Bölüm
14

JİNEKOLOJİK KANSER VE KANAMA

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GİRİŞ

Genital bölge kanamaları, kadınlarda genellikle vajinal kanama şeklindedir. Klinikte çoğunlukla uterus kaynaklı olmakla beraber, alt genital sistem(vulva, vajina, serviks) veya üst genital sistem (uterus korpus, fallopian tüp, over) kaynaklı olabilir. Anormal uterin kanamaya (AUK) neden olan jinekolojik kanserler, International Federation of Gynecology and Obstetrics Menstrual Disorders Committee (FIGO MDC) tarafından etyolojiye yönelik yapılan PALM-COEIN (polip, adenomyozis, leiomyom, malignensi ve hiperplazi, koagülopati, ovulatuar disfonksiyon, endometrial disfonksiyon, iyatrojenik, ve sınıflandırılmamış) sınıflamasında M ile simgelenmiştir (1). Jinekolojik kanserler, AUK dışında serviks, vajen, vulvanın primer kanserleri olması veya metastaz yapmasıyla da kanama sebebi olabilir. Yine bazı over primer veya metastatik kanserleri intraabdominal kanamaya neden olabilmekte ve bazen de östrojen salgılayarak endometriyal hiperplazi veya endometrium kanserine sebebiyet verip anormal uterin kanama yapabilmektedir. Tanı veya tedavi amaçlı yapılan insizyonel veya eksizyonel işlemler sonrası jinekolojik kanserlerin sebep olduğu kanamalar olabilmektedir. Jinekolojik kanserlerin sebep olduğu kanamaların yönetimi inoperabıl veya fertilite koruyucu yaklaşımlarda riskli ve zor olabilir.

UTERUS KORPUS KANSERLERİ VE KANAMA

Endometrıum kanseri, gelişmiş ülkelerde ve ülkemizde en sık, gelişmekte olan ülkelerde ikinci sırada görülen jinekolojik kanserdir. Yaşam boyu bir kadının endometrium kanser riski %2,6'dır. İnsidans 60-70 yaşlar arasında pik yapmakta, 40 yaş öncesinde %2-5 görülmektedir (2). Obezitenin artması, progestinli hormon

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AUK ile karışabilir. Muayenede genellikle fornikslerde veya suburetral alanda damarlanma artışı şeklinde görülür, kanama çok fazla olabileceği için GTN'nin vajinal metastaz bölgesinden biyopsi yapılmamalıdır. Molar gebelik sonrası olan GTN tanısı için; 3 hafta plato seyreden, 2 hafta %10 artış olan veya 6 ay boyunca negatifleşmeyen BHCG değerleri gereklidir. GTN, metastazın görüntüleme yöntemleriyle gösterilmesi veya küretaj materyalindeki patolojik incemeyle de tanı alabilir. Uterin kanamaya sebep olduğunda küretaj veya histerektomi yapılabilir. Farklı organlara metastaza bağlı kanamalarda metastaz alanına yönelik cerrahi veya embolizasyon seçenekleri değerlendirilebilir. Ciddi kanamaya neden olmayan GTN'lerde tedavi kemoterapidir. Evre 1'de tek ajan metotreksat tedavisi başarılıyken, evre 4 hastalar WHO risk skorlamasına göre genelde yüksek riskli hastalardır ve kombine kemoterapi alması gerekir. Evre 2 ve 3 hastalar; WHO risk skorlamasında 6 ve altı puan aldığında tek ajan, 7 ve üzeri puan aldığında kombine kemoterapi almalıdır.

SONUÇ

Jinekolojik kanamaların yönetiminde; kanamayı durdurmanın yanında kanamaya neden olan tanıyı koymak özellikle kanser şüphesi varsa çok önemlidir. Anormal uterin kanama, endometrium kanserli hastaların %75-90'ında başvuru sebebi olmasıyla en sık görülen semptomdur, görüntülemenin yanında endometriyal örnekleme yapılmalıdır. Overyan kanserler, kitlenin rüptür olmasıyla batın içine veya hormonal etkiyle uterin kanamaya neden olabilir. Overyan kanser şüphesi olanlarda, anormal uterin kanama veya endometriyal kalınlık saptanması durumunda olası eşlik eden endometriyal kanseri tanısı için de endometriyal örnekleme önerilir. Özellikle postkoital kanama tarifleyen hastada servikal kanser akılda tutulmalı, smear veya HPV testi yapılmalıdır. Vulva ve vajen kanserleri daha nadir görülmekle birlikte, uterin kaynaklı olmayan jinekolojik kanamaya sebep olabilir. Kanama tarifleyen hastada BHCG bakmak, olası gebelik durumu hakkında bilgi verdiği gibi gestasyonel neoplazi için uyarıcı olmalıdır, gestasyonel neoplaziler oldukça kanamaya meyilli kitlelerle karşımıza çıkabilir bu nedenle biyopsi yapılmadan önce akılda tutulmalıdır.

REFERANSLAR

1. Munro MG, Critchley HO, Broder MS, et al. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. *Int J Gynaecol Obstet*, 113(1):3-13. Doi: 10.1016/j.ijgo.2010.11.011
2. Constantine GD, Kessler G, Graham S, et al. Increased Incidence of Endometrial Cancer Following the Women's Health Initiative: An Assessment of Risk Factors. *J Womens Health (Larchmt)* 28 (2), 237-243. Doi: 10.1089/jwh.2018.6956.
3. Cote ML, Ruterbusch JJ, Olson SH, et al. The Growing Burden of Endometrial Cancer: A Major Racial Disparity Affecting Black Women. *Cancer Epidemiol Biomarkers Prev* 24 (9), 1407-15. doi: 10.1158/1055-9965.EPI-15-0316.

4. Felix AS, Weissfeld JL, Stone RA, et al. Factors associated with Type I and Type II endometrial cancer. *Cancer Causes Control*. 21(11), 1851-6. Doi: 10.1007/s10552-010-9612-8.
5. Kwon JS, Scott JL, Gilks CB, et al. Testing women with endometrial cancer to detect Lynch syndrome. *J Clin Oncol*, 29 (16), 2247-52. Doi: 10.1200/JCO.2010.32.9979.
6. Iversen L, Sivasubramaniam S, Lee AJ, et al. Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study. *Am J Obstet Gynecol*, 216 (6), 580.e1-580.e9. Doi: 10.1016/j.ajog.2017.02.002.
7. Husby A, Wohlfahrt J, Melbye M. Pregnancy duration and endometrial cancer risk: nationwide cohort study. *BMJ,* 366, l4693. Doi: 10.1136/bmj.l4693.
8. Gu M, Shi W, Barakat RR, et al. Pap smears in women with endometrial carcinoma. *Acta Cytol*, 200; 45:555.
9. Desai VB, Wright JD, Gross CP, et al. Prevalence, characteristics, and risk factors of occult uterine cancer in presumed benign hysterectomy. *Am J Obstet Gynecol*, 39.e1-39.e14. Doi: 10.1016/j.ajog.2019.02.051.
10. Dijkhuizen FP, Mol BW, Brölmann HA, et al. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. *Cancer,* 2000; 89:1765.
11. Clark TJ, Mann CH, Shah N, et al. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review. *BJOG,* 2002; 109:313.
12. Clark TJ, Mann CH, Shah N, et al. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial hyperplasia. *Acta Obstet Gynecol Scand*, 2001; 80:784.
13. Deckardt R, Lueken RP, Gallinat A, et al. Comparison of transvaginal ultrasound, hysteroscopy, and dilatation and curettage in the diagnosis of abnormal vaginal bleeding and intrauterine pathology in perimenopausal and postmenopausal women. *J Am Assoc Gynecol Laparosc*, 2002; 9:277.
14. Trimble CL, Method M, Leitao M, et al. Management of endometrial precancers. *Obstet Gynecol,* 2012; 120:1160.
15. Yazbeck C, Dhainaut C, Batallan A, et al. Diagnostic hysteroscopy and risk of peritoneal dissemination of tumor cells. *Gynecol Obstet Fertil*, 2005; 33:247.
16. Seebacher V, Schmid M, Polterauer S, et al. The presence of postmenopausal bleeding as prognostic parameter in patients with endometrial cancer: a retrospective multi-center study. *BMC Cancer,* 2009; 9:460.
17. Clarke MA, Long BJ, Del Mar Morillo A, et al. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. *JAMA Intern Med*, 2018; 178:1210.
18. Burbos N, Musonda P, Giarenis I, et al. Age-related differential diagnosis of vaginal bleeding in postmenopausal women: a series of 3047 symptomatic postmenopausal women. *Menopause Int*, 2010; 16:5.
19. Cote ML, Ruterbusch JJ, Ahmed Q, et al. Endometrial cancer in morbidly obese women: do racial disparities affect surgical or survival outcomes? *Gynecol Oncol*, 2014; 133:38.
20. Salman MC, Bozdag G, Dogan S, Yuce K. Role of postmenopausal bleeding pattern and women's age in the prediction of endometrial cancer. *Aust N Z J Obstet Gynaecol,* 2013; 53:484.
21. Munro MG, Southern California Permanente Medical Group's Abnormal Uterine Bleeding Working Group. Investigation of women with postmenopausal uterine bleeding: clinical practice recommendations. *Perm J*, 2014; 18:55.
22. Vargas R, Rauh-Hain JA, Clemmer J, et al. Tumor size, depth of invasion, and histologic grade as prognostic factors of lymph node involvement in endometrial cancer: a SEER analysis. *Gynecol Oncol,* 133 (2), 216-20. Doi: 10.1016/j.ygyno.2014.02.011.
23. WHO Classification of tumours of the female reproductive organs, 4, Kurman RJ, Carcangiu ML, Herrington CS, Young RH (Eds), *World Health Organization*, 2014. p.126, 150.
24. Conlon N, Leitao MM Jr, Abu-Rustum NR, et al. Grading uterine endometrioid carcinoma: a proposal that binary is best. *Am J Surg Pathol*, 38 (12), 1583-7. Doi: 10.1097/PAS.0000000000000327.

25. Xiong J, He M, Jackson C, et al. Endometrial carcinomas with significant mucinous differentiation associated with higher frequency of k-ras mutations: a morphologic and molecular correlation study. Int *J Gynecol Cancer*, 23 (7), 1231-6. Doi: 10.1097/IGC.0b013e31829ea82f.
26. Huang CY, Tang YH, Chiang YC, et al. Impact of management on the prognosis of pure uterine papillary serous cancer - a Taiwanese Gynecologic Oncology Group (TGOG) study. *Gynecol Oncol,* 133 (2), 221-8. Doi: 10.1016/j.ygyno.2014.02.010.
27. Quddus MR, Sung CJ, Zhang C, et al. Minor serous and clear cell components adversely affect prognosis in ''mixed-type" endometrial carcinomas: a clinicopathologic study of 36 stage-I cases. *Reprod Sci,* 17 (7), 673-8. Doi: 10.1177/1933719110368433.
28. Berton-Rigaud D, Devouassoux-Shisheboran M, Ledermann JA, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for uterine and ovarian carcinosarcoma. *Int J Gynecol Cancer* , 24 (9 Suppl 3), S55-60. Doi: 10.1097/IGC.0000000000000228.
29. Tropé CG, Abeler VM, Kristensen GB. Diagnosis and treatment of sarcoma of the uterus. A review. *Acta Oncol*, 51 (6), 694-705. Doi: 10.3109/0284186X.2012.689111.
30. Munro MG.Uterine polyps, adenomyosis, leiomyomas, and endometrial receptivity. *Fertil Steril*, 11 (4), 629-640. Doi: 10.1016/j.fertnstert.2019.02.008.
31. Sherman ME, Devesa SS. Analysis of racial differences in incidence, survival, and mortality for malignant tumors of the uterine corpus. *Cancer*, 2003; 98:176.
32. Liao Q, Wang J, Han J. Clinical and pathological analysis on 106 cases with uterine sarcoma. *Zhonghua Fu Chan Ke Za Zhi*, 2001; 36:104.
33. Bansal N, Herzog TJ, Burke W, et al. The utility of preoperative endometrial sampling for the detection of uterine sarcomas. *Gynecol Oncol,* 2008; 110:43.
34. Leibsohn S, d'Ablaing G, Mishell DR Jr, et al. Leiomyosarcoma in a series of hysterectomies performed for presumed uterine leiomyomas. *Am J Obstet Gynecol*, 1990; 162:968.
35. Lee NK, Cheung MK, Shin JY, et al. Prognostic factors for uterine cancer in reproductive-aged women. *Obstet Gyneco,l* 2007; 109:655.
36. Li J, Zhu Q, Yang B, et al. Risk factors for ovarian involvement in young and premenopausal endometrioid endometrial cancer patients. *Eur J Obstet Gynecol Reprod Biol*, 222, 151-154. Doi: 10.1016/j.ejogrb.2018.01.030.
37. Kumar S, Medeiros F, Dowdy SC, et al. A prospective assessment of the reliability of frozen section to direct intraoperative decision making in endometrial cancer. *Gynecol Oncol*,127 (3), 525-31. Doi: 10.1016/j.ygyno.2012.08.024.
38. Orbo A, Vereide A, Arnes M, et al. Levonorgestrel-impregnated intrauterine device as treatment for endometrial hyperplasia: a national multicentre randomised trial. *BJOG*, 121 (4), 477-86. Doi: 10.1111/1471-0528.12499.
39. Ushijima K, Yahata H, Yoshikawa H, et al. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. *J Clin Oncol,* 2007; 25:2798.
40. Eftekhar Z, Izadi-Mood N, Yarandi F, et al. Efficacy of megestrol acetate (megace) in the treatment of patients with early endometrial adenocarcinoma: our experiences with 21 patients. *Int J Gynecol Cancer*, 2009; 19:249.
41. Thigpen JT, Brady MF, Alvarez RD, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. *J Clin Onco,l* 1999; 17:1736.
42. Park JY, Kim DY, Kim JH, et al. Long-term oncologic outcomes after fertility-sparing management using oral progestin for young women with endometrial cancer (KGOG 2002). *Eur J Cancer*, 2013; 49:868.
43. Montz FJ, Bristow RE, Bovicelli A, et al. Intrauterine progesterone treatment of early endometrial cancer. *Am J Obstet Gynecol*, 2002; 186:651.
44. Baker J, Obermair A, Gebski V, et al. Efficacy of oral or intrauterine device-delivered progestin in patients with complex endometrial hyperplasia with atypia or early endometrial adenocarcinoma: a meta-analysis and systematic review of the literature. *Gynecol Oncol*, 2012; 125:263.

45. Yan J, Milosevic M, Fyles A, et al. A hypofractionated radiotherapy regimen (0-7-21) for advanced gynaecological cancer patients. *Clin Oncol (R Coll Radiol),* 2011;23:476-81.
46. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, 2018; 68:394.
47. Wentzensen N, Poole EM, Trabert B, et al. Ovarian Cancer Risk Factors by Histologic Subtype: An Analysis From the Ovarian Cancer Cohort Consortium. *J Clin Oncol*, 34 (24), 2888-98. Doi: 10.1200/JCO.2016.66.8178.
48. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65:87.
49. Hoskins WJ, Bundy BN, Thigpen JT, et al. The influence of cytoreductive surgery on recurrence-free interval and survival in small-volume stage III epithelial ovarian cancer: a Gynecologic Oncology Group study. *Gynecol Oncol,* 1992; 47:159.
50. Zivanovic O, Sima CS, Iasonos A, et al. Exploratory analysis of serum CA-125 response to surgery and the risk of relapse in patients with FIGO stage IIIC ovarian cancer. *Gynecol Oncol*, 115 (2), 209-14. Doi: 10.1016/j.ygyno.2009.06.038.
51. Crawford SC, Vasey PA, Paul J, et al. Does aggressive surgery only benefit patients with less advanced ovarian cancer? Results from an international comparison within the SCOTROC-1 Trial. J *Clin Oncol*, 2005; 23:8802.
52. Segal R, DePetrillo AD, Thomas G. Clinical review of adult granulosa cell tumors of the ovary. *Gynecol Oncol*, 1995; 56:338.
53. Young R, Clement PB, Scully RE. The ovary. In: Surgical Pathology, Sternberg SS (Ed), Raven Press, *New York* 1989. p.1687.
54. Evans AT 3rd, Gaffey TA, Malkasian GD Jr, Annegers JF. Clinicopathologic review of 118 granulosa and 82 theca cell tumors. *Obstet Gynecol*,1980; 55:231.
55. Cronjé HS, Niemand I, Bam RH, et al. Review of the granulosa-theca cell tumors from the emil Novak ovarian tumor registry. *Am J Obstet Gynecol,* 1999; 180:323.
56. Jobling T, Mamers P, Healy DL, et al. A prospective study of inhibin in granulosa cell tumors of the ovary. *Gynecol Onco*l, 1994; 55:285.
57. Liu H, Hao SH, Li WM. Giant malignant ovarian fibrothecoma involved with retroperitoneal structures mimicking a retroperitoneal sarcoma. *Arch Gynecol Obstet*, 2009; 279:763.
58. Tewari K, Cappuccini F, Disaia PJ, et al. Malignant germ cell tumors of the ovary. *Obstet Gynecol*, 2000; 95:128.
59. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*, 1999; 189:12.
60. Quinn M, Babb P, Jones J, Allen E. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. *BMJ,* 1999; 318:904.
61. International Collaboration of Epidemiological Studies of Cervical Cancer. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. *Int J Cancer*, 2007; 120:885.
62. Castellsagué X, Bosch FX, Muñoz N, et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. *N Engl J Med*, 2002; 346:1105.
63. Franco EL, Schlecht NF, Saslow D. The epidemiology of cervical cancer. *Cancer J*, 2003; 9:348.
64. Liu L, Yang X, Chen X, et al. Association between TNF-α polymorphisms and cervical cancer risk: a meta-analysis. *Mol Biol Rep*, 2012; 39:2683.
65. Look KY, Brunetto VL, Clarke-Pearson DL, et al. An analysis of cell type in patients with surgically staged stage IB carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol,* 1996; 63:304.
66. Lea JS, Coleman RL, Garner EO, et al. Adenosquamous histology predicts poor outcome in low-risk stage IB1 cervical adenocarcinoma. *Gynecol Oncol*, 2003; 91:558.
67. Partridge EE, Abu-Rustum NR, Campos SM, et al. Cervical cancer screening. *J Natl Compr Canc Netw*, 2010; 8:1358.

68. D'Alessandro P, Arduino B, Borgo M, et al. Loop Electrosurgical Excision Procedure versus Cryotherapy in the Treatment of Cervical Intraepithelial Neoplasia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Gynecol Minim Invasive Ther*, 7 (4), 145-151. Doi: 10.4103/GMIT.GMIT_56_18.
69. Liontos M, Kyriazoglou A, Dimitriadis I, et al. Systemic therapy in cervical cancer: 30 years in review. *Crit Rev Oncol Hematol*, 137, 9-17. Doi: 10.1016/j.critrevonc.2019.02.009.
70. Tripathi A, Rawat S. Comparative Study of Neoadjuvant Chemotherapy Followed by Definitive Chemoradiotherapy Versus Definitive Chemoradiotherapy Alone in Locally Advanced Carcinoma of Cervix. *J Obstet Gynaecol India*, 69 (6), 546-552. Doi: 10.1007/s13224-019-01236-0.
71. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020.
72. Schuurman MS, van den Einden LC, Massuger LF, et al. Trends in incidence and survival of Dutch women with vulvar squamous cell carcinoma. *Eur J Cancer*, 49 (18), 3872-80. Doi: 10.1016/j.ejca.2013.08.003.
73. Madsen BS, Jensen HL, van den Brule AJ, et al. Risk factors for invasive squamous cell carcinoma of the vulva and vagina--population-based case-control study in Denmark. Int J Cancer 2008; 122:2827.
74. de Sanjosé S, Alemany L, Ordi J, et al. Worldwide human papillomavirus genotype attribution in over 2000 cases of intraepithelial and invasive lesions of the vulva. *Eur J Cancer*, 2013; 49:3450.
75. Collins CG, Lee FY, Roman-Lopez JJ. Invasive carcinoma of the vulva with lymph node metastasis. *Am J Obstet Gynecol*, 1971; 109:446.
76. Thorneycroft IH, Gibbons WE. Vaginal bleeding patterns in women receiving hormone replacement therapy. Impact of various progestogen regimens. *J Reprod Med*, 1999 Feb;44(2 Suppl):209-14.
77. Liang Y, Chen M, Qin L, et al. A meta-analysis of the relationship between vaginal microecology, human papillomavirus infection and cervical intraepithelial neoplasia. *Infect Agent Cancer*, 14:29. Doi: 10.1186/s13027-019-0243-8.
78. Gerstl B, Sullivan E, Vallejo M, et al. Reproductive outcomes following treatment for a gynecological cancer diagnosis: a systematic review. *J Cancer Surviv*, 13 (2), 269-281. Doi: 10.1007/s11764-019-00749-x
79. Lian J, Dundas G, Carlone M, et al. Twenty-year review of radiotherapy for vaginal cancer: an institutional experience. *Gynecol Oncol*, 2008; 111:298.
80. Al-Kurdi M, Monaghan JM. Thirty-two years experience in management of primary tumours of the vagina. Br J Obstet Gynaecol 1981; 88:1145.
81. Ngan S, Seckl MJ. Gestational trophoblastic neoplasia management: an update. *Curr Opin Oncol*, 2007; 19:486.
82. Altieri A, Franceschi S, Ferlay J, et al. Epidemiology and aetiology of gestational trophoblastic diseases. *Lancet Oncol*, 2003; 4:670.
83. Goldstein DP, Berkowitz RS. Current management of gestational trophoblastic neoplasia. *Hematol Oncol Clin North Am*, 2012; 26:111.
84. Lurain JR. Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. *Am J Obstet Gynecol*, 2010; 203:531.
85. Osborne R, Dodge J. Gestational trophoblastic neoplasia. *Obstet Gynecol Clin North Am,* 2012; 39:195.
86. Berkowitz RS, Goldstein DP. Pathogenesis of gestational trophoblastic neoplasms. *Pathobiol Annu* , 1981; 11:391.
87. Berkowitz RS, Goldstein DP. Chorionic tumors. *N Engl J Med*, 1996; 335:1740.
88. Lim AK, Agarwal R, Seckl MJ, et al. Embolization of bleeding residual uterine vascular malformations in patients with treated gestational trophoblastic tumors. *Radiology*, 2002; 222:640.