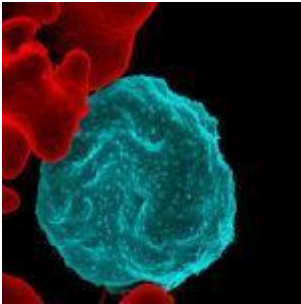


17 year old male with fever and decreased level of consciousness



- [Patient presentation](#)
- [History](#)
- [Differential diagnosis](#)
- [Examination](#)
- [Investigations](#)
- [Discussion](#)
- [Treatment](#)
- [Final outcome](#)
- [Evaluation - Questions & answers](#)

Patient presentation

A 17 year old adolescent presents to a refugee camp infirmary obtunded. He has been febrile for the last 4 days and has been complaining of back pain and stomach aches accompanied with diarrhoea.

Acknowledgement

This case study was kindly provided by Barclay Stewart, Medical University of South Carolina, Fogarty International Clinical Research Scholar, Nairobi, Kenya

History

The patient is a refugee from the northern part of Sudan who was relocated to a northern Ugandan refugee camp. On arrival 2 months ago he received a comprehensive medical exam. He was noted to be undernourished but not suffering from any acute or chronic illnesses. He was placed on a nutrition supplementation program during his first month at the camp and given all appropriate vaccinations.

He was fine until 4 days ago when he told one of the staff that he was having back and stomach pains. He was taken to the camp clinic, examined, given medication and released. He later admitted he had not taken the medication. A gentleman staying in the bed next to him alerted the clinic staff because he was concerned about the patient's shivering and mumbling. The clinic staff came to see him and immediately had him taken to the infirmary.

Differential diagnosis

- Encephalitis
- Meningitis
- Endocarditis
- Gastroenteritis with secondary severe dehydration
- Malaria
- Pneumonia
- Toxic Shock Syndrome
- Typhoid Fever
- Brucellosis
- Relapsing Fever
- Katayama Fever

Examination

On Admission

The young man is thin, drenched in sweat, and obtunded

Vitals

- Pulse-124
- Respiratory Rate-34
- Temperature-40.1
- Blood Pressure- not recorded
- Pulse-Oxygen-91%

Head and Neck

- Jaundice seen in sclera.
- Eyes sunken and unresponsive.
- No papillidema.
- Non-inflamed nasal passage without discharge.
- Oral mucosa pale, without lesions.
- No cervical lymphadenopathy, midline trachea

Respiratory System

- Chest is symmetrical in appearance, no scars.
- Breathing deep and rapid.
- No vocal or tactile fremitus.
- Clear on auscultation bilaterally.

Cardiovascular System

- Non displaced, bounding apex beat.
- Tachycardic with a regular rhythm.
- Normal S1 and S2.
- Radial, femoral and dorsalis pedis pulses present and bounding.
- Capillary refill within 2 seconds.

Abdomen

- Normal upon inspection.
- No masses palpable.
- No hepatosplenomegally.
- Bowel sounds diminished but present.

Neurological

- GCS 9/15
- Young man obtunded, not following commands although appears to attempt to by moving slightly on the initial command.
- Localises to pain.
- Eyes open in response to pain

Investigations

Examination	Value	Normal Limits
WBC	12	(4-12 x 10 ⁹ /l)
HB	7.2	(12.1-15.2 g/l)
HCT	0.22	(.31 - .42)
Platelets	222	(140-450 x 10 ⁹ /l)
LDH	294	(70-250 U/l)
Haptoglobin (Free Serum)	23	(27-139 mg/dl)
Reticulocyte Count	4	(0.8-4% RBC)
Complete Metabolic Panel		
AST	52	(5-35 U/l)
ALT	101	(5-35 U/l)
Total Bilirubin	7	(3-7 umol/l)
Direct Bilirubin	0.1	(0.0-0.3 mg/dl)
Sodium	143	(135 – 147 mmol/l)
Potassium	4.0999999999999996	(3.5 – 5.1 mmol/l)
Bicarbonate	25	(22-33 mmol/l)
Chloride	93	(95 – 107 mmol/l)

Examination	Value	Normal Limits
Lactate	6.4	(0.3 – 4 mmol/l)
Creatinine (serum)	160	(70 – 150 umol/l)
BUN (serum)	7	(2.5 – 6.7 mmol/l)
Glucose (serum)	3	(3.5 – 6.5 mmol/l)
Urine Analysis		
Color	Tea	
Spec. Gravity	1.0289999999999999	(1.010 – 1.030)
pH	6.3	(4.8 – 7.5)
Ketones	Trace	Absent
Protein	Trace	Absent
Urobilinogen	High	(0.3 – 2.1 units/2hours)
Bilirubin	Trace	Absent
Glucose	Absent	Absent
RBC	Trace	Absent
WBC	Trace	Absent
Malaria Rapid Diagnostic Test – Positive for P. falciparum		

Discussion

The pathophysiology of *Plasmodium sp.*, is considered to arise from one of two possible mechanisms. One advocates the mechanical hypothesis of insufficient tissue oxygenation resulting in sequestration of the parasitized red blood cells in the microvasculature. The second advocates the cytokine hypothesis in which the exuberant release of pro-inflammatory cytokines is the basis of the disease and accompanying

mortality. This case study discussion focuses on the cytokine hypothesis.

Generally it is thought that the pro-inflammatory cytokines are central to the pathophysiology of systemic disease caused by infectious and non-infectious agents. These cytokines bring about symptoms which include anorexia, malaise, myalgia, arthralgia and fever, which patients experience during systemic disease such as malaria. Furthermore, the release of these cytokines in large amounts are responsible for severe illnesses. Of special note is TNF- α . When this cytokine is produced in appropriate concentrations it is vital to the immune response and subsequent clearance of malaria. However, pathology ensues when TNF is produced in large amounts. Many systemic diseases, both infectious and non-infectious, have been linked to this superabundant pro-inflammatory cytokine release. Effects of this release, seen in malaria, sepsis and tissue injury syndromes, include metabolic acidosis , hyperlactatemia and encephalopathy.

During the blood stage, infection with *Plasmodium falciparum* is associated with high levels of pro-inflammatory cytokines such as IL-1, IL-6, TNF- α , IL-12 and INF- γ and low levels of anti-inflammatory cytokines IL-10 and TGF-B causing symptoms associated with malaria such as fever and anaemia. Although it is also true that lysis of infected red cells, splenic removal of infected red cells and red-cell occlusion in blood vessels contributes to anaemia, cytokines, particularly IL-1 and TNF- α , play an additive role by causing mitochondrial dysfunction, bone marrow suppression and upregulation of endothelial adhesion molecules.

Furthermore, inflammatory cytokines upregulate endothelial cell adhesion molecules in order to entice circulating blood elements to undergo diapedesis and intercellular migration. In many disease states, including malaria, these blood elements which include activated leukocytes and platelets promote coagulation. In malaria, circulating monocytes, placental

macrophages and thrombin enhance adhesion by increasing CD36, a receptor known to bind parasitized erythrocytes on platelet surfaces. These adherent cells set up local foci of inflammation which produces more inflammatory cytokines. In combination with the effects of systemic inflammation, these local inflammatory reactions cause a cycle of endothelial integrity loss, vascular permeability, cellular destruction and inflammatory cytokine release. These responses can result in complications such as decreased consciousness and coma.

Treatment

The patient was given a full course of quinine and recovered well.

Final outcome

After the course of malaria treatment he was begun on weekly malaria prophylaxis with mefloquin because the region of Sudan from which he came was not a malaria endemic region, unlike the area surrounding the refugee camp in northern Uganda.

Evaluation – Questions & answers

What is the diagnosis?

Severe *Plasmodium falciparum* malaria, which has progressed to cerebral malaria

Which two mechanisms have been proposed to cause disease in *falciparum* malaria cases?

The first is the mechanical hypothesis, based on the idea that insufficient tissue oxygenation is a result of parasitized red blood cell sequestration in the microvasculature. The second mechanism is the cytokine hypothesis in which the exuberant release of pro-inflammatory cytokines is the root of disease and mortality.

What contributes to the anaemia seen in malaria?

Malaria causes anemia through multiple mechanisms including lysis of infected red cells, splenic removal of infected red cells and red-cell occlusion in blood vessels as well as cytokine effects which cause mitochondrial dysfunction, bone marrow suppression and upregulation of endothelial adhesion molecules.

What is the relationship between parasitized red cell adhesion, inflammatory cytokines, and coma?

Sequestration at sensitive sites, such as the cerebral capillaries, creates high local concentrations of inflammatory cytokines triggered by parasite molecules which further causes endothelial cell, platelet and leukocyte activation, amplifying the site specific inflammation, vaso-occlusion, secondary cytokine effects, and increasing blood-brain barrier permeability causing cerebral edema and coma.

In sepsis and malaria , what are some of the consequences of greatly increased TNF- α levels?

Consequences include metabolic acidosis , hyperlactatemia and encephalopathy.

What symptoms do pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-1 bring about?

The symptoms these cytokines cause include anorexia, malaise, myalgia, arthralgia and fever which patients experience during systemic disease.