavities and air-space opacities in the left lung involving the upper lobe (Fig. 1), the lingula, and the lower lobe. There is loss of volume in the left lung, with a slight shift of the mediastinum to the left. The left heart border and the mediastinum are partially obscured by the opacities in the left lung. There is also focal consolidation in the right upper lobe adjacent to the minor fissure. There is pleural thickening or a small pleural effusion on the left side.

Multifocal asymmetric involvement of the lungs



Figure 1. Radiograph of the Chest.

There are multiple cavities and air-space opacities in the left lung involving the upper lobe, the lingula, and the lower lobe. There is loss of volume in the left lung, with a slight shift of the mediastinum to the left. The left heart border and the mediastinum are partially obscured by opacities in the left lung. There is pleural thickening or a small pleural effusion on the left side. There is focal consolidation in the right upper lobe adjacent to the minor fissure.

favors an infectious disease. The presence of cavities and loss of volume suggests a subacute to chronic process, such as a mycobacterial or fungal infection. In an immunocompromised patient, such as this one, opportunistic infections such as chronic *P. jirovecii* pneumonia can have an appearance similar to that seen in this patient. It is difficult to rule out acute infection superimposed on the background of chronic lung disease, since there are no earlier radiographs for comparison.

Dr. Wilson: I am aware of the diagnosis in this case, which illustrates many of the diagnostic and therapeutic challenges encountered in resource-limited settings in southern Africa. This young woman with HIV infection was in a DOTS program that should have ensured adherence to first-line therapy for tuberculosis, but she had sputum smears that were persistently positive for acid-fast bacilli; there is a paucity of other laboratory information, such as culture results and drug-sensitivity testing. Common causes of sputum smears that are persistently positive for acid-fast bacilli in HIV-infected adults are shown in Table 2, and causes of nonresponse to antituberculosis therapy are shown in Table 3.

ABNORMAL LABORATORY-TEST RESULTS

A review of this patient's blood-test results shows several abnormalities. Her normocytic anemia is most likely anemia of chronic disease, due to both untreated HIV infection and tuberculosis, and would be expected to improve with effective treatment of the underlying cause. Routine iron supplementation for anemic patients with tuberculosis is not recommended.¹ Mild-to-moderate thrombocytopenia is frequently observed in patients with advanced HIV infection; it is usually attributed to marrow suppression by HIV but may be due to autoimmune thrombocytopenia (usually seen early in the course of the disease) or to platelet consumption in a patient with coagulopathy. Thrombocytopenia can also be caused by rifampin.

Hyponatremia in a euvolemic patient suggests inappropriate secretion of antidiuretic hormone, in this case probably caused by lung disease. The hypoalbuminemia may be due to malnutrition, and the hypergammaglobulinemia can be attributed to chronic infection and to HIV-mediated polyclonal B-cell activation.² Mildly elevated trans-

aminase levels are commonly seen in patients taking antituberculosis therapy. Causes of moderately elevated lactate dehydrogenase levels include tuberculosis, lymphoma, hemolysis, and *P. jirovecii* pneumonia. Abnormal renal function could be caused by HIV-related nephropathy,³ acute tubular necrosis due to sepsis, or rifampin, which has been associated with renal tubular, interstitial, and glomerular disease. Initial evaluation should include urinary dipstick testing, microscopy for casts, and renal ultrasound scan, and if renal function continued to deteriorate, a kidney biopsy may be needed.

CAUSES OF PERSISTENTLY POSITIVE SPUTUM SMEARS

This patient's sputum smears were positive for acid-fast bacilli, and causes other than persistent tuberculosis need to be considered (Table 2). Colonization and invasion of bronchiectatic lung tissue by nontuberculous mycobacteria is possible; diagnosis requires identification of the species in a positive culture.⁴ *Nocardia* species are partially acid-fast and cause cavitating lung disease; however, the absence of skin involvement, the lack of focal neurologic signs, and the absence of a clinical response to high-dose trimethoprim-sulfamethoxazole make this diagnosis unlikely.

CAUSES OF WORSENING RESPIRATORY DISEASE

HIV infection evolves over a period of months to years, with gradual weight loss, fatigue, chronic diarrhea, oral pain, and skin rash. Superimposed localized or systemic infections may cause clinical deterioration over a period of days to several weeks, as seen in this patient. Her 6-week respiratory deterioration suggests a new pulmonary infection. *P. jirovecii* is an important cause of subacute pneumonia in southern Africa, and an induced sputum specimen for direct fluorescent antibody testing or polymerase-chain-reaction assay for *P. jirovecii* would be helpful to evaluate this possibility. Other possible pathogens include *Legionella pneumophila*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*; this patient was taking rifampin, which has activity against legionella and chlamydia but does not have an effect on mycoplasma. A tetracycline or macrolide such as azithromycin could have been added to cover this atypical pathogen, although there are potential interactions between the macrolides and rifampin.⁵ Fluoroqui-

Table 2. Causes of Sputum Smears That Are Persistently Positive for Acid-Fast Bacilli in HIV-Infected Adults.

<i>Mycobacterium tuberculosis</i>
Erratic adherence to antituberculosis therapy
Poor drug absorption
Limited drug penetration into pulmonary cavities and fibrous tissue
Nonviable organisms shed into respiratory secretions
Drug-resistant strains
Bacteria other than <i>M. tuberculosis</i>
Nontuberculous mycobacteria (colonization or invasive infection)
<i>Nocardia</i> *
<i>Rhodococcus</i> *

* This species is partially acid-fast.

Table 3. Causes of Nonresponse to Antituberculosis Therapy in HIV-Infected Adults.

Incorrect original tuberculosis diagnosis
Nonadherence to antituberculosis therapy
Resistance to mycobacterial drugs
Post-tuberculosis lung disease (bronchiectasis)
Superimposed infection or tumor
Progression of HIV disease
Immune reconstitution syndrome (after starting antiretroviral therapy)
Deterioration due to other conditions (e.g., heart failure, renal disease, or diabetes)

nonolones should not be used for the treatment of bacterial infections of the respiratory tract in settings with a high incidence of tuberculosis, since activity against *Mycobacterium tuberculosis* can mask culture-positive disease and promote the development of resistance. On admission, the patient was appropriately treated for a bacterial infection of the lower respiratory tract and *P. jirovecii* pneumonia.

This patient was isolated only after spending a week in an open ward. It is essential to isolate all patients with positive sputum smears at the time of admission,⁶ but this may be difficult to achieve in a resource-limited setting. Negative-pressure rooms are not available, and physically separating an acutely ill patient from the rest of the ward in a side cubicle (if one is available) may restrict access to nursing care without greatly reducing the risk of infection. Cough hygiene and the use of surgical masks by patients with smear-

positive infection are recommended but can be difficult to implement for patients who are delirious or who require supplemental oxygen therapy (oxygen can be delivered by means of nasal prongs under a surgical mask unless the patient is severely hypoxemic). Reporting of the results of the inpatient sputum smear may have been delayed by difficulties with specimen collection, an overburdened laboratory with a long turnaround time, and a paper-based results system with the potential for erratic delivery and misfiling. Institutional infection-control policies that address practical and logistical issues such as these are crucial in resource-scarce settings.

Patients with HIV infection often have more than one cause of fever, and the positive smears for acid-fast bacilli do not rule out other diagnoses. Results of bacterial cultures are not available; however, it is likely that this patient met the criteria for the diagnosis of fever of unknown origin.⁷ The elevated C-reactive protein level suggests an infection but may also occur in deep-vein thrombosis or lymphoma. In the absence of extrapulmonary symptoms, it is debatable how much further to pursue the workup for fever of unknown origin. An abdominal ultrasound examination to look for intraabdominal lymph nodes, hepatic or splenic lesions, ascites, or pericardial effusion may be helpful, as would blood culture in a liquid medium that is suitable for bacterial, mycobacterial, and fungal growth. Bone marrow biopsy for histologic examination and culture could be considered if the hematologic characteristics continue to deteriorate. The use of ceftriaxone and gentamicin would provide more extended gram-negative coverage, suitable for empiric treatment of nontyphoidal salmonellosis.⁸ However, tuberculosis is the predominant cause of fever of unknown origin in HIV-infected adults in southern Africa, and is likely in this case.

The patient's confusion that developed shortly before death was probably caused by multiple factors, including untreated infection, hyponatremia, azotemia, and HIV encephalopathy. Both HIV and tuberculosis cause a thrombophilic state. Pulmonary embolism arising from deep-vein thrombosis in the left leg could have been the immediate cause of death, and this complication emphasizes the importance of heparin prophylaxis in nonambulatory medical inpatients.

SUMMARY

In this patient with extensive lung disease, positive sputum smears, and clinical deterioration, progressive tuberculosis was the most likely diagnosis. Her lack of a response to first-line anti-tuberculosis therapy could have been due to any of several factors (Table 3), but the predominant concern should be about either multidrug-resistant or extensively drug-resistant tuberculosis. Mycobacterial culture and testing for drug sensitivity with the use of conventional methods can take months. Responding to the possibility of multidrug-resistant tuberculosis in this seriously ill patient is difficult and controversial. How should infection-control issues be managed? Should her antituberculosis treatment have been empirically broadened to cover multidrug-resistant tuberculosis, followed by initiation of antiretroviral therapy for HIV? Did palliative care techniques adequately address her symptoms? For clinicians who work in southern Africa, these issues will continue to pose challenges for the foreseeable future.

CLINICAL DIAGNOSIS

Pulmonary infection with drug-resistant *M. tuberculosis*, either multidrug resistant or extensively drug resistant, in a patient with HIV infection.

PATHOLOGICAL DISCUSSION

Dr. Wilson: Three months after the patient's death, a sputum culture that had been obtained during her hospitalization was reported to show *M. tuberculosis* that was resistant to isoniazid, rifampin, ethambutol, streptomycin, kanamycin, and ciprofloxacin.

DISCUSSION OF MANAGEMENT

Dr. Rocío M. Hurtado: This patient's case illustrates the challenges associated with the diagnosis and management of HIV infection and extensively drug-resistant tuberculosis (defined as tuberculosis that is resistant to at least isoniazid and rifampin plus one second-line injectable drug [amikacin, capreomycin, or kanamycin] and a fluoroquinolone) that are faced by clinicians in resource-limited settings where the burden of these intersecting epidemics is high and the diagnostic and therapeutic options

are often limited. This case is of particular relevance to clinicians in South Africa, where extensively drug-resistant tuberculosis has been confirmed in all nine provinces. Genotyping studies have shown that many patients with extensively drug-resistant tuberculosis in this patient's province of KwaZulu-Natal have been infected with the highly transmissible F15/LAM4/KZN strain, which developed resistance to as many as seven drugs over the span of a decade since its original fingerprinting, in 1994.⁹

CAUSES OF INFECTION WITH EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS

This patient could have primary infection with a strain of extensively drug-resistant tuberculosis,¹⁰ a mixed infection, or reinfection with a resistant strain while on first-line treatment.^{11,12} Her history of a previous prolonged hospitalization raises the possibility of nosocomial transmission, a well-described mode of acquisition of drug-resistant tuberculosis in HIV-positive patients.¹⁰ Finally, she might have been exposed during that hospitalization to fluoroquinolones, injectable antibiotics, or both for treatment of bacterial infections such as invasive pneumococcal disease or nontyphoidal salmonellosis, which are not uncommon in HIV-positive patients. Such exposures may contribute to the evolution of resistance to these agents in a patient with undiagnosed or inadequately treated tuberculosis.

There are three aspects of this patient's treatment that should be explored further. These include timely diagnosis of drug-resistant tuberculosis; chemotherapeutic management of extensively drug-resistant tuberculosis, including adjunctive interventions; and management of HIV/AIDS in this coinfecting patient.

DIAGNOSIS OF DRUG-RESISTANT TUBERCULOSIS

First, the delay in diagnosis of drug-resistant tuberculosis was an obstacle to proper medical care for this patient. Unfortunately, it is the most common roadblock to accessing appropriate second-line antimycobacterial therapy for patients coinfecting with HIV and drug-resistant tuberculosis in resource-limited settings. As is standard in these settings, this patient's diagnosis of tuberculosis was based on smear microscopy and clinical criteria, without sputum cultures and drug-susceptibility testing. Although cultures and drug-suscep-

tibility testing are not possible for all patients, this patient's lack of clinical response (persistent cough) and the presence of smear-positive disease after 2 months or more of therapy should have prompted such cultures and drug-susceptibility testing. In the context of a DOTS program, persistent smear-positive disease after more than 2 months of therapy increases, by a factor of 12, the likelihood of multidrug resistance¹³ and is a well-established indication for culture and testing for drug susceptibility according to South African guidelines.¹⁴ Even with a confirmed positive smear after 6 months of therapy, she did not undergo culture and testing for drug susceptibility until her final hospitalization. In addition, after a culture was sent, the diagnosis of extensively drug-resistant tuberculosis was not reported until 3 months later. Thus, multiple opportunities for earlier diagnosis of drug-resistant tuberculosis were missed.

The use of rapid diagnostic tests for tuberculosis at the time of the patient's original diagnosis would have had benefits for both her and the community, because of decreased risk of transmission. Rapid diagnostic methods under evaluation in resource-limited settings include the microscopic-observation drug-susceptibility (MODS) assay and line-probe assays. These have a high degree of concordance with drug-susceptibility testing in the detection of resistance to isoniazid and rifampin, especially in smear-positive disease, and a reduced time to diagnosis as compared with conventional methods (7 days for MODS and 1 to 2 days for the line-probe assay, as compared with 22 to 68 days for conventional liquid and solid mediums).^{15,16} Current versions of rapid diagnostic tests do not detect resistance to fluoroquinolones and injectable drugs. Therefore, the confirmation of extensively drug-resistant tuberculosis still requires access to drug-susceptibility testing for second-line tuberculosis drugs. A two-step strategy, which could have been used for this patient, would involve the use of rapid diagnostic tests to screen for multidrug-resistant tuberculosis, followed by expedited referral of the isolate, once drug resistance was detected, for expanded second-line drug susceptibility testing.

MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS IN A RESOURCE-LIMITED SETTING

In addition to evaluating and treating the patient for other concomitant diagnoses, should we con-

sider empiric therapy for multidrug-resistant tuberculosis? In most resource-limited settings, documentation of multidrug resistance is required before the initiation of treatment for multidrug-resistant tuberculosis, since unregulated use of second-line antimycobacterial agents can lead to the development of extensively drug-resistant tuberculosis. The issue is even more complex for this patient, who actually had extensively drug-resistant tuberculosis, since most empirical regimens for the treatment of multidrug-resistant tuberculosis in resource-limited settings provide only partial coverage for extensively drug-resistant tuberculosis. Empirical therapy for extensively drug-resistant tuberculosis could have been considered, given the presence of extensively drug-resistant tuberculosis in her community, but such empirical treatment may not be feasible for most communities in South Africa. Unfortunately, until diagnostic tests improve and treatment capacity increases, many patients such as this one will die of tuberculosis.

Constructing a regimen for treating extensively drug-resistant tuberculosis in this patient would have been based on the strategies for multidrug-resistant tuberculosis,^{17,18} including an induction phase with the use of at least four (preferably five) active drugs (excluding amithiozone [formerly called thiacetazone], which is contraindicated in patients coinfecting with HIV), use of an injectable drug for a minimum of 6 months (preferably at least 6 months after conversion to a negative culture, and in many cases, well beyond 6 months), continuation of therapy for a minimum of 18 months after culture conversion, and supervised therapy. Some programs have included newer quinolones such as moxifloxacin.^{19,20} Although these treatment strategies are derived from retrospective experience and not from randomized, controlled trials, a regimen of capreomycin, moxifloxacin, cycloserine, and para-aminosalicylic acid as the core agents would have been an appropriate starting point for this patient. Other agents such as clofazimine and amoxicillin-clavulanate, with some *in vitro* activity yet with uncertain efficacy, would probably have been included. Linezolid, not available in resource-limited settings because of its cost, has been used in small numbers of patients with multidrug-resistant or extensively drug-resistant tuberculosis.²¹ There are reports of peripheral neuropathy and adverse ef-

fects on bone marrow, and the drug has not been evaluated in patients coinfecting with HIV. In this patient, with HIV and a compromised bone marrow, linezolid would not have been a favorable choice. High-dose isoniazid has been shown to increase negative sputum cultures in patients with multidrug-resistant tuberculosis,²² but it has not been formally evaluated in patients with extensively drug-resistant tuberculosis or in patients who are coinfecting with HIV.²³

If an adequate antimycobacterial regimen is used concomitantly, corticosteroids can be beneficial in patients with tuberculosis who have respiratory distress²⁴ and might have been considered in this patient. I am not aware of any controlled trials that have involved patients with drug-resistant tuberculosis, and the weaker regimens used in the treatment of patients with extensively drug-resistant tuberculosis who are in an immunosuppressed state could result in adverse outcomes in patients coinfecting with HIV. If this patient's condition had improved after several months of treatment, and if she had relatively localized disease and adequate pulmonary reserve, resection of affected lung tissue could have been considered. Resection has been associated with improved outcomes in several cohorts with multidrug-resistant and extensively drug-resistant tuberculosis (including those in resource-limited settings).²⁵⁻²⁷ In view of the extensive lung disease present on admission, it seems unlikely that resection would have been an option for this patient.

ANTIRETROVIRAL THERAPY

A third important component of this patient's care is the use of antiretroviral therapy for HIV. Antiretroviral therapy has been associated with improved survival in patients coinfecting with multidrug-resistant tuberculosis and HIV.²⁸ Initiation of antiretroviral therapy was indicated, given this patient's advanced immunosuppression, if she had no adverse effects associated with the antimycobacterial regimen. To my knowledge, no randomized, controlled trials of timing of antiretroviral therapy in patients with multidrug-resistant tuberculosis have been undertaken. However, in view of the significantly higher rates of death among patients with multidrug-resistant tuberculosis who are HIV-positive as compared with those who are HIV-negative, I would strongly consider early initiation of antiretroviral therapy in such coinfecting

patients, regardless of CD4+ T-cell count. The choice of regimen is important, since antiretroviral drugs and antimycobacterial drugs have many overlapping adverse effects, including nephrotoxicity (injectable drugs and tenofovir), peripheral neuropathy (injectable drugs and nucleosides), and neuropsychiatric effects (efavirenz and cycloserine). Thus, a major component of the patient's treatment plan would have included careful monitoring for drug-related adverse events while she was taking medications for concomitant tuberculosis and HIV infection.

Monitoring for a treatment response of both tuberculosis and HIV infection, as well as for the development of new intercurrent illnesses or immune-reconstitution inflammatory syndromes, would be essential. Supervising the treatment of both tuberculosis and HIV infection, ensuring uninterrupted supplies of drugs, and providing nutritional and psychosocial support would also have been key to improving the clinical outcome for this patient. Community-based programs, which have been successfully implemented in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis even in resource-limited set-

tings, would have been helpful for this patient, once she was clinically stabilized.^{20,29}

In summary, a delay in diagnosis that caused a delay in therapy for extensively drug-resistant tuberculosis, coupled with advanced immunosuppression and several poor prognostic factors (respiratory insufficiency, coinfection, fibrocavitary disease), led to this young patient's death. The challenges of caring for patients such as this one in resource-limited settings remain formidable.

ANATOMICAL DIAGNOSIS

Extensively drug-resistant *Mycobacterium tuberculosis* infection in a patient with HIV/AIDS.

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