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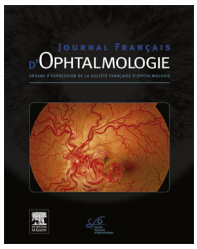

GENERAL REVIEW

Fungal keratitis☆

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Summary Fungal keratitis, or keratomycoses, are corneal infections which must be considered in cases of corneal trauma, prior corneal surgery, chronic ocular surface disease, topical corticosteroids or contact lens wear. Filamentous fungi or yeasts may be involved. Presenting clinical features such as corneal infiltrates with feathery edges and/or raised surface, intact epithelium with deep stromal involvement, satellite lesions, endothelial plaques, lack of improvement with antibiotics and worsening with steroids are suggestive of fungal keratitis.

Corneal scraping for laboratory examination is mandatory. Medical management with antifungal eye drops and systemic agents should be started as soon as possible. Surgical interventions are required in a significant number of cases to control the infection. The prognosis of fungal keratitis is worse than that of bacterial keratitis.

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Organisms

Over 70 species of fungus have been identified in the setting of keratitis [1]. Fungi may be classified as filamentous fungi or yeasts (Table 1). A third group consisting of dimorphic fungi having both a filamentous phase and a yeast phase is responsible for deep tissue mycoses but rarely keratitis. Filamentous fungi are ubiquitous in the environment, present on plants, in soil, in water and in the air in the form of spores. Yeasts are also widely distributed in the environment (soil, water, objects, food), the digestive or genital tract, and skin.

Infections due to filamentous fungi occur primarily in tropical climates: southern United States, Mexico, Central America, South America, Africa, Middle East, China, India, southeast Asia [2,3]. In these regions, fungal keratitis may represent up to 80% of infectious keratitis.

Yeast-related keratomycoses are, in the very large majority of cases, due to *Candida* or *Cryptococcus*. Local or systemic immunosuppression constitutes the primary risk factor. Yeasts represent approximately 30 to 52% of fungal keratitis observed in countries with temperate climates: Europe, northern United States, Australia [4—7]. In these regions, fungal keratitis represents between 1 and 5% of infectious keratitis.

Pathogenesis

The occurrence of a fungal infection implies an alteration in one or more of the cornea's anti-infectious defense systems (epithelial barrier, tear film, blinking). The inflammatory response to the infection depends on fungal reproduction, mycotoxins, secreted proteolytic enzymes and fungal antigens [8]. Fungi may penetrate the stromal lamellae, attack Descemet's membrane, spread into the anterior chamber and provoke endophthalmitis. The formation of biofilm is an important factor in the pathogenesis, notably for filamentous fungi such as *Fusarium* [9]. Corticosteroids and other immunosuppressive agents facilitate the development of fungal infections by inhibiting transcription of pro-inflammatory cytokines and chemokines. They also decrease the anti-infectious activity of macrophages as well as the ability of neutrophils to adhere [10].

Risk factors

Filamentous fungal infections occur most commonly in healthy corneas in the context of contact lens wear (risk factor found in 25 to 40% of series of keratomycoses) [3—5,11], followed by corneal surgery or corneal trauma with plant material. This may be an indoor or outdoor plant or other types of plant matter (tree branches, fruits, vegetables). Certain professions involving outdoor activities (farming, agriculture, landscaping) are thus particularly at risk, which explains the male preponderance of filamentous fungal infections. There are also seasonal variations, with cases being more frequent in spring and autumn, during the harvest season [2]. Corneal traumas by the fingers, nails, metallic foreign bodies, insects, cow tails and food products have also been reported.

Local or systemic immunosuppression constitutes the primary risk factor for yeast infections [12]. *Candida* and other yeasts are opportunistic fungi, which infect diseased ocular surfaces such as those of corneal grafts, atopic keratoconjunctivitis, severe keratitis sicca, stromal herpes, fibrosing conjunctivitis, neurotrophic keratitis or exposure keratopathy. Certain causes of systemic immunosuppression may be associated with keratomycoses: diabetes, HIV infection, cancer and medication-induced immunosuppression.

Rare cases of fungal keratitis (yeasts and filamentous fungi) have been reported after corneal refractive surgery: LASIK, keratotomies, intracorneal ring segments, corneal cross-linking, or cataract surgery [11].

Clinical diagnosis

One or several risk factors are generally present on the patient's history. Functional signs of keratitis are present and of variable intensity depending on the degree of inflammation. Decreased visual acuity is variable depending on the location of the corneal lesions (infiltrate, edema) with respect to the visual axis, anterior chamber reaction, the presence of secretions and/or tearing reflex.

Biomicroscopy should look for signs suggestive of an active corneal infection: lid edema, conjunctival injection, chemosis, peripheral ring infiltrate, epithelial defect, localized (abscess) or diffuse (keratitis) suppurative stromal infiltrate. The location, color, density, dimensions, shape, edge regularity and depth of the infiltrate should be noted, as well as the existence of areas of melting, necrosis, stromal thinning, peri-lesional edema, satellite infiltrates, neovascularization, endotheliitis, or an anterior chamber reaction (Tyndall effect, hypopyon, fibrin, endothelial plaque). Examination of the cornea adjacent to the infected zone, the contralateral cornea, the lids, conjunctiva, sclera, tear film, anterior chamber and vitreous allow identification of ocular surface disease and/or complications associated with the corneal infection. Corneal sensitivity should be tested if a neurotrophic keratitis is suspected. All of these signs should be recorded in a detailed diagram performed at the initial exam and repeated throughout the follow-up.

Certain signs suggest fungal keratitis (Fig. 1) [13]:

- grayish corneal epithelium with an ulcerated or infiltrated surface; the epithelium is sometimes intact, healed over the stromal infiltrate which extends deeper;
- stromal infiltrate with irregular edges, showing little or no inflammation, which on high magnification may sometimes exhibit filamentous fungal hyphae, explaining the ''fluffy'' appearance of the edges of the infiltrate;
- heaped infiltrate;
- microinfiltrates ''satellite lesions'' disseminated throughout the cornea;