كلية : التربية للعلوم الصرفة

القسم او الفرع : علوم الحياة

المرحلة: دكتوراه

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اسم المادة باللغة العربية : علم النسج المرضية

اسم المادة باللغة الإنكليزية : histopathology

اسم المحاضرة الأولى باللغة العربية: الامراض الاستوائية

اسم المحاضرة الأولى باللغة الإنكليزية : SELECTED TROPICAL DISEASES

VII. Malaria

Malaria is caused by the intracellular protozoan parasite called Plasmodium species and plasomodium Faliprium is the worldwide infections that affect 100 million people and kill 1 to 1.5 million people yearly. P.Falciparium and P.Vivax, P. ovale, and P.malarie represent 60%, 49 %, <1.0% and reported cases respectively in Ethiopia. P. falciparum cause high parasitmias, severe anemia, cerebral symptoms, and pulmonary edma and death.

Pathogenesis (P.Falciparum):

Infected humans produce gametocytes that mosquitoes acquire on feeding. Within these insects' body, the organism produces sporozites, which the mosquito transmits to human when it feeds.

③ Malarial sporozites after being released in the blood within minutes attach to a serum protein thrombosroridin and properidine located on the basolateral surface of hepatocytes. These sporozites multiply and release merozytes by rupturing liver cells.

③ Once released, P. falciparum merozites bind by a parasite lactin like molecule to on the surface of red blood cells

③ Within 2 to3 weeks of hepatic infection, merozites rupture from their host hepatocytes and invade erythrocytes establishing erytrocytic phase of malarial infection.

③ The merozites feed on hemoglobin grow and reproduce within erythrocytes. Repeated cycles of parasitemia occur with subsequent ruptures of these cells with resultant clinical manifestations such as chills, fever etc.

③ P. Vivax merozites however, bind by homologous lectin to the Duffy antigen on RBC so many cases who are Duffy negative are resistant to this infection.

③ HLA –B53 associated resistance in some Africans is related to the ability of HLA – B53 to present the liver stage specific malarial antigen to cytotoxic T-cells, which then kill malarial, infected hepatocytes.

③ Individuals with sickle cell trait are resistant to malaria because the red cells that are parasitized in these individuals are removed by the spleen.

③ Most malarial parasites infect new RBC & some develop to sexual form called gametocytes and the mosquito when it takes this blood meal the cycle continues.

Morphology:

③ Spleen enlarged upto 1000gm (normally 150grams) and this splenomegaly can be attributed to increased phagocytosis in splenic reticuloendothelial cells in chronic malaria. The parenchyma imparts grey or blue discolouration due to hemozoin.

③ Liver kuffer cells are heavily laden with malarial pigments, parasites, and cellular debris. Pigmented phagocytes may be dispersed through out bone marrow, lymph nodes, subcutaneous tissues and lungs.

③ Malignant cerebral malaria: Patients with cerebral malaria have increased amount of inter-cellular adhesion molecules (ICAM- 1). These patients manifest diffuse symmetric encephalopathy; brain vessels are plugged with parasitized red cells. There are ring hemorrhages related to local hypoxia. Cerebral involvement by *P. falciparum* causing 80% of childhood death is due to adhesion of the P. falciparum parasite to endothelial cells with in the brain.

Hypoglycemia- result from failure of hepatic gluconeogenesis & glucose consumption by the host and the parasite lactic acidosis -due to anaerobic glycolysis, non cardiogenic pulmonary edema, renal impairment, anemias etc

P. falciparum, the cause of malignant malaria produces much more aggressive and lethal disease than the other human malarias. This organism is distinguished from other malarial parasites in four aspects.

1) It has no secondary exoerythocytic (hepatic) stage

2) It parasitizes erythrocytes of any stage, causing marked parasitmia and anemia. In other types of malaria only subpopulations of erythrocytes are parasitized, and thus low level parasitemias and more modest anemias occur. P. Vivax and P>Ovale attack immature erythrocytes while P. malarie attack senescent cells.

3) There may be several parasites in single erythrocyte

4) P. falciparum alters the flow characteristics and adhesive qualities of infected erythrocytes so that they adhere to the endothelial cells of small blood vessels frequently produce severe ischemia. Infected red cells sequester inside the small blood vessels at the same time P. falciparum infected RBCS may also adhere to uninfected red cells to form rosettes. The process of cytoadhernce and rosetting are central to the pathogenesis of falcparum malaria in the other three " benign" malarias sequestrations does not occur and all stages of parasites' development are evident on peripheral blood smears.

P. falciparum invades erythroytes of all ages and is associated with high level parasitemia whereas, P. vivax, P.ovale and P.malariae show predilection for either old red cells or reticuloytes & level of parasitmias seldom exceeds 2 percent.

Malaria in pregnancy

In pregnancy, malaria may be associated with hypoglycemia, fetal distress syndrome and low birth weight. Congenital malaria can occur rarely. P. falcparum malaria is an important cause of fetal death. Congenital malaria occurs in fewer than 5% of newborns.

Malaria in children

Most of the estimated 1-3 million persons who die of falciparum malaria each year are young African children. Convulsion, coma, hypoglycemia, metabolic acidosis and severe anemia are relatively common.

Transfusion malaria

Malaria can be transmitted by blood transfusion, needle -stick injury, sharing of needles by infected drug addicts, or organ transplants. The incubation period is short because there is no pre-erythrocytic stage of development**.**

Complications of malaria include:

Tropical splnomegaly syndrome (**Hyperreactive** malarial splenomegaly), Burkitt's lymphoma and EBV infection

Quartan malarial nephropathy

Black water fever

Algid malaria

VIII. Leishmaniasis

Definition: Chronic inflammatory disease of skin, mucous membranes or viscera caused by obligate intracellular Kinetoplastid protozoal parasites (Leishmania species) transmitted through infected sand fly.

③ Leishmanial infections like with other intracellular organism (including mycobactria, histoplasma, toxoplasma and tryprosoma) is exacerbated by AIDS.

③ Different leishmanial parasites in new and old world appeared to show tropism related to temperature, because parasites that cause visceral disease grow at 37% in vitro whereas parasite that cause multiple diseases grow only at 340c.

③ Leishmania are phagocytozed by macrophage and acidity within phagolysosome induces them to transform into amastigate from promatigate by losing flagella.

③ Leismanial amastigotes are the only protozoal parasites that survive and reproduce in macrophage phagolysosomes, which have a PH of 4.5. Amastigotes are protected from the intravascular acid by a proton -transforming ATPase which maintains the intracellular parasite PH at 6.5

③ Leismanial parasites have two glycocongugates, which appeared important in their virulence. The first is lipophosphoglycans that are glycolipids & bind C3b and iC3b.

Organisms resist lysis by complement C5-9 but are phagocytozed by macrophages through complement receptors CR1 and CR3

③ Lipophosphoglycans may also protect the parasite within phagolysosomes by supplying oxygen radical and by inhibiting lysosmal enzymes.

③ Like *M. laprae* severity of disease is determined by host immune response.

Parasites specific to CD+T-cells of TH1 class may secrete interferon gamma which along with TNF-α secreted by other macrophages activates phagocytes to kill the parasites through toxic metabolites of oxygen or nitric acid (or both). In contrast, down regulation of the immune response that lead to anergy and progressive diseases may be caused by arasite specific CD4+T cells of T helper class 2 that secrete IL-4 which inhibits macrophages activation by interferon gamma and inhibits secretion of TNF α .

Morphology:

③ Visceral leishmaniasis (L.donovanni & L.chagasi) macrophages of RES are invaded so hepatosplenomegly, lymphadenopathy, pancytopenia, fever & weight loss, hyperpigmentation of the skin (kalazar, black fever) glomerulonephritis (mesangioproliferative) and in advanced cases amyloid deposits**.**

Cutaneous leishmaniasis

Localized single ulcer on exposed skin (slowly expanding and irregular borders, usually heals within 6 months by involution. The lesion is granulomatous.

Diffuse cutaneous leishmaniasis

Lesions of diffuse cutaneous leishmaniasis resembles lepromatous leprosy nodules. The lesions do not ulcerate but contain vast aggregates of foamy macrophages filled with leishmania. The patients are usually anergic not only to Leshmania but also to other skin antigens and the disease respond poorly to therapy.

IX. Schistosomiasis

It is the most important helmenthic disease infecting 200 million people & killing 250,000 annually.

Life cycle: Schistosomal larval, (cercaria) & penetrate human skin. Ghycocalyx that protect the organism from osmotic is shed but it activates complement by alternative pathway. Schistosoms migrate into peripheral vasculature transverse to the lung and little in the portal venous system where they develop into adult male and female schistosomes. Females produce hundreds of eggs per day around which granulmas and fibrosis form the major manifestation in schistosomiasis. Some schist some eggs are passed from the portal veins through the intestinal wall into the colonic lumen are shed with the feces and released into fresh water, form to miracidia that infect the snail to complete the life cycle.

Pathogenesis:

1. S. mansoni eggs cause liver disease in multiple ways. The schistosome eggs are direct hepatotoxicity.

2. Carbohydrate antigens of the eggs induce macrophage accumulation and granulomas formation mediated by TNF only TH1 and TH2 helper cells.

TH2 helper T-cells are responsible for eosinophilla mastocytosis and high level of serum in human schistosomiasis, because these cells secrete IL-3 and IL-4, which stimulate mastocytosis and IL-5, which is the growth factor for eosinophils. Resistance to reinfection by schistosomes after treatment correlates with IgE levels whereas, eosinophile major basic proteins may destroy larvae schistsomula.

3. Eggs release factors that stimulate lymphocytes to secrete a lymphokine that stimulate fibroblast proliferation and portal fibrosis the exuberant fibrosis which is out of proportion to the injury caused by the eggs and granucoma, occurs in 5% of persons infected with schistosomes and cause severe portal hypertension esophageal varicoses and ascites - the hallmark of severe schistosomiasis.

Morphology:

White granulomas scattered in the liver and gut. The center of the granuloma is the schistosome eggs. The granuloma degenerate overtime and undergo fibrosis and calcification. The liver is darken by regurgitated pigments from the schistosome gut which like malaria pigment are iron negative and accumulate in kuffer cells and splenic macrophages.

Severe infection (s. mansoni & S. Japanicum)

Colonic pseudopolyps

Liver surface is bumpy and its cut section shows granuloma and wide spreading fibrous portal enlargement without distortion of the intervening parenchyma.

Portal fibrosis (PIPE-stem fibrosis) many of these portal triads lack a vein lumen causing perisinusoidal portal hypertension and severe congestive splenomegaly, esophageal varices. Schistome eggs diverted to the lungs through portal collateral may produce granulomatous pulmonary arteritis with intimal hyperplasia progressive arterial obstruction and ultimately heart failure (cor pulmonale).

Patients with hepatosplenic Schistosomiasis have also increased frequency of mesangio proliferative glomerulonephritis or membranous glomerulonepritis in which glomeruli contain deposits of immunoglobulins and compliments but rarely schstosomal antigens.

S. hamatobium infection

Massive egg depositions and early granuloma formation that when erode the vasculature (hamaturia). Latter the granuomas calcify and develop a sandy appearance and in severe cases, it causes concentric rim on the wall of the bladder forming calcified bladder on x-rays films.

When the urinary inflammation involves the ureteral orifices, it causes obstructive hydronephrosis and chronic pylonehphritis. Urinary schistosomiasis is also associated with squamous cell carcinoma of the bladder that is commonly seen in Egypt.

X. Fungal Infections

There are 100,000 known fungi and only few infect humans mostly opportunistically. Only few are involved in human diseases because most fungi are destroyed by cell-mediated

immune responses however, humoral immunity plays little or no role. Predisposing factors for fungal infections include:

③ Corticosteroid administration, acquired or congenital immunodeficiency states, defects in neutrophillic and macrophage functions

③ Fungal infections are divided into superficial and deep fungal infections (mycosis). Here are few examples of systemic fungal infections

1. Candidiasis (Moniliasis)

Normally found in mouth, skin and gastrointestinal tracts. It is the most common fugal infection mostly caused by (C. albicans). It affects locally the skin, nail and mucous membranes and it grows best in warm, moist surface and cause vaginitis, diaper rash & oral trush. Systemic candidiasis widespread in persons with depressed immune responses including lymphohemopiotic malignancy, immunosuppressive therapies and broad-spectrum antibiotic usage as well as patients with dialysis, cardiac surgery, IV drug abusers.

Pathogenesis:

Candida has molecules on its surface that mediates its adherence to tissues including 1) A homologue to human CR3 integrin

2) A lectin that binds sugars on epithelial cells

3) Mannose containing protein that binds to lectin like molecule on epithelial cells

Finally, the transition of yeast to hyphal forms is important to fungal virulence because the hyphae appear to spear their way out of cells, which engulf them.

Morphology:

• **Oral trush & vaginitis** are superficial lesions characterized by white patches (or fluffy membrane)

• **Cutaneous eczematous lesion**: Seen in moist area such as between fingers, & toes and in inguinal areas, inflamammary folds and ano-genital regions. These lesions may contain acute and chronic inflammations with micro abscesses but in their chronic states granulomatous inflammations may develop.

• **Invasive candidiasis**: seen in Immunosuppression. Many organs may be involved for examples include kidney with micro abscesses in 90%, and right side candida endocarditis. The brain, liver subcutis etc may be involved with micro abscesses.

2. Cryptococcosis

Cryptococcos neoformans is encapsulated yeast. It causes menigioencephalitis in normal individuals but more frequently in patients with AIDS, leukemias, lymphomas, SLE, Hodgkin's lymphomas and transplant recipients and those on steroid therapy.

Pathogenesis:

③ Found in soil and droppings of birds (peogons): Three factors associated with virulence

1) Capsular polysaccharides

2) Resistant to killing by alveolar macrophages

3) Production of phenol oxidase, which consumes host epinephrine oxidase system. This enzyme consumes host epinephrines in the synthesis of fungal melanin thus, preventing the fungus from epinephrine oxidase system

C. neoformans affect brain because of CSF lacks the alternative pathway complement components that binds to carbohydrate capsule and facilitates phagocytosis and killing by Polymorphonuclear leukocytes.

Morphology:

Lung is the primary site of localization with minor or asymptomatic presentation; here solitary granulomatous lesions may appear.

The major pathologic changes are in the CNS involving meninges, cortical grey matter and basal ganglia. The tissue response to C. neoformans is extremely variable. In immunosupressed patients, the organisms may evoke no inflammatory reactions so; gelatinous masses of fungi grow in the meninges or in small cysts within the grey matter (soap bubble lesion)