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Editorial

Scourge and Pestilence-Histoplasmosis

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Histoplasmosis is a global disease encountered within diverse continents. The condition is engendered due to fungus Histoplasma capsulatum of class Ascomycetes, order Onygenales and family Ajellomycetaceae. The species Histoplasma capsulatum var capsulatum commonly induces histoplasmosis whereas species Histoplasma capsulatum var duboisii induces African histoplasmosis. Histoplasma capsulatum is a dimorphic mould fungus inducing environmental, mould-forming, tuberculate macroconidia with a classic 'ship's wheel' architecture. Histoplasma capsulatum emerges as a causative agent inducing histoplasmosis which arises within environmental niche comprised of nitrogen rich soils and dark, dingy attics infested with bird or bat droppings [1,2]. With primate body temperatures an intracellular, uniform, miniature, elliptical yeast demonstrating exceptional, narrow 'budding' is observed [1,2]. Afflicted immunocompetent individuals delineate tuberculosis-like illness configuring necrotizing granulomas whereas immunocompromised subjects display disseminated infectious disease accompanied by inferior prognostic outcomes [1,2]. Pulmonary parenchyma depicts solitary nodules simulating various pulmonary neoplasms. Mediastinal lymph nodes may demonstrate features recapitulating lymphoma. Cutaneous lesions simulate lesions of Molluscum contagiosum. Lesions arising upon tongue may expound as ulcerative lesions accompanied by edges raised by 'heaped' epithelium. Bone marrow infection induces anaemia of unknown origin [2,3]. Immunocompromised individuals display disseminated disease. The condition is induced by inhalation of fungal spores which germinate into yeasts. Subsequently, alveolar macrophages and neutrophils appear incompetent in decimating the infection [2,3]. Yeast forms persist within macrophages and disseminate into lymphatics. Immunocompetent subjects with infection expound T cell activation which assists efficacious configuration of 'granuloma'. Immunocompromised individuals delineate perpetual proliferation of organisms within the reticulo-endothelial system with subsequent dissemination [2,3].

Clinically, pulmonary histoplasmosis appears as asymptomatic infection or may emerge as a self limiting, respiratory illness. Typically, acute disease expounds cough, pyrexia with chills or dyspnoea. Subacute disease represents as persisting, community acquired pneumonia which may be unresponsive to specific antibiotic therapy. Chronic disease represents with cough with expectoration, low grade pyrexia, loss of weight and night sweats [2,3]. Mediastinal histoplasmosis exemplifies lymphadenitis of mediastinal lymph nodes. The condition is commonly asymptomatic and self limiting. However, pyrexia and lymphadenopathy may ensue. Granuloma formation may occur within the mediastinum [3,4]. Aggregates of paratracheal or subcarinal lymph nodes appear coalesced and necrotic and manifest as a semiliquid, conglomerate mass, designated as 'caseation necrosis' [3,4]. Fibrosing mediastinitis represents as a dense, fibrotic tumefaction which may obstruct pulmonary vasculature or airways. Progressive disseminated histoplasmosis emerges within immunocompromised subjects and is associated with pyrexia, fatigue, night sweats, dyspnoea and loss of weight. The infection may disseminate into hepatic parenchyma, spleen, gastrointestinal tract and bone marrow [3,4]. Upon microscopy, miniature, uniform, elliptical, narrow, budding yeasts delineating eccentric, intracellular, acorn-like nuclei appear amalgamated within histiocytes. Immune response with granuloma formation varies from an absent reaction within immunocompromised subjects to occurrence of enlarged, necrotizing granulomas. Additionally, aggregates of organisms may persist beyond demise of host cell [3,4]. Organisms may be challenging to ascertain upon haematoxylin and eosin

stain wherein a retraction artefact is characteristic. Gomori methanamine silver (GMS) or periodic acid Schiff's (PAS) stain may be appropriate for highlighting the organisms. Morphological tissue alterations may simulate modifications encountered with organisms as Candida glabrata, Talaromyces marneffei or amastigotes of Leishmania and Trypanosoma spp [3,4]. Yeasts which appear to lack pseudo-hyphae formation may induce inflammation with neutrophilic exudate. Yeasts configured with T. marneffei may undergo binary fission with characteristic septa demarcating the dividing cells. Amastigotes of Leishmania and Trypanosoma may expound a secondary dot or kinetoplast inculcated within singular cell. Molecular assays as Hologic Gen-Probe hybridization assay or Accu Probe may be beneficially employed for confirming fungal presence within cultures [3,4]. Nucleic acid hybridization technique employs single-stranded DNA probe with chemiluminescent label, a feature which adheres to fungal rRNA and configures a stable DNA:RNA hybrid. Additionally, internal transcribed spacer (ITS) / 28S rRNA sequencing may be appropriate in discerning species specific organisms [3,4].

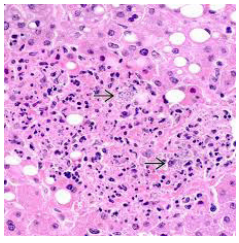

Figure 1: Histoplasmosis depicting intracellular aggregates of yeasts with budding and eccentric nuclei amalgamated within histiocytes [9].

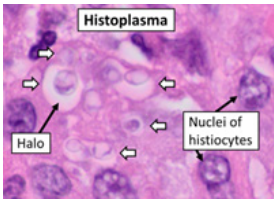

Figure 2: Histoplasma capsulatum engulfed within histiocytes with fungal organisms incorporated with abundant, eosinophilic cytoplasm, eccentric nuclei and a halo. Surrounding inflammatory exudate is minimal [10].

Ann Arbor staging of Non Hodgkin's Lymphoma [2,3].

- stage I with involvement of singular lymph node region ~stage IE with involvement of singular extra-lymphatic organ or site
- stage II with involvement of ≥2 lymph node regions on one side of diaphragm ~stage IIE with localized involvement of an extra-lymphatic organ or site and ≥ one lymph node region upon one side of diaphragm
- stage III with involvement of lymph node regions on opposite sides of diaphragm ~stage IIIS with involvement of spleen ~stage IIIE with involvement of extra-lymphatic site
- stage IV with diffuse or disseminated involvement of ≥one extra-lymphatic organ or tissue along with or devoid of associated lymph node involvement. Occurrence of systemic symptoms within preceding six months are designated as fever, night sweats or >10% loss of body weight. Absence of systemic symptoms is designated 'A' whereas presence of systemic symptoms is denominated as 'B' within Ann Arbor staging of non-Hodgkin's lymphoma. Incriminated extra-nodal sites are designated as ~M+ with involvement of bone marrow ~L+ with involvement of pulmonary parenchyma ~H+ with involvement of hepatic parenchyma ~P+ with involvement of pleura ~O+ with involvement of bone ~D+ with involvement of cutaneous and subcutaneous tissue.

Histoplasmosis requires segregation from conditions as acute illness denominated by community acquired pneumonia, chronic illness as tuberculosis, infection with non tubercular mycobacterium and diverse acid fast organisms, blastomycosis, coccidioidomycosis or sarcoidosis [5,6]. Direct smear examination obtained from various exudates depicts miniature, uniform, narrow filaments and clusters of budding yeasts permeated within host cells. Yeasts gradually progress into fluffy, white, mouldy colonies within weeks [5,6]. Preliminary tape sample preparations display yeast cells of magnitude 2 µ metres to 4 µ metres. Few yeast cells depict transformation into fungal hyphae [6,7]. Preliminary hyphae simulate hyphal forms of Blastomyces or Paracoccidioides and may depict lollipop-like configurations as aleurioconidia of diameter between 2 µmetres to 4 µ metres [6,7]. Fungal cultures obtained from delayed

disease stage characteristically demonstrate enlarged, tuberculate macroconidia of magnitude between 8µ metres to 16 µ metres [7,8]. Disease confirmation with diverse molecular techniques as Gen-Probe appears mandatory in order to exclude the occurrence of non pathogenic environmental moulds which simulate Histoplasma, especially Sepedonium species on morphological grounds [7,8]. Non invasive diagnostic methodologies or antigen tests may be adopted as ~evaluation of Histoplasma galactomannan may be obtained with serum and urine assays, a procedure which ensures non invasive ascertainment of active disease. ~enzyme immunoassay manifests as a quantitative outcome which may be beneficial for assessing acute or disseminated disease or subjects with human immune deficiency virus (HIV) infection along with an absence of discernible antibodies against the fungus [7,8]. Appropriate detection of granulomas of significant duration may be challenging. The fungus depicts a definitive cross reactivity with Blastomyces, Paracoccidioides and antigens from various fungi. Serological parameters are pre-eminently employed for antigen screening within urine [7,8]. Asymptomatic infection with Histoplasma capsulatum or mild disease and incidentally discovered granulomas of significant duration or 'histococcomas' may not necessitate cogent therapy. Precise therapy may range from 6 weeks to 12 months. Immunosuppressed individuals may mandate lifelong therapy. Agents such as itraconazole are pre-eminently employed as first line therapy. Severe disease may be managed with liposomal amphotericin B [7,8].

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10. Image 1 Courtesy: Basic medical key.

11. Image 2 Courtesy: Wikipedia.com.