Early Presentation of Subcutaneous Aspergillus Infection in the Lower Extremity

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Abstract

We present a case of eumycetoma with aspergillus as a causative organism. The patient presented at an early stage and was successfully treated after a combination of surgical excision and medical treatment.

INTRODUCTION

Mycetoma is a chronic infection of the subcutaneous tissue caused by either Actinomycetoma bacteria (actinomyctoma) or fungal (eumycetoma). The result of the infection is a granulomatous inflammatory response in the subcutaneous or deep dermis. When actinomycetoma or eumycetoma occurs in the foot it is termed Madura foot. Madura foot was first coined by Colebrook in 1946 to describe an abnormal growth that was frequently noted on feet of natives of the Madurai District in India [1,2]. Mycetoma commonly affects population who live in the belt between latitudes 30°N and 15°S, which is commonly called "the mycetoma belt". This belt includes Sudan, Somalia, Senegal, India, Yemen, Mexico, Venezuela, Columbia, Argentina and other surrounding countries [3,5]. The most common cause of mycetoma in the United States is due to Pseudallescheria boydii [3]. However, the prevalence is unknown as this condition usually presents in immigrant who came from countries listed above. This condition usually affects field workers who come in contact and work with soil. As a result, the clinical manifestations are frequently seen on lower limb (82%) and hands (7%) [6].

Today, the World Health Organization considers mycetoma as a neglected tropical disease and attributes this problem to lack of resources and international attentiveness [7].

There are several methods for diagnosis. The different causative agent can be identified by visually inspecting the drainage, microscopically evaluating the organism or by culture. The color and texture of the discharge grain can be suggestive of specific organisms [9]. However, it is often difficult identify the specific causative agent as these organisms are very slow growing and are easily contaminated [10]. When discharge is not present, a punch biopsy to the subcutaneous level or local excision with histopathological examination is the next step. Under the microscope, Eumycetoma shows branching septate hyphae with extensive surrounding supplicative granulomas and fibrotic reaction. Actinomycetoma shows poorly defined filamentous structures with variable size granules [11]. A more superior method for analysis is polymerase chain reaction, which can provide rapid diagnosis and identification of the causative organism [12].

Treatment options for mycetoma are optimally a combination of medical and surgical therapy. Medical treatment is usually optimized after identification of causative organism. In case of Eumycetoma, the gold standard is itraconazole 400 mg per day, divided into two dosages of 200 mg every morning and every evening. The duration of this treatment depends on clinical response and side effects, but ranges from 9 to 18 months [9,13-15]. Benefits of triazoles, such as itraconazole and ketoconazole,
is that they help to localize the disease by encapsulating the lesion, which later assists in easier excision. In uncomplicated actinomycetoma the primary treatment is with trimethoprim-sulfamethoxazole for 6 months or 2Years. If there is lack of clinical response, amoxicillin-clavulanic acid can be used for 6 months. In more severe cases with lack of response to the above treatments, combined treatment of amikacin for 3 weeks with trimethoprim-sulfamethoxazole for 5 weeks is indicated. This cycle is repeated until complete cure is achieved. Local wide excision is useful when there is lack of response to medical treatment or in early stages of the infection. Amputation is reserved for advance stages of infection or if there is bony involvement and often serves as a lifesaving procedure [16]. We will present a case of eumycetoma in the foot caused by aspergillus and different clinical presentations of subcutaneous and cutaneous infection.

CASE PRESENTATION

46-year-old Mexican-American male presented with a 10 years’ history of a soft tissue mass on the dorsolateral aspect of his left foot. He reported occasional itching and irritation in closed toe shoes. He noticed progressive growth of the lesion mainly in the past 7 months. He denied any history trauma or any open wounds on his foot. He also denied any drainage from the lesion or pain. He has not received prior medical treatments. The patient had an unremarkable past medical history, which are negative for immune compromised state or prior infection history. At the time of his presentation, he was not taking any medications. He had no known drug allergies, family history of major illnesses, or history of any surgeries. He did not smoke, drink or use illicit drugs. He was born in Guadalajara, Mexico, and moved to California about 10 years ago. He worked as a gardener. On physical exam, he was well nourished, well developed and in no apparent distress. His vital were stable. His lower extremities were normal. There was no open lesions or drainage noted. The lesion did not Trans illuminate. No erythema or increased warmth noted peri-lesion. However, the lesion was mildly painful on direct palpation. His foot pulses were palpable and light touch sensation was intact. There were no pain with range of motion or no gross structural deformities of his foot/ankle noted. He had no inguinal or popliteal lymphadenopathy. No other similar lesions were noted on his upper extremities or trunk.

His initial radiographic findings were consistent with a non-specific dorsolateral forefoot soft tissue prominence (not shown). No calcification noted within the soft tissue mass on the radiograph. Magnetic resonance imaging (MRI) revealed a loculated infiltrative soft tissue mass in the dorsolateral forefoot with numerous internal cystic-facing spaces (Figure 1).

The case was discussed with the radiology service. Patient underwent an incisional biopsy, obtaining a 0.5cm specimen. The intraoperative report noted a fibro fatty tissue with no evidence of grains, discharge or vasculature involvement. The pathology report noted fibrotic tissue with patchy acute and chronic inflammation, granulation tissue and a few multinucleated giant cells. Findings were discussed with the patient, who wished to just monitor the lesion. However, 4 months post-op, he returned to clinic with complaints of occasional pain and pinpoint bleeding from the soft tissue lesion. He denied any discharge, enlargement of mass or constitutional symptoms. On exam, the lesion size was unchanged compared to previous visits (Figure 2). However, there was newly noted pinpoint bleeding from multiple areas of the lesion beyond the biopsy site. There was no erythema or increased warmth. Based on the new findings, patient agreed to proceed with an incisional/excisional biopsy.

The intraoperative findings noted a firm multilayered soft tissue mass with loculated septae extending into the fourth interspace of the left foot. Black debris was present in the subcutaneous tissue surrounding the soft tissue mass. Clear drainage was noted but no pus or purulence found. A 4.0x4.0x3.1 cm soft tissue mass (Figure 3) was sent to pathology.

The pathology report read that the skin surface was grossly unremarkable, but cut sections through soft tissue showed a few scattered darkly pigmented pinpoint spots, 1-2 mm each, in the background of a yellow adipose tissue (Figure 1). No definitive mass lesion was seen. Microscopically, many micro abscesses and necrotizing granulomas were present in the deep subcutaneous tissue, with associated pigmented structures, consistent with fungal colonies (Figure 2). High power view of these colonies showed innumerable pigmented fungal hyphae with septation and sharp angle branching (Figure 3). Many granulomas had palisading histolytic and multinucleated giant cell reaction (Figure 4). Grocott Methenamine Silver (GMS) histochemical stain for fungal organisms was confirmatory (Figure 5).
Infectious disease was consulted due to concerns for Eumycetoma. The patient completed a course of itraconazole 200 mg bid for approximately 8 weeks. An MRI was performed 5 weeks post excisional biopsy, which showed subcutaneous edema consistent with postoperative finding, no fluid collections or bony involvement noted (Figure 4). Three months postoperative exam showed complete healing of his tissue uneventfully without further recurrence or other pedal complaints.

**DISCUSSION**

There are more than 30 known causative agents of mycetoma and subcutaneous aspergillosis (SA) is one of these many types [17]. This type of infection differs from the cutaneous form of aspergillosis, which is a sub type of a more common and widespread disease called invasive aspergillosis (IA). The most common organisms of IA are Aspergillus fumigatus, A. flavus, A. niger, A. terreus, and A. nidulans [18]. In SA the most common reported types of are A. nidulans [3] and A. flavus [19]. Both are rare with unknown prevalence.

The clinical manifestation in cutaneous aspergillosis (CA) is different than the subcutaneous form. Similar to other causative organisms of mycetoma, SA will present clinically with a triad of tumefaction, fistulation of abscess and extrusion of colored grains [3]. Specifically, in aspergillosis, the grains will be white [20]. Cutaneous aspergillosis can be of either primary or secondary origins. Primary skin lesions are usually caused by intravenous access site, trauma, burns or surgery. Secondary skin lesions usually result from a contiguous extension to the skin from a

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**Figure 3** Soft tissue mass excised with loculated appearance.

**Figure 4** Many granulomas with palisading histolytic and multinucleated giant cell reaction.

**Figure 5** Grocott Methenamine Silver (GMS) histochemical stain shows fungal organism.
deep wide spread infection or blood-borne infection that seeds to the skin. The respiratory tract is the most common portal of entry. Other portals include the cornea, ear and damaged skin [18]. In CA, the initial skin presentation may be macular, papular, nodular or plaque. Pustules are less common and may be seen in nevomata. In primary infection, the patient will present with a fever, swelling, in duration and tenderness. In secondary infection, the lesion will initially appear as an erythematous macule that can later develop into hemorrhagic bullae or ulcerative nodule and might present similarly to pyoderma gangrenosum [18,21].

Subcutaneous and cutaneous aspergillus also differs in risk factors: Most cutaneous infections occur in immune compromised patient such as those with HIV/AIDS, neonates, cancer patients, and recipient of transplant tissue or organs. The same risk factors also apply to subcutaneous infections. However, there are other risk factors that are associated with CA, such as minor trauma due to prick or abrasion, walking barefoot, and working in agriculture or farm environment with exposure to soil [4].

The radiographic presentation of IA depends greatly on the anatomic source of the infection. Since most IA patients present with pulmonary disease, chest x-ray and computerized tomography (CT) can be utilized in the diagnosis of IA. The cutaneous form rarely invades into deep layers when it presents in the limbs. The use of radiographic imaging such as x-ray, CT or MRI is not commonly utilized in the diagnosis of the disease and the primary diagnosis occurs through skin biopsy.

In SA, the disease is more localized but tends to spread vertically within a specific location. Diagnostic tools such as x-ray, MRI and CT scan can support with diagnosis. On x-ray, early stages appear as a dense shadow that can represent a granuloma. As the disease develops there is periosteal reaction that is seen as Codman triangle and sun ray appearance. In late stage, there is formation of cavities with normal bone density. In the terminal stage, there will be bone lysis with “melting snow appearance” [3,13,22]. Computed tomography and MRI are diagnostic tools that provide better visualization and extent of the infection. Computed tomography is more sensitive than MRI in early stages and demonstrates soft tissue infiltration, osteolysis and irregular periosteal reaction. The benefit of MRI is that it provides information regarding the depth and extent of tissue invasion, which aids in surgical planning. In addition, MRI presents with a classic dot-in-circle sign: a 2.5 mm hypointense foci that indicates the presence of grains and is highly specific for mycetoma [23-25]. However, radiological presentations are not specific to one organism, but rather has a general appearance that is seen all type of mycetoma.

As discussed earlier, the gold standard treatment of eumycetoma including SA is Itraconazole. In comparison, the treatment for CA that is secondary to disseminated infection, the Infectious Diseases Society of America recommends systemic voriconazole as the primary therapy. Alternative agents include liposomal amphotericin B, posaconazole, itraconazole, caspofungin or micafungin [26].

The prognosis of mycetoma depends on the stage of infection, availability of antimicrobial treatment and adequate surgical excision. As a result, the prognosis will vary significantly between third world and western countries. The recurrence rate varies from 25-50% and can be local or distant at the regional lymph nodes [13]. A study in Sudan investigated the prognostic factor for healing and amputation in actinomycetoma and eumycetoma. Their findings of eumycetoma cases (N=1242), 321 (25.9%) were cured, 35 (2.8%) had amputations and 671 (54%) were dropped from the study due to various reasons. One of these reasons was dissatisfaction with side effects from triazoles such as hepatic toxicity, gynecomastia and skin discoloration. They showed that medical treatment was a predominant factor in determining healing of actinomycetoma. On the other hand, eumycetoma therapy outcome was more dependent upon combination of medical and surgical treatment, where the size of the lesion was an important factor: patients with lesions greater than 5 cm had a higher chance for undergoing amputation [27].

A retrospective study in France aimed to provide prognostic data regarding primary and secondary cutaneous invasive aspergillosis. The number of subjects was 5 primary cutaneous invasive aspergillosis (PCIA) and 10 secondary cutaneous invasive aspergillosis (SCIA), totaling of 15. Hematological malignancies were the main the underlying condition for these subjects (12/15). All 5 PCIA subjects were treated with antifungal therapy and 2 of the 5 had surgical removal of skin necrosis. Six of the 10 SCIA subjects were treated with antifungal therapy based in skin culture findings. The three-month survival was 100% for PCIA and 30% for SCIA. They concluded that early diagnosis of PCIA was associated with better prognosis. In addition, survival in SCIA remains poor compared to PCIA due to vascular invasion mostly in lungs and brain [27].

CONCLUSION

We present a case of eumycetoma with aspergillus as a causative organism. The patient presented at an early stage and was successfully treated after a combination of surgical excision and medical treatment.

A high index of suspicion should be present when patients present with a soft tissue mass and risk factors such exposure of skin to soil and country origin from the “mycetoma belt”. Tissue biopsy and culture should be completed. It is important to catch the infection at an early stage, as it will determine the prognosis and avoid devastating outcome.

REFERENCES

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