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Mucormycosis: Identify Symptoms, Diagnosis and Treatment of Black Fungus.

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Abstract
Mucormycoses are devastating fungal infections that mainly afflict immunosuppressed patients. The infection is caused by fungi of the order Mucorales. Treatment of mucormycosis is reliant on reversal of underlying predisposing factors, surgical debridement of infected tissues and appropriate antifungal therapy. Rapid and reliable diagnostic methods are lacking and current diagnosis is dependent on culture and histopathological examination. Recent major advances in gene manipulation and genomics have produced several promising targets for novel therapeutic interventions. We discuss the disease, its current management, the recent advances in molecular pathogenesis, diagnostics and potential new modalities of treatment.

Introduction :-
Mucormycosis (sometimes called zygomycosis) is a serious but rare fungal infection caused by a group of molds called mucormycetes. These fungi live throughout the environment, particularly in soil and in decaying organic matter, such as leaves, compost piles, or rotten wood (Richardson, 2009).
Several different types of fungi can cause mucormycosis. These fungi are called mucormycetes and belong to the scientific order Mucorales. The most common types that cause mucormycosis are Rhizopus species and Mucor species(Roden*et al*., 2005).Other examples include Rhizomucor species, Syncephalastrum species, Cunninghamellabertholletiae, Apophysomyces, Lichtheimia (formerly Absidia), Saksenaea, and Rhizomucor.(Al-Ajam, *et al*., 2006).
It is generally spread by breathing in, eating food contaminated by, or getting spores of molds of the Mucorales type in an open wound (Reid*et al*., 2020). These fungi are frequently present in decomposing organic matter such as rotting fruit and vegetables, leaves, and animal manure, but do not usually affect people.It is not transmitted between people (CDC, 2021). Risk factors include diabetes, lymphoma, organ transplant, iron overload, HIV/AIDS and long-term steroids or immunosuppressants use (Hernández & Buckley, 2021).
he fungal spores are in the environment, can be found on for instance moldy bread and fruit and are breathed in frequently, but cause disease only in some people (Helen & Gary, 2005).In addition to being breathed in to be deposited in the nose, sinuses and lungs, the spores can also enter the skin through a cut or open wound, or grow in the intestine if eaten (McDonald, 2018).

Symptoms:-
Mucormycosis depend on where in the body the fungus is growing. Contact your healthcare provider if you have symptoms that you think are related to mucormycosis.
Symptoms of rhinocerebral (sinus and brain) mucormycosis include: One-sided facial, swelling. Headache, Nasal or sinus congestion, Black lesions on nasal bridge or upper inside of mouth that quickly become more severe and Fever (Petrikkos*et al* ., 2012, Lewis *et al* ., 2013).

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While Symptoms of pulmonary (lung) mucormycosis include:Fever, Cough, Chest pain and Shortness of breath.Cutaneous (skin) mucormycosis can look like blisters or ulcers, and the infected area may turn black. Other symptoms include pain, warmth, excessive redness.after a burn, or other skin injury, in people with leukaemia, poorly controlled diabetes, Graft-versus-host disease, HIV and intravenous drug use (Helen & Gary, 2005).
Symptoms of gastrointestinal mucormycosis include:Abdominal pain, Nausea and vomiting , Gastrointestinal bleeding, Disseminated mucormycosis typically occurs in people who are already sick from other medical conditions, so it can be difficult to know which symptoms are related to mucormycosis. Patients with disseminated infection in the brain can develop mental status changes or coma (, Ribes *et al* ., 2000, Spellberg *et al* ., 2005).

Laboratory diagnosis:-
Diagnosis of mucormycosis relies on direct morphologic identification of mycotic elements and recovery of Mucorales organisms in culture from specimens obtained from the site of presumed involvement. Presence of broad (6-16μm), ribbon-like, somewhat irregular nonseptate hyphae that branch in perpendicular angles facilitates identification of the fungus (Walsh*et al* ., 2012). Tissue samples may show hyphae invading tissue and blood vessels with or without thrombosis. Histologic detection of Mucorales organisms is enhanced by use of periodic acid-Schiff and Gomorimethanamine silver stains. The diagnosis of entomophthoramycosis is usually made on clinical presentation. Culture and identification of fungal elements on biopsy is frequently hampered by the intense reactive fibrosis. The Splendore-Hoepli phenomenon may be evident within the chronic inflammatory infiltrate. Final species identification requires culture and should be attempted whenever possible as it bears important therapeutic implications (Richardson*et al* ., 1999). The recovery rate of Mucorales organisms in culture is enhanced if the tissue is sliced into small pieces instead of grinded. Molecular methods to improve diagnosis and identification of clinically relevant Mucorales organisms are under development (Hammond *et al* ., 2011; Bernal *et al* ., 2013).

Treatment :-
If mucormycosis is suspected, Amphotericin B is initially given slowly into a vein, then given daily for the next 14 days (BMJ Group and the Pharmaceutical, 2021).Amphotericin B is sometimes continued for longer (Cornely, 2019). Without a randomised control trial, the FDA approved Isavuconazole as a treatment for mucormycosis (McDonald, 2021). Posaconazole is an alternative (Dannaoui&Lackner 2020).
Surgical removal of the "fungus ball" is then indicated. The disease must be monitored carefully for any signs of reemergence (Rebecca, 2008; McDonald,2018).Surgery can be very drastic, and in some cases of disease involving the nasal cavity and the brain, removal of infected brain tissue may be required. Removal of the palate, nasal cavity, or eye structures can be very disfiguring (MedlinePlus, 2008).Sometimes more than one operation is required (McDonald, 2018) .Hyperbaric oxygen has been used as an adjunctive therapy, because higher oxygen pressure increases the ability of neutrophils to kill the fungus (Spellberg *et al* ., 2005). The efficacy of this therapy is uncertain (CDC, 2021) .

Risk factors :
Almost all patients with invasive mucormycosis have some underlying disease that both predisposes to the infection and influences the clinical presentation. The most common underlying diseases are (Farmakiotis&Kontoyiannis, 2016).

- Diabetes mellitus, particularly with ketoacidosis
- Treatment with glucocorticoids(Kontoyiannis*et al* ., 2000).
- Hematologic malignancies (Trifilio*et al* ., 2007).

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- Hematopoietic cell transplantation (Kontoyiannis*et al* ., 2000).
- Solid organ transplantation (Lanternier*et al* ., 2012).
- Treatment with deferoxamine
- Iron overload (Maertens*et al* ., 1999).
- AIDS
- Injection drug use
- Trauma/burns (Legrand*et al* ., 2016).
- Malnutrition

Coronavirus disease 2019-associated:

There have been case reports of mucormycosis in patients diagnosed with coronavirus disease 2019 (COVID-19), but the relationship of these two infections is unclear. Some of the infections of mucormycosis were diagnosed several days to a couple weeks after being admitted for COVID-19, and it seems reasonable to assume that the mucormycosis (rhinocerebral and pulmonary in these cases) was a secondary infection arising in a critically-ill patient on steroids (Mehta & Pandey,2020 ; Placik*et al* ., 2020). The other case reports describe patients who were diagnosed with rhinocerebralmucormycosis and COVID-19 simultaneously (Mekonnen *et al* ., 2021; Werthman, 2021) and one patient who was diagnosed with gastric mucormycosis five days after admission for COVID-19 treated with both steroids and tocilizumab(Monte *et al* ., 2020).

Recommendation:

- Mucormycosis is manifested by a variety of syndromes, particularly in immunocompromised patients and those with diabetes mellitus. Devastating rhino-orbital-cerebral and pulmonary infections are the major syndromes caused by these fung.
- The diagnosis of mucormycosis relies upon the identification of organisms in tissue by histopathology with culture confirmation. However, culture often yields no growth, and histopathologic identification of an organism with a structure typical of Mucorales may provide the only evidence of infection. A clinician must think of this entity in the appropriate clinical setting and pursue invasive testing in order to establish a diagnosis as early as possible. The polymerase chain reaction with sequencing may be useful for identifying the causative species when histopathology is positive but cultures are negative.
- Treatment of mucormycosis involves a combination of surgical debridement of involved tissues and antifungal therapy. Aggressive surgical debridement of involved tissues should be undertaken as soon as the diagnosis of rhino-orbital-cerebral mucormycosis is suspected. Elimination of predisposing factors for infection, such as hyperglycemia, metabolic acidosis, deferoxamine administration, and neutropenia, is also critical.
- The drug of choice for initial therapy of mucormycosis is a lipid formulation of amphotericin B. The usual starting dose is 5 mg/kg daily of liposomal amphotericin B or amphotericin B lipid complex, and many clinicians will increase the dose up as high as 10 mg/kg daily in an attempt to control this infection.
- For patients who have responded to a lipid formulation of amphotericin B, posaconazole or isavuconazole can be used for oral step-down therapy. We continue amphotericin B until the patient has shown signs of improvement; this usually takes several weeks. When switching to oral posaconazole, we favor the use of posaconazole delayed-release tablets (300 mg every 12 hours on the first day, then 300 mg once daily) taken with food. We do **not** use the oral suspension of posaconazole since it is not highly bioavailable and requires fatty food for absorption. Loading doses of 200 mg (ie, two capsules) of oral isavuconazole (equivalent to 372 mg of isavuconazonium sulfate) should be given every 8

hours for six doses, followed by 200 mg orally once daily starting 12 to 24 hours after the last loading dose.

Reference :-

1. Al-Ajam, MR, Bizri, AR, Mokhbat, J, Weedon, J, Lutwick, L. Mucormycosis in the Eastern Mediterranean: a seasonal diseaseexternal icon. Epidemiol Infect. 2006 Apr 134(2):341-6.
2. About Mucormycosis". www.cdc.gov. May 25, 2021.
3. Bernal-Martínez L, Buitrago MJ, Castelli MV, Rodriguez-Tudela JL, Cuenca-Estrella M. Development of a single tube multiplex real-time PCR to detect the most clinically relevant Mucormycetes species. Clin Microbiol Infect. 2013;19:E1-7. [PubMed].
4. BMJ Group and the Pharmaceutical Press. September 2021 – March 2021. p. 629-635. ISBN 978-0-85711-369-6.
5. Cornely, Oliver A. (December 1, 2019). "Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium". The Lancet Infectious Diseases. 19 (12): e405–e421. doi:10.1016/S1473-3099(19)30312-3. ISSN 1473-3099. PMID 31699664. (several authors).
6. Dannaoui, Eric; Lackner, Michaela (March 2020). "Special Issue: Mucorales and Mucormycosis". Journal of Fungi. 6 (1): 6. doi:10.3390/jof6010006.
7. Farmakiotis D, Kontoyiannis DP. Mucormycoses. Infect Dis Clin North Am 2016; 30:143.
8. For Healthcare Professionals | Mucormycosis | CDC". www.cdc.gov. June 17, 2020. Retrieved May 25, 2021.
9. Hammond SP, Bialek R, Milner DA, Petschnigg EM, Baden LR, Marty FM. Molecular methods to improve diagnosis and identification of mucormycosis. J Clin Microbiol 2011;49:2151-2153. [PubMed.
10. Helen Ogden-Grable; Gary W. Gill (2005-08-17). "Selecting The Venipuncture Site". American Society for Clinical Pathology. P. 4. Retrieved 2008-12-22
11. Hernández, JL; Buckley, CJ (January 2021). "Mucormycosis". PMID 31335084.
12. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis 2000; 30:851
13. Lanternier F, Sun HY, Ribaud P, et al. Mucormycosis in organ and stem cell transplant recipients. Clin Infect Dis 2012; 54:1629.
14. Mubark, N. N., Jalil, A. T., &Dilfi, S. H. (2020). DESCRIPTIVE STUDY OF HYDATIDIFORM MOLE ACCORDING TO TYPE AND AGE AMONG PATIENTS IN WASIT PROVINCE, IRAQ. Global Journal of Public Health Medicine, 2(1), 118-124.
15. Legrand M, Gits-Muselli M, Boutin L, et al. Detection of Circulating Mucorales DNA in Critically Ill Burn Patients: Preliminary Report of a Screening Strategy for Early Diagnosis and Treatment. Clin Infect Dis 2016; 63:1312.
16. Lewis RE, Kontoyiannis DP. Epidemiology and treatment of mucormycosisexternal icon. Future Microbiol. 2013 Sep;8(9):1163-75.
17. Jalil, A. A. T. EPIDEMIOLOGY OF CERVICAL CANCER AND HIGH RISK OF HUMAN PAPILLOMA VIRUS IN PATIENT. ББК 28.6 З, 85(7).
18. McDonald, Philip J. (September 10, 2018). "Mucormycosis (Zygomycosis): Background, Etiology and Pathophysiology, Epidemiology". Medscape.
19. Maertens J, Demuynck H, Verbeken EK, et al. Mucormycosis in allogeneic bone marrow transplant recipients: report of five cases and review of the role of iron overload in the pathogenesis. Bone Marrow Transplant 1999; 24:307.

20. McDonald, Philip J. (September 10, 2018). "What is the role of isavuconazole (Cresemba) in the treatment of mucormycosis (zygomycosis)?".www.medscape.com. Retrieved May 25, 2021.
21. JALIL, A. T., DILFY, S. H., KAREVSKIY, A., & NAJAH, N. (2020). Viral Hepatitis in Dhi-Qar Province: Demographics and Hematological Characteristics of Patients. International Journal of Pharmaceutical Research, 12(1).
22. MedlinePlus Medical Encyclopedia: Mucormycosis". Retrieved May 19, 2008.
23. Mehta S, Pandey A. Rhino-Orbital Mucormycosis Associated With COVID-19. Cureus 2020; 12:e10726.
24. Mezal, E. H., Yousif, A. F., Hanan, Z. K., Hanan, A. K., & Jalil, A. (2020). Isolation, Assessment of Antimicrobial Sensitivity of Bacterial Pathogens from Post-Cesarean section Infection of patients in Thi-Qar Province. European Journal of Molecular & Clinical Medicine, 7(3), 958-964.
25. Mekonnen ZK, Ashraf DC, Jankowski T, et al. Acute Invasive Rhino-Orbital Mucormycosis in a Patient With COVID-19-Associated Acute Respiratory Distress Syndrome. Ophthalmic PlastReconstrSurg 2021; 37:e40.
26. Monte Junior ESD, Santos MELD, Ribeiro IB, et al. Rare and Fatal Gastrointestinal Mucormycosis (Zygomycosis) in a COVID-19 Patient: A Case Report. ClinEndosc 2020; 53:746.
27. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosisexternal icon. Clin Infect Dis. 2012 Feb;54 Suppl 1:S23-34.
28. Placik DA, Taylor WL, Wnuk NM. Bronchopleural fistula development in the setting of novel therapies for acute respiratory distress syndrome in SARS-CoV-2 pneumonia. Radiol Case Rep 2020; 15:2378.
29. Dilfy, S. H., Hanawi, M. J., Al-bideri, A. W., & Jalil, A. T. (2020). Determination of Chemical Composition of Cultivated Mushrooms in Iraq with Spectrophotometrically and High Performance Liquid Chromatographic. Journal of Green Engineering, 10, 6200-6216.
30. Rebecca J. Frey. "Mucormycosis". Health A to Z. Archived from the original on May 18, 2008. Retrieved May 19, 2008.
31. Jaleel, A. T. (2018). SURVEY THE PREVALENCE OF VIRAL HEPATITIS A, B, C INFECTION IN DHI-QAR PROVINCE (IRAQ). ББК 20.1 А43 Редакционнаяколлегия: ИБ Заводник (отв. ред.), АЕ Каревский, ОВ Янчуревич, ОВ Павлова, 95.
32. Reid, Gail; Lynch, Joseph P.; Fishbein, Michael C.; Clark, Nina M. (February 2020). "Mucormycosis". Seminars in Respiratory and Critical Care Medicine. 41 (1): 99–114. Doi:10.1055/s-0039-3401992. ISSN 1098-9048. PMID 32000287.
33. Jalil, A. T. (2020). COVID-19 most affected age groups and lethality in Europe, Glob. J. Public Health Med, 2, 179-184.
34. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human diseaseexternal icon. Clin Microbiol Rev 2000; 13:236-301
35. Richardson M. The ecology of the Zygomycetes and its impact on environmental exposureexternal icon. ClinMicrobiol Infect. 2009 Oct;15 Suppl 5:2-9.
36. Jalil, A. T., &Karevskiy, A. (2020). The Cervical Cancer (CC) Epidemiology and Human Papillomavirus (HPV) in the Middle East. International Journal of Environment, Engineering & Education, 2(2), 7-12.
37. Richardson MD, Shankland GS. Rhizopus, Rhizomucor, Absidia, and other agent of systemic and subcutaneous zygomycosis. In: Murray PR, Baron EJ, Pfaller MA, Tenover

FC, Yolken RH (eds): Manual of Clinical Microbiology, ed 7. Washington D.C, ASM Press, 1999:1242-1258.
38. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported casesexternal icon. Clin Infect Dis. 2005 Sep 1;41(5):634-53.
39. Spellberg B, Edwards Jr. J, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and managementexternal icon. Clin Microbiol Rev. 2005 Jul;18(3):556-69.
40. Trifilio SM, Bennett CL, Yarnold PR, et al. Breakthrough zygomycosis after voriconazole administration among patients with hematologic malignancies who receive hematopoietic stem-cell transplants or intensive chemotherapy. Bone Marrow Transplant 2007; 39:425.
41. Walsh TJ, Gamaletsou MN, McGinnis MR, Hayden RT, Kontoyiannis DP. Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis(zygomycosis). Clin Infect Dis 2012;54:S55-60. [PubMed].
42. Werthman-Ehrenreich A. Mucormycosis with orbital compartment syndrome in a patient with COVID-19. Am J Emerg Med 2021; 42:264.e5.
43. Marofi, F., F. Abdul-Rasheed, O., SulaimanRahman, H., Setia Budi, H., Jalil, A. T., ValerievichYumashev, A., ... &Jarahian, M. CAR-NK cell in cancer immunotherapy; A promising frontier. Cancer Science.
44. Hanan, Z. K., Saleh, M. B., Mezal, E. H., & Jalil, A. T. (2021). Detection of human genetic variation in VAC14 gene by ARMA-PCR technique and relation with typhoid fever infection in patients with gallbladder diseases in Thi-Qar province/Iraq. Materials Today: Proceedings.
45. Saleh, M. M., Jalil, A. T., Abdulkareem, R. A., & Suleiman, A. A. (2020). Evaluation of immunoglobulins, CD4/CD8 T lymphocyte ratio and interleukin-6 in COVID-19 patients.
46. Jalil, A. T., Al-Khafaji, A. H. D., Karevskiy, A., Dilfy, S. H., & Hanan, Z. K. (2021). Polymerase chain reaction technique for molecular detection of HPV16 infections among women with cervical cancer in Dhi-Qar Province. Materials Today: Proceedings.