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Reactivation of Hepatitis B in a Patient Coinfected with Hiv/Hbv Undergoing Therapy Without the use of Tenofovir: A Case Report

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Abstract

Coinfection with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) is a significant clinical challenge, especially during changes in antiretroviral therapy. Tenofovir is a key drug for the simultaneous suppression of HIV and HBV, and its suspension can lead to HBV reactivation in individuals with latent or occult infection. This study reports a case of hepatitis B reactivation after tenofovir withdrawal. The patient was a 68-year-old male diagnosed with HIV in 1985, on antiretroviral therapy since 1998, and with an undetectable HIV viral load for several years. In February 2024, tenofovir disoproxil fumarate was discontinued due to renal changes and osteopenia. Three months after withdrawal, the patient presented with a significant elevation of liver transaminases. Initially, drug-induced hepatotoxicity was considered; however, investigation revealed HBsAg, total anti-HBc, and HBeAg reactants, in addition to an HBV viral load of 16,100,000 copies, confirming viral reactivation. The introduction of tenofovir alafenamide resulted in a progressive reduction in HBV viral load and laboratory improvement. The case highlights the need for complete serological evaluation for hepatitis B before changes in the antiretroviral regimen and the risk associated with inadvertent suspension of tenofovir in coinfecting patients.

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Introduction

Chronic hepatitis B virus infection remains an important public health problem, especially among people living with human immunodeficiency virus, in whom coinfection is frequent and clinically relevant. ^[1, 2] HIV infection alters the natural history of hepatitis B, favoring greater viral replication, accelerated progression of liver fibrosis, and increased risk of clinical complications. ^[3, 4] In this context, antiretroviral therapy plays a central role, particularly when it includes drugs with dual activity against HIV and HBV, such as tenofovir, which has established itself as a pillar of coinfection treatment due to its high antiviral efficacy and high genetic barrier. ^[5, 6]

However, the growing adoption of tenofovir-sparing antiretroviral regimens, motivated by toxicities, comorbidities, and the aging of the population living with HIV, has exposed coinfecting patients to a significant risk of HBV reactivation. ^[7, 8] Withdrawal of tenofovir is associated with the reappearance of viral replication, elevated transaminases, and, in severe cases, liver failure, even in individuals with previously controlled or occult infection. ^[9, 10] Despite national and international guidelines recommending the maintenance of active agents against HBV, episodes of reactivation still occur in clinical practice, reinforcing the importance of complete serological evaluation, continuous virological monitoring, and caution when modifying therapeutic regimens. ^[1, 2]

Objectives

General Objective

To report and analyze a clinical case of facial verrucous sporotrichosis with atypical presentation and delayed diagnosis, discussing its clinical, histopathological, epidemiological, and therapeutic aspects in the context of an endemic area.

Specific Objectives

1. To describe the patient's clinical evolution from the onset of lesions to complete resolution after prolonged antifungal treatment.
2. To correlate the clinical findings with the histopathological, immunohistochemical, and serological results obtained during the diagnostic investigation.
3. To identify factors associated with delayed diagnosis, including the absence of obvious feline exposure and similarity to other facial dermatoses.
4. Discuss the main differential diagnoses of chronic verrucous facial lesions in regions hyperendemic for sporotrichosis.
5. Evaluate the therapeutic response to itraconazole in a prolonged regimen, highlighting the need to individualize treatment duration in extensive presentations.
6. Contribute to the expansion of clinical recognition of atypical facial forms of sporotrichosis, aiming to reduce morbidity and aesthetic sequelae.

Methodology

This is a descriptive case report study with a qualitative approach and retrospective analysis of clinical data from a patient treated at a specialized infectious disease service at the Emílio Ribas Institute of Infectious Diseases, São Paulo, Brazil.

Information extracted from medical records was analyzed, including:

- Clinical and epidemiological data
- Temporal evolution of lesions
- Initial diagnostic hypotheses
- Laboratory and histopathological tests
- Complementary methods (immunohistochemistry, special stains, and serology)
- Therapeutic approach and clinical response

The diagnosis was established based on clinical-pathological correlation, considering:

- Presence of chronic verrucous facial lesion compatible with subcutaneous mycosis
- Histopathological findings of granulomatous inflammatory process with suppurative foci
- Identification of yeasts compatible with *Sporothrix* spp. in special stains (Grocott and PAS)
- Immunohistochemical positivity for *Sporothrix* spp.
- Reactive serum serology

Although fungal culture was performed, it remained negative, which was interpreted in light of the literature describing variable sensitivity in chronic or paucifungal lesions.

A narrative review of the literature was performed in the PubMed, SciELO, and Google Scholar databases, using descriptors related to “sporotrichosis,” “facial

sporotrichosis,” “verrucous sporotrichosis,” and “misdiagnosis,” with selection of recent publications addressing atypical presentations and facial involvement.

The report complies with the ethical principles of confidentiality, with complete anonymization of the patient's data, with no identifying elements.

Case Report

A 68-year-old male patient diagnosed with HIV infection since 1985 had undergone prolonged clinical follow-up and satisfactory adherence to antiretroviral therapy, initiated in 1998, with sustained virological suppression, in line with current criteria for therapeutic success.^[3, 11] The patient was referred to a new specialized service, maintaining an antiretroviral regimen consisting of tenofovir disoproxil fumarate, lamivudine, dolutegravir, darunavir, and ritonavir, with no available records of previous genotyping, a situation not uncommon in individuals with a long therapeutic history.^[13, 2]

The presence of tenofovir disoproxil fumarate conferred concomitant antiviral activity against HBV, even though, at that time, there was no known diagnosis of chronic infection with this virus, which may underestimate the protective role of the drug in coinfection or occult infection.^{5, 6} In December 2023, initial serology tests showed non-reactive HBsAg, non-reactive anti-HBs, non-reactive serology for hepatitis C, reactive hepatitis A IgG, and non-reactive IgM, a profile consistent with the absence of acquired immunity against hepatitis B, but without further investigation of total anti-HBc at that time.^[14, 2]

The absence of reactive anti-HBs, associated with the lack of previous vaccination records, placed the patient in a situation of susceptibility or possible previous uncharacterized infection, particularly relevant in people living with HIV, in whom the serological response may be atypical or incomplete.^[15, 16]

In February 2024, during follow-up, elevated urinary albumin/creatinine ratio and osteopenia were identified, findings consistent with possible adverse effects associated with prolonged use of tenofovir disoproxil fumarate, especially in elderly individuals and those with long-term exposure.^[10]

Given this scenario, and in the absence of apparent changes in the viral serologies known at the time, it was decided to withdraw tenofovir disoproxil fumarate from the antiretroviral regimen, while maintaining dolutegravir, darunavir, and ritonavir, a strategy in line with therapeutic simplification and toxicity reduction practices, but one that requires caution in patients with a potential risk of HBV infection.^[7, 22]

This withdrawal inadvertently led to the suspension of the only drug with effective activity against HBV in the therapeutic regimen, creating a favorable environment for viral reactivation in individuals with possible latent or occult infection.^[9, 24]

After approximately three months, the patient presented a marked elevation of aminotransferases (AST 339 U/L; ALT 756 U/L), characterizing acute biochemical hepatitis and raising initial differential hypotheses, including drug-induced hepatotoxicity.^[25, 30] Given the coexistence of motor neuron syndrome and recent use of riluzole, drug-associated hepatotoxicity was considered, and the drug was discontinued.^[25]

However, after one month, persistent liver changes were

observed, progressively ruling out isolated drug toxicity and reinforcing the need for further etiological investigation. [30, 20]

A new serological evaluation revealed HBsAg reactive, total anti-HBc reactive, anti-HBc IgM non-reactive, HBeAg reactive, and anti-HBs non-reactive, a profile compatible with reactivation of chronic HBV infection, without characteristics of acute primary infection. [14, 24]

HBeAg positivity indicated intense replicative activity, later corroborated by high HBV viral load, a finding described in episodes of reactivation after withdrawal of suppressive antiviral therapy. [9, 23]

The HBV viral load was 16,100,000 copies, confirming exuberant replication and explaining the magnitude of the elevation of aminotransferases. [8, 19] This finding is consistent with evidence that withdrawal of tenofovir can trigger rapid recovery of HBV replication even after long periods of suppression. [10, 9]

Given the diagnosis of reactivation, antiviral therapy was reintroduced with the inclusion of tenofovir alafenamide, based on its efficacy and more favorable renal and bone safety profile. [5, 6]

The virological response was progressive, with a reduction in HBV viral load to 6,440 copies in eight weeks and 604 copies in twelve weeks, in addition to laboratory improvement. [23, 8]

From a clinical standpoint, the patient remained stable, with no signs of liver failure, encephalopathy, or decompensation. [30, 20] Additional evaluations did not reveal any laboratory or radiological criteria for liver cirrhosis or hepatocellular carcinoma, a relevant finding given the increased risk of these complications in coinfection. [31, 4]

The case illustrates the risk associated with tenofovir

withdrawal in patients with incomplete hepatitis B serology, especially when anti-HBc is not previously documented. [14, 24]

The absence of reactive anti-HBs and the lack of adequate prior vaccination reinforce the importance of complete serological evaluation before changes in the antiretroviral regimen. [21, 2]

The results demonstrate that HBV infection can remain silent for long periods under pharmacological suppression, being revealed only after withdrawal of the active antiviral agent. [24, 26]

Figure 1 presents the patient's clinical timeline, summarizing the main milestones related to the diagnosis of human immunodeficiency virus infection, the evolution of antiretroviral therapy, and the episode of hepatitis B reactivation. It can be seen that the patient was diagnosed with HIV in 1985 and started antiretroviral therapy in 1998, maintaining sustained virological suppression for several years. In February 2024, after changing the antiretroviral regimen to one without tenofovir, there was a significant increase in liver transaminases in the following months, culminating in the identification of hepatitis B virus reactivation in June 2024, with a high viral load.

The reintroduction of specific antiviral therapy with tenofovir alafenamide resulted in a progressive reduction in HBV viral load, as evidenced by laboratory tests performed in September and October 2024. This chronological representation facilitates understanding of the temporal relationship between tenofovir withdrawal and viral reactivation, reinforcing the role of this drug in suppressing HBV in coinfecting patients. [19, 18, 23]

Table 1: Timeline

1985	1998	February/2024	May/2024	June/2024	September/2024	October/2024
Diagnosis of HIV infection	Start of ART	Switch from ART to DTG + DRV + ritonavir	Elevated transaminases and suspension of riluzole	HBsAg reactive HBV viral load: 16,100,000 copies Introduction of TAF	HBV CV: 6,440 copies	HBV CV: 604 copies

Source: Authors

Discussion

HBV reactivation in people living with HIV is a recognized complication, particularly after changes in antiretroviral regimens involving the withdrawal of drugs with anti-HBV activity, such as tenofovir. [3, 13, 11]

HIV/HBV coinfection alters the natural history of hepatitis B and is associated with an increased risk of liver disease progression and outcomes such as cirrhosis and hepatocellular carcinoma. [4, 31]

The absence of HBsAg and anti-HBs in initial evaluations does not rule out previous HBV infection, especially in people living with HIV, in whom atypical serological patterns and isolated anti-HBc positivity may occur and represent a risk of reactivation after withdrawal of antiviral pressure. [14, 24, 26]

The switch to nucleos(t)ide-sparing regimens has been associated with reactivation and HBV-related events in settings of high endemicity and during therapeutic transitions, reinforcing the need for complete serological screening and anti-HBV coverage when indicated. [17, 7]

Elevated transaminases weeks to months after tenofovir withdrawal are consistent with the described interval for reactivation, and the differential diagnosis with drug-induced

hepatotoxicity is often challenging. [25, 19, 30]

Once reactivation is confirmed, reintroduction of tenofovir therapy tends to restore virological control, with a progressive decline in viral replication markers. [5, 23]

The case reinforces guideline recommendations for caution in modifying antiretroviral regimens, maintaining drugs active against HBV whenever possible, and virological and biochemical monitoring after therapeutic changes, especially in patients with current or past evidence of HBV infection. [1, 2, 21]

From a pathophysiological point of view, HBV reactivation after tenofovir discontinuation in people living with HIV reflects the abrupt loss of antiviral pressure on hepatic reservoirs of the virus, associated with a dysfunctional immune response characteristic of coinfection. HIV infection compromises CD4+ T cell-mediated cellular immunity, which is essential for controlling HBV replication, favoring silent replication even in the absence of detectable HBsAg. [13, 19, 29]

In this context, prolonged use of nucleos(t)ides with anti-HBV activity, such as tenofovir, can suppress viral replication for years, masking latent or occult infection, which manifests clinically only after withdrawal of the drug.

[9, 18, 24] Studies show that rapid recovery of HBV replication after therapeutic interruption can occur even in patients with adequate immunovirological control of HIV, emphasizing that viral suppression is not equivalent to virus eradication. [23, 26]

From a clinical standpoint, this case reinforces the relevance of tenofovir alafenamide as a safe and effective therapeutic alternative for patients with contraindications to the use of tenofovir disoproxil fumarate. Recent evidence shows that TAF maintains high antiviral potency against HBV, with less impact on renal function and bone mineral density, making it the preferred option in aging populations with multiple comorbidities. [5, 10, 23]

This report contributes to the literature by illustrating that the decision to withdraw tenofovir should always be preceded by a complete serological evaluation for hepatitis B, including HBsAg, anti-HBs, and total anti-HBc, as well as planning an alternative antiviral strategy when there is any evidence of current or previous infection. [1, 2, 21]

Thus, the experience presented reinforces guidelines that recommend continuous surveillance and an individualized approach to simplifying antiretroviral therapy, avoiding potentially serious and preventable events such as HBV reactivation. [17, 20]

Conclusion

This case report clearly and didactically highlights the risk of hepatitis B reactivation in HIV/HBV coinfecting patients undergoing modification of their antiretroviral regimen with withdrawal of tenofovir. Although the therapeutic change was motivated by adverse events related to renal function and bone health, the absence of a complete serological evaluation for hepatitis B prior to discontinuation of the drug with anti-HBV activity contributed to the onset of clinically significant viral reactivation.

The case reinforces that prolonged HBV suppression in coinfecting patients can mask latent or occult infections, with the withdrawal of antiviral pressure being a determining factor for the resumption of viral replication. The marked elevation of transaminases, associated with high HBV viral load, illustrates the potential severity of this event, even in patients with adequate virological control of HIV.

The favorable response after reintroduction of tenofovir alafenamide confirms the efficacy of tenofovir in suppressing HBV and highlights the role of TAF as a safe alternative in individuals with limitations to the use of TDF. Thus, this report contributes to clinical practice by reinforcing the need for continuous surveillance, complete serological evaluation, and caution in adopting tenofovir-sparing antiretroviral regimens in patients at risk for HBV infection.

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