

Endometrial carcinoma in women 40 year old or younger: a case report and literature review

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Abstract. – Endometrial cancer is the most frequent gynecologic cancer. Although it mainly occurs in menopausal women, it can hit younger patients as well. Only few cases of affected women under the age of 30 are reported. A case of a 23-year-old patient with endometrioid carcinoma grade II-III is presented. Hysterectomy is considered the standard treatment and it could represent a problem for those young women who desire to preserve fertility. A conservative management can be offered to these patients when the tumor is well differentiated and advanced stage is excluded. Several studies are available in literature about fertility sparing approach. Progestin treatment, combined or not with hysteroscopic ablation seem to be the most validated conservative management. Anyhow this treatment is not free risk, because it is not always effective and disease progression during or after treatment is possible. Then a strict evaluation and selection of patients before starting treatment is mandatory.

Key Words:

Endometrial carcinoma, Menopausal women, Hysterectomy.

Introduction

Endometrial cancer is the most common gynecologic cancer in developed countries, with a mortality rate of 2.4 per 100,000.

Although most women diagnosed with endometrial cancer have already gone through menopause, 25% are premenopausal and roughly 4% are 40 years old or younger¹⁻³. The youngest patients affected by endometrial cancer reported in literature were 14 years old^{4,5}. Although young patients are only few cases, the physician should rule out endometrial cancer anytime there is an abnormal vaginal bleeding at any age.

The standard treatment for endometrial carcinoma is total hysterectomy³. Although this treatment is considered appropriate for all affected women in menopause and in those who do not care to preserve fertility, it could represent conversely a problem for all young affected women

who want to preserve their fertility. A medical treatment with progestins could be a reasonable option to propose to young patients with grade I, stage IA endometrial carcinoma, who desire to retain fertility, but patients should be informed about all risks these treatments include^{3,6}.

As only few cases of affected women under the age of 30 are reported, we present a case of a very young patient with endometrioid adenocarcinoma grade II-III.

Case

A nulliparous patient of 23-year-old with a 10 months history of abnormal vaginal bleedings was referred on July 2012. Menarche was at age 13 and menses were irregular. The patient did not suffer dysmenorrhea, nor other gynecologic disease.

Her body mass index was normal, she was not affected by diabetes mellitus, nor other conditions related to a hyperestrogenism and her family history was negative for ovarian, uterine and colonic cancer.

After several months of irregular bleeding, a transvaginal sonography was carried out and a thickened endometrium with apparently normal ovaries was demonstrated. Hysteroscopy revealed a friable, sessile bulgy mass inside the uterine cavity with atypical vascularization. Isthmus and cervix were unaffected. Endometrial biopsy showed endometrioid adenocarcinoma grade II. Magnetic resonance imaging revealed a myometrial invasion. Lymph nodes were not involved. Conservative treatment was not recommended and laparoscopic hysterectomy was performed. The pathological examination showed a white bulgy friable mass involving the fundus, the anterior and posterior wall of the uterus and microscopic examination revealed a grade II endometrioid adenocarcinoma and some areas with grade III, infiltrating more than 50% of myometrium (Figure 1). Infiltration of cervical stroma and neoplastic embolization of peritumoral blood vessels spreading up to 1 mm from serosa were also found. Computerized tomography scan performed after hysterectomy did not show pelvic or abdominal lymphadenopathies.

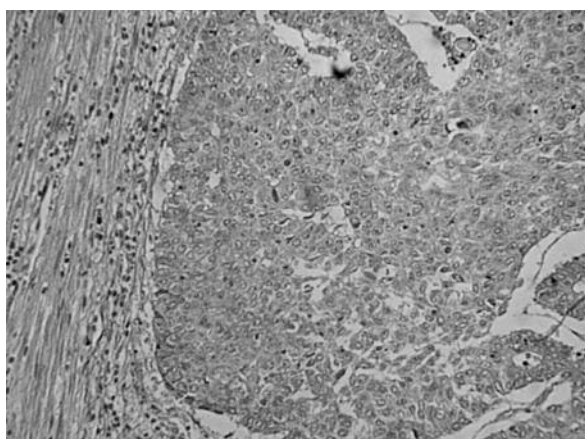


Figure 1. Myometrial infiltration of endometrial cancer.

The patient is currently in good health and until today no sign of recurrence was revealed.

Literature Review

Risk Factors

Obesity and any condition that cause a hyperestrogenic state are the main risk factors for endometrial cancer in young women², but anytime women refer abnormal vaginal bleeding (menorrhagia, irregular menses, menometrorrhagia) endometrial cancer should be suspected.

A literature review, about fertility sparing treatment in young women with endometrial cancer, reported that the majority of patients had a history of anovulation, infertility, ovarian dysfunction, nulliparity and obesity⁷.

Among young patients, lean women seem to have a more advanced stage compared to those who are obese. Indeed, Duska et al⁸ demonstrated that patients with a BMI lower than 25 were more likely to have advanced disease and high risk histology (clear cell, uterine serous papillary) compared with those women with a BMI over 25, although no differences were found in the estrogen receptor expression and Her3neu positivity between the two groups.

Furthermore, Gallup and Stock⁹ in 1984 reported that young women who were obese, nulliparous, hypertensive or diabetic, tended to have a well-differentiated tumor more frequently compared to those patients without metabolic or cardiovascular complications. More than 31% of patients belonging to the first group presented a polycystic ovarian syndrome.

A comparison of the disease in young and older women is mandatory and differences between

the two groups were demonstrated in a study of Evan-Metcalf et al¹⁰. The distribution of stage from I to IV and the histological type were similar, but grade I endometrial cancer seemed to occur more frequently in young patients with less aggressive behavior.

They also demonstrated a higher prevalence of contemporary ovarian malignancies in the younger group, showing, at the same time, that nulliparity is an independent risk factor for the development of ovarian malignancy¹⁰.

The higher prevalence of synchronous ovarian cancer in younger women is demonstrated in several studies. Walsh et al¹¹ reported a rate of 25%, while Gitsch et al¹² reported a rate of 29%.

Management

Although hysterectomy represents the standard treatment for endometrial cancer, it is often not accepted when the patient is young and desires a pregnancy in the future. Then, a fertility-sparing approach could be offered as an alternative option to accurately selected patients. Hormonal therapy alone or combined with hysteroscopic ablation are identified in literature as the most used and effective conservative treatments¹³. Anyhow, patients must be informed that data about medical treatment are incomplete because of the limited number of treated patients³, and that there is a risk of disease progression during treatment or after initial response¹³.

Either oral and intrauterine hormonal treatment are reported in literature. Saegusa and Okayasu¹⁴ suggested the use of progestins when positive progesterone receptors are detected in well differentiated endometrial cancer. Medroxyprogesterone acetate (400 mg/day) and megestrol acetate (160 mg/day) were the more frequently progestins used for oral treatment¹³.

Chiva et al¹⁵ in 2008 reported a total of 133 patients treated with conservative treatment from 1966 until 2007, mainly with progestins. He reported that 76% patients responded to the treatment, 66% never relapsed and 24% women did not respond to treatment. Most patients with relapsed disease underwent hysterectomy, but 30% of them received a second line hormonal therapy with a response of 80%.

Ricciardi et al¹⁶ reported a study of 15 patients with early stage endometrial cancer or atypical hyperplasia, 40 years old or younger, treated with hormonal therapy. Medroxyprogesterone acetate (500-1000 mg/day), or megestrol acetate (80-160 mg/day) were used for at least 12 weeks. First

hysteroscopic biopsy was performed after one month and then repeated every three months of treatment and then at 4, 8 and 12 months after delivery in all patients who achieved childbearing. Of 15 women, 11 had complete remission and 4 of them attained pregnancy with 4 live births. Three patients manifested disease progression and received definitive surgery and one did not have any response to treatment with further hysterectomy.

In a more recent experience, Koskas et al¹⁷ performed a retrospective study evaluating the outcome of 22 patients with atypical hyperplasia or endometrial carcinoma who underwent conservative treatment with progestin. Before starting treatment a radiological staging was performed. The follow-up lasted for at least one year. Seventeen patients responded to conservative management but three of them relapsed. Ten pregnancies were achieved in eight patients and one woman diagnosed with atypical hyperplasia had disease progression to stage IIIA endometrial cancer.

A retrospective study of Park et al¹⁸ demonstrated the effectiveness of high dose progestin therapy in the conservative management of endometrial cancer in young patients when limited to the endometrium.

Yamazawa et al¹⁹ in a prospective study from 1999 to 2005, assessed the outcome of nine women aged between 22 and 40 years, with grade I, stage IA endometrial cancer conservatively treated. Medroxyprogesterone acetate (400 mg/day) was administered and continued for 6 months. Seven women had complete response and two of nine patients partially responded to treatment. Although two women manifested relapsing disease with synchronous ovarian cancer, all nine patients were alive and recovered completely for a mean of 39 months. Moreover, of eight patients who sought to conceive, four had a pregnancy and three of them delivered. It has been suggested that complete response was related to positive progesterone receptors.

In a case reported by Mitamura et al²⁰, a 14 years old girl with a grade II endometrial cancer was treated with medroxyprogesterone acetate for a month. After one month of treatment, endometrial biopsy revealed no hormonal response and hysterectomy was performed. The uterine examination showed myometrial invasion which was not revealed by previous CT scan and MRI. In this study the endometrial cancer was a grade II, hormonal approach lasted only for one month and seemed to be not effective, unlike the other reports in which progestin was given for a longer period (at least three months) and women had a grade I tumor.

Several studies²¹⁻²⁴ are available in literature about progestin-releasing intrauterine devices (IUDs), as an alternative option to oral administration in the conservative management of endometrial cancer.

A study performed by Montz et al²¹ in 2002, in which thirteen patients were treated with intrauterine progesterone, demonstrated that this conservative treatment was able to cure definitely some cases of grade I, stage IA endometrial cancer.

Kim et al²³ demonstrated that intrauterine progestin (Levonorgestrel) could be used in combination with oral medroxyprogesterone in the conservative treatment of endometrial cancer. Four of five treated patients and one of them had complete and partial response respectively. All women had early stage disease and follow-up lasted from 6 to 16 months.

Two recent studies^{25,26} introduced a new fertility sparing approach combining hysteroscopic ablation and progestin treatment. Six patients with grade I, stage IA endometrial cancer with positive estrogen and progesterone receptor²⁵ underwent resectoscopic eradication of the lesion, ablation of the closer endometrium and the underlying myometrium. After hysteroscopy, all patients started therapy with megestrol acetate (160 mg/day) for six months. All patients had complete remission and four of them achieved pregnancy.

In the second study²⁶ fourteen women with the desire of childbearing underwent hysteroscopic ablation of the tumor and then hormonal therapy with megestrol acetate (160 mg/day) or levonorgestrel (52 mg) intrauterine device for six months. In all cases there was a grade I stage IA endometrioid endometrial cancer, all patients were younger than 40 years of age and the tumor had positive estrogen and progesterone receptors. All but one responded to treatment. The patient who showed recurrent disease received hysterectomy. Only one patient manifested atypical hyperplasia which definitely resolved in the further biopsies. Three patients tried to conceive and one achieved childbearing.

Although in the majority of the literature about fertility-sparing management reported treated patients with grade I stage IA endometrial cancer, Brown et al²⁴ in 2012 reported a case of an 18 years old girl with grade II endometrioid adenocarcinoma, treated with Levonorgestrel IUD. Endometrial biopsy performed every 3 months revealed a complete regression of endometrial cancer and hyperplasia.

This case demonstrated that there are not clear guidelines in the selection of patients and in some cases a grade II endometrial cancer can respond to conservative treatment.

Patient's Selection

A fertility sparing approach is a reasonable option for young women wishing to reserve their fertility, but every patient should be strictly selected. Benshushan³ considered conservative treatment only for early endometrial cancer (stage I, grade I) with MRI or transvaginal ultrasound staging, before starting treatment. CA 125 should be also taken. Moreover, he considered a clear counseling mandatory, informing the patient about risks and benefits, including that hormonal therapy is not the standard treatment for endometrial cancer and disease progression during treatment is possible.

Several diagnostic tools can be used for endometrial cancer staging. MRI and transvaginal ultrasonography seemed to be more accurate than CT scan in staging^{27,28}. On the contrary, MRI and endovaginal ultrasound showed a similar grade of accuracy in both myometrial invasion and cervical extension²⁹ but only MRI with contrast seems to be reliable for detecting the myometrium invasion and the involvement of the cervix³⁰.

Bovicelli et al¹³ suggested hysteroscopic tumor excision in evaluating myometrial invasion and CA 125 with transvaginal ultrasound in order to rule out synchronous ovarian cancer.

Recommendations were expressed by Eskander et al³¹, whereby only patients with grade I, stage IA endometrial cancer and expression of progesterone receptors could start conservative treatment. Moreover, it was necessary to exclude myometrial invasion, lymph vascular space invasion, metastatic disease and suspicious synchronous ovarian cancer^{31,32}.

Chiva et al¹⁵ emphasized that selection of patients for conservative treatment should include a well-differentiated tumor, with no invasion of the myometrium, and absence of contemporary ovarian cancer and nodes involvement.

In conclusion, hormonal treatment for a conservative management is possible, but it is not free of risks: only selected patients should accede and a strict follow-up is needed to avoid disease progression.

Conservative treatment with IUDs is a valid option in some cases of early stage endometrial cancer in young women, but clear guidelines in the selection of patients does not exist and in some cases a grade II endometrial cancer can respond to conservative treatment.

Follow up

Although today no clear guidelines about follow up for women who undergo conservative treatment have been expressed, most authors consider to perform the first endometrial biopsy after three months of hormonal therapy.

Chiva et al¹⁵ reported that a strict follow up with endometrial evaluation should be taken after 12 weeks of treatment. When a positive biopsy occurs, another biopsy should be performed after 24 weeks of treatment. If the second biopsy results positive, a radical treatment should be carried out. On the contrary the patient could start to attempt conception with a negative biopsy. Then, endometrial sampling could be taken every 3-4 months. He also recommended to perform biopsy during the preovulatory period.

Eskander et al³² suggested an endometrial evaluation with curettage after three months of treatment. In case of disease progression or persistence of cancer, he recommended hysterectomy. If response to conservative management is confirmed, hormonal therapy should be continued for 6 to 9 months.

Bovicelli et al¹³ in a review suggested a close follow up ranged from 3 to 12 months with a median of 40 months.

Pregnancy Outcomes

The pregnancy outcome represents an important issue in patients with positive response to conservative treatment.

A total of 53 women conceived after cancer regression and 35 of them achieved pregnancy through assisted reproductive techniques¹⁵. In another study³³, ten of twelve patients with early stage endometrial cancer and complete remission after treatment with medroxyprogesterone acetate and megestrol acetate achieved pregnancies; eight of them had live births. A review of eleven studies, in which women with endometrial cancer treated with fertility sparing approach were considered, showed that 81% of patients had remission and, among those patients who tried to conceive, 47% had live births³².

Several studies demonstrated the usefulness of assisted reproductive technologies in achieving pregnancy after a conservative approach for endometrial cancer, but until today no clear evidence of safety of the hormonal treatment has been demonstrated.

In a study of Mao et al³⁴, three of four patients with complete remission and assisted reproductive techniques conceived. Mao et al³⁴ and Gaducci et al³⁵ reported that childbearing was easily

achieved when assisted procreation was completed. In an other study³⁶, 41.9% of women with early stage endometrial cancer successfully treated with sparing fertility approach, conceived spontaneously and artificially.

Hysterectomy After Successful Treatment

Several authors suggested to perform hysterectomy when patients have completed their fertility plans.

A small risk of disease progression after or during conservative treatment is described, therefore hysterectomy should be considered after pregnancy³.

A recent literature review reported that hysterectomy was not justified for all women after pregnancy was achieved, due to the low risk of recurrence (35%)¹³.

Conclusions

Even though endometrial carcinoma is mainly diagnosed after menopause, it may occur in young women as well and anytime a young woman complains abnormal bleeding, endometrial carcinoma should be ruled out and all diagnostic tools should be used to exclude the pathology. This is particularly true if risk factors for endometrial carcinoma are present.

The standard treatment for endometrial cancer is total hysterectomy. Although this procedure is usually performed in women in menopause, conservative treatment could be a reasonable option to propose to young patients with stage IA grade I endometrial cancer and endometrial hyperplasia who desire to retain fertility³⁷. A strict evaluation of grade, stage, histology type, hormonal receptors expression, myometrial invasion and metastatic diffusion is necessary before introducing hormonal therapy as alternative treatment.

Today the majority of controlled studies about the conservative treatment concerns patients with endometrial hyperplasia and endometrioid adenocarcinoma grade I. There are only few cases with grade II endometrial carcinoma reported and there are not available cases with grade III carcinoma treated with hormones. The case we described was a very young patient with a grade II-III endometrioid adenocarcinoma with myometrial invasion and therefore not suitable for hormonal treatment.

There is often a debate when cancer is diagnosed in young patients who wants to preserve fertility: risks and benefits of conservative treatment should be widely discussed with patients.

Non surgical approach is a valid option but indications and eligibility of different therapies must be carefully considered and strictly followed.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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