Efficacy of 2 drug (Intensive phase) and 1 drug (Eradication phase) regimen for Rhino-facial Entomophthoromycosis: our experience and review of 5-year literature

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Abstract

Introduction: Conidiobolomycosis of the face is a rare infection seen in tropical countries worldwide. It usually affects immunocompetent individuals. Though the entity has been described since long, the exact duration of treatment and the efficacy of single Vs multi-drug regimen, with or without debridement has not been defined. The rarity of the disease is a major hurdle in creating universal management protocols with good reliability. This paper shall review our institutional experience in management of this disease with a fixed 2 drug regimen and its possible universal applicability.

Case series: We present 5 patients treated between May 2013 to May 2020 in our institute with a 2 drug intensive phase and a single drug eradication phase

Results: All the 5 patients received 6 months of supersaturated potassium iodide solution (KI) and Itroconazole, followed by 4 months of supersaturated potassium iodide solution mono therapy. All the patients responded well to treatment and are disease free on a minimum follow up of 2 years post treatment. 1 patient with history of surgery received additional 2 months of KI drops monotherapy due to persistence of induration.

Conclusion:

Rhino-facial entomophthoromycosis should be considered in the differential diagnosis for subcutaneous facial swellings and granulomatous diseases of face. Medical management with 2 drug regimen yielded good results in our experience. Surgical intervention aids dissemination of fungus and delays response to treatment and should be avoided.

Highlights:

- Rhino-facial entomophthoromycosis should be considered in the differential diagnosis for rhino facial swellings
- Biopsy is required for diagnosis
- 2 drug therapy for 6 months (Rapid response phase), followed by 4 months of monotherapy (Eradication phase) provides early response and prevents delayed recurrence
- Persistent sub cutaneous induration is an early sign of residual or recurrent disease and would warrant prolonged therapy till complete resolution of induration
- Surgery induces dissemination of fungus and delays response to medical management, thus it should be avoided.

Background

Entomophthoromycosis is a rare subcutaneous fungal infection of immunocompetent individuals caused by *Conidiobolus coronatus*, *C. incongruus*, and *C. lampraugesa*. It is commonly seen in Africa, South America and Asia. Our initially treated patients had mixed response to treatment, with many having slow response and delayed recurrence beyond 1 year of follow up. This article describes our experience with a modified protocol. The drug regimen is aimed at providing early response (Intensive phase) and preventing delayed recurrence (Eradication phase), which is common on long term follow up. This study tries to establish a universal treatment protocol which can treat and prevent delayed recurrence of the disease.

Case series

We report results in 5 cases treated over the past 5 years in our institute. (Table 1)

Table 1: The summarized patient data (KI, Potassium Iodide, FESS; functional endoscopic sinus surgery)

S No.	AGE /SEX	SURGICAL INTERVENTION	MANAGEMENT	TREATMENT DURATION (IN MONTHS)	COMPLICATIONS WITH MEDICAL MANAGEMENT	RESPONSE	DURATION OF FOLLOWUP (Months)
1	**42/M**	Biopsy	KI + Itraconazole	10	Skin rashes	Complete	48
2	**18/F**	Biopsy	KI + Itraconazole	10	Hypothyroidism	Complete	36
3	**45/M**	Biopsy	KI + Itraconazole	10	None	Complete	32
4	**35/M**	FESS	KI + Itraconazole	12	None	Complete	28

5	**58/M**	Biopsy	KI + Itraconazole	10	None	Complete	24

All our patients presented with progressive facial swelling and nasal obstruction over 3-6 months (Figure 1). Sub-labial biopsy was performed to ascertain the diagnosis. All the patients underwent complete haematological and clinical evaluation to rule out systemic co-morbidities. All were found to be immunocompetent.

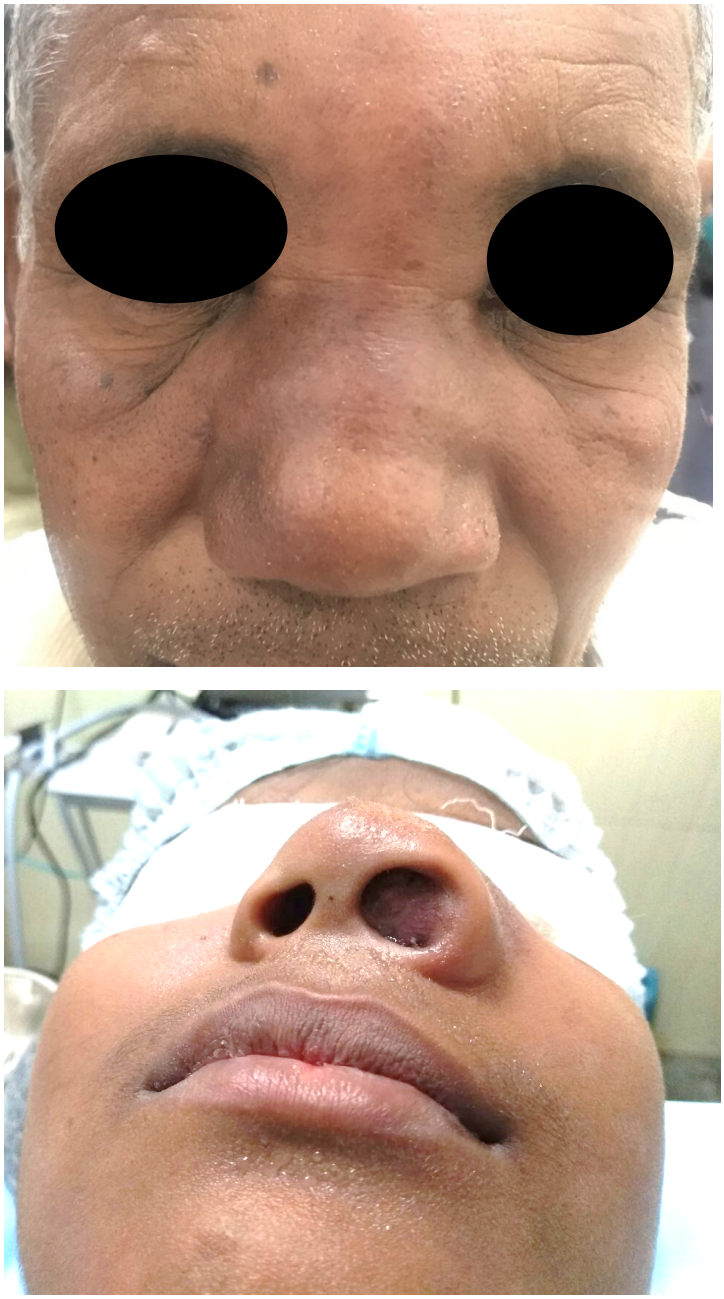

Figure 1: Common presentation in all our patients was subcutaneous facial swelling with nasal obstruction decreased sensation over the area of swelling. The induration typically extended beyond the swelling.

The culture of the biopsy showed conidia with papillate base, confirmatory for entomophthoromycosis (Figure 2). After the confirmation of the diagnosis, patients were initiated on supersaturated potassium iodide solution. Solution was prepared by dissolving KI in absolute alcohol[1gm/ml] i.e. 1 drop ~ 67 mg. They dose was titrated for adverse effects, initially starting with 3 drops thrice daily and progressively increasing up to 20 drops based on tolerance of skin and gastrointestinal side effects. Patients were simultaneously initiated on oral Itraconazole therapy, at 400mg twice daily for 2 days as loading dose, followed by 200 mg twice daily for 6 months [1]. This dosage schedule was used in our pilot patient, a 16 year old girl who had good response to this protocol and needed 4 months of mono therapy for complete resolution. She also had presence of fungal elements in her induration post 6 months of therapy [1]. Thyroid, liver and renal function were monitored. KI solution drops were continued for a further period of 4 months after completion of 6 months' therapy.

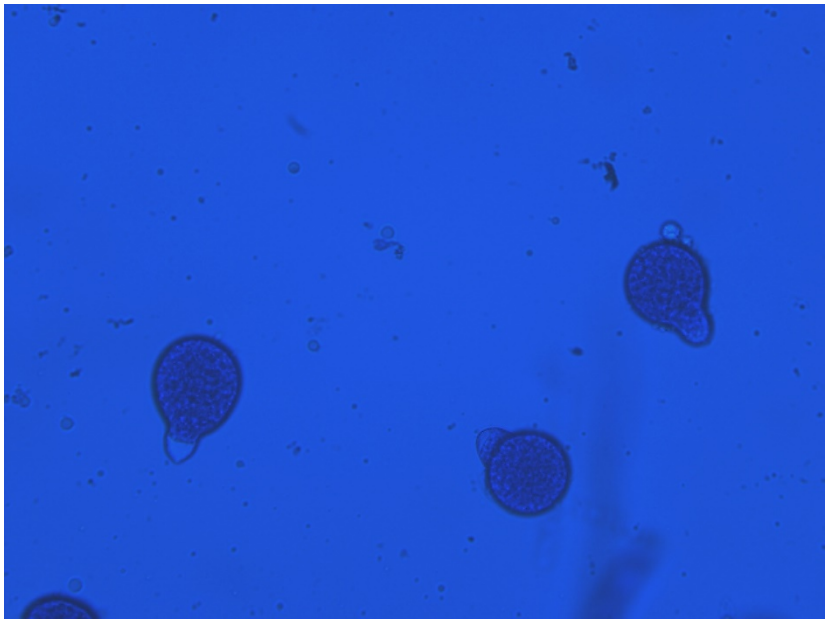

Figure 2: Microbiological review of culture specimen in Lactophenol Cotton blue staining under 40X magnification revealed conidia with papillate base

All patients responded well to treatment with no recurrence noted over a minimum follow up period of 24 months. 1 patient who underwent surgery prior to being referred to us needed 2 months of extra KI drops therapy as biopsy from his residual induration revealed fungus (Figure 3). Our criteria for complete resolution was complete resolution of swelling and induration. During the course of therapy, one patient developed transient skin rashes and another hypothyroidism, which were managed with antihistamines and thyroxine supplementation. The patient had transient hypothyroidism which settled down over the next 36 months.

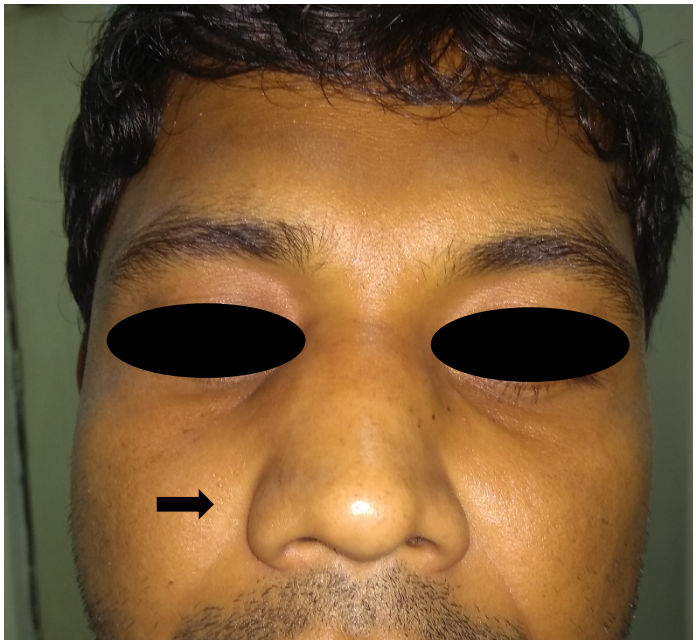

Figure 3: Presence of minimal induration even after resolution of swelling was suggestive of residual lesion in our series, as we discovered fungal elements from the induration (Black arrow).

Discussion

As Entomophthoromycosis is a rare entity, clinically, it should be differentiated from other neoplastic lesions [2].

With limited anti-fungal medications available, we should use the most appropriate agent. The recent 5-year English literature search with keywords of rhino-facial fungal infection, entomophthoromycosis, conidiobolomycosis yielded 13 studies which were reviewed (Table 2) [3-15].

Table 2: Review of 5 years' literature

S. NO	AUTHORS	NUMBER OF PATTIENTS	TREATMENT MODALITIES	DRUGS USED	DURATION OF TREATMENT (IN MONTHS)
1	Yu WN , Chen CJ ét al (2014)	1	Surgery + Medical	Itraconazole	3+6 (9)
2	Raveenthiran V, Mangayarkarasi V et al. (2015)	16	Surgery + Medical	Potassium iodide and in 1 case Itraconazole was added	4.7 (2-8)
3	Cherian LM, Varghese L et	1	Surgical + Medical	Itraconazole and	6

S. NO	AUTHORS	NUMBER OF PATTIENTS	TREATMENT MODALITIES	DRUGS USED	DURATION OF TREATMENT (IN MONTHS)
	al (2015)			terbinafine	
4	Arora N, Bhargava EK et al (2016)	1	Medical	Potassium iodide and itraconazole	1
5	Gupta M, Narang T et al (2016)	10	Medical	Potassium iodide, itraconazole, Amphotericin B, Fluconazole	6-9
6	Cunwei Cao, Jazeer A. Khader (2018)	1	Medical	Potassium iodide, Trimethoprim - Sulfamethoxazole, Itroconazole	6
7	Deak L, Mudalagiriyappa S et al (2018)	1	Surgical + Medical	Itraconazole	18
8	Gupta N, Kumar R et al (2018)	2	Medical	Potassium iodide + itraconazole/ Voriconazole	5& 6
9	Sudip Kumar Das, Chiranjib Das et al (2019)	6	Medical	Potassium iodide, Itrocanazole, Fluconazole, Ketaonazole, terbinafine, Steroids	5-6
10	Chaiyasate S, Salee P et al (2020)	3	Medical	Itraconazole + Potassium iodide/Cotrimoxazole	6 -12
11	Wankhade AB, Patro P et al (2020)	2	Surgical + Medical	Amphotericin	1

S. NO	AUTHORS	NUMBER OF PATTIENTS	TREATMENT MODALITIES	DRUGS USED	DURATION OF TREATMENT (IN MONTHS)
12	Sigera LSM, Janappriya GHDC et al (2020)	3	Surgical + Medical	Itraconazole + terbinafine/amphotericin	4 to 6
13	Somashree Dutta, Somenath Sarkar et al (2020)	1	Medical	Potassium iodide and itraconazole	6

The treatment was primarily medical, excepting 6 studies where surgical debridement was also performed [3,4,5,9,13,14]. The medical management included Potassium iodide, itraconazole, Amphotericin B, Fluconazole, terbenafine, Cotrimoxazole and ketoconazole. The treatment duration ranged from a minimum of 1 month to a maximum of 18 months. In majority of the studies, the duration was 6 months. This clearly demonstrates a lack of uniformity in approach. As the infection is typically seen in immunocompetent individuals, surgical debridement is not warranted and may in fact cause more resistance due to dissemination and tissue scarring. This was seen in our case who underwent surgery before being referred to us. He required 2 months of extended mono therapy for persistent induration. The use of inappropriate anti-fungal medication for inadequate time period leads to partial response and resistance. This can be very dangerous for the patient, considering the availability of limited anti-fungal medications. Debridement also helps in dissemination of the disease and prevents early resolution. Our study emphasizes the need to use appropriate anti-fungal medication for adequate duration, so as to prevent resistance and ascertain a complete response. The surgical debridement should also be limited to rare scenarios where there is no response to treatment and as a last resort.

This report presents our standardised protocol of management, with a defined time period (Table 3). We have divided the treatment into 2 phases. The initial 2 drug therapy is for rapid response and the mono therapy provides for eradication of the fungus to prevent recurrence. Our 2 drug therapy in our initial experience has eradicated the disease and prevented delayed recurrence, which was common over long term follow up. The side effects were transient and settled with dose adjustment. The use of 2 drugs to start with helps in obtaining a rapid response and avoids a need for surgery. The mono therapy was used in our protocol as we noticed minimal persistence of induration even after good response and this ultimately led to delayed recurrence over 1 -2 years. Our definition of response is complete resolution of induration as we found fungal elements in the minimal residual induration. The biopsy from the induration invariably displays fungal elements requiring prolonged therapy.

Table 3: Our protocol for management after diagnosis is confirmed on pathological or microbiological evaluation. In case of non-resolution of swelling, a microbiological analysis should be performed to identify the most appropriate drug.

0-6 months (Rapid response/Intensive phase)	7-10 months (Eradication phase)
KI solution drops; initially starting with 3 drops thrice daily and progressively titrated to 18 drops thrice daily or more based on tolerability. Oral Itroconazole: 400mg twice daily for 2 days, followed by 200mg twice daily for 6 months.	KI solution drops: 18 drops thrice daily for 4 months

Potassium iodide has been observed to have an antifungal action in infections with Splendore-Hoeppli reaction viz. Sporotrichosis, Entomophthoromycosis, Chromoblastomycosis and Mycetomas [16]. It is hypothesized to enhance the outcome of complement fixation dependent cytolysis either enhancing or retarding the reaction [17]. Contraindications to KI include pregnancy or hypersensitivity to iodide or acute infections like Tuberculosis or bronchitis [18]. Dose limiting adverse reactions include hypothyroidism, parotitis, acneiform skin eruptions, nausea or vomiting [19]. Adding a second anti-fungal helps in enhancing the response with early disappearance of swelling and induration. The recurrence over period of months is due to the incomplete resolution of induration which harbours the fungus. This has led us to include complete resolution of induration as a marker for eradication of fungus. Surgery induces dissemination of the fungus and is associated with poorer response to treatment and need prolonged treatment. The 4 months of KI drops helps in eradication of the fungus and is vital to prevent delayed recurrence.

CONCLUSION

The primary treatment modality for entomophthoromycosis is with potassium iodide solution in titrating doses. The addition of synergistic antifungals like Itraconazole has provided early resolution. The total duration of treatment was 10 months with 2 drug therapy (KI and Itraconazole) for 6 months as intensive phase and mono therapy with KI drops for further 4 months as eradication phase. Early cessation of treatment was associated with delayed recurrence. Reappearance of induration is an early sign of recurrence and should be evaluated. Hypothyroidism can result and needs regular follow up during therapy. Surgical debridement should be avoided as it has detrimental effects in the long run. Delayed response to treatment would warrant microbiological analysis with reconfirmation of diagnosis and its sensitivity pattern.

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