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Case Report

Verrucous and ulcerovagitant facial chromo-blastomycosis with nasal bridge destruction, cleaving upper lip deformity and exuberant eyelid squamous cell carcinoma- rare debilitating sequel of facial chromoblastomycosis in a non-endemic region: A case report

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Abstract Chromoblastomycosis, refers to a chronic granulomatous and suppurative subcutaneous dematiaceous fungal infection, resulting from traumatic skin inoculation by melanized fungi of Herpotrichiellaceae family, including Fonsecaea pedrosoi, Cladophialophora carrionii, accounted as the most commonly prevalent endemic etiological species in tropical and temperate regions. Chromoblastomycosis is therapeutically challenging executing varied clinical forms with recalcitrant and intractable disease nature, frequent recurrence and debilitating sequel. We report a case of verrucous and destructive Facial Chromoblastomycosis in an 8yrs old male child, who initially presented with a 3yrs history of progressive appearance of hyperkeratotic and cauliflower like vegetative mycosis over bilateral extensor forearm and legs prevailing for years with constitutional symptoms, later evolved into verrucous, ulcerovegetant gritty plaques involving ear lobule and pinna, bilateral cheeks, with subsequent nasal bridge destruction, cleaving upper lip deformity and recently unfolded a papillomatous exuberant lower eyelid SCC. Histopathological evidence of cutaneous biopsy was consistent with Chromoblastomycosis while protruding eyelid mass revealed an SCC.

Key words
Facial Chromoblastomycosis; Squamous cell carcinoma.

Introduction

Chromoblastomycosis (CBM) refers to a granulomatous and suppurative chronic mycosis involving cutaneous and subcutaneous cellular tissue, prevalent in endemic tropical and temperate regions of the entire world, is caused by the traumatic implantation of dematiaceous fungi of the order Chaetothyriales and Herpotrichiellaceae family found in soil and rotting wood.[1]

Immunopathogensis is conferred with predominantly cellular in addition to humoral immune dysregulation and cytokine profile deliberating TH1 and TH2 response with abundance of IL-10 and IL-17 typically documented in verrucous type,[2] that clinically represent as has dry hyperkeratotic lesions with characteristic cauliflower appearance and pigmented dots, most notorious for causing ulceration with relatively abundant CBM agents. As the disease severity increases, IL-10 production is evident with drastic decrease in

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Table 1 [4]

Nodular	Fibrotic, erythematous-violaceous nodules, with smooth or hyperkeratotic surface.
Verrucous or warty	Cauliflower-like, dry, hyperkeratotic lesions with black dots.
Plaque (infiltrative or erythematous)	Erythematous or violaceous plaques, infiltrated, circumscribed, irregular, sharp and elevated edges, with black dots.
Tumoral	Isolated or coalescent lobulated lesions, smooth or vegetative-like surface.
Cicatricial or atrophic	Annular, serpiginous, or irregular lesions.

gamma IFN and T-cell proliferation,[3]expressed by atrophic type along with Langerhans cells**.** Other factors that contribute to chronicity include presence of thickened sclerotic bodies or muriform cells, tolerance to heat, intensive melanin expression and certain inter cellular adhesive properties. Chromoblastomycosis holds an insidious disease course, is clinically polymorphic and exhibits five distinct appearances **(Table 1)**.[4]

CBM most commonly infects lower extremities, through contact with soil via traumatic inoculation, especially in agricultural workers in endemic areas however, uncommon sites and rare clinical features that have been reported in literature to date include localized annular form, diffuse cutaneous form, abdominal, axillary, scapular, auricular, corneal and conjunctival mycosis triggering melanomic neoplasm, facial phagedenic ulcer,[5-9] nonetheless fatal oral chromoblastomycosis has been accounted.[10]

Although extracutaneous involvement is infrequent, yet contiguous lymphatic and hematogenous dissemination often leads to lymph node metastasis and pulmonary seeding,[11,12] causing extensive tissue fibrosis and lymphedema, and at times local osseous invasion into subsequent lytic or cystic lesions and ankylosis.[13] Studies have found immunocompromised patients encounter dreadful cerebral abscesses pulmonary, gastrointestinal mycosis with F. pugnacious and monophora.[14] A delayed diagnosis and lapse in prompt treatment may render carcinomatous degeneration into squamous cell carcinoma (SCC), depicted as the most serious complication.[15]

We report a case of recalcitrant CBM infection with debilitating sequel in a young child who developed significant facial disfigurement because of prevalent verrucous and ulcerovegetant lesions invading ear lobes, bilateral cheeks with resultant nasal bridge destruction, cleaving upper lip deformity and lower eyelid SCC.

Case Report

An 8 yrs. old, young male child presented to us with a 3 years history of multiple itchy hyperkeratotic verrucous plaques wide spread on extensor forearm, elbows and left upper thigh and ulcerovegetant lesions extensively involving ear lobule and pinna, bilateral cheeks, nasal bridge, chin and upper lip. However neck trunk and genitalia were relatively spared.

It started off as small solitary unilateral painless papules over extremities, progressively evolved over years into well-defined hyperkeratotic erythematous plaques that grew in size and number and spread to involve his face entirely with ulcerovegetant lesions. There was significant history of recalcitrant disease with indolent course of progression evident from his repeated admissions with recurrent supper imposed cutaneous exudative infection, bone pains and constitutional symptoms. He later developed debilitating sequel over the past year as he noticed cauliflower like gritty plaques on ear lobules, tragus and pinna, markedly

Figure 1 Hyperkeratotic cauliflower like verruous and ulcerovegitant plaques on ear lobules, cheeks and chin with cleaving upper lip deformity, nasal bridge destruction and exuberant lower eyelid growth.

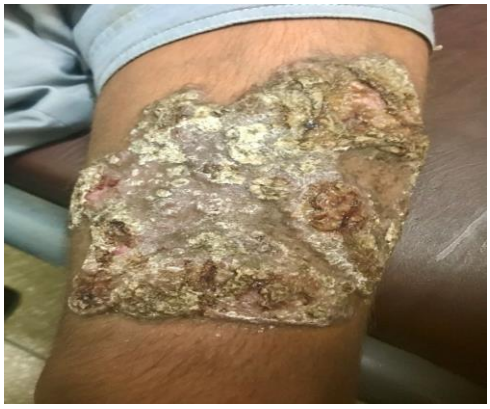

Figure 2 15x6cm verrucous, dry, hyperkeratotic plaque on left upper thigh with induration, purulent exudate and woody hardening.

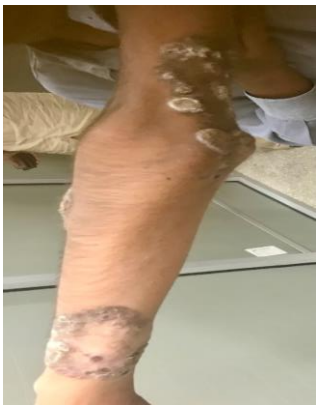

Figure 3 Multiple hyperkeratotic plaques on variable shapes and sizes located around the elbow, upper arm and wrist.

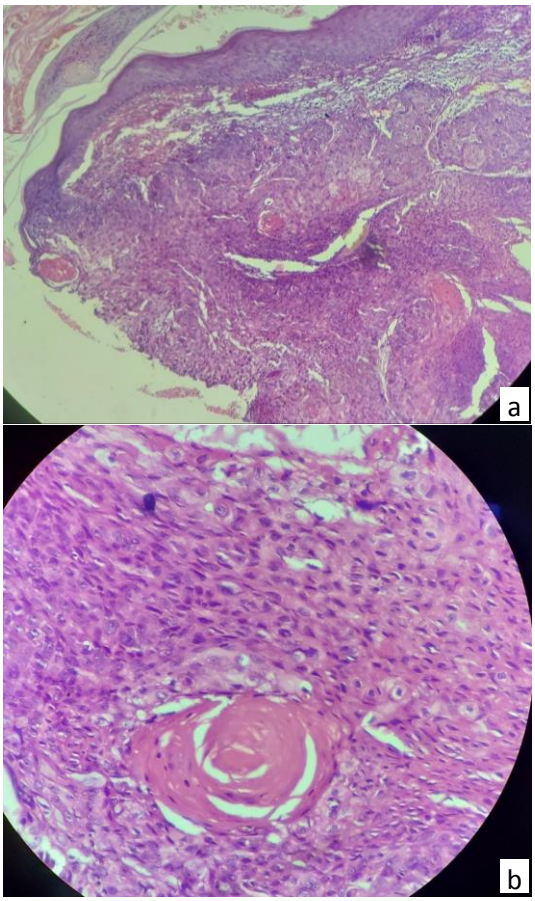

Figure 4 (a,b): SCC-lower eyelid.

infiltrated nasal bridge, mutilating nasal tip and invaded upper lip with cleaving deformity. Nonetheless recently unfolded painless exuberant filiform mass protruding over right lower lid hindering his ocular movements and multiple painful bony cysts in patellar region. The young child had no comorbidities or coexisting autoimmune condition and denied any traumatic skin exposure.

On cutaneous examination, multiple isolated well defined hyperkeratotic dry crusted plaques of variable sizes were noted on extremities (extensor forearm, elbow, upper outer arm and thighs) the largest being 15*6cm on left upper thigh with verrucous appearance, purulent exudate, woody hardening and induration, limiting knee mobility while a small palpable firm patellar cyst was an incidental finding. However, trunk (back and abdomen), genitalia and neck were relatively spared **(Figure 2, 3)**.

Examination of the face revealed auricular hyperkeratosis, confluent cauliflower plaques on helical rim extending to the ear lobules and tragus. There were verrucous pigmented ulcerovegetant lesions appreciated on bilateral cheeks and chin, invading nasal bridge with destructive nasal tip and cleaving upper lip deformity. An exuberant peduncular lower eye lid growth was exacerbated on blinking with resultant ectropion **(Figure 1)**.

The clinical polymorphism made the differentials mandatory as disseminated paracoccidioidomycosis exhibiting verrucous cutaneous lesions, sporotrichosis with nodular and tumoral morphologies, moreover, atypical mycobacterium, leishmaniosis, cutaneous sarcoidosis and squamous cell carcinoma were made into account.

Diagnostic workup included bacterial and AFB cultures, which were negative. Complete blood picture had occasional neurotrophic lymphocytosis because of repeated secondary infections. Tissue culture with KOH mount and histopathological findings of multiple cutaneous Biopsies revealed fungamoid cells, pseudoepitheliomatous hyperplasia, giant cells, and the presence of pigmented sclerotic bodies with cross walls (copper pennies), typical of Chromoblastomycosis. There was unavailability of fungal culture and genomic sequencing. Whereas Excision Biopsy of lower eyelid mass was suggestive of moderately differentiated squamous cell carcinoma evident from the presence of epidermal squamous epithelial cells exhibiting pleomorphism with dermal invasion.

The treatment plan was tailored addressing Oral voriconazole in a calculated dose, considering recalcitrant disease course, yet it hindered clinical use as the patient reported frequent adverse effects as visual blurring and impairment along with photosensitivity expressing eczematous cutaneous reactions though minimal derangements in liver and renal profile. However, Lower eye lid SCC was excised. A multidisciplinary approach was followed for proposed skin grafting and facial reconstruction concerning marked cosmetic disfigurement and psychosocial impact, unfortunately had drawbacks with suspected graft reinfection.

Discussion

Considering the fact that CBM is less likely cured, being notorious for frequent relapses specially in more severe clinical forms, treatment mainly depends on the causative dematiaceous agent, extent of cutaneous involvement, chronicity, severity defining clinical distribution, geographic endemicity and dissemination rendering complications.

Treating CBM has been challenging particularly recalcitrant lesions even resistant to vigorous treatment regimen. Localized cutaneous lesions at early stages are removed with wide surgical resection and often combined with antifungal agents prior to surgery to reduce mycotic focus and later to prevent relapse. As the severity increases with diverse disease distribution and incidence of low cure and greater relapse is evident, treatment is confined to long term antifungal agents.

Clinical criteria defining complete resolution hereby leaving scars for chromoblastomycosis.[16]

Clinical
Complete resolution of all lesions with atrophic scarring
Disappearance of symptomatology
Follow-up observation period of at least two years without recurrence
Mycological
Absence of fungal agents on direct examination
Failure to isolate the etiologic agent from biopsied tissues
Persistence of these findings in three consecutive monthly biopsies
Histologic
Absence of muriform cells and micro abscesses
Replacement of active granulomatous infiltrate in the dermis by a chronic inflammation and dense fibrosis
Atrophy of the epidermis
Persistence of all these findings in three consecutive monthly biopsies.

Physical treatments as cryotherapy, thermotherapy and carbondioxide laser are adjunct to chemotherapy. However, electro dissection is least preferred due to risk of lymphatic invasion.[17] Among systemic Antifungals, first line regimen include a six to twelve months aggressive treatment with Itraconazole (200mg-400mg a day) and Terbinafine (500mg-1000mg a day).[18] Itranonazole Pulses are highly efficacious with recommended dose of 400mg a day for seven consecutive days a month.[19] Moreover, Voriconazole is utilized in recalcitrant forms of deep melanised mycosis and well recognized for providing significant clinical improvement but detrimental adverse reactions as ocular impairment and photosentivity are a setback besides exorbitantly higher cost rendering poor adherence.[20] Similarly Posaconazole in dose of 800mg a day is acclaimed favorable in impervious endemic dermatomycosis.[21] However, nephrotoxic Ketoconazole and Fluconazole are nearly absolute in configured disease prevalent regions.[22]

Studies have revealed evolution of Chemotherapeutic agents altering fungal DNA as Flurocytosine to be efficacious only in synergism with Itraonazole in recalcitrant cases, yet is notorious for substantial myelotoxicity and hepatic fibrosis.[23] When it comes to treating debilitating Facial CBM sequel as Squamous cell carcinoma, Mohs Micrographic Surgery is exotic and readily implicated in cutaneous oncology, promising for treating mycotic focus with malignant alteration, with an absolute cure and least post procedure cosmetic disfigurement particularly face which is indeed a matter of concern addressing to eliminate psychosocial disease implications as evident in our patient.[24]

Recent advances in emergent Immunotherapy is modulated elucidating host immune response for a better cure rate. Clinical trials have discovered utilizing exogenously administered topial Imiquimod, that helps restoring TRL (toll like receptors) recognize mycotic activity, while establishing strong cytotoxic, immunomodulatory and antiviral potential when advised subsequently with Itraonazole.[25] Nonetheless, weekly administration of injectable 5-Gluagon induces host immunomodulation through selective cytokine enhancement of TNF alpha and gamma, activation of dendritic cells and macrophages, increasing T cell proliferation and PMN lymphocytosis as adjunct to oral antifungal.[26]

Conclusion

CBM is a recalcitrant dematiaceous mycosis encountered in morbid individuals, often crucial to treat in severe extensive disease distribution. A delayed diagnosis and lapse in prompt treatment may render debilitating sequel and even carcinomatous degeneration. Any atypical changes as recognition of ulceration, rapid disease progression or poor response to treatment should promptly raise the skepticism of cutaneous neoplasm. Our patient a young child, had rare destructive facial chromoblastomycosis that slowly progressed to lower eyelid Squamous Cell Carcinoma. Nonetheless timely aggressive management with systemic antifungals associated with physical and immutherapy should be modulated elucidating host immune response for a better cure rate.

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