High levels of xenoestrogens in patients with low-grade endometrial stromal sarcoma - report of two cases

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Summary

Background: Endometrial stromal sarcomas (ESS) are rare uterine tumors with unknown etiological risk factors, but estrogen-dependent growth promotion. *Cases:* We present two patients with advanced ESS, who had increased levels of p,p-DDE; hexachlorobenzene; PCB 28; PCB 52; PCB 101; PCB 138; PCB 153 and PCB 180 in abdominal adipose tissue. Other xenoestrogens were within expected limits for the non-exposed European population. *Conclusion:* Increased levels of xenoestrogens in patients with ESS may be involved in the pathogenesis of ESS. Chronic exposure to xenoestrogens may be a risk factor for tumor progression.

Key words: Endometrial stromal sarcoma; Estrogen; Xenoestrogen; Pathogenesis.

Introduction

Endometrial stromal sarcomas (ESS) are rare uterine tumors, representing less than 1% of all gynecological malignancies. They have no known etiological risk factors such as exogeneous carcinogenic agents. Only one cell culture study with normal endometrial stromal cells reports a sarcomatous transformation after treatment with the carcinogen N-methyl-nitro-N-nitrosoguanidine [1]. The individual steps involved in malignant transformation of endometrial stromal cells are largely unknown, but progression of disease is estrogen-dependent [2].

Hyperestrogenism may occur due to endogeneous and exogeneous factors. Endogenous hyperestrogenism can occur either locally within endometriotic tissues or systemically due to pregnancy, adiposity and polycystic ovarian syndrome. Exogenous hyperestrogenism can be induced by ovulation-stimulating drugs in protocols of assisted reproduction and estrogen-containing hormone replacement therapy [2]. Some environmental substances are also known to induce exogeneous hyperestrogenism. Such xenoestrogens are a heterogeneous group of chemicals that differ from naturally occurring estrogens. Of particular concern are hormonally active environmental agents such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD= dioxin) and other persistent compounds such as polychlorinated biphenyls (PCBs) and organochlorine pesticides that bioaccumulate and magnify within the food chain [3].

We analyzed the following xenoestrogens in two patients with advanced EES: p,p-DDE, o,p-DDD; p,p-DDD; o,p-DDT; p,p-DDT; alpha endosulfan; beta endosulfan; dieldrin; endrin; isodrin; cis-chlordane; trans-chlordane, alachlor; o,p-methoxychlor; p,p-methoxychlor; 1,2,3-tricholorbenzol; 1,2,4-trichlorbenzol; 1,3,5-trichlorbenzol; 1,2,3,5-tetrachlorbenzol; 1,2,4,5-tetrachlorbenzol; 1,2,3,4-tetrachlorbenzol; pentachlorobenzene, hexachlorobenzene; alpha-HCH; beta-HCH; gamma HCH; delta HCH; hexachlorobutadiene; trifluralin; PCB 28; PCB 52; PCB 101; PCB 138; PCB 153 and PCB 180.

After freeze drying of the homogenized and freeze dried formalin (3%) fixed tissue the samples were soxhlet extracted by toluene/ethanol. An aliquot of the extract was used for lipid determination. Further sample treatment comprised a multi-step cleanup by column liquid chromatography. Measurement of the analytes was done by GC/HRMS (dioxins and dioxin-like PCBs) and GC/LRMS (indicator-PCBs, organochlorine pesticides) respectively. The quantification was done by isotope dilution using ^{13}C-labeled standards, which were added prior to extraction.

Case Reports

Case 1: A patient had presented with FIGO Stage I ESS at age 38. She had two recurrences at age 46 and 50 years resulting in a colectomy. Formalin-fixed adipose tissue from the second recurrence revealed increased levels of the following xenoestrogen: p,p-DDE: 370 mg/g; hexachlorobenzene: 300 ng/g; PCB 28: 84 ng/g; PCB 52: 86 ng/g; PCB 101: 420 ng/g; PCB 138: 150 ng/g; PCB 153: 320 ng/g; PCB 180: 120 ng/g.

Case 2: A 62-year-old woman presented with FIGO Stage III ESS. Formalin-fixed tissue of the omentum was analyzed. The following xenoestrogens were increased: p,p-DDE: 3100 ng/g; p,p-DDT 250 ng/g, hexachlorobenzene: 410 ng/g; gamma-HCH 86 ng/g; PCB 28: 34ng/g; PCB 52: 44 ng/g; PCB 101: 190 ng/g; PCB 138: 840 ng/g; PCB 153: 2000 ng/g; PCB 180: 880 ng/g.

Both patients had levels of dioxin which are considered within normal limits for non-exposed Europeans.

Discussion

The ubiquitous occuring xenostrogene can be either ingested via the food chain or inhaled when bound to dust. Some xenoestrogens can cross the placenta and are present in breast milk. The lipophilic characteristics of these compounds allow bioaccumulation in animals and particularly in humans, who represent the end of the food

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chain. Xenostrogens have been linked to increased cancer risk in exposed people [4] and their toxicity has led to a ban in many countries world wide (e.g. PCBs). This is the first time that hormonally active environmental agents have been demonstrated in the abdominal adipose tissue of patients with advanced ESS. In particular p,p-DDE, p,p-DDT, hexachlorobenzene and Lindan (γ-HCH) were demonstrated in significantly higher concentrations than those considered "normal" in European countries [5]. The observed concentrations compared to those of acutely exposed people living close to production plants and storage facilities of organochlorine pesticides [6].

Progression of most ESS is influenced by steroid hormones after binding to their receptors, in particular estrogen receptor isoform alpha, which has been demonstrated in 80% of ESS [7]. Exogenous and endogenous estrogens as well as xenoestrogens may lead to a growth stimulation of tumor cells. At present it is unclear if and how xenoestrogens are involved in tumor progression of ESS. Sequence variations of enzymes can account for differences in effects of xenoestrogen. Martuci and Fishman [8] suggest that genetic polymorphisms in cytochrome P450 (CYP) 1A1 and CYP1B1 are associated with interindividual susceptibility to organochlorines. CYP1A1 and CYP1B1 are phase I drug-metabolizing enzymes that are critical to both metabolism of xenobiotic and naturally occurring estrogens. Furthermore, the C1558-T polymorphism of the aromatase gene CYP19A1 has been associated with increased susceptibility to estrone and estradiol. The prevalence of the mutated T/T phenotype is similar in the general Caucasian population and 20 analyzed European ESS patients (personal unpublished data). It has also been suggested that exposure to DDE, a metabolite of DDT, and other pesticides may cause conformational changes in the estrogen receptor alpha [9].

In conclusion, xenoestrogens were demonstrated in increased concentrations in both analyzed patients with ESS. Chronic exposure to xenoestrogens may be involved in the pathogenesis of ESS and/or associated with an increased risk of tumor progression.

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