GLYCODELIN (A) IN PATIENTS WITH ENDOMETRIAL CANCER

Thesis
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Entessar Abd El-Kader Abd El-Sattar

List of Abbreviations

α2-PEG	Pregnancy-Associated Endometrial α2 Globulin
AP	Adriamycin, Cisplatin
ASTEC	A Study in the Treatment of Endometrial Cancer
BMI	Body Mass Index
BRAF	v- raf murine sarcoma viral oncogene homolog B1
CAP	Cyclophosphamide, Adriamycin, Cisplatin
Chromosome 9^{q34}	Chromosome 9 Short Arm 34
COC	Combined Oral Contraceptives
COH	Controlled Ovarian Hyperstimulation
D&C	Dilatation & Curettage
EIC	Endometrial Intraepithelial Carcinoma
EIN	Endometrial Intraepithelial Neoplasia
EM_{42}	Human Endometrial Endothelial Cells
ER	Estrogen Receptors
FDGPET	Fluorine-18 Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography
FIGO	International Federation of Obstetrics & Gynecology
GOG	Gynecologic Oncology Group
GP	Antiglycodelin Peptide
hCG	Human Chorionic Gonadotrophin
HER-2/neu	Human epidermal growth factor receptor
HIV	Human Immune Deficiency Virus
hMG	Human Menopausal Gonadotrophin
hMLH1	Human mut-L homologue 1
HNPCC	Hereditary Non Polyposis Colon Cancer
HPC	Hydroxy Progesterone Caproate
HRT	Hormone replacement Therapy
HUVECs	Human Endometrial Carcinoma Cells
IGFBP-1	Insulin Growth Factor Binding Protein 1
IL1, 11	Interleukin 1, 2
IUD	Intrauterine Device
IVF	In Vitro Fertilization
JGOG	Japan Gynecologic Oncology Group
Kb	Kilo Base
KDa	Kile Dalton
LASS	Laparoscopic Assisted Surgical Staging
LGL	Large Granular Lymphocyte
LH	Luteinizing Hormone
LHRH	Luteinizing Hormone Releasing Hormone

LPF	Lower Power Field
LVSI	Lymph Vascular Space Invasion
MCF-7, MDA-MB231	Human Breast Adenocarcinoma cell line
MFE280	Endometrial carcinoma Cell Line
MGA	Megestrol Acetate
MPA	Medroxy Progesterone Acetate
MRI	Magnetic Resonance Imaging
MSI	Microsatellite Instability
NCOR	Nuclear Receptor Core Pressor
NK cell	Natural Killer Cell
OS	Overall Survival
OVCAR-3	Human Ovarian Carcinoma Cells
P_{27}	Protein 27
PAEP	Progesterone Associated Endometrial Protein
PaLA	Para Aortic Lymphadenectomy
PCO	Polycystic Ovarian Syndrome
PCR	Polymerase Chain Reaction
PEP	Progesterone-Dependant Endometrial Protein
PFS	Progression Free Survival
PLA	Pelvic Lymphadenectomy
PMB	Postmenopausal Bleeding
PORTEC	Postoperative Radiotherapy Treatment of Endometrial Cancer
PR	Progesterone Receptors
PTEN	Phosphatase & Tensin Homolog
P53	Protein 53
Rb	Retinoblastoma
PP_{14}	Placental Protein 14
SHBG	Sex Hormone Binding Globulin
SP_1	Promoter Specific Transcription Factor 1
TA	Paclitaxel, Adriamycin
TAH & BSO	Total Abdominal Hysterectomy & Bilateral Salpingo-Oophorectomy
TAP	Paclitaxel, Adriamycin, Cisplatin
Tj	Paclitaxel, Carboplatin
TVU	Trans Vaginal U/S
VEGF	Vascular Endothelial Growth Factor
VH	Vaginal Hysterectomy
WHO	World Health Organization

Aim Of The Work To study serum level , tissue expression of glycodelin in patients with cancer endometrium and its potential role in diagnosis and prognosis of endometrial cancer .

Materials And Methods Three groups of patients were included in the study: Group A : comprised thirty patients with established cancer endometrium. Group B : comprised ten postmenopausal patients with hyperplastic endometrium. Group C : comprised seven premenopausal patients with proliferative endometrium. Group A represented the group of cases while group B and C represented the group of controls.

All patients were subjected to the following : full history taking ,thorough clinical (general & pelvic) examination , full laboratory investigations (complete blood picture, coagulation profile, liver and kidney function tests) ,trans vaginal ultrasound for measuring endometrial thickness and body mass index calculation. Then preoperative endometrial samples were taken using Pipelle or Novak,s cannula as out patient procedure or sharp curette under anaethesia to establish the diagnosis before surgery. From all patients blood samples were collected,centrifugated to separate the serum that was stored at -70 degree till analysis by ELISA technique. Also endometrial tissue samples were collected following hysterectomy ,stored at -70 degree till analysed by Immunohistochemistery technique.

Introduction

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Endometrial cancer is the most common gynecologic malignancy, the 4th most common cancer in women in U.S.A and the 8th most common malignant neoplasm world wide. Incidence ranges from 5.9 per 100.000 in China, to 44 per 100.000 in U.S.A *(Randall and Trimble, 1999)*.

The etiology of endometrial cancer is hypothesized to be a hormone mediated process, through long standing stimulation of the endometrium by unopposed estrogen ***(Randall and Trimble,1999)***.

Seventy per cent of cases are presented early (stage I) and of good prognosis while thirty per cent are presented late (stage IV) and of bad prognosis ***(Randall and Trimble,1999)***. The key stone for diagnosis of endometrial cancer in women with postmenopausal bleeding is endometrial biopsy through fractional curettage or office hysteroscopy. This followed by surgical staging according to the 1988 FIGO criteria to determine the extent of the disease and the selection of any adjuvant therapy ***(Randall and Trimble,1999)***.

So there is still a place for diagnostic and prognostic tumor markers to search for to help us to detect early and hence good prognosis of endometrial cancer ***(Randall and Trimble, 1999)***. Of these potential makers suggested a glycoprotein called " Glycodelin -A" (placental protein 14 or progesterone associated endometrial protein) ***(Li et al., 1998)***. It is synthesized in the secretory and decidualized endometrium ***(Horowitz et al., 2001)***.

Glycodelin was reported in normal and malignant glandular epithelium outside the reproductive tract, namely, the breast, hideradenoma , parabronchial glands, sweat glands and pancreatic cystadenoma ***(Kämäräinen et al, 1997)***.

Glycodelin A has important biological activities such as: Immunosuppression through inhibiting N.K cell activity suggests a role of Glycodelin in tumor biology ***(Okamoto et al., 1991)***. Also it could be important for the feto- embryonic defense system ***(Clark et al., 1996)***. Contraception through inhibiting the interaction of spermatozoa with oocytes ***(Oehninger et al., 1995)***. Angiogenisis promoting vascularization during pregnancy ***(Horowitz et al. , 2001)***.

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To study serum level, tissue expression of glycodelin in patients with cancer endometrium and its potential role in diagnosis and prognosis of endometrial cancer.

Review of Literature

Chapter 1

ENDOMETRIAL CANCER

Introduction:

Cancer of the endometrium is the second commonest gynaecological tumour reported in the United Kingdom (UK) but in the European Union (EU) as a whole it ranks above ovarian cancer as the commonest tumour. The overall incidence in developed countries has risen in recent years. The death rate, around 20% overall, is lower than that of other gynaecological cancers, due principally to early presentation by means of post-menopausal bleeding. There are no practical preventative strategies currently available, so changes in incidence generally reflect demographic and lifestyle changes. Treatment has remained relatively unchanged over the last 40 years relying principally on surgery to achieve cure. During the last 10 years interest in endometrial cancer has increased considerably and investigations into the optimal use of adjuvant radiotherapy, the effect of tamoxifen, the role of chemotherapy, the effectiveness of lymphadenectomy, genetic predisposition to the disease and the influence of less common histotypes have all helped to increase our understanding of how we could reduce the risk of acquiring the disease and how best to use the surgical and non-surgical treatments available to us ***(Kitchener, 2006).***

Incidence:

Endometrial carcinoma is the most common malignancy of the female genital tract, with more than 40.000 estimated cases diagnosed in 2005 in the United States. Endometrial carcinoma is responsible for 7.310 deaths each year making it

the eighth leading site of cancer related death among American women ***(Jemal et al., 2005)***.

The incidence of endometrial cancer in the UK in 2000 was 13/100,000/year and the death rates 2.5/100,000/year. There is variation between EU countries with overall incidence and death rates of 17/100,000/year and 3.5/100,000/ year, respectively. The lowest incidence was reported from Greece and the highest from Luxembourg with rates of 8.8/ 100,000/year and 29.7/100,000/year, respectively ***(Cancer Stats, 2004)***. The incidence in Egypt is 370 cases/ year & Deaths are 293 cases/ year & the incidence rate is about 3/100.000/year while the death rate is about 1.2/ 100.000/ year ***(IARC, 2002)***.

Epidemiology:

Endometrial adenocarcinoma occurs during the reproductive and menopausal years. The median age for adenocarcinoma of the uterine corpus is between 60-65 years. Approximately 5% of women will have adenocarcinoma before the age of 40 years, and 20% will be diagnosed before the menopause ***(Kitchener, 2006).***

The incidence has increased during the past 20 years due to (a) increased life-expectancy, (b) obesity, which increases circulating oestrogens, and (c) tamoxifen, a widely prescribed adjuvant treatment for breast cancer which increases incidence by as much as 6-8-fold. Another high-risk group is those women with hereditary non-polyposis colon cancer (HNPCC). These observations suggest that unopposed hyperoestrogenism provides a pathway to endometrial carcinogenesis ***(Kitchener, 2006)***.

Factors that decrease the risk of development of endometrial cancer:

- Increasing data note that the use of combination oral contraceptives (C.O.C) decreases the risk for development of endometrial cancer. This protection occurred in women who used oral contraceptive pills for at least 12 months, and protection continued for at least 10 years after oral contraceptive use. Protection was most notable for nulliparous women ***(Creasman, 2005).*** The risk of developing endometrial cancer decreased markedly with increasing duration of c.o.c use (8 years). Some protective effect may continue for more than 20 years after stopping ***(Vessey and Painter, 2006)***

- In a population-based case-control study of women aged 40-60 years, cigarette smoking apparently decrease the risk for development of endometrial cancer. The relative risk decreased by about 30% when one pack of cigarette was smoked per day, and by another 30% when more than one pack was smoked per day ***(Amant et al., 2005).*** The protective effect of smoking on endometrial cancer risk in women using estrogen replacement therapy supports a peripheral extra ovarian anti estrogenic biological mechanism that can be expressed in post menopausal women as well ***(Baron et al.,1990)***.

  N.B: This advantage is strongly out weighed by the increased risk of lung cancer and other major health problems associated with cigarette smoking.