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Abstract
Phaeohyphomycosis is an infection caused by pigment-producing saprophytic fungi. Systemic infections may occur in the immunocompromised patient. Infection in healthy individuals may result in subcutaneous abscess formation. Oral lesions appear to be rare. A case of intraoral phaeohyphomycosis presenting as a well-demarcated, painful nodule of the anterior hard palate in a 12-year-old healthy male is described. The mass was excised and the diagnosis was established following histopathologic examination of the tissue.

Keywords
Oral, Mycosis, Dematiaceous, Cyst, Infection

Introduction
Many species of fungi demonstrate some degree of pigmentation of their cell wall. However, those fungi that are routinely characterized by intense melanin-like pigmentation of their cell walls that is

readily observed in hematoxylin and eosin stained sections are known as phaeoid or dematiaceous fungi [1, 2]. Dematiaceous fungi are ubiquitous saprophytes of the soil, wood and decaying vegetable matter [2]. While considered poorly pathogenic, they may cause skin infection by either traumatic inoculation or by colonization of altered skin [3]. Inhalation of airborne spores is a primary and common route of exposure and accounts for allergic fungal sinusitis by these fungi [1, 2]. Systemic infection is secondary to impaired host resistance [3, 4].

Dematiaceous fungi can produce three different types of infections in humans including phaeohyphomycosis, chromoblastomycosis, and mycetoma. The latter usually presents as a chronic infectious process of the foot [4].

While subcutaneous infections by dematiaceous fungi secondary to traumatic implantation have been described in human subjects, intraoral infection by these microorganisms has been previously reported in at least two cases, one involving the lower labial mucosa [5] and the other infecting a third molar extraction socket [6]. We present a case of oral phaeohyphomycosis within an epithelium-lined cyst of the anterior midline hard palate.

Case Report

A 12-year-old healthy male presented with a painful swelling of the midline of the anterior palate of four days duration. 16 weeks prior to this presentation, the patient had concluded a rapid maxillary expansion appliance therapy and was continuing to receive additional orthodontic treatment. On clinical examination, an oval to fusiform, sessile, midline swelling of the anterior hard palate just posterior to the incisive papilla region, measuring 1.0 cm × 0.5 cm was noted. The mucosa over the swelling was pink in color and had a smooth, uninterrupted surface (Fig. 1). The swelling was soft to palpation and mildly tender to touch. The teeth of the entire maxillary dentition were vital, free from caries and periodontal disease. No other intraoral soft tissue pathology was noted. A maxillary anterior occlusal radiograph showed no intrabony changes (Fig. 2). In the absence of an obvious focus of infection, a provisional diagnosis of an inflammatory condition of unknown etiology was rendered. An excisional biopsy was performed to establish a definitive diagnosis and to plan treatment. The mass appeared brown-black on its deep surface and approximated the content of the posterior most portions of the incisive foramen. During the surgery, a small amount of purulent discharge was noted. Mild saucerization of the underlying bone was observed but there was no evidence of palatal erosion or perforation.

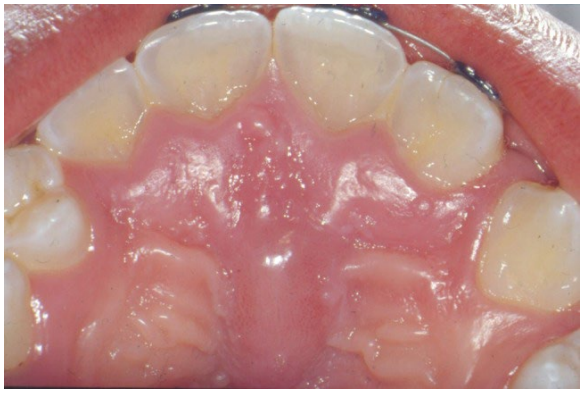

Fig. 1 Oval to fusiform swelling of midline, anterior hard palate

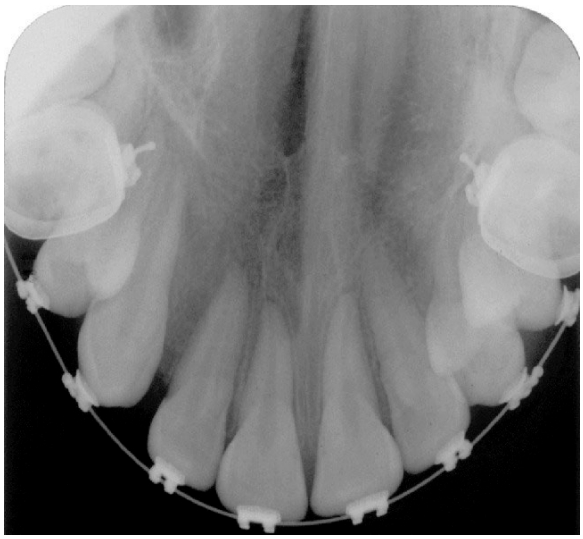

Fig. 2 Maxillary occlusal view X-ray showing no cystic changes

Hematoxylin and eosin stained sections of formalin-fixed tissue revealed an acutely inflamed connective tissue underlying the surface epithelium. Deeper portions of the connective tissue showed a cyst lined by non-keratinized stratified squamous epithelium. The lumen of the cyst was filled with colonies of brownish pigmented fungal forms (Fig. 3 bold arrow). A prominent nerve bundle was observed within the cyst wall (Fig. 3 interrupted arrow). At higher magnification and with Gomori methenamine silver stain (GMS), budding, septated, thick-walled, fungal hyphae were readily identified (Fig. 4a, b). A diagnosis of oral phaeohyphomycosis occurring within a midline soft tissue cyst of the anterior palate was made. The lesion was removed in its entirety and fixed in formalin and therefore a fungal culture was not obtained for species determination.

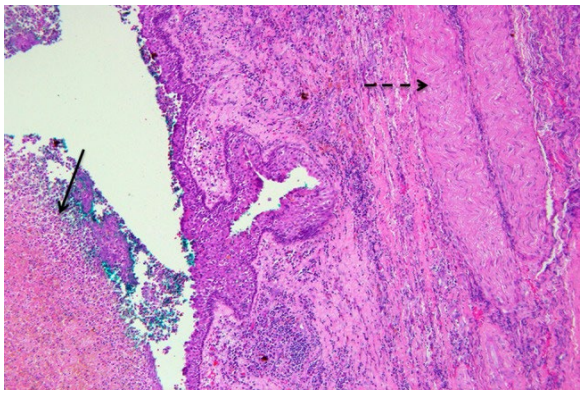

Fig. 3 Epithelium-lined cystic cavity containing mass of fungal organisms [*bold arrow*]. Wall of cyst showing large nerve bundle [*interrupted arrow*] (H&E, ×100)

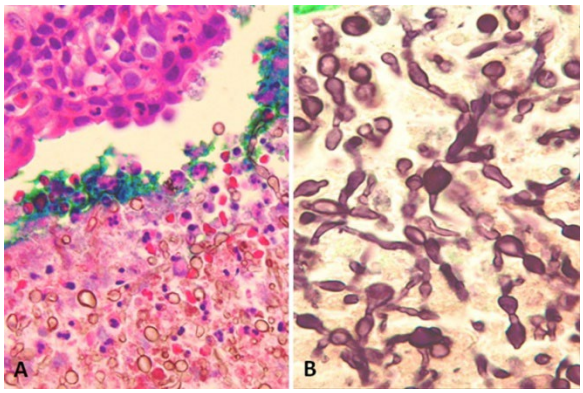

Fig. 4 **a** Naturally pigmented fungal organisms intermixed with neutrophils. (H&E, ×400). **b** Budding, septated fungal hyphae (GMS, ×400)

Due to the unusual nature of this process, the child was questioned further. He revealed that in response to the sensation of the rapid maxillary expansion appliance therapy, he had resorted to rubbing his palate with a twig and may have injured the mucosal surface. The child was immunocompetent and in very good overall health. Excisional removal of the oral lesion was considered curative. One week post-operative healing was uninterrupted and a six week recall visit showed no signs or symptoms of residual or recurrent infection.

Discussion

Opportunistic fungal pathogens are important causes of morbidity and mortality among bone marrow and solid organ transplant patients, those receiving anticancer chemotherapy, and in those with primary or acquired immunodeficiency states. *Candida albicans, Aspergillus fumigatus, Cryptococcus neoformans, Coccidioides immitis* and *Histoplasma capsulatum* are examples of common opportunistic pathogens. The term 'emerging' fungal pathogens has been used to describe uncommon organisms that are increasingly reported due to an enlarging pool of immunocompromised hosts.

Dematiaceous fungi represent a part of these emerging potential pathogens. Invasive and fatal infections due to dematiaceous fungi have also been reported in individuals with an "intact" immune system. The mechanism of disease in immunocompetent individuals is not known [1]. In dematiaceous fungi, melanin localized to the cell wall has been cited as a potential virulence factor, as it is resistant to a variety of agents including free radicals, ionizing radiation, and drying. Melanin may scavenge superoxides, hypochlorite and other free radicals produced by macrophages rendering them ineffective in oxidative digestion. Melanin may also bind to hydrolytic enzymes and antifungal chemotherapeutic agents and suppress their action. Therefore, it is likely that melanin plays a pivotal role in the pathogenesis of disease even in immunocompetent hosts [1, 7].

Dematiaceous fungi can produce three major types of clinical syndromes in humans including chromoblastomycosis, eumycetoma and phaeohyphomycosis. The salient features of these human infections are presented in Table 1. Chromoblastomycosis and eumycetoma are encountered more frequently in the tropics, while clinical syndromes associated with phaeohyphomycosis are universal.

Table 1 Salient features of dematiaceous fungal infections in humans [1, 2, 7]

Disease and common associated fungal genus and species	Clinical syndrome	Histopathology	Treatment
Chromoblastomycosis *Fonsecaea pedrosoi, Fonsecaea compacta, Phialophora verrucosa, Cladophialophora carrion, Rhinocladiella aquaspera*	Chronic subcutaneous mycosis. Preceded by minor trauma. Over years, nodular lesions form large verrucous plaques over feet, legs and exposed areas of the body Dissemination of lesions by extension or autoinoculation through scratching. Development of squamous cell carcinoma in long-standing lesions	Thick walled (sclerotic) yeast form with internal septation (Medlar bodies or "copper pennies"). 5–12 µm in diameter Cellular division by internal septation and not by budding. No hyphal forms in tissue. Infection is superficial Dermal granulomas Intraepidermal abscesses and transepithelial elimination of fungal bodies	Extends several months–years. Surgery, cryotherapy, thermotherapy, laser therapy all found useful in removal of local/limited disease. Systemic antifungals in moderate to severe or widespread disease. Itraconazole and terbinafine are first line drugs. Ketoconazole, flucytosine and amphotericin B offer variable cure rates
Eumycetoma *Madurella mycetomatis, Pyrenochaeta romeroi, Leptosphaeria senegalensis* Note: The term "Eumycetomas" is reserved for a true fungal infection and must be distinguished from "mycetomas" that are caused by filamentous bacteria as in actinomycetomas. Eumycetomas show gram negative septate hyphae while mycetoma (actinomycetoma) grains have gram negative centers with fine radiating gram positive fringes	Chronic granulomatous infection of skin and subcutaneous tissue characterized by tumefaction, draining sinuses and black grains or sclerotia in tissue and exudate. The organisms are present in soil and are implanted into host tissue following trauma. The foot is most susceptible. Lesions start as painless papules that enlarge and discharge an exudate. Lesions spread contiguously and form multiple draining sinuses. Grains in the exudate may be seen clinically	Grains are clusters of small filamentous hyphae Type I reaction: grains surrounded by neutrophils. Granulation tissue, macrophages, lymphocytes and plasma cells lie around the neutrophils. Fibrosis and perivascular sclerosis Type II reaction: neutrophils replaced by macrophages and multinucleated giant cells that phagocytize the grain material Type III reaction: characterized by well-organized granulomas	Requires prolonged systemic antifungal therapy in addition to surgery unlike chromoblastomycosis which may be cured by surgical therapy alone. Ketoconazole and itraconazole show consistent antifungal activity. Voriconazole and posaconazole have also been used successfully. Amphotericin B is ineffective

Phaeohyphomycosis can be divided into several groups of disease **Superficial and cutaneous disease** Tinea nigra: *Hortaea werneckii, Stenella araguata* Onychomycosis: *Alternaria, Scopulariopsis* **Corneal or mycotic keratitis** Keratitis: *Curvularia, Bipolaris, Exserohilum* **Subcutaneous disease** Subcutaneous nodules: *Alternaria, Exophiala* **Allergic disease** Allergic fungal sinusitis: *Bipolaris, Curvularia* Allergic bronchopulmonary mycosis: *Bipolaris, Curvularia* **Invasive, systemic and cerebral disease** Bone and joint infection: *Scedosporium prolificans, Alternaria* Peritonitis: *Curvularia, Exophiala, Alternaria* Pneumonia: *Ochroconis, Exophiala* Brain abscess: *Cladophialophora bantiana, Rhinocladiella mackenziei, Ochroconis* Disseminated disease: *Scedosporium*	Fungi grow on soil, wood and decaying plant material and organic matter. Portals of entry into the body include inoculation into skin and subcutaneous tissue through trauma, inhalation of fungus with lung and sinus infection, ingestion of contaminated food followed by penetration through the gastrointestinal tract and via contaminated vascular catheters and needles. Superficial and subcutaneous infections are the most common and onychomycosis mostly affects toe nails manifesting as cysts or abscesses. Fungal ocular keratitis is most prevalent in the tropics. Allergic sinusitis caused by dematiaceous fungi is more common than aspergillus sinusitis. Disseminated disease is seen in immunocompromised patients. More than half the cases of brain abscess due to dematiaceous fungi are in patients with no immunodeficiency	3 different patterns: (1) Keratotic plaques and nodules show epidermal hyperplasia and microabscesses. Brown yeast-like cells and hyphae are seen among epithelioid cells, giant cells and neutrophils. (2) Intradermal, multiloculated cystic cavities lined by granulomas and neutrophils. Yeast-like cells and hyphae among the cellular infiltrate. (3) Well-defined dermal cyst surrounded by dense fibrous tissue. Cyst cavity shows necrotic debris and neutrophils. Fragments of vegetable matter may be seen inside cyst. Granulomas and pigmented fungi in wall of cyst Fungal walls are yellow to brown and pigment is dihydroxynaphthalene melanin. Morphological characteristics and colony characteristics of a list of dematiaceous fungi are documented in reference [1], Table 1, 888–890	Tinea nigra confused with nevi, syphilis, or melanoma. Diagnosis is made by scraping lesions and culture. Simple scraping or abrasion may be curative. Topical therapy and systemic itraconazole and terbinafine are effective in onychomycosis. Surgical resection is curative in many subcutaneous infections. Fungal keratitis due to trauma, prior eye surgery, diabetes or contact lens abrasion receives topical agents like 5 % natamycin in combination with an azole. Oral ketoconazole is also used. Diagnosis of allergic disease depends on demonstration of fungus in mucin. Management consists of surgical removal of the tenacious mucous, followed by systemic steroids and itraconazole. Disseminated infections are uncommon and are a management challenge

prolificans, Bipolaris, Exophiala			

Traumatic implantation of fungi by a wooden splinter, thorn or other foreign object can result in subcutaneous, localized phaeohyphomycosis. Subcutaneous phaeohyphomycosis in healthy individuals may present as solitary or multiple, firm to fluctuant, painless abscesses over exposed skin surfaces. Lymphangitis and regional lymphadenopathy are unusual and so is progressive dissemination of the infection [2, 4]. Systemic or cerebral phaeohyphomycosis is seen in the immunocompromised or debilitated hosts who have inhaled the airborne conidia into the respiratory system [2].

Oral phaeohyphomycosis is rare. From our case, as well as the presentation in other cases [5, 6], oral involvement appears to have resulted from inoculation by plant/foliage matter. The lesions in our case and of the lower labial mucosa [5] were deeply submucosal, well-delineated, and with an intact surface. Pain and tenderness were variable. Given the non-specific clinical findings, diagnosis was made by microscopic examination of lesional tissue.

Given the clinical setting of the current case, we felt there were at least two plausible explanations for its pathogenesis. First, the lesion could have represented secondary infection of a pre-existing nasopalatine duct cyst or alternatively, a cyst of the incisive papilla [8]. The latter possibility was considered most likely due to the absence of surgical or radiographic evidence of an associated intrabony cavity. Second, the soft tissue cyst could have resulted from traumatic implantation of surface oral epithelium associated with the child's habit of scraping or pressing against his palate with a twig. With either explanation of cyst formation, acquisition of the uncommon fungal infection was likely associated with the child's parafunctional habit.

The diagnosis of phaeohyphomycosis depends upon direct microscopic detection of typical forms in tissue [2]. Demonstration of hyphae in tissue may be the only evidence of disease because growth in cultures may be severely suppressed in individuals receiving antifungal therapy [1].

Rapid direct microscopic examination may be done using the Gram stain or potassium hydroxide (KOH) preparations. Routine hematoxylin and eosin stains demonstrate strongly pigmented forms in tissue sections while the melanin Fontana-Masson stain may be used to demonstrate the presence of lightly pigmented hyphae [1]. The practicality of demonstrating dark hyphae against a green background is offered by the GMS stain but this stain does not differentiate between melanized and non-pigmented fungi [1].

During microscopic examination, the possibility of myospherulosis must be entertained, especially in a clinical setting where a recent surgical procedure has been performed and the surgical site has been packed with an antibiotic in a petrolatum base. Myospherulosis may arise in the paranasal sinuses and associate with pigmented resident fungal organisms [8].

Over 150 species and 70 genera of pigmented fungi have been associated with human disease. Based on the clinical presentation, and with a high degree of suspicion, the lesional tissue needs to be cultured for examination of phenotypic features of the fungal isolates for species or genus

determination [1]. More recently, molecular techniques such as PCR assays have been used in the classification of pigmented fungi rather than in the diagnosis of infections [1, 7].

Itraconazole has been used to treat systemic cases of phaeohyphomycosis [1, 3, 4, 9]. Localized subcutaneous lesions however do not require antibiotics and surgical excision of infected tissue is typically curative. Caution should be exercised during surgery to prevent reimplantation of the fungus [3, 4]. Table 1 describes the treatment for the different clinical syndromes associated with dematiaceous fungal infections in humans.

The clinical presentation as well as prognosis of infections by these and other emerging pathogens depends on the virulence of the microorganism and the level of host resistance. To our knowledge, the current case represents the first report of intraoral phaeohyphomycosis, occurring as an infection of a cyst of the soft tissue of the midline anterior maxilla.

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