

RESEARCH

Open Access



Association between atypical endometriosis and ovarian malignancies in the real world

Kyeong A So^{1,2}, Sung Ran Hong^{3,4}, Nae Ri Kim¹, Eun Jung Yang¹, Seung-Hyuk Shim¹, Sun Joo Lee¹ and Tae Jin Kim^{1,2*}

Abstract

Background: To evaluate the clinical outcome of atypical endometriosis and its association with ovarian malignancy.

Methods: This retrospective study included patients diagnosed with atypical endometriosis between January 2001 and December 2017. All patients had received surgical treatment for ovarian tumor. The clinical characteristics and histopathological results of all patients were reviewed.

Results: Atypical endometriosis was diagnosed in 101 patients. We analyzed 98 patients with a mean age of 34.8 years (range: 16–58 years). Ten patients (10.2%) had previously undergone endometriosis surgery more than once. In total, 12 (12.2%) patients had atypical endometriosis-associated ovarian malignancy—nine had carcinomas and three had borderline tumor. The tumors were pathologically classified as follows: five, clear cell carcinomas; two, endometrioid adenocarcinomas; one, mixed clear cell and endometrioid adenocarcinoma; one, seromucinous carcinoma; two, mucinous borderline tumors; and one, seromucinous borderline tumor.

Conclusion: Atypical endometriosis is most frequently associated with clear cell carcinoma and endometrioid adenocarcinoma. To identify the risk of ovarian malignancy and manage patients with endometriosis, diagnosing atypical endometriosis and recognizing its precancerous potential are important.

Keywords: Atypical endometriosis, Ovarian malignancy, Clear cell carcinoma, Adenocarcinoma

Background

Endometriosis is defined as the presence of endometrial tissue outside the uterus [23]. It is a common gynecological disease that is estimated to occur in 5–8% of reproductive-aged women [20]. Although endometriosis is considered as a benign disease, it has a unique ability to metastasize and invade other tissues [27]. Some cases of endometriosis are closely related to ovarian malignancy [27]. In 1925, Sampson first described the criteria to diagnose a malignant tumor arising from endometriosis, which were as follows: evidence of endometriosis close to

the tumor, exclusion of invasion from other sources, and presence of tissue resembling endometrial stroma surrounding characteristic epithelial glands [17]. In addition, in 1953, Scott indicated that transition of endometriosis from benign to malignant should be confirmed histologically [19].

Atypical endometriosis was first described by Czer-nobilsky and Morris in 1979 [3]. Atypical endometriosis is considered to have premalignant potential, is characterized by dysplastic features with cellular atypia, and is different from typical endometriosis [10]. Endometriosis-associated tumorigenesis involves pathophysiological progression of endometriosis to atypical endometriosis, followed by formation of a well-defined borderline tumor and development of ovarian malignancy [23]. However, it is difficult to diagnose accurately the atypical endometriosis. In the real world, there are few cases diagnosed as

*Correspondence: kimonc111@naver.com

¹ Department, of Obstetrics and Gynecology, Konkuk University School of Medicine, 120-1, Neungdong-ro, Gwangjin-gu, Seoul 05030, Republic of Korea

Full list of author information is available at the end of the article



© The Author(s) 2021. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

atypical endometriosis, so clinicians do not fully understand the clinical significance of atypical endometriosis. In this study, we investigated the clinical feature of atypical endometriosis and the association between atypical endometriosis and endometriosis-associated ovarian malignancy.

Methods

This retrospective study included patients diagnosed with atypical endometriosis at Cheil General Hospital & Women’s Healthcare Center between January 2001 and December 2017. All patients had undergone surgical treatment for ovarian mass and were diagnosed with atypical endometriosis. Patients with a history of malignant disease were excluded. Medical charts were reviewed for clinical characteristics and laboratory findings. Further, histopathological results were reviewed by an expert gynecologic pathologist. The study was approved by the Institutional Review Board (No. CGH-IRB-2018–22). All procedures performed in this study were in accordance with the ethical standards of the institution and with the 1964 Helsinki declaration and its later amendments.

Statistical analyses

Categorical variables are presented as numbers and percentages, and continuous variables are presented as means and standard deviations. Continuous and categorical variables were analyzed using a t-test and chi-square test, respectively. A *p*-value of less than 0.05 was considered statistically significant. Data analyses were performed using SPSS for Windows (version 17.0; SPSS Inc., Chicago, IL, USA).

Results

A total of 101 patients were diagnosed with atypical endometriosis in the study period. Among them, two patients had endometrial adenocarcinoma and one patient had received treatment for ovarian mucinous borderline tumor 10 years ago. These three patients were excluded and remaining 98 patients were included in the study. During the same period, 13,074 patients were surgically diagnosed with endometriosis in this hospital. Therefore, the prevalence of atypical endometriosis was approximately 0.8%.

Clinical characteristics of the patients with atypical endometriosis are presented in Table 1. The mean age of patients was 34.8 years. In total, 88 (89.8%) patients were diagnosed with atypical endometriosis during their first surgery for endometriosis. Ten patients (10.2%) had previously undergone endometriosis surgery more than once. The mean duration from first surgery to diagnosis of atypical endometriosis was 7.4 years (range:

Table 1 Patient characteristics of atypical endometriosis (N = 98)

Category	Number
Age (years, range)	34.8 ± 7.3 years (16 ~ 58 years)
Parity (range)	0.5 ± 0.9 (0 ~ 3)
Infertility history	17 (17.3%)
Number of previous surgery for endometriosis	
0	88 (89.8%)
1	9 (9.2%)
2	1 (1.0%)
Largest diameter (cm, range)	7.2 ± 2.7 (2 ~ 15.5)
Tumor marker (U/mL)	
CA-125	87.0 ± 100.2
CA-19-9	58.0 ± 60.2
Location of atypical endometriosis	
Right ovary	54 (55.1%)
Left ovary	35 (35.7%)
Both ovaries	8 (8.2%)
Pelvic peritoneum	1 (1.0%)
Histopathology	
Atypical endometriosis (AE)	86 (87.7%)
AE + Borderline tumor	3 (3.1%)
AE + Carcinoma	9 (9.2%)

3–24 years). One patient was diagnosed with atypical endometriosis during the third surgery for ovarian endometriosis. The mean diameter of the ovarian cyst was 7.2 cm (range: 2–15.5 cm). Atypical endometriosis was found in the right ovary (55.1%), left ovary (35.7%), both ovaries (8.2%), and pelvic peritoneum (1%). Serum tumor markers were found to be elevated (CA-125: 87.0 U/mL, CA-19–9: 58.0 U/mL). Most of the atypical endometriosis cases were found to be benign endometriosis (87.7%); however, twelve cases (12.3%) of atypical endometriosis were found to be associated with malignant ovarian tumor.

Characteristics of atypical endometriosis with ovarian malignancy are presented in Table 2. The mean age of patients was 36.3 years and the mean diameter of the cyst was 8.8 cm (1.2–15 cm) in atypical endometriosis with ovarian malignancy. Malignant tumors associated with atypical endometriosis were borderline tumors (three cases) and invasive carcinoma (nine cases). These tumors were pathologically classified as follows: five, clear cell carcinoma (stage Ic); two, endometrioid adenocarcinoma (stage Ib and Ic); one, seromucinous carcinoma (stage IIb); and one, mixed carcinoma (clear cell and endometrioid; stage IIb).

The mean follow-up period for atypical endometriosis, except for patients with atypical endometriosis-associated ovarian malignancy, was 44.5 months. Seven of the 12 patients who were diagnosed with recurrent ovarian

Table 2 Characteristics of atypical endometriosis with ovarian malignancy ($N=12$)

Category	Number
Age (years, range)	36.3 ± 5.2 (29~46)
Parity (range)	0.8 ± 1.0 (0~2)
Tumor size (cm, range)	8.8 ± 3.1 (1.2~15)
Tumor marker (U/mL)	
CA-125	122.9 ± 113.1
CA-19-9	43.8 ± 65.3
Location of atypical endometriosis	
Right ovary	6
Left ovary	6
Histopathology	
Borderline malignancy ($n=3$)	Mucinous ($n=2$), Seromucinous ($n=1$)
Invasive carcinoma ($n=9$)	
Clear cell carcinoma (5)	Stage Ic
Endometrioid adenocarcinoma (2)	Stage Ib, Ic
Mixed (clear cell + endometrioid) (1)	Stage IIb
Seromucinous carcinoma (1)	Stage IIb

Table 3 Comparison between atypical endometriosis (AE) alone and AE with ovarian malignancy

Category	AE alone ($n=86$)	AE + ovarian malignancy ($n=12$)	<i>p</i> -value
Age (years)	34.6 ± 7.5	36.3 ± 5.2	0.452
Parity	0.5 ± 0.8	0.8 ± 1.0	0.344
Tumor size (cm)	7.0 ± 2.6	8.8 ± 3.1	0.025
Tumor marker (U/mL)			
CA-125	97.4 ± 13.0	122.9 ± 113.1	0.222
CA-19-9	43.8 ± 65.3	43.8 ± 65.3	0.464

endometriosis by ultrasound underwent additional surgery. Two patients were diagnosed with recurrent atypical endometriosis. Two patients were diagnosed with recurrent atypical endometriosis after 4 years of the first surgery. One of these two patients had received gonadotropin-releasing hormone agonist treatment for 6 months after the first surgery, whereas the other did not receive any hormonal therapy after the first surgery

Comparison between atypical endometriosis alone and atypical endometriosis with ovarian malignancy is presented in Table 3. The mean size of ovarian cyst in atypical endometriosis with malignant tumor was significantly larger than that in atypical endometriosis alone ($p = 0.025$). No statistical differences in mean age, parity, and serum tumor maker levels were noted between the groups.

Discussion

Previous studies have reported that ovarian endometriosis may develop into primary malignant ovarian tumor. The risk of malignant transformation of endometriosis occurs in 0.7–4.5% of patients [1, 7, 21]. Endometriosis is associated with an increased risk of epithelial ovarian cancer development, especially clear cell and endometrioid carcinoma. Although clear cell and endometrioid subtypes are rare among all epithelial ovarian cancers, they are most common in endometriosis-associated ovarian cancer (EAO) [8, 9, 16]. In our study, clear cell and endometrioid subtypes were found in 8 of 9 patients with invasive carcinoma. Clear cell carcinoma was the most common and was found in six patients. Several studies have indicated that patients with EAO are more likely to be younger and to have longer disease-free survival than those with epithelial ovarian carcinoma not associated with endometriosis [2, 22]. In addition, EAO is more likely to be diagnosed at an early stage and with low grade of tumor [6, 9, 12].

Incidence of ovarian atypical endometriosis is not well known. Two studies reported the incidence of atypical endometriosis to be approximately 1.7% and 5.9% in 255 and 339 benign ovarian endometriosis cases, respectively [5, 15]. The incidence of atypical endometriosis is found to be high (61–78%) in EAO [5, 14]. In our study, the incidence of atypical endometriosis was approximately 0.8% in 13,074 patients diagnosed with benign endometriosis. The frequency of atypical endometriosis was low in our study because our study included considerably more cases than the previous studies. In addition, atypical endometriosis was diagnosed by extensive sections of specimen in previous studies. However, in real clinical practice, performing extensive pathological examination for each specimen is difficult. Therefore the real incidence of atypical endometriosis may be higher than 0.8% in the present study.

Atypical endometriosis represents a transition from endometriosis to carcinoma that may occur in the process of endometriotic tissue undergoing chronic inflammation and oxidative stress [11]. Several molecular and genetic mechanisms have been demonstrated to support that endometriosis may lead to epithelial ovarian carcinoma. EAO is associated with overexpression of vascular endothelial growth factor (VEGF), and VEGF expression in atypical endometriosis may be associated with the malignant transformation of endometriosis [4]. Somatic mutations such as *ARID1A*, *PTEN*, and *PIK3CA* have been reported in patients displaying atypical endometriosis and development of endometrioid and clear cell carcinomas [13, 18, 25]. Activation of oncogenic KRAS and PIK3CA pathways and inactivation of tumor suppressor genes, *ARID1A* and *PTEN*, are observed in

clear cell and endometrioid ovarian carcinomas, respectively [26].

The large size of atypical endometriotic cyst was associated ovarian malignancy ($p=0.025$) in our study. Serum tumor marker levels did not distinguish patients with malignant ovarian tumors associated with atypical endometriosis. The risk of ovarian malignancy in patients with atypical endometriosis was not completely understood because of small sample size. However, atypical endometriosis has been implicated in the development of ovarian malignant tumor—a small number of patients will progress along the continuum from endometriosis to EAO. It is not necessary for patients with endometriosis to be screened for cancer. However, if they are diagnosed with atypical endometriosis, they should be counseled for the potential risk of progression to endometriosis-associated ovarian malignancy [24].

Conclusions

Diagnosing atypical endometriosis and recognizing its precancerous potential are important for identifying the risk of ovarian malignancy and managing patients with endometriosis. Results showed that the large size of atypical endometriotic cyst was associated ovarian malignancy. Further, careful long-term follow-up of the patients with large atypical endometriosis is required.

Abbreviations

EAO: Endometriosis-associated ovarian cancer; VEGF: Vascular endothelial growth factor.

Acknowledgements

Not applicable

Authors' contributions

SO KA: conception and the design of the study, drafting the manuscript. Hong SR: acquisition of data, interpretation of data. Kim NR and Yang EJ: analysis of data. Shim SH and Lee SJ: interpretation of data. Kim TJ: conception and the design of the study and final approval of the version to be published.

Funding

Not applicable.

Availability of data and materials

The datasets used and/or analyzed in the present study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Cheil General Hospital and Women's Healthcare Center (No. CGH-IRB-2018–22).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department, of Obstetrics and Gynecology, Konkuk University School of Medicine, 120-1, Neungdong-ro, Gwangjin-gu, Seoul 05030, Republic of Korea. ²Department of Obstetrics and Gynecology, Cheil General Hospital & Women's Healthcare Center, Seoul, Republic of Korea. ³Department of Pathology, CHA Ilsan Medical Center, CHA University, Gyeonggi-do, Republic of Korea. ⁴Department of Pathology, Cheil General Hospital & Women's Healthcare Center, Seoul, Republic of Korea.

Received: 6 January 2021 Accepted: 30 May 2021

Published online: 28 August 2021

References

1. Aris A. Endometriosis-associated ovarian cancer: A ten-year cohort study of women living in the Estrie Region of Quebec, Canada. *J Ovarian Res.* 2010;3:2.
2. Bai H, Cao D, Yuan F, Sha G, Yang J, Chen J, et al. Prognostic value of endometriosis in patients with stage I ovarian clear cell carcinoma: Experiences at three academic institutions. *Gynecol Oncol.* 2016;143(3):526–31.
3. Czernobilsky B, Morris WJ. A histologic study of ovarian endometriosis with emphasis on hyperplastic and atypical changes. *Obstet Gynecol.* 1979;53(3):318–23.
4. Del Carmen MG, Smith Sehdev AE, Fader AN, Zahurak ML, Richardson M, Fruehauf JP, et al. Endometriosis-associated ovarian carcinoma: differential expression of vascular endothelial growth factor and estrogen/progesterone receptors. *Cancer.* 2003;98(8):1658–63.
5. Fukunaga M, Nomura K, Ishikawa E, Ushigome S. Ovarian atypical endometriosis: its close association with malignant epithelial tumours. *Histopathology.* 1997;30(3):249–55.
6. Kim HS, Kim TH, Chung HH, Song YS. Risk and prognosis of ovarian cancer in women with endometriosis: a meta-analysis. *Br J Cancer.* 2014;110(7):1878–90.
7. Kobayashi H. Ovarian cancer in endometriosis: epidemiology, natural history, and clinical diagnosis. *Int J Clin Oncol.* 2009;14(5):378–82.
8. Kobayashi H. Screening, epidemiology, molecular biology, and treatment strategies for endometriosis-associated ovarian cancer. *Reprod Med Biol.* 2010;9(1):17–22.
9. Kurman RJ, Shih IM. The dualistic model of ovarian carcinogenesis: revisited, revised, and expanded. *Am J Pathol.* 2016;186(4):733–47.
10. LaGrenade A, Silverberg SG. Ovarian tumors associated with atypical endometriosis. *Hum Pathol.* 1988;19(9):1080–4.
11. Munksgaard PS, Blaakaer J. The association between endometriosis and ovarian cancer: a review of histological, genetic and molecular alterations. *Gynecol Oncol.* 2012;124(1):164–9.
12. Noli S, Cipriani S, Scarfone G, Villa A, Grossi E, Monti E, et al. Long term survival of ovarian endometriosis associated clear cell and endometrioid ovarian cancers. *Int J Gynecol Cancer.* 2013;23(2):244–8.
13. Obata K, Hoshi H. Common genetic changes between endometriosis and ovarian cancer. *Gynecol Obstet Invest.* 2000;50:39–43.
14. Ogawa S, Kaku T, Amada S, Kobayashi H, Hirakawa T, Ariyoshi K, et al. Ovarian endometriosis associated with ovarian carcinoma: a clinicopathological and immunohistochemical study. *Gynecol Oncol.* 2000;77(2):298–304.
15. Prefumo F, Todeschini F, Fulcheri E, Venturini PL. Epithelial abnormalities in cystic ovarian endometriosis. *Gynecol Oncol.* 2002;84(2):280–4.
16. Rossing MA, Cushing-Haugen KL, Wicklund KG, Doherty JA, Weiss NS. Risk of epithelial ovarian cancer in relation to benign ovarian conditions and ovarian surgery. *Cancer Causes Control.* 2008;19(10):1357–64.
17. Sampson J. Endometrial carcinoma of the ovary arising in endometrial tissue in that organ. *Arch Surg.* 1925;10:1–72.
18. Sato N, Tsunoda H, Nishida M, Morishita Y, Takimoto Y, Kubo T, et al. Loss of heterozygosity on 10q23.3 and mutation of the tumor suppressor gene PTEN in benign endometrial cyst of the ovary: possible sequence progression from benign endometrial cyst to endometrioid carcinoma and clear cell carcinoma of the ovary. *Cancer Res.* 2000;60(24):7052–6.
19. Scott R. Malignant change in endometriosis. *Obstet Gynecol.* 1953;2(3):283–9.
20. Somigliana E, Vigano P, Parazzini F, Stoppelli S, Giambattista E, Vercellini P. Association between endometriosis and cancer: a comprehensive review

- and a critical analysis of clinical and epidemiological evidence. *Gynecol Oncol.* 2006;101(6):331–41.
21. Van Gorp T, Amant F, Neven P, Vergote I, Moerman P. Endometriosis and the development of malignant tumours of the pelvis. A review of literature. *Best Pract Res Clin Obstet Gynaecol.* 2004;18(2):349–71.
 22. Wang S, Qiu L, Lang JH, Shen K, Yang JX, Huang HF, et al. Clinical analysis of ovarian epithelial carcinoma with coexisting pelvic endometriosis. *Am J Obstet Gynecol.* 2013;208(5):413.e1–5.
 23. Wei JJ, William J, Bulun S. Endometriosis and ovarian cancer: a review of clinical, pathologic, and molecular aspects. *Int J Gynecol Pathol.* 2011;30(6):553–68.
 24. Wilbur MA, Shih IM, Segars JH, Fader AN. Cancer implications for patients with endometriosis. *Semin Reprod Med.* 2017;35(1):110–6.
 25. Wiegand KC, Shah SP, Al-Agha OM, Zhao Y, Tse K, Zeng T, et al. ARID1A mutations in endometriosis-associated ovarian carcinomas. *N Engl J Med.* 2010;363(16):1532–43.
 26. Worley MJ, Welch WR, Berkowitz RS, Ng SW. Endometriosis-associated ovarian cancer: a review of pathogenesis. *Int J Mol Sci.* 2013;14(3):5367–79.
 27. Zondervan KT, Becker CM, Koga K, Missmer SA, Taylor RN, Vigano P. Endometriosis. *Nat Rev Dis Primers.* 2018;4(1):9.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

