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When infection and malignancy intersect in Rwanda: A diagnostic challenge in the tropics—Case Report

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ABSTRACT

CASE PRESENTATION: We describe a 38-year-old Rwandan male patient who presented to the hospital with a two-week history of left axillary lymphadenopathy, fever, weight loss, and one-year history of dysphagia. Lymph node fine needle aspirate was consistent with tuberculous lymphadenitis. Peripheral blood smear suggested a concomitant diagnosis of Acute Myeloid Leukemia (AML), which was confirmed by bone marrow biopsy. Although several cases of concurrent pulmonary tuberculosis and AML exist, fewer cases of concomitant tuberculous lymphadenitis and AML have been reported.

CONCLUSION: This case highlights the need to keep a high suspicion for malignancy in a patient with lymphadenopathy, leukocytosis, and constitutional symptoms; at the same time, a coexisting opportunistic infection such as tuberculosis should not be overlooked in the tropical clinical setting.

Keywords (MeSH): Tuberculous Lymphadenitis; Acute Myeloid Leukemia; Lymphadenopathy; Immune Reconstitution Inflammatory Syndrome; Fine-Needle Biopsy; Immunohistochemistry; Leukocytosis; Pulmonary Embolism; Splenomegaly

CASE PRESENTATION

A 38-year-old Rwandan male presented to University Teaching Hospital of Kigali with a two-week history of a new-onset, painful left axillary mass. He reported a six out of ten grade in severity of left-sided chest pain and left axillary pain. Additionally, over the past year, he had experienced symptoms of pain and difficulty when swallowing solids, which eventually progressed to difficulty swallowing solids and liquids. These symptoms were associated with persistent fevers and unintentional weight loss for the past month. For three days prior to admission, he endorsed intermittent episodes of emesis and nausea. He denied cough, sick contacts, or exposure to contacts with tuberculosis.

He was a farmer from Karongi District with a remote history of malaria. Ten days prior to his presentation, he had been evaluated at an outside hospital for the aforementioned symptoms. At the district hospital, he was noted to have an initial leukocytosis of 30,000 cells/μL. A chest x-ray was reportedly unremarkable. Due to unclear etiology, he was treated for presumed sepsis with antibiotics including ceftriaxone for ten days. He also received hydrocortisone for three days. Subsequently, he was transferred to our hospital for hematologic evaluation due to concerns regarding persistent leukocytosis and dysphagia.

On physical examination, he was asthenic and cachectic, in no acute distress. He had a temperature of 40°C, heart rate of 106 bpm, blood pressure of 91/50 mmHg, respiratory rate of 20 cpm, and oxygen saturation of 92% on room air. He had a palpable, fixed, 4-cm diameter left anterior axillary mass, which was tender to palpation. He had dry oral mucosa with white coating on his tongue. The cardiopulmonary, abdominal, and neurologic examinations

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were unremarkable. Laboratory data revealed leukocytosis with a white blood cell count of 48,800 cells/µL with 68% eosinophils, 23% monocytes, 6% lymphocytes, and 3% neutrophils. Hemoglobin was 9.1 g/dL with mean corpuscular volume of 101 fL, and his platelet count was 88,000 cells/µL. He had a serum sodium of 133 mmol/L, potassium of 4.3 mmol/L, chloride of 95 mmol/L, urea of 5.1 mmol/L, creatinine of 73 µmol/L, and glucose of 4.45 mmol/L. He had an aspartate transaminase of 44 U/L, alanine transaminase of 106.4 U/L, gamma-glutamyl transferase of 85 U/L, and lactate dehydrogenase of 524 U/L. C-reactive protein was elevated at 169.65 mg/dl. Rapid human immunodeficiency virus test and malaria thick smear were negative.

Blood cultures revealed no growth. He was unable to produce sputum for Gene Xpert testing for evaluation of pulmonary tuberculosis (TB).

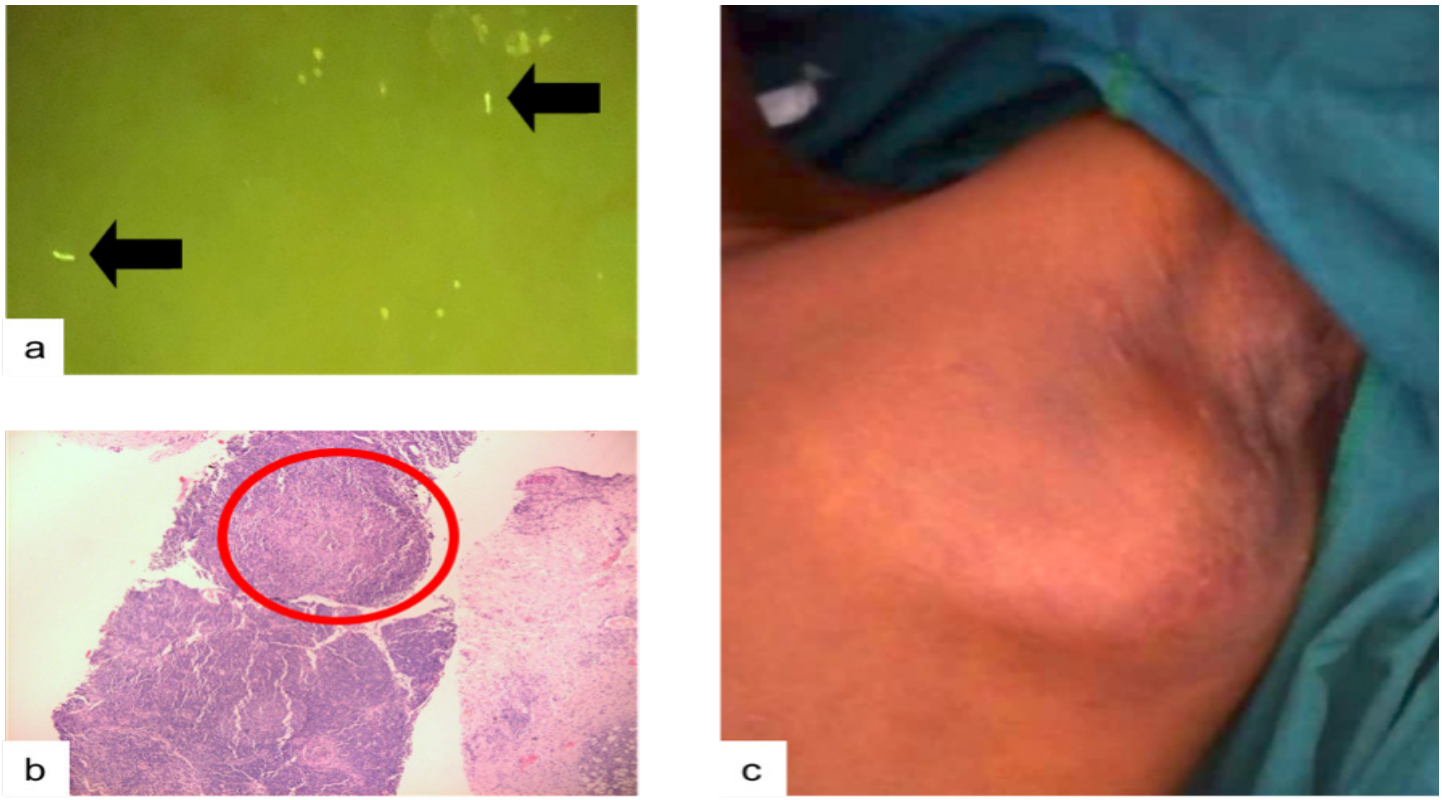

Figure 1. a) *Auramine O stain of the axillary lymph node fine needle aspirate cytology confirmed presence of 1+ acid-fast bacilli concentration (black arrows) via fluorescence microscopy, supporting the diagnosis of tuberculous lymphadenitis.* ***b)*** *A core lymph node biopsy of the axillary lymph node revealed granulomas with areas of central necrosis (outlined in red), consistent with tuberculous lymphadenitis.* ***c)*** *The patient demonstrated features of Tuberculosis-Immune Reconstitution Inflammatory Syndrome, as the lymph node enlarged rapidly and significantly after treatment of tuberculous lymphadenitis. On day 26 of his total hospitalizations, after receiving approximately four weeks of therapy for tuberculous lymphadenitis, the left axillary lymph node grew to three times the initial size on presentation, with a maximum diameter of 12cm.*

On day one of hospitalization, cefotaxime was initiated and later broadened to ceftazidime for empiric coverage, in the setting of neutropenic fever. Fluconazole was initiated for oral thrush. He received intravenous fluids as well as morphine for pain control. A fine needle aspiration (FNA) was performed on the left axillary mass.

On day two of hospitalization, the left axillary mass FNA cytology revealed lymphocytes, loose granulomatous formations, and multinucleated giant cells in a proteinaceous-necrotic background, highly suspicious for tuberculous lymphadenitis.

On day three of hospitalization, an Auramine O stain (Figure 1a) of the axillary lymph node FNA cytology was positive, detecting 1+ acid-fast bacilli concentration due to presumptive Mycobacterium tuberculosis, which supported the diagnosis of tuberculous lymphadenitis. He was started on rifampicin, isoniazid, pyrazinamide, and ethambutol therapy for treatment of tuberculous lymphadenitis, along with pyridoxine.

On day four of hospitalization, the peripheral blood smear (Figure 2a) demonstrated 95% immature myeloid and monocytic blast cells with a high nucleus to cytoplasmic ratio, consistent with a diagnosis of Acute Myelomonocytic Leukemia, which is a subtype of Acute Myeloid Leukemia. Thus, he was newly diagnosed with concurrent tuberculous lymphadenitis and Acute Myelomonocytic Leukemia.

On day eight of hospitalization, a spiral computed tomography (CT) scan of the chest revealed multiple enlarged left axillary and subpectoral lymph nodes (Figure 3a), some necrotic and measuring up to 3.6 cm; bilateral segmental pulmonary emboli; and a 1.6 cm right upper lobe pulmonary nodule (Figure 3b). A CT scan of the abdomen and pelvis demonstrated mild splenomegaly, with a span of 13.5 cm (Figure 3c).

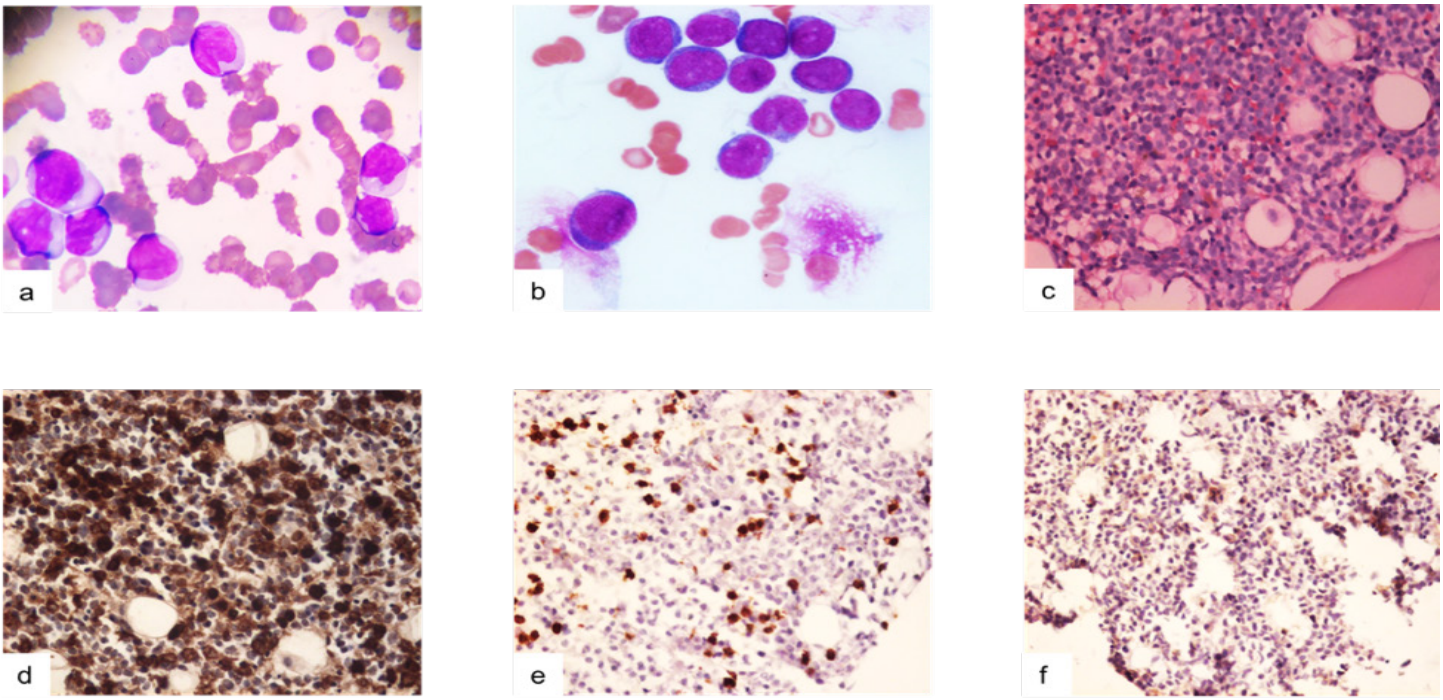

Figure 2. a) *Peripheral blood smear demonstrated 95% immature blast cells with a high nucleus to cytoplasmic ratio, consistent with Acute Myeloid Leukemia.* ***b)*** *The bone marrow aspirate was hypercellular and spicular with a diffuse infiltrate of myeloid and monocytic blasts, exhibiting a high nucleus to cytoplasm ratio and prominent nucleoli.* ***c)*** *The bone marrow core tissue was also hypercellular, consisting of less than five percent of a fat component, with a diffuse infiltrate of myeloid and monocytic blasts and markedly reduced myeloid maturing elements.* ***d)*** *Anti-lysozyme antibody staining was positive in all blasts.* ***e)*** *Immunohistochemical staining was negative for the immunohistochemical marker of CD3.* ***f)*** *Immunohistochemical staining was negative for the immunohistochemical marker of CD19.*

Full-dose enoxaparin was initiated for the treatment of pulmonary emboli. He received omeprazole after he underwent an upper endoscopy revealing grade II ulcerative esophagitis and bilious gastroesophageal reflux.

For the remainder of the ten-day hospital course at University Teaching Hospital of Kigali, he continued to display dysphagia and fever. Intermittent high-grade fevers persisted, with Tmax of 39.9°C. On day ten of hospitalization, his leukocytosis fell to 11,700 cells/µL with 68% monocytes, 16% basophils, 12% lyphocytes, 3% neutrophils, and 1% eosinophils. Hemoglobin fell to 6.67 g/dL and platelets fell to 57,200 cells/µL. He received a transfusion of two units of packed red blood cells.

The patient was then transferred to Butaro Hospital in the northern province of Rwanda, because of its ability to provide free cancer care. During the hospital course, he remained afebrile. He continued treatment for tuberculous lymphadenitis, at which time the axillary lymph node was noted to enlarge rapidly. His hospital course was complicated by anemia and thrombocytopenia, which interrupted the anticoagulation therapy he was receiving for treatment of pulmonary embolism. He received three additional units of packed red blood cells and four units of platelets.

On day five at Butaro Hospital, a bone marrow biopsy was performed. The bone marrow biopsy confirmed the diagnosis of Acute Myelomonocytic Leukemia. The bone marrow aspirate was hypercellular with bone spicules and a diffuse infiltrate of myeloid and monocytic blasts, exhibiting a high nucleus to cytoplasm ratio and prominent nucleoli (Figure 2b). The bone marrow core tissue was also hypercellular, consisting of less than five percent of a fat component, with a diffuse infiltrate of myeloid and monocytic blasts and markedly reduced myeloid maturing elements (Figure 2c). Anti-lysozyme antibody staining was positive in all blasts (Figure 2d). Immunohistochemical staining was negative for the immunohistochemical markers of CD3 (Figure 2e), CD19 (Figure 2f), and CD20. CD34 and TdT that are normally part of the panel of immunohistochemistry stains were not available at Butro Hospital, but this did not impact the final diagnosis.

After two weeks of therapy for treatment of tuberculous lymphadenitis, the left axillary lymph node continued to rapidly enlarge. After four weeks of therapy for tuberculous lymphadenitis, the aillary lymph node grew to three times the initial size on presenttion, with a maximum diameter of 12cm (Figure 1c).

A core needle biopsy of the lymph node at Butaro Hospital demonstrated lymphoid tissue with extensive necrosis and poorly formed granulomas, some with areas of central necrosis (Figure 1b), consistent with tuberculous lymphadenitis. Clinically the patient demonstrated features of Tuberculosis-Immune Reconstitution Inflammatory Syndrome (TB-IRIS), as the lymph node enlarged rapidly and significantly after treatment of tuberculous lymphadenitis.

Currently, treatment for Acute Myeloid Leukemia is unavailable at Butaro Hospital but available at a different hospital in Kigali. The cost of such chemotherapy is generally quite high for patients in

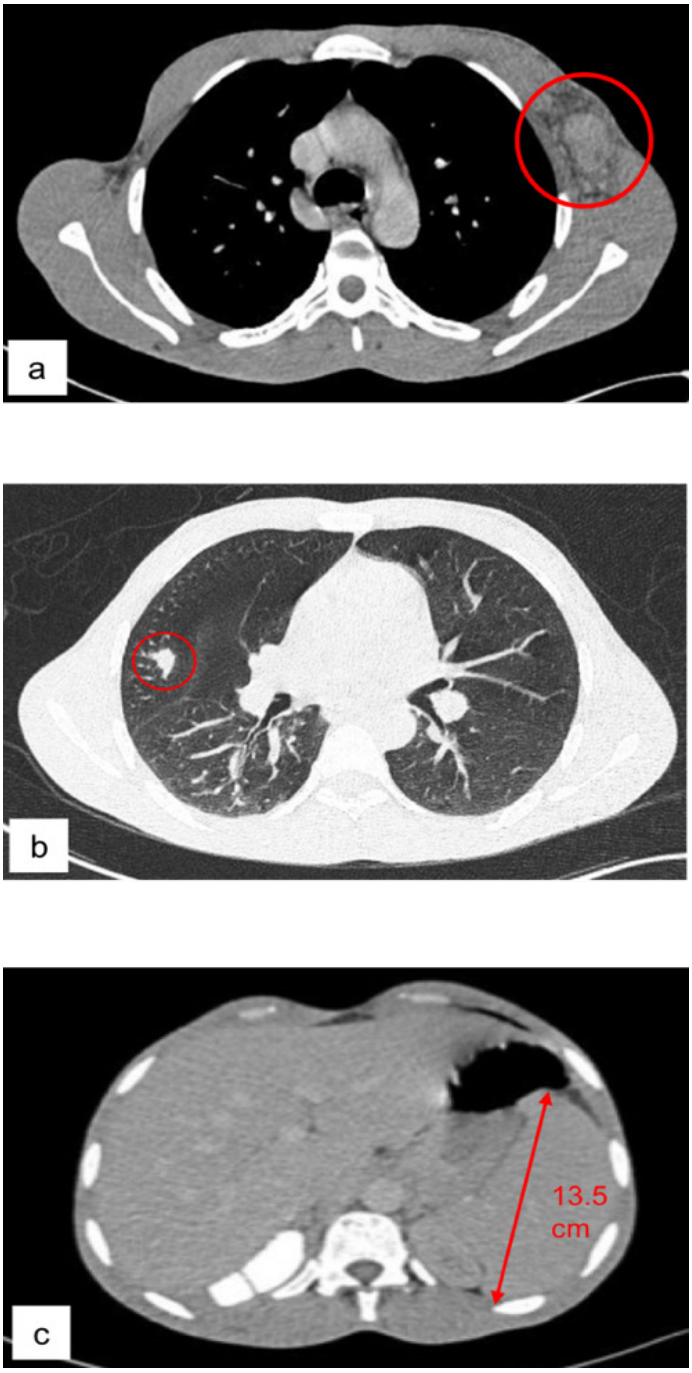

Figure 3. a) *Computed tomography scan of the chest demonstrated multiple enlarged left axillary and subpectoral lymph nodes (outlined in red), some of which were necrotic measuring up to 3.6 cm.* ***b)*** *Computed tomography scan of the chest demonstrated a 1.6 cm right upper lobe pulmonary nodule (outlined in red).* ***c)*** *Computed tomography scan of the abdomen demonstrated mild splenomegaly, with a span of 13.5 cm.*

patients in Rwanda which may prompt to seek chemotherapy-for Acute Myeloid Leukemia outside of the country. In this case, the patient declined chemotherapy. He was discharged from the hospital to home with palliative care.

DISCUSSION

Several case series exist demonstrating pulmonary tuberculosis (TB) and concomitant Acute Myeloid Leukemia [1,2]. However, fewer case reports exist regarding patients with tuberculous lymphadenitis and concurrent Acute Myeloid Leukemia [3]. In 2017, the estimated incidence of TB was 57 cases per 100,000 people in Rwanda [4]. The estimated incidence of leukemia in Rwanda was 370 new cases in 2018 [5].

Hematologic malignancies have been reported to increase the relative risk for TB infection by 2-40 fold that of the population [6]. The immune system responds to TB infection by initially releasing macrophages, which phagocytose aerosolized Mycobacterium tuberculosis, and subsequently produce cytokines. These cytokines are cellular signals which draw in inflammatory cells—including neutrophils, macrophages, natural killer cells, and T cells—resulting in an inflammatory cascade and remodeling of tissue, which leads to granuloma formation [7]. Patients with hematologic malignancies have an underlying alteration in immunity leading to immunodeficiency, which may result in progression from latent to active TB and development of other types of infections [6].

Tuberculous lymphadenitis, a form of extrapulmonary TB, typically occurs due to reactivation of TB at a hematogenously seeded site during primary TB infection [8]. Young adults generally present with chronic lymphadenopathy which is non-tender [9]. On physical exam, a firm, discrete mass or collection of nodes may be present [8]. A diagnosis is made via acid-fast bacilli smear via FNA or excisional lymph node biopsy [9], [10]. Culture of mycobacteria is the gold standard for tuberculosis diagnosis. Treatment for tuberculous lymphadenitis is rifampicin, isoniazid, ethambutol, and pyrazinamide for two months, followed by rifampicin and isoniazid for four months. TB-Immune Reconstitution Inflammatory Syndrome (IRIS) occurs as an exaggerated response to Mycobacterium tuberculosis antigen, and may present as a paradoxical worsening of prior tuberculous lesions or development of new tubercular lesions after TB therapy initiation [11].

During TB therapy administration or even after its completion, TB-IRIS may occur in HIV-uninfected or HIV-infected individuals. TB-IRIS may occur independently in HIV-infected individuals after antiretroviral therapy initiation [11]. Symptoms of TB-IRIS may include fever, enlarging lymphadenopathy, or worsening respiratory status. There is a noted increased risk of IRIS in those with extrapulmonary or disseminated TB, which is thought to be due to the elevated quantity of bacilli present [11]. The median timeframe for such a response to begin is generally between three to eight weeks in HIV-negative individuals, but can even occur after treatment [11]. Corticosteroids may reduce the inflammation associated with TB-IRIS, and may be considered in patients with significant symptoms, especially in severe cases, such as in patients with neurologic involvement [12].

Acute Myeloid Leukemia (AML), a type of leukemia which occurs due to abnormal proliferation of a clonal population of myeloid stem cells, is the most common acute leukemia in adults [13,14]. Patients may present with anemia, dyspnea, excessive bleeding or bruising. Physical exam may reveal pallor, ecchymosis, or splenomegaly. Lymphadenopathy is reportedly uncommon [13]. AML is diagnosed by bone marrow aspirate and biopsy. Blast forms, which must be identified as cells of myeloid lineage, generally must be

greater or equal to 20% of bone marrow biopsy cellularity or of the peripheral white blood cell count, except in certain circumstances [13,14]. Acute Myelomonocytic Leukemia, a subtype of Acute Myeloid Leukemia classified as M4 under the French-American-British classification system, is an acute leukemia characterized by differentiation of both myeloid and monocytic cell lines [15].

The induction chemotherapy regimen for treatment of AML may include cytarabine plus an anthracycline [13]. Consolidation therapy may consist of cytarabine or hematopoietic stem cell transplant [13]. AML is generally rapidly fatal without chemotherapy [13,14].

CONCLUSION

Arriving at a concomitant diagnosis of malignancy and tuberculous lymphadenitis in a tropical setting can be challenging. Clinical suspicion for malignancy should be high in a patient with marked leukocytosis, constitutional symptoms, and persistent high-grade fevers. However, in this case, the suspicion for tuberculous lymphadenitis also remained high due to the presence of necrotic lymphadenopathy in the context of the patient's symptoms and location in a tuberculosis-endemic region. When initial evidence supported the diagnosis of tuberculous lymphadenitis for this patient, further workup for an alternative, concomitant diagnosis based on his clinical presentation continued.

It is important to keep in mind that premature closure may lead to conclusions that fit preexisting expectations, while confirmation bias could allow for potential coexisting diagnoses to be overlooked. An important lesson to highlight from this case is to not overlook concurrent opportunistic infections, such as tuberculosis—particularly in endemic regions in Africa—in the tropical clinical setting in Rwanda.

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