Fluconazole, an effective treatment for Parinaud oculoglandular syndrome associated with Sporotrichosis - case reports and literature review.

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Abstract

Background: Parinaud oculoglandular syndrome is a unilateral granulomatous, follicular conjunctivitis associated with ipsilateral lymphadenopathy, observed in various bacterial, viral and fungal infections. Fluconazole belongs to the azole class of antifungals and it is used to treat a variety of fungal and yeast infections.

Objective: To report two patients with Parinaud oculoglandular syndrome associated with Sporotrichosis, who were successfully treated with oral Fluconazole.

Methods: Retrospective case reports.

Results: Two healthy female patients presented to our centre with follicular conjunctivitis associated with enlarged ipsilateral pre-auricular and submandibular lymph nodes. Both the patients had a history of contact with cats. They were diagnosed with Parinaud oculoglandular syndrome, associated with sporotrichosis and were successfully treated with oral Fluconazole 200 mg once daily for 2-3 months.

Conclusion: Fluconazole is an effective alternative to itraconazole in treating Parinaud oculoglandular syndrome associated with sporotrichosis.

Keywords: Parinaud oculoglandular syndrome, Sporotrichosis, granulomatous, follicles, Cat, Fluconazole

EyeSEA 2023;18(1)1-5

Introduction

Parinaud oculoglandular syndrome is a unilateral granulomatous, follicular conjunctivitis associated with ipsilateral lymphadenopathy. It is associated with bacterial (cat-scratch disease, tularaemia, tuberculosis and syphilis), viral (mumps, infectious mononucleosis and herpes simplex) and fungal infections (sporotrichosis). Sporotrichosis is commonly caused by Sporothrix schenckii, a dimorphic fungus which can be found not only in water, soil, plant and organic matter, but also in infected animals such as cats, rabbits, horses and rats.[2-3,5,7,9-10] It is usually found in tropical and subtropical countries, most cases of ocular sporotrichosis are from Peru, China and Brazil but a few have also been reported in Thailand and Japan.[3,9,10] The disease has good prognosis but requires anti-fungal therapy from weeks to months.

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Received: April 23rd, 2022
Accepted: May 5th, 2023
Published : June 30th, 2023

Case 1

A 25-year-old lady was referred to our centre from a district hospital. She presented with an erythematous and swollen right lower lid for 1 month. She had already been treated with oral Doxycycline for 3 weeks, followed by tablet Azithromycin for 2 weeks prior to our review. However, the symptoms did not

improve. She had 9 cats at home and had been recently scratched by one of them. Ocular examination revealed follicular conjunctivitis and a granulomatous lesion over the right lower palpebral conjunctiva (Figs:1A-1B). Systemic examination revealed pre-auricular and submandibular lymphadenopathy with right cheek swelling and also purple nodular skin lesions over her arms and hands bilaterally (Fig.1C). We started her on oral Doxycycline 200mg once daily while awaiting Bartonella serology. When her Bartonella serology came back as negative, she was treated as having ocular sporotrichosis and started on oral Fluconazole 200mg once daily. This patient did not have any confirmatory test for sporotrichosis. Her symptoms improved markedly and treatment was continued for 3 months, after which she had complete resolution of symptoms.

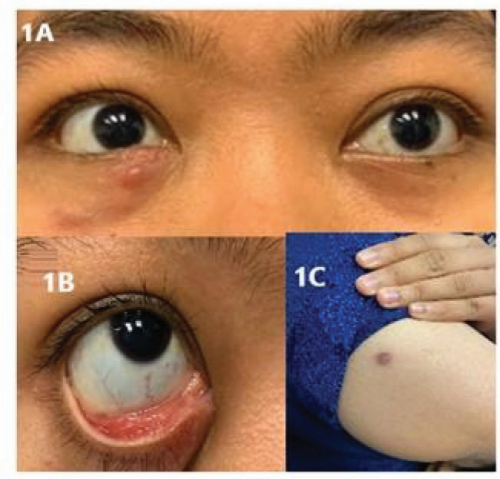

Figure 1: A: Granulomatous lesion over right lower lid. 1B: Follicles over right lower palpebral conjunctiva. 1C: Nodular skin lesion on right arm.

Case 2

A 37-year-old lady presented to us with a complaint of right eye discomfort and redness for 3 months. She was treated by a general practitioner with gutt. Dexamethasone and occ. Chloramphenicol prior to our review. However, her symptoms did not resolve. At home, her siblings and their pet cat were recently diagnosed with sporotrichosis and were on anti-fungal medication. This patient claimed that her symptoms began after water splashed into her eyes while bathing her sick cat. Ocular examination revealed follicles at the right palpebral and superior bulbar conjunctiva (Figure 2), as well as right submandibular and pre-auricular lymphadenopathy. Her conjunctival swab results confirmed Sporotrix schenckii infection. She was started on oral Fluconazole 200mg once daily and treatment was continued for 2 months, after which she had resolution of symptoms.

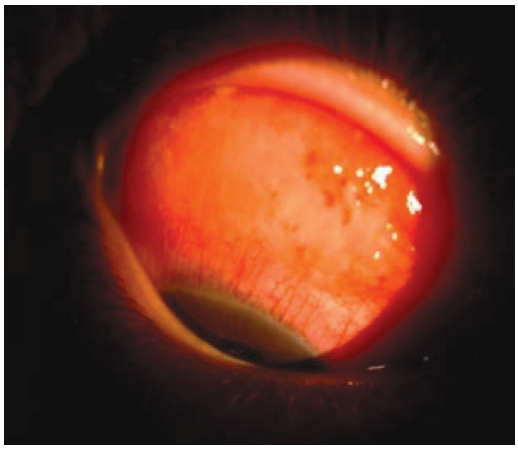

Figure 2: Follicles at bulbar conjuctiva

Discussion

Sporotrichosis can be classified into cutaneous and extracutaneous forms.[3] The cutaneous form can be further divided into lymphocutaneous, fixed and disseminated forms.[3] The lymphocutaneous form is the most common form observed in our Malaysian population, with a slight female preponderance but no age preponderance.[9] It spreads from the area of traumatic implantation through regional lymph nodes. The fixed cutaneous form has no regional lymphatic spreading, while the disseminated form is rare and only occurs in immunocompromised patients. On the other hand, extracutaneous sporotrichosis includes ocular, pulmonary and osteoarticular infections.[3]

Ocular Sporotrichosis can be classified into Sporotrichosis of ocular adnexa, and intraocular disease. Sporotrichosis of ocular adnexa includes infection of the eyelids, conjunctiva and lacrimal sac.[3] Intraocular sporotrichosis causes endophthalmitis which can be exogenous or endogenous which is usually seen in immunocompromised patients

with disseminated disease.[3] The most common species found in Malaysian humans and felines are Sporotrix schenckii, which cause skin and ocular infections.[4-8] Less than 10 cases of ocular sporotrichosis have been reported so far in Malaysia.[3-7] However, there is a possibility that the cases are under reported, as features of the disease may be mistaken for other types of conjunctivitis.[5]

Sporotrix spreads not only via traumatic inoculation by infected cats or plants, but also through droplets.[9-10] Ocular inoculation from splashed culture material in laboratory workers has also been described before which is similar to our second patient.[1] When conjunctival sporotrichosis is associated with ipsilateral pre-auricular and submandibular lymphadenopathy, it can be described as Parinaud oculoglandular syndrome.[3] The other feature of this syndrome is fever, but both of our patients did not present with it. About 50% of cases of conjunctival sporotrichosis from previous case reports and case series were Parinaud oculoglandular syndrome.[3] Most of the cases reported were from Brazil as it is endemic there.[3]

The recommended treatment for sporotrichosis is oral Itraconazole 200 mg twice daily, based on the Infectious Diseases Society of America Clinical Practice Guidelines for the Management of Sporotrichosis: 2007.[12] According to this, Itraconazole is an effective treatment for various cutaneous and extracutaneous forms of sporotrichosis. However, treatment for ocular sporotrichosis was not specifically mentioned in this guideline.[12] In most of the articles available, Itraconazole was used as the treatment of choice for ocular sporotrichosis.[1-6,8-9] Both our cases were treated with tablet Fluconazole 200 mg once daily, as tablet Itraconazole was not available at our centre, which proved to be an effective alternative in treating ocular sporotrichosis. We did not use any topical antifungal eyedrops for both our patients.

Both Fluconazole and Itraconazole belong to the triazole group of anti-fungal drugs and are fungistatic in nature. The mechanism of action of this group of drugs is by impairment of ergosterol biosynthesis in fungal cell membranes, leading to increased permeability of cell membranes and inhibition of fungal growth. The particle size of fluconazole is 305 microns, while itraconazole is 706 microns.[12] The percentage of plasma protein binding is 12% for Fluconazole and 99.8% for Itraconazole.[12] Since Fluconazole is a small polar compound with low plasma protein binding, it achieves better penetration into aqueous sites such as the anterior chamber of the eye, while the more lipophilic Itraconazole compound has much larger volume of distribution and tends to penetrate tissues with high lipid content better.[12] Since, the ocular penetration of fluconazole is better than itraconazole, it might be a better option for ocular sporotrichosis. The half-life of both drugs are about 30 hours and both medications are well tolerated orally.

Other treatments for Sporotrichosis include Potassium Iodide, Terbinafine and Amphotericin B.[3] Amphotericin B is usually reserved for disseminated disease and in cases of endophthalmitis in immune-compromised patients.[3] A case has been successfully treated in Thailand with occ.Terramycin (Oxytetracycline hydro-chloride with polymyxin B sulfate) QID for 2 months and ointment Maxitrol (neomycin sulfate with polymyxin B sulfate and Dexamethasone) nocte for 1 month without systemic anti-fungal treatment.[10]

From our literature review (Table 1), we found that there was a female preponderance in the cases reported in Malaysia.[4-7] This may be due to the fact that women might have more frequent contact with pet cats than men. Out of the 9 cases previously reported in Malaysia, 8 cases had history of exposure to cats and only 1 patient presented after gardening.[4-7] Lymphadenopathy was not mentioned in 8 patients and 1 patient had no lymphadenopathy, in contrast with both of our patients who presented with ipsilateral lymphadenopathy.[4-7] Oral Itraconazole was the treatment of choice for 8 patients, while 1 patient had intralesional Amphotericin B due to pregnancy.[4-7] Most of the patients were immunocompetent, except for 1 patient with retro viral disease.[4-7] All the patients reported had resolution of symptoms with treatment.[4-7]

Table 1: Case reports and case series of ocular sporotrichosis In Malaysia.

Author	Cases/Age /Sex	Risk factor	Co-Morbidities	Clinical Manifestation	Isolated Species	Treatment	Resolution
Ling et al [6]/2018	18/Female	Contact with Sporotix infected cat.	Nil	LE generalised granulomatous palpebral conjunctival lesion.	S.shenckii	Oral Itraconazole 200mg twice daily	Resolved after 5 months.
Lee et al [4]/2020	15/Female	Had 3 pet cats at home.	Post renal transplant	LE granulomatous conjunctival lesion with overlying ulceration at medial canthal lesion. (No Lymphadenopathy)	S.shenckii	Oral Itraconazole 200mg Twice daily	Resolved after 3 weeks.
Lau et al [7]/2021	35/Female	Exposure to infected cat.	RVD positive. Pregnant.	RE granulomatous lesion over palpebral conjunctiva.	S.shenckii	Intralesional Amphoterecin B 5 mg Gutt. Fluconazole 2 hourly, then tapered to 4 hourly.	Resolved.
Ahmad-Fauzi et al [5]/2021	6 Cases 17-61 years old (Mean Age 36.5 years old) 4 females /2 males	4 patients: Contact with cats. 1 patient: Scratched by cats. 1 patient: History of gardening without trauma.	Nil	5 patients with lobulated/granulomatous conjunctival lesions. 1 patient with eyelid granuloma.	S.shenckii	Oral Itraconazole 200mg twice daily	2 patients resolved with symblepharon. 1 patient resolved with scarring.

Conclusion

Ocular sporotrichosis should be considered in patients presenting with Parinaud oculoglandular syndrome, especially in those with a history of cat exposure. Fluconazole is an effective alternative to itraconazole in treating Parinaud oculoglandular syndrome associated with sporotrichosis.

Declaration

Consent for Publication

Informed consent was obtained from patient for the publication of the clinical data and images contained in this case report.

Conflict of Interests

None to declare.

Funding

None to declare.

Acknowledgements

None to declare.

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