CASE REPORT

A report of a successfully treated case of ABPA in an HIV-infected individual

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SUMMARY

Aspergillus fumigatus is a ubiquitous fungus responsible for a variety of pulmonary diseases, ranging from infection of a pre-existing cavity as in aspergilloma to highly invasive disease in immunocompromised hosts. Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity response mounted against antigens of *A. fumigatus* manifesting as poorly controlled asthma and bronchiectasis. Although ABPA is not uncommon, occurrence of ABPA in HIV-affected individuals is distinctly rare. We describe the occurrence of ABPA in a 35-year-old woman with poorly controlled asthma since childhood and HIV-1 infection of 11 years duration. This is the second documented case of ABPA in a HIV-affected individual, and the first reported case to be successfully managed with antifungal therapy alone. We also discuss the complex management issues involved in treating ABPA in HIV-affected individuals.

BACKGROUND

The devastating effects of HIV on the immune system and its consequences are well known. The common presentation of HIV-related AIDS is with a variety of opportunistic infections. With the development of effective antiretroviral therapy, significant improvement in survival and quality of life has been achieved. A hypersensitivity reaction is an exaggerated immune response to exogenous or endogenous antigens. Allergic bronchopulmonary aspergillosis (ABPA) is a manifestation of hyperexaggerated immune response to *Aspergillus fumigatus*,¹ whereas HIV/AIDS is a typical example of immunodeficiency. A combination of both is not only challenging with regards to management but also throws light on the intricacies of the immune system. We report a case of acute exacerbation of ABPA in an HIV-affected individual with long-standing asthma.

CASE PRESENTATION

A 35-year-old woman was diagnosed with HIV-1 infection 11 years earlier. She was started on antiretroviral drugs (zidovudine, lamivudine, nevirapine) 4 years ago as her CD4 count dropped to 320 cells/ μ L. After antiretroviral therapy, her CD4 count gradually increased to reach a recent value of 597 cells/ μ L. There was no history of tuberculosis, other opportunistic infections, recurrent pneumonias, intravenous drug abuse or blood transfusion. There was history of poorly controlled asthma since childhood and seasonal rhinitis. Currently, she presented to our chest clinic with worsening cough, wheeze and breathlessness. Auscultation of

the chest revealed presence of bilateral diffuse rhonchi. The rest of the examination was unremarkable. Her symptoms were partially controlled with inhaled formoterol-budesonide (6/200 μ g two puffs twice a day) and a course of oral amoxicillin-clavulanate. The patient had significant relief from rhinitis after montelukast at a dose of 10 mg daily was started, however, she still had persistent wheezing and breathlessness.

INVESTIGATIONS

Screening for ABPA with *A. fumigatus*-specific IgE antibody was done, which turned out to be positive (100 kUA/L). Further investigations showed an elevated peripheral blood eosinophil count (1958 cells/ μ L), positive type 1 skin test reaction to *A. fumigatus* and a total IgE concentration of 29 600 IU/mL. CT of the chest revealed the presence of central bronchiectasis and centrilobular nodules, supporting the diagnosis of ABPA (figure 1). Spirometry disclosed severe obstruction with significant bronchodilator reversibility.

TREATMENT

A final diagnosis of ABPA complicating asthma was made. In view of the underlying immunodeficiency, further immune suppression with corticosteroids was avoided. Itraconazole was started at a dose of 200 mg twice a day.

OUTCOME AND FOLLOW-UP

At the end of 2 months, the patient noted significant improvement in symptoms and specific IgE decreased from 100 to 48.3 kUA/L. Therapy with inhaled bronchodilators and itraconazole was continued. After 6 months of therapy, the patient was asymptomatic. A repeat CT scan (figure 1) performed after 6 months of itraconazole therapy showed significant improvement compared with the baseline CT and total IgE levels dropped to 4424 IU/mL (about 85% decrease from baseline value). Antiretroviral therapy was continued throughout the course of treatment. No opportunistic infections were noted and the liver functions remained normal during therapy with itraconazole. The patient has been continued on itraconazole with a plan to stop therapy at 12 months after clinical reassessment and IgE values.

DISCUSSION

In contrast to the invasive diseases caused by *Aspergillus*, ABPA is an immunological disease entity occurring in genetically susceptible individuals as a result of hypersensitivity to antigens of

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Figure 1 Pretreatment and post-treatment (6 months after itraconazole treatment) high resolution CT of the chest of the index case showing considerable improvement in the pulmonary opacities.

A. fumigatus.² ABPA commonly occurs in individuals with asthma and cystic fibrosis, although recent data also suggest chronic obstructive pulmonary disease and pulmonary tuberculosis-related fibrocavitary disease to be potential risk factors for *Aspergillus* sensitisation (and probably ABPA).^{3–4} Allergens released by *A. fumigatus* are presented to the T cells in the bronchial mucosa by the antigen presenting cells. A Th2 immune response develops in individuals predisposed to ABPA resulting in secretion of several cytokines including interleukin (IL)-4, IL-5 and IL-13.⁵ These cytokines ultimately lead to the various clinical, radiological and immunological manifestations seen in ABPA.^{6–7} Among the various diagnostic tests employed in diagnosing ABPA, an elevated IgE against *A. fumigatus* has been found to be the most sensitive, and has been recommended for screening, as was done in the index case.^{2–8}

A systematic search of the PubMed and EMBASE databases using the following free text terms: (“abpa”[ti] OR “allergic bronchopulmonary aspergillosis”[ti] OR “allergic bronchopulmonary mycosis”[ti]) AND (“hiv”[ti] OR “aids”[ti] OR “acquired immunodeficiency syndrome”[ti] OR “human immunodeficiency virus”[ti] OR “retrovirus”[ti] OR “htlv”[ti]), revealed that the occurrence of ABPA in AIDS has been reported only once in the literature, so far.⁹ AIDS is an immunodeficient state in which invasive infections from opportunistic fungi are well known. Among them *Candida*, *Histoplasma* and *Cryptococcus* are very common, although invasive aspergillosis in AIDS is also not unknown.¹⁰ Dysregulated cytokine production by T-helper cells seen during advanced HIV infection may result in blunted antifungal activity of neutrophils, thereby possibly explaining the increased occurrence of invasive aspergillosis in individuals with a CD4 count of <50 cells/ μ L.¹¹ Despite the development of AIDS, presence of an intact Th2 system probably explains the occurrence of ABPA in our index patient.¹²

The index case highlights the difficulty encountered in managing such patients. ABPA is generally managed with corticosteroids,² and can be used in HIV-affected individuals. However, in those with an already compromised immune system, especially in advanced HIV/AIDS, it is difficult to justify another insult to the immune system by treating ABPA with corticosteroids. We chose monotherapy with azoles because of the high prevalence of tuberculosis in our country, especially in HIV-affected individuals, and the fact that corticosteroids would further amplify that risk. Monotherapy with azoles has also been found to be effective in ABPA, but the evidence is weaker than that available for corticosteroids.¹³ Inhaled amphotericin and anti-IgE therapy have also been tried in treatment of ABPA with varying degrees of success.^{14–15} Although the previous reported patient of ABPA with HIV was managed with corticosteroids,⁹ it may not always be safe. Our index patient had long-standing HIV and development of tuberculosis was always a concern; hence, treatment with azoles was considered instead of corticosteroids. Voriconazole is recommended for invasive aspergillosis,¹⁶

however, in ABPA there is good data with itraconazole and limited data with voriconazole.¹³ Hence, our patient was started on itraconazole with which she demonstrated good clinical, radiological as well as immunological response.

Finally, using itraconazole in place of steroids may have avoided a few problems but it also has the potential to create a few more. Especially important is the drug interaction between antiretroviral drugs and itraconazole. Itraconazole is a substrate as well as a strong inhibitor of cytochrome P450 (CYP3A4) enzyme, and is thus prone to several drug interactions. For instance, the majority of the HIV protease inhibitors are also CYP3A4 inhibitors, which can increase the concentration of azoles and vice versa. The effect of antiretroviral drugs on itraconazole and vice versa are summarised in tables 1 and 2, respectively. Therapeutic drug monitoring of itraconazole is useful in these situations, not only because of the drug interaction but also due to the erratic absorption of itraconazole, and is strongly recommended. A serum itraconazole concentration greater than 17.1 μ g/mL was associated with higher chances of itraconazole toxicity in a study performed in individuals receiving itraconazole for chronic pulmonary aspergillosis and ABPA.¹⁷ Among the antiretroviral drugs that the index patient received, lamivudine and zidovudine have no significant interaction with itraconazole. However, with nevirapine being a

Table 1 The effect of antiretroviral drugs on serum itraconazole levels

Antiretroviral drug class	Itraconazole levels		
	No change	Increased	Decreased
Nucleoside and nucleotide reverse transcriptase inhibitors	Abacavir Emtricitabine Zidovudine Lamivudine Stavudine Tenofovir		Didanosine (affects itraconazole absorption. Should be given 2 h apart)
Non-nucleoside reverse transcriptase inhibitors	Rilpivirine	Delavirdine	Efavirenz Nevirapine Etravirine
Protease inhibitors		Darunavir Fosamprenavir Indinavir Lopinavir Nelfinavir Ritonavir Saquinavir Tipranavir	
Fusion inhibitor	Enfuvirtide		
Integrase inhibitors	Elvitegravir Raltegravir Dolutegravir		
Chemokine receptor type 5 antagonist	Maraviroc		

Table 2 Itraconazole increases the serum concentration of these antiretroviral drugs

Antiretroviral drug class	Drugs
Non-nucleoside reverse transcriptase inhibitors	Rilpivirine
Protease inhibitors	Atazanavir Darunavir Indinavir Saquinavir Elvitegravir
Chemokine receptor type 5 antagonist	Maraviroc

potential enzyme inducer, reduction in the serum level of itraconazole could have occurred, but this could not be ascertained as therapeutic drug level monitoring was not available at our facility. Our patient had a clinical improvement as well as decline in IgE levels after itraconazole therapy, possibly indicating that there was no therapeutic failure arising from the drug interaction. She tolerated itraconazole and antiretroviral therapies well, her liver functions remained normal and there were no breakthrough opportunistic infections. Our experience illustrates that azoles alone may be used as a safer alternative in individuals with HIV AIDS (or other immune suppressive state) presenting with ABPA, particularly in countries with a high burden of tuberculosis. The use of glucocorticoids for ABPA may be avoided in advanced HIV AIDS, as the risk of infections related to therapy may outweigh the potential benefit of treating ABPA.

Learning points

- Owing to the longevity offered by antiretroviral therapy, complications of other long-standing diseases (such as allergic bronchopulmonary aspergillosis (ABPA) complicating asthma) may be seen more often in patients living with HIV.
- Th2-related disorders may occur with similar frequency in HIV AIDS compared with the general population.
- Apart from the well-known invasive fungal infections in HIV AIDS, these individuals can also go on to develop hypersensitivity disorder to fungal antigens such as ABPA.
- In HIV-affected individuals, itraconazole monotherapy can be used effectively as an alternate to corticosteroids in the management of ABPA. However, the potential for drug interaction with antiretroviral drugs should be borne in mind and therapeutic drug level monitoring for itraconazole should be performed wherever available.

Contributors VM was involved in patient management, drafted and revised the manuscript. RA conceived the idea, was involved in patient management and drafted and revised the manuscript for intellectual content.

Competing interests None.

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