

Bölüm 2

SERÖZ TÜMÖRLER

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SERÖZ KİSTADENOM, ADENOFİBROM VE OVERİN YÜZEY PAPİLLOMU

Tanım

Seröz kistadenom, adenofibrom ve yüzey papillomu, tuba epiteline benzeyen overin benign seröz tümörleridir (1).

Epidemiyoloji ve Etiyoloji

Bu tümörler overin en sık görülen seröz tümörleridir. Benign over epitelyal tümörlerinin 2/3'ünü oluştururlar. Herhangi bir yaş grubunda görülebilmekle birlikte hastaların ortalama yaşının 40 ile 60 arasında değiştiği bildirilmiştir. Etiyolojisi bilinmemektedir (2).

Patogenez

Patogenezinde stromal fibromatöz hücrelerde ve nadiren epitelyal hücrelerde DNA kopya sayısındaki değişikliklerin rol alabildiği gösterilmiştir (3-4).

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Ayırıcı tanı

Yüksek dereceli seröz karsinomlar, belirgin nükleer atipi (nükleer boyutta >3 kat artış), belirgin nükleollerin varlığı ve artmış mitoz (>12 mitoz/10 BBA, ancak genellikle çok daha yüksek) ile düşük dereceli seröz karsinomlardan ayrılır. Düşük dereceli seröz karsinomlar genellikle mikropapilla ve küçük yuvalarla daha düzenli bir yapıya sahiptir; solid alanlar nadirdir. Tipik olarak p53 mutasyonlarından ve dolayısıyla yüksek dereceli seröz karsinomların p53 boyama paterninden yoksundur (2).

Overin yüksek dereceli endometrioid karsinomları seröz karsinomlar ile morfolojik olarak benzeyebilir. Bu olgularda immunhistokimyasal incelemede güçlü ve yaygın östrojen ve progesteron reseptörü ekspresyonu, wild tip p53 boyanması, WT-1 ve p16 negatifliği endometrioid karsinom lehine değerlendirilmelidir (2).

Overin berrak hücreli karsinomu seröz karsinomlardan farklı olarak tanı anında daha düşük evrelerde ve genellikle unilateraldir. Tübulokistik patern, papiller yapılarda hiyerarşik dallanma veya belirgin hücresel tomurcuklanma/stratifikasyon olmaması, berrak hücreler, hobnail hücreler ve stromal hyalinizasyon berrak hücreli karsinom lehine bulgulardır. Ayrıca bu tümörler yaygın olarak yüksek dereceli nükleusların yokluğu; düşük mitotik oran, Napsin A ve HNF1p pozitifliği, östrojen reseptörü ve WT1 negatifliği; wild tip p53 boyanması sergilerler (5, 62).

Overe metastaz yapan tümörler, özellikle kolorektal karsinomlar sıklıkla müsinöz veya endometrioid tip over karsinomlarını taklit etmelerine rağmen, nadiren seröz karsinoma benzer morfoloji sergileyebilirler. CK7/CK20 boyanma paterni bu olguların ayırımında yardımcı olur (2).

KAYNAKÇA

1. Longacre TA, Davidson B, Kong CS, Mal pica A, Vang R. Serous cystadenoma, adenofibroma, and surface papilloma of the ovary. In: Cheung AN, Ellenson LH, Gilks CB, Kim K-R KC, Lax SF, Longacre TA, et al., editors. Female Genital Tumours, WHO Classification of Tumours. 5 ed. France: International Agency for Research on Cancer (IARC); 2020. p. 36.
2. Seidman JD, Ronnett BM, Shih I-M, Cho KR, Kurman RJ. Epithelial Tumors of the Ovary. In: RJ Kurman, LH Ellenson, Ronnett B, editors. Blaustein's Pathology of the Female Genital Tract. 7 ed. Switzerland: Springer; 2019. p. 841-966.
3. Hunter SM, Anglesio MS, Sharma R, et al. Copy number aberrations in benign serous ovarian tumors: a case for reclassification? Clin Cancer Res. 2011 Dec 1;17(23):7273-82.

4. Cheng EJ, Kurman RJ, Wang M, et al. Molecular genetic analysis of ovarian serous cystadenomas. *Lab Invest.* 2004 Jun;84(6):778-84.
5. Clement PB, Stall JN, Young RH. *Atlas of Gynecologic Surgical Pathology.* Fourth edition; 2020.
6. Vang R, Davidson B, Kong CS, Longacre TA, Malpica A. Serous borderline tumour of the ovary In: Cheung AN, Ellenson LH, Gilks CB, Kim K-R KC, Lax SF, Longacre TA, et al., editors. *Female Genital Tumours, WHO Classification of Tumours.* 5 ed. France: International Agency for Research on Cancer (IARC); 2020. p. 38.
7. Folkins AK, Longacre TA Low-grade serous neoplasia of the female genital tract. *Surg Pathol Clin.* 2019 Jun;1 2(2):481-513.
8. Allison KH, Swisher EM, Kerkering KM, et al. Defining an appropriate threshold for the diagnosis of serous borderline tumor of the ovary: When is a full staging procedure unnecessary? *Int J Gynecol Pathol.* 2008 Jan;27(1):10-7.
9. Hannibal CG, Vang R, Junge J, et al. A nationwide study of serous "borderline" ovarian tumors in Denmark 1 978-2002: centralized pathology review and overall survival compared with the general population. *Gynecol Oneal.* 2014 Aug; 134(2):267-73.
10. Singer G, Old! R 3rd, Cohen Y, et al. Mutations in BRAF and KRAS characterize the development of low-grade ovarian serous carcinoma. *J Natl Cancer Inst.* 2003 Mar 19;95(6):484-6.
11. Ho CL, Kurman RJ, Oehari R, et al. Mutations of BRAF and KRAS precede the development of ovarian serous borderline tumors. *Cancer Res.* 2004 Oct 1;64(19):6915-8.
12. Abeler VM, Vergote IB, Kjørstad KE, et al. Clear cell carcinoma of the endometrium. Prognosis and metastatic pattern. *Cancer.* 1996 Oct 15;78(8):1 74 0-7.
13. Jones S, Wang TL, Kurman RJ, et al. Low-grade serous carcinomas of the ovary contain very few point mutations. *J Pathol.* 2012 Feb;226(3):41 3-20.
14. Hunter SM, Anglesio MS, Ryland GL, et al. Molecular profiling of low grade serous ovarian tumours identifies novel candidate driver genes. *Oncotarget.* 2015.
15. Xing D, Suryo Rahmanto Y, Zeppernick F, et al. Mutation of NRAS is a rare genetic event in ovarian low-grade serous carcinoma. *Hum Pathol.* 2017 Oct;68:87-91.
16. Seidman JD, Soslow RA, Vang R, et al. Borderline ovarian tumors: diverse contemporary viewpoints on terminology and diagnostic criteria with illustrative images. *Hum Pathol.* 2004 Aug;35(8) 91 8-33,918-933.
17. Vang R, Hannibal CG, Junge J, et al. Long-term behavior of serous borderline tumors subdivided into atypical proliferative tumors and noninvasive low-grade carcinomas: a population-based clinicopathologic study of 942 cases. *Am J Surg Pathol.* 2017 Jun;41 (6):725- 37.
18. Bell DA, Scully RE. Ovarian serous borderline tumors with stromal microinvasion: a report of 21 cases. *Hum Pathol.* 1990 Apr;21(4):397-403.
19. Sangoi AR, McKenney JK, Dadrás SS, et al. Lymphatic vascular invasion in ovarian serous tumors of low malignant potential with stromal microinvasion: a case control study. *Am J Surg Pathol.* 2008 Feb;32(2):261--8.
20. Seidman JD, Savage J, Krishnan J, et al. Intratumoral heterogeneity accounts for apparent progression of noninvasive serous tumors to invasive low-grade serous carcinoma: a study of 30 low-grade serous tumors of the ovary in 18 patients with peritoneal carcinomatosis. *Int J Gynecol Pathol.* 2020 Jan;39(1):43-54.

21. McKenney JK, Gilks CB, Kalloger S, et al. Classification of extraovarian implants in patients with ovarian serous borderline tumors (tumors of low malignant potential) based on clinical outcome. *Am J Surg Pathol*. 2016 Sep;40(9): 1155-64.
22. Brierley JD, Gospodarowicz MK, Wittekind C, editors. *TNM classification of malignant tumours*. 8th ed. Oxford, UK: Wiley-Blackwell; 2017.
23. Singer G, Stöhr R, Cope L, et al. Patterns of p53 mutations separate ovarian serous borderline tumors and low- and high-grade carcinomas and provide support for a new model of ovarian carcinogenesis. *Am J Surg Pathol* 2005;29:218–224.
24. Ho CL, Kurman RJ, Dehari R, et al. Mutations of BRAF and KRAS precede the development of ovarian serous borderline tumors. *Cancer Res* 2004;64:6915–6918.
25. Ardighieri L, Zeppernick F, Hannibal CG, et al. Mutational analysis of BRAF and KRAS in ovarian serous borderline (atypical proliferative) tumours and associated peritoneal implants. *J Pathol* 2014;232:16–22.
26. Horn L-C, Höhn AK, Eibenkel J, et al. Monoclonal origin of peritoneal implants and lymph node deposits in serous borderline tumors with high intratumoral homogeneity. *Int J Gynecol Pathol* 2014;33:592–597.
27. Sieben NLG, Roemen GMJM, Oosting J, et al. Clonal analysis favours a monoclonal origin for serous borderline tumours with peritoneal implants. *J Pathol* 2006;210:405–411.
28. Zuo T, Wong S, Buza N, et al. KRAS mutation of extraovarian implants of serous borderline tumor: Prognostic indicator for adverse clinical outcome. *Mod Pathol* 2018;31:350–357.
29. Longacre TA, Davidson B, Folkins AK, Kong CS, Malpica A, Vang R. Low-grade serous carcinoma of the ovary. In: Cheung AN, Ellenson LH, Gilks CB, Kim K-R, Lax SF, Longacre TA, et al, editors. *Female Genital Tumours, WHO Classification of Tumours*. 5 ed. France: International Agency for Research on Cancer (IARC); 2020. p. 43.
30. Ahn G, Folkins AK, McKenney JK, et al. Low-grade serous carcinoma of the ovary: clinicopathologic analysis of 52 invasive cases and identification of a possible noninvasive intermediate lesion. *Am J Surg Pathol*. 2016 Sep;40(9): 1165-76.
31. Hunter SM, Anglesio MS, Ryland GL, et al. Molecular profiling of low grade serous ovarian tumours identifies novel candidate driver genes. *Oncotarget*. 2015 Nov 10;6(35):37663-77.
32. Tsang YT, Deavers MT, Sun CC, et al. KRAS (but not BRAF) mutations in ovarian serous borderline tumour are associated with recurrent low-grade serous carcinoma. *J Pathol*. 2013 Dec;231 (4):449-56.
33. Malpica A, Deavers MT, Lu K, et al. Grading ovarian serous carcinoma using a two-tier system. *Am J Surg Pathol*. 2004 Apr;28(4):496-504.
34. Gilks CB, Bell DA, Scully RE. Serous psammocarcinoma of the ovary and peritoneum. *Int J Gynecol Pathol* 1990;9:110–121.
35. Weir MM, Bell DA, Young RH. Grade 1 peritoneal serous carcinomas: A report of 14 cases and comparison with 7 peritoneal serous psammocarcinomas and 19 peritoneal serous borderline tumors. *Am J Surg Pathol* 1998;22:849–62.
36. McCluggage WG. Morphological subtypes of ovarian carcinoma: a review with emphasis on new developments and pathogenesis. *Pathology*. 2011 Aug;43(5):420-32.

37. Kobel M , Luo L , Grevers X , e t al. Ovarian carcinoma histotype: strengths and limitations of integrating morphology with immunohistochemical predictions. *Int J Gynecol Pathol.* 2019 Jul;38(4):353-82.
38. Jones S, Wang TL, Kurman RJ et al (2012) Low-grade serous carcinomas of the ovary contain very few point mutations. *J Pathol* 226:413–420.
39. Soslow RA, Brenton JO, Davidson B, Folkins AK, Kong CS, Malpica A, Soerjomataram I, Vang R. High-grade serous carcinoma of the ovary In: Cheung AN, Ellenson LH, Gilks CB, Kim K-R KC, Lax SF, Longacre TA, et al., editors. *Female Genital Tumours, WHO Classification of Tumours.* 5 ed. France: International Agency for Research on Cancer (IARC); 2020. p. 45.
40. Peres LC, Cushing-Haugen KL, Anglesio M, et al. Histotype classification of ovarian carcinoma: a comparison of approaches. *Gynecol Oneal.* 2018 Oct;151(1):53-60.
41. Hunn J, Rodriguez GC. Ovarian cancer: etiology, risk factors, and epidemiology. *Clin Obstet Gynecol.* 2012 Mar;55(1):3- 23.
42. Pelucchi C, Galeone C, Talamini R, et al. Lifetime ovulatory cycles and ovarian cancer risk in 2 Italian case-control studies. *Am J Obstet Gynecol.* 2007 Jan;196(1):83. e1-7.
43. Permuth-Wey J, Sellers TA. Epidemiology of ovarian cancer. *Methods Mai Biol.* 2009;472:413-37.
44. Singh N, Gilks CB, Wilkinson N, et al. Assessment of a new system for primary site assignment in high-grade serous carcinoma of the fallopian tube, ovary, and peritoneum. *Histopathology* 2015;67:331–337.
45. Ahmed AA, Etemadmoghadam D, Temple J, et al. Driver mutations in TP53 are ubiquitous in high grade serous carcinoma of the ovary. *J Pathol.* 2010 May;221(1):49-56.
46. Verhaak RG, Tamayo P, Yang JY, et al. Prognostically relevant gene signatures of highgrade serous ovarian carcinoma. *J Clin Invest.* 2013 Jan;123(1):517-25.
47. Jones MR, Kamara D, Karlan BY, et al. Genetic epidemiology of ovarian cancer and prospects for polygenic risk prediction. *Gynecol Oncol.* 2017 Dec;147(3):705-13.
48. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature.* 2011 Jun 29;474(7353):609-15.
49. Morency E, Leitao MM Jr, Soslow RA. Low-stage high-grade serous ovarian carcinomas: support for an extraovarian origin. *Int J Gynecol Pathol.* 2016 May;35(3):222-9.
50. Che M, Tomas C, Deavers MT, et al. Ovarian mixed-epithelial carcinomas with a microcystic pattern and signet-ring cells. *Int J Gynecol Pathol.* 2001 Oct;20(4):323-8.
51. Imamura H, Ohishi Y, Aman M, et al. Ovarian high-grade serous carcinoma with a noninvasive growth pattern simulating a serous borderline tumor. *Hum Pathol.* 2015 Oct;46(10):1455-63.
52. Ritterhouse LL, Nowak JA, Strickland KC, et al. Morphologic correlates of molecular alterations in extrauterine Mullerian carcinomas. *Mod Pathol.* 2016 Aug;29(8):893-903.
53. Altman AD, Nelson GS, Ghatage P, et al. The diagnostic utility of TP53 and CDKN2A to distinguish ovarian high-grade serous carcinoma from low-grade serous ovarian tumors. *Mod Pathol.* 2013 Sep;26(9):1255-63.

54. Milea A, George SH, Matevski D, et al. Retinoblastoma pathway deregulatory mechanisms determine clinical outcome in high-grade serous ovarian carcinoma. *Mod Pathol*. 2014 Jul;27(7):991-1001.
55. Karamurzin Y, Leitao MM, Soslow RA (2013) Clinicopathologic analysis of low-stage sporadic ovarian carcinomas: a reappraisal. *Am J Surg Pathol* 37:356–367.
56. Yemelyanova A, Vang R, Kshirsagar M et al (2011) Immunohistochemical staining patterns of p53 can serve as a surrogate marker for TP53 mutations in ovarian carcinoma: an immunohistochemical and nucleotide sequencing analysis. *Mod Pathol* 24:1248–1253.
57. Taube ET, Denkert C, Sehouli J et al (2017) Cytokeratin 5/6 expression, prognosis, and association with estrogen receptor α in high-grade serous ovarian carcinoma. *Hum Pathol* 67:30–36.
58. Kobel M, Kalloger SE, Carrick J, et al. A limited panel of immunomarkers can reliably distinguish between clear cell and high-grade serous carcinoma of the ovary. *Am J Surg Pathol*. 2009 Jan;33(1):14-21.
59. Garg K, Levine DA, Olvera N et al (2013) BRCA1 immunohistochemistry in a molecularly characterized cohort of ovarian high-grade serous carcinomas. *Am J Surg Pathol* 37:138–146.
60. Gottlieb C, Ring K, Mills A. PD-L1 expression in tumor-associated macrophages in primary and metastatic high-grade serous ovarian carcinoma. Abstract. *Mod Pathol* 2017;30:287A.
61. Hetland TE, Holth A, Kaern J, et al. HMGA2 protein expression in ovarian serous carcinoma effusions, primary tumors, and solid metastases. *Virchows Arch* 2012;460:505–513.
62. DeLair D, Han G, Irving JA, et al. HNF-1 β in ovarian carcinomas with serous and clear cell change. *Int J Gynecol Pathol* 2013;32:541–546.