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CASE REPORT

Fluconazole-resistant oral candidosis in a repeatedly treated female AIDS patient

Fluconazol-resistente orale Candidose bei einer wiederholt behandelten AIDS-Patientin

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Key words. Candidosis, oral infection, antimycotic chemotherapy, fluconazole, resistance.
Schlüsselwörter. Candidose, orale Infektion, antimykotische Chemotherapie, Fluconazol, Resistenz.

Summary. A 29-year-old female suffering from full-blown AIDS received fluconazole 400 mg day^{-1} for a long period for treatment of oral candidosis, pseudomembranous type. She had previously received this drug repeatedly for the same reason, yet manifest disease persisted. She was therefore put on parenteral amphotericin B, which led to clinical, but not mycological, cure in the short term. IC_{30} testing revealed a minimum inhibitory concentration (MIC) > 128 μg ml^{-1} for fluconazole. The isolate, however, was susceptible *in vitro* to ketoconazole, itraconazole and amphotericin B. The same antimicrobial susceptibility pattern was found with a second isolate obtained later. Resistance to fluconazole might become a major problem in HIV-infected patients receiving this drug for long periods.

Zusammenfassung. Eine 29-jährige manifest an AIDS erkrankte Patientin erhielt 400 mg Fluconazol per os über längere Zeit zur Behandlung einer oralen Candidose vom pseudomembranösen Typ. Eine daraufhin erfolgte Umstellung der Therapie auf Amphotericin B parenteral führte zur klinischen, nicht aber zur mykologischen Heilung in der kurzen Frist. Die IC_{30}-Testung des *Candida albicans*-Isolates erbrachte eine minimale Hemmkonzentration (MHK) für Fluconazol von > 128 μg ml^{-1}. Das Isolat war demgegenüber *in vitro* empfindlich gegenüber Ketoconazol, Itraconazol und Amphotericin B. Korrespondierende Empfindlichkeit wies auch ein konsekutives Isolat aus. Fluconazol-Resistenz könnte ein größeres Problem bei HIV-infizierten Patienten werden, die dieses Medikament über längere Zeit erhalten.

Introduction

Oral candidosis is considered to be one of the earliest signs of HIV infection. It develops in one-third to one-half of HIV-seropositive persons according to a recent in-depth review [1]. The frequency of oral candidosis seems to be linked to the stage of HIV infection and to the T4/T8 ratio [2]. It has been speculated that candidosis may adversely influence the prognosis of the patient because of the immunosuppressive effect of *Candida* species [3]. Early treatment of oral candidosis in HIV-infected patients is also considered mandatory to prevent spread of fungal disease [4].

Nowadays a variety of antimycotics are available for the treatment of oral candidosis in HIV-infected patients [5]. For initial therapy ketoconazole, itraconazole and fluconazole are particularly recommended. In this context the daily dose of antimycotic is least with fluconazole, amounting to 50 mg [5]. In fact, in a comparative clinical trial fluconazole proved to be slightly superior to ketoconazole [6]. More recently, fluconazole 100 mg day^{-1} has also been proven to be superior

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to ketoconazole 200 mg day^{-1} in *Candida* oesophagitis in AIDS patients [7]. Yet higher efficacy *in vivo* is not linked to higher activity *in vitro*. Minimum inhibitory concentrations using a macro-broth dilution assay revealed fluconazole to be about 16-fold less active than ketoconazole against 35 *Candida albicans* isolates [8].

Although fluconazole seems to be efficacious in most patients suffering from oral candidosis associated with HIV infection, this cannot be expected in every patient. In recent years clinical failure with fluconazole has repeatedly been traced back to inadequate *in vitro* activity as expressed by high minimum inhibitory concentrations (MICs) [9–13]. In the following we report on a further case recently observed.

Case report

History

A 29-year-old female had undergone blood transfusion for hypermenorrhoea-associated anaemia at the age of 21 years. Three years later, in 1987, she suffered from weight loss, relapsing fever and nocturnal sweating. In 1988 the patient for the first time attended the Department of Internal Medicine, and AIDS-related complex was diagnosed on both clinical and serological grounds. At that time oral candidosis was manifest, the patient was anergic in the Meriéux test and the CD4 count was 56 μl^{-1}. For 1 year, the patient was put on zidovudine. Owing to relapsing oral candidosis the patient was repeatedly treated with topical amphotericin B, oral ketoconazole and fluconazole. Moreover, the patient was once treated with amphotericin B parenterally. This was because of elevated liver enzymes in the blood linked to the application of fluconazole. In July 1990 *Candida* oesophagitis was successfully treated with oral ketoconazole.

In August 1989 the patient suffered from persistent herpes simplex of the disseminated type. Thus the diagnosis of full-blown AIDS was established. In April 1991 atypical mycobacteriosis of the disseminated type due to *Mycobacterium kansasii* infection was found.

From February 1992 onwards the patient suffered from persistent oral candidosis refractory to various treatment protocols including fluconazole 400 mg day^{-1} orally and also fluconazole parenterally.

Clinical findings

When the patient was referred to the outpatient department of the Department of Dermatology, inspection of the oral cavity revealed whitish plaques surrounded by marked erythema mainly on the tongue and the hard and soft palate but to a certain extent also in the buccal region (see Fig. 1). The diagnosis of oral candidosis of the pseudomembranous type was established on clinical and mycological grounds.

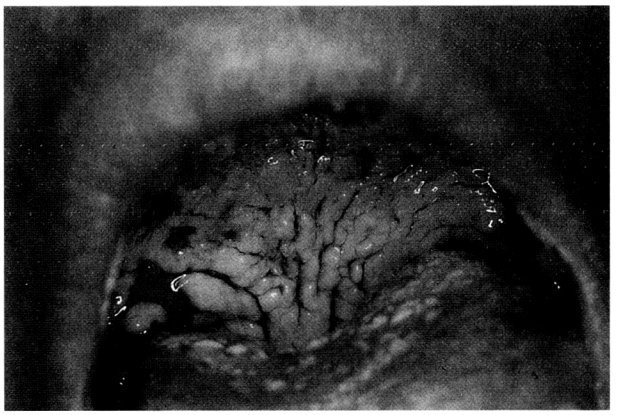

Figure 1. Oral candidosis in a patient suffering from full-blown AIDS. Whitish plaques surrounded by marked erythema at the tongue and the palate.

Treatment and course of disease

In the Department of Internal Medicine the patient was put on parenteral amphotericin B. This led to clinical cure in the short term. After relapsing the patient was again referred to the Department of Dermatology and material was obtained for identifying the causative organism and characterizing its antimicrobial susceptibility. The analysis was repeated 4 weeks later.

Laboratory findings

In both cases a yeast was grown using standard cultural techniques. The species *Candida albicans* was identified by germ tube assay. Antimicrobial susceptibility to various antimycotics was determined using the IC_{30} test as described by Johnson *et al.* [13]. The MIC values of ketoconazole, itraconazole, fluconazole and amphotericin B are shown in Table 1.

Discussion

The *in vitro* susceptibility of *Candida albicans* isolates from HIV-infected patients has been demonstrated to differ according to the stage of HIV infection of the host in that inhibitory concentrations are higher with isolates from patients with manifest AIDS [2]. Recently, an association between reduced susceptibility to ketoconazole and high

Table 1. Antimicrobial susceptibility of *Candida albicans* strains (μg ml^{-1}) according to the IC_{30} test

Strain*	Ketoconazole	Itraconazole	Fluconazole	Amphotericin B
1	0.25	0.25	>128	2
2	4	8	>128	2

*Consecutive isolates.

activity of a protease characteristic of strains isolated from HIV-infected patients was demonstrated [14]. Moreover, in a clinical trial a change from susceptibility to resistance against ketoconazole, which was also clinically relevant, could be demonstrated [15]. In this case, the definitory requirement for development of azole resistance by *Candida albicans* as postulated by Warnock [16] was fulfilled. However, Fan-Havard *et al.* [17] were not able to detect a generally higher resistance of *Candida* isolates from HIV-infected patients with oral candidosis. Yet in an individual case *in vitro* resistance to ketoconazole, fluconazole and amphotericin B was linked to corresponding *in vivo* resistance. In the cases of fluconazole resistance of *Candida albicans* from the oral cavity of HIV-infected patients, fluconazole resistance was either isolated [9–11] or paralleled by a lack of susceptibility to ketoconazole [9]. Currently, the relevance of such an *in vitro* finding is the subject of debate. In particular, it has been questioned if the difference in the MICs between fluconazole and other azoles such as ketoconazole is a true one or results from current not entirely adequate testing procedures [16].

Yet it must be remembered that the question of azole resistance of *Candida albicans* strains from patients with both HIV infection and oral candidosis was raised at the time when fluconazole was introduced into the treatment of this entity on a large scale. In addition, it cannot be overlooked that prophylactic treatment has particularly been suggested since fluconazole became available, and in fact a remarkable number of the cases of fluconazole resistance that have been reported have occurred in this context [10, 12]. Taking a relatively low *in vitro* activity of fluconazole for granted, it is tempting to speculate that in particular low-dose oral fluconazole might in future cause a problem of more widespread resistance. And one cannot currently exclude the possibility that decreased activity of fluconazole might also be paralleled by reduced activity of other azoles such as ketoconazole. This appears to be even more relevant as the mechanism of resistance of all azoles is considered to be the same [16].

The experience of fluconazole resistance *in vitro* in individual patients not responding to corresponding therapy clinically implies that antimicrobial susceptibility testing using adequate methods should be implemented in more clinical centres in future. Although the ideal method has certainly not yet been identified [16, 18], the method to be used in general should be defined in an international consensus conference. From our own experience we would suggest a microdilution test with objective reading and comparison with a control such as the IC_{30} test [19].

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