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Abstract (oral session)

Phenotypic and molecular resistance patterns of Candida species in patients with candidaemia and haematologic malignancies

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Background: During a prospective, observational, multicenter study of candidemia in patients with hematological malignancies, we observed that candidemia emerged commonly during antifungal therapy. The mechanisms underlying these breakthrough infections are not well understood. Methods: In vitro susceptibility was performed by CLSI M27A3 microbroth dilution on all 30 isolates of Candida spp. causing bloodstream infection (BSI). The molecular mechanisms of resistance of 12 of these BSI isolates were further characterized by sequencing specific regions of FKS1, FKS2 and ERG11 genes. Results: There were 13 C. parapsilosis(43%), 5 C. albicans(17%), 4 C. glabrata(13%), 3 C. tropicalis(10%), 2 C. guilliermondii(7%), and one(3%) each of C. lusitaniae, C. krusei and C. famata; 18(60%) caused BSIs during antifungal therapy. Eight(27%) emerged during amphotericin B (AmB)therapy. The median MIC for these isolates was 0.25 µg/ml(0.25-1.0 µg/ml); whereas, the median MLC=2 µg/ml(2-8 µg/ml) and median MLC/MIC ratio=4 µg/ml(2-8 µg/ml), consistent with resistance to the fungicidal effect of AmB. During the course of an antifungal triazole, breakthrough BSI occurred in 10(33%) cases(4 posaconazole, 6 fluconazole). All isolates were susceptible to both triazoles; however, 8 of 10 isolates were C. parapsilosis, suggesting a role for vascular catheters. Breakthrough BSI developed in 2 cases receiving echinocandins (caspofungin and anidulafungin); both were caused by echinocandin-resistant C. parapsilosis(MIC>=2 mg/L) with the proline-to-alanine amino acid change in the FKS1 protein(P660A). Six other isolates of C. parapsilosis showed phenotypic resistance against echinocandins(MIC range,2-8 mg/L): 4 C. parapsilosis de novo, 1 C. parapsilosis on fluconazole, 1 C. parapsilosis on AmB. Thus, 8 (62%) of 13 isolates of C. parapsilosis demonstrated phenotypic resistance to echinocandins, 4 of which demonstrated P660A in FKS1. By comparison, the multidrug resistant isolate of C. guilliermondii with MICs>=4 mg/L to all echinocandins did not demonstrate any critical FKS1 gene mutations. Conclusions: This study demonstrates new patterns of breakthrough Candida BSIs in patients with hematological malignancies: the emergence of C. parapsilosis and C. guilliermondii; echinocandin resistance with P660A FKS1; high-level resistance to the fungicidal effect of AmB; and emergent candidemia during triazole therapy despite susceptible profiles.