Review

Alternaria Infections in Immune-Compromised and Transplant Patients: A Review of Case Studies and Treatment Methods

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Alternaria Infections in Immune-Compromised and Transplant Patients: A Review of Case Studies and Treatment Methods

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Abstract: Alternaria alternata is a saprophyte and is also known to cause many opportunistic infections in humans. Alternaria infections are important factors of morbidity and mortality in immune-compromised and solid organ transplant (SOT). Sensitivity to the airborne fungus Alternaria alternata is also believed to be a common cause of allergic asthma. Therapies are limited by the lack of knowledge about the role of individual fungal gene products and symptoms in immune-compromised and transplant patients. This review summarizes the published case studies on Alternaria alternata infections in transplant patients.

Keywords: Alternaria alternata; host-pathogen interactions; immune-compromised; transplant patients; asthma

1. Introduction

Alternaria species are fungi widely distributed in nature. As opportunistic pathogens, they can cause many plant diseases. They are also weak parasites, saprophytes and endophytes. The species is the principle contaminating fungi in several food and food products. Alternaria spores are the predominant spores in the atmosphere and act after inhalation. Fungal spore's concentration in the atmosphere is 1000-fold more than pollen and can cause prolonged exposure overtime [1,2]. Its spores, while preferring warm and humid climate, can also grow at low temperatures and thus pose a major risk to humans and animals [3–6].

Alternaria alternata is a saprophyte and is also known to cause many opportunistic infections in humans. Alternaria infections are also important factors of morbidity and mortality in immune-compromised and solid organ transplant (SOT). Alternaria is a common genus for invasive infection in transplants patients. About 33.3% of transplant patient die due to the fungal infection [7]. In this group, lung graft patients have the highest incidence of fungal infections. A table of incidence of fungal infections in organ transplants is given in Table 1.

A. alternata can cause invasive infections such as keratomycosis, cutaneous alternariosis, paranasal sinusitis, granulomatous pulmonary nodule, peritonitis and phaeohyphomycosis. A. alternata can also affect patients that are immune-compromised by HIV. A 31-year-old man with AIDS developed necrotic lesions in nasal septum due to the fungus A. alternata. The patient was effectively treated with surgical excision and amphotericin B. This suggests the importance of innate cell-mediated immunity in host defense against this organism [8].

Table 1. Rate of Incidence of fungal infections in solid organ transplant. [9].

Solid Organ Transplant	Rate of Incidence (%)
Lung	7.9
Heart	3.4
Liver	3.1
Kidney	1.1
Pancreas	0.7

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2. Alternaria alternata and Cutaneous Infections

Nearly 4.5-6% of organ transplant patients are prescribed with tacrolimus. However, this application is not without risks as about 66-67% of patients developed fungal infections due to its usage. The incidence of Alternaria fungal infections has increased the mortality rate of the patients. Cutaneous alternariosis is an opportunistic infection that occurs in patients being treated with systemic corticosteroids and in a few rare cases in patients with HIV. High cortisol levels induce fragility in cutaneous lesions that permit direct infections from fungi like A. alternata and A. infectoria [10]. The treatment methods are also not standardized and can be difficult. A. alternata is also reported to be partially unresponsive to amphotericin B, miconazole, itraconazole, ketoconazole and imazalil [11].

Patients with cutaneous A. alternata infections (Alternariosis) and on tacrolimus monotherapy show poor response to surgical excision and itraconazole alone. Reduction of immunosuppressive drug dosage provides better results. In Alternaria infections surgical excision followed by treatment with amphotericin B provides a more effective therapy. Voriconazole provided an effective treatment response to A. alternata skin lesions in liver transplant patients as seen in a 62-year old patient with hepatic cirrhosis with a history of hepatocarcinoma [12]. Alternaria infections are also harder to diagnose based on histopathology or morphology alone. DNA testing provides a more effective diagnosis [13].

Another 60-year old male patient reported skin lesions nine months after a heart transplant due to dilated cardiac myopathy with an underlying squamous cell carcinoma. The lesions were later identified to be A. alternata hyphae. Alternaria was also cultured from the broncho-alveolar lavage in the left lung with computed tomography angiography after a progressive dyspnea was reported. The patient was first treated with reduced tacrolimus, an immunosuppressant, levels and daily dose of 400mg voriconazole and then changed to 800mg posaconazole upon persistent infection in the lung. The treatment was effective and no relapse was seen after 2 months [14].

A 56-year-old cardiac transplant patient developed an Alternaria skin infection 9 months after surgery. This case illustrates the difficulties in treating invasive Alternaria infections and a unique case of treatment of fungal infections with curettage and cautery in absence of anti-fungal therapy. Initial treatment of oral fluconazole 200mg for 5 weeks was unsuccessful. One year after onset of skin infection, skin biopsy showed progression with hyperkeratosis and pseudo-epitheliomatous hyperplasia with a dermal granulomatous infiltrate. After unsuccessful treatment with itraconazole, intravenous methylprednisolone and an increased dose of tacrolimus and mycophenolate mofetil, the infection was treated with curettage and cautery and double freeze-thaw cryotherapy. [15]

Alternaria infections are also common in children when on an immunosuppressive regimen as in the case of a 12-year-old male patient with Fanconi's anemia was reported to have an Alternaria infection 33 days after allogeneic hematopoietic stem cell transplantation. An anti-fungal prophylaxis treatment was performed with 600mg posaconazole orally and caspofungin for 4 days before the transplant. Skin biopsy of the nodules seen in the lower limb identified them as invasive A. alternata hyphae infection as the culprit. A treatment combination of posaconazole and liposomal amphotericin B provided complete resolution of skin lesions. These results raise the question of most appropriate drug for prophylaxis treatment as well as the importance of the synergy of several drugs for treatment of A. alternata infections. [16]

Cutaneous infections with Alternaria usually occur on the extremities. Invasive fungal infections by A. alternata and A. infectoria are becoming more common as the rate of organ transplants grow along with increased use of immune suppressive regimens. In chronic lymphocytic leukemia (CLL), the patient is heavily immune compromised. CLL itself is associated with immune deficiency due to loss of both cell-mediated and humoral immunity. A 58-year old male farmer was admitted complaining of fever, rigors, and night sweats with a greenish-blue nodule on the right hand. With prior history of chemotherapy and immunotherapy due to CLL, the patient was at considerable risk of death by an opportunistic infection. The fungal elements on the nodule were identified to be A. alternata. The nodule invaded the subcutaneous tissue and had to be surgically removed. The surgical bed was then irrigated with amphotericin B. Oral anti-fungal's like voriconazole and

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posaconazole failed to have any effect before surgery. In soft tissue infections like this, medical therapy seems to be failing in treating an aggressive fungal infection. This case suggests that a combination of surgical and anti-fungal therapy is recommended for immune-compromised patients for successful outcomes. Identifying the fungal species is also very important for optimal treatment of systemic infections [17].

Another 65-year old male liver transplant patient developed an invasive A. infectoria infection. The patient was successfully treated with fluconazole. A combinatorial therapy comprising anti-fungal azole based drugs and a reduction of immune suppressive drugs seems to be the cornerstone for invasive fungal infections in solid organ transplant patients [18].

Persistent thermotherapy was applied in the rare case of a patient with a subcutaneous infection with an underlying history of renal transplant. Amphotericin B could not be used because of the potential renal toxic effects. Warmth therapy proved to be more effective in this case and the fungal colonies were reduced after six months of therapy [19].

Another 56-year old female liver transplant patient developed pulmonary nocardiosis two months after an episode of liver rejection and a series of cytomegalovirus infections. Culture examination confirmed the presence of Alternaria alternata. Oral Voriconazole resolved the skin infection with complete remission highlighting the importance of early screening for Alternaria alternata. [30]

3. Alternaria alternata and Phaeohyphomycosis

A 65-year-old male Caucasian patient with a history of a liver transplant within 4 months and under immunosuppressive therapy reported nodules on the right leg and dorsal of the left hand. Microscopic analysis identified the biopsy isolates as Alternaria spp. even though there was slight difference in the biopsy material from the hand and the leg. Molecular sequencing and corresponding analysis identified A. alternata as the species in the leg and A. infectoria as the species in the hand. The infection was defined as Phaeohyphomycosis and is one of the first cases of cutaneous co-infection with two different species of Alternaria in the world. The patient treatment consisted of surgical excision and oral itraconazole. No relapse was reported. [9]

Phaeohyphomycotic infections are also increasing prevalent in immune compromised patients. It manifests clinically as lesions or ranges up to disseminated infections. Treatment options involve Itraconazole for subcutaneous infections but if the infection is systemic, amphotericin B is required [20].

4. Alternaria alternata in Corneal Transplants

Keratomycosis was detected in 21 cases of infection of the eye. All of the cases were limited to cornea. After a corneal transplant, a 53-year-old Japanese woman was reported to have contracted an ulcer in the right eye. A. alternata was detected in the culture of the ulcerated tissue. Five drugs were used for treatment: Thimerosal, Pimaricin, Amphotericin B and Nystatin. Out of these, Thimerosal was most effective. [21]

Another case of Alternaria associated keratomycosis was reported in a 66-year old female patient with the corneal transplant of the right eye. A second keratoplasty was performed as the consequence of corneal melting by the fungal infection. A local and systemic anti-fungal treatment resulted in complete resolution of the fungus and minimized the risk of permanent eye loss. [22] A record of opportunistic infections caused by Alternaria species is given in Table 2. [27,28]

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Table 2. A summary of case studies involving invasive infections caused by Alternaria species and their underlying defect.

Patient Details	*Alternaria* infection	Immune Defect	Treatment	Outcome	Ref.	Organism
31/M	Visceral and mucosal infections	AIDS	Amphotericin B	No Relapse	8	*A. alternata*
65/M	Phaeohyphomycosis	Liver transplant, Tacrolimus immune suppressive therapy and diabetes	Itraconazole	No Relapse	9	*A. alternata and A. infectoria*
70/M	Cutaneous	Cadaveric renal transplantation , ulceration and vascular graft rejection	Itraconazole	cerebrovascular accident	11	*A. alternata*
62/M	Cutaneous	Liver Transplant	Voriconazole	No relapse	12	*A. alternata*
66/M	Cutaneous	Liver Transplant due to hepatic carcinoma	Surgical excision, Tacrolimus	No relapse	13	*A. alternata*
60/M	Cutaneous and Pulmonary infection	Heart transplant due to dilated cardiac myopathy	Posaconazole	No Relapse	14	*A. alternata*
55/M	Cutaneous alternariosis	Cardiac Transplant	Intravenous methylprednisolone, Tacrolimus, Cryotehrapy,Curettage and cautery	Recurrent	15	*A. alternata*
12/M	Invasive Alternariosis	Allogeneic hematopoietic stem cell transplantation for Fanconi anaemia	Posaconazole and amphotericin B	Recurrent	16	*A. alternata*
58/M	Progressive subcutaneous infection	Chronic Lymphocytic Leukemia	Surgical Excision and Posaconazole	Recurrent	17	*A. alternata*
65/M	Multiple crusty ulcerative skin lesions	Liver Transplant	Fluconazole	No Relapse	18	*A. Infectoria*
55/M	Cutaneous	Renal Transplant	Thermotherapy	No relapse	19	*A. alternata*
53/F	Keratomycosis	Corneal Transplant	Thimerosal, Pimaricin, Amphotericin B and Nystatin	No Relapse	21	*A. alternata*
66/F	Keratitis	Corneal Transplant	Keratoplasty, cefazolin	No Relapse	22	*A. alternata*
61/M	Cutaneous alternariosis	Renal Transplant	Amphotericin B wet-packing and systemic	Recurrent	23	*A. alternata*

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			anti- fungal therapy with oral voriconazole			
10/F	Rhinocerebral zygomycosis	Allogeneic stem cell transplantation for severe aplastic anaemia	Surgical Excision, liposomal amphotericin B and posaconazole	No Relapse	24	*A. alternata*
47/M	Cutaneous Alternariosis	CREST (calcinosis, Raynaud's phenomenon, oesophageal dysfunction, sclerodactyly and telangiectasia) syndrome with pulmonary hypertension	itraconazole	No Relapse	25	*A. alternata*
6/M	Granulomas with fungal elements	Aplastic anemia presented with generalized erythematous papules	Anti-fungals	No Relapse	26	*A. alternata*
56/F	Cutaneous Alternariosis	Liver Transplant	Voriconazole	No Relapse	30	*A. alternata*

5. Conclusions

In conclusion, this review highlights the various types of opportunistic infections caused by Alternaria alternata in transplant patients. This review also summarizes symptoms, treatment methods, and challenges in diagnosis and infection management in the host to emphasize the importance of early intervention as well as initiating anti-fungal therapy immediately.

Conflicts of Interest: The authors declare no conflict of interest.

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