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CASE REPORT

Endometrial Adenocarcinoma in a 27-Year-Old Woman

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Abstract

Background: Endometrial adenocarcinoma usually occurs after menopause, but in 2%–14% of cases, it occurs in young patients (less than 40 years of age) who are eager to preserve their fertility. Its treatment includes hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy, and, in some cases, radiation therapy.

Aim: To describe a case of endometrial adenocarcinoma occurring in a young woman and to undertake a literature review of risk factors and therapeutic options proposed for young women wishing to preserve their fertility.

Case: We report a case of endometrial cancer in a 27-year-old woman treated for resistant menorrhagia and cared for in our department as well as in the Salah Azaiez Institute.

Conclusion: Endometrial adenocarcinoma rarely occurs in young women. In such cases, other therapeutic options can be proposed: progesterone therapy and LH-RH (Luteinzing-Hormone-Releasing-Hormone) agonists therapy in order to preserve fertility in younger patients.

Keywords: conservative treatment, endometrial adenocarcinoma, fertility, progestins, young women

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Introduction

Endometrial adenocarcinoma usually occurs after menopause. However, in 2%–14% of cases, it occurs in young women (less than 40), most of whom wish to preserve their fertility.[1–4] In a literature review, Vaccarello et al[5] observed that the majority of cases of endometrial adenocarcinoma in young women were of endometrioid type, well differentiated (Grade 1) and at early stages with a superficial invasion (Stage I). Therefore, these carcinomas had a good prognosis (survival rate at five years: >93%).

The classic treatment consists of a total hysterectomy and/or a salpingo-oophorectomy with or without a pelvic or aortic lymphadenectomy. However, there is a therapeutic alternative for young women wishing to become pregnant in the future. In fact, a certain number of publications report attempts to find a conservative treatment for young women carrying endometrial adenocarcinoma at Stage IA, Grade 1.[3,6–14] These kinds of therapies are not standard management and should not be recommended routinely. Patients must be informed of the oncological risks (failure, progression of the disease, ovarian metastasis, etc.).[15]

We report the case of a 27-year-old patient with an endometrial cancer diagnosed at Stage Ic grade 1 according to the FIGO (International Federation of Gynecology and Obstetrics) 2000 classification of endometrial cancer.[16]

Observation

A 27-year-old patient who was nulliparous and overweight (body mass index = 28) was referred to us by her regular doctor for menorrhagia that was resistant to progestogens. A verbal examination revealed that the patient required blood transfusion for treating her menorrhagia, which had continued for a period of about five years. The physical examination revealed little. A trans-vaginal ultrasound led us to suspect an endometrial hypertrophy and the presence of an endometrial polyp. A hysteroscopy was scheduled but we lost trace of the patient. She presented five months later for metrorrhagia associated with fetid hydrorrhea. A hysteroscopy revealed an area of endometrial polyposis reaching the uterine isthmus. A haemostatic uterine curettage was performed successfully. The histological examination confirmed the presence of an endometrial adenocarcinoma of endometrioid type that was well differentiated and Grade 1. During the extent's assessment, an MRI scan revealed a focal myometrial invasion of more than 50% without extension to the serous membrane and infracentimetric bilateral hypogastric and inguinal lymph nodes. The other abdominal organs were lesion-free.

The patient underwent a total hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy. The pathological exam showed an adenocarcinoma of endometrioid type (Stage IC and Grade 1 according to the FIGO 2000 classification of endometrial cancer) that had invaded the whole uterine cavity, and a focal fundic myometrial infiltration reaching the outer third of the wall without reaching the serosa; the cervical canal, lymph nodes, fallopian tubes and ovaries were lesion-free. The surgery was followed by vaginal curietherapy and external radiotherapy. The follow-up, three years after the end of radiotherapy, was uneventful.

Discussion

Most endometrial adenocarcinomas occur after menopause. However, 20%–25% of them are diagnosed before the menopause and 2%–14% occur among younger women (less than 40).[1–4] The most reported risk factors of endometrial cancer are anovular cycles associated with polycystic ovarian syndrome (PCD), hypertension, diabetes, obesity, the sole use of estrogens and the use of tamoxifen.[17] Several authors[4,18–23] have tried to individualize the risk factors of endometrial adenocarcinoma related specifically to women under 40. Younger patients with endometrial carcinoma tend to have a history of estrogen use or hormone-related disorders such ovarian dysfunction, chronic anovulation, infertility, obesity and PCO (odds ratio: 3.1; 95% confidence interval: 1.1–7.3).[23] Our patient had problems with excess weight and infertility. An association between PCO and endometrial cancer in younger women is consistent with the hypothesis that the stimulatory effect of estrogen on the endometrium, if unopposed by progesterone, can induce endometrial carcinogenesis. PCO is also associated with hyperinsulinaemia and insulin resistance (insulin and IGF-I stimulate endometrial carcinoma cells *in vitro*), and with hyperandrogenism by enhancing aromatase activity. These endocrine factors may underpin the association

between PCO and endometrial carcinoma.[24] Endometrial carcinomas associated with PCO do not seem to have a better prognosis than those with normal ovaries.[23,24]

It is estimated that 2%–5% of endometrial cancer may be attributed to an inherited predisposition to cancer. Lynch syndrome (hereditary nonpolyposis colorectal cancer syndrome) accounts for the majority of inherited endometrial cancers and for 6% of all endometrial cancers, especially in young patients.[25–27] Germline mutations in one of the DNA mismatch repair genes *hMLH1*, *hMLH2*, *hMSH6* or *hPMS2* have been identified in patients with Lynch syndrome. These mutations are inherited in an autosomal dominant fashion. Individuals with Lynch syndrome inherit one nonfunctional allele; when subsequent loss of the corresponding allele occurs, genetic DNA repairs are defective in target tissues such as the endometrium.[3,25]

The most important prognosis factors of endometrial adenocarcinomas are the histological grade, the cancer stage and the myometrial invasion. This gives rise to the question whether there are specific prognosis factors in young women with endometrial cancer. Several studies[19,20,21,28] have not observed a difference in the frequency of Stage I carcinomas (approximately 70% in both groups). According to the studies of Evans-Metcalf et al[19] and Fahri et al[22] it seems that the frequency of Grade 1 tumors was higher in young women, reaching 90%. Another study[21] reports a myometrial invasion rate that was more than 50% lower in young women (24% vs. 49% in older women). Two studies[19,28] have shown that the association of endometrial adenocarcinoma with ovarian one seems to be more frequent in younger women than older ones (29% vs. 4.6%).

Surgery is the classic treatment for endometrial cancer. It consists of total hysterectomy and bilateral salpingo-oophorectomy, with a pelvic and aortic lymphadenectomy if required. Curietherapy and radiotherapy are indicated when there is a high risk of recurrence. The young women affected by endometrial cancer are often nulliparas with a past history of infertility and thus are very anxious to preserve their fertility. This constitutes a dilemma for the patients as well as their physicians.

Fortunately, 70% of the endometrial adenocarcinomas in young women are at Stage I and 90% of them are Grade 1 carcinomas, which have a good prognosis and offer other therapeutic possibilities instead of the standard radical treatment.

Some authors[29,30] have proposed repeated endometrial curettages or hysteroscopic resection of cancerized polyps; however, most conservative treatments are inspired by the hormone-dependence of endometrial adenocarcinomas. In fact, a large proportion of endometrial cancers express estrogen and progestogen receptors.[31] Both estrogen and progesterone exert their effects through intra-nuclear receptors, estrogen receptors (ER; α and β) and progesterone receptors (PR; A and B).[15] The expression of ER and PR is generally considered to be coordinated because transcription of the PR gene is induced by estrogen and inhibited by progesterone in the great majority of estrogen responsive cells.[15] During the secretory phase when circulating concentrations of progesterone are maximal, activation of PR results in reduced proliferative and increased cellular differentiation.[32] It has been demonstrated that in endometrial cancer from clinical Stages III–IV, ER and PR concentrations are lower than those in Stage I endometrial cancer. Also, in Stage I samples, higher concentrations of receptors were measured in the well and moderately differentiated samples.[32] The detection of PR in endometrial adenocarcinomas is associated with a better disease-free survival, while the loss of expression of PR isoforms may result in more aggressive biological characteristics in human endometrioid endometrial carcinomas that can play an important role in the prognosis and/or recurrence in these patients.[15] Endometrial carcinomas, especially of the well-differentiated endometrioid type, often express PR and their growth is suppressed by progestins. In general, the effect of progestins is considered to be mediated through PR, because the response rate to progestins in PR-positive carcinoma was higher (70%) compared with PR-negative tumors (16%).[33,34] It has recently been shown that they express Gn-RH (Gonadotropin-Releasing Hormone) receptors,[35] which implies that progestins and Gn-RH agonists are the most useful medicines in the framework of conservative treatment of endometrial cancer (Stage I, Grade 1).

The progestogens have been used for a long time for palliative treatment in advanced endometrial cancers, with a response rate ranging from 20% to 40% (this limited response likely to be related to a lack of receptors in the tumor cells of advanced stage

cancers).[36] Their first use in the context of conservative treatment of endometrial adenocarcinoma in young women dates back to 1968 in a study by Kempson and Pokorny.[37] Since then, several short series (with an average follow-up of 32 months) have shown high response rates with the possibility of future full-term pregnancies.[1,6–8,22,38,39] The response rate varies from 57 to 75% and the recurrence rate ranges from 11% to 50%.[1] These rates seem to be quite encouraging. However, we should not ignore the side effects of progestogens given at high doses, notably embolism associated with deep-vein thrombosis (5%–10%),[40,41] disturbance of the lipid metabolism, the risk of atherogenesis, reduced sexual drive (libido) and mood disorders.

The literature analysis shows no established consensus regarding:

- the choice of the progestogen to use, even though medroxyprogesterone acetate and megestrol acetate seem to be the most used;
- the dose of progestogen to prescribe, even though most studies report a dose of 600 mg of medroxyprogesterone acetate per day, taken in 200 mg amounts three times a day;[42]
- the duration of the treatment, which varies according to the authors from 3 to 9 months.[6,7] A duration of six months seems to be an acceptable compromise.[2]

The Gn-RH agonists have been used principally in the management of metastatic and recurrent endometrial cancers after unsuccessful surgery and/or radiotherapy. Remission rates up to 57% have been reported.[31,36,43] As far as the patients younger than 40 are concerned, only nine cases have been reported.[1,44] These nine patients have been treated for a period of 3 to 6 months, culminating in normal endometrial biopsies. Five patients became pregnant, and four carried their babies to term. The principal side effect of the Gn-RH agonist is bone demineralization, especially when the treatment exceeds 3 to 4 months.[45] Other side-effects of Gn-RH agonists such as vaginal dryness, hot flushes, reduced sexual interest, insomnia, headache, depression, nausea and vomiting are intolerable in about 10% of patients.[1] Add-back therapy with tibolone has been proposed in order to limit this demineralization. However, this approach should be carried out carefully because of the absence of data concerning the effects of tibolone on neoplastic cells, even if it is admitted that it does not result in endometrial proliferation.[46,47] The results obtained with Gn-RH agonists seem encouraging, yet literature on the subject remains scarce.

In 2002, Montz et al[9] have published a series about 12 women with an endometrial cancer (Stage I, Grade 1) treated with a progestogen intra-uterine device for one year with normalization of the endometrium in six of them after a period of six months. As this is a series of insufficient size, we cannot draw any conclusions, even though the results seem to be convincing. More recently, other cases have been reported[48–50] with results that are somewhat convincing.

Aromatase inhibitors such as anastrozole (Arimidex™, manufactured by Astra Zeneca) are able to effectively stop the peripheral conversion of androgens to estrogens. Such a conversion is the major source of estrogens in obese patients with endometrial cancer. Anastrozole seems to be able to reduce aromatase activity by 96%, thus dropping estradiol and estrone levels by 80%. To our knowledge, no study dealing with the use of only aromatase inhibitors in the early stage of endometrial adenocarcinoma has been published to date.[51] However, Burnett et al[52] reported the successful use of a combination of Anastrozole (an aromatase inhibitor) and medroxyprogesterone acetate (an anti-estrogen) in the treatment of Stage IA Grade 1 endometrial carcinoma in two obese pre-menopausal women (19 and 39 years old). Such an association should reduce the duration of treatment, so women will be more able to conceive, particularly if they are approaching the upper ages of reproductive potential. Aromatase inhibitors have been also used in patients having an endometrial adenocarcinoma at an advanced stage.[1]

Despite the disappearance of endometrial lesions in 57% to 75% of the cases after conservative treatment, the recurrence rate after stopping the treatment is about 40% for a follow-up ranging between 7 and 22 months[42] and about 67% after a follow-up of 30 months.[53] This relatively high rate can be explained by an initial mis-diagnosis of the cancer stage, a poor diagnostic sensitivity during the follow-up or by progressive resistance of the tumor to the treatment,[2] or else by the reappearance of the same factors that induced endometrial cancer in the first place upon discontinuation of progestogen therapy, e.g. a defect

in mismatch repair genes or other tumor suppressor genes.[54]

According to the international literature, it appears that the most important factor for conservative treatment is selecting the "ideal patient".[55] That is:

- a well-differentiated endometrial carcinoma that does not deeply invade the myometrium,
- absence of suspicious pelvic or pre-aortic nodes.
- absence of synchronous ovarian tumors,
- no contraindications for medical treatment,
- the patient understands and accepts that this is not a standard treatment,
- the patient should show her desire to complete the follow-up protocol.

Optimized evaluation of the FIGO stage in these young patients, whom we do not wish to operate on, uses a combination of some or all of hysteroscopy, curettage, a pelvic trans-vaginal ultrasound scan, MRI scanning and serum CA125 measurements (extra-uterine invasion is indicated if the CA125 concentration is over 35 UI/mL) even though the latter is not specific enough, as it can also be caused by endometriosis, fibroids, liver disease etc.[2,56–59] Preoperative assessment of the histological grade, using endometrial biopsy or curettage, has only a moderate ability to predict final pathology. Tumor grade at diagnosis matches the tumor grade determined after hysteroscopy in 58% of patients diagnosed via endometrial biopsy (Pipelle) and 77% of the patients diagnosed via dilatation and curettage (D & C).[60] Hysteroscopy is thus essential; it allows the lesion and biopsy to be seen directly. However, the risk of spreading cancer cells is not theoretically zero.[61] The depth of myometrial invasion can be estimated with surrogate staging techniques, such as those using ultrasound and MRI scanning. However, MRI has limited sensitivity to differentiate between stage IA and stage IB disease.[62] The accuracy of T2-weighted images in the determination of myometrial invasion varies between 68% and 82%.[1,35,63] The use of a dynamic study after administration of intravenous contrast increases the accuracy of myometrial invasion to 85%–91%.[2,35,63] An ultrasound is necessary to view the appearance, the thickness of the endometrium, the depth of endometrial invasion (with a sensitivity of 88%) and the ovaries.[64] Synchronous ovarian malignancies have been observed in up to 25% of the cases of endometrial cancer in younger women compared with only 2% in older patients. This high incidence of coexisting ovarian malignancies and the young age at diagnosis suggest an increased susceptibility of the reproductive organs to carcinogenic transformation.[12,60,65–69] A literature review indicates that surgical exploration by the means of laparoscopy could be helpful to verify the absence of suspicious macroscopic lesions on the ovaries; furthermore, a laparoscopy allows us to make a macroscopic assessment of the peritoneal cavity (peritoneal cytology) and to ensure temporary occlusion by laparoscopy of the tubes where they emerge, thus avoiding the risk of cancer cells migrating to the peritoneal cavity during hysteroscopy. Laparoscopy also makes a lymphadenectomy possible, thus increasing the accuracy of the assessment of the cancer's extent.[2,61,70] Cervical involvement can be assessed by the means of MRI scanning. Indeed, the accuracy, sensitivity and specificity of MRI scans were 80%, 33% and 100% (when compared to surgical staging of endometrial carcinoma). The use of a dynamic study after administration of intravenous contrast is helpful in the cases where the junctional zone is not clearly visualized.[71] Hysteroscopy seems to be more reliable than MRI and transvaginal ultrasound scan in excluding cervical canal involvement, while MRI is the most reliable technique for predicting cervical involvement (positive predictive value of hysteroscopy: 58% vs. 71% for MRI; specificity 88% vs. 95%).[72,73] According to Almog,[74,75] fractional D & C appears to be the best method to predict cervical involvement adequately.

The same diagnostic arsenal (i.e. hysteroscopy, endometrial curettage, endo-vaginal ultrasound scan, MRI) is used in post-therapeutic follow-up. However, there is no consensus regarding its modalities (periodicity: 12 to 24 weeks; hysteroscopy with guided biopsy or D & C).[55,61]

The principal aim of conservative treatment in endometrial adenocarcinoma is the preservation of the patients' fertility [Table 1]. Following regression of endometrial cancer as documented by D & C, women without a history of infertility can immediately try to conceive naturally;[2,76] the spontaneous pregnancy rate in such situation is about 25%.[2,61] After a period of three months with no pregnancy, a preliminary infertility appraisal is appropriate. In the case of a history of infertility, it seems logical to proceed to assisted

Table 1. Publications concerning medical treatment in endometrial adenocarcinoma and pregnancy outcome.

	No of patients	Initial response	Recurrence	Progestogens (type and dose)	Fertility treatment	Pregnancy	Births
Farhi et al[22]	6	6	–	MPA/Norethindrone	None	1	1
Muechler et al[79]	1	1	–	–	Cc/hMG	1	0
Paulson et al[80]	1	1	0	Megestrol acetate	IVF	2	1
Lai et al[81]	1	1	0	Megestrol acetate	None	1	1
Randall & Kurman[7]	12	9	0	Megestrol acetate: 40–160 mg/J	None	5	5
Kim et al[6]	21	13	3	Megestrol acetate: 160 mg/J and others	None	6	6
Sardi et al[12]	4	3	0	MPA: 200–500 mg/J	None	–	3
Kaku et al[10]	12	9	2	MPA: 200–800 mg/J	Cc	2	1
Imai et al[14]	14	8	3	MPA: 400–800 mg/J	None	–	3
Pinto et al[82]	1	1	0	Megestrol acetate	IVF	1	1
Wang et al[11]	9	8	4	Various products	None	3	3
Lowe et al[13]	2	2	0	Megestrol acetate: 80 mg/J	–	–	7
Gotlieb et al[8]	13	13	6	Megestrol acetate: 160 mg/J or MPA: 200–600 mg/J	–	–	9
Jadoul & Donnez[1]	7	7	–	Gn-RH agonists	6 IVF	–	4
Niwa et al[53]	12	12	8	Medroxyprogesterone acetate 400–600 mg/day	None	8	6
Ferrandina et al[83]	1	1	1	Dihydrogesterone 20 mg/day	None	1	1
Ota et al[4]	12	6	3	MPA 600 mg/day	None	4	2
Park et al[84]	1	1	0	Megestrol acetate 600 mg/day	IVF	1	1
Wu et al[85]	1	1	1	Megestrol acetate 160 mg/day	IVF	1	1
Yamazawa et al[34]	9	7	2	MPA 400 mg/day	3 IVF	4	3
Total	**130**		**–**	**–**	**–**	**–**	**58**

Abbreviations: MPA, medroxyprogesterone acetate; Cc, Clomiphene citrate; hMG, human chorionic gonadotropins; IVF, *in vitro* fertilization.

reproduction techniques (ART) as a solution for these infertile patients aged 35 and older. Even if the FSH (Follicle stimulating hormone) increases the estrogen rate because of ovarian stimulation, this increase is of short duration and is not significant enough to lead to tumor development. In addition, a correlation between induction of ovulation and the emergence of an endometrial cancer has not been proved.[76] Although the delay between the end of treatment and attempts to achieve pregnancy has not been established, it seems logical to implement ART as soon as possible.[77]

After bringing a pregnancy to term, a radical treatment should be proposed and discussed with the patient.[2] If radical treatment is refused or if other pregnancies are desired, there is no consensus on the appropriate management of the woman's condition. However, a continuing treatment by estro-progestogen contraception or by Depo-Provera™ (150 mg of medroxyprogesterone acetate every 12 weeks via intra-muscular injection) is recommended with a close follow-up (every 12–24 weeks) of the endometrium by hysteroscopy with biopsy or D & C and trans-vaginal ultrasound or MRI for myometrial invasion.[6,7,78]

Conclusion

According to this review, it seems that endometrial cancer is not that rare in women aged less than 40. Hence, we can conclude that a conservative treatment for endometrial carcinoma at Stage IA with

a low histological grade is possible if a complete pre-therapeutic assessment is achieved and if a rigorous follow-up during and after the treatment is pursued, achieving a complete response rate of 75%. A recurrence rate of 25% is seen after a temporary response.

However, no consensus has been drawn concerning the ideal treatment, its dose or its duration, even though medroxyprogesterone and megestrol acetate are the most used and the best explored. Furthermore, it should be kept in mind that every delay in implementing radical treatment can increase the rate of recurrence or the development of metastasis, which will systematically worsen the prognosis. Radical treatment should be indicated as soon as the desire to carry a pregnancy to term is fulfilled.

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Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material. Written consent was obtained from the patient or relative for publication of this study.

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