
ACQUIRED RESISTANCE AND REVERSIBILITY OF *ASPERGILLUS FUMIGATUS* TO ITRACONAZOLE

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In this study, we report on the development of resistance to itraconazole of *Aspergillus fumigatus* in a patient following prolonged itraconazole therapy and the reversion of resistance after the drug was discontinued.

The patient was a 46-year-old man who had a history of pulmonary tuberculosis with cavitation and fibrosis in the lesion for five years. He was admitted in December 2001 because of expectoration, hemoptysis and dyspnea. Acid fast staining of his sputum for *Mycobacterium tuberculosis* was negative. A large number of hyaline and septate hyphae were seen in KOH preparations of the sputum. *A. fumigatus* was isolated from his sputum and was named isolate "A" in this study. A large cavity was found in his left lung by CT scanning. Itraconazole, 200 mg/day combined with antituberculosis agents Protionamide, Rifapentine and sodium para-aminosalicylate were started and continued for 6 months. In July 2002, hyphae were again seen in the sputum. *A. fumigatus* was isolated from his sputum and this strain was named isolate "B". In August 2002, two months after discontinuing the itraconazole (by himself), the patient was hospitalized again. Sputum was positive for hyphae and *A. fumigatus* was recovered from his sputum (named isolate C).

All three of the *Aspergillus fumigatus* isolates were evaluated for antifungal susceptibility using NCCLS M38-A procedures. Itraconazole MICs against the pre-treatment isolate "A" was 0.25 mg/L, while the second isolate ("B"), recovered after 6 months of itraconazole therapy, had itraconazole MICs of >16 mg/L. The third isolate (C), isolated two months after the therapy was discontinued, had itraconazole MICs of 0.5 mg/L. The ITS sequence of the three aspergilli isolates had 100% identity. The three isolates were typed by random amplified polymorphic DNA (RAPD) with five different primers. RAPD patterns obtained for each were identical.

These results suggesting that the same strain was recovered each time and it developed resistance to itraconazole under the pressure of the drug: it then reverted to being susceptible when the pressure was eliminated.