ORO-ESOPHAGEAL CANDIDIASIS IN A PATIENT WITH AIDS

You met Carol in 1994 when she first came to you from an outside clinic. She was 24 years old at the time, diagnosed with HIV in 1991. Her risk factor was a history of injection heroin use. She was in a methadone program when you met her and had been clean for two years. She had two children and delivered a third in 1995. She was married to a man who was also HIV-infected. He had not given up his heroin addiction and left their marriage in 1996. He died of complications from AIDS in 1998.

Carol had the support of her mother and sisters and came to her medical appointments fairly consistently over the years. She had a hard time with medication adherence as she didn't like taking pills. In 1994 she was started on zidovudine. Her CD4 cell count was 61/mmm. She was also diagnosed with Hepatitis C at that time. Various drug regimens were tried over the next 7 years and her CD4 cell count peaked in 2001 at 158/mmm during a brief time when she was taking efavirenz. Her viral load was never fully suppressed. She took her medication sporadically despite your encouragement and the nurses' calls and her poor numbers. Her only symptoms during that 7 year period came from recurrent episodes of oral thrush. She took fluconazole for this. You encouraged her also to take prophylaxis for PCP but she was not always adherent.

In late 2001 she dropped out of sight and didn't return for more than a year. During that absence she took no medication except an occasional sulfamethoxazole and/or fluconazole. A week prior to her return she'd come to the emergency room in your hospital with severe thrush. She was treated with fluconazole and a follow-up appointment with you was made. In your office for the first time in 15 months she

claimed she'd been feeling fine in the intervening period and hadn't needed to see you. She acknowledged that since she didn't want to take any pills, it was easier not to come to see you, despite what the numbers were showing.

Her weight on that visit in early 2003 was down 3 kg from her baseline 54 kg. She was 5'2". She denied fevers, headaches, shortness of breath or other physical complaints other than a sensation of a lump in her chest when she swallowed. Her thrush was better since getting the fluconazole in the emergency room but the previous week it had been so bad she'd almost stopped eating. She had not been able to taste anything and it had been very hard to swallow although not particularly painful. She said she brushed thick coating off the sides of her mouth and the back of her throat every morning. In your office there was a thin coating of whitish material on her palate, posterior pharynx, tonsils and the back of her throat. She had a complete upper denture in place. When you asked her to remove this she had more white coating on her upper palate. She said that she rarely removed her upper plate, even to sleep. The rest of Carol's exam was essentially normal. You ordered an update of her blood tests and continued her on a twice a day course of fluconazole.

Carol's CD4 cell count was 95/mmm and her viral load was 28,000 copies/ml when you'd last seen her in 2001. Upon her return in early 2003 her CD4 cell count was 10/mmm and her viral load was 463,000 copies/ml. An HIV genotype revealed no mutations – consistent with her having been off all medications for the previous many months. Knowing the results of a genotype done in March, 2001, you gave her prescriptions for lopinavir/ritonavir, abacavir and didanosine. Her Hepatitis C viral load at this time was 1.3 million copies/ml. You discussed the need for a liver biopsy but

decided with her that her HIV needed to be under better control before this would be pursued.

Carol's thrush resolved on the increased dose of fluconazole but quickly recurred. An endoscopy with culture and biopsy revealed invasive *Candida albicans*. You switched the patient from fluconazole to itraconazole. She claimed there was minor improvement in symptoms but only briefly. In late April you admitted her for treatment with amphotericin B. Within 24 hours the patient improved and by 48 hours she noted no dysphagia. No thrush could be seen on her palate. You advised her to remove her dentures for sleeping but she was unwilling to do this at home. She didn't want her children to see her without her teeth. After 3 days of intravenous amphotericin Carol insisted on going home. You prescribed an oral amphotericin solution for swish and spit.

Carol missed her follow-up appointment and returned to the hospital in July for admission with recurrent thrush and severe dysphagia. She reported that the oral solution had worked well for several weeks but when she'd run out she was unable to get more. The pharmacy reported that it was no longer being made. Carol also admitted to frequently missing her antiretroviral medication. While her viral load had dropped to 34,000 copies/ml in March, on admission in July it was back to 470,000 copies/ml. Carol spent a week in the hospital getting amphotericin and once again had a rapid, excellent response. She left the hospital on fluconazole and her thrush recurred shortly after discharge. Her CD4 cell count remained below 20/mmm. She claimed adherence to her PCP and MAC prophylaxis but by the fall she said she hadn't taken any antiretrovirals for months.

In October, 2003, Carol was admitted once more for dysphagia, chest pain, weight loss and severe oro-esophageal candidiasis. After 10 days of liposomal amphotericin B her thrush was only partially improved. At this time a new antriretroviral regimen was initiated with once-a-day medication. She was discharged with an indwelling intravenous catheter (peripherally inserted central catheter: PICC) through which she continued to receive amphotericin three times a week. After ten days at home she called to say ther thrush was no better. She was eating poorly, had trouble keeping her medications down and complained of anterior chest pain. At this point you readmitted her for initiaton of treatment with caspofungin. Carol responded well to this new medication; within 4 days her symptoms were gone and there was no evidence of thrush on exam. She was unhappy about continued intravenous therapy but agreed to have it three times a week at home for a month. She did well at home and her symptoms did not recur. Her ARV adherence also improved during this time although it was never 100%. Carol asked to be switched to an oral medication at the end of the month. Her caspofungin was stopped and she was started on voriconazole. After one week she called to say that her thrush was fine but she was having problems with her vision. She described seeing colored lights and floaters as well as blurry vision and what she called “blank vision”. You sent her to the ophthalmologist but their exam yielded no abnormalities. Carol’s complaints were consistent with side effects of the voriconazole. This was discontinued and the caspofungin was restarted. In late February, 2004 she had been on caspofungin for 6 weeks three times a week and remained symptom-free. She claimed to be taking her ARVs as prescribed but her CD4 cell count remained at 16/mmm and her viral load was 34,000 copies/ml. Another six weeks passed and she returned to your office noting

leakage from the catheter. You pulled the line and sent her home again on fluconazole. She was thrilled to have the PICC line out. You were nervous about what would happen. One week later Carol returned noting that her thrush recurred the day after the line was pulled. She did not want it replaced. She wanted to try the voriconazole again despite her previous visual complaints. You agreed and gave her a loading dose of 300mg twice a day for the first day followed by 200 mg in the morning and 100 mg at night for maintenance. A week later she reported good control of her thrush and no visual side effects.

What Happens Next?

Carol suffers from antifungal resistant *Candida albicans*. Candida is the most common fungal infection and *C. albicans* is the most common opportunistic yeast pathogen in humans and in most animals as well [1]. Up to 55% of healthy individuals carry Candida in their oral cavity [2] but there are a number of conditions which facilitate carriage of the organism and/or enhance the development of the more aggressive hyphal phase of the organism. These conditions include age, diabetes mellitus, antibiotics, corticosteroids, local trauma and immune dysfunction. Wearing dentures, Carol was vulnerable to one of the most common forms of Candida-associated disease. Denture stomatitis is noted much more frequently in women and is present in up to 60% of denture wearers. Her thrush could have started from this. More likely, however, is the role played by her advanced immunosuppression. The AIDS epidemic heralded a dramatic rise in mucosal Candidal infections. Oro-esophageal candidiasis occurred in

nearly 90% of patients infected with HIV in the mid-1980s [3]. While Candida can and does occur in patients with CD4 cell counts greater than 200/mmm, AIDS-defining esophageal candidiasis infrequently occurs in patients with more that 100 CD4 cells/mmm. Defects in T cell function predispose to mucosal candidiasis. Once colonized, Carol would have had little in the way of host defenses against esophageal candidiasis given her very low CD4 cell count. Opportunistic fungal infections occur in other immunocompromised settings and the frequency of these infections in increasing as medical advances in organ transplants, cancer therapy and use of indwelling vascular devices increases.

Resistant Organisms

In the 1990s, use of azole antifungal compounds in the treatment of oral and esophageal candidiasis increased markedly. Fluconazole became the most commonly used of the azole compounds for its ease of administration, low toxicity and rapid response rate. Along with this increased use came increased resistance to the treatment. *Candida albicans* accounts for the majority of candida species found in oral isolates. Non-albicans Candida species (NACS) have become more commonly isolated in recent years as C. *glabrata* and *C. krusei*, for example, are less susceptible to fluconazole [4]. Resistance to azole compounds, and to fluconazole in particular, in patients with HIV came about as a result of both the chronic and intermittent use of these drugs. In those patients whose immune function steadily worsened, the likelihood of azole resistance increased, despite augmenting the doses used [5].

The use of HAART has seen an overall decrease in the rates of oro-esophageal candidiasis but for individual patients such as Carol, HAART (or the lack of it) has not been able to help her. The intermittent use of fluconazole over the years led to azole resistance. Her inability to tolerate or adhere to an effective antiretroviral regimen further encouraged the ongoing disease process.

When Carol's antifungal treatment was switched to amphotericin B she initially had an excellent response. Her symptoms recurred after a certain interval and the amphotericin B was effective a second time. The third time it was used to treat the esophageal candidiasis it was ineffective. There are no current standard methods to test for susceptibility of Candida spp. to amphotericin B [6]. Her lack of clinical response is clear, however.

Newer Antifungals

Both amphotericin B and fluconazole affect membrane ergosterol in the Candida organism. Voriconazole is a second generation derivative of fluconazole and inhibits the enzyme lanosterol 14-a-demethylase of *C.albicans* more effectively than does fluconazole. It also inhibits 24-methylene dihydrolanosterol demethylation in some yeasts and fungi which makes this drug effective against some Candida which are resistant to fluconazole [4]. Like fluconazole, voriconazole is fungistatic and already there have been cross-resistant strains reported [7]. For now Carol is responding to this newly approved medication. Her previous visual disturbances, recognized side effects of this medication, did not recur when she tried the medication a second time.

Glucan synthesis inhibitors are among a new class of antifungals that inhibit cell wall synthesis. This makes these drugs fungicidal and avoids cross-resistance [4]. Echinocandins are glucan synthesis inhibitors that are in clinical trials and caspofungin is a recently approved echinocandin. Caspofungin was demonstrated to have an efficacy, safety and tolerability profile that was similar to that of fluconazole. Caspofungin has to be given intravenously but in a study of HIV-infected patients with Candida esophagitis, it was as safe and as effective as oral fluconazole. Caspofungin was proposed as a "comparably effective but less toxic parenteral alternative" to amphotericin B [8].

Combination Treatment

It is interesting to note that combination therapy has been commonly used and to great effect in some bacterial, mycobacterial and viral infections. The use of combination antifungal therapy has not been widely investigated although the concept seems sensible. There have been some situations when combined antifungal agents have been used. Flucytosine has been used with both fluconazole and amphotericin B in small trials against cryptococcal meningitis and candidal peritonitis [4]. Amphotericin B with fluconazole, itraconazole and caspofungin has been evaluated in small studies against various fungal pathogens but there is as yet no concensus on the effective use of combined antifungal agents.

It is conceivable that for Carol, combination therapy is a future option. It is one of few. Unfortunately, Carol's most recent HIV genotype demonstrated a pan-resistant organism. It is therefore unlikely that she will achieve viral suppression adequate to

allow any significant T cell recovery. Without T cells, antifungals are her only means of relief from the relentless recurrence of oroesophageal candidiasis. As this case demonstrates, oral-esophageal candidiasis can still be a chronic and dramatic problem in some patients with AIDS. HAART has decreased the proportion of those vulnerable to this condition but for those patients who cannot or will not tolerate HAART, severe candidiasis remains a challenging entity.

References

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