·Letter to the Editor·

A rare pigmented keratitis caused by *Aspergillus fumigatus*

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Dear Sir,

I am Mauricio Vélez, from the Department of Ophthalmology, Cornea Service Director, Universidad Pontificia Bolivariana in Medellín, Colombia. Below, I would like to share an interesting case I managed recently, which I've entitled "A rare pigmented keratitis caused by *Aspergillus fumigatus* ".

Fungi are a relatively uncommon cause of microbial keratitis in developed countries. The importance of fungal keratitis resides not only on their challenging diagnosis and management, but also on their association with disastrous functional sequelae [1]. For such infection to develop, fungi must gain access to the corneal stroma *via* a defect on the epithelial barrier. Such a breach can develop due to a number of reasons, including prior surgery, prolonged contact lens wear [2-4], or, commonly, trauma. Corticosteroids use, and the presence of systemic of local diseases have also been linked as predisposing factors for the infection[4].

Fungi that cause infectious keratitis have been divided in four groups: yeasts (*Candida spp*, *Trichosporon beigelii*, *Pichia ohmeria*), filamentous septated with nonpigmented hyphae (*Fusarium spp*, *Aspergillus spp*, *Acremonium spp*, *Cilindocarpon spp*, among others), filamentous septated with pigmented hyphae (dematiaceous) (*Alternaria spp*, *Curvularia spp*, *Cladosporium spp*) and filamentous nonseptated (*Mucor spp* and *Rhizopus spp*).

Up next, the authors describe the case of a female patient from Cundinamarca, Colombia (warm, tropical area), who was evaluated at the cornea service of our institution because of a pigmented fungal keratitis, in whom a final diagnosis of *Aspergillus fumigatus (A. fumigatus)* infection was reached.

The authors consider this case to be of great interest for two main reasons: first, the fact that *A. fumigatus* is considered a non-pigmenting type of fungi, which was not compatible with the patient's clinical presentation of an obviously pigmented corneal abscess. Second, the topical application of diclofenac coupled with prolonged ultraviolet-radiation exposure may have caused such pigmentation; the authors present current evidence supporting this notion.

CLINICAL CASE

Female, 42-year-old patient, house-keeper, who attends the Cornea Service of our institution complaining of a two months history of burning and itching on her left eye. Before attending our institution, she had already been evaluated at another center in a different city, of which we have no information regarding initial visual acuity or any other aspect of her physical examination. All we are aware is that, due to a presumptive diagnosis of fungal keratitis, she had received topical amphotericin B and fluconazole and systemic itraconazole as empiric therapy. There had been no positive clinical evolution. By the time we first evaluated her, she was also on auto-formulated diclofenac 0.1% (3A Ofteno® - *Laboratorios Sophia*, Jalisco-México) four times a day and benoxinate chlorhydrate 0.4% (OQ Seina® - *Oftalmoquimica*, Bogotá-Colombia) as needed.

On initial evaluation, her uncorrected visual acuity was 20/25 (LogMAR 0.10) on both eyes. A slit lamp examination showed a nodular lesion in her left eye. Such lesion was located near the corneal periphery, was pigmented, with feathery borders, measuring about 0.3×0.3 cm. There was also some associated mucous secretion. Tyndall was negative (Figure 1). No other such lesions were found. There was no history of corneal foreign body of any kind, and she did not have exposure to any source of metallic dust or any other element which could constitute a metallic foreign body.

A diagnosis of infectious keratitis caused by a pigmenting fungi was made, and material was taken from the lesion borders for KOH, Gram, and cultures (blood, chocolate, Sabouraud and mycocel agar, and brain-heart-infusion broth) The patient was started on natamycin 5% every two hours and gatifloxacin 0.3% every four hours. All other drugs were stopped. The patient is re-evaluated numerous times at intervals of 24-48h, but after 11d of treatment, with no clinical response and all cultures being reported as negative, she underwent excisional cornea biopsy.

Biopsy studies confirmed *A. fumigatus* infection in corneal biopsy. This finding was double-checked by laboratory staff

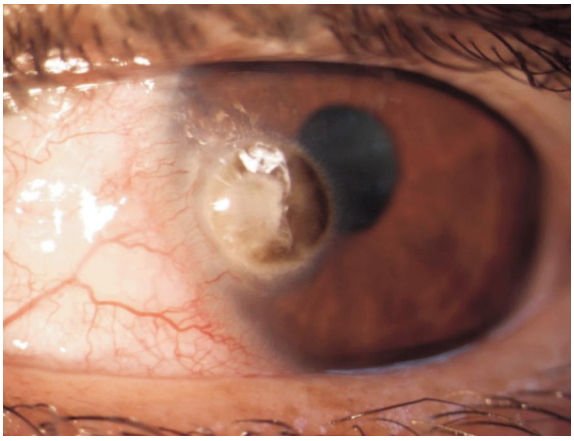

Figure 1 Patient at the moment of initial presentation. A pigmented corneal abscess is seen.

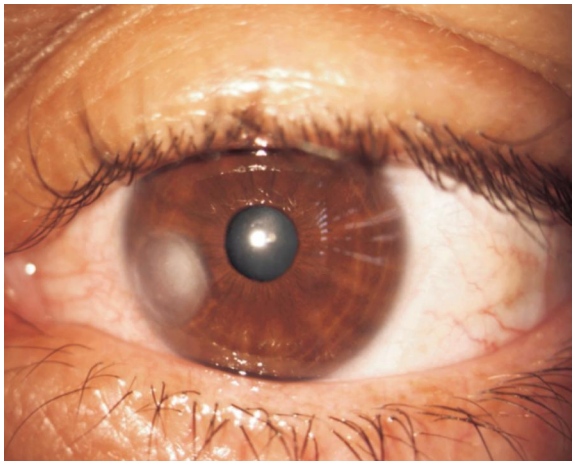

Figure 2 Patient after surgical and medical treatment, with a corneal leukoma and no signs of active infection.

at our institution. The treatment was adjusted to natamicyn every hour, moxifloxacin 0.4% every six hours, and itraconazole 200 mg per mouth every twelve hours.

On later evaluations, the patient is found to have an excellent clinical evolution. No signs of active infectious disease in cornea are found. On sixth week of treatment, a gradual tapering of natamicyn, itraconazole and moxifloxacin is started. With a complete certainty of fungal eradication, prednisolone 1% is started every 24h, with a progressive increase in dose.

Seventy-nine days after surgery, the patient is evaluated again. Her visual acuity is 20/20 (LogMAR 0) in both eyes. Her cornea has quite a small leukoma, with no clinical signs of fungal infection (Figure 2). Topical treatment is stopped, and the patient is programmed for a new clinical evaluation six months from that time. She is yet to be seen again.

DISCUSSION

Altough fungi are considered as an unusual ethiologic agent for keratitis in developed countries, their importance in third world countries is remarkable, specially owing to the difficulties in their diagnosis and management, coupled with their potential for causing disastrous functional sequelae[5]. As of today, there are no Colombian studies regarding local epidemiological behavior of fungal keratitis; but some very important Latin-American information can be taken from the recent paper by Cariello *et al* [6], who studied all cases of fungal keratitis managed at a referral center in Sao Paulo (Brazil). These authors reported fungi to be responsible of 5.3% of all cases where an ethiological agent could be isolated; the most common ones being *Fusarium spp*, *Candida albicans* and *Aspergillus spp*, with 51.9%, 10.7%, 9.1%, respectively[6].

This article discusses the clinical case of a Colombian resident with infectious keratitis in whom infection by *A. fumigatus* was proved. Regarding this case, there are two specific points authors believe deserve special attention. First of all, as was evident upon clinical evaluation (and as can be seen in the photographs that accompany this article), the patient's clinical picture was that of a microbial keratitis caused by fungi considered as *pigmentary* (the most common of which would be *Curvularia spp*)[7]. Nevertheless, biopsy studies proved such lesion to be caused by *A. fumigatus*, considered to be related to the development of non-pigmented rather than pigmented hyphae.

To the best of the authors' knowledge, there is no report in international literature of a case of pigmented fungal keratitis caused by *A. fumigatus*. The authors are well aware there are two specific strains of *Aspergillus spp* which can cause pigmented fungal keratitis(*A. niger* and *A. Tubingensis*)[12,13]. Therefore, we have double-checked the typification regarding the fungi isolated from our patient and are completely sure that it is, certainly, an *A. fumigatus*. The authors have considered a number of theories for this behavior, but most of them have been considered by us to be unlikely. The first potential point considered was the possibility of a concomitant infection with a second agent which may have caused seen pigmentations; nevertheless, biopsy studies gave definitive information regarding this point, and excluded the possibility of another etiological agent besides the one we report.

Also, there could exist the possibility of a spontaneous mutation in the *Aspergillus*' genome which could cause it to alter their metabolism and start expressing a pigmentation phenotype and clinical behavior. Nevertheless, the authors are yet to found a second similar case either in literature or local practice, and therefore, proving such assumption represents a challenge and seems pretty unlikely.

Upon patient reevaluation and interrogation, it became clearly apparent that she had been applying auto medicated Diclofenac 0.1% on the affected eye four times a day for a couple of weeks. To the best of authors' knowledge, there is no published paper to prove a connecting relationship between Diclofenac use and pigmentation of fungal colonies;

nevertheless, it is important to note this anti-inflammatory agent has been proved to act as a photosensitizer in a number of clinical and environmental contexts. Both natural luminical stimulation as well as simulated sunlight exposure have been proved to modify Diclofenac's structure and transform it into a composite which is toxic to a number of algae, including *Scenedesmus vacuolatus* [8]. Some other, similar studies have proven diclofenac to be subject to phototransformation even when exposed to relatively low levels of ambient irradiation (such as those found in the European winter). As may be expected the same studies have shown this transformation to be quicker in the presence of a higher amount of solar irradiation, which could be compared with the Colombian geographic characteristics[9].

On the other hand, phototoxicity induced in human cells by non-steroidal anti-inflammatory drugs (the group diclofenac belongs to) had already been described since 1987. Studies performed at that time had shown that, when incubated in a diclofenac-containing solution and exposed to ultraviolet irradiation, human leukocytes liberated exaggerated amounts of histamine and leukotrienes[10,11].

Although there are no published reports linking diclofenac photochanges and pigmentations of fungal colonies, it is readily evident the former to respond to luminic stimulation, generating reactions that affect both human and vegetable cells [8,10]. Due to this, the authors consider it possible that the topical application of diclofenac induced changes in the intrinsic metabolism (possibly mutations or other changes) of the *A. fumigatus*, getting it to express a pigmented colony, instead of the non-pigmented one that could be expected. Obviously, there is still the need for research articles focused on this specific matter for the authors to be able to prove this theory.

CONCLUSION

Fungal keratitis is a relatively uncommon disease, which imposes challenging diagnosis and management. Although it is well known that some fungal families are capable of producing pigmented colonies, *A. fumigatus* has not been described to have such capability. The present article describes the clinical case of a female Colombian patient, with a pigmented corneal abscess in whom an *A. fumigatus* infection was proved by anatomopathologic examination of the corneal lesion. The authors discuss a theory in which the topical application of diclofenac, coupled with prolonged ultraviolet-radiation exposure may have caused such pigmentation.

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Conflicts of Interest: Vélez M, None; **Balparda K,** None; **Díaz AM,** None.

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