Breakthrough zygomycosis during voriconazole treatment for invasive aspergillosis

Haematologica 2004; 89:(12)e140

Voriconazole is active against Aspergillus and other filamentous fungi, but it has no activity against Zygomycetes.[1] Iowa and Boston groups reported an increase in the incidence of zygomycosis in patients given prophylactic voriconazole.[2,3] Long-term use of voriconazole might exert selective pressure for growth of resistant organisms[4] however, reviews of data from several transplantation centers show an apparent increase in the incidence of zygomycosis that began before the introduction of voriconazole.[5] At present, it remains unknown whether increases in the incidence of zygomycosis are attributable to the use of voriconazole. We experienced a patient who developed breakthrough zygomycosis after prolonged use of voriconazole for invasive aspergillosis.

A 61-year man with acute myeloid leukemia received induction chemotherapy comprising cytarabine and idarubicin in February 2004. Antibiotic-resistant fevers developed during neutropenia, and computed tomography (CT) of the chest showed multiple nodules with halo. Circulating Aspergillus antigen using an enzyme-linked immunosorbent assay and plasma (1, 3)-beta-D-glucan (BDG) assay tested positive. Based on histopathological and microbiological examination, invasive aspergillosis caused by A. fumigatus was diagnosed. We initiated micafungin 150 mg. He achieved complete remission. His condition improved with the recovery from myelosuppression. He thereafter received cytarabine 2 g/m^2 twice a day for 4 days as consolidation. Invasive aspergillosis did not recur with prophylactic voriconazole 200 mg. The second course of intermediate dose of cytarabine was given in July 2004. Neutropenic fevers developed 12 days after initiation of the chemotherapy. We initiated ceftazidime and amikacin, but the fever persisted. Since the size of multiple nodules increased on the chest CT scan, recurrence of invasive aspergillosis was suspected. Intravenous micafungin 150 mg was initiated, but to no avail. Circulating galactomannan antigen assay and BDG assay remained negative. Transbronchial lung biopsy revealed thickened walls of the pulmonary vessels with organized thrombi. There were hyphae which were twisted, woven, and broad without regular septation. These organisms were identified as Zygomycetes based on the characteristic morphology. Despite aggressive antifungal therapy including amphotericin-B, he finally died of invasive zygomycosis in September 2004.

His clinical courses support the association between voriconazole use and zygomycosis. Such clinical courses were comparable to previous reports.[6,7] The Seattle group reported that 4 of 6 patients who had zygomycosis between 1998 and 2003, had received voriconazole for the treatment of aspergillosis or fusariosis.[7] History of invasive aspergillosis might have significantly contributed to the development of zygomycosis. Several possibilities can be postulated on the pathogenesis of aspergillosis and zygomycosis in this patient. Interestingly, the major infectious sites of Aspergillus and Zygomycetes were almost identical on repeated chest CT scans. The lung tissue damaged by invasive aspergillosis probably became the infectious focus of Zygomycetes, which might selectively proliferate with the long-term use of voriconazole. The other possibility is a mixed mycosis at the onset of the infection during induction chemotherapy. This patient developed aspergillosis and zygomycosis concomitantly; the former was cured with micafungin and voriconazole, and the latter progressed despite antifungal treatments using voriconazole and micafungin. Both agents are effective against Aspergillus, but lack activities against Zygomycetes.[8,9] Zygomycosis might have been an undiagnosed, not a breakthrough, fungal infection.

The standard treatment of deep fungal infection has been amphotericin-B which is active for both Aspergillus and Zygomycetes. Voriconazole is effective against Aspergillus; however, their drawback is the reduced activity against Zygomycetes.[9] The more frequently we use the agent, the more Zygomycetes infection may become apparent. Patients with a history of invasive aspergillosis who had long been treated with voriconazole might have a risk of zygomycosis.

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We thank to Dr. Koichi Makimura in Teikyo University Institute of Medical Mycology for advice on this case report.

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