

Bölüm 19

Paraneoplastik Allerjik Reaksiyonlar

Gürgün Tuğçe VURAL SOLAK¹

GİRİŞ

Allerji bağışıklık sistemimizin normalde zararsız olarak bilinen maddelere karşı oluşturduğu aşırı duyarlılık reaksiyonlarıdır. Günümüzde allerjik hastalıkların sıklığı giderek artmaktadır. Allerji ile sistemik hastalıklar arasındaki ilişki ise merak edilen konular arasındadır. Kansere ve allerjik hastalıklar arasındaki ilişki ise uzun zamandır bilinmektedir. Ancak etki eden mekanizmalar netlik kazanmamıştır. Doku ve kanda azalan histamin düzeylerinin tümör progresyonunda risk artışına neden olduğu, eozinofil ve Th2 hücreleri kaynaklı sitokinler olan interlökin-4 (IL-4) ve interlökin-10 (IL-10)'un ise antitümör etkinliği olduğu bilinmektedir (1, 2). Kansere ile ilgili yapılan epidemiyolojik çalışmalarda kendi içinde çelişkiler bulunmaktadır. Atopinin prostat ve testis kanserinde bir risk faktörü olduğunu belirten çalışmalar olmakla birlikte, atopinin lösemi, lenfoma ve beyin tümörlerinde daha az olduğunu gösteren çalışmalar da mevcuttur (3-6).

Allerjik hastalıklar başta solunum sistemi ve deri olmak üzere birçok sistemi etkiler, bu kapsamda inatçı öksürük, geçmeyen deri döküntüleri ve kaşıntı şikayetlerinde allerjik durumların araştırılması önem arz etmektedir. Ancak altta yatan sebep araştırılmadan hastaya verilen antihistaminik tedavi ve sistemik steroid tedavisi tanı konusunda bizleri yanılgıya sokabilir. Bu kapsamda allerjik semptomları olan her hastaya "allerjik" demeden önce göz önünde bulundurulması gereken konulardan biri de paraneoplastik sendromlardır. Kansere ile ve ilişkili semptomları ile uğraşan hekimlerin paraneoplastik sendromları onları taklit eden iyi huylu hastalıklardan ayırt edebilmesi gerek-

¹ Uzm. Dr., Ankara Atatürk Sanatoryum Eğitim ve Araştırma Hastanesi, İmmünoloji ve Allerji Hastalıkları Kliniği, g.tugcevural@hotmail.com

Basit allerjik reaksiyonların sadece basit allerjik hastalıklarla ilişkili olmayıp, malignite öncülü olabileceği veyahut malignitede nüksü gösteren bir alarm semptomu olabileceği her zaman akılda tutulmalıdır.

KAYNAKLAR

1. Reali E, Greiner JW, Corti A, et al. IgEs targeted on tumor cells: therapeutic activity and potential in the design of tumor vaccines. *Cancer research*. 2001;61(14):5517-5522.
2. Mocellin S, Wang E, Marincola FM. Cytokines and immune response in the tumor microenvironment. *Journal of immunotherapy*. 2001;24(5):392-407.
3. McWhorter WP. Allergy and risk of cancer. A prospective study using NHANESI followup data. *Cancer*. 1988;62(2):451-455.
4. Swerdlow A, Huttly S, Smith P. Testicular cancer and antecedent diseases. *British journal of cancer*. 1987;55(1):97-103.
5. Severson RK, Davis S, Thomas DB, et al. Acute myelocytic leukemia and prior allergies. *Journal of clinical epidemiology*. 1989;42(10):995-1001.
6. Grulich AE, Vajdic CM, Kaldor JM, et al. Birth order, atopy, and risk of non-Hodgkin lymphoma. *Journal of the National Cancer Institute*. 2005;97(8):587-594.
7. Forga L, Anda E, Martínez de Esteban J, editors. Paraneoplastic hormonal syndromes. *Anales del Sistema Sanitario de Navarra*; 2005.
8. Yosipovitch G, Bernhard JD. Chronic pruritus. *New England Journal of Medicine*. 2013;368(17):1625-1634.
9. Stander S, Weisshaar E, Mettang T, et al. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. *ACTA DERMATOVENEREOLÓGICA-STOCKHOLM*. 2007;87(4):291.
10. Ständer S, Streit M, Darsow U, et al. Diagnostic and therapeutic procedures in chronic pruritus. *Journal der Deutschen Dermatologischen Gesellschaft= Journal of the German Society of Dermatology: JDDG*. 2006;4(4):350-370.
11. Alpsoy E. Paraneoplastik kaşıntı (pruritus) ve eritrodermi. *TÜRKDERM-Deri Hastalıkları ve Frenji Arşivi*. 2013;47(2):65-68.
12. Weisshaar E, Weiss M, Mettang T, et al. Paraneoplastic itch: an expert position statement from the Special Interest Group (SIG) of the International Forum on the Study of Itch (IFSI). *Acta dermato-venereologica*. 2015;95(3).
13. Twycross R, Greaves M, Handwerker H, et al. Itch: scratching more than the surface. *Qjm*. 2003;96(1):7-26.
14. Rowe B, Yosipovitch G. Malignancy-associated pruritus. *European Journal of Pain*. 2016;20(1):19-23.
15. Dalal S, Smith TJ, FASCO F. Overview of pruritus in palliative care.
16. Abdel-Naser M, Gollnick H, Orfanos C. Aquagenic pruritus as a presenting symptom of polycythemia vera. *Dermatology*. 1993;187(2):130-133.
17. Misery L. Pruritus in cutaneous T-cell lymphomas. *Itch: Mechanisms and Treatment* Boca Raton, FL: CRC Press/Taylor and Francis Group, LLC. 2014:119-128.
18. Singer EM, Shin DB, Nattkemper LA, et al. IL-31 is produced by the malignant T-cell population in cutaneous T-Cell lymphoma and correlates with CTCL pruritus. *The Journal of investigative dermatology*. 2013;133(12):2783-2785.
19. Kılıç A, Gül Ü, Soylu S. Skin findings in internal malignant diseases. *International journal of dermatology*. 2007;46(10):1055-60.
20. Weisshaar E, Kucenic MJ, Fleischer Jr AB. Pruritis: A Review. *Acta Dermato-Venereologica*. 2003;83.

21. CORMIA FE. Pruritus, an uncommon but important symptom of systemic carcinoma. *Archives of dermatology*. 1965;92(1):36-39.
22. Yosipovitch G. Chronic pruritus: a paraneoplastic sign. *Dermatologic therapy*. 2010;23(6):590-596.
23. King N, Siriwardana H, Coyne J, et al. Intractable pruritus associated with insulinoma in the absence of multiple endocrine neoplasia: a novel paraneoplastic phenomenon. *Scandinavian journal of gastroenterology*. 2003;38(6):678-680.
24. Padda SK, Shrager JB, Riess JW, et al. Pruritus as a paraneoplastic symptom of thymoma. *Journal of Thoracic Oncology*. 2015;10(11):110-112.
25. Valley JJ, Hudson KE, Locke SC, et al. Pruritus in patients with solid tumors: an overlooked supportive care need. *Supportive Care in Cancer*. 2019;27(10):3897-3904.
26. Paul R, Paul R, Jansen CT. Itch and malignancy prognosis in generalized pruritus: a 6-year follow-up of 125 patients. *Journal of the American Academy of Dermatology*. 1987;16(6):1179-1182.
27. Demierre MF, Gan S, Jones J, et al. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: results of a 2005 National Cutaneous Lymphoma Foundation Survey. *Cancer*. 2006;107(10):2504-2511.
28. Saini KS, Patnaik MM, Tefferi A. Polycythemia vera-associated pruritus and its management. *European journal of clinical investigation*. 2010;40(9):828-834.
29. Yosipovitch G. Epidemiology of itching in skin and systemic diseases. *BASIC AND CLINICAL DERMATOLOGY*. 2004;27:183-192.
30. Etter L, Myers SA. Pruritus in systemic disease: mechanisms and management. *Dermatologic clinics*. 2002;20(3):459-472.
31. Meyer N, Paul C, Misery L. Pruritus in cutaneous T-cell lymphomas: frequent, often severe and difficult to treat. *Acta dermato-venereologica*. 2010;90(1).
32. Siegel FP, Tauscher J, Petrides PE. Aquagenic pruritus in polycythemia vera: characteristics and influence on quality of life in 441 patients. *American journal of hematology*. 2013;88(8):665-669.
33. Fett N, Haynes K, Propert KJ, et al. Five-year malignancy incidence in patients with chronic pruritus: a population-based cohort study aimed at limiting unnecessary screening practices. *Journal of the American Academy of Dermatology*. 2014;70(4):651-658.
34. Johannesdottir S, Farkas D, Vinding G, et al. Cancer incidence among patients with a hospital diagnosis of pruritus: a nationwide Danish cohort study. *British Journal of Dermatology*. 2014;171(4):839-846.
35. Ständer S, Weisshaar E, Luger TA. Neurophysiological and neurochemical basis of modern pruritus treatment. *Experimental dermatology*. 2008;17(3):161-169.
36. Rokhsar S. Malignancy Presenting as Paraneoplastic Itch. *Proceedings of UCLA Health*. 2018;22.
37. Radonjic-Hoesli S, Hofmeier KS, Micaletto S, et al. Urticaria and angioedema: an update on classification and pathogenesis. *Clinical reviews in allergy & immunology*. 2018;54(1):88-101.
38. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73(7):1393-1414.
39. Kaplan AP. Chronic Urticaria and Angioedema. *New England Journal of Medicine*. 2002;346(3):175-179.
40. Greaves MW. Chronic urticaria. *New England Journal of Medicine*. 1995;332(26):1767-1772.
41. Powell R, Du Toit G, Siddique N, et al. BSACI guidelines for the management of chronic urticaria and angio oedema. *Clinical & Experimental Allergy*. 2007;37(5):631-650.
42. Daniel B, Murrell D. Chronic Urticaria Resolving after Resection of Mucinous Breast

- Cancer. *J Clin Exp Dermatol Res*. 2010;1(103):2.
43. Greiner D, Schofer H, Boehncke W-H. Urticaria associated with a small cell carcinoma of the lung. *CUTIS-NEW YORK*-. 2002;69(1):49-.
 44. Clore Jr LS, Stafford CT, editors. Chronic urticaria as a presenting sign of hairy cell leukemia. *Allergy and Asthma Proceedings*; 1999: OceanSide Publications.
 45. Murota H, Shoda Y, Ishibashi T, et al. Improvement of recurrent urticaria in a patient with Schnitzler syndrome associated with B-cell lymphoma with combination rituximab and radiotherapy. *Journal of the American Academy of Dermatology*. 2009;61(6):1070-1075.
 46. Manganoni A, Tucci G, Venturini M, et al. Chronic urticaria associated with thyroid carcinoma: report of 4 cases. *Journal of Investigational Allergology and Clinical Immunology*. 2007;17(3):192.
 47. Reinhold U, Bruske T, Schupp G. Paraneoplastic urticaria in a patient with ovarian carcinoma. *Journal of the American Academy of Dermatology*. 1996;6(35):988-989.
 48. Shamsadini S, Varesvazirian M, Shamsadini A. Urticaria and lip fasciculation may be prodromal signs of brain malignancy. *Dermatology Online Journal*. 2006;12(3):23-.
 49. Bo ek A, Rachowska R, Krajewska J, et al. Carcinoid syndrome with angioedema and urticaria. *Archives of dermatology*. 2008;144(5):691-2.
 50. De P, Abbasi R, Senadhira T, et al. Urticaria and large cell undifferentiated carcinoma of lung. *Dermatology Online Journal*. 2005;11(3).
 51. Larenas-Linnemann D, Saini S, Azamar-Jácome A, et al. Chronic urticaria can be caused by cancer and resolves with its cure. *Allergy*. 2018;73(7):1562-1566.
 52. Lindelöf B, Sigurgeirsson B, Wahlgren C, et al. Chronic urticaria and cancer: an epidemiological study of 1155 patients. *British Journal of Dermatology*. 1990;123(4):453-456.
 53. Chen Y-J, Wu C-Y, Shen J-L, et al. Cancer risk in patients with chronic urticaria: a population-based cohort study. *Archives of dermatology*. 2012;148(1):103-108.
 54. Ciaccio CE. Angioedema: an overview and update. *Missouri Medicine*. 2011;108(5):354.
 55. Cicardi M, Zanichelli A. Acquired angioedema. *Allergy, Asthma & Clinical Immunology*. 2010;6(1):1-5.
 56. Gunatilake SSC, Wimalaratna H. Angioedema as the first presentation of B-cell non-Hodgkin lymphoma—an unusual case with normal C1 esterase inhibitor level: a case report. *BMC Research Notes*. 2014;7(1):1-4.
 57. Kang M, Bhatia N, Sauder A, et al. Angioimmunoblastic T cell lymphoma mimicking chronic urticaria. *Case Reports in Medicine*. 2016;2016.
 58. Boussetta N, Ghedira H, Hamdi M, et al. Acquired Angioedema Revealing a B cell Non Hodgkin Lymphoma in a Tunisian Man. *Intern Med*. 2017;7(259):2.
 59. Rodolfo A, Pina F, Miranda M. Urticaria-angioedema paraneoplastic syndrome associated with renal cell carcinoma. *Rev Port Imunoalergologia*. 2020;28(2):111-114.
 60. Lewis LM. Angioedema: etiology, pathophysiology, current and emerging therapies. *The Journal of emergency medicine*. 2013;45(5):789-96.
 61. Agostoni A, Aygören-Pürsün E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *Journal of Allergy and Clinical Immunology*. 2004;114(3):S51-S131.
 62. Zingale LC, Castelli R, Zanichelli A, et al. Acquired deficiency of the inhibitor of the first complement component: presentation, diagnosis, course, and conventional management. *Immunology and Allergy Clinics*. 2006;26(4):669-690.
 63. Postorino M, Pupo L, Guarino MD, et al. Acquired Angioedema and Large Granular T-Cell Leukemia. 2017.
 64. Harrison NK, Twelves C, Addis BJ, et al. Peripheral T-cell lymphoma presenting with angioedema and diffuse pulmonary infiltrates. *Am Rev Respir Dis*. 1988;138(4):976-980.
 65. Castelli R, Zanichelli A, Cicardi M, et al. Acquired C1-inhibitor deficiency and lymphoma.

- hoproliferative disorders: a tight relationship. *Critical reviews in oncology/hematology*. 2013;87(3):323-332.
66. Foti R, Fazio P, Lizzio G, et al. Angioedema: first manifestation of non-Hodgkin's lymphoma. *Annali Italiani di Medicina Interna: Organo Ufficiale Della Societa Italiana di Medicina Interna*. 2002;17(3):185-188.
 67. Wu MA, Castelli R. The Janus faces of acquired angioedema: C1-inhibitor deficiency, lymphoproliferation and autoimmunity. *Clinical Chemistry and Laboratory Medicine (CCLM)*. 2016;54(2):207-214.
 68. Zanichelli A, Bova M, Coerezza A, et al. Icatibant treatment for acquired C1 inhibitor deficiency: a real-world observational study. *Allergy*. 2012;67(8):1074-1077.
 69. Davis MD, Brewer JD. Urticarial vasculitis and hypocomplementemic urticarial vasculitis syndrome. *Immunology and Allergy Clinics*. 2004;24(2):183-213.
 70. Zuberbier T, Maurer M. Urticarial vasculitis and Schnitzler syndrome. *Immunology and Allergy Clinics*. 2014;34(1):141-7.
 71. Peroni A, Colato C, Zanoni G, et al. Urticarial lesions: if not urticaria, what else? The differential diagnosis of urticaria: part II. Systemic diseases. *Journal of the American Academy of Dermatology*. 2010;62(4):557-570.
 72. Wilson D, McCluggage W, Wright G. Urticarial vasculitis: a paraneoplastic presentation of B-cell non-Hodgkin's lymphoma. *Rheumatology*. 2002;41(4):476-477.
 73. Sprossmann A, Müller R. Urticaria-vasculitis syndrome in metastatic malignant testicular teratoma. *Der Hautarzt; Zeitschrift fur Dermatologie, Venerologie, und Verwandte Gebiete*. 1994;45(12):871-874.
 74. Kassim J, Igali L, Levell N. A 14-year paraneoplastic rash: urticarial vasculitis and dermal binding bullous pemphigoid secondary to chronic lymphocytic leukaemia. *Clinical and Experimental Dermatology*. 2015;40(4):391-394.
 75. Di Stefano F, Siriruttanapruk S, Di Gioacchino M. Exercise-induced urticarial vasculitis as a paraneoplastic manifestation of cystic teratoma. *Rheumatology*. 2003;42(11):1418-1419.
 76. Marsaudon E, Ksiyer S, Louarn A, et al. Paraneoplastic urticarial vasculitis and recurrence of prostatic adenocarcinoma. *J Case Rep Stud*. 2018;6(5):502.
 77. Klion AD, Ackerman SJ, Bochner BS. Contributions of eosinophils to human health and disease. *Annual Review of Pathology: Mechanisms of Disease*. 2020;15:179-209.
 78. Wen T, Rothenberg ME. The regulatory function of eosinophils. *Microbiology spectrum*. 2016;4(5):4.5. 06.
 79. Gleich GJ. Mechanisms of eosinophil-associated inflammation. *Journal of Allergy and Clinical Immunology*. 2000;105(4):651-663.
 80. Kato M, Kephart GM, Talley NJ, et al. Eosinophil infiltration and degranulation in normal human tissue. *The Anatomical Record: An Official Publication of the American Association of Anatomists*. 1998;252(3):418-425.
 81. Valent P, Klion AD, Horny H-P, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *Journal of Allergy and Clinical Immunology*. 2012;130(3):607-612.
 82. Galiuto L, Enriquez-Sarano M, Reeder GS, et al., editors. Eosinophilic myocarditis manifesting as myocardial infarction: early diagnosis and successful treatment. *Mayo Clinic Proceedings*; 1997: Elsevier.
 83. Wright BL, Leiferman KM, Gleich GJ. Eosinophil granule protein localization in eosinophilic endomyocardial disease. *New England Journal of Medicine*. 2011;365(2):187-188.
 84. Chen Y-YK, Khoury P, Ware JM, et al. Marked and persistent eosinophilia in the absence of clinical manifestations. *Journal of allergy and clinical immunology*. 2014;133(4):1195-1202.
 85. Gotlib J. World Health Organization-defined eosinophilic disorders: 2017 update

- on diagnosis, risk stratification, and management. *American journal of hematology*. 2017;92(11):1243-1259.
86. Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2019 update on diagnosis, risk stratification, and management. *American journal of hematology*. 2019;94(10):1149-1167.
 87. Samoszuk M. Eosinophils and human cancer. *Histology and histopathology*. 1997.
 88. Balian A, Bonte E, Naveau S, et al. Intratumoral production of interleukin-5 leading to paraneoplastic peripheral eosinophilia in hepatocellular carcinoma. *Journal of hepatology*. 2001;34(2):355-356.
 89. Anagnostopoulos GK, Sakorafas GH, Kostopoulos P, et al. Disseminated colon cancer with severe peripheral blood eosinophilia and elevated serum levels of interleukine-2, interleukine-3, interleukine-5, and GM-CSF. *Journal of surgical oncology*. 2005;89(4):273-275.
 90. Manelis G, Aderka D. Eosinophilia associated with malignant tumors of the bronchus and stomach. *Harefuah*. 1976;90(5):213-215.
 91. Ando J, Sugimoto K, Tamayose K, et al. Cytokine-producing sarcoma mimics eosinophilic leukaemia. *European journal of haematology*. 2007;78(2):169-170.
 92. Rojas G, Castro D, Vigo-Guevara G, et al. Hypereosinophilic encephalopathy with multiple cerebral infarctions in neighbouring vascular territories associated with prostate cancer. *Revista de Neurologia*. 2006;43(12):762-764.
 93. Fridlender ZG, Shalit M, Simon H-U. Metastatic carcinoma presenting with concomitant eosinophilia and thromboembolism. *The American journal of the medical sciences*. 2003;326(2):98-101.
 94. Watanabe M, Ono K, Ozeki Y, et al. Production of granulocyte—macrophage colony-stimulating factor in a patient with metastatic chest wall large cell carcinoma. *Japanese journal of clinical oncology*. 1998;28(9):559-562.
 95. Rothenberg ME. Eosinophilia. *New England Journal of Medicine*. 1998;338(22):1592-1600.
 96. Lowe D, Jorizzo J, Hutt M. Tumour-associated eosinophilia: a review. *Journal of Clinical Pathology*. 1981;34(12):1343-1348.
 97. Chang W, Liaw C, Wang P, et al. Tumor-associated hypereosinophilia: report of four cases. *Changgeng Yi Xue Za Zhi*. 1996;19(1):66-70.
 98. Isaacson Nh, Rapoport P. Eosinophilia in malignant tumors: its significance. *Annals of Internal Medicine*. 1946;25(6):893-902.
 99. Harbaum L, Pollheimer MJ, Kornprat P, et al. Peritumoral eosinophils predict recurrence in colorectal cancer. *Modern Pathology*. 2015;28(3):403-413.
 100. McNeel DG, Gardner TA, Higano CS, et al. A transient increase in eosinophils is associated with prolonged survival in men with metastatic castration-resistant prostate cancer who receive sipuleucel-T. *Cancer immunology research*. 2014;2(10):988-999.
 101. Aldebert D, Lamkhioed B, Desaint C, et al. Eosinophils express a functional receptor for interferon alpha: inhibitory role of interferon alpha on the release of mediators. 1996.
 102. Schleimer RP, Bochner BS. The effects of glucocorticoids on human eosinophils. *Journal of Allergy and Clinical Immunology*. 1994;94(6):1202-1213.
 103. Balducci L, Chapman SW, Little DD, et al. Paraneoplastic eosinophilia. Report of a case with in vitro studies of hemopoiesis. *Cancer*. 1989;64(11):2250-2253.
 104. Albitar HAH, Egan AM, Alkhateeb H, et al. Marked hypereosinophilia secondary to endometrioid ovarian cancer presenting with asthma symptoms, a case report. *Respiratory Medicine Case Reports*. 2020;31:101178.