GSC Advanced Research and Reviews
eISSN: 2582-4597 CODEN (USA): GARRC2
Cross Ref DOI: 10.30574/gscarr
Journal homepage: https://gsconlinepress.com/journals/gscarr/

(CASE REPORT)

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Cutaneous alternariosis: A case report

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GSC Advanced Research and Reviews, 2026, 27(02), 031-035

Publication history: Received on 25 March 2026; revised on 04 May 2026; accepted on 07 May 2026

Article DOI: https://doi.org/10.30574/gscarr.2026.27.2.0102

Abstract

Alternariosis are phaeohyphomycoses with a predominantly cutaneous localisation; they primarily affect immunocompromised individuals. The objective of this work is to review the mycological characteristics of alternariosis and the factors favouring transmission. We report the case of a diabetic patient presenting with a myelodysplastic syndrome and suspicious cutaneous lesions. The mycological examination of the biopsy sample revealed a cutaneous alternariosis. The treatment consisted of a combination of surgical excision of the lesions and antifungal therapy.

Keywords: Cutaneous Alternariosis; Phaeohyphomycosis; Immunosuppression; antifungal

1. Introduction

Alternariosis are opportunistic mycoses caused by filamentous fungi of the genus *Alternaria*. They are included amongst the phaeohyphomycoses, whose pathogens are black fungi or dematiaceous fungi. The latter share the presence of melanin-like brown pigments in the cell walls of their hyphae or conidia, or both. This is considered a major virulence factor that allows them to resist environmental stresses and host phagocytosis mechanisms. These saprophytic and phytopathogenic fungi are increasingly recognised as causes of human infection. [1, 2] Fungi of the genus *Alternaria* are primarily responsible for dermal cutaneous lesions. They are rare, but the number of reported cases is constantly increasing, particularly in immunocompromised individuals. [3] The present work aims to review the mycological characteristics of cutaneous alternariosis and to study the factors favouring their transmission, as well as the basis of therapeutic management.

2. Case Report

This involves a 64-year-old male patient, with type 2 diabetes on insulin for 12 years, who underwent cataract surgery 2 months ago. The patient presented with a myelodysplastic syndrome with a high risk of leukaemic transformation (MDS-EB1) and was scheduled for chemotherapy. He was hospitalised for facial cellulitis, which began approximately 1 month prior with the appearance of a nasal discharge followed by bilateral nasal obstruction associated with erythema and facial swelling. The progression was marked by the onset of stomatitis with necrotic deposits in the oral cavity (Figure 1), and an extension to the cheek and eye with plaques of necrosis around the eye, all evolving within a febrile context and a deterioration of his general condition with asthenia and weight loss. On physical examination, the swelling of the hemiface was very pronounced on the left, with a bulging of the inner canthus of the eye topped by a ruptured bulla, and an extensive inflammatory patch on the cheek and upper lip with tearing. The CT scan was indicative of left hemifacial cellulitis secondary to a collected dacryocystitis.

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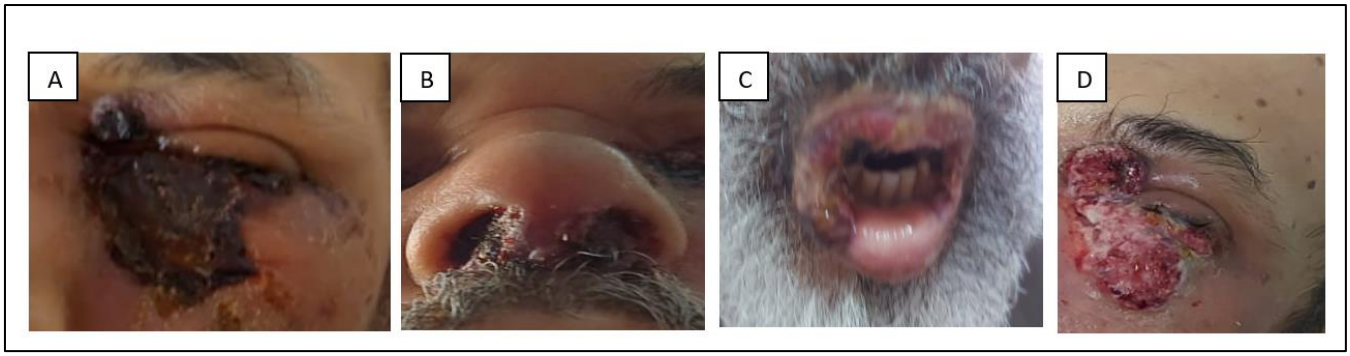

Figure 1 A: Necrotic deposits on the eyelid/ B: Bilateral nasal obstruction/ C: Necrotic deposits in the oral cavity/ D: Surgical excision of the necrotic deposits around the eye

Surgical excision of the necrotic deposits and a biopsy of the underlying lesion were performed. The mycological examination of the biopsy fragments revealed the presence of mycelial filaments upon direct examination. The culture on Sabouraud agar was positive after 7 days of incubation at 30°C, with the colonies appearing brown and fluffy upon macroscopic examination. The microscopic appearance of the colonies under a light microscope after staining with Lactophenol cotton blue showed long, sometimes melanised, septate mycelial filaments; amidst the filaments, brown structures were visible: conidia or dictyospores often arranged in chains, with a beaked extremity, an appearance suggestive of *Alternaria* sp.

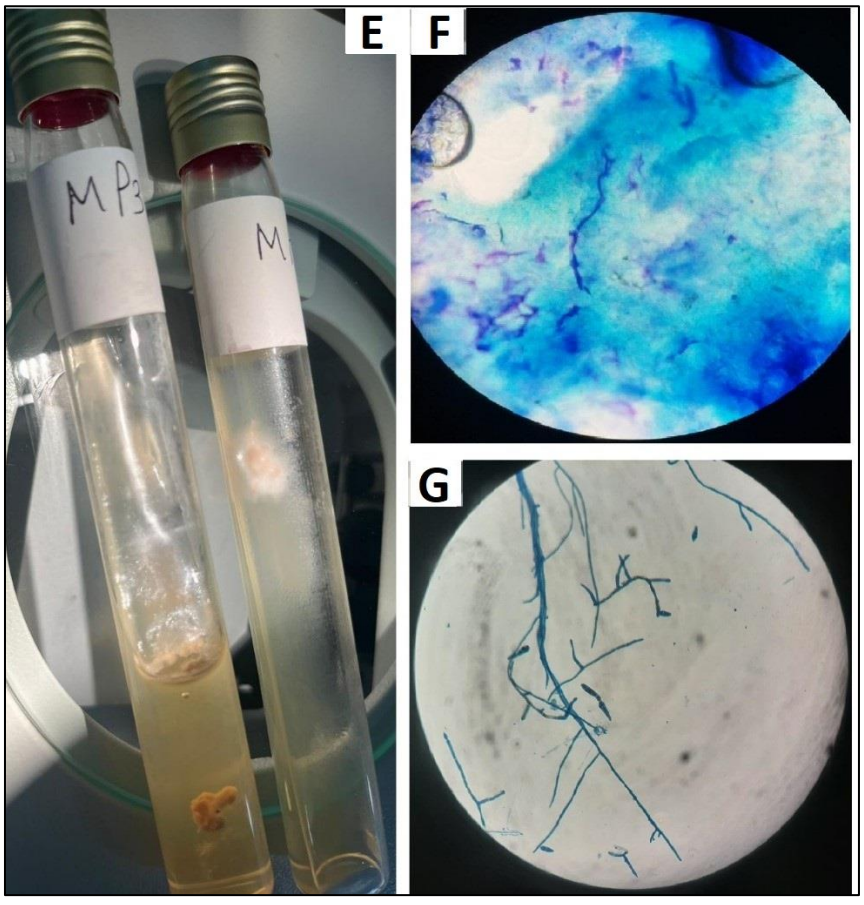

Figure 2 E: Macroscopic appearance of the colonies in mycological culture/ F: Direct examination of a biopsy fragment, MGG stain: mycelial filaments/ G: Microscopic appearance of the colonies, Lactophenol blue stain

The patient was initially treated with Amphotericin B (0.5 mg/kg/day) for 15 days (empiric treatment), then with echinocandins (caspofungin 50 mg/day) for 7 days, and finally with voriconazole (400 mg/day). The patient also

underwent surgical excision of the lesions, combined with local care and preventive measures against potential superinfections. Despite optimal medical and surgical management, the progression was marked by a good clinical improvement, but given the background of immunosuppression, death occurred in a context of severe anaemia with hypovolaemic shock.

3. Discussion

Alternariosis is a phaeohyphomycosis that most often occurs in immunocompromised patients. Phaeohyphomycoses are classified into two groups according to the depth of invasion (epidermal versus dermal): semi-deep/deep phaeohyphomycoses and superficial ones [4; 5]. Two routes of cutaneous infection are possible: from an exogenous or an endogenous source. The exogenous source is either the consequence of traumatic inoculation (most cases) or the colonisation of damaged skin. The endogenous source originates from the inhalation of spores that have disseminated within the body and results in secondary involvement of the skin (the lesions therefore having a sporotrichoid distribution) [6, 7, 8]. Interestingly, some authors have hypothesised that skin fragility induced by corticosteroids could increase the risk of percutaneous inoculation. [8] *Alternaria* are saprophytes or plant parasites widely distributed in nature. Their spores are dispersed by air currents. The fungus is introduced following microtrauma, which explains the higher frequency of alternariosis in patients from tropical areas, in immunocompromised patients, and in rural dwellers, as well as their preferential localisations on exposed areas: knees, wrists, and the back of the hands. Their appearance is polymorphic and varies according to the evolutionary stage. The most common appearance is that of purplish, erythematous-crusted nodules. [7, 2]. In very rare cases where multiple and disseminated foci were observed, dissemination via the bloodstream was discussed. [9] According to a literature review, the main predisposing factor is long-term systemic corticosteroid therapy, sometimes associated with immunosuppressants or cytotoxics. The conditions justifying such treatments were diverse: autoimmune diseases, renal and hepatic transplants, haematological malignancies, neoplasia, nephrotic syndromes, asthma… More rarely, exclusively topical corticosteroid therapy was reported. Other underlying conditions may be noted: Cushing's disease, diabetes, and rarely HIV infection. For patients receiving systemic or topical corticosteroid therapy, as well as those with Cushing's disease, the skin fragility induced by hypercortisolism acted as a cofactor by facilitating the direct inoculation of the fungus. Regardless of the extent of immunosuppression, neither visceral invasion nor positive blood cultures have been described, and the observed deaths were due to the underlying disease. [10, 11]. Mycological examination must not be neglected as it allows the lesion to be rapidly attributed to a fungal infection. The diagnosis relies on the pathological and mycological examination of a skin biopsy. Due to the frequency of the fungus in nature, both of these examinations must be positive in order to confirm its pathogenicity. The histological appearance is that of well-demarcated, mixed granulomas located in the superficial dermis and potentially reaching the deep dermis and hypodermis. The fungus appears as rounded elements and/or short, septate filaments, the walls of which are well stained by PAS and Gomori-Grocott stains. The identification of the genus *Alternaria* relies on mycological culture. Molecular biology facilitates species diagnosis, particularly when there is no conidial formation in culture. Purely epidermal cases of alternariosis are debatable. Fungi of the genus *Alternaria* can cause onychomycoses. [12, 13, 14, 15]. The treatment is not standardised, and there are no precise guidelines. Indeed, the great diversity of dematiaceous fungi makes it impossible to recommend a uniform approach in the treatment of phaeohyphomycoses [1, 12, 16]. The duration of treatment and the choice of intervention (surgery, systemic antifungal treatment, or a combination of both) are based on the clinical presentation, the host's underlying condition, and the initial response to treatment [1]. Surgical excision followed by oral antifungal treatment is recommended by most authors [16]. Antifungal treatment without excision is generally not sufficient [16]. Surgical excision without systemic treatment can be an effective treatment in localised and superficial forms of phaeohyphomycosis [5, 17]. The reduction of immunosuppression, when possible, is also an interesting therapeutic approach [8]. In all cases, long-term follow-up must be implemented in order to address late recurrences [17]. Oral treatment with itraconazole is the most commonly used antifungal and should be the oral treatment of choice with a duration exceeding two months; it is usually continued for 1 month after the disappearance of the lesion and for 4 months if the lesion has been excised [7, 5, 8, 12]. The doses used range from 100 mg/day to 600 mg/day [5]. Some cases of therapeutic failure with itraconazole have been reported even though in vitro susceptibility had been demonstrated [5]. In our patient, the duration of treatment was 15 days for amphotericin B (0.5 mg/kg/day) (empiric treatment) and 7 days for echinocandins (caspofungin 50 mg/day) before a supply disruption, which affected compliance with the echinocandin treatment and necessitated the administration of voriconazole (400 mg/day). In the literature, Bajwa et al. used itraconazole as the treatment of choice in monotherapy for a duration exceeding two months but encountered a resistance rate of 40%, requiring an additional agent. Voriconazole as a monotherapy or in combination with surgery or topical antifungals has yielded the best results (79% response rate) [5]. Finally, posaconazole would overcome the disadvantages of itraconazole, particularly regarding drug interactions (no inhibition of CYP450) [5]. Furthermore, imidazole antifungals inhibit cytochrome P450 3A4/5; it is recommended to decrease the doses of immunosuppressive treatment and to monitor the concentrations of these molecules during antifungal therapy [7]. Cohorts and in vivo studies have shown that by inhibiting calcineurin, agents such as tacrolimus and sirolimus could

inhibit the growth of these pathogens. Interestingly, tacrolimus has demonstrated antifungal properties. The use of these calcineurin inhibitors could provide some protection against these frequently found species [16].

4. Conclusion

This clinical case shows that cutaneous alternariosis is a condition not to be neglected and must be considered in immunocompromised individuals. The clinical examination, particularly the dermatological one, must be meticulous because the cutaneous presentations of alternariosis are heterogeneous. The contribution of direct examination of biopsy appositions is significant in the detection of mycological characteristics; Therapeutic strategies remain variable and are not yet codified, but they primarily rely on surgical excision, prolonged antifungal treatment, and the reduction of immunosuppression.

Compliance with ethical standards

Acknowledgments

Our sincere gratitude goes to Oukoujane El mustapha from Mycology Laboratory of ARRAZI Hospital, which performed the mycological examinations of this case.

Disclosure of conflict of interest

There is no conflict of interest

Statement of informed consent

Informed consent was obtained from all individual participants included in the study by signing the Free and Informed Consent Form.

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