Pathology of Rhino-orbito-cerebral Mucor Mycosis

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Mucormycosis is a life-threatening infection that occurs in patients who are immunocompromised because of impair host defences which permit growth and dissemination of fungus. The risk factors for invasive disease are uncontrolled diabetes mellitus with ketoacidosis; malignancies (haematological and solid organ); hematopoietic stem cell transplantation (HSTC); solid organ transplantation; high dose corticosteroids/immuno-suppression; deferoxamine therapy, malnutrition, neonatal prematurity etc. Immunocompetent individuals gets infected when there is a breach in body defence mechanism. Like skin injuries, burns, contaminated bandages. (1)

The fungal spores enter the body via inhalation; implantation in injured skin by trauma/burns/surgery; percutaneous route by contaminated needles or catheters or ingestion of contaminated food. (2)

Healthy individual resist this infection with help of various defences like intact skin/mucosal barrier and innate immunity. The mucosal barrier has cilia trap for the spores as well as antimicrobial properties. They are also poor in nutrients. Host also has nutrient immunity by which it keeps nutrient iron firmly bound to the serum proteins to restrict access to pathogens. Macrophages phagocytes spores and kill them. If macrophages fail to kill; spores germinates and hyphae act as chemo attractant to neutrophils which damage hyphae and phagocyte them. Neutrophils produce reactive oxygen metabolites, cationic peptides enzymes, perforin and kill the spores and hyphae. (3) Neutrophils also secretes proinflammatory cytokines like INF-γ; TNF-α and IL-1b which further activates T cells. The toll-like receptors (TLR) are expressed on phagocytes and bind to the pathogen-associated molecular patterns (PAMP) on the fungi. This activates intracellular signalling and mediates inflammation. (4) Platelet also take part in host defences by secreting granules that have pro-inflammatory and anti-inflammatory properties; cytokines and chemokines. Platelets get activated by adhering to spores and hyphae. This leads to the aggregation of platelets and clot formation which prevents dissemination of infection. They also express molecules to adhere to endothelial cells, monocytes and dendritic cells and activate them. (5)

Mucormycosis secretes various lytic enzymes; mycotoxins, alkaloids which helps in tissue invasion and angioinvasion. (6) Mucormycosis needs free iron for its growth. Due to angioinvasive nature, it takes up heme intracellularly and with the help of heme oxygenase which is present in cytoplasm it separates ferric ion. Other method by which it obtains ferric ion is by the action of
reductase-permease system (copper oxidase–iron permease (FTR1) complex). In patients with diabetic ketoacidosis, acidic pH causes displacement of ferric iron from transferrin which is transferred intracellularly by the reductase-permease. Iron chelators like deferoxamine directly chelates iron from transferrin and forms iron-deferoxamine complex (ferrioxamine). The ferrous iron is liberated by fungus from ferrioxamine by reduction at the cell surface. (7)

The main risk factor for mucormycosis is uncontrolled diabetes. Hyperglycemia causes glycosylation of transferrin, ferritin, and lactoferrin which reduces their affinity for binding iron and cause proton mediated displacement of ferric iron. This increases free iron levels even without acidosis. (6) Hyperglycaemia also affects innate immunity. It causes dysfunction of phagocytic activity. Uncontrolled diabetes also increases level of β-hydroxy butyrate which further lowers the pH in the blood vessel. Lowering of pH further impairs the ability of transferrin to chelate iron.(8) Glucose, iron, and β-hydroxy butyrate induce the expression of GRP78 and CotH (homologous protein).Increased expression promotes the growth and invasion of the fungus leading to the endothelium injury. Overall effect leads to the suppression of T lymphocyte induction, IFN-γ production, and phagocyte-mediated killing. Ketoacidosis also impairs neutrophil function leading to disseminated disease.(9) Mucormycosis down regulates the genes involved in various defence mechanism like pathogen recognition, innate immunity and tissue repair.(10)
Depending upon anatomical location mucormycosis is classified into rhinocerebral, rhinoorbital, cutaneous, pulmonary, gastrointestinal and disseminated. Rhinocerebral Mucormycosis is the most common form of the disease occurring in uncontrolled diabetic patients. It enters from mucosa of nose and nasopharynx and spread to adjacent areas. Fungus further spreads to sphenoid sinus, cavernous sinus, orbits and also invades the brain (11). Mucormycosis is highly angiotropic and invades arteries like internal carotid, sinuses and in orbit leading to the thrombosis and infarcts at multiple sites. (12) It also spreads by retrograde extension along nerves. The mucormycosis causes characteristic features like hemorrhage, thrombosis, infarction along with tissue necrosis. The inflammation is predominantly neutrophilic, sometimes causing suppuring granulomas. Multinucleated giant cells are also seen in some cases. (13)

References


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