Endometrial stromal sarcoma - Observational evidence of a genetic background?

O. Reich[1], *M.D.*; **S. Regauer**[2], *M.D.*

Departments of [1]*Obstetrics and Gynecology and* [2]*Pathology, Medical University of Graz (Austria)*

Summary

Background: Endometrial stromal sarcomas (ESS) constitute only 0.2% of all gynecological malignancies, and risk factors or genetic associations are largely unknown. We are in contact with more than 100 patients with ESS via an internet support group, and our aim was to analyze the personal and familial medical histories of this large patient group for possible familial cancers aggregations in ESS patients.

Methods: A questionnaire regarding the personal and familial medical history was circulated among the members of the internet group, which was returned by 64 patients.

Results: At diagnosis of ESS the average age was 42 years. Fifty percent had a history of long-term hormonal treatment. One patient each had a previous history of breast carcinoma, thyroid cancer and cutaneous malignant melanoma. One familial case of ESS was observed. At least one malignancy in the family was reported by 47% of patients, and the mother or father were affected in 26%. Multiple familial cancers were observed in 25% of ESS patients. The most frequent familial cancer was breast cancer (25%) followed by endometrial (8%), lung (7%) and prostate carcinoma (5%).

Conclusions: Patients are young, report hormonal treatments and have a familial history of hormone-dependent carcinomas. This suggests a strong genetic predisposition in the oncogenesis of ESS. Patients with ESS may suffer from an inherited genetic predisposition similar to familial breast and prostate carcinoma which may render them susceptible to hormone-dependent growth promotion and/or to cellular damage from particular estrogen metabolites of endometrial cells resulting in a ESS.

Key words: Familial cancer; Hormone sensitive tumors; Genetic predisposition; Genetic polymorphism.

Introduction

Endometrial stromal sarcomas (ESS) are rare uterine estrogen-dependent tumors in young women, representing only 0.2% of all gynecological oncological diseases [1, 2]. The individual steps involved in malignant transformation of endometrial stromal cells are largely unknown, but hormonal treatments have been implicated [3,4]. ESS have no known etiological risk factors such as exogeneous carcinogenic agents [5]. Only one cell culture study with normal endometrial stromal cells reports sarcomatous transformation after treatment with the carcinogen N-methyl-nitro-N-nitrosoguanidine [6]. The low incidence of ESS in elderly women speaks against a cumulative effect of exogenous carcinogenic agents. Due to the rarity of the disease and the small study groups, next to nothing is known about the role of genetic factors in the development of ESS [7]. In this study, we present the personal and familial oncological background of 64 patients with ESS. These patients are members of the "Endometrial Stromal Sarcoma Health Group", an internet support group for women with ESS, which was originally started in 2001 by David Hughes (http: www.Global HealthNetwork.org). This group has members from the U.S.A., Australia, New Zealand and the United Kingdom. We learned about this discussion group in January 2004 when we were contacted by a member of this group regarding our previous publication on aromatase expression in ESS [8]. Since reports on large series of patients with ESS are rare, we took advantage of this large patient cohort and designed a questionnaire about the patient's personal medical history, hormonal treatment and a detailed family history of oncological diseases.

Material and Methods

A questionnaire was circulated among 120 members of the ESS group via e-mail. The questions pertained to the following aspects: age at diagnosis, organs involved at diagnosis and stage of ESS, clinical course including recurrences and metastases; age at menarche, menopause, number of children, pregnancies, hormonal treatments, other hormone-dependent diseases, synchronous oncological diseases and oncological family history.

Results

The questionnaire was returned by 64 patients (57 women from the U.S.A., 2 from Canada, 2 from Australia, 2 from the U.K. and 1 from New Zealand). At diagnosis of ESS, 58/64 patients were premenopausal, only 6/64 patients were postmenopausal, with an average age of 42 years (age range 26 to 72 years). Sixteen patients (25%) were younger than 40 years. The extent of the ESS at primary presentation corresponded to Stage I in 47/64 patients, Stage II in 4/64 patients, Stage III in 6/64 patients and Stage IV in 7/64 patients. Slightly more than 50% of patients were nulliparous (34/64 patients), while ten patients were primiparous and 20 patients were mul-

Revised manuscript accepted for publication January 28, 2005

tiparous. Twenty-two of 64 patients had used oral contraception for more than one year. Four patients received estrogen replacement therapy before the diagnosis of ESS, two patients had a history of diethylstilbestrol treatment and eight patients had undergone in-vitro fertility treatments. One patient had polycystic ovary syndrome. Leiomyomas and endometriosis were identified in 27/64 patiens. One patient had a history of pelvic irradiation. Several patients had metachronous oncological diseases: patient #20 had lobular breast carcinoma and cutaneous squamous cell carcinoma; patient #25 had cutaneous malignant melanoma; patient #54 had thyroid cancer and patients #12, 38 and 44 had a high grade CIN.

The questions regarding family history of oncological diseases were answered by 62 patients only (Table 1). One case of familial ESS (patient #21) was identified. There was an oncological family history in 29/62 patients (47%) with ESS. An oncological disease in one parent was reported by 16/62 patients (26%) and in both parents by 1/62 patients (2%). Among the parental oncological diseases, breast carcinoma was the most common cancer in six mothers, followed by carcinomas of the prostate (2) and colon (2). Multiple familial malignancies were reported by 15/62 patients (25%; Table 1). Breast carcinoma was the most prevalent familial cancer in 15/62 patients (25%), followed by endometrial carcinoma in 5/62

Table 1. — *Familial aggregation of oncological diseases in patients with ESS.*

Pt.	Paternal side	Oncological disease	Maternal side	Oncological disease	Brother/Sister	Oncological disease
#2	Father	Bladder cancer	Grandmother	Endometrial carcinoma		
	Grandfather	Gastric cancer	Aunt	Endometrial carcinoma		
	Aunt	Gastric cancer	Great-grandmother	Endometrial carcinoma		
#6	Grandmother	Breast cancer	Grandmother	Lung cancer		
#7			Grandmother	Cervical cancer		
#8	Father	Colon cancer				
#9	Aunt	Breast cancer				
#10	Grandmother	Breast cancer	Mother	Breast cancer		
	Aunt	Breast and colon cancer				
#12			Mother	Breast, endometrial and colon cancer, Hodgkin lymphoma		
#14	Grandfather	Gastric cancer				
#15	Grandfather	Colon cancer				
#17	Grandmother	Breast cancer				
	Aunt	Breast cancer				
	Aunt	Multiple myeloma				
#19	Father	Liver cancer				
#20			Mother	Breast cancer	Pt. herself	Breast cancer
#21	Father	ALL	Cousin	ESS	Sister	Cutaneous SCC
#23	Aunt	Endometrial carcinoma				
#25			Aunt	Breast cancer		
			Grandmother	Colon cancer		
#26			Mother	Renal cell carcinoma		
#28			Grandmother	Breast cancer		
			Mother	Ovarian cancer		
			Cousin	Breast cancer		
#32			Aunt	Breast cancer		
			Aunt	Breast cancer		
			Aunt	Breast cancer		
			Cousin	Breast cancer		
			Cousin	Prostate cancer		
			Cousin	Pancreatic cancer		
#33	Aunt	Breast cancer				
#35	Father	Prostate carcinoma	Mother	Lymphoma		
#36	Father	Lung cancer				
#45	Father	Prostate carcinoma			Sister	Breast cancer
					Pt. herself	Breast cancer
#48	Grandmother	Breast cancer	Mother	Breast cancer		
#49			Mother	Breast cancer		
#50			Mother	Brain tumor		
			Grandmother	Endometrial carcinoma		
#57			Mother	Basal cell carcinoma	Brother	Gastric cancer
#59	Grandmother	Lung cancer				
#62	Grandfather	Lung cancer	Aunt	Breast cancer		
	Father	Colon cancer	Grandmother	Endometrial carcinoma		
#63			Mother	Breast cancer		

patients (8%), lung cancer in 4/62 patients (7%) and prostate cancer in 3/62 patients (5%). Breast carcinomas in several family members was observed in six patients. In families affected by multiple cancers, breast carcinomas were associated with endometrial carcinoma (2/62), prostate carcinoma (2/62), colon cancer (2/62), ovarian carcinoma (1/62), and multiple myeloma (1/62).

Discussion

Inherited cancer susceptibility confers a significant risk for development of various gynecological malignancies such as breast and ovarian cancer [5]. The current dogma of cancer research holds accumulations of heritable or acquired gene mutations responsible for the development and progression of human cancers. At present, no such predisposing genes have been identified for ESS. However, the results of this survey suggest a strong genetic predisposition in the oncogenesis of ESS: over 90% of women with ESS were young and premenopausal with an average age of 42 years at initial diagnosis; almost one third of ESS patients reported that one or both parents had an oncological disease; one quarter of ESS patients reported the existence of familial breast carcinoma, followed by endometrial and prostate carcinoma; one quarter of ESS occurred in the setting of multiple familial cancers; and, familial clustering of ESS was observed in one patient. At least 50% of patients with ESS had hormone related conditions and/or treatments, such as polycystic ovary syndrome, premature menarche, hormonal birth control, in-vitro fertilization treatments and estrogen replacement therapy before diagnosis of ESS.

There was a striking incidence of familial breast carcinomas in patients with ESS, followed by other hormone dependent carcinomas such as endometrial and prostate carcinoma. Breast carcinoma and ESS are characterized by long-term exposure to exogenous and endogenous estradiol [10-12]. The prevailing theory proposes that estrogen increases cell proliferation via receptor-mediated transcription, thereby increasing the number of errors occurring during DNA replication. An alternative hypothesis proposes that estradiol is metabolized to quinone derivatives which react with DNA and remove bases from DNA through a process called depurination. Error prone DNA repair then results in point mutations. Both processes (increased cell proliferation and genotoxic metabolite formation) may act in an additive or synergistic fashion to induce ESS. Estrogenic growth stimulation of ESS can occur via autocrine regulation systems, among which is aromatase, a key enzyme complex of estrogen biosynthesis. A gene polymorphism of the CYP gene has been implicated in the hormone-dependent growth promotion of breast carcinoma and familial prostate cancer [13, 14], but also in endometrial cancer [15]. This enzyme complex consists of the CYP19 gene product aromatase cytochrome P450 and a flavoprotein NADPH-cytochrome P450 reductase and is involved in androgen-estrogen conversion, in estrogen biosynthesis and metabolism, and in the metabolism of environmental carcinogens.

Our observation of the high incidence of familial hormone dependent cancers, particularly breast, endometrial and prostate cancer in patients with ESS suggests that patients with ESS are possibly carriers of a so-far unknown gene mutation which renders them susceptible to hormone-dependent growth promotion and/or to cellular damage from particular estrogen metabolites. Molecular genetic studies are needed to test this hypothesis.

References

[1] Chu M.C., Mor G., Lim C., Zheng W., Parkash V., Schwartz P.E.: "Low-grade endometrial stromal sarcoma: hormonal aspects". *Gynecol. Oncol.*, 2003, *90,* 170.
[2] Reich O., Regauer S., Urdl M., Lahousen M., Winter R.: "Estrogen and progesterone receptor content in low-grade-stromal sarcomas". *Br. J. Cancer*, 2000, *82,* 1030.
[3] Beer T.W., Buchanan R., Buckley C.H.: "Uterine stromal sarcoma following tamoxifen-treatment". *J. Clin. Pathol.*, 1995, *48,* 596.
[4] Martin-Loeches M., Rius J., Orti R.M.: "Uterine sarcoma associated with tamoxifen use: case report". *Eur. J. Gynecol. Oncol.,* 2003, *24,* 202.
[5] Chang K.L., Crabtree G.S., Lim-Tan S.K., Kempson R.L., Hendrickson M.R.: "Primary uterine endometrial stromal neoplasms. A clinicopathologic study of 117 cases". *Am. J. Surg. Pathol.,* 1990, *14,* 415.
[6] Walton L.A., Siegfried J.M., Nelson K.G., Siegal G., Kaufman D.G.: "Endometrial stromal cells in culture: an attempt to understand the genesis of biologic activity of uterine sarcomas". *Gynecol. Oncol.,* 1986, *24,* 247.
[7] Hendrickson M.R., Tavassoli F.A., Kempson R.L., McCluggage W.G., Haller U., Kubik-Huch R.A.: "Mesenchymal tumours and related lesions". In: Tavassoli F.A. (ed.), Tumors of the Breast and Female Genital Organs. WHO, Lyon, France, IARC Press, 2003, 233.
[8] Reich O., Regauer S.: "Aromatase expression in low-grade endometrial stromal sarcomas: an immunohistochemical study". *Mod. Path.*, 2004, *17,* 104.
[9] Goldgar D., Stratton M.R.: "Familial aggregation of cancers of the breast and female genital organs". In: Tavassoli F.A. (ed.), Tumors of the Breast and Female Genital Organs, WHO, Lyon, France, IARC Press, 2003, 336.
[10] Briand P., Hou-Jensen K., Thorpe S.M., Rose C.: "Hormone dependent uterine sarcomas in GR mice". *Eur. J. Cancer*, 1981, *17,* 635.
[11] Ellis I.O., Schnitt S.J., Sastre-Garau X., Bussolati G., Tavassoli F.A., Eusebi V., Peterse J.L. *et al.*: "Invasive breast carcinoma". In: F.A. Tavassoli (ed.), Tumors of the Breast and Female Genital Organs, WHO, Lyon, France, 2003, 13.
[12] Press M.F., Scully R.E.: "Endometrial 'sarcomas' complicating ovarian thecoma, polycystic ovarian disease and estrogen therapy". *Gynecol. Oncol.*, 1985, *21,* 135.
[13] Miyoshi Y., Ando A., Hasegawa S., Ishitobi M., Yamamura J., Irahara N. *et al.*: "Association of genetic polymorphisms in CYP19 and CYP1A1 with the oestrogen receptor-positive breast cancer risk". *Eur J Cancer*, 2003, *39,* 2531.
[14] Suzuki K., Nakazato H., Matsui H., Koike H., Okugi H., Kashiwagi B. *et al.*: "Genetic polymorphisms of estrogen receptor alpha, CYP19, catechol-O-methyltransferase are associated with familial prostate carcinoma risk in a Japanese population". *Cancer,* 2003, *98,* 1411.
[15] Berstein L.M., Imyanitov E.N., Kovalevskij A.J., Maximov S.J., Vasilyev D.A., Buslov K.G. *et al.*: "CYP17 and CYP19 genetic polymorphisms in endometrial cancer: association with intratumoral aromatase activity". *Cancer Lett.,* 2004, *207,* 191.

Address reprint requests to:
O. REICH, M.D.
Department of Obstetrics and Gynecology
Auenbruggerplatz 14
Medical University of Graz
A-8036 Graz (Austria)