73

A 21-Year-Old Male Migrant from Rural Mali With Massive Splenomegaly

CAMILLA ROTHE

Clinical Presentation

History

A 21-year-old male migrant from rural Mali is referred to the tropical medicine department of a university hospital in Germany. He has just been worked-up for splenomegaly and bicytopenia at the haematology department. However, the underlying condition could not be established.

Clinically, the patient is quite well, he only reports intermittent fever, and some "heaviness" on the left side of his abdomen for some time (the duration is difficult to specify). There are no night sweats and his weight appears to be stable.

The patient migrated from rural Mali to Germany and arrived 1 year prior. During his journey he crossed Niger and spent a few weeks at a detention centre in Libya until he made his way across the Mediterranean and through Italy to Germany. He comes from a poor family and is unable to read and write.

Clinical Findings

21-year-old young man, who appears clinically well. Temperature 36.1°C (96.98°F), BP 120/80mmHg, pulse 64 bpm. The spleen is massively enlarged (around 15 cm below the left costal margin), but there is no clinical anaemia and no lymphadenopathy. Heart sounds are clear and there are no murmurs. The rest of the examination is normal.

Abdominal Ultrasound

Spleen 21.8 cm in longitudinal diameter, the parenchyma appears homogenous. The liver is normal in size and the parenchyma looks normal. The flow of the portal and splenic veins is normal. There is no lymphadenopathy and no free fluid.

Laboratory Results

The laboratory results are shown in Table 73.1.

TABLE 73.1 Laboratory Results at First Presentation

Parameter	Patient	Reference Range
WBC ($\times 10^9$/L)	3.3	4–10
Neutrophils ($\times 10^9$/L)	2.29	1.8–7.2
Lymphocytes ($\times 10^9$/L)	1.4	1.5–4
Monocytes ($\times 10^9$/L)	0.28	0.2–0.5
Eosinophils ($\times 10^9$/L)	0.12	<0.5
Haemoglobin (g/dL)	13.8	13–15
Platelets ($\times 10^9$/L)	124	150–350
LDH (U/L)	185	<220
Total bilirubin (mg/dL)	0.5	0.2–1.2
IgM (g/l)	8.59	0.4–2.3
CRP	0.5	<0.5
ESR mm/h	9/21	<15/30
Plasmodium spp. (thick and thin film)	negative	negative
P. falciparum IFAT	1:256	<1:32

Questions

1. What are the most important differential diagnoses in this patient?
2. How would you manage him?

Discussion

A 21-year old migrant from rural Mali presents with massive splenomegaly, causing a feeling of heaviness in his abdomen and reports intermittent fever. The symptoms have been present for some time.

At presentation he appears well and is afebrile. Gross splenomegaly is the only abnormal finding confirmed by ultrasound, which otherwise yields no pathological results. Laboratory results show mild bicytopenia, normal LDH and almost 4-fold increased immunoglobulin M (IgM). The systemic inflammatory markers are not elevated. Blood films for malaria parasites are negative, but malaria serology is positive.

Answer to Question 1

What Are the Most Important Differential Diagnoses in This Patient?

Lymphoma or leukaemia is an important differential diagnosis to have in a patient with splenomegaly and fever anywhere in the world. However, in our patient it seems unlikely, because the differential count is normal, LDH, CRP and ESR are not elevated and the specialist work-up elsewhere did not yield a cause for his complaints.

Visceral leishmaniasis (VL) can present with massive hepatosplenomegaly, generalized lymphadenopathy and pancytopenia. Patients usually have a history of fever and weight loss and appear severely ill, which our patient did not.

Schistosomiasis is common in many parts of sub-Saharan Africa. Chronic *S. mansoni* infection causes liver fibrosis and secondary portal hypertension with splenomegaly and hypersplenism.

Liver fibrosis in schistosomiasis (so called "pipestem fibrosis") is usually easy to detect on ultrasound. In our patient, the liver appeared normal, and the flow of portal and splenic veins was normal as well, making portal hypertension of any cause unlikely.

Bacterial endocarditis and brucellosis may cause fever and splenomegaly; however, the spleen tends to be only moderately increased in size and there were no murmurs on ardiac examination.

EBV and CMV infections may cause ongoing fever and splenomegaly. Typical laboratory features include relative and absolute lymphocytosis, elevated LDH and liver transaminases, which our patient does not have. In Africa, most people will be exposed to both viruses already in childhood.

Our patient shows remarkably high IgM titres, positive malaria serology and a negative blood film. The most likely differential diagnosis for this patient therefore is hyperreactive malarial splenomegaly (HMS). HMS is the most common cause of massive splenomegaly in tropical areas with stable malaria transmission.

Answer to Question 2

How Would You Manage the Patient?

An HIV test should be ordered in any patient from Africa with a history of fever and/or thrombocytopenia. Serologies for schistosomiasis and visceral leishmaniasis should be done and blood cultures taken for *Brucella* species and bacterial endocarditis.

For HMS, malaria PCR should be ordered and antimalarial treatment attempted. If splenomegaly remains unexplained, a bone marrow aspirate should be done to rule out a haematological disorder and look for intracellular *Leishmania* promastigotes.

The Case Continued…

HIV serology was negative; EBV and CMV serologies indicated previous infection. Serologies for schistosomiasis and leishmaniasis were also negative, and the blood culture did not yield any pathogens. There were no ova of *S. mansoni* found in the stool.

Despite the negative blood film, PCR for *P. falciparum* came back positive, making a diagnosis of hyperreactive splenomegaly very likely.

The patient received one single course of dihydroartemisinin/piperaquine and the reported episodes of fever subsided. Malaria PCR was still positive at follow-up 2 weeks later, but has remained negative since then.

Shortly after treatment, authorities threatened to deport the patient back to Mali. A medical letter indicating that he was at high risk for splenic rupture, which at his home in rural Mali would mean certain death, was recognized and he was permitted to stay.

The patient has been monitored for a total of 2.5 years at the time of writing. IgM levels took 2 years to get back to normal. The size of the spleen slowly decreased; but at his last visit, remained slightly enlarged (14 cm in diameter).

At his last visit, the young man was well and spoke fluent German. He went to school in Germany and has learned to read and write. He planned to start vocational training to become a house painter.

SUMMARY BOX

Hyperreactive Malarial Splenomegaly (HMS)

HMS, formerly known as tropical splenomegaly syndrome (TSS), is one of the most common causes of massive splenomegaly in tropical regions with stable malaria transmission. Other important causes include lymphomas, chronic myeloid leukaemia, myelofibrosis, haemoglobinopathies, schistosomiasis and visceral leishmaniasis.

HMS is caused by an abnormal immune response to repeated infections with *Plasmodium falciparum, P. malariae* or *P. vivax* that results in an overproduction of polyclonal IgM. IgM forms aggregates and immune complexes, which are phagocytosed by the reticuloendothelial system, leading to massive splenomegaly and hypersplenism.

HMS is more common in women than in men and mainly affects the age group between 20 and 40 years. There seems to be a genetic background, with ethnic and familial clustering. HMS has also been described in expatriates residing in malaria-endemic regions, and more and more cases are being described in refugees and migrants from malaria-endemic areas.

Diagnostic criteria were proposed by Fakunle in 1982 and include splenomegaly extending >10cm below the left costal margin without any other cause, elevated IgM, elevated antimalarial antibodies and favourable response to antimalarial prophylaxis.

Even though commonly quoted in the literature, Fakunle's criteria are of limited practical use for clinicians practicing in

resource-constrained settings, where HMS is naturally most common because malaria serology and IgM levels are usually unavailable. Under those circumstances, clinicians are often limited to presumptive treatment with antimalarials of a patient with massive splenomegaly, and HMS may be difficult to differentiate from lymphoma.

Patients most commonly present with symptoms of anaemia and abdominal heaviness or discomfort, some report episodes of low-grade fever. Full blood count usually shows anaemia, bi- or pancytopenia reflecting hypersplenism. Malaria microscopy is usually negative, because parasitaemia is kept at bay and therefore very low. However, molecular methods such as PCR may be able to detect low-level parasitaemia, as highlighted in this case.

Treatment of HMS is effective with antimalarials for the duration of exposure, i.e. in endemic settings, lifelong. In migrants living in malaria non-endemic countries, one treatment course of antimalarials is enough to eliminate parasites as shown in this case, and repeated courses are not required. However, even after clearanc of infection splenic size and increased IgM may still take a long time to get back to normal ranges.

Further Reading

1. White NJ. Malaria. In: Farrar J, editor. Manson's Tropical Diseases. 23rd ed. London: Elsevier; 2013 [chapter 43].
2. Fakunle YM. Tropical splenomegaly. Part 1: Tropical Africa. Clin Haematol 1981;10:963–75.
3. Bedu-Addo G, Bates I. Causes of massive tropical splenomegaly in Ghana. Lancet 2002;360(9331):449–54.
4. Leoni S, Buonfrate D, Angheben A, et al. The hyper-reactive malarial splenomegaly: a systematic review of the literature. Malar J 2015;14:185.
5. Bisoffi Z, Leoni S, Angheben A, et al. Chronic malaria and hyperreactive malarial splenomegaly: a retrospective study on the largest series observed in a non-endemic country. Malar J 2016;15:320.