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Rhinosporidiosis ,a chronic granulomatous infection of humans, and animals, is caused by an agent of uncertain taxonomy *Rhinosporidium seeberi*. Recent molecular evidence has indicated that the organism earlier considered as fungus is now a protistan parasite.The disease is recorded from many counties of the world but it is endemic in India, and Sri Lanka. Rhinosporidiosis affects both sexes with preponderance in males. How the disease is acquired still remains a great enigma. The principal site of infection is usually the nasal mucous membranes, and infrequently the skin, and other tissues of humans, and animals. The natural habitat of *R.seeberi* is thought to be stagnant water. Many attempts to isolate the pathogen on various cultural media were unsuccessful.The diagnosis of this pseudofungal infection is mainly based on the demonstration of characteristic structure on histopathological examination of tissue. Cytological examination of aspirates from lumps or smears of secretions with PAS technique is also very useful to detect *R.seeberi*. Hence, cytodiagnosis can be recommended as a simple, economical, and reliable method to confirm the disease both in humans and animals in laboratories with no facility for histopathology. Surgical excision of the lesions is considered the main stay of management of the disease, though recurrence may occur in the absence of complete excision. Further studies on the ecology, epidemiology, pathogenesis, diagnosis , and chemotherapy are needed to understand this enigmatic disease.

Key words: Animal**,** human, nasal mucosa, Mesomycetozoa, pseudoparafungal, Rhinosporidiosis, *Rhinosporidum seeberi*

INTRODUCTION

Rhinosporidiosis is a non-contagious, sporadic, benign, usually nonfatal, and chronic granulomatous disease of humans and animals (Pal,2007).The disease is caused by *Rhinosporidium seeberi*, an organism that was previously classified as a fungus but has been regrouped into the class Mesomycetozoa (family *Rhinosporideacae*). This class consists of several parasitic and saprophytic organisms, most of which infect fish and amphibians; only *R. seeberi* infects mammals (Adl *et al*, 2005). Rhinosporidiosis is endemic to India and Sri Lanka, although cases have been reported in Africa, the Americas, and Europe (Karunaratne,1964; McClatchie and

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Bremner,1969; Fredricks *et al*, 2000; Ali *et al*, 2001; Loh *et al*, 2001; Hussein and Rashad,2005; Pfaller and Diekema,2005; Pal, 1995, 2007). Most affected patients have a history of temporary or permanent residence within rhinosporidiosis- endemic areas. Rhinosporidiosis is predominantly a human disease, however, it has been documented in many other species, including cats, dogs, equine, cattle, and waterfowl (Pal, 2007). Disease commonly causes single or multiple, sessile or pedunculated, papillomatous lesions on the nasal mucosa and less frequently the ocular mucosa. These masses are painless, slow-growing, and non-infiltrating. Surgical excision of the polypoid growth is the only treatment to provide relief to the patient (Pal , 2007).

The natural habitat of *R. seeberi* is thought to be stagnant water, although isolation of the organism from such environments has not been successful so far (Arseculeratne, 2005; Pal, 2007). Nonetheless, epidemiologic evidence supports this hypothesis; the only report of an outbreak originating within Europe was associated with persons bathing in a lake in Serbia (Vukovic *et al*, 1995). The infection is linked to swimming or bathing in freshwater ponds, lakes or rivers (Kennedy *et al*,1995; Pal,2007). The typical location of *R. seeberi* associated lesions in all species is the nasal mucosa, and therefore, drinking from contaminated water is likely the source of infection (Kennedy *et al*, 1995), possibly through superficial wounds in the mucosa (Pal, 2007). In addition, dust particles are possible fomites for endospores of *R.seeberi* to cause ocular disorder (Arseculeratne, 2005).The present paper is an attempt to highlight the significance of *R. seebei* as an enigmatic pseudofungal pathogen of humans and animals.

ETIOLOGY

The disease is caused by *Rhinosporidium seeberi*, an unusual unicellular pathogen that is difficult to culture, and whose taxonomic classification has been controversial. *R.seeberi* had first been regarded as a sporozoon by Malbran, its discoverer, in 1892, and then as a protozoan by Seeber who first published a description of the pathogen, and later, as a Phycomycete (Ashworth, 1923). Through molecular biological analysis of the organism's ribosomal DNA classified the organism in a new clade, which was named as the *Mesomycetozoa*. It includes fish and amphibian pathogens in the former DRIP clade (*Dermocystidium*, the rossette agent, *Ichthyophonus* and *Psorospermium*). It is of interest that the histopathology of these fish and amphibian diseases closely resembles that of rhinosporidiosis. In addition, the morphological similarities were noted between *R.seeberi* and these pathogens. It was speculated by Herr and co-investigators (1999) that some of these pathogens could be classified in the genus *Rhinosporidium* with the suggestion that *Rhinosporidium* is a monotypic genus. An independent group of workers supported this conclusion concerning taxonomy, in that their analysis of *R.seeberi* 18S rRNA from infected tissue showed that this organism is a protist "from a novel clade of parasites that infect fish and amphibians". These studies finally resolve the debate on the taxonomy of *R.seeberi*, particularly that it is not a classic fungus "but rather the first known human pathogen from the DRIPs clade, a novel clade of aquatic protistan parasites (Fredricks *et al*, 2000).

HOST

Rhinosporidiosis is reported in humans from several countries (Pal, 2007). Naturally occurring infections have also been diagnosed in buffaloes ,cats, cattle, dogs, ducks, geese, goats, horses, mules, swans, and water fowls (Rao *et al*,1975; Pal and Rao,1989 Pal *et al*,1984; Caniatti *et al*,1998; Leeming *et al*, 2007; Pal, 1995, 2007).

TRANSMISSION

Hitherto, the exact nature of transmission of infection in humans and animals is not known. It is presumed that direct contact of traumatized epithelium, most commonly the nostrils with natural aquatic habitats may act the prime mode of entry of pathogen to the susceptible host (Pal and Rao, 1989; Pal,2007). The occurrence of rhinosporidiosis in river sand workers in India and in Sri Lanka, is particularly relevant to such a mode of infection, through abrasions caused by the sand particles with the pathogen in the putative habitat – ground water. Trauma from *R.seeberi* contaminated stones used for mopping-up residual drops of urine is claimed to be responsible for anterior urethral rhinosporidiosis in the male. The spore of the fungus is present in the cow dung of animal. If people take bath in the contaminated pond or river, they become infected with the spores (Pal,2007).

The mode of transmission of this disease could be

droplet infection that is by close contact with infected humans and animals, contaminated sources like air, soil and water. The spores of *R. seeberi*, which are dormant in the saprophytic sources, become active on implantation over live tissues. The fact that nose is the commonest site of infection strengthens the theory of droplet transmission. Involvement of adjacent sites in the same individual is explained by auto-inoculation (Ahmed *et al,* 2013).The spillage of endospores from the polyps after trauma or surgery is thought to be followed by auto-inoculation through the adjacent epithelium (Karunaratne,1964).

There is evidence for haematogenous spread of rhinosporidiosis to anatomically distant sites (Rajam and Viswanathan,1955) The development of subcutaneous granulomata in the limbs, without breach of the overlying skin, could be attributed to such haematogenous dissemination, from a subclinical, upper respiratory focus of infection. The mode of lymphatic spread of *R.seeberi* infection, however, is controversial. The first report on the occurrence of inguinal lymphadenitis in a case of disseminated rhinosporidiosis, which involved the lower limbs, was described by Arseculeratne in 2002.It is emphasized that the diverse mechanisms of immune evasion by *R.seeberi* needs further detailed studies.

CLINICAL SPECTRUM

Humans

Rhinosporidiosis manifests primarily with the development of red, swollen polyps in the nasal mucosa or the ocular conjunctivae. The polyps are deep red or pink, are sessile or pedunculated, and tend to bleed easily. They are seldom observed outside the nasal cavity in a nasal infection. Gray or yellow spots, which represent the sporangia form of *R. seeberi*, can also often be observed in the polyps. The feeling is most commonly described as foreign body being felt in the nasal passages, while the development of polyps in the ocular conjunctivae is readily visible. The polyps can lead to unilateral nasal obstruction as well as bleeding, although symptoms are variable depending on the location of the polyps. In eye infection, increased tearing can occur as the disease progresses. Photophobia and redness of the eye can also occur.

The nose and nasopharynx are the most common sites of infection, occurring in about 70% of cases (Pal, 2007). The infection of the eye is noticed in about 10% of cases (Arora., 2001).Rarely, the involvement of the skin, ears, genitals, and rectum have also been observed with the development of wart-like lesions in these areas. The lesions in the mouth and upper airways can lead to obstruction, cough, haemoptysis, or painful swallowing (Rivitta 1999). Cutaneous infection is rare, and is often associated with adjacent mucocutaneous infection. In rare cases, profuse dissemination occurs throughout the body, which can be life threatening. Local secondary bacterial infection can also contribute to mortality from the disease, although this is a rare complication.Disseminated rhinosporidiosis is extremely very rare but has been reported by Ho and Tay (1986).

Animals

Clinical findings include wheezing, sneezing, unilateral seropurulent nasal discharge, and epistaxis (Pal, 1995). Polypoid lesions may be visible in the nares, and may also be visualized by rhinoscopy in the nasal cavity. Single or multiple polyps ranging in size from a few millimeters up to 3 cm are pink, red, or pale gray and covered by numerous pinpoint white yellowish granules (sporangia). Polyps may be sessile or pedunculated, and the superficial surface is irregular, glistening, and possibly ulcerated (Caniatti *et al*, 1998).

EPIDEMIOLOGY

The epidemiology of rhinosporidiosis is poorly defined because the exact information on the natural habitat of the causative agent is still not well established. Disease has been reported from about 70 countries of the world with highest incidence from India and Sri Lanka (Jain,1967; McClatichie and Bremner, 1969; Hutt *et al*,1971; Hussein and Rashad,2005;Pal,2007; Deshpande *et al*.,2009). Approximately, 90% of all known cases of disease occur in both the country, where 1.4 % prevalence is estimated (Moses and Shanmugham,1987). Though most cases of human rhinosporidiosis in western temperate and middle eastern countries occurred in expatriate Indians, who probably acquired the disease in their native lands, a few cases have been reported in persons, living in the west, who have never travelled to endemic areas. The disease is not contagious, as there is no evidence of direct transmission from man to man or animal

to man (Pal, 2007). In addition to numerous cases in humans, rhinosporidiosis has also been documented in several species of farm, domestic and wild animals. The natural infection is recorded in several species of mammals and avians (Rao *et al,* 1975; Pal, 1995; Caniatti *et al*,1998; Leeming *et al,* 2007; Pal, 2007). Most bovines, equines and canines cases are reported from India, and USA (Caniatti *et al*,1998).The majority of cases are sporadic. The single outbreak of ocular and nasal rhinosporidiosis in humans was recorded in Serbia by Vukovic and others (1995), and the lake where all the patients took bath, was incriminated as the source of *R. seeberi*. Kennedy and co-workers (1995) described an outbreak of ocular and cutaneous rhinosporidiosis in swans from Florida, USA. Though hundreds of persons bathe in the stagnant waters, only a few develop progressive disease. Comprehensive and systematic studies should be conducted to elucidate the reason/s for the rare occurrence of disease in persons, who often come in contact with contaminated water.

DIAGNOSIS

Rhinoscopy can reveal nasal polypoid lesions both in humans and dogs (Caniatti *et al*.,1988). The definitive diagnosis of rhinosporidiosis is made by histopathology of biopsied or resected tissues, with the identification of the pathogen in its diverse stages.

Cytodiagnosis on aspirates from rhinosporidial lumps or on smears of secretions from the surfaces of accessible polyps and fine-needle aspirates from lumps provide, with suitable stains, distinctive diagnostic features has been recommended (Arseculeratne, 2002; Sinha *et al,* 2012).The periodic acid-Schiff stain will discriminate between these, as the endospores stain markedly magenta while the epithelial cells are PAS-negative. The presence of electron dense bodies in the endospores is useful in confirmation of rhinosporidial identity (Kennedy *et al*, 1995; Thianprasit and Thagernpol, 1989).

TREATMENT

Although spontaneous regression have been recorded in few cases, the mode of treatment remains surgical. The recurrence of disease occurs in 5 to 10 % of cases (Pal, 2007). In order to avoid recurrence, total excision of the polyp, preferably by electrocautery, is recommended (Pal, 2007). Pedunculated polyps permit of radical removal, while excision of sessile polyps with broad bases of attachment to the underlying tissues are sometimes followed by recurrence due to spillage of endospores on the adjacent mucosa. Extensive growths, as on the penis, might require amputation of the affected site. The failure to propagate *R.seeberi* in vitro from clinical and environmental samples on various nutrient media (Pal *et al.,*1984), and the inability to establish experimental rhinosporidiosis, have prevented the determination of the sensitivity of *R. seeberi* to drugs that might have clinical application. Several anti-bacterial and anti-fungal drugs have been tested clinically, but without any success. The only drug, which was found to have some anti-rhinosporidial effect is dapsone (Pal 2007). This drug appears to arrest the maturation of the sporangia, and to promote fibrosis in the stroma, when used as an adjunct to surgery. Hence, there is a special need to develop drug therapies, which can be safely used to treat humans and animals without any side effects. In animals, the surgical excision of the lesions is considered standard, but recurrence is common. Amphotericin B, Ketaconazole and Itraconazole have been described for treatment, but are generally not as effective as surgery (Pal, 2007).

PREVENTION AND CONTROL

Currently, no vaccine or chemotherapeutic agent is commercially available to manage the cases of rhinosporidiosis in humans or animals. The identification of *R. seeberi* in a deposit of ground water suggest that preventive measures against the acquisition of rhinosporidial infection by bathers may include the avoidance of trauma from vigorous immersion in the water. It is surmised that spicules, derived from sand particles, could act as a predisposing factor for colonization. Sand-workers, who are among those predisposed to nasal rhinosporidiosis, could be advised to avoid collection of river-bed sand by diving, and to use a sand-scoop attached to a long handle, actuated from above the surface of the water, instead. Avoid swimming in stagnant fresh water ponds, lakes, or rivers, and also use cleaned ponds water areas for animals as well as humans (Pal, 2007; Kumara *et al*, 2008). The person with trauma on the mucosa of the nose, nasopharynx, or eye should not come in direct contact with contaminated water (Pal, 2007).

CONCLUSION

Rhinosporidiosis is endemic to India and Sri Lanka, although cases have been reported in Africa,

America, and Europe. It is predominantly a human disease, however, it has been described in several animal species, including cats, dogs, and cattle. The etiological agent, *Rhinosporidium seeberi*, in recent studies has been established as an aquatic protistan parasite. The definitive diagnosis of rhinosporidiosis is by histopathology of biopsied or resected tissues, with the identification of the pathogen in its diverse stages, rather than the stromal, and cellular responses of the host. Cytology is useful where facility of histopathology is non-existent. The pathogen should be differentiated from *Chrysosporium parvuam*, and *Coccidioides immitis*. Pharmacologic treatment has not been successful, probably because of the impenetrability of the sporangial wall. The natural habitat, transmission and cultural characteristics remain poorly understood. The trauma to the mucous membrane is considered an important risk factor that may predispose the humans as well as animals to the infection. The source and reservoir of *R. seeberi* infection are not clearly known. Hence, it seems highly imperative to undertake comprehensive studies to elucidate the exact source, and reservoir of infection so that the strategies to control the disease in humans as well as in animals can be undertaken.

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