

BÖLÜM

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MİKOZİS FUNGOİDESİN TARİHÇESİ VE ETYOPATOGENEZİ

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GİRİŞ

Kutanöz T hücreli lenfomalar (KTHL), kronik olarak enflamatuvar deri lezyonlarında malign T hücrelerinin birikmesi ile karakterize, heterojen ekstranodal, non-Hodgkin lenfoma grubudur. Mikozis Fungoides (MF), KTHL'nin en sık görülen tipidir. Gelişimi karmaşık yolaklarla açıklanmaya çalışılan MF'in etyopatogenezinde genetik, epigenetik, çevresel ve immunolojik faktörlerin bir arada rol oynadığı düşünülmektedir. Ancak şimdiye kadar spesifik bir neden belirlenmemiştir.

MİKOZİS FUNGOİDES'İN TARİHÇESİ

Mikozis Fungoides (MF), ilk olarak 1806 yılında Fransız dermatolog Alibert tarafından yaws hastalığına (Ekvator frengisi) benzerliği nedeniyle 'yaws mantarı' anlamına gelen 'pian fungoide' olarak isimlendirilerek tanımlanmıştır. Daha sonra 1835 yılında tümöral lezyonların mantar şeklinde benzemesi nedeniyle ismi 'mikozis fungoides' olarak kullanılmaya başlanmıştır (Farber et al., 1957, Mahalingam et al., 2015, Willemze, 2018). Bazin tarafından 1870 yılında hastalığın seyrinin sırasıyla yama-plak ve tümör evreleri şeklinde ilerlediği tariflenmiştir (Willemze, 2018, Willemze et al., 2006.).

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rin protümürijenik özellik gösterdiği düşünülmektedir (Pileri et al., 2021). İleri evre MF lezyonlarında immunsupresif hücre özelliği gösteren MDSH sayısı ve aktivitesinde artış saptandığı bildirilmektedir. Regülatuvardan T ve B hücrelerinin fonksiyonları, MF/SS'da halen tam olarak anlaşılamamıştır.

SONUÇ

MF ve SS'nun etyopatogenezi ile ilişkili yapılan çok sayıda çalışmadan elde edilen ve giderek artan kanıtlar, malign, stromal ve epidermal etkileşimlerin, hastlığın patogenezinde önemli bir rol oynadığını göstermektedir. Tümör hücreleri, kertinositler ve fibroblastlar arasındaki karmaşık sinyal ağları, STAT proteinlerinin malign aktivasyonu, Th2 baskın enflamatuar bir mikroçevrenin gelişimi, tümör dokusunun neovaskülarizasyonu ve deride yapısal değişiklikleri içeren çeşitli patolojik süreçler besleyebilir. Bu süreçlerin farklı yolaklar aracılığıyla antitümör reaksiyonları engellerken, malign proliferasyonu ve hastlığın yayılmasını kolaylaştırıldığı düşünülmektedir (Stolearence et al., 2020, Krejsgaard et al. 2017). Bununla birlikte KTHL'nin patogenezinin daha net anlaşılabilmesi için ileri çalışmalar gereksinim olduğu açıktır.

KAYNAKLAR

- Farber EM, Schneidman HM, Llerena J. (1957). The natural history of mycosis fungoides. Calif Med.87(4):225-30.
- Mahalingam M, Reddy VB. (2015) Mycosis Fungoides, Then and Now... Have We Travelled? Adv Anat Pathol.22(6):376-83. <https://doi.org/10.1097/PAP.0000000000000092>
- Willemze R. (2018) Cutaneous T-Cell Lymphoma In Bolognia JL, Schaffer JV, Cerroni L, eds. Dermatology. 4th ed. China: Elsevier; p.2127-47.
- Willemze R, Meijer CJ. (2006). Classification of cutaneous T-cell lymphoma: from Alibert to WHO-EORTC. J Cutan Pathol ;33 Suppl 1:18-26.
- Bagherani N, Smoller BR (2016). An overview of cutaneous T cell lymphomas. F1000Res.;5:F1000 Faculty Rev-1882.<https://doi.org/10.12688/f1000research.8829.1>
- Larocca C, Kupper T. (2019). Mycosis Fungoides and Sézary Syndrome: An Update. Hematol Oncol Clin North Am;33(1):103-120. <https://doi.org/10.1016/j.hoc.2018.09.00>
- Damsky WE, Choi J. (2016) Genetics of Cutaneous T Cell Lymphoma: From Bench to Bedside. Curr Treat Options Oncol. 17(7):33. <https://doi.org/10.1007/s11864-016-0410-8>

- García-Díaz N, Piris MÁ et al. (2021). Mycosis Fungoides and Sézary Syndrome: An Integrative Review of the Pathophysiology, Molecular Drivers, and Targeted Therapy. *Cancers.* 13(8), 1931. <https://doi.org/10.3390/cancers13081931>.
- Walia R, Yeung CCS. (2020) An Update on Molecular Biology of Cutaneous T Cell Lymphoma. *Front Oncol.* 9:1558. <https://doi.org/10.1007/s11864-016-0410-8>
- Hara N, Sawada Y. (2022) Epigenetics of Cutaneous T-Cell Lymphomas. *Int J Mol Sci.* 23(7):3538. <https://doi.org/10.3390/ijms23073538>
- Phyo ZH, Shanbhag S, Rozati S. (2020) Update on Biology of Cutaneous T-Cell Lymphoma. *Front Oncol.* 10:765. <https://doi.org/10.3389/fonc.2020.00765>
- Stolarenc V, Namin MRJ, Hasselager SS, Gluud et al. (2020) Cellular Interactions and Inflammation in the Pathogenesis of Cutaneous T-Cell Lymphoma. *Front Cell Dev Biol.* 8:851. <https://doi.org/10.3389/fcell.00851>.
- Krejsgaard, T, Lindahl, L.M, Mongan, N.P. et al. (2017). Malignant inflammation in cutaneous T-cell lymphoma a hostile takeover. *Semin Immunopathol.* 39, 269–282. <https://doi.org/10.1007/s00281-016-0594-9>.
- Hodak E, Klein T, Gabay B, et al (2005). Familial mycosis fungoides: report of 6 kindreds and a study of the HLA system. *J Am Acad Dermatol.* 52:393–402. doi: 10.1016/j.jaad.2003.12.052.
- Jackow CM, McHam JB. (1996). HLA-DR5 and DQB1*03 class II alleles are associated with cutaneous T-cell lymphoma. *J Invest Dermatol;* 107: 373– 376.
- Odum N, Lindahl LM, Wod M, et al. (2017) Investigating heredity in cutaneous T-cell lymphoma in a unique cohort of Danish twins. *Blood Cancer J.* 7(1):e517.
- Bobrowicz M, Fassnacht C, Ignatova D. (2020) Pathogenesis and Therapy of Primary Cutaneous T-Cell Lymphoma: Collegium Internationale Allergologicum (CIA) Update *Int Arch Allergy Immunol.* 181(10):733-745.
- Jonak C, Tittes J, Brunner PM, Guenova E. (2021) Mycosis fungoides and Sézary syndrome. *J Dtsch Dermatol Ges :JDDG,* 19(9), 1307–1334. <https://doi.org/10.1111/ddg.14610>.
- Durgin JS, Weiner DM, Wysocka M, Rook AH. (2021) The immunopathogenesis and immunotherapy of cutaneous T cell lymphoma: Pathways and targets for immune restoration and tumor eradication. *J Am Acad Dermatol.* 84(3):587-595. <https://doi.org/10.1016/j.jaad.2020.12.027>
- Bastidas Torres AN, Cats D, Mei H, Szuhai K, et al., (2018). Genomic analysis reveals recurrent deletion of JAK-STAT signaling inhibitors HNRNPK and SOCS1 in mycosis fungoides. *Genes Chromosomes Cancer.* Dec;57(12):653-664. <https://doi.org/10.1002/gcc.22679>
- Gluud M, Willerslev-Olsen A, Gjerdrum LMR et al. (2020). MicroRNAs in the Pathogenesis, Diagnosis, Prognosis and Targeted Treatment of Cutaneous T-Cell Lymphomas. *Cancers (Basel).*12(5):1229. <https://doi.org/10.3390/cancers12051229>.
- Sandoval J, Díaz-Lagares A, Salgado R et al. (2015). MicroRNA expression profiling and DNA methylation signature for deregulated microRNA in cutaneous T-cell lymphoma. *Journal of Investigative Dermatology,* 135(4), 1128-1137.

- Lindahl LM, et al. (2016). STAT5 induces miR-21 expression in cutaneous T cell lymphoma. *Oncotarget*, 7(29),45730- 45744. <https://doi.org/10.18632/oncotarget.10160>
- Willerslev-Olsen A, Gjerdrum LMR, Lindahl LM et al. (2021). *Staphylococcus aureus* Induces Signal Transducer and Activator of Transcription 5-Dependent miR-155 Expression in Cutaneous T-Cell Lymphoma. *J Invest Dermatol*. Oct;141(10):2449-2458.
- Han Q, Liu D, Convertino M, Wang Z et al. (2018). miRNA-711 binds and activates TRPA1 extracellularly to evoke acute and chronic pruritus. *Neuron*, 99(3), 449-463.
- van Kester MS, Ballabio E, Benner MF, et al. (2011) miRNA expression profiling of mycosis fungoides. *Mol Oncol*. 5(3):273-280.
- Manso R, Martínez-Magunacelaya N, et al (2018). Mycosis fungoides progression could be regulated by microRNAs. *PLoS One*. Jun 12;13(6):e0198477. <https://doi.org/10.1371/journal.pone.0198477>.
- Lindahl, L. M., Besenbacher, S., Rittig, A. H., et al. (2018). Prognostic miRNA classifier in early-stage mycosis fungoides: development and validation in a Danish nationwide study. *Blood*, 131(7), 759–770. <https://doi.org/10.1182/blood-2017-06-788950>
- Ghazawi, F. M., Alghazawi, N., Le, M., Netchiporouk, E., et al.(2019). Environmental and Other Extrinsic Risk Factors Contributing to the Pathogenesis of Cutaneous T Cell Lymphoma(CTCL). *Frontiers in oncology*, 9, 300. <https://doi.org/10.3389/fonc.2019.00300>
- Litvinov, I. V., Shtreis, A. & Duvic, M. (2016). Investigating potential exogenous tumor initiating and promoting factors for Cutaneous T-Cell Lymphomas (CTCL), a rare skin malignancy. *Oncoimmunology*, 5(7),e1175799.<https://doi.org/10.1080/2162402X.2016.1175799>
- Aschebrook-Kilfoy B, Cocco P. (2014) Medical History, Lifestyle, Family History, and Occupational Risk Factors for Mycosis Fungoides and Sézary Syndrome: The InterLymph Non-Hodgkin Lymphoma Subtypes Project. *JNCI Monographs*, 48, 98-105. <https://doi.org/10.1093/jncimonographs/lgu008>
- Chang HC, Tsai TY. (2022) Is smoking associated with mycosis fungoides and Sézary syndrome? *J Eur Acad Dermatol Venereol*. 36(5):e381-e384. <https://doi.org/10.1111/jdv.17923>
- Paul, L J, Duvic, M. (2012). Mycosis fungoides following skin trauma. *Journal of the American Academy of Dermatology*, 67(4), e148.<https://doi.org/10.1016/j.jaad.2011.11.953>
- Jahan-Tigh, R. R., Huen, A, & Duvic, M. (2013). Hydrochlorothiazide and cutaneous T cell lymphoma: prospective analysis and case series. *Cancer*, 119(4), 825–831. <https://doi.org/10.1002/cncr.27740>
- Morales-Suárez-Varela, M. M., et al. (2006). Occupational sun exposure and mycosis fungoides: a European multicenter case-control study. *Journal of occupational and environmentalmedicine*, 48(4), 390–393. <https://doi.org/10.1097/01.jom.0000194160.95468.20>

- Jones, C. L., Degasperi, A., Grandi, V., et al. (2021). Spectrum of mutational signatures in T-cell lymphoma reveals a key role for UV radiation in cutaneous T-cell lymphoma. *Scientific reports*, 11(1), 3962. <https://doi.org/10.1038/s41598-021-83352-4>
- Talpur, R., Cox, K. M., Hu, M., Geddes., et al. (2014). Vitamin D deficiency in mycosis fungoides and Sézary syndrome patients is similar to other cancer patients. *Clinical lymphoma, myeloma-leukemia*, 14(6), 518–524. <https://doi.org/10.1016/j.cml.2014.06.023>.
- Jost, M., & Wehkamp, U. (2022). The Skin Microbiome and Influencing Elements in Cutaneous T-Cell Lymphomas. *Cancers*, 14(5), 1324. <https://doi.org/10.3390/cancers14051324>.
- Zhang, Y., Seminario-Vidal, L., Cohen, L., Hussaini, M., et al (2022). “Alterations in the Skin Microbiota Are Associated With Symptom Severity in Mycosis Fungoides”. *Frontiers in cellular and infection microbiology*, 12, 850509. <https://doi.org/10.3389/fcimb.2022.850509>
- Lindahl LM, Iversen L, Ødum N, Kilian M. (2022) Staphylococcus aureus and Antibiotics in Cutaneous T-Cell Lymphoma. *Dermatology*. 238(3):551-553. <https://doi.org/10.1159/000517829>
- Willerslev-Olsen A, Krejsgaard T, Lindahl LM et al. (2016) Staphylococcal enterotoxin A (SEA) stimulates STAT3 activation and IL-17 expression in cutaneous T-cell lymphoma. *Blood*. Mar 10;127(10):1287-96. . <https://doi.org/10.1182/blood-2015-08-662353>
- Wilcox RA. (2017). Cutaneous T-cell lymphoma: update on diagnosis, risk-stratification, and management. *Am J Hematol*. Oct;92(10):1085-1102. <https://doi.org/10.1002/ajh.24876>
- Pileri A, Guglielmo A, Grandi V et al. (2021). The Microenvironment's Role in Mycosis Fungoides and Sézary Syndrome: From Progression to Therapeutic Implications. *Cells*. 10(10):2780. <https://doi.org/10.3390/cells10102780>
- Liu Z, Wu X, Hwang ST, Liu J. (2021). The Role of Tumor Microenvironment in Mycosis Fungoides and Sézary Syndrome. *Ann Dermatol*. 33(6):487-496. . <https://doi.org/10.5021/ad.2021.33.6.487>