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Case Report

Primary Cutaneous Dermatosis Due to *Alternaria alternata*, Case Report in an Immunocompromised Patient

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KEYWORDS

primary cutaneous dermatosis, Alternaria alternata, immunosuppression

ABSTRACT

Cutaneous alternariosis is an unusual opportunist infection with the complexity of its polymorphous manifestations that occur in circumstances of immunosuppression. We present a case of a 66-year-old female patient with type 2 diabetes mellitus, who had a nephrectomy, who presents a dermatosis of 2 months of evolution, consisting of papules and vesicles that affect the right cheek and neck. Histopathological study was performed with hematoxylin and eosin stains and Schiff's periodic acid, mycological (direct examination with KOH and cultures) and molecular biology. Diagnosis of *Alternaria alternata* infection was made based on histopathological, mycological and molecular biology studies. Treatment with itraconazole 200 mg/day and topical ketoconazole was indicated, with resolution at 3 months. Cutaneous alternariosis is a rare pheohyphomycosis with potentially invasive and fatal implications.

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1. Introduction

Feohyphomycosis is an uncommon fungal disease caused by a group of heterogeneous fungi that produce melanin-like pigment. The condition manifests in both immunocompetent and immunosuppressed patients (1, 2).

The genera implicated include species of *Alternaria*, which are fungi found worldwide in soil, air, and other habitats. These organisms are classified as opportunistic pathogens, capable of infecting humans, animals, and plants. The clinical manifestations of this condition are diverse, encompassing a wide spectrum of presentations, including but not limited to eye disease, sinusitis, onychomycosis, dermatosis, and unusual forms such as pulmonary and disseminated disease (3).

The underlying factor associated with skin and subcutaneous conditions is impaired immunity, induced by organ transplant treatment, Cushing's syndrome, and the use of various immunosuppressive agents (3).

2. Clinical case

A 66-year-old female patient, a native of Guadalajara, Jalisco, Mexico, was diagnosed with uncontrolled type 2 diabetes mellitus (fasting glucose of 126 mg/dl) and treated with linagliptin 5 mg/day. She also had a history of nephrectomy due to pyelonephritis.

The patient exhibited a condition that had been developing for two months, characterized by dermatosis affecting the right cheek, lateral neck, and supraclavicular region. The dermatosis manifested as erythematous papules and vesicles that converged to form plaques and some punctiform hematoma scabs. These lesions were located on irregularly distributed erythematous patches and were associated with mild pain on palpation (Fig. 1). Upon further inquiry, the patient declined to report any history of trauma, systemic symptoms, or involvement of other organs. The remainder of the examination revealed no adenomegaly or other findings suggestive of systemic involvement. He sought consultation with a physician, who prescribed an unspecified treatment for suspected herpes. This treatment did not result in any improvement.

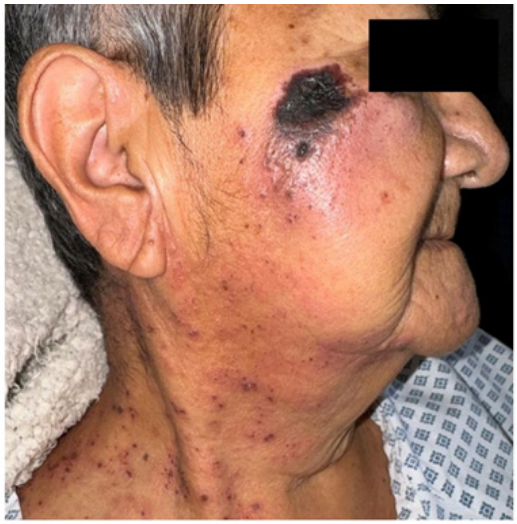


Fig. 1. *Dermatosis on the right cheek consisting of erythematous papules and vesicles forming plaques, punctate crusts and progression to a scar.*

A histopathological evaluation of the cheek skin biopsy, which had been stained with hematoxylin and eosin (H&E) and periodic acid-Schiff (PAS), revealed an inflammatory infiltrate consisting of neutrophils and lymphocytes, areas of necrosis, and septate hyphae with a diameter of 4 to 6 µm and branching. This finding is was suggestive of cutaneous mycosis (Fig. 2).

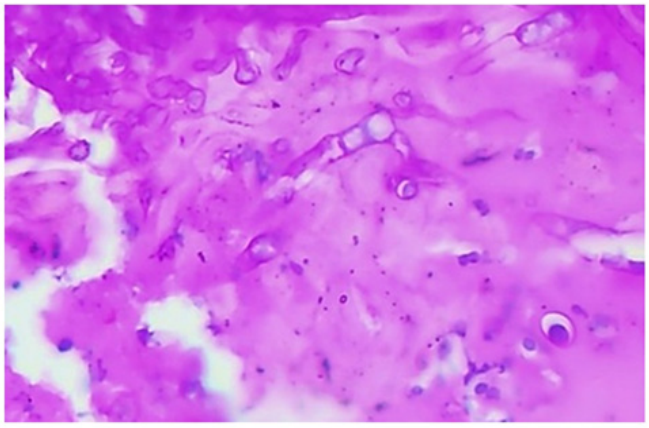


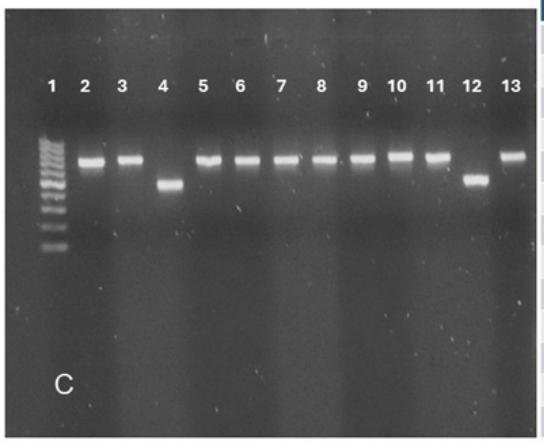
Fig. 2. *Histopathological study with PAS staining (40x), where septate and branched figs of 4 to 6 microns in diameter are were observed.*

A comprehensive evaluation encompassing blood biometry and blood chemistry tests was conducted, which revealed the presence of normocytic normochromic anemia and chronic kidney disease, classified as stage G3a according to the CKD-EPI classification system, (Chronic Kidney Disease Epidemiology Collaboration classification), with a glomerular filtration rate of 41 ml/min/1.73 m.

A scraping of the necrotic lesion was performed for direct examination with 20% KOH, where macroconidia, septate, demateaceous hyphae measuring 4 to 6 microns in diameter were observed. The sample was cultured in six tubes with Sabouraud dextrose agar at 28 and 30°C. After five days, the sample developed unlimited colonies with a velvety green appearance. Microscopic examination revealed the presence of brown septate dictyoconidia with pores arranged in short chains, characteristics that are indicative of *Alternaria* species (Fig. 3A and 3B).

Fig. 3 A. *Limited, velvety, greenish colony on plain Sabouraud agar*; **B.** *Microscopy with septate dictyoconidia and short chains of Alternaria sp.*

The extraction of deoxyribonucleic acid (DNA) was carried out using the Exgene Plant SV mini kit (GeneAll®). The genetic material obtained was quantified by spectrophotometry (EPOCH) and subjected to agarose gel electrophoresis (1.5% agarose; run at 80 V for 1 hour; stained with RedGel). After the procurement of DNA at an acceptable concentration and quality, end-point PCR amplification was performed targeting the ITS1/ITS4 region of the ribosomal DNA. The amplified product was then subjected to a purification process using a ZymocleanTM gel DNA recovery kit (Zymo Research, USA®). The agarose gel under consideration was derived from a low-melting-point source. The obtained fragment was subjected to de novo sequencing using the Sanger chain termination method in a Biosystems 3500 series genetic analyzer (Thermo Fisher Scientific®). This sequence was then compared with the Genbank database, which revealed 100% identity with *Alternaria alternata* (Fig. 3C).



Carril	Producto	[DNA] ng/µl	Tamaño (pb)
1	Marcador		
2	Caso clínico	89.05	750
3	7	52.55	750
4	9	58.9	450
5	10	54.05	750
6	12	44.45	750
7	13	42.55	750
8	14	48.3	750
9	15	49.6	750
10	16	52.8	750
11	18	54.75	750
12	19	53.1	450
13	20	34.4	750

Fig. 3 C. *1.5% agarose gel; purified amplified PCR product ready for sequencing. (lane 2, 750bp length, ITS2/ITS4 primers.*

The diagnosis of primary cutaneous alternariosis was made, and treatment with itraconazole 200 mg/day orally and topical ketoconazole 2% on the affected area was indicated, with complete resolution at 3 months (Fig. 4).

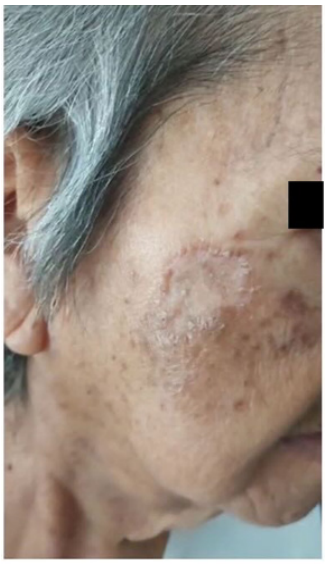


Fig. 4. *Treatment with itraconazole, resolution in three months with clear regression of the lesion.*

3. Discussion

Reports of this disease are rare because this genus is commonly considered a contaminating fungus, thus diminishing its medical importance. Furthermore, molecular identification is required to confirm the precise identity of the agent and, consequently, the diagnosis (4).

The main predisposing factor for *Alternaria* infection is a decreased immune response induced by immunosuppressants, as in the case of post-transplant patients, carriers of autoimmune diseases, steroid use, and diabetes mellitus (5). The patient has been diagnosed with uncontrolled type 2 diabetes mellitus and chronic kidney disease, with a history of nephrectomy, making her susceptible to disease caused by this fungus (3).

Diseases in humans caused by *Alternaria* spp. have been reported, affecting the eyeball, paranasal sinuses, oral mucosa, skin, subcutaneous tissue, joints, and disseminated forms. There are cases of hypersensitivity pneumonitis explained by the inhalation of conidia (4, 6).

The species *Alternaria alternata* is reported as the causative agent in most skin conditions, although A. *infectoria*, A. *tenuissima*, A. *alternatum*, and A. *tenuis* have also been described (7). Two routes of infection have been proposed for cutaneous alternariosis: exogenous infection through trauma with contaminated plant material (implantation mycosis), although there is not always a history of trauma prior to infection, and endogenous contamination through inhalation of fungal conidia with subsequent hematogenous spread to other organs, including the skin (disseminated alternariosis or invasive fungal disease) is possible (8).

The clinical presentation on the skin manifests in exposed areas, predominantly on the lower extremities, forearms, and chest, and less frequently on the face. Clinically, erythematous nodules, keratotic plaques, recurrent cellulitis, irregular and/or necrotic ulcers, and erythematous-violaceous nodular neoplasms may be present; therefore, the differential diagnosis with other dermatoses is broad. The average time from the onset of clinical symptoms to the diagnosis of alternariosis is approximately 3.7 months (9).

The diagnosis is made based on mycological studies such as direct examination and culture, as well as histopathological study demonstrating the presence of fungal structures in the tissue. Currently, molecular methods, such as endpoint PCR RPLF®, and proteomics such as MALDI-TOF®, are used to identify the species involved (6, 7, 9-11).

Treatment consists of azoles for a period of 3 to 12 months, depending on the severity of the disease, the type of condition, and the patient's immune response. In disseminated cases, with relapses, osteoarticular involvement, and osteomyelitis, the required treatment may be prolonged for 1 to 2 years (9). The antifungals used mainly include itraconazole and amphotericin B (in cases of dissemination), although voriconazole has also been used in immunocompromised patients, which can be combined with topical antifungals (for skin conditions). A surgical approach has been reported in invasive cases, where the involvement is not only in the skin and localized, including the use of Mohs micrographic surgery with PAS staining in the sections. In our case, there was an excellent response to oral itraconazole and topical ketoconazole for 3 months, in addition to adequate metabolic control with oral hypoglycemic agents (4, 9, 12).

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