Commentary

Cutaneous zygomycosis: major concerns

Till two decades back zygomycosis due to fungi belonging to the class Zygomycetes and the order Mucorales was considered rare fatal opportunistic fungal infection. In the recent past, zygomycosis is emerging throughout the world in part due to continued rise of diabetics and the increased use of immunosuppressive agents, but the rise in India is phenomenal. The rise in incidence had been reported systematically from one tertiary care center in India (13 cases/year during 1990-1999, to 35 cases/year during 2000-2004, and to 50 cases/year during 2006-2007). However, the awareness about the rise in cases of zygomycosis is restricted only to a few centers in India, and the rise is largely associated with uncontrolled diabetes mellitus. Based on clinical presentation and involvement of particular anatomical site, the disease is categorized into six clinical types: rhino-orbito-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous. With increased awareness about the disease in recent years, the clinicians to certain extent recognize zygomycosis in differential diagnosis of opportunistic infections in particular group of patients like uncontrolled diabetes, haematological malignancy undergoing chemotherapy, haematological stem cell transplant recipients. However, the diagnosis of cutaneous zygomycosis, though easy as the infection occurs in exposed part of the body, is frequently either missed or delayed due to lack of awareness and absence of any underlying illness in nearly 50 per cent of patients.

Cutaneous zygomycosis may be primary by direct inoculation in skin or secondary to dissemination from a distant focus seeding the bloodstream. Although dissemination from the skin to other organs is relatively common, the dissemination to the skin from distant focus (reverse dissemination) is rare. In the review by Roden et al. of 176 cases of cutaneous zygomycosis only 3 per cent patients had this reverse dissemination.

The cutaneous zygomycosis is described with underlying disease such as haematological malignancies, uncontrolled diabetes, solid organ transplantation, steroid or other immunosuppressive therapies, and metabolic acidosis. In infants and neonatal patients, prematurity and low birth weights
(< 1500 g at birth) are important underlying conditions. However, a large proportion (30-50%) of patients is apparently immunocompetent. Similarly the series of Chander et al had only one patient with diabetes mellitus. To develop cutaneous zygomycosis breach of skin is essential for the zygomycetes to enter, as intact cutaneous barrier serves as structural defense against tissue invasion. Trauma in general is the major cause of cutaneous zygomycosis especially in immunocompetent host and it may be minor injury like insect bite, stings and even pecking of birds; or may be major like road traffic accidents or crush injuries. Contact with soil and vegetation containing the zygomycetes greatly enhances the chance of cutaneous zygomycosis. The disease has also emerged as nosocomial infection. In the review of 78 cases of cutaneous zygomycosis, 36 per cent patients acquired the infection in hospitals. Poor infection control practices associated with injury due to intravenous access, adhesive tapes, occlusive dressings, burn wound, and post-operative wound are considered as mode of entry of zygomycetes in hospital. Interestingly from India or other developing countries many cases of cutaneous zygomycosis were reported at the site of intramuscular injection. In the series of Chander et al, 44 per cent patients developed cutaneous zygomycosis at injection sites. This is very disturbing and indicates poor medical care practices in the developing countries. Surgical wound zygomycosis or infections after occlusive plaster equally highlights the requirement of improvement of hospital care practices.

The cutaneous zygomycosis proceed through three stages depending on host competence and virulence of the fungi. Initially it produces localized disease when the infection is confined to cutaneous or subcutaneous tissue. Without any management intervention or depending on host immunity, the infection may invade muscle, tendon or bone, which is classified as deep extension of infection or it may spread through blood vessels to non-contiguous site as disseminated infection. Diagnosis at the early stage of the disease is desirable as the mortality varies at 4-10 per cent in localized infection, 26-29 per cent in deep extension and 83-94 per cent in disseminated disease. All patients in the report presented with necrotizing lesions (necrotizing fasciitis) and had 55 per cent mortality. The mortality was high due to delay in diagnosis.

*Rhizopus oryzae* is the commonest fungus isolated from zygomycosis including cutaneous form. Other fungi occasionally isolated include *Mucor* species, *Absidia corymbifera*, *Rhizomucor pusillus*, *Apophysomyces elegans*, *Saksenaea vasiformis*, *Mucor* species, and *Cunninghamella bertholletiae*. It is important to note that Chander et al isolated *A. elegans* from four of their six patients. *A. elegans* is an emerging zygomycete in India. The fungus is found abundantly in tropics and subtropical areas. Besides India, *A. elegans* infections have been documented from southern USA, North and Western Australia, Mexico, Caribbean islands, Colombia, Venezuela. However, of nearly 100 cases with *A. elegans* infections published in literature, a major portion (~60%) of cases was reported from India. The fungus does not readily sporulate in standard laboratory media and the microbiologist may find it difficult to identify. A special nutrient deficient growth medium, a high temperature and prolonged incubation may be used to induce *A. elegans* isolates to sporulate. Given this problem in delay in identification, DNA based molecular techniques show enormous potential for rapid and accurate identification of the fungus. *S. vasiformis*, another difficult to sporulate fungus, also produces cutaneous zygomycosis and has been isolated from multiple centers of this country.

Awareness amongst the clinicians, as has been stressed earlier, is the key factor for early diagnosis of cutaneous zygomycosis. Confirmation of diagnosis depends on obtaining tissues for histopathology, direct microscopy and culture. The biopsy specimen should be taken from the centre of the lesion especially from black eschar area and include subcutaneous fat, as zygomycetes frequently invade blood vessels of the dermis and subcutis. Though zygomycetes rapidly grow on ordinary media, in a high proportion of cases with cutaneous zygomycosis cultures do not yield a fungus. Broad asceptate ribbon shaped hyphae on direct microscopy helps in diagnosis in such cases. Occasionally concomitant Gram-negative bacterial infection is associated with cutaneous zygomycosis.

The best management strategy for cutaneous zygomycosis is extensive surgical debridement combined with antifungal therapy and control of the underlying illness where possible. The lesion should be closely monitored and at the first indication of disease progression debridement should be repeated. Amputation may occasionally be required in extensive infection over extremities. Amphotericin B (conventional or liposomal) is chosen as the first line of therapy. Posaconazole as a substitute for amphotericin B is gaining popularity in recent years especially as
salvage therapy, though the drug is still not available in Indian market. In conclusion, a high index of suspicion and early aggressive management may improve the outcome in cutaneous zygomycosis.

Arunaloke Chakrabarti
Department of Medical Microbiology
Postgraduate Institute of Medical Education & Research
Chandigarh 160 012, India
arunaloke@hotmail.com

References


