Letter to Editor

Intracranial Mucormycosis (Zygomycosis): An emerging opportunistic infection

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Sir,

We would like to address the health care impact of Mucormycosis (Zygomycosis) and the need to formulate the national health policy.

Mucormycosis is a potentially life threatening angioinvasive opportunistic infection caused by a group of relatively ubiquitous fungi belonging to the order Mucorales. It affects immunocompromised and diabetic individuals commonly presenting as rhino-orbito-cerebral and pulmonary mucormycoses.

It is the third most common invasive mycosis with an annual economic burden of $50 million in United States alone. This burden is expected to rise with an increase in prevalence of the major risk factors viz. diabetes, aggressive cancer treatment and increasing transplant procedures.[1,2] In the 929 cases of mucormycosis observed between 1940 to 2003 the most common risk factors were; diabetes mellitus (36%), hematologic malignancies (17%) and hematologic cell transplantation (12%).[3] However studies conducted later have indicated a sustained decline in diabetes mellitus as a risk factor due to the concomitant use of statins that have a fungistatic role in-vitro.[4]

The clinically important genera of Mucorales are Rhizopus, Mucor, Rhizomucor, Cunninghamella, Absidia, Saksenaea, and Apophysomyces; Rhizopus oryzae being most common. The fungi are relatively ubiquitous and found abundantly in soil and decaying organic matter. Microscopically, they have broad, non-septate irregularly branched hyphae.

Despite having abundant exposure to the spores, humans rarely contract mucormycosis which is a hallmark of an intact immune system. Diabetes mellitus is the commonest risk factor for mucormycosis, esp. with most cases having ketoacidosis; since high glucose and acidic conditions promote the growth of the fungus. Hematologic malignancies, associated chemotherapy, hemopoetic cell transplant (HCT), immunosuppressive therapy and graft versus host disease are all known risk factors for mucormycosis due to reduced host immune response. Prolonged Voriconazole prophylaxis given with HCT is an independent risk factor.[5]

Deferoxamine administered as an iron-chelating agent in iron overload esp. after recurrent blood transfusions have known to increase chances of mucormycosis both independent of each other. Feroxamine, (Deferoxamine after iron-chelation) serves as a siderophore promoting fungal growth. Other iron-chelators, Deferasirox and Deferiprone don't serve as siderophores and might reduce tissue fungal load.[6,7] Catheters, adhesive bandages, endoscopes and also contaminated linen have been known to be associated with nosocomial mucormycosis.[8,9] A case of necrotizing enterocolitis has been reported after contaminated probiotic administration to a premature neonate due to Rhizopus oryzae.[10] Apophysomyces trapeziformis infection was

observed in form of mucormycosis of soft tissue injuries after 2011 Joplin tornado in Missouri, US. Mucormycosis manifest as locally and sometimes invades the surrounding tissue and blood vessel due to its affinity for and ability to dissolve elastin in the tunica intima. Rhino-orbito-cerebral mucormycosis (39%) starts with spore infection of the sinuses, destroys the turbinates and the palate. Nasal mucormycosis presents as perinasal swelling, palatal and nasal eschars. It may also erode the walls of the ethmoidal sinus and impinge on the frontal lobe causing obtundation. Invasion of the orbit may cause proptosis, periorbital edema and even blindness. Contiguous invasion into the sphenoidal sinus and adjacent cavernous sinus results in cranial nerve palsies and cavernous sinus thrombosis. Pulmonary mucormycosis (24%) involves spore inhalation into the alveoli that invades the blood vessels. Dermatological mucormycosis (19%) and gastrointestinal mucormycosis are associated with soft tissue ulcers and eschars.

Diagnosis of mucormycosis is based on clinical judgment and microscopic observation of broad (5-15 nm) non-septate irregularly branched hyphae of Mucorales c.f. narrow, septate regularly branched Aspergillus. It is generically typed by PCR and confirmed on biopsy of the tissue on autopsy which serves as a 'gold standard' diagnosis. Intracranial Mucormycosis is a potentially life threatening local and invasive disease and warrants urgent surgical and medical intervention. The first line therapy includes surgical debridement of the eschar and IV liposomal Amphotericin B. Oral Posaconazole is used as a step-down maintenance therapy for Amphotericin responsive patients. Elimination of underlying predisposing factors such as diabetes ketoacidosis, Deferoxamine is also a prudent strategy. IV Posaconazole can be used as salvage therapy for patients unresponsive or not tolerating IV Amphotericin B.

Despite of early diagnosis and treatment mortality remains high with mucormycosis. In disease limited to sinuses it has the best outcomes. In rhino-orbito-cerebral mycosis it ranges from 25-62% depending on the degree of CNS involvement.[3] Pulmonary disease has a much higher mortality ranging from 70- 85%.[3] This is in part due to inability to excise the deep tissue. Disseminated disease have the least favorable outcomes with mortality as high as 90-100%.[3] Even in the patients who have survived there is considerable morbidity and the risk of re-infection persists. There is emphasis being made on the development of a vaccine for high risk patients.

We would like to emphasize the results of the study on economic feasibility by Ibrahim, Edwards et al, targeted deployment of an anti-mucormycosis vaccine that would result in a net cost per quality adjusted life year saved (QUALY) of $17,249. The vaccine priced between $150-300 (adjusted for inflation) would likely be cost effective and marketable.[11] So far such an attempt is yet to be made.

Most of the current studies are retrospective and limited. Larger prospective studies directed to accurate diagnosis are necessary to device a diagnostic protocol for physicians. It will improve chances of increased ante-mortem diagnosis and hence management in currently underdiagnosed conditions like gastrointestinal mucormycosis (25%).[12] Clinicians must have high degree of suspicion in patients with risk factors. For example, any diabetic patient with headache and visual changes is a candidate for prompt evaluation using imaging studies and nasal endoscopy to rule out mucormycosis.[12]

Also, there is need for a national disease registry for reporting cases of mucormycosis. It will help in devising effective prognostic criteria, identifying the incidence and disease burden, trends and health impact of mucormycosis. Collaboration of prospective data from Centers for Disease Control and Prevention TRANSNET network monitoring transplant patients

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and PATH Alliance working with immunosuppressed patients needs to be done to device public health strategies fortified by epidemiological evidence. [13]

References :

1. Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev. 2005 Jul;18(3):556-69.

2. Kontoyiannis DP, Lionakis MS, Lewis RE, Chamilos G, Healy M, Perego C, Safdar A, Kantarjian H, Champlin R, Walsh TJ, Raad II. Zygomycosis in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis. 2005 Apr 15;191(8):1350-60.

3. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP, Walsh TJ. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005 Sep 1;41(5):634-53.

4. Lanternier F, Dannaoui E, Morizot G, Elie C, Garcia-Hermoso D, Huerre M, Bitar D, Dromer F, Lortholary O; French Mycosis Study Group. A global analysis of mucormycosis in France: the RetroZygo Study (2005-2007). Clin Infect Dis. 2012 Feb;54 Suppl 1:S35-43.

5. Kontoyiannis DP, Lionakis MS, Lewis RE, Chamilos G, Healy M, Perego C, Safdar A, Kantarjian H, Champlin R, Walsh TJ, Raad II. Zygomycosis in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis. 2005 Apr 15;191(8):1350-60.

6. Ibrahim AS, Edwards JE Jr, Fu Y, Spellberg B. Deferiprone iron chelation as a novel therapy for experimental mucormycosis. J Antimicrob Chemother. 2006 Nov;58(5):1070-3. Epub 2006 Aug 23. PubMed PMID: 16928702.

7. Ibrahim AS, Gebermariam T, Fu Y, Lin L, Husseiny MI, French SW, Schwartz J, Skory CD, Edwards JE Jr, Spellberg BJ. The iron chelator deferasirox protects mice from mucormycosis through iron starvation. J Clin Invest. 2007 Sep;117(9):2649-57.

8. Rammaert B, Lanternier F, Zahar JR, Dannaoui E, Bougnoux ME, Lecuit M, Lortholary O. Healthcare-associated mucormycosis. Clin Infect Dis. 2012 Feb;54 Suppl 1:S44-54.

9. Kanamori H, Rutala WA, Sickbert-Bennett EE, Weber DJ. Review of fungal outbreaks and infection prevention in healthcare settings during construction and renovation. Clin Infect Dis. 2015 Aug 1;61(3):433-44.

10. Vallabhaneni S, Walker TA, Lockhart SR, Ng D, Chiller T, Melchreit R, Brandt ME, Smith RM; Centers for Disease Control and Prevention (CDC). Notes from the field: Fatal gastrointestinal mucormycosis in a premature infant associated with a contaminated dietary supplement--Connecticut, 2014. MMWR Morb Mortal Wkly Rep. 2015 Feb 20;64(6):155-6.

11. Ibrahim AS, Edwards JE Jr, Bryant R, Spellberg B. Economic burden ofmucormycosis in the United States: can a vaccine be cost-effective? Med Mycol. 2009;47(6):592-600.

12. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis. 2012 Feb;54 Suppl 1:S23-34.

13. Bitar D, Lortholary O, Le Strat Y, Nicolau J, Coignard B, Tattevin P, Che D, Dromer F. Population-based analysis of invasive fungal infections, France, 2001-2010. Emerg Infect Dis. 2014 Jul;20(7):1149-55.