General Section

Frequency of endometriosis and adenomyosis in patients with leiomyomas, gynecologic premalignant, and malignant neoplasias

R.S. Nomelini[1], F.A. Ferreira[1], R.C. Borges[1], S.J. Adad[2], E.F.C. Murta[1]

[1]Oncological Research Institute (IPON), Discipline of Gynecology and Obstetrics,
[2]Discipline of Special Pathology; Federal University of the Triângulo Mineiro, Uberaba, MG (Brazil)

Summary

Objective: This study investigated the association between gynecological neoplasms, endometriosis, and adenomyosis in women who underwent surgical treatment for gynecological cancer and uterine leiomyoma during reproductive years or after menopause. *Materials and Methods:* Information was collected from patient records from the Hospital's database from 1985 to 2007. The study included 502 women, of which 375 were premenopausal and 132 were postmenopausal. *Results:* A significant association was observed between the occurrence of adenomyosis in cancer in women with four or more pregnancies, and in women aged over 40 years ($p < 0.0001$). The frequency of adenomyosis was significantly higher than the frequency of endometriosis for cancer in two sites ($p = 0.0419$) or for leiomyomas ($p < 0.0001$). *Conclusion:* Therefore adenomyosis is more frequently found than endometriosis in women with leiomyomas or cancer in two sites in premenopausal women, and clinicians need to be aware of patients with adenomyosis and the risk of cancer.

Key words: Adenomyosis; Endometriosis; Cancer association; Leiomyoma.

Introduction

Malignant transformation of endometriosis was first described in 1925 by Sampson and supported by additional evidence in further studies [1-10]. This transformation is described in various organs but occurs mainly in the ovaries [11].

Women with endometriosis have an increased risk for some types of malignancies and up to one percent develop cancer associated with these lesions [5]. Those who are diagnosed early in life and whose affected site is the ovary, have the highest risk for cancer in that organ [4].

Ovarian neoplasms, mainly endometrioid adenocarcinomas and clear cell carcinomas, are associated with the presence of ectopic endometrial tissue [1, 2]. The association between endometriosis and ovarian adenocarcinomas was supported by a study using a combination of clinical, pathological, and molecular data [3]. Data from molecular genetics and genetic aberrations, such as mutation type or loss of heterozygosity mutation, also provide evidence that endometriosis is a precursor of ovarian cancer [6, 8-10].

Ectopic endometrium undergoes malignant transformation, but how often this transformation occurs remains unknown [7]. Nonetheless, the causal relationship between endometriosis and specific types of ovarian cancer should be recognized [12]. Women with cancers associated with endometriosis probably represent a different group of patients than those who have traditional ovarian cancer and may require different therapeutic treatments [5, 13]. The elucidation of the true relationship between endometriosis and the development of malignancies is likely to have an impact on treatment options and follow-up of these patients [4].

The relationship between endometriosis and cancer is well-described in literature. The associative frequency of these conditions is an important issue requiring further information regarding this association and its impact in addressing cases with a known association. Therefore, the objective of this study was to verify the presence of endometriosis and adenomyosis in patients undergoing surgery for gynecological cancer and uterine leiomyoma.

Materials and Methods

Patient selection

A retrospective study from 1985 to 2007 was carried out in the Oncological Research Institute (IPON), Discipline of Gynecology and Obstetrics of the University of Triângulo Mineiro. Data were collected from medical records of patients who underwent surgical treatment for gynecological cancer or uterine leiomyoma in the University Hospital of the Federal University of Triângulo Mineiro.

The study included 502 women (375 premenopausal and 132 postmenopausal). Surgical procedures were performed and the presence or absence of adenomyosis and/or endometriosis-associated malignancy was evaluated.

Diagnosis was leiomyoma and gynecologic cancer for 37 and 85 surgeries, respectively. Wertheim-Meigs surgery was used for cervical cancer. Total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, multiple biopsies, and pelvic lymphadenectomy were performed for endometrial or ovarian cancer. Patients with cervical intraepithelial neoplasia (CIN) 3 were submitted to a hysterectomy when there was no technical condition for conization. All surgeries were performed by a gynecologist or gynecologic oncologist with experience,

Revised manuscript accepted for publication February 17, 2012

including one or two residents in gynecology at the Discipline of Gynecology and Obstetrics. Age, parity, menarche, and menopausal age, use of oral contraceptives at diagnosis, family history of cancer, surgical procedure, staging of endometriosis, cancer staging, and main symptoms were recorded.

Statistical analysis and ethical approval

Data were analyzed using GraphPad Instat software Chi-square (χ^2) and Fisher tests were used for statistical analysis with the significance level set at a p less than 0.05.

The Research Ethics Committee of Federal University of Triângulo Mineiro approved this research.

Results

The mean age of premenopausal patients was 39.06 years (range 13 to 55). The mean age of menopausal women was 58.67 years (range 42 to 79). The main symptoms presented by premenopausal patients were: increased abdominal size (9.33%), abdominal pain (30.4%), metrorrhagia (37.07%), menstrual irregularity (7.2%), no symptoms (51%), and other symptoms (2.4%). The main symptoms presented by postmenopausal patients were: increased abdominal size (18.18%), abdominal pain (28.79%), postmenopausal bleeding (29.55%), and no symptoms (23.48%).

Data analysis: premenopausal patients

Adenomyosis was found in 79 (21.07%) of 375 patients. The age with the highest association of cancer with adenomyosis was 41 - 50 years with 79.75% of cases (63 / 79). Patients under 30 years of age showed no association. A significant association was observed between the occurrence of adenomyosis in cancer in women with four or more pregnancies, and in women aged over 40 years ($p <$ 0.0001). The association of adenomyosis and cancer was more frequent among women not using oral contraceptives (86.08% of cases; 68 / 79) and among those with a negative family history (83.54% of cases; 66 / 79 (Table 1).

Endometriosis was seen in 26 (6.93%) of 375 women, and in 12 / 26 (46.15%) of women aged 41-50 years. The association in nulliparous women was 30.77% (8/26). Patients with one to three pregnancies were 50% of cases (13 / 26). Endometriosis associated with cancer predominated in patients with no family history of cancer (65.38% of cases; 17 / 26) and who were not using oral contraceptives at the time of surgery (80.77% of cases; 21 / 26) (Table 2). Endometriosis stagings (American Society for Reproductive Medicine, 1996) were Stage I: 42.31%; Stage II: 26.92%; Stage III: 11.54%; Stage IV: 3.85%; other sites: 15.38%.

Adenomyosis was associated with 17.14% of uterine cervical cancers and 2.5% of ovarian cancers. No endometrial cancers were associated with adenomyosis and endometriosis. Endometriosis was associated with 4.17% of ovarian cancer cases, and 5.71% of all cervical cancer cases. In patients with leiomyoma, adenomyosis was present in 32.62%, and endometriosis in 9.09%. For cancer at two sites, adenomyosis was found in 30% of adenomyosis cases and 6.67% of endometriosis cases.

Table 1. — *Frequency of adenomyosis related to age, parity, oral contraceptives use, family history, and menarche age in premenopausal patients.*

	Adenomyosis (+)	Adenomyosis (–)	n	%	*p*
Age					
< 40	10	163	173	5.78	
≥ 40	69	133	202	34.16	< 0.0001
Parity					
G0	7	51	58	12.07	
G1-3	31	174	205	15.12	
G4+	41	71	112	36.61	< 0.0001
Oral contraceptives					
Yes	11	52	63	17.46	0.5016
No	68	244	312	21.79	
Family history					
Yes	13	49	62	20.97	1.0
No	66	247	313	21.09	
Menarche					
< 12	11	64	75	14.67	
12-13	36	143	179	20.11	
> 13	32	89	121	26.45	0.1319 / 0.0444*

*χ^2 for trend.

Table 2. — *Frequency of endometriosis related to age, parity, oral contraceptives use, cancer family history, and menarche age in premenopausal women.*

	Endometriosis (+)	Endometriosis (–)	n	%	*p*
Age					
< 40	12	161	173	6.94	
≥ 40	14	188	202	6.93	
Parity					
G0	8	50	58	13.79	
G1-3	13	192	205	6.34	0.0672 / 0.0371*
G4+	5	107	112	4.46	
Oral contraceptives					
Yes	5	58	63	8.62	0.7850
No	21	291	312	6.73	
Family history					
Yes	9	56	65	13.85	0.0275
No	17	293	310	5.48	
Menarche					
< 12	3	72	75	4	
12-13	13	166	179	7.26	0.5060
> 13	10	111	121	8.26	

*χ^2 for trend.

Table 3. — *Adenomyosis and endometriosis by site of gynecologic premalignant and malignant neoplasia in premenopausal patients.*

Site	Adeno-myosis	Total	%	Endo-metriosis	Total	%	*p*
Cervix	6	35	17.14	2	35	5.71	0.2595
Ovary	3	120	2.5	5	120	4.17	0.72
Endometrium	0	3	0	0	3	0	–
Two sites	9	30	30	2	30	6.67	0.0419
Leiomyomas	61	187	32.62	17	187	9.09	< 0.0001
Total	79	375		26	375		

The frequency of adenomyosis was significantly higher (p = 0.0419) than the frequency of endometriosis ($p <$ 0.0001) for related cancers in two sites and for leiomyomas (Table 3).

The histological subtypes and staging found in menacme were: 28.58% CIN 3 (Stage 0); 35.72% uterine cervical squamous cell carcinoma (Stages IA2, IB1, and IB2); 7.14% uterine cervical villoglandular adenocarcinoma (Stage IB1); 7.14% uterine cervical endometrioid adenocarcinoma (Stage IB2); 7.14% borderline ovarian serous cystadenoma (Stage IA); 7.14% borderline ovarian Brenner tumor (Stage IC); and 7.14% ovarian granulosa cell tumor (Stage IA).

Data analysis of menopausal women

Adenomyosis was present in 15 of 132 (11.36%) of postmenopausal women. An association between adenomyosis and cancer was found in 66.66% in the age group 41 - 60 years (10/15). Women with four or more pregnancies were 9 of 15 cases (60%), while only one was nulliparous (6.67%). No patients with an association had used oral contraceptives and 86.67% (13 / 15) had no family history of cancer (Table 4). Only two cases of endometriosis were seen among 132 patients (1.52%) (Table 5). The stagings of endometriosis (American Society for Reproductive Medicine, 1996) in postmenopausal women were Stage II: 50%; other sites: 50%.

Uterine cervical cancer and ovarian cancers were associated with adenomyosis in 22.22% and 5% of cases, and with endometriosis in 18% and 60% cases, respectively. No endometrial cancer was associated with adenomyosis and endometriosis. Endometriosis was associated with only one (20%) case of leiomyoma and one (21%) case of cancer in two sites (Table 6). Leiomyomas and cancer in two sites were associated with adenomyosis in 30% and 9.52% cases, respectively, and associated with endometriosis in 5% and 4.76% cases, respectively.

Histological subtypes and staging found in menopausal women were: 54.55% CIN 3 (Stage 0); 36.36% uterine cervical adenocarcinoma (Stages IB2 and IIA); and 9.09% ovarian serous cystadenocarcinoma (Stage IIC).

Discussion

Adenomyosis is a common benign disease of the uterus that is seen in 15% - 30% of histopathological evaluations of hysterectomy [14]. In this study, the frequency of adenomyosis in the patient group was 21.07% for patients of reproductive age and 11.36% for menopausal patients. The exact incidence of endometriosis was unknown, because diagnosis depended on surgical procedure. Approximately 3% to 10% of women of reproductive age and 2% to 5% of postmenopausal women have endometriosis [15, 16]. In this present study, the frequency of endometriosis in patients with gynecological cancer was 6.93% for patients of reproductive age and 1.52% of menopausal patients.

Age, multiparity, high levels of follicle-stimulating hormone (FSH), prolactin, and smoking are risk factors for adenomyosis [17]. This study demonstrated a significant association between the occurrence of adenomyosis in cancer in women with one to three pregnancies, and in women over 40 years of age ($p < 0.0001$) in the premenopausal group. Endometriotic lesions can predispose to clear cell and endometrioid ovarian cancers; advancing age and the size of endometriomas were independent pre-

Table 4. — *Frequency of adenomyosis related to age, parity, oral contraceptives use, cancer family history, and menarche age in menopausal patients.*

	Adenomyosis (+)	Adenomyosis (–)	n	%	*p*
Age					
< 60	10	70	80	12.5	0.7808
≥ 60	5	47	52	9.61	
Parity					
G0	1	16	17	5.88	
G1-3	5	50	55	9.09	0.4546
G4+	9	51	60	15	
Oral contraceptives					
Yes	0	8	8	0	0.5960
No	15	109	124	12.10	
Family history					
Yes	2	30	32	6.25	0.5217
No	13	87	100	13	
Menarche					
< 12	3	22	25	12	
12-13	7	51	58	12.07	0.9493
> 13	5	44	49	10.20	

Table 5. — *Frequency of endometriosis related to age, parity, oral contraceptives, cancer family history, and menarche age in menopause patients.*

	Endometriosis (+)	Endometriosis (–)	n	%	*p*
Age					
< 60	1	79	80	1.25	0.3441
≥ 60	1	51	52	1.92	
Parity					
G0	0	17	17	0	
G1-3	1	54	55	1.82	0.8587
G4+	1	59	60	1.67	
Oral contraceptives					
Yes	0	8	8	0	1
No	2	122	124	1.61	
Family history					
Yes	0	32	32	0	1
No	2	98	100	2	
Menarche					
< 12	0	25	25	0	0.7818
12-13	1	57	58	1.72	
> 13	1	48	49	2.04	

Table 6. — *Adenomyosis and endometriosis by site of gynecologic premalignant and malignant neoplasia in menopausal women.*

Site	Adeno-myosis	Total	%	Endo-metriosis	Total	%	*p*
Cervix	4	18	22.22	0	18	0	0.1039
Ovary	3	60	5	0	60	0	0.2437
Endometrial	0	13	0	0	13	0	–
Two sites	2	21	9.52	1	21	4.76	1.0
Leiomyomas	6	20	30	1	20	5	0.0915
Total	15	132	–	2	132	–	–

dictors of development of ovarian cancer among women with ovarian endometrioma [18].

Endometriosis is a common disease that affects quality of life and fertility, and its prevalence is increasing [19]. Although considered a benign disorder, it has some malignant characteristics in terms of progression such as invasion and metastasis, which often affect other organs. Immune response abnormalities and inflammation have been shown in women with endometriosis, predisposing them to cancer and infections [20]. Cancer may be promoted by growth factors, cytokines, and inflammatory mediators that reach the ovarian epithelium during retrograde menstruation. Endocrine-disrupting environmental toxins that modify the inflammatory process can be associated with endometriosis [21].

Endometriosis is a progressive disease that is often debilitating because it causes chronic pelvic pain and infertility [22, 23]. The frequency of endometriosis associated with a neoplasm was 6.93% in premenopausal patients treated by surgery and 1.52% in patients undergoing surgery at menopause. Varma *et al*. (2004) found this association in 10% - 15% in women of reproductive age. The present study found an association of endometriosis with ovarian cancer in 4.17% cases [23].

The frequency of endometriosis in endometrioid and clear cell types has been demonstrated to be higher than in the general population [16, 24]. Genetic alterations in ovarian cancers and adjacent endometriosis, such as p53 and bcl gene mutations, show a possible malignant genetic transition. Endometriosis is associated with chronic inflammation and cytokines can induce or repress their own synthesis and cause unregulated mitotic division, growth, differentiation, migration, or apoptosis similar to malignant mechanisms [16]. Gemmil *et al*. demonstrated a higher prevalence of recurrent upper respiratory or vaginal infections, melanoma, and ovarian cancer in patients with endometriosis than in the general population [25].

Adenomyosis is characterized by the presence of an ectopic endometrium with or without hyperplasia of the surrounding myometrium. Adenomyosis and leiomyomas can usually coexist [17, 26] and patients with these conditions may have more chronic pelvic pain [27]. The relationship between endometriosis and cancer is shown in several studies, but only two case studies have reported adenocarcinomas developing within adenomyosis [28, 29].

Adenomyosis associated with neoplasia was significantly higher than endometriosis in premenopausal patients with two-site tumors ($p = 0.0419$) and leiomyomas ($p < 0.0001$). Ovarian cancers were more frequently associated with endometriosis than with adenomyosis, but this was not significant. This fact could be explained by the small number of cases in this study or because they included benign neoplasias.

The role of genetic alterations has been discussed in relation to putative oncogenes and tumor suppressor genes that may be involved in endometriosis [30]. Mucin 1 (MUC1) glycoprotein is present in eutopic human endometrial glands, and in ectopic lesions of ovarian endometriosis, and is overexpressed in endometrioid and clear cell ovarian tumors. Changes in MUC1 expression in endometriosis could promote adaptive anti-MUC1 immunity that might play a role in malignant progression [31]. Pathological changes can reflect genetic alterations; in clear cell carcinoma, K-ras mutations were associated with malignant transformation of clear cell carcinoma [32]. Bischoff *et al*. demonstrated that perturbations of chromosome 17 in general and the p53 locus in particular, occur frequently in severe/late stage endometriosis [33]. Some genetic alterations that induce p53 mutations in endometriosis can affect malignant transformation of endometriosis in ovarian clear cell carcinoma [34]. Amemiya *et al*. demonstrated that K-ras mutations and microsatellite instability are associated with malignant transformation from endometriosis to ovarian endometrioid carcinoma [35]. Adenomyosis might be considered a special form of endometriosis. However, uterine adenomyosis rarely responds to hormonal therapy and its cure usually requires hysterectomy. Oehler *et al*. suggested that mutation-related silencing of estrogen responsiveness might render endometriotic cells resistant to hypoestrogenic conditions, accounting for failure of estrogen-ablative therapy in adenomyosis [36]. In contrast, Wang *et al*. found no positive recurrent gene copy number alterations in 25 cases of pathologically-proven adenomyosis utilizing comparative genomic hybridization; they concluded that genetic changes might be extremely rare in adenomyosis, or comparative genomic hybridization was not sensitive enough to detect candidate genes [37].

The present study detected a significantly higher frequency of adenomyosis, compared to endometriosis in cancer in two sites, which has not yet been reported by other studies. Further research is needed to better understand the relationship of genetic alterations in adenomyosis predisposing to cancer, which is already well-established in cases of endometriosis.

Conclusion

The authors demonstrated that adenomyosis is more frequently found than endometriosis in women with leiomyomas or cancer in two sites in premenopausal women. This emphasizes the need for clinicians to be aware of patients with adenomyosis and the risk of developing cancer, and new studies on neoplasms and adenomyosis are needed to elucidate this relationship.

Acknowledgments

The authors wish to acknowledge funding received from the CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) and the FAPEMIG (Fundação de Amparo à Pesquisa do Estado de Minas Gerais).

References

[1] Heaps J., Nieberg R., Berek J.: "Malignant neoplasms arising in endometriosis". *Obstet. Gynecol.,* 1990, *75,* 1023.

[2] 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*, 298.

[3] Brinton L.A., Sakoda L.C., Sherman M.E., Frederiksen K., Kjaer S.K., Graubard B.I. *et al*.: "Relationship of benign gynecologic diseases to subsequent risk of ovarian and uterine tumors". *Cancer Epidemiol. Biomarkers Prev.,* 2005, *14,* 2929.
[4] Melin A., Sparén P., Persson I., Bergqvist A.: "Endometriosis and the risk of cancer with special emphasis on ovarian cancer". *Hum. Reprod.,* 2006, *21,* 1237.
[5] Benoit L., Arnould L., Cheynel N., Diane B., Causeret S., Machado A. *et al*.: "Malignant extraovarian endometriosis: a review". *Eur. J. Surg. Oncol.,* 2006, *32,* 6.
[6] Prowse A.H., Manek S., Varma R., Liu J., Godwin A.K., Maher E.R. *et al*.: "Molecular genetic evidence that endometriosis is a precursor of ovarian cancer". *Int. J. Cancer*, 2006, *119,* 556.
[7] Somigliana E., Viganò 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*, 331.
[8] Ali-Fehmi R., Khalifeh I., Bandyopadhyay S., Lawrence W.D., Silva E., Liao D. *et al*.: "Patterns of loss of heterozygosity at 10q23.3 and microsatellite instability in endometriosis, atypical endometriosis, and ovarian carcinoma arising in association with endometriosis". *Int. J. Gynecol. Pathol.,* 2006, *25,* 223.
[9] Christie M., Oehler M.: "Molecular pathology of epithelial ovarian cancer". *J. Br. Menopause Soc.,* 2006, *12,* 57.
[10] Brinton L.A., Lamb E.J., Moghissi K.S., Scoccia B., Althuis M.D., Mabie J.E., Westhoff C.L.: "Ovarian cancer risk associated with varying causes of infertility". *Fertil. Steril.,* 2004, *82*, 405.
[11] Valenzuela P., Ramos P., Redondo S., Cabrera Y., Alvarez I., Ruiz A.: "Endometrioid carcinoma of the ovary and endometriosis". *Eur. J. Obstet. Gynecol. Reprod. Biol.,* 2007, *134,* 83.
[12] Viganò P., Somigliana E., Parazzini F., Vercellini P.: "Bias versus causality: interpreting recent evidence of association between endometriosis and ovarian cancer". *Fertil. Steril.,* 2007, *88,* 588.
[13] Komiyama S., Aoki D., Katsuki Y., Nozawa S.: "Proliferative activity of early ovarian clear cell adenocarcinoma depends on association with endometriosis". *Eur. J. Obstet. Gynecol. Reprod. Biol.,* 2006, *127,* 130.
[14] Seidman J., Kjerulff K.: "Pathologic findings from the Maryland Women's Health Study: practice patterns in the diagnosis of adenomyosis". *Int. J. Gynecol. Pathol., 1996, 15,* 217.
[15] Van Gorp T., Amant F., Vergote N.: "Endometriosis and the development of malignant tumors of the pelvis. A review of literature". *Best Pract. Res. Clin. Obstet. Gynaecol.*, 2004, *18*, 349.
[16] Nezhat F., Datta M.S., Hanson V., Pejovic T., Nezhat C., Nezhat C.: "The relationship of endometriosis and ovarian malignancy: a review". *Fertil. Steril.,* 2008, *90*, 1559.
[17] Parazzini F., Vercellini P., Panazza S., Chatenoud L., Oldani S., Crosignani P.G.. "Risk factors for adenomyosis". *Hum. Reprod.,* 1997, *12*, 1275.
[18] Kobayashi H., Sumimoto K., Kitanaka T., Yamada Y., Sado T., Sakata M. *et al*.: "Ovarian endometrioma - risks factors of ovarian cancer development". *Eur. J. Obstet. Gynecol. Reprod. Biol.,* 2008, *138,* 187.
[19] Nezhat C., Nezhat F.: "A simplified method of laparoscopic presacral neurectomy for the treatment of central Pelvic pain due to endometriosis". *Brit. J. Obstet. Gynaecol.*, 1992, *99*, 659.
[20] Giudice L., Kao L.: "Endometriosis". *Lancet,* 2004, *364,* 1789.
[21] Bruner-Tran K.L., Yeaman G.R., Crispens M.A., Igarashi T.M., Osteen K.G.: "Dioxin may promote inflammation-related development of endometriosis". *Fertil. Steril.,* 2008, *89,* 1287.
[22] Ota H., Maki M., Shidara Y., Kodama H., Takahashi H., Hayakawa M. *et al*.: "Effects of danazol at the immunologic level in patients with adenomyosis with special reference to autoantibodies: A multi-center cooperative study". *Am. J. Obstet. Gynecol.,* 1992, *167*, 481.
[23] Varma R., Rollason T., Gupta J.K., Maher E.R.: "Endometriosis and the neoplastic process". *Reproduction,* 2004, *127,* 293.
[24] Nagle C.M., Olsen C.M., Webb P.M., Jordan S.J., Whiteman D.C., Green A.C. *et al*.: "Endometrioid and clear cell ovarian cancers: a comparative analysis of risk factors". *Eur. J. Cancer,* 2008, *44,* 2477.
[25] Gemmill J., Stratton P., Cleary S., Ballweg M.L., Sinaii N.: "Cancers, infections, and endocrine diseases in women with endometriosis". *Fertil. Steril.,* 2010, *94,* 1627.
[26] Vercellini P., Parazzini F., Oldani S., Panazza S., Bramante T., Crosignani P.G.: "Adenomyosis at hysterectomy: a study on frequency distribution and patient characteristics". *Hum. Reprod.,* 1995, *10,* 1160.
[27] Taran F.A., Weaver A.L., Coddington C.C., Stewart E.A.: "Characteristics indicating adenomyosis coexisting with leiomyomas: a case-control study". *Hum. Reprod.*, 2010, *25,* 1177.
[28] Koshiyama M., Suzuki A., Ozawa M., Fujita K., Sakakibara A., Kawamura M. *et al*.: "Adenocarcinoma arising from uterine adenomyosis: a report of four cases". *Int. J. Gynecol. Pathol.,* 2002, *21*, 239.
[29] Motohara K., Tashiro H., Ohtake H., Saito F., Ohba T., Katabuchi H.: "Endometrioid adenocarcinoma arising in adenomyosis: elucidation by periodic magnetic resonance imaging evaluations". *Int. J. Clin. Oncol.,* 2008, *13*, 266.
[30] Gogusev J., Bouquet de Jolinière J., Telvi L., Doussau M., Stojkoski A., Levardon M.: "Cellular and genetic constitution of human endometriosis tissues". *J. Soc. Gynecol. Investig.,* 2000, *7,* 79.
[31] Budiu R.A., Diaconu I., Chrissluis R., Dricu A., Edwards R.P., Vlad A.M.: "A conditional mouse model for human MUC1-positive endometriosis shows the presence of anti-MUC1 antibodies and Foxp3+ regulatory T cells". *Dis. Model Mech.,* 2009, *2,* 593.
[32] Sekizawa A., Amemiya S., Otsuka J., Saito H., Farina A., Okai T., Tachikawa T.: "Malignant transformation of endometriosis: application of laser microdissection for analysis of genetic alterations according to pathological changes". *Med. Electron Microsc.,* 2004, *37*, 97.
[33] Bischoff F., Heard M., Simpson J.: "Somatic DNA alterations in endometriosis: high frequency of chromosome 17 and p53 loss in late-stage endometriosis". *J. Reprod. Immunol.,* 2002, *55*, 49.
[34] Akahane T., Sekizawa A., Purwosunu Y., Nagatsuka M., Okai T.: "The role of p53 mutation in the carcinomas arising from endometriosis". *Int. J. Gynecol. Pathol.*, 2007, *26,* 345.
[35] Amemiya S., Sekizawa A., Otsuka J., Tachikawa T., Saito H., Okai T.: "Malignant transformation of endometriosis and genetic alterations of K-ras and microsatellite instability". *Int. J. Gynaecol. Obstet.,* 2004, *86*, 371.
[36] Oehler M.K., Greschik H., Fischer D.C., Tong X., Schuele R., Kieback D.G.: "Functional characterization of somatic point mutations of the human estrogen receptor alpha (hERalpha) in adenomyosis uteri". *Mol. Hum. Reprod.*, 2004, *10*, 853.
[37] Wang P.H., Shyong W.Y., Lin C.H., Chen Y.J., Li Y.F., Chao H.T., Yuan C.C.: "Analysis of genetic aberrations in uterine adenomyosis using comparative genomic hybridization". *Anal. Quant. Cytol. Histol.,* 2002, *24*, 1.

Address reprint requests to:
E.F.C. MURTA, M.D.
Oncological Research Institute (IPON)
Discipline of Gynecology and Obstetrics
UFTM, Av. Getúlio Guaritá, s/n, Bairro
Abadia, 38025-440 Uberaba-MG (Brazil)
e-mail: eddiemurta@mednet.com.br