

DERMATOLOJİK PROBLEMLER VE COVID-19

Rabia ÖZTAŞ KARA¹
Bahar SEVİMLİ DİKİCİER²

GİRİŞ

COVID-19 pandemisinin patlak vermesinin ardından Guan ve arkadaşları tarafından yapılan araştırmada ilk kez hastalık ile ilişkili dermatolojik bulgular bildirilmiştir. Ardından COVID 19 ilişkili deri bulguları; olgu sunumları ve serileri ile bildirilmeye devam etmiştir[1]. COVID-19'a neden olan şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) virüsü dermatopik olmamasına rağmen tek başına deri üzerinde muazzam bir etkiye sahiptir. Dermatolojik belirti insidansının %0.2 ile %20 arasında olduğu çalışmalarda bildirilmektedir[2].

Bu bölümde COVID-19 salgınında görülen dermatolojik problemler; COVID-19 ile ilişkili dermatolojik bulgular, COVID-19'u önlemede cilt bakımının yeri, immüsupresif kullanan dermatoloji hastalarının sorunları, COVID-19'un dermatolojik ilaçlarla tedavisi ve kullanılan tedavi ajanlarının dermatolojik yan etkileri başlıkları altında incelenecektir.

COVID-19 ile ilişkili Dermatolojik Bulgular

Vaka serileri; pernio benzeri, eritematöz papüller, eritematöz maküler, ürtikeryal morbiliform, varisellaform, papüloskuamöz lezyonlar, peteşiyal erüpsiyonlar, livedo retikularis benzeri eritemler, purpurik lezyonlar, akrokemik lezyonlar, retiform purpura gibi dermatolojik bulgular olarak dökümente edilmektedir[2]. Gelecekte COVID-19 ile ilişkili pruritus, eritrodermi, eritema nodozum, eritema multiforme gibi farklı döküntülerin de bildirilebileceği, viral aşı sonrası ürtiker, skleroderma, makülopapüler döküntülerin gelişebileceği düşünülmektedir[3].

COVID-19' daki kutanöz belirtiler patofizyolojik olarak; viral nükleotidlere karşı gelişen viral ekzantemler ve COVID-19'un neden olduğu sistemik etkilere sekonder gelişen özellikle vaskülit ve trombotik vaskülopatinin aracılık ettiği sekonder deri döküntüleri olmak üzere 2 ana grupta incelenebilir. Bunun haricinde tedavide kullanılan

¹ Uzm.Dr. Sakarya Eğitim Araştırma Hastanesi, r.oztas.kara@gmail.com

² Doç.Dr.Sakarya Üniversitesi, Tıp Fakültesi, bsevimidikicier@gmail.com

Kullanılan Tedavi Ajanlarının Dermatolojik Yan Etkileri

COVID-19 enfeksiyonu tedavisi altında iken makülopapüler döküntüler gibi deri reaksiyonlarının enfeksiyonla mı, yoksa anti-COVID-19 ilaçla ilişkili mi olduğu konusunu ayırmak oldukça önemlidir. Ayrıntılı bir anamnez almak büyük önem taşımaktadır. Tam kan incelemesinde atipik lenfositöz, nötrofili, eozinofili, deri biyopsisinde eozinofili, ödem ve inflamasyon saptanması kutanöz ilaç erupsiyonunu destekler nitelikte olacaktır. Kutanöz ilaç erupsiyonunun erken tanısı, sorumlu ilacın tespiti ve ilaç tedavisine devam edilip edilmeyeceği konusunda yardımcı olacaktır. Ayrıca kutanöz ilaç reaksiyonların tedavisinde topikal kortikosteroidler ve antihistaminikler genellikle yeterli olup dirençli vakalarda sistemik steroid, siklosporin ve intavenöz immunglobulin tedavileri verilebilir. İlaçların kutanöz yan etkileri tablo 1'de özetlenmiştir.

Akılda kalması gerekenler:

- COVID-19'a neden olan şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) virüsü tek başına deri üzerinde birçok etkiye sahiptir.
- Kutanöz COVID-19 belirtileri genellikle COVID-19'un klasik semptomlarından sonra veya klasik semptomlarla eş zamanlı ortaya çıkmaktadır.
- Pernio benzeri lezyonu olanların, göreceli olarak daha hafif COVID-19 geçirdikleri; diğer COVID-19 semptomlarını daha az gösterdikleri ve daha az hospitalize oldukları saptanmıştır. Buna rağmen, fix livedo racemosa, retiform purpura ve akral iskemi bulguları daha çok, durumu ciddi hastalarda görülmüştür.
- Dermatolojik hastalıklarının tedavisinde immünsüpresif ve immünmodülatör ilaç kullanan hastaların aktif enfeksiyon varlığı dışında mevcut tedavilerinin devam edilmesi gerektiği kabul edilmektedir.
- COVID-19 enfeksiyonu tedavisi altında iken gelişen ilaç erüpsiyonu reaksiyonu olabilmekte ve ilaç tedavisine devam edilip edilmeyeceği konusunda karar vermek gerekmektedir.

KAYNAKÇA

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020;382(18):1708-20.
2. Freeman EE, McMahon DE, Lipoff JB, Rosenbach M, Kovarik C, Desai SR, et al. The spectrum of COVID-19-associated dermatologic manifestations: an international registry of 716 patients from 31 countries. 2020, medRxiv.
3. Türsen Ü, Türsen B, Lotti T. Coronavirus-Days in Dermatology. *Dermatologic Therapy.* 2020.
4. Suchonwanit P, Leerunyakul K, Kositkuljorn C. Cutaneous manifestations in COVID-19: Lessons learned from current evidence. *J Am Acad Dermatol.* 2020.
5. Casas CG, Catala A, Hernandez GC, Jimenez PR, Nieto DF, Lario ARV, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol.* 2020;183:71-77.
6. Fiehn C. Familial chilblain lupus what can we learn from type I interferonopathies? *Curr Rheumatol Rep.* 2017;19:61.
7. Jamilloux Y, Henry T, Belot A, Viel S, Fauter M, Jammal TE, et al. Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. *Autoimmun Rev.* 2020;19:102567.
8. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol.* 2020;34:e212-e213.
9. van Damme C, Berlingin E, Saussez S, Accaputo O. Acute urticaria with pyrexia as the first manifestations of a COVID-19 infection. *J Eur Acad Dermatol Venereol.* 2020. DOI: 10.1111/jdv.16523.
10. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy.* 2020.
11. Kolivras A, Dehavay F, Delplace D, Feoli F, Meiers I, Milone L, et al. Coronavirus (COVID-19) infection-induced chilblains: A case report with histopathologic findings. *JAAD Case Rep.* 2020;10.1016/j.jdc.2020.04.011.
12. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvas-

- cular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. *Transl Res.* 2020;220:1-13.
13. Yan Y, Chen H, Chen L, Cheng B, Diao P, Dong L, et al. Consensus of Chinese experts on protection of skin and mucous membrane barrier for health-care workers fighting against coronavirus disease 2019. *Dermatol Ther.* 2020;e13310.
 14. Lan J, Song Z, Miao X, Li H, Li Y, Dong L, et al. Skin damage among health care workers managing coronavirus disease-2019. *J Am Acad Dermatol.* 2020;82(5):1215-6.
 15. Tan KT, Malcolm WG. N95 acne. *Int J Dermatol.* 2004;43(7):522-23.
 16. Saric-Bosanac S, Clark AK, Sivamani RK, Shi VY. The role of hypothalamus-pituitary-adrenal (HPA)-like axis in inflammatory pilosebaceous disorders. *Dermatol Online J.* 2020;26(2): 13030.
 17. Kaçar N, Balcı DD. COVID-19 ve dermatolojik bulgular. Dursun R, editör. *Dermatoloji ve COVID-19.* 1. Baskı. Ankara: Türkiye Klinikleri; 2020. p.9-13.
 18. WHO (2020). Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected: Interim Guidance. (12/02/2020 tarihinde [https://www.who.int/publications-detail/infection-prevention-and-control-during-health-care-when-novel-coronavirus-\(ncov\)-infection-is-suspected-20200125](https://www.who.int/publications-detail/infection-prevention-and-control-during-health-care-when-novel-coronavirus-(ncov)-infection-is-suspected-20200125) adresinden ulaşılmıştır).
 19. Kownatzki E. Hand hygiene and skin health. *J Hosp Infect.* 2003;55:239-245. 10.1016/j.jhin.2003.08.018.
 20. EADV (2020). Guidance for patients with Autoimmune Blistering Diseases during the COVID-19 pandemic. (17/04/2020 tarihinde <https://www.eadv.org/cms-admin/show-file2> adresinden ulaşılmıştır).
 21. http://turkdermatoloji.org.tr/media/files/file/psoriasis_Hastalarinda_Covid-19_Onerileri.pdf
 22. <https://www.dermatoimmunolojiwealerjidernegi.com/>
 23. <http://www.psoriasisdernegi.org/>
 24. <https://www.aad.org/member/practice/coronavirus/registry>
 25. <https://ilds.org/covid-19/guidance-psoriasis-atopic-dermatitis/>
 26. Wang C, Rademaker M, Baker C, Foley P. COVID-19 and the use of immunomodulatory and biologic agents for severe cutaneous disease: An Australia/New Zealand consensus statement. *Australasian journal of Dermatology.* 2020.
 27. Rademaker M, Baker C, Foley P, Sullivan J, Wang, C. Advice regarding COVID-19 and use of immunomodulators, in patients with severe dermatological diseases. *Australasian Journal of Dermatology.* 2020;61(2):158-9.
 28. Price KN, Frew JW, Hsiao JL, Shi VY. COVID-19 and immunomodulator/immunosuppressant use in dermatology. *J Am Acad Dermatol.* 2020;82(5):e173-e175.
 29. Ataseven A. COVID-19 ve psoriasis. Dursun R, editör. *Dermatoloji ve COVID-19.* 1. Baskı. Ankara: Türkiye Klinikleri; 2020. p.18-22.
 30. Damiani G, Pacifico A, Bragazzi NL, Malagoli P. Biologics increase the risk of SARS-CoV-2 infection and hospitalization, but not ICU admission and death: real-life data from a large cohort during RED-ZONE declaration. *Dermatol Ther.* 2020;e13475.
 31. Tursi A, Vetrone LM, Papa A. Anti-TNF- α Agents in Inflammatory Bowel Disease and Course of COVID-19. *Inflamm Bowel Dis.* 2020; May 8: 114. doi: 10.1093/ibd/izaa114.
 32. Bardazzi F, Loi C, Sacchelli L, Di Altobrando A. Biologic therapy for psoriasis during the covid-19 outbreak is not a choice. *Journal of Dermatological Treatment.* DOI: 10.1080/09546634.2020.1749545.
 33. Kasperkiewicz M, Schmidt E, Fairley JA, Joly P, Payne AS, Yale ML, et al. Expert recommendations for the management of autoimmune bullous diseases during the COVID-19 pandemic. *J Eur Acad Dermatol Venereol.* 2020 Apr 25. doi: 10.1111/jdv.16525.
 34. Dermatology Advice Regarding Medication Acting on the Immune System: Adults, Paediatrics and Young People. 23/03/2020 tarihinde <https://www.bad.org.uk/shared/get-file.ashx?itemtype=document&id=6674> adresinden ulaşılmıştır).
 35. Zhao ZT, Ji CM, Yu WJ, Meng L, Hawro T, Wei JF, et al. Omalizumab for the treatment of chronic spontaneous urticaria: A meta-analysis of randomized clinical trials. *J Allergy Clin Immunol.* 2016;137(6):1742-50 e1744.
 36. Carugno A, Raponi F, Locatelli AG, Vezzoli P, Gambini DM, Di Mercurio M, et al. No evidence of increased risk for COVID-19 infection in patients treated with Dupilumab for atopic dermatitis in a high-epidemic area-Bergamo, lombardy, Italy. *Journal of the European Academy of Dermatology and Venereology.* 2020.
 37. Gautret P, Van Thuan Hoang SH, Roussel Y, Million M, Lagier JC, & Raoult D. (2021). Response to the use of hydroxychloroquine in combination with azithromycin for patients with COVID-19 is not supported by recent literature. *International Journal of Antimicrobial Agents,* 57(1), 106241.
 38. Malek AE, Granwehr BP (2021). Doxycycline as an alternative to azithromycin in elderly patients. *International Journal of Antimicrobial Agents,* 57(1), 106168.
 39. Valerio Pascua F, Diaz O, Medina R, Contreras B, Mistroff J, Espinosa D, et al. A multi-mechanism approach reduces length of stay in the ICU

- for severe COVID-19 patients. *Plos one*, 16(1), e0245025.
40. Salido M, Joven B, D'Cruz Dp, Khamashta MA, Hughes GR. Increased cutaneous reactions to hydroxychloroquine (plaquenil) possibly associated with formulation change: comment on the letter by Alarcón. *Arthritis Rheum*. 2002;246(12):3392-6.
 41. Das A, Sancheti K, Podder I, Das NK. Azithromycin induced bullous fixed drug eruption. *Indian J pharmacol*. 2016;48(1):83-5.
 42. An I, Demir V, Akdeniz S. Lichenoid drug eruption induced by colchicine: case report. *Cut Ocul Toxicol* 2017;36:199-200
 43. Grein J, Ohmagari N, Shin D, Diaz G Compassionate Use of Remdesivir for patients with Severe Covid-19. *N Engl J Med*. 2020;10: 2007016.
 44. Zuo W, Wen Ip, li J, Mei D, Fu Q, Zhang B. Oseltamivir induced Stevens-Johnson syndrome/toxic epidermal necrolysis-case report. *Medicine (Baltimore)*.2019;98(19): e15553 15.
 45. Kalsi T, Stevenson J, Wade p, Kinirons M. Tongue swelling in association with oseltamivir (Tamiflu). *BMJ Case Rep*. 2011; 4;2011.
 46. Russell B, Moss C, George G, et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. *E cancer Medical Science*. 2020;14:1022.
 47. Chen C, Huang J, Yin p Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. *MedRxiv* 2020;doi: <https://doi.org/10.1101/2020.03.17.20037432>.
 48. Gupta M, Aggarwal M, Bhari N. Acneiform eruptions: An unusual dermatological side effect of ribavirin. *Dermatol Ther*. 2018;31(5):e12679.
 49. Verma p, Dayal S, Jain VK, Amrani A. Alopecia universalis as a side effect of pegylated interferon α -r combination therapy for hepatitis C: a rare case report. *J Chemother*. 2017; 29(6):380-2.
 50. Iorcy S, Gaudy-Marqueste C, Botta D, et al. Cutaneous adverse events oftelaprevir/peginterferon/ribavirin therapy for chronic hepatitis C: A multicenter prospective cohort study. *Ann Dermatol Venereol*. 2016;143(5):336-46
 51. Bush AE, Hymes SR, Silapunt S. Lichenoid Dermatitis From Interferon alpha-2a in a patient With Metastatic Renal Cell Carcinoma and Seronegative HCV. *J Drugs Dermatol*. 2017;16(7):714-16
 52. Introcaso CE, Hines JM, Kovarik Cl. Cutaneous toxicities of antiretroviral therapy for HIV: part I. lipodystrophy syndrome, nucleoside reverse transcriptase inhibitors, and protease inhibitors. *J Am Acad Dermatol*. 2010; 63(4):549-61.
 53. Sharma A, Vora R, Modi M, Sharma A, Marfatia Y. Adverse effects of antiretroviral treatment. *Indian J Dermatol Venereol Leprol*. 2008; 74(3):234-7.
 54. Spada F, Barnes TM, Greive KA. Comparative safety and efficacy of topical mometasone furoate with This article is protected by copy- right. All rights reservedother topical corticosteroids. *Australas J Dermatol*. 2018;59:e168- e174.
 55. Koumaki D, Koumaki V, Iagoudaki E, Bertias G. Palmoplantar pustulosis like Eruption Induced by Baricitinib for Treatment of Rheumatoid Arthritis. *Eur J Case Rep Intern Med*. 2019;7(1):001383.
 56. Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase iii trial. *Crit Care Med*. 2016; 44: 275-81.
 57. Vastert SJ, Jamilloux Y, Quartier P, Ohlman S, Koskinen LO, Kullenberg T, et al. Anakinra in children and adults with Still's disease. *Rheumatology (Oxford)*. 2019;58(Suppl 6):vi9-vi22.
 58. Kullenberg T, Löfqvist M, Leinonen M, Goldbach-Mansky R, Olivecrona H. Long-term safety profile of anakinra in patients with severe cryopyrin-associated periodic syndromes. *Rheumatology (Oxford)*. 2016; 55(8): 1499-506.
 59. Markatseli TE, Theodoridou A, Zakalka M, Koukli E, Triantafyllidou E, Tsalavos S, et al. Persistence and Adherence during the First Six Months of Tocilizumab Treatment Among Rheumatoid Arthritis patients in Routine Clinical practice in Greece. Results from the Single Arm REMISSION II Study (NCT01649817). *Mediterr J Rheumatol*. 2019; 30(3):177-85.
 60. Matsushima Y, Hayashi A, Mizutani K, Kondo M, Nakai Y, Habe K, et al. Psoriasiform Dermatitis Developing during Treatment of Juvenile Idiopathic Arthritis with Tocilizumab. *Case Rep Dermatol*. 2019; 11(3):317-21.
 61. Sehgal R, Stratman EJ, Cutlan JE. Biologic AgentAssociated Cutaneous Adverse Events: A Single Center Experience. *Clin Med Res*. 2018;16(1-2):41-6.
 62. Brannagan TH, Nagle KJ, Iange DJ, Rowland LP. Complications of intravenous immune globulin treatment in neurologic disease. *Neurology*. 1996;47:674-7.