BÖLÜM

11 SİSTEMİK FUNGAL ENFEKSİYONLAR

Murat ÜNSEL [1]
Güldem TURAN [2]

GİRİŞ

Sistemik fungal infeksiyon (SFİ) sıklığı son yıllarda giderek artmakta ve yoğun bakım ünitelerinde (YBÜ) genellikle nonspesifik klinik tabloya neden olarak yüksek mortalite ve morbitideye yol açan hastalıklar arasında yer almaktadır. Özellikle immünosüprese hastalarda öldürücü olabilen derin yerleşimli sistemik fungal infeksiyonların tanısında ve yönetim süreçlerinde güçlükler yaşanmaktadır (1). Bu duruma zemin hazırlayan faktörler arasında, hematopoetik kök hücre veya solid organ nakli ve HIV infeksiyonu gibi immünosüpresyona neden olan hastalıkların ve yaşlı hasta popülasyonunun artması; geniş spektrumlu antibiyotiklerle uzun süreli tedaviler, immün sistemi baskılayan ilaçların kullanımının ve santral venöz kateter gibi invaziv erişim yollarının kullanımının yaygınlaşması sayılabilir (2).

YBÜ'lerde invaziv fungal enfeksiyonların büyük coğunluğundan Candida spp. (%52.9) sorumludur. Azalan sıklıkla Aspergillus spp. (%18.8), Cryptococcus, diğer küfler, endemik mantarlar, Zygomycetes ve Pneumocystis etyolojide yer almaktadır(3).

[1] Uzm. Dr., Başakşehir Çam ve Sakura Şehir Hastanesi, Yoğun Bakım Kliniği, muratunsel@hotmail.com
[2] Prof. Dr., Başakşehir Çam ve Sakura Şehir Hastanesi, Yoğun Bakım Kliniği, gturanmd@yahoo.com

primer tedavisinde vorikanazol, lipozamal AmB ya da ekinokandinler önerilmektedir. MSS'ye çok iyi geçmesinden dolayı serebral aspergillozun tedavisinde ilk seçenek vorikonazoldür (54). Varikanazol ile tedaviye cevap alınamadığı zaman tedaviye ekinokandin veya AmB eklenmelidir. Tedavi lezyonlar iyileşene ve nötropeni düzelene kadar devam etmelidir (55). Yine solid organ nakli yapılmış İA olgularında da ilk seçenek vorikonazol ve isavukonazoldur.

İNVAZİV MUKORMİKOZ ENFEKSİYONLARI

Mukormikoz en sık hematolojik malignite, uzun süreli ve ciddi nötropeni, kontrolsüz diabetes mellitus, demir yüklenmesi, ciddi travma, uzun süreli ve yüksek dozda kortikosteroid kullanımı, ciddi beslenme bozukluğu gibi durumlarda görülür. Hematolojik malignite ve alojenik kök hücre nakli hastalarında kandidiyaz ve aspergillozdan sonra en sık görülen invaziv mikozdur (56,57). Mukormikoz etkenleri vazotropiktir; konak dokularında hiflerin damarlara invazyonu sonucunda ortaya çıkan infarkt ve nekrozla karakterizedir. En sık görülen formu rino-orbito-serebral infeksiyondur. Duyarlı bir konakta sporların paranazal sinüslere inhalasyonuyla başlar; hızla komşu dokulara yayılabilir. Klasik olarak en sık altta yatan durum olan diyabetik ketoasidozda veya kontrolsüz diabetes mellitus hastalarında tanımlanmıştır (56,59). Lösemi hastalarında genellikle birlikte diabetes mellitus varlığında veya yüksek doz kortikosteroid kullanımında ortaya çıkar. Akciğer mukormikozu klinik ve radyolojik olarak akciğer aspergillozuna benzer. Mukormikozun en sık görülen ikinci formudur. Sporların inhalasyonu yoluyla ortaya çıkar. Kavitasyonlar ve hemoptizi ile seyreder. Tedavide merkezi sinir sistemi enfeksiyonu için L-AmB (Lipozomal AmB) kullanılır.

Sonuç olarak, YBÜ'lerde yüksek morbidite ve mortaliteye sahip invaziv mantar enfeksiyonlarında amaç, uygun tedaviyi hastada en kısa sürede başlamaktır. Tedavi başlanacak hastanın en kısa sürede belirlenebilmesi için klinik risk faktörleriyle kültüre dayalı olmayan laboratuvar testlerinin birlikte kullanımı, klinik yönlendirme için önemlidir. Ancak kültüre dayalı olmayan laboratuvar testlerinin antifungal tedavi sürecinin yönlendirilmesinde kullanımıyla ilgili yeterli bilgi yoktur.

KAYNAKLAR

1. Webb BJ, Ferraro JP, Rea S, Kaufusi S, Goodman BE, Spalding J. Epidemiology and clinical features of invasive fungal infection in a US health care network. Open Forum Infect Dis. 2018; 5(8): ofy187. [CrossRef]
2. Enoch DA, Yang H, Aliyu SH, Micallef C. The changing epidemiology of invasive fungal infections. *Methods Mol Biol.* 2017; 1508: 17-65. [CrossRef]
3. Paramythiotou E, Frantzeskaki F, Flevari A, Armaganidis A, Dimopoulos G Invasive fungal infections in the ICU: how to approach, how to treat. Molecules 2014;19(1):1085-119.
4. Mean M, Marchetti O, Calandra T. Bench-to-bedside review: Candida infections in the intensive care unit. *Crit Care*. 2008; 12(1): 204. [CrossRef]

5. Marchetti O, Bille J, Fluckiger U, *et al.* Epidemiology of candidemia in Swiss tertiary care hospitals: secular trends, 1991-2000. *Clin Infect Dis*. 2004; 38(3): 311-20.
6. Warnock DW. Trends in the epidemiology of invasive fungal infections. Nihon Ishinkin Gakkai Zasshi. 2007; 48(1): 1-12.
7. Horn DL, Neofytos D, Anaissie EJ, et al. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin Infect Dis. 2009; 48(12): 1695-703.
8. Falagas ME, Roussos N, Vardakas KZ. Relative frequency of albicans and the various non-albicans Candida spp among candidemia isolates from inpatients in various parts of the world: a systematic review. Int J Infect Dis. 2010; 14(11): e954-66.
9. Pfaller MA, Diekema DJ, Turnidge JD, Castanheira M, Jones RN. Twenty years of the SENTRY antifungal surveillance program: Results for Candida species from 1997-2016. Open Forum Infect Dis. 2019; 6(Suppl. 1): S79-94.
10. Schmiedel Y, Zimmerli S. Common invasive fungal diseases: an overview of invasive candidiasis, aspergillosis, cryptococcosis, and Pneumocystis pneumonia. *Swiss Med Wkly*. 2016; 146: w14281.
11. Satoh K, Makimura K, Hasumi Y, Nishiyama Y, Uchida K, Yamaguchi H. Candida auris spp. a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital. Microbiol Immunol, 2009; 53: 41–4.
12. Chauhan R, Loonker S. Synthesis. Characterization and biological evaluation of chitosan epoxy n-methyl piperazine as antimicrobial agent. Int J Pharm Sci Rev Res, 2017; 45:266–70.
13. Anonymous. https://www.cdc.gov/fungal/ candida-auris/tracking-c-auris.html, (Erişim Tarihi: 15.05. 2019).
14. Gudlaugsson O, Gillespie S, Lee K, et al. Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis. 2003; 37(9): 1172-7.
15. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospital: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis. 2004; 39(3): 309-17.
16. Glöckner A, Karthaus M. Current aspect of invasive candidiasis and aspergillosis in adult intensive care patients, Mycoses 2011 ;54(5):420-33.
17. Yang SP, Chen YY, Hsu HS, Wang FD, Chen LY, Fung CP. A risk factor analysis of healthcare-associated fungal infections in an intensive care unit: a retrospective cohort study. BMC Infect Dis. 2013; 13: 10.
18. Jordà-Marcos R, Alvarez-Lerma F, Jurado M, et al. Risk factors for candidemia in critically il patients: a prospective surveillance study. Mycoses. 2007; 50(4): 302-10.
19. Guastalegname M, Russo A, Falcone M, Giuliano S, Venditti M. Candidemia subsequent to severe infection due to Clostridium difficile: is there a link? Clin Infect Dis. 2013; 57(5): 772-4. [CrossRef]
20. Papadimitriou-Olivgeris M, Spiliopoulou A, Fligou F, et al. Association of KPC-producing Klebsiella pneumoniae colonization or infection with Candida isolation and selection of non-albicans species. Diagn Microbiol Infect Dis. 2014; 80(3): 227-32.
21. Matthaiou DK, Christodoulopoulou T, Dimopoulos G. How to treat fungal infections in ICU patients. BMC Infect Dis. 2015; 15: 205.
22. Arendrup MC. Epidemiology of invasive candidiasis. Curr Opin Crit Care. 2010; 16(5): 445-52.
23. Pittet D, Monod M, Suter PM, Frenk E, Auckentaler R. Candida colonization and subsequent infections in critically ill surgical patients. *Ann Surg*. 1994; 220(6): 751-8.
24. Eggimann P, Pittet D. Candida colonization index and subsequent infection in critically ill surgical patients. 20 years later. *Intensive Care Med*. 2014; 40(10): 1429-48.
25. Piarroux R, Grenouillet F, Balvay P, Tran V, Blasco V, Milloin M, et al. Assessment of preemptive treatment to prevent severe candidiasis in critically ll surgical patients. Crit Care Med. 2004; 32(12): 2443-9.
26. Leon C, Ruiz-Santana S, Saavedra P, et al. A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with Candida colonization. Crit Care Med. 2006; 34(3): 730-7.
27. Ostrosky-Zeichner L, Pappas PG, Shoham S, *et al*. Improvement of a clinical prediction rule for clinical trials on prophylaxis for invasive candidiasis in intensive care unit. *Mycoses*. 2011; 54(1): 46-51.

28. Ullmann AJ, Aguado JM, Arıkan-Akdağlı S, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect. 2018; 24(Suppl. 1): e1-38.
29. Wheat JL. Approach to the diagnosis of invasive aspergillosis and candidiasis. Clin Chest Med. 2009; 30(2): 367-77.
30. Mikulska M, Calandra T, Sanguinetti M, Poulain D, Viscoli C, Third European Conference on Infections in Leukemia Group. The use of mannan antigen and anti-mannan antibodies in the diagnosis of invasive candidiasis: recommendations from the Third European Conference on Infections in Leukemia. *Crit Care*. 2010; 14(6): R222.
31. McMullan R, Metwally L, Coyle PV, et al. A prospective clinical trial of real-time polymerase chain reaction assay for the diagnosis of candidemia in nonneutropenic, critically ill adults. Clin Infect Dis. 2008; 46(6): 890-6.
32. Khot PD, Fredricks DN. PCR-based diagnosis of human fungal infections. Expert Rev Anti Infect Ther. 2009; 7(10): 1201-22.
33. Neely LA, Audeh M, Phung NA, et al. T2 magnetic resonance enables nanoparticle mediated rapid detection of candidemia in whole blood. Sci Transl Med. 2013; 5(182): 182ra54.
34. Mylonakis E, Clancy CJ, Ostrosky-Zeichner L, et al. T2 magnetic resonance assay for the rapid diagnosis of candidemia in whole blood: a clinical trial. Clin Infect Dis. 2015; 60(6): 892-9.
35. Baykara N, Akalın H, Arslantaş MK, et al. Epidemiology of sepsis in intensive care units in Turkey: a multicenter, point-prevalence study. Crit Care. 2018; 22(1): 93.
36. Gudlaugsson O, Gillespie S, Lee K, et al. Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis. 2003; 37(9): 1172-7.
37. Lortholary O, Renaudat C, Sitbon K, et al. Worrisome trends in incidence and mortality of candidemia in intensive care units (Paris area, 2002-2010). Intensive Care Med. 2014; 40(9): 1303-12.
38. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016; 62(4): e1-50.
39. Cornely OA, Bassetti M, Calandra T, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect. 2012; 18(7): 19-37.
40. Beed M, Sherman R, Holden S. Fungal infections and critically ill adults. Continuing Education in Anaesthesia Critical Care & Pain. 2014; 14(6): 262-7.
41. Garnacho-Montero J, Díaz-Martín A, García-Cabrera E, Ruiz Pérez de Pipaón M, Hernández-Caballero C, Lepe-Jiménez JA. Impact on hospital mortality of catheter removal and adequate antifungal therapy in Candida spp. bloodstream infections. J Antimicrob Chemother. 2013; 68(1): 206-13.
42. Kuhn DM, George T, Chandra J, Mukherjee PK, Ghannoum MA. Antifungal susceptibility of Candida biofilms: unique efficacy of amphotericin B lipid formulations and echinocandins. Antimicrob Agents Chemother. 2002; 46(6): 1773-80.
43. Muilwijk EW, Schouten JA, van Leeuwen HJ, et al. Pharmacokinetics of caspofungin in ICU patients. J Antimicrob Chemother. 2014; 69(12): 3294-9. [CrossRef]
44. Grau S, Luque S, Campillo N, et al. Plasma and peritoneal fluid population pharmacokinetics of micafungin in post-surgical patients with severe peritonitis. J Antimicrob Chemother. 2015; 70(10): 2854-61.
45. Karthaus M. Prophylaxis and treatment of invasive aspergillosis with voriconazole, posaconazole and caspofungin: review of the literature. Eur J Med Res 2011 ;16 (4):145-152
46. Kosmidis C, Denning DW. The clinical spectrum of pulmonary aspergillosis. *Thorax*. 2015; 70(3): 270-7.
47. Kauffman CA. Epidemiology and clinical manifestations of invasive aspergillosis. [İnternet].Waltham,MA:UpToDate, Inc. [erişim 29 Haziran 2019]. https://www.uptodate.com/contents/epidemiology-and-clinical-manifestations-of-invasive-aspergillosis.
48. Munoz P, Guinea J, Bouza E. Update on invasive aspergillosis: clinical and diagnostic aspects. Clin Microbiol Infect. 2006; 12 (Suppl. 7): 24-39.
49. Horvath JA, Dummer S. The use of respiratory-tract cultures in the diagnosis of invasive pulmonary aspergillosis. Am J Med. 1996; 100(2): 171-8.

50. Lamoth F, Calandra T. Early diagnosis of invasive mould infections and diseas. J Antimicrob Chemother. 2017; 72 (Suppl. 1): i19-28.
51. Schelenz S, Barnes RA, Barton RC, et al. British Society for Medical Mycology best practice recommendations for the diagnosis of serious fungal diseases. Lancet Infect Dis. 2015; 15(4): 461-74.
52. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016; 63(4): e1-60.
53. Cornely OA, Maertens J, Winston DJ, *et al*. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007; 356(4): 348-59.
54. Mousset S, Buchheidt D, Heinz W, *et al*. Treatment of invasive fungal infections in cancer patients - updated recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol*. 2013; 93(1): 13-32
55. Walsh TJ, Anaissie EJ, Denning DW, et all Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America. Clin. Infec.Dis.2008;46 (3):327-60.
56. Cornely OA, Bangard C, Jaspers NI. Hepatosplenic candidiasis. *Clin Liver Dis (Hoboken)*. 2015; 6(2): 47-50.
57. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. *Clin Infect Dis*. 2012; 54(Suppl. 1): 23-34.
58. Prabhu RM, Patel R. Mucormycosis and entomophthoramycosis: a review of the clinical manifestations, diagnosis and treatment. *Clin Microbiol Infect*. 2004; 10(Suppl. 1): 31-47.
59. Cox GM. Mucormycosis (zygomycosis) [İnternet]. Waltham, MA: UpToDate, Inc. [erişim 29 Haziran 2019]. https://www.uptodate.com/contents/mucormycosis-zygomycosis.