29

A 35-Year-Old Woman from Malawi With Fever and Severe Anaemia

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Clinical Presentation

History

A 35-year-old Malawian woman presents to a local hospital because of fever and weakness.

The fever started 3 days earlier, but the weakness has progressed over the past several months. There is no cough and no night sweats, but she reports some weight loss. There is no diarrhoea, no dysuria and no history of abnormal bleeds.

Two months earlier she presented to a local health centre because of her weakness. She was found to be clinically pale and was prescribed iron tablets, which she took. Nevertheless, the weakness progressed. Otherwise, the patient does not report any abnormalities.

She is divorced, with three children (17, 15 and 12 years old), who are all well. She works as a small-scale farmer and sells vegetables on the local market. The family can afford three meals a day and occasionally meat or fish.

Clinical Findings

A 35-year-old woman, wasted, body mass index 17 kg/m^2. Blood pressure 90/60 mmHg (difficult to measure because of the low upper arm circumference), pulse 110 bpm, temperature 37.8°C (100°F), respiratory rate 25 breath cycles per minute, oxygen saturation 97% on ambient air, Glasgow Coma Scale 15/15.

Her conjunctivae are very pale, but there is no jaundice. The examination of her mouth is normal, there is no oral thrush, no Kaposi's sarcoma lesions and no oral hairy leukoplakia. The chest is clear. The abdomen is soft, with slight diffuse tenderness, but no guarding. The spleen is palpable 3 cm below the left costal margin. The rectal examination is normal.

Investigations

The malaria rapid diagnostic test is negative. The HIV serology comes back positive.

TABLE 29.1 Laboratory Results on Admission

Parameter	Patient	Reference
WBC ($\times 10^9$/L)	3.0	4–10
Haemoglobin (mg/dL)	4.8	12–14
MCV (fL)	90	80–99
Platelets ($\times 10^9$/L)	112	150–400

The results of her full blood count are shown in Table 29.1.

Questions

1. What is the suspected diagnosis?
2. How would you manage this patient?

Discussion

A 35-year-old Malawian woman presents in a state of sepsis without any clear focal symptoms. She is wasted and severely anaemic and she newly tests HIV-positive.

This is a very common clinical scenario in a high-prevalence setting for HIV in sub-Saharan Africa.

Answer to Question 1

What is the Suspected Diagnosis?

The patient presents with a septic picture without a clear focus; she is newly diagnosed HIV-positive and her wasting and anaemia suggest advanced immunosuppression and/or possible concomitant tuberculosis (TB).

The most common cause of sepsis in HIV-positive adults in many parts of sub-Saharan Africa is infection with invasive non-typhoidal *Salmonellae* (iNTS). The slight abdominal tenderness and her splenomegaly would also fit with this diagnosis.

Enteric fevers (typhoid or paratyphoid) are clinically indistinguishable from infection with iNTS, they are

however far less common than iNTS in HIV-positive patients in sub-Saharan Africa. The reason for this is unclear.

Severe anaemia led to the non-specific feeling of progressive 'weakness' in this patient. It is most likely a consequence of infection of her bone marrow with HIV, *Salmonellae* and possibly also with *Mycobacterium tuberculosis.*

Other causes of severe anaemia, such as iron deficiency, helminth infections and malaria, are less common in an HIV-positive urban adult population but may have to be considered in other patients, in particular children, pregnant women or in the rural poor. Thalassaemia usually leads to a microcytic anaemia.

Severe anaemia is very common in sub-Saharan Africa. Patients commonly present to healthcare facilities late, at times only when they are developing heart failure secondary to severe anaemia.

Visceral leishmaniasis may also cause fever and pancytopenia as seen in this patient. It usually causes gross hepatosplenomegaly which our patient does not have. It also appears not to be endemic in Malawi, but should be considered in other parts of Africa, e.g. South Sudan, Northern Uganda and Northern Kenya, Ethiopia or Somalia.

Answer to Question 2

How Would You Manage This Patient?

Fluids and broad-spectrum antibiotics need to be started immediately. Before starting antibiotic treatment, blood cultures should be taken. Because bacteraemia may be low, it is important to inoculate a decent volume of blood (at least 20–40ml) for culture.

Severe anaemia in an HIV-infected person commonly is a sign of TB. Therefore the patient should be assessed for underlying tuberculosis. A chest radiograph and an abdominal ultrasound scan should be done. If the CD4-count is <100 cells/μl, a lateral flow urine lipoarabinomannan (LAM) may also help confirm TB.

Of note, anaemia may be the only finding in a patient with TB hiding in the bone marrow; and even if all routine investigations are unremarkable, TB should still be high on the list of possible diagnoses if the patient does not make a satisfactory recovery, i.e. remains febrile and/or anaemic or continues to lose weight.

The baseline CD4 count should be checked and the patient should be started on co-trimoxazole preventive treatment as prophylaxis against *Pneumocystis pneumonia,* toxoplasmosis and other opportunistic infections. Antiretroviral therapy (ART) should be started as soon as possible, once the acute infection is under control and concomitant opportunistic infections have been ruled out. The latter is important to prevent unmasking immune reconstitution inflammatory syndrome (IRIS). Her children and her current and past sexual partners should be encouraged to go for an HIV test.

The Case Continued…

Blood cultures were taken and the patient was started on IV ceftriaxone 2 g od, as well as on fluid resuscitation. Blood cultures grew *Salmonella enterica* var Typhimurium. Her antibiotic treatment was changed to oral ciprofloxacin 500 mg tds which was continued for 14 days. TB screening revealed prominent hilar lymph nodes and the patient was also commenced on antituberculous treatment and on antiretroviral therapy. She also received co-trimoxazole prophylaxis, vitamin B_6 to prevent peripheral neuropathy and therapeutic feeding.

She was discharged after 4 weeks in hospital. On review in ART clinic 3 months later she was feeling much better. She had gained weight and her haemoglobin levels were picking up. Her three children tested negative for HIV. Her ex-husband refused to go for HIV-testing.

SUMMARY BOX

Invasive Non-Typhoidal Salmonellae (iNTS) Infection

S. enterica is a leading cause of community-acquired bloodstream infection in Africa and Asia. Typhoidal *Salmonella* species cause typhoid and paratyphoid, i.e. enteric fever. They are restricted to human hosts. Non-typhoidal *Salmonellae* are host generalists, colonizing and infecting a broad range of vertebrate animals.

Non-typhoidal salmonellae (NTS) usually cause a self-limiting enterocolitis in immunocompetent individuals. In contrast, in sub-Saharan Africa (SSA) NTS commonly cause invasive disease resulting in sepsis and death. Important populations at risk for development of iNTS infection are infants and children living in areas of high transmission intensity for falciparum malaria and/or with severe malnutrition, and adults with advanced HIV-infection.

In Asia, enteric fever still prevails as a cause of invasive salmonellosis, which may be associated with the lower prevalence of iNTS risk factors in the population.

Both the reservoir and source of infection for iNTS remain unclear. S. Typhimurium and S. Enteritidis are the most common serovars, but it is unknown if the same strains cause invasive and diarrhoeal disease and if the modes of transmission are the same.

Infection with iNTS commonly presents as a non-specific febrile illness. Some patients report abdominal pain or a history of diarrhoea, but often the focus remains clinically unclear. Mild splenomegaly occurs in more than one-third of patients, hepatomegaly is less common. About 30% of patients with iNTS have a concomitant lower respiratory tract co-infection, with pathogens such as *M. tuberculosis* or *Streptococcus pneumoniae.* Severe anaemia is common and should prompt the clinician to look carefully for signs of TB co-infection.

Blood culture remains the diagnostic standard; however, it is not widely available in many African settings. Also, sensitivity of blood culture is suboptimal because of the low magnitude of bacteraemia (median <1 CFU/mL). Care should therefore be taken to inoculate large enough volumes of blood for culture.

Antimicrobial resistance among iNTS strains in Africa is increasing. Empirical management is similar to enteric fever and includes either a fluoroquinolone or azithromycin, depending on the local resistance pattern and drug availability. If oral intake is not possible, a third-generation cephalosporin should be administered. Effective antibiotic treatment should be given for 10 to 14 days. Antiretroviral therapy should be started urgently to prevent relapse. The case fatality rate of patients with iNTS is much higher than in enteric fever (22–47% vs 1%).

Further Reading

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