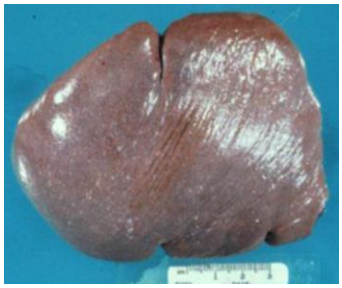
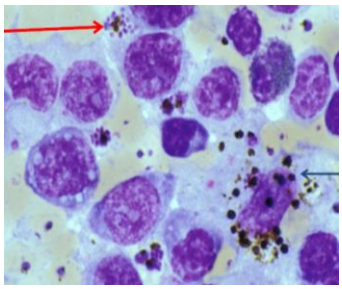
Problem 5 – Unit 6 – Pathology of Malaria

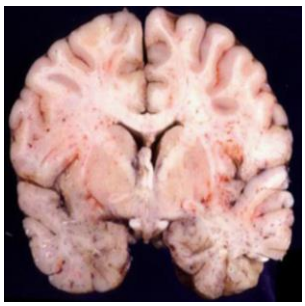
- **There are four species of plasmodium:**
  - P.vivax
  - P.malariae.
  - P.falciparum
  - P.ovale
- **Notes:**
  - P.vivax & P.ovale produce a latent form (hypnozoite) in the liver; this is the cause of relapses seen in these both species.
  - P.malariae causes nephrotic syndrome (membranous nephropathy & membranoproliferatice GN).
  - Disease caused by P.malariae is called quartan malaria (the timing of the fever cycle is 72 hours).
  - Tertian malaria is subdivided into malignant malaria, caused by P.falciparum, and benign malaria, caused by P.vivax & P.ovale. (the fever cycle of these 3 Plasmodia is every 48 hours)
- **Malaria pathophysiology:**
  - When schizonts rupture → they release merozoites and a lot of proteins (from the destroyed RBCs and parasites) → this will lead to the activation of macrophages which will release cytokines (TNF & IL-1). Note: IL-1 causes fever by producing PGE_2 which will reset the set point that is regulating the temperature of the body in the hypothalamus.
  - P.falciparum causes severe form of the disease → it infects RBCs (of all stages of development) resulting in high-level of parasitemia → leading to more severe hemolytic anemia.
  - Infected RBCs with P.falciparum will express (plasmodium falciparum erythrocyte membrane protein 1) which will aid in the adherence of RBCs to the endothelial cells of the capillaries & in the agglutination of RBCs (clumping). This clumping will block small blood vessels leading to organ ischemia (cerebral malaria, organ damage…etc).
  - **Clinical manifestations of a patient infected with P.falciparum:**
    - ✓ Fever, chills, headache, myalgias & arthralgias (resulting from the rupture of schizonts which will release merozoites).
    - ✓ Cerebral malaria and cardiac abnormalities (as a result of the occlusion of blood vessels).
    - ✓ Hemolytic anemia with excessive increase in free Hb (which is toxic). This free Hb will be removed by the kidneys leading to hemoglobinuria (blackwater fever).
    - ✓ Splenomegaly: because of the engorgement of sinusoids with RBCs and hyperplasia of lymphocytes and macrophages.
- **Resistance to malaria:**
  - **Sickle cell trait (HbA/HbS)**: due to reduced ATPase activity which will provide insufficient energy for supporting the growth of the parasite.
  - **Duffy antigen**: it is negative in Africa (especially Gambia) so there will be resistance to P.vivax.
  - **HLA-B53**: present liver-stage specific malaria antigens to cytotoxic T-lymphocytes that destroy infected hepatocytes.
- **Premunition**: partial immunity based on humoral antibodies block merozoites from invading the red cells occurs in infected individuals. A low level of parasitemia and low-grade symptoms result.
- **Pathology of organs in malaria:**
  - **Spleen:**
    - ✓ Splenomegaly (it will be massive especially with repeated infections. Weight exceeding 1000g. normal weight of the spleen is 150g).
    - ✓ In infection with P.vivax → there is a risk of rupture of the spleen.

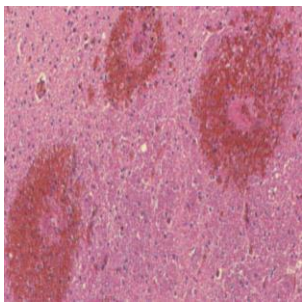




- ✓ The spleen is characterized by: thick capsule which is dark-brown in color (due to the malarial pigment: hemozoin).
  Note: Hb → α-hematin (toxic) → β-hematin (hemozoin – crystalline form). Antimalarial drugs act by inhibiting this conversion.
- ✓ There is also reticuloendothelial cells hyperplasia.
- ✓ *Hyperreactive malarial splenomegaly:*
  * Common in areas where malaria is endemic (with P.malariae).
  * Patients present with splenomegaly without other typical feature of malaria.
  * There is increased level of IgM.
  * Also, there is portal hypertension.
  * Feature of a benign lymphoproliferative disorder:↑ lymphocytes count in blood & in sinusoids of the liver and spleen.
  * Parasites are rarely demonstrated.
  * There is response to anti-malarial therapy.

- **Liver:**
  - ✓ Enlarged (hepatomegaly).
  - ✓ Pigmented with hemozoin (they will be found specially in kupffer cells).
- **Kidneys**:
  - ✓ Acute renal failure especially with hemoglobinuria (which will cause acute tubular necrosis) → this condition is known as blackwater fever and is seen in infection with P.falciparum. Note that blackwater fever can also be caused by G6PD deficiency and immune hemolytic anemia with use of quinine.
  - ✓ Renal pathology is associated with poor prognosis.
  - ✓ P.malariae will cause nephrotic syndrome (membranous nephropathy/ membranoproliferative GN).
- **Hematologic manifestations:**
  - ✓ *Anemia*: due to the rupture of infected RBCs. Sometimes it might be due to the presence of anti red cells antibody. Another cause of anemia is G6PD which is triggered by infections or the use of anti-malarial drugs.
  - ✓ *Thrombocytopenia*: due to immune complexes (antibodies binding to malaria-antigens) deposited on platelets.
  - ✓ *Variable leukocyte counts.*
- **Bone marrow and lymph nodes:**
  - ✓ Parasite and pigment-laden phagocytic cells & hemophagocytosis.
- **Cerebral malaria:**
  - ✓ It occurs in infection with P.falciparum.
  - ✓ Lumbar puncture is done to examine the CSF which will show increased pressure and increased proteins & little pleocytosis.
  - ✓ There will be cerebral edema: characterized by flattened gyri.
  - ✓ In addition, there will be ring hemorrhages (commonly seen in white matter).
  - ✓ Focal inflammatory lesions: Durck granuloma → microglial growth results in the formation of small perivascular granulomas.





- **Lungs:**
  - ✓ Pigment-laden macrophages.
  - ✓ Pulmonary edema.
  - ✓ Intra-alveolar hyaline membrane formation (ARDS: Acute Respiratory Distress Syndrome).
- **Heart:**
  - ✓ Focal hypoxic lesions (non-specific).