

12. BÖLÜM

Mesane Ürotelyal Karsinom Varyantları

Oğuzhan OKCU¹
Buket Bambul SIĞIRCI²

GİRİŞ

Ürotelyal karsinomlar (ÜK) mesane karsinomlarının %90'ından fazlasını oluşturmaktadır. Ürotelyal epitelin farklı embriyolojik yapılardan köken alması ve yüksek metaplastik değişim kapasitesi çok farklı morfolojik görünümlere sebep olmaktadır (1,2). Dünya Sağlık Örgütü (DSÖ) 2016 üriner sistem tümörleri sınıflamasında 3 farklı diferansiyasyon ve 10 farklı varyant tanımlanmıştır. Geçmiş yıllarda farklı başlık altında sınıflanan bazı varyantlar benzer morfolojik ve prognostik özellikleri sebebiyle DSÖ 2016 üriner sistem tümörleri sınıflamasında tek başlık altında isimlendirilmiştir. DSÖ üriner sistem kanserleri 2016 sınıflamasında yer alan ürotelyal karsinom varyantları tablo 1 de gösterilmiştir (3).

Ürotelyal karsinom varyantları çok farklı morfolojik özellikleri sebebiyle rutin patoloji işleyişinde ayırıcı tanıda ve primer-metastaz ayrımında oldukça zorluk oluşturabilmektedir. İngilizce yazılı literatürde ÜK olgularının %25-40'ında ÜK varyantlarının izlendiği bildirilmiştir. Ürotelyal karsinom varyantlarının farklı prognostik öneme sahip olmaları ve lenfoepitelyoma benzeri ÜK olgularında olduğu gibi farklı tedavi yaklaşımları gerektirebilmeleri nedeniyle morfolojik olarak tanınmaları ve patoloji raporlarında toplam tümör hacmi içerisindeki oranlarıyla birlikte bildirilmesi gerekmektedir (4).

Literatürde bildirilen olgular arasında en sık skuamöz ve glandüler diferansiyasyon ve mikropapiller varyant izlenmektedir. Nested, berrak hücreli, lipitten zengin ve lenfoepitelyoma vb. varyantlar çok daha nadiren saptanmaktadır (3).

¹ Uzm. Dr., Recep Tayyip Erdoğan Üniversitesi Eğitim ve Araştırma Hastanesi, Tıbbi Patoloji Kliniği, oguzhanokcu@hotmail.com

² Uzm. Dr., Bahçelievler Devlet Hastanesi, Tıbbi Patoloji Kliniği buketbambul@hotmail.com

KAYNAKLAR

1. Lopez-Beltran A, Henriques V, Montironi R et al. Variants and new entities of bladder cancer. *Histopathology*. 2019 Jan;74(1):77-96. doi: 10.1111/his.13752. PMID: 30565299.
2. Lobo N, Shariat SF, Guo CC et al. What Is the Significance of Variant Histology in Urothelial Carcinoma? *Eur Urol Focus*. 2020 Jul 15;6(4):653-663. doi: 10.1016/j.euf.2019.09.003. Epub 2019 Sep 15. PMID: 31530497
3. Moch H, Humphrey PA, Ulbright TM et al. WHO classification of tumours of the urinary system and male genital organs. Lyon: International Agency for Research on Cancer; 2016
4. Aron M. Variant Histology in Bladder Cancer-Current Understanding of Pathologic Subtypes. *Curr Urol Rep*. 2019 Nov 28;20(12):80. doi: 10.1007/s11934-019-0949-6. PMID: 31781939
5. Scosyrev E, Ely BW, Messing EM et al. Do mixed histological features affect survival benefit from neoadjuvant platinum-based combination chemotherapy in patients with locally advanced bladder cancer? A secondary analysis of Southwest Oncology Group-Directed Intergroup Study (S8710). *BJU Int*. 2011 Sep;108(5):693-9. doi: 10.1111/j.1464-410X.2010.09900.x. Epub 2010 Nov 24. PMID: 21105991; PMCID: PMC3117124.
6. Mitra AP, Bartsch CC, Bartsch G Jr et al. Does presence of squamous and glandular differentiation in urothelial carcinoma of the bladder at cystectomy portend poor prognosis? An intensive case-control analysis. *Urol Oncol*. 2014 Feb;32(2):117-27. doi: 10.1016/j.urolonc.2012.08.017. Epub 2013 Mar 7. PMID: 23477878.
7. Kulkarni GS, Hermanns T, Wei Y et al. Propensity Score Analysis of Radical Cystectomy Versus Bladder-Sparing Trimodal Therapy in the Setting of a Multidisciplinary Bladder Cancer Clinic. *J Clin Oncol*. 2017 Jul 10;35(20):2299-2305. doi: 10.1200/JCO.2016.69.2327. Epub 2017 Apr 14. PMID: 28410011
8. Nagumo Y, Kojima T, Shiga M et al. A single-institute experience of trimodal bladder-preserving therapy for histologic variants of urothelial carcinoma. *Int J Clin Oncol*. 2020 Feb;25(2):354-361. doi: 10.1007/s10147-019-01553-4. Epub 2019 Oct 8. PMID: 31595343.
9. Moschini M, D'Andrea D, Korn S, et al. Characteristics and clinical significance of histological variants of bladder cancer. *Nat Rev Urol*. 14(11):651-668. doi:10.1038/nrurol.2017.125
10. Lopez-Beltran A, Requena MJ, Alvarez-Kindelan J, et al. Squamous differentiation in primary urothelial carcinoma of the urinary tract as seen by MAC387 immunohistochemistry. *J Clin Pathol*. 2007;60(3):332-335. doi:10.1136/jcp.2006.038802
11. Liu Y, Bui MM, Xu B. Urothelial Carcinoma With Squamous Differentiation Is Associated With High Tumor Stage and Pelvic Lymph-Node Metastasis. *Cancer Control*. 2017;24(1):78-82. doi:10.1177/107327481702400113
12. Li G, Hu J, Niu Y. Squamous differentiation in pT1 bladder urothelial carcinoma predicts poor response for intravesical chemotherapy. *Oncotarget*, 9(1), 217 DOI: 10.18632/18563. 2018
13. Gofrit ON, Yutkin V, Shapiro A, et al. The Response of Variant Histology Bladder Cancer to Intravesical Immunotherapy Compared to Conventional Cancer. *Front Oncol*. 2016;6:43. Published 2016 Mar 15. doi:10.3389/fonc.2016.00043
14. Li G, Yu J, Song H, et al. Squamous differentiation in patients with superficial bladder urothelial carcinoma is associated with high risk of recurrence and poor survival. *BMC Cancer*. 2017;17(1):530. Published 2017 Aug 8. doi:10.1186/s12885-017-3520-1
15. Gulmann C, Paner GP, Parakh RS, et al. Immunohistochemical profile to distinguish urothelial from squamous differentiation in carcinomas of urothelial tract. *Hum Pathol*. 2013;44(2):164-172. doi:10.1016/j.humpath.2012.05.018
16. Paner GP, Annaiah C, Gulmann C, et al. Immunohistochemical evaluation of novel and traditional markers associated with urothelial differentiation in a spectrum of variants of urothelial carcinoma of the urinary bladder. *Hum Pathol*. 2014;45(7):1473-1482. doi:10.1016/j.humpath.2014.02.024

17. Alexander RE, Hu Y, Kum JB, et al. p16 expression is not associated with human papillomavirus in urinary bladder squamous cell carcinoma. *Mod Pathol.* 2012;25(11):1526-1533. doi:10.1038/modpathol.2012.103
18. Vail E, Zheng X, Zhou M, et al. Telomerase reverse transcriptase promoter mutations in glandular lesions of the urinary bladder. *Ann Diagn Pathol.* 2015;19(5):301-305. doi:10.1016/j.anndiagpath.2015.06.007
19. Yang Z, Epstein JI. Urothelial Carcinoma In Situ of the Bladder With Glandular Differentiation: Report of 92 Cases. *Am J Surg Pathol.* 2018;42(7):971-976. doi:10.1097/PAS.0000000000001073
20. Mitra AP, Bartsch CC, Bartsch G Jr, et al. Does presence of squamous and glandular differentiation in urothelial carcinoma of the bladder at cystectomy portend poor prognosis? An intensive case-control analysis. *Urol Oncol.* 2014;32(2):117-127.
21. Kim SP, Frank I, Cheville JC, et al. The impact of squamous and glandular differentiation on survival after radical cystectomy for urothelial carcinoma. *J Urol.* 2012;188(2):405-409. doi:10.1016/j.juro.2012.04.020
22. Lee YJ, Moon KC, Jeong CW, et al. Impact of squamous and glandular differentiation on oncologic outcomes in upper and lower tract urothelial carcinoma. *PLoS One.* 2014;9(9):e107027. Published 2014 Sep 5. doi:10.1371/journal.pone.0107027
23. Zhao G, Wang C, Tang Y, et al. Glandular differentiation in pT1 urothelial carcinoma of bladder predicts poor prognosis. *Sci Rep.* 2019;9(1):5323. Published 2019 Mar 29. doi:10.1038/s41598-019-41844-4
24. Douglas J, Sharp A, Chau C, et al. Serum total hCG β level is an independent prognostic factor in transitional cell carcinoma of the urothelial tract. *Br J Cancer.* 2014;110(7):1759-1766. doi:10.1038/bjc.2014.89
25. Monn MF, Kaimakliotis HZ, Pedrosa JA, et al. Contemporary bladder cancer: variant histology may be a significant driver of disease. *Urol Oncol.* 2015;33(1):18.e15-18.e20. doi:10.1016/j.urolonc.2014.10.001
26. Kinoshita Y, Takasu K, Yuri T, et al. Cytological findings in urothelial carcinoma of the bladder with trophoblastic differentiation. *Cytopathology.* 2013;24(6):405-408. doi:10.1111/j.1365-2303.2012.00993.x
27. Amin MB. Histological variants of urothelial carcinoma: diagnostic, therapeutic and prognostic implications. *Mod Pathol.* 2009;22 Suppl 2:S96-S118. doi:10.1038/modpathol.2009.26
28. Weyerer V, Weisser R, Moskalev EA, et al. Distinct genetic alterations and luminal molecular subtype in nested variant of urothelial carcinoma. *Histopathology.* 2019;75(6):865-875. doi:10.1111/his.13958
29. Legesse T, Matoso A, Epstein JI. PAX8 positivity in nested variant of urothelial carcinoma: a potential diagnostic pitfall. *Hum Pathol.* 2019;94:11-15. doi:10.1016/j.humpath.2019.09.012
30. Hacıhasanoğlu E, Behzatoğlu K. Large nested urothelial carcinoma: A clinicopathological study of 22 cases on transurethral resection materials. *Ann Diagn Pathol.* 2019;42:7-11. doi:10.1016/j.anndiagpath.2019.06.005
31. Brimo F, Dauphin-Pierre S, Aprikian A, et al. Inverted urothelial carcinoma: a series of 12 cases with a wide morphologic spectrum overlapping with the large nested variant. *Hum Pathol.* 2015;46(10):1506-1513. doi:10.1016/j.humpath.2015.06.010
32. Allory Y, Beukers W, Sagrera A et al. Telomerase reverse transcriptase promoter mutations in bladder cancer: high frequency across stages, detection in urine, and lack of association with outcome. *Eur Urol.* 2014 Feb;65(2):360-6. doi: 10.1016/j.eururo.2013.08.052. Epub 2013 Sep 7. PMID: 24018021
33. Warrick JI, Kaag M, Raman JD, et al. FOXA1 and CK14 as markers of luminal and basal subtypes in histologic variants of bladder cancer and their associated conventional urothelial carcinoma. *Virchows Arch.* 2017;471(3):337-345. doi:10.1007/s00428-017-2190-3
34. Wasco MJ, Daignault S, Bradley D, et al. Nested variant of urothelial carcinoma: a clinicopathologic and immunohistochemical study of 30 pure and mixed cases. *Hum Pathol.* 2010;41(2):163-171. doi:10.1016/j.humpath.2009.07.015

35. Compérat E, McKenney JK, Hartmann A, et al. Large nested variant of urothelial carcinoma: a clinicopathological study of 36 cases. *Histopathology*. 2017;71(5):703-710. doi:10.1111/his.13280
36. Beltran AL, Cheng L, Montironi R, et al. Clinicopathological characteristics and outcome of nested carcinoma of the urinary bladder. *Virchows Arch*. 2014;465(2):199-205. doi:10.1007/s00428-014-1601-y
37. Mally AD, Tin AL, Lee JK, et al. Clinical Outcomes of Patients With T1 Nested Variant of Urothelial Carcinoma Compared to Pure Urothelial Carcinoma of the Bladder [published online ahead of print, 2017 Jul 14]. *Clin Genitourin Cancer*. 2017;S1558-7673(17)30199-4. doi:10.1016/j.clgc.2017.07.002
38. Linder BJ, Frank I, Chevillon JC, et al. Outcomes following radical cystectomy for nested variant of urothelial carcinoma: a matched cohort analysis. *J Urol*. 2013;189(5):1670-1675. doi:10.1016/j.juro.2012.11.006
39. Lopez Beltran A, Montironi R, Cheng L. Microcystic urothelial carcinoma: morphology, immunohistochemistry and clinical behaviour. *Histopathology*. 2014;64(6):872-879. doi:10.1111/his.12345
40. Young RH, Zukerberg LR. Microcystic transitional cell carcinomas of the urinary bladder. A report of four cases. *Am J Clin Pathol*. 1991;96(5):635-639. doi:10.1093/ajcp/96.5.635
41. Zhong M, Tian W, Zhuge J, et al. Distinguishing nested variants of urothelial carcinoma from benign mimickers by TERT promoter mutation. *Am J Surg Pathol*. 2015;39(1):127-131. doi:10.1097/PAS.0000000000000305
42. Compérat E, Roupret M, Yaxley J, et al. Micropapillary urothelial carcinoma of the urinary bladder: a clinicopathological analysis of 72 cases. *Pathology*. 2010;42(7):650-654. doi:10.3109/00313025.2010.522173
43. Sangoi AR, Beck AH, Amin MB, et al. Interobserver reproducibility in the diagnosis of invasive micropapillary carcinoma of the urinary tract among urologic pathologists. *Am J Surg Pathol*. 2010;34(9):1367-1376. doi:10.1097/PAS.0b013e3181ec86b3
44. Nassar H, Pansare V, Zhang H, et al. Pathogenesis of invasive micropapillary carcinoma: role of MUC1 glycoprotein. *Mod Pathol*. 2004;17(9):1045-1050. doi:10.1038/modpathol.3800166
45. Guo CC, Dadhania V, Zhang L, et al. Gene Expression Profile of the Clinically Aggressive Micropapillary Variant of Bladder Cancer. *Eur Urol*. 2016;70(4):611-620. doi:10.1016/j.eururo.2016.02.056
46. Watts KE, Hansel DE. Emerging concepts in micropapillary urothelial carcinoma. *Adv Anat Pathol*. 2010;17(3):182-186. doi:10.1097/PAP.0b013e3181d97851
47. Lopez-Beltran A, Montironi R, Blanca A, et al. Invasive micropapillary urothelial carcinoma of the bladder. *Hum Pathol*. 2010;41(8):1159-1164. doi:10.1016/j.humpath.2009.11.018
48. Willis DL, Fernandez MI, Dickstein RJ, et al. Clinical outcomes of cT1 micropapillary bladder cancer. *J Urol*. 2015;193(4):1129-1134. doi:10.1016/j.juro.2014.09.092
49. Schneider SA, Sukov WR, Frank I, et al. Outcome of patients with micropapillary urothelial carcinoma following radical cystectomy: ERBB2 (HER2) amplification identifies patients with poor outcome. *Mod Pathol*. 2014;27(5):758-764. doi:10.1038/modpathol.2013.201
50. Giannico GA, Gown AM, Epstein JI, et al. Role of SATB2 in distinguishing the site of origin in glandular lesions of the bladder/urinary tract. *Hum Pathol*. 2017;67:152-159. doi:10.1016/j.humpath.2017.07.002
51. Zinnall U, Weyerer V, Compérat E, et al. Micropapillary urothelial carcinoma: evaluation of HER2 status and immunohistochemical characterization of the molecular subtype. *Hum Pathol*. 2018;80:55-64. doi:10.1016/j.humpath.2018.05.022
52. Figueroa JD, Ye Y, Siddiq A, et al. Genome-wide association study identifies multiple loci associated with bladder cancer risk. *Hum Mol Genet*. 2014;23(5):1387-1398. doi:10.1093/hmg/ddt519

53. Nguyen D, Taheri D, Springer S, et al. High prevalence of TERT promoter mutations in micropapillary urothelial carcinoma. *Virchows Arch.* 2016;469(4):427-434. doi:10.1007/s00428-016-2001-2
54. Amin MB, Ro JY, Lee KM, et al. Lymphoepithelioma-like carcinoma of the urinary bladder. *Am J Surg Pathol.* 1994;18(5):466-473. doi:10.1097/00000478-199405000-00005
55. Lopez-Beltrán A, Luque RJ, Vicioso L, et al. Lymphoepithelioma-like carcinoma of the urinary bladder: a clinicopathologic study of 13 cases. *Virchows Arch.* 2001;438(6):552-557. doi:10.1007/s004280000378
56. Rodríguez-Cabello MA, Méndez-Rubio S, Sanz-Miguelañez JL, et al. Lymphoepithelioma-Like Bladder Carcinoma: A Diagnostic and Therapeutic Challenge. Contribution Using a New Case and Review of the Literature. *Clin Genitourin Cancer.* 2017;15(3):e507-e515. doi:10.1016/j.clgc.2016.12.023
57. Tamas EF, Nielsen ME, Schoenberg MP, et al. Lymphoepithelioma-like carcinoma of the urinary tract: a clinicopathological study of 30 pure and mixed cases. *Mod Pathol.* 2007;20(8):828-834. doi:10.1038/modpathol.3800823
58. Yoshino T, Ohara S, Moriyama H. Lymphoepithelioma-like carcinoma of the urinary bladder: a case report and review of the literature. *BMC Res Notes.* 2014;7:779. Published 2014 Nov 4. doi:10.1186/1756-0500-7-779
59. Yang AW, Pooli A, Lele SM, et al. Lymphoepithelioma-like, a variant of urothelial carcinoma of the urinary bladder: a case report and systematic review for optimal treatment modality for disease-free survival. *BMC Urol.* 2017;17(1):34. Published 2017 Apr 27. doi:10.1186/s12894-017-0224-4
60. Lopez-Beltran A, Requena MJ, Montironi R, et al. Plasmacytoid urothelial carcinoma of the bladder. *Hum Pathol.* 2009;40(7):1023-1028. doi:10.1016/j.humpath.2009.01.001
61. Ricardo-Gonzalez RR, Nguyen M, Gokden N, et al. Plasmacytoid carcinoma of the bladder: a urothelial carcinoma variant with a predilection for intraperitoneal spread. *J Urol.* 2012;187(3):852-855. doi:10.1016/j.juro.2011.10.145
62. Kaimakliotis HZ, Monn MF, Cary KC, et al. Plasmacytoid variant urothelial bladder cancer: is it time to update the treatment paradigm?. *Urol Oncol.* 2014;32(6):833-838. doi:10.1016/j.urolonc.2014.03.008
63. Fox MD, Xiao L, Zhang M, et al. Plasmacytoid Urothelial Carcinoma of the Urinary Bladder: A Clinicopathologic and Immunohistochemical Analysis of 49 Cases. *Am J Clin Pathol.* 2017;147(5):500-506. doi:10.1093/ajcp/aqx029
64. Al-Ahmadie HA, Iyer G, Lee BH, et al. Frequent somatic CDH1 loss-of-function mutations in plasmacytoid variant bladder cancer. *Nat Genet.* 2016;48(4):356-358. doi:10.1038/ng.3503
65. Wang X, Lopez-Beltran A, Osunkoya AO, et al. TERT promoter mutation status in sarcomatoid urothelial carcinomas of the upper urinary tract. *Future Oncol.* 2017;13(8):705-714. doi:10.2217/fo-2016-0414
66. Dayyani F, Czerniak BA, Sircar K, et al. Plasmacytoid urothelial carcinoma, a chemosensitive cancer with poor prognosis, and peritoneal carcinomatosis. *J Urol.* 2013;189(5):1656-1661. doi:10.1016/j.juro.2012.11.084
67. Cheng L, Zhang S, Alexander R, et al. Sarcomatoid carcinoma of the urinary bladder: the final common pathway of urothelial carcinoma dedifferentiation. *Am J Surg Pathol.* 2011;35(5):e34-e46. doi:10.1097/PAS.0b013e3182159dc
68. Sanfrancesco J, McKenney JK, Leivo MZ, et al. Sarcomatoid Urothelial Carcinoma of the Bladder: Analysis of 28 Cases With Emphasis on Clinicopathologic Features and Markers of Epithelial-to-Mesenchymal Transition. *Arch Pathol Lab Med.* 2016;140(6):543-551. doi:10.5858/arpa.2015-0085-OA
69. Lopez-Beltran A, Pacelli A, Rothenberg HJ, et al. Carcinosarcoma and sarcomatoid carcinoma of the bladder: clinicopathological study of 41 cases. *J Urol.* 1998;159(5):1497-1503. doi:10.1097/00005392-199805000-00023

70. Vetterlein MW, Wankowicz SAM, Seisen T, et al. Neoadjuvant chemotherapy prior to radical cystectomy for muscle-invasive bladder cancer with variant histology. *Cancer*. 2017;123(22):4346-4355. doi:10.1002/cncr.30907
71. Berg S, D'Andrea D, Vetterlein MW, et al. Impact of adjuvant chemotherapy in patients with adverse features and variant histology at radical cystectomy for muscle-invasive carcinoma of the bladder: Does histologic subtype matter?. *Cancer*. 2019;125(9):1449-1458. doi:10.1002/cncr.31952
72. Samaratunga H, Delahunt B, Egevad L, et al. Pleomorphic giant cell carcinoma of the urinary bladder: an extreme form of tumour de-differentiation. *Histopathology*. 2016;68(4):533-540. doi:10.1111/his.12785
73. Lopez-Beltran A, Blanca A, Montironi R, et al. Pleomorphic giant cell carcinoma of the urinary bladder. *Hum Pathol*. 2009;40(10):1461-1466. doi:10.1016/j.humpath.2009.02.016
74. Solomon JP, Lowenthal BM, Kader AK, et al. Challenges in the Diagnosis of Urothelial Carcinoma Variants: Can Emerging Molecular Data Complement Pathology Review?. *Urology*. 2017;102:7-16. doi:10.1016/j.urology.2016.10.014
75. Samaratunga H, Delahunt B. Recently described and unusual variants of urothelial carcinoma of the urinary bladder. *Pathology*. 2012;44(5):407-418. doi:10.1097/PAT.0b013e3283560172
76. Priore SF, Schwartz LE, Epstein JI. An expanded immunohistochemical profile of osteoclast-rich undifferentiated carcinoma of the urinary tract. *Mod Pathol*. 2018;31(6):984-988. doi:10.1038/s41379-018-0012-z
77. Lopez-Beltran A, Amin MB, Oliveira PS, et al. Urothelial carcinoma of the bladder, lipid cell variant: clinicopathologic findings and LOH analysis. *Am J Surg Pathol*. 2010;34(3):371-376. doi:10.1097/PAS.0b013e3181cd385b
78. Kojima Y, Takasawa A, Murata M, et al. A case of urothelial carcinoma, lipid cell variant. *Pathol Int*. 2013;63(3):183-187. doi:10.1111/pin.12027
79. Mihai I, Taban S, Cumpănas A, et al. Clear cell urothelial carcinoma of the urinary bladder - a rare pathological entity. A case report and a systematic review of the literature. *Bosn J Basic Med Sci*. 2019;19(4):400-403. Published 2019 Nov 8. doi:10.17305/bjbms.2019.4182
80. Knez VM, Barrow W, Lucia MS, et al. Clear cell urothelial carcinoma of the urinary bladder: a case report and review of the literature. *J Med Case Rep*. 2014;8:275. Published 2014 Aug 14. doi:10.1186/1752-1947-8-275
81. Yamashita R, Yamaguchi R, Yuen K, et al. Urothelial carcinoma (clear cell variant) diagnosed with useful immunohistochemistry stain. *Int J Urol*. 2006;13(11):1448-1450. doi:10.1111/j.1442-2042.2006.01569.x
82. Dadhania V, Czerniak B, Guo CC. Adenocarcinoma of the urinary bladder. *Am J Clin Exp Urol*. 2015;3(2):51-63. Published 2015 Aug 8.
83. Mai KT, Bateman J, Djordjevic B, et al. Clear Cell Urothelial Carcinoma. *Int J Surg Pathol*. 2017;25(1):18-25. doi:10.1177/1066896916660195