

# Atypical Form of Primary Cutaneous Aspergillosis in HIV<sub>1</sub> Infected Individual

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**Abstract Background:** Primary Cutaneous Aspergillosis (PCA) is a relatively rare condition in people living with HIV (PLWHIV). Of the 25 cases reported in the literature, only one patient had advanced immunosuppression and none of the reported cases involved a black African subject. The objective of this work was to provide additional data to the scientific literature regarding cases of PCA in HIV- infected individuals. **Observation:** We report a case of PCA due to Aspergillosis Niger in a black PLWHIV subject who did not present any of the known factors associated with Aspergillosis, namely venous approach, neutropenia and trauma. The patient had an HIV1 / hepatitis C coinfection and consulted for finely scaly, pruritic, hyper-pigmented lesions forming a cupboard with a clear vesicular border in places that extended from the upper third of the trunk to the lower 2/3 of the thighs taking in the buttocks and external genitalia. The patient presented a good evolution of the lesions under treatment. **Conclusion:** Our observation describes a rare case of primary cutaneous aspergillosis in a subject immunosuppressed to HIV. Although rare in PLHIV, primary cutaneous aspergillosis, given the immunocompromised profile of patients, exposes them to systematic complications, potentially morbid. Hence the interest for the clinician to think of Primary Cutaneous Aspergillosis in the face of suggestive or atypical skin lesions for early diagnosis and management.

**Keywords** Cutaneous aspergillosis, Aspergillus Niger, HIV, Togo

## 1. Introduction

Immunosuppression due to HIV is associated with numerous opportunistic infections, among which mycotic infections play a significant role. The skin is one of the prominent organs affected by various ailments of which fungal infections occupy a privileged place. Aspergillosis are ubiquitous germs. While pulmonary and systemic aspergillosis remains widely described in the literature, this is not the case for primary cutaneous Aspergillosis, especially in people living with HIV (PLWHIV). The first case of cutaneous Aspergillosis in a PLWHIV was reported post-mortem in 1984 [1]. To date, the review of data in the literature between 1984 and 2012 regarding cases of primary cutaneous aspergillosis in PLWHIV has only enabled us to identify a total of 25 published cases (see Table 1) among which there were no cases involving a black subject [1–11].

We report a case of primary cutaneous Aspergillosis in a PLWHIV which caught our attention because of its clinical features. The purpose of this observation is to make an additional contribution regarding the primary cutaneous Aspergillosis in HIV immunocompromised subject, especially in black individuals.

## 2. Observation

This is a 53-year-old male subject, received in consultation in the Infectious Diseases Department of the Sylvanus Olympio University Hospital Center in Lomé, for pruritic dermatosis on HIV immunocompromised ground.

Historically, the disease would have started about a year ago with pruritic papules that gradually evolved in a centrifugal manner invading almost the entire integument associated with persistent pruritus. The patient had HIV<sub>1</sub> / hepatitis C co-infection and had been on antiretroviral therapy (Tenofovir / Lamivudine / Efavirenz) for the past 07 months with an initial CD4 count of 435cel / mm<sup>3</sup>.

He had no other known medical condition. The patient was self-reliant and had a stable general condition. Clinical

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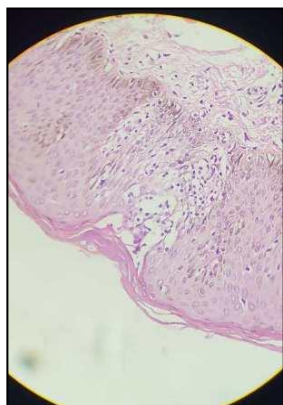
examination of the skin revealed finely scaly, pruritic, hyperpigmented lesions with local excoriations and scratch marks, forming a cupboard with a clear vesicular border in places. This cupboard extended from the upper third of the trunk to the lower 2/3 of the thighs, taking the buttocks and external genitals without spaces of healthy skin (Figure 1).

Elsewhere, lesions with the same characteristics were found in the upper limbs but separated by small spaces of healthy skin.



**Figure 1.** Aspects of dermatological lesions

Examination of the mucous membranes and integuments was normal, as was the examination of the digestive, cardiovascular, pleuro-pulmonary and spleno-ganglionic systems. Faced with this clinical presentation, which a priori suggested a mycosis but was not typical of cutaneous candidiasis, a biopsy sample was taken for an anatomopathological analysis. The results of this examination revealed in the epidermis, a hyperkeratosis, orthokeratotic, Malpighi's mucosal body being the site of a psoriasiform acanthosis. The analysis also noted spongiosis, sometimes with formation of a vesicle and exocytosis of polymorphous inflammatory cells, the papillary dermis being the site of a superficial, polymorphous peri-vascular inflammatory infiltrate, (Figure 2). Standard staining did not reveal any aspergillary filaments.



**Figure 2.** Image of a histological section of the biopsy

In the view of this histological aspect of a spongiotic and inflammatory dermatosis that may be part of a superficial cutaneous mycosis, a microbiological culture of a sample was carried out and allowed the isolation of a strain of *Aspergillus Niger*.

The patient was offered treatment based on fluconazole 300 mg / week and ketoconazole in a foam bath solution. The evolution was already good after 3 weeks of treatment (Figure 3).



**Figure 3.** Patient seen after three months of treatment

### 3. Discussion

*Aspergillus* is ubiquitous germs. The first case of cutaneous Aspergillosis in a PLWHIV was reported in 1984 and was a post-mortem finding. Since then 24 cases of primary Aspergillosis affecting PLWHIV have been reported.

Table 1 presents the characteristics of the 25 cases we were able to find in the literature. Primary cutaneous aspergillosis in PLWHIV appears to be the prerogative of patients with severe immunosuppression since out of 19 of the patients whose CD4 counts were reported, 18 had CD4 count below 200 cells / mm<sup>3</sup>.

The presence of a venous catheter was reported in 79% of cases (19 cases out of 24). Neutropenia appears to be a factor in the occurrence of cutaneous Aspergillosis since certain ARVs such as Zidovudine and Ganciclovir have been proven to be myelotoxic, just as HIV itself is also thought to be involved in bone marrow dysfunction [12]. In previously reported cases, neutropenia was found in 14 of the 19 cases that reported neutropenia data. However, our case is similar to that reported by Guedela *et al.* in 2012 [2], who had neither a venous approach nor neutropenia but a CD4 count between 400 and 500 cel / mm<sup>3</sup>.

The various lesions described in the literature in relation to primary cutaneous Aspergillosis in PLHIV included a pruritic rash, fluctuating papule, nodules, vesiculopustular plaques, indurated erythema, and warty plaque with micro pustules or multiple umbilical or erythematous papules.

The singularity of the lesional extension of the case that we report deserves to be dwelled on since the atypical lesion presents in the form of a hyperpigmented, scaly and pruritic cupboard extending from the upper third of the trunk to the lower 2/3 of the thighs, taking the buttocks and external genitals without healthy skin spaces.

Based on the history of the disease, we hypothesized that with regard to the initial lesions that were characterized by pruritus associated with papules, the patient would likely have presented prurigo, which is very common in black HIV

immunocompromised individuals [13]. Prurigo scratching would have resulted in excoriations lesions that secondarily would have provided the gateway for *Aspergillus* conidia. The emancipation of these *Aspergillus* conidia would have

been facilitated by the underlying immune system failure due to HIV but probably also to HCV. Indeed, conidiospores of *Aspergillus* circulate in the air and reach peak concentrations at seasonally variable times.

**Table 1.** Characteristics of the cases of cutaneous *Aspergillus* in PLWHIV reported in the literature

N°Patient [Ref.]/ Âge, ans	CD4 Rate	Neutropenia	Antifungal used before Diagnostic	Veinous catether	Wound	Seat of the lesion	Characteristics of the lesion	Germs isolated	Treatment received (Issue)
1[2]/30	462	NR	N	N	N	Jambe	puritic rash	A.fumigatus	Itraconazole, 200 PD (Healed)
2[3]/40	NR	Y	Itraconazole	Y	N	Bras		A.fumigatus	Incision, Itraconazole, 200 TPD (Healed)
3[3]/46	4	Y	Fluconazole	Y	N	Bras		A.fumigatus	Incision, Itraconazole, 200 TPD (Died after 03 month)
4[3]/35	5	Y	Fluconazole	Y	N	Poitrine		A.fumigatus	Incision, Itraconazole, 400 PD (recidivism and healed)
5[3]/58	0	N	Fluconazole	N	Y	Bras		Negative	Incision, Itraconazole, 200mg TPD (Healed)
6[3]/47	4	Y	Fluconazole	Y	N	Bras	Fluctuating papul, nodule, vésiculo pustular plaque	A.fumigatus	Incision, Itraconazole, 200mg TPD, terbinafine (Healed)
7[3]/32	NR	N	Fluconazole	Y	N	Bras		Species of A..	Incision, Itraconazole, 200mg TPD (Healed)
8[3]/41	3	Y	Fluconazole	Y	N	Bras		A.fumigatus	Incision, Itraconazole, 200mg TPD, (MAC,asp.) (Died)
9[3]/38	13	Y	Fluconazole	Y	N	Bras		Négative	Incision, Itraconazole, 200mg TPD (Healed)
10[3]/35	0	N	NR	Y	N	Bras		Négative	Incision, Itraconazole, 400mg PD (Healed)
11[3]/42	0	Y	Fluconazole	Y	N	Bras		Non réalisé	Incision, (Healed)
12[3]/39	6	Y	Fluconazole	Y	N	Bras		A.fumigatus	Incision, Itraconazole, 200mg TPD (Healed)
13[1]/30	NR	NR	NR	NR	NR	NR	NR	NR	Post-mortem
14[4]/38	NR	Y	Fluconazole	Y	N	Bras		A.fumigatus	NR
15[5]/14	143	NR	NR	N	Y	Jambe	Ulcer	A.glaucus	Incision, Amphotéricine B, Itraconazole, 200mg TPD(Healed)
16[5]/10	2	Y	NR	Y	N	Poitrine	Nodule	A.fumigatus	Incision, Amphotéricine B, (Healed)
17[6]/26	24	Y	Fluconazole	Y	N	Poitrine	indurated erythema	A.fumigatus	Amphotéricine B, Itraconazole, 200mg TPD(Died after one month)
18[7]/37	67	NR	NR	Y	N	Poitrine	warty plaque with micro pustules or	A.fumigatus	Biopsie, Amphotéricine B, (Died after 03 month)
19[8]/27	14	Y	Fluconazole	Y	N	Poitrine	multiple umbilical	A.fumigatus	Biopsie, local treatment, (Died after 04 month)
20[8]/43	NR	NR	NR	Y	N	Poitrine	Umbilical papules	Aucun	Fluconazole (MAC), (Died after few months)
21[9]/44	NR	NR	NR	N	N	Cuire chevelu	NR	A.fumigatus	Amphotéricine in intravenous injection and in a foam bath solution, (Healed)
22[10]/NR	15	Y	NR	Y	N	Bras	Nodule	A.fumigatus	Incision, Itraconazole 200mg TPD, (Healed)

N°Patient [Ref.]/ Â ge, ans	CD4 Rate	Neutropenia	Antifungal used before Diagnostic	Veinous catether	Wound	Seat of the lesion	Caracteristics of the lesion	Germes isolated	Treatement received (Issue)
23[10]/NR	0	Y	NR	Y	N	Bras	Nodule	A.fumigatus	Amphotéricine B, Itraconazole 200mg TPD, Died after 02 weeks)
24[11]/57	145	N	NR	N	Y	Pénis	Erythematous papules	A.fumigatus	Amphotéricine B (Died after 02 month)
25[11]/38	51	N	NR	Y	N	Bras	Erythematous papules	A.fumigatus	Incision, (Healed after 03 month)

TPD: Twice per day; mg: Milligram; MAC: Mycobacterium Avium Complex; N: No; NR: No Reported; PD: Per day; Ref: Reference; Y:Yes;

An intact skin barrier provides effective protection against the penetration of conidiospores into the body. In the event of skin damage, Langerhans cells and other inflammatory cells (polynuclear neutrophils and monocytes) are capable of phagocytosis and intracellular destruction of the spores which manage to penetrate the deep layers of the skin [14].

Thus, the causes of phagocyte cell dysfunction such as chronic granulomatous diseases, HIV, high-dose corticosteroid therapy, lead to an imbalance between lymphocytes T helper 1(Th1) and lymphocytes T helper 2 (Th2) with an excess of Th2 lymphocytes signaling pathways and may prevent the inhibition of inoculated spores promoting their germination into hyphae [14]. Specifically in people with HIV, a reduction in the antifungal activity of neutrophils has been described [15]. Similarly, a dysfunction of monocytes derived from macrophages has also been described in PLWHIV [16].

Another cause of this functional failure is the decrease in CD4 count associated with the synthesis of inhibitory factors by TCD8 lymphocytes [17].

In addition, cytokine dysfunction with increased production and activity of cytokines including interleukin 10 appears to be related to decrease anti-Aspergillus activity of macrophages and neutrophils [18,19]. Furthermore, in subjects with chronic hepatitis C, the antigen presenting cells, the dendritic cells, in which the HCV seems to multiply, could also be involved in this functional failure of the immune response to Aspergillus invasion. Indeed, it has recently been shown that despite a normal phenotype and intact antigen-capturing capacity, the ability of dendritic cells to activate allogeneic T lymphocytes was profoundly impaired in patients with chronic hepatitis C in contrast to healthy subjects [20–22]. In addition, subjects with chronic hepatitis C also had an increased tendency to synthesize pro-inflammatory Th2 cytokines (IL-4, IL-5 and L-10) [23,24].

All of these immunological phenomena could have contributed in addition to the decrease in HIV-related CD4 count, to the drastic decrease in the anti-aspergillary activity of the macrophages and neutrophils described above and thus to a real invasion of skin tissue by Aspergillosis in our patient.

We isolated a strain of *Aspergillus Niger* from our patient to our knowledge, no case of *Aspergillus Niger* Aspergillosis

on HIV immunocompromised ground had yet been reported. Indeed, in cultures carried out among the 24 previously reported cases, *Aspergillus Fumigatus* is by far the most isolated strain in 9 out of 10 cases. One case of *Aspergillus Glaucus* was reported by Shetty et al. in 1997 [5].

Given the accessibility of the molecules in our context, we opted for a combination of oral Fluconazole combined with a topical treatment based on Ketoconazole with an evolution that was favorable for our patient with regression of the lesions. Among the cases reported in the literature, 13 cases were on antimycotic drugs prior to the diagnosis of cutaneous Aspergillosis of which 12 patients were already on Fluconazole and one patient on Itraconazole, suggesting resistance of Aspergillosis to these molecules.

Nevertheless, it is essentially Itraconazole alone or in combination with Amphotericin B that has been used as a molecule in the care of subjects with a good evolution of the clinical picture in general. However, deaths occurring between two weeks and 12 weeks post- treatment have been reported depending on the case as a result of hematogenous dissemination of Aspergillosis either due to an underlying opportunistic infection such as *Mycobacterium avium* complex, Kaposi disease, toxoplasmosis., Cryptosporidiosis or leukemia.

## 4. Conclusions

The study observation describes a rare case of primary cutaneous Aspergillosis in an HIV immunocompromised subject. Skin biopsy and microbiological exploration allowed us to isolate a strain of *Aspergillus Niger*. This clinical case is of interest for two reasons. The first is the extensive nature that primary cutaneous Aspergillosis can take in people with HIV. The second is the interest of skin biopsy as the first option for exploring atypical skin lesions in PLHIV in order to guide the etiological diagnosis and ensure optimal patient care.

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