CASE REPORT

Iatrogenic immunosuppression may favour *Alternaria* skin lesion flares

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SUMMARY

Alternaria spp may cause opportunistic mycoses in the skin after cutaneous inoculation or through blood dissemination in immune-suppressed patients. Here, we describe a case of cutaneous infection with *Alternaria* spp in a 62-year-old man, presenting with multifocal papules and erythematous nodules involving distal limbs bilaterally. The absence of inflammatory bowel disease was confirmed by a gastroenterologist. The patient was under treatment for uveitis of unknown origin with immunosuppressive doses of cyclosporin and prednisolone for approximately 3 months. The diagnosis was based on clinical signs, demonstration of fungal elements in skin biopsies and deep fungal culture. Complete clinical remission was achieved by oral and systemic treatment with antifungal drugs. However, because cessation of the immunosuppressive medication was not possible, his clinical history was characterised by multiple flares requiring each time oral and intravenous antifungal treatment.

BACKGROUND

Phaeohyphomycoses (PHMs) are diseases caused by fungi able to produce melanin. The black fungi may cause different types of infection in humans, ranging from superficial, involving the stratum corneum, keratinised tissues and cornea, to deep-seated infections called PHMs.¹ The infection, generally mild, in immune-compromised hosts may disseminate after inhalation with subsequent lung infection.^{1–3} Agents that most frequently cause human infections are *Alternaria* spp, *Exophiala* spp, *Phialophora* spp and *Wangiella* spp.^{1,4} Since the course of disease may vary according to different host and fungal species, the most important step in diagnosing PHMs is first to suspect the infection on the basis of clinical features including the presence of nodular lesions, suppurative granulomatous infiltrate, oval-to-round bodies at the histology examination and a positive culture.

Traditional therapy for multiple subcutaneous lesions includes oral antifungal drugs such as itraconazole, voriconazole, posaconazole and amphotericin B.¹ Photodynamic therapy, cryotherapy and laser are an alternative or coadjuvants to conventional antifungal agents.

However, in order to obtain a sustained remission, any effort should be attempted to remove the cause of immune suppression.

We present a case of disseminated cutaneous infection caused by *Alternaria* spp in an immune-compromised patient.

CASE PRESENTATION

A 62-year-old man, white Caucasian, was referred to our clinic by the ophthalmology specialist for the presence of erythematous nodules on the lower legs. In the previous year, the patient experienced an uveitis of unknown origin. The gastroenterologist confirmed the absence of inflammatory bowel disease. The patient was treated for 3 months with cyclosporin 200 mg/daily and prednisolone 50 mg tapering dose. In addition, the patient was diagnosed with type 2 diabetes. He denied any recent travel abroad. Clinical examination showed several erythematous and/or purple infiltrated nodules, some of which with a scaly-crusty surface involving the lower extremities symmetrically (figure 1). Skin lesions occurred 2 months earlier. There was no history of recent trauma. Eight years before, the patient was treated with brachytherapy for prostate cancer.

INVESTIGATIONS

Laboratory tests including full blood count and lymphocytic subpopulations, urine and electrolytes, liver profile, C3, C4, autoantibodies (anti-nuclear antibody, extractable nuclear antigens and antineutrophil cytoplasmic antibodies), inflammatory markers (C-reactive protein and erythrocyte sedimentation rate), serological testing for syphilis (venereal disease research laboratory and *Treponema pallidum* haemagglutination assay) and chest X-Ray were all negative. QuantiFERON-TB gave positive result. A deep cutaneous biopsy for histology and culture for tubercular and non-tubercular mycobacteria, fungi and other bacteria was performed. Biopsy specimens stained with H&E showed a thick infiltrate containing histiocytes,

Figure 1 Erythematous-violaceous nodules with a crusty and scaly surface bilaterally distributed.

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Figure 2 Histiocytic infiltrate with an area of suppuration. Presence of oval-to-round bodies.

lymphocytes and neutrophils involving the whole dermis and subcutis. There were suppurative areas within a not well-defined granulomatous pattern (figure 2). Moreover, a number of round-to-oval bodies, highlighted with Grocott's stain were observed (figure 3). Ziehl-Nielsen stain was negative. Growth of *Alternaria* spp was observed in culture media. On the contrary, tubercular and non-tubercular bacteria were not observed.

DIFFERENTIAL DIAGNOSIS

Based on clinical presentation and medical history, an extensive differential diagnosis was required including sarcoidosis, vasculitis, erythema nodosum, Bazin's erythema induratum, cutaneous manifestation in inflammatory bowel diseases and infections such as syphilis, cutaneous tubercular and non-tubercular and fungal infections. However, negative blood investigations, positive QuantiFERON-TB and the histology characterised by the presence of granulomas suggested an infectious process caused by fungi or tubercular or non-tubercular mycobacteria. Moreover, the presence of oval-to-round bodies in biopsy specimens highlighted by Grocott's stain, strongly supported a diagnosis of deep mycotic infection. Finally, culture confirmed the presence

of *Alternaria* spp and the absence of tubercular and non-tubercular mycobacteria.

TREATMENT

Based on histological features of a fungal infection, an empirical treatment with itraconazole 200 mg/daily was started and continued for 8 weeks. Subsequently, intravenous voriconazole was added followed by oral voriconazole 200 mg/daily according to antibiotic sensitivity test results.

OUTCOME AND FOLLOW-UP

Lesions resolved completely after 1 month of treatment and voriconazole was stopped. However, after 2 months, the lesions recurred. In the attempt to remove the immunosuppression as trigger, the patient was switched from cyclosporin to azathioprine, and, at the same time, intravenous amphotericin B 300 mg/daily was administered for 2 weeks. The clinical effect on skin lesions was weak and the clinical course of the disease was characterised by recurrent flares requiring antifungal treatment.

DISCUSSION

Alternaria spp are widely distributed in the environment.³ Spores are present in soil, water, indoor⁵ and as pathogen of plants.⁶ *Alternaria* is a well-known cause of allergies³ but rarely may cause infection in healthy individuals, although a few cases have been reported.⁶ Usually, *Alternaria* may infect immune-compromised hosts, mostly transplanted patients,² patients with advanced acquired HIV syndrome, hosts with malignancies, autoimmune disease, iatrogenic immunosuppression, patients with poorly controlled diabetes mellitus and other severe comorbidities.^{2,7} In these subgroups of patients, skin injuries may facilitate pathogen inoculation.⁵⁻⁷ In addition, a systemic dissemination through blood may occur, after inhalation of the pathogen, and in this case lesions are multiple, not contiguous, bilaterally spread.⁴⁻⁸ Widespread *Alternaria* infection may be fatal because of involvement of multiple organs including brain.¹ Erythematous macules, violaceous papules or nodules and ulcers occur in the dorsal surface of hands, fingers, feet, knees and pretibial areas in the cutaneous syndrome.¹

The typical histological hallmark is a suppurative and granulomatous dermatitis or cellulitis.⁷ Suppurative granulomas are the most frequent type, but sarcoid-like or plasma-cell rich granulomas can occasionally be observed. Black hyphae are usually present.¹ There is no standard treatment for cutaneous infections by *Alternaria*. Surgical excision, when possible, is recommended.^{1,3,6} Itraconazole, voriconazole, posaconazole, amphotericin B and terbinafine are suggested treatments.^{1,6} High dosage of echinocandins, fluconazole and flucytosine showed to be also effective.¹ Intralesional amphotericin B or imidazole may be used in some cases. Treatment is necessary until clinical resolution and should be continued for additional 3–6 months.⁹ Removing the cause of immune suppression, when possible, is mandatory in order to achieve a definitive cure.

In our patient, the bilateral distribution of multiple lesions, suggested a disseminated form of infection, although pulmonary symptoms were absent and the chest X-ray was negative. Due to disease dissemination, a correct diagnosis was mandatory in order to avoid a catastrophic outcome for the patient. However, because of the risk of serious eye damage, it was not feasible to stop the immunosuppressive therapy, and since surgical option was excluded owing to the systemic

Figure 3 Grocott's methenamine silver stain identified several fungal organisms.

Patient's perspective

- I greatly appreciate the approach among all doctors in taking care of my illness. Although a complete resolution of the infection has not been reached, I am confident that they will do everything to avoid further complications.

Learning points

- *Alternaria* spp is a well-known cause of allergies being widespread in the environment and rarely may cause cutaneous infection.
- Disseminated infection may occur in immune-compromised hosts and, if not diagnosed and appropriately cured, may be fatal.
- The most important step in the treatment of the disease is to remove the underlying cause of immunosuppression, when possible.
- Antifungal therapy remains the only valuable option to treat recurrences.

nature of infection, a definitive cure of the disease was not achieved.

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