FEMALE GENITAL SYSTEM PATHOLOGY

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The efficiency of diltiazem in prevention of monosodium glutamate toxicity on ovaries in rats

ABSTRACT

Sustained high concentrations of MSG (monosodium glutamate) could induce to persistent depolarization and altered ionic permeability of neural membranes. The excessive activation of glutamate receptors and the overloading of intracelullar Ca2+ lead to neural death. The purpose of this investigation was to study if pretreatment with diltiazem (L-calcium channel blocker) prevents the effects of monosodium glutamate (MSG) on ovaries in rats. Female Wistar rats were administered subcutaneously with: 0,9% sodium chloride (I group), 4 mg/g b.w. MSG (II group), 5 mg/g b.w. diltiazem (III group) and 5 mg/g b.w. diltiazem and 60 minutes later with 4 mg/g b.w. MSG (IV group) at 2nd, 4th, 6th, 8th and 10th day of the life. The rats were sacrificed when they were six months old and morphometric examinations and ovarian histology were performed. Treatment with MSG resulted in cystic degeneration of ovaries. In MSG rats ovaries contained many atretic follicles, but no corpora lutea. Ovarian histology in II, III and IV group of treated animals was normal. The pretreatment with diltiazem prevents the development of damages caused by MSG in ovaries of rats. Our results sugest the importance of calcium channel blockade in prevention of MSG toxicity.

KEYWORDS: Sodium Glutamate+toxicity; Diltiazem; Drug Toxicity+prevention and control; Ovary

INTRODUCTION

MSG is widely used as food additive. It has been demonstrated that subcutaneous administration of MSG during the neonatal period to animals (mice, rats, rabbits) results in acute degeneration of cells in the inner layer of retina, the arcuate nuclei of hypothalamus and circumventricular organs. Adult rats treated neonataly exhibit a number of endocrine related disorders. The most prominent disorders are: obesity, stunted growth and abnormal reproductive function. The aim of the study was to determine if pretreatment with diltiazem (L-calcium channel blocker) prevents the effects of monosodium glutamate (MSG) on ovaries in rats.

MATERIALS AND METHODS

The present study was carried out on female Wistar rats. The animals were administered subcutaneously interscapulary with: 0,9% sodium chloride (I group), 4 mg/g b.w. MSG (II gro up), 5 mg/g b.w. diltiazem (III group) and 5 mg/g b.w. diltiazem and 60 minutes later with 4 mg/g b.w. MSG (IV group) at 2nd, 4th, 6th, 8th and 10th day of life. Rats were housed under controled conditions with constant temperature (23+/-2 0C) and humidity 55-65%) and 14h light:10h dark cycle (lights on at 06.00). All animals were weaned after 28 days of age. They had free access to tap water and standard laboratory chow pellets („Veterinarski zavod“, Zemun). The animals were sacrificed at the age of 6 months under phentobarbital anesthesia and histological and morphometric examinations were carried out.

RESULTS

Treatment with MSG resulted in cystic degeneration of ovaries in rats. Ovaries contained many atretic folicles, but no corpora lutea, fibrotic changed stroma and hyalinosis of arteriola. Ovarian histology in II, III and IV group of treated animals was normal.

DISCUSSION

Neurotoxic properties of MSG result from its ability to induce depolarization of cell membrane (Olney, 1970). Glutamate functions physiologically as neurotransmitter (Curtis, 1969) and it would be expected that postsynaptic region would be particularly sensitive to its increased extracellular concentrations. Sustained high concentrations of MSG infiltrating the synaptic cleft region could lead to persistent depolarization, altered ionic permeability of neural membranes and to neuronal necrosis. Neuronal destruction in the brain is apparent in areas where blood-brain barrier is leaky (the circumventricular organs and contiguous structures) (Eskay et al, 1972; Tokuyama and Himms-Hagen, 1986.). The excessive activation of glutamate receptors and the overloading of intracellular Ca2+ lead to neuronal death (Gao et al, 1994; Kubo et al, 1993). In this study is shown that the pretreatment with diltiazem (L-calcium channel blocker) prevents the effects of MSG on ovaries in rats.

CONCLUSION

The pretreatment with diltiazem prevents the development of damages caused by MSG in ovaries of rats. Our results sugest the importance of calcium channel blockade in prevention of MSG toxicity.

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Endometrial carcinoma with and without associated endometrial hyperplasia

ABSTRACT

The presence of endometrial hyperplasia is the most favorable nontumor-related prognostic factor for the survival of patients with endometrial carcinoma. The aim of this study was to compare the histopathologic features and surgical stage of endometrial carcinoma with and without associated endometrial hyperplasia. Histologic slides of surgical specimens of 62 consecutive patients who underwent surgery as a primary treatment for endometrial carcinoma were reviewed. Twenty-four of 62 patients (39%) with endometrial carcinoma had concomitant endometrial hyperplasia. Endometrial carcinomas associated with hyperplasia were less often in advanced surgical stage, better differentiated, of lower nuclear grade and less invasive into the myiometrium than carcinomas without associated hyperplasia. Lymph-vascular space invasion, cervical involvement, and spread to the adnexa were found more frequently in endometrial carcinoma without concomitant hyperplasia. The presence or absence of associated endometrial hyperplasia was strongly correlated with the surgical stage and histopathologic feature of endometrial carcinoma.

KEYWORDS: Endometrial Neoplasms; Endometrial Hyperplasia; Neoplasm Staging

INTRODUCTION

Some authors have distinguisehed two main groups of endometrial carcinomas: those with and those without associated endometrial hyperplasia (1,3,4). Some of these reports were based on clinical staging or clinical stage I endometrial carcinoma and the prognostic influence of endometrial hyperplasia in patients with endometrial carcinoma was not asessed in all studies (1). The aim of this study was to compare the histopathologic features and surgical stage of endometrial carcinoma with and without concomitant hyperplasia.

MATERIALS AND METHODS

Histologic slides of the surgical specimens of 62 consecutive patients who underwent total hysterectomy with bilateral salpingo-oophorectomy as a primary treatment for endometrial carcinoma from 1996 through 1998 were reviewied at the Institute of Pathology in Niš. Between 7 and 20 slides were

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reviewed per case. Endometrial carcinoma was staged according to the 1988 classification of the International Federation of Gynecology and Obstetrics (FIGO) (5,6). The histologic type, histologic and nuclear grade, depth of myometrial invasion, transmural invasion of the uterine serosa, lymph-vascular space invasion, cervical involvement, presence or absence of associated endometrial hyperplasia, and adnexal involvement were documented. The patients were divided into two groups depending on the presence or absence of associated endometrial hyperplasia. Endometrial hyperplasia was classified according to the World Health Organization. Statistical analysis was performed with Chi square test and Fisher exact test.

RESULTS

Twenty-four of 62 patients (39%) had concomitant endometrial hyperplasia in the adjacent endometrium or within the carcinomatous area and 38 patients (61%) had no concomitant hyperplasia. Of 24 cases with concomitant endometrial hyperplasia 19 (79%) had atypical hyperplasia, 4 (17%) had complex hyperplasia, and 1 (4%) had simple hyperplasia. Endometrial carcinomas with associated hyperplasia were found less often in advanced stages of the disease (p`0,0001), and showed better differentiation (p`0,01), lower nuclear grade (p`0,001) and less myometrial invasion (p`0,0001) than carcinomas without concomitant hyperplasia. Lymph-vascular space invasion, cervical involvement, and spread to the adnexa were significantly more common in the patients with endometrial carcinoma without associated hyperplasia (p`0,0001; p`0,05; p`0,001).

DISCUSSION

The existence of two fundamentally different pathogenetic types of endometrial carcinoma (estrogen-related, type I, and nonestrogen-related, type II) has been postulated (2,5,6). The estrogen-related carcinomas are usually better differentiated, less invasive into the myometrium, less aggressive than nonestrogen-related carcinomas, and appear in younger women (5,6). Concomitant adenomatous hyperplasia has been found more frequently in type I endometrial carcinoma (1). Deligdisch and Holinka (2) reported that progesterone receptor levels, which are increased by estrogen, were significantly higher in endometrial carcinomas with concomitant hyperplasia than in those without concomitant hyperplasia.

In our study, significant differences in the surgical stage, histologic and nuclear grade, myometrial invasion, transmural invasion of the uterine serosa, cervical involvement, lymph-vascular space invasion, and spread to the adnexa between patients with endometrial carcinoma with concomitant hyperplasia and those without hyperplasia were found and this is consistent with previous reports (2-4). Some authors (2,4) reported that the presence of endometrial hyperplasia was significantly correlated with the less virulent histological subtypes of endometrial carcinoma but in our series there were rather few patients with poor prognosis histologies (i.e., clear cell, serous) to evaluate these as a separate group.

CONCLUSION

In conclusion, the presence or absence of concomitant endometrial hyperplasia was strongly correlated with the surgical stage and histopathologic features of endometrial carcinoma.

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Radiotherapy of cervical adenocarcinoma - initial experiences of the Clinic of Oncology , Knez Selo

ABSTRACT

Contrary to the traditional opinion in clinical practice that adenocarcinoma of the uterine cervix is radioresistant, probably originating from the analogy with relative resistance of healthy glandular tissues, most reports on the subject suggest that there is no significant difference in survival between squamous cell carcinoma and adenocarcinoma. We are trying here to show our own experiences with radiation therapy of the cervical adenocarcinoma and to establish any existing differences in survival in relation to the squamous cell carcinoma form. From August 1990 to August 1992 there were 106 patients at the Clinic of Oncology in Knez Selo irradiated for the uterine cervix carcinoma (comprising all histopathologic forms). There were 45 patients treated postoperatively; 61 patients were radically and palliatively treated. By the FIGO classification there were: I A - 9 patients, I B - 27 patients, II A - 9 patients, II B - 27, III A - 1, III B - 29 and st. morbi ignotus - 4 patients. Squamous cell carcinoma was found in 97/106 (92%) patients, adenocarcinoma in 4/106 (4%), and adenosquamous carcinoma in 5/106 (4%). Five-year survival for all stages was 43/106 (41%). Distribution of the histopathologic forms was as follows: squamous cell carcinoma 37/43 (86%), adenocarcinoma 3/43 (7%), adenosquamous carcinoma 3/43 (7%). Five-year survival correlated to the histopathologic form was as follows: squamous cell carcinoma 37/97 (38%), adenosquamous carcinoma 3/5 (60%) and adenocarcinoma 3/4 (75%). Using the Fisher test we did not found any statistically significant difference among the groups with squamous cell carcinoma and adenocarcinoma in the 5-year survival rates ($p = 0.154$). In our material we have not found that a histopathologic form of the uterine cervix carcinoma influences the 5-year survival rate of irradiated patients.

KEYWORDS: Adenocarcinoma; Cervix Neoplasms; Radiotherapy; Survival Rate; Carcinoma, Adenosquamous

INTRODUCTION

In addition to the disease volume and stage, numerous other factors are of prognostic significance in the radiotherapy of malignant uterine cervix tumours: histopathologic type of the lesion, vascular or lymphatic invasion, anemia, hypertension, simultaneous inflammations within the pelvis etc. Contrary to the traditional opinion in the clinical practice that cervical adenocarcinoma is radioresistant, probably originating from the analogy with the relative radioresistance of the healthy glandular tissues, most reports on the subject suggest that there is no significant difference in survival between squamocellular and adenocarcinoma (1-3). The aim of this work is to present our own experiences with radiotherapy of the cervical adenocarcinoma and to detect the difference, if any, in the 5-year survival rates of adeno- and squamocellular carcinoma.

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MATERIALS AND METHODS

From August 1990 to August 1992 at the Clinic of Oncology in Knez Selo, Dept. of Radiotherapy, there were 106 patients with cervical cancers (all histopathologic types). In order to analyze the initial results we took this period for at least 2 reasons. First, on account of almost uniform radiotherapeutic approaches and almost identical treatments of squamocellular and adenocarcinoma of the uterine cervix. Second, this was the longest period of a relative stability in the work of our linear accelerators - there were no malfunctions and interruptions longer that 1/10 of the time needed for radiotherapy application (otherwise, corrections of the total dose fractionation would be required). Out of the total number of patients, postoperatively irradiated were 45, and radically and palliatively (without any prior surgery) 61 patients. By the FIGO classification there were: I A - 9 patients, I B - 27, II A - 9, II B - 27, III A - 1, III B - 29 and stadium morbi ignotus - 4 patients.

RESULTS

Squamocellular cancer was found in 97/106 (92%) patients, adenocarcinoma in 4/106 (4%), while 5/106 (4%), according to pathologist's report, had a mixed form (ÓCarcinoma adenosquamosum cervicis uteriÓ). Other histopathologic forms were not detected. Overall 5-year survival for all stages was 43/106 (41%). Histopathologic forms distribution was: squamocellular carcinoma 37/43 (86%), adenocarcinoma 3/43 (7%) and adenosquamous 3/43 (7%). This means that within the period of 5 years after radiotherapy, out of the total number of deaths (63) there were 60 (95%) squamocellular cervical cancers, 2/63 (3%) were mixed pathology, while there was only one case - 1/63 (2%) of ÓpureÓ adenocarcinoma. Five-year survival, for each histopathologic form, was as follows: 37/97 (38%) for planocellular cancer, 3/5 (60%) for adenosquamous cancer and 3/4 (75%) for adenocarcinoma. With the Fisher test we have found that there was not any statistically significant difference in 5-year survival rates between the groups with squamocellular and adenocarcinoma ($p=0.154$).

DISCUSSION

Adenocarcinoma arises from the cyllindrical mucosa of the endocervix or the mucus-secreting endocervical glands. The endocervical adenocarcinoma may form mucosal glands lined by high columnar cells and produce tubular folds oriented in many directions. The stroma surrounds the epithelial formations. As the tumor becomes less differentiated, the cells become more bizzare, contain more mitoses, and do not have a glandular appearance. Sometimes it is difficult to differentiate a primary endocervical carcinoma from an endometrial tumor (1). Adenocarcinoma of the cervix can be subdivided into pure adenocarcinomas and mixed adenosquamous carcinomas. Mixed carcinomas can be further subdivided into mature, „signet-ring“ and glassy-cell types (2). Adenosquamous carcinoma is relatively rare (2% to 5% of all cervical carcinomas) and consists of intermingled epithelial cell cores and glandular structures. The squamous component is frequently nonkeratinizing (1). Cervical adenocarcinoma is a relatively rare histopathologic form. Authors report differing incidences, usually below 10%. In a study of 1484 patients with an invasive cervical cancer, treated primarily with irradiation, adenocarcinoma was found in 65 (4.4%) (4). Another group of authors report

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the incidence of adenocarcinoma of 5.1% out of 2489 patients, with additional 7.9% for the mixed type and 87% for squamocellular carcinoma. (2). Information from the literature on the influence of histopathology on 5-year survival are contradictory. Some studies suggest the prognostic value of histologic features in patients treated with radiotherapy; some other studies do not confirm such a relationship (2,5,6). The 19th FIGO Annual Report showed an inferior 5-year survival for patients with adenocarcinoma, whether treated by radiation alone or by surgery with or without radiation (2). There are even speculations about the prognostic groups - adenosquamous and large-cell non-keratinizing reputedly carry the best prognosis, adenocarcinoma and keratinizing squamocellular slightly worse, while small-cell and glassy-cell types carry the worst prognosis (7). In several reports quite contradictory attitudes are presented, with retrospective analyses of treatment results denying any direct influence of the histopathologic type of the tumour on survival, simultaneously denying the thesis that adenocarcinoma of the uterine cervix is a tumour with worse prognosis compared to squamocellular type. (2,5). Out of 9/106 (8%) patients irradiated at the Clinic of oncology in Knez Selo, with adenosquamous or adenocarcinoma, 6 were alive for more than 5 years after their therapy. One patient with „pure“ adenocarcinoma of the uterine cervix with a lethal outcome had the clinical II B stage (FIGO), ie the disease was inoperable, so that she received radical radiotherapy. Other three patients with „pure“ adenocarcinoma are alive for more than 5 years free of disease; two of them had stage I B disease (with postoperative radiotherapy) and one with III B stage (with radical radiotherapy administered). Such a small number of treated patients does not make it possible for us to bring forth any definitive conclusions. However, we agree more with the authors sharing the opinion that histopathologic features are not a factor of significance for survival rate since the results are not significantly better nor worse from those obtained for much more common squamocellular carcinoma. Prognostical significance should be sought, above all, in the disease stage and tumour volume.

CONCLUSION

Adenocarcinoma of the uterine cervix is a rare histopathologic form (9/106; 8%). ÓPureÓ adenocarcinoma was found in 4/106 (4%). Contribution of adenocarcinoma in patients who were alive after 5 years is 6/43 (14%); contribution of ÓpureÓ adenocarcinoma was 3/43 (7%). We may conclude, from our material, that there is no statistically significant difference among the groups with squamocellular and adenocarcinoma in the 5-year survival rate (p=0.154). Small number of treated patients with adenocarcinoma of the uterine cervix does not allow any definitive inferences, but we are inclined to agree with most authors dealing with the subject, that histopathology is not the factor of significance for survival.

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Brenner tumor of the ovary and transitional cell neoplasms of the urinary bladder: a comparative histochemical and immunohistochemical analysis

ABSTRACT

The modern classification of ovarian tumors based on histogenetic principles is clinically important in the prognosis evaluation and differential therapy. The histogenesis of the Brenner Tumor (BT) has not been yet fully clarified. Since in the recent years the histogenesis of BT has been linked with the urothelial nature, the purpose of this study was to compare the histochemical and immunohistochemical patterns of BT with transitional cell carcinoma (TCC) of the urinary bladder. Out of the total of 1312 ovarian tumors diagnosed over the period between 1989 and 1999, there were only 9 BTs: 7 BTs were typical benign, 1 was metaplastic, and 1 was proliferating. In addition to the hematoxylin and eosin, periodic acid-Schiff and alcian blue were also utilized. Selected sections were immunostained for cytokeratin, carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA), neuron-specific enolase (NSE), chromogranin and serotonin. The same methods were utilized for selected TCC grade I - II. Epithelial cells of BT and TCC revealed the presence of glycogen in all cellular layers and an alcianophilic surface mucous coat. Immunohistochemically, CEA, EMA, keratin, chromogranin and NSE reactivity were found in BT and TCC. Serotonin was negative in all of the cases of BT and TCC. The common histochemical and antigenic pattern of BT cells and TCC of the bladder point to their common origin. This is an indirect confirmation of the hypothesis that BT cells derive directly from the Mullerian system, which, due to the relationship of the gonadal ridge to the mesonephros, preserves the ability to undergo transitional cell differentiation.

KEYWORDS: Brenner tumor; Carcinoma, Transitional Cell; Immunohistochemistry

INTRODUCTION

The modern classification of ovarian tumors based on histogenetic principles is clinically important in the prognosis evaluation and differential therapy. The histogenesis of the Brenner tumor (BT) has not been yet fully clarified. The origin of this tumor was originally linked with the follicular epithelium, and later with Walthard rests, rete ovarii, mesonephric duct remnants, and the celomic epithelium, while the hypothesis according to which BT is a variety of teratoma, persisted for a long time (1-3). Since in the recent years the histogenesis of the BT has been linked with the urothelial nature, the purpose of this study was to compare the histochemical and immunohistochemical patterns of BT with transitional cell carcinoma (TCC) of the urinary bladder.

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PATIENTS, MATERIALS AND METHODS

Out of the total of 1312 ovarian tumors diagnosed over the period between 1989 and 1999, there were only 8 patients with BT. These 8 patients harbored 9 BTs, as in one instance the tumor was bilateral. 7 BTs were typical benign, 1 was metaplastic, and 1 was proliferating. There were 4 pure BTs and 3 mixed tumors in which the Brenner elements were intermixed with mucinous cystadenoma (in 2 cases) and mature cystic teratoma (in one case). One of pure BTs was associated with serous cystadenoma of the contralateral ovary. Tumor size ranged from 7 mm to 15 cm. All microscopic slides were reviewed, and in most instances the original paraffin blocks were recut and stained with hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), and alcian blue stains. Selected sections were immunostained for cytokeratin, carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA), neuron-specific enolase (NSE), chromogranin and serotonin. The same methods were utilized for 10 selected cases of bladder tumors of the transitional cell type grade I-II. Antibodies used for immunohistochemistry are summarized in Table 1. Immunohistochemistry was routinely performed, using the avidin-biotin-peroxidase technique. The percentage of positive staining tumor cells was estimated and categorized as negative (no staining at all), focal (1-10% staining tumor cells), partial (10-50% staining tumor cells), and subtotal/total (more than 50% staining tumor cells).

Table 1. Characteristics of the antibodies used in this study

Antibody	Pre-treatment	Dilution	Source	Positive control
Pan-CK (5/6/8/18)	Trypsin	1 : 100	Vector	Skin
CK 19	Trypsin	1 : 100	Vector	Skin
CEA	Trypsin	1 : 200	Vector	Colon carcinoma
EMA	-	1 : 500	Vector	Breast cancer
NSE	High temp.	1 : 7500	Dako	Oat cell carcinoma
Chromogranin A	High temp.	1 : 2500	Dako	Adrenal medulla
Serotonin	-	1 : 5		Carcinoid tumor

RESULTS

Epithelial cells of BT and TCC revealed the presence of glycogen in all cellular layers, and an alcianophilic surface mucous coat. The results of the percentage of positive staining tumor cells with different antibodies are presented in Table 2.

Semi-quantitative staining results of Brenner tumor and transitional cell tumor of urinary bladder

		Pan-CK	CK 19	CEA	EMA	NSE	Chromogranin	Serotonin
Brenner tumor N=9	Negative	0	0	0	1	0	0	9
	Focal	3	1	7	7	7	6	0
	Partial	3	2	2	1	1	0	0
	Total	3	6	0	0	1	3	0
TCC N=10	Negative	0	0	0	2	2	2	10
	Focal	3	0	6	6	6	3	0
	Partial	4	4	4	2	2	5	0
	Total	3	6	0	0	0	0	0

In almost all of the BT cases (88.8%) the presence of all the tested antigens except serotonin was immunohistochemically con-

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firmed, while in TCC the presence of the above mentioned antigens was confirmed in 80% of the cases. 2 TCCs revealed negative staining for EMA, NSE and chromogranin. Serotonin was negative in all of the cases of BT and TCC.

DISCUSSION

The resemblance of BT epithelium and the epithelium of the urinary tract was first detected and described by Schiller as early as 1934 (3). Numerous histologic, histochemical, and ultrastructural studies done since then confirmed that BT contains urothelial-type epithelium (3-5). An identical or nearly identical immunohistochemical profile of BT and TCC has been described by a number of authors (3,6-8). Santini et al. (7) quote results similar to those included in this study, the difference being that they confirm the presence of serotonin storing cells in both BT and the urothelium. Soslow et al. (8) also confirm the presence of an almost identical antigenic pattern of BT and TCC, but with the different percentage of individual antigens, which leads them to conclude that TCC of the bladder and the ovarian BT constitute an immunophenotypically distinct form of transitional cell proliferations. We, however, believe that the differences in the intensity of immunohistochemical staining and the frequency of antigens are small and insignificant and that the obtained results point to the fact that they are antigenically identical. The common histochemical and antigenic pattern of BT cells and TCC of the bladder point to their common origin. This is an indirect confirmation of the hypothesis that BT cells derive directly from the Mullerian system which, due to the relationship of the gonadal ridge to the mesonephros, preserves the ability to undergo transitional cell differentiation.

CONCLUSION

The common histochemical and antigenic pattern of BT cells and TCC of the bladder point to their common origin. This is an indirect confirmation of the hypothesis that BT cells derive directly from the Mullerian system, which, due to the relationship of the gonadal ridge to the mesonephros, preserves the ability to undergo transitional cell differentiation.

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Expression and distribution of Sialyl-Tn-antigen (STN) in mucinous and serous ovarian tumors

ABSTRACT

Rare studies about distribution of Sialyl-Tn-antigen (STN) in ovarian neoplasms aimed our investigation toward examination of expression of this antigen in mucinous and serous ovarian tumors, as well as in bordeline types of these neoplasms. Surgical material of 125 patients with a previous clinical diagnosis of ovarian tumor was used. Specimens obtained by ovariectomy or ovariectomy with histerectomy were routinely processed. Five micrometer thin sections were stained with a routine H/E method for pathohistologic verification of the lesions and with immunocytochemical SAB method with anti TKH2 antibodies (1:300). Weak or strong immunoreactivity was found in all mucinous tumors (benign, bordeline and malignant). Benign serous tumors showed strong multifocal reactivity on STN antigen that was always in the inverse proportion with the degree of displasia.

In the mucinous parts of sero-mucinous adenocarcinomas STN showed a strong reaction, but serous parts of these tumors were STN-negative. Endothelial stromal cells of all investigated neoplasms contained STN-antigen. Normal ovarian tissue was STN-negative. Our results indicate that STN is a good marker for mucinous diferentiation in cystadenomas, the cystadenomas with displasia and an excellent marker for mucinous cystadenocarcinomas. The absence of this antigen in normal tissue emphasizes a differential-diagnostic significance of this marker.

KEYWORDS: Ovarian Neoplasms; Immunohistochemistry; Antigens, Tumor Associated, Carbohydrate

INTRODUCTION

STN antigen belongs to the group of carbohidrate antigens bounded to the cell membrane and is product of early glycosilation. Kjeldsen et al. (1988) were the first who isolated monoclonal antibody TKH2 that is used for detection of STN antigen (5). The normal human tissue shows STN-reactivity localised in excretion ducts of salivatory glands, tonsills epithelium, oxintic gastric cells, duodenal goblet cells, Leydig cells in testis, endometrium and capillary endothelium (11). Sialyl-Tn-antigen can be verified in serum

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and other body fluids also, where its normal value is lower than 39 U/ml (2,7). Numerous studies indicate that neoplastic cells of various origin show a reaction on anti-STN-antibodies in great percentage, especially malignant tumors of the digestive tract, urinary bladder, prostate, breast, uterine cervix and endometrium (2,8). Considering rare reports on the presence of this marker in the ovarian tumors, the aim of our study was to examine the expression and distribution of STN in mucinous and serous tumors.

MATERIALS AND METHODS

During the study, the surgical material from Obstetrical-Gynecology Clinic of Medical Faculty in Kragujevac was used. Specimens obtained by ovariectomy or ovariectomy with histerectomy from 125 patients with previously clinically diagnosed ovarian tumor were delivered to the Institute of Pathology of the Medical faculty in Kragujevac. After microscopic examination, specimens were fixed in 10% formalin for 24 hours, routinelly processed and embedded in paraffin. On 5 micrometer thin sections, a routine H/E method for verification of the lesions and differentiation of the histologic subtypes of tumors as well as the immunocytochemical SAB (streptavidin-biotin) method (Histofine SAB pro Kit, Nichirei, Tokyo) with anti TKH2 antibodies (1:300) for detection of the STN-antigen were applied.

RESULTS

The routine H/E method showed that of 125 cases 34 specimens were benign mucinous tumors (27.2%), 11 specimens were malignant mucinous tumors (8.8%) and 8 cases were borderline mucinous tumors (6.4%).The serous tumors group contained 43 cases of benign serous tumors (34.4%), 18 cases of malignant serous neoplasms (14.4%) and 11 cases of serous borderline tumors (8.8%). The immunocytochemical investigation of the STN-antigen showed that this marker was weakly or strongly present in all mucinous tumors (benign with or without displasia as well as malignant types with various degree of differentiation). Benign serous tumors showed strong multifocal reactivity on STN antigen that was always in inverse proportion with the degree of displasia. So, strong immunoreactivity of this marker was present in well differentiated epithelium, but weak reaction was found in altered cells. Mixed, sero-mucinous adenocarcinomas were positive on STN-antigen in mucinous parts, but negative in serous parts of the neoplasms. The presence of STN-antigen was verified in stromal endothelial cells of all examined tumors, while the normal ovarian tissue showed a complete absence of this marker.

DISCUSSION

Our results concerning expression of the STN-antigen in epithelial ovarian tumors are in correlation with the findings of other researchers (2,4,9,10). We verified STN immunoreactivity in all mucinous tumors, including benign with or without displasia and malignant lessions with various degree of diferentiation. In the contrast to the findings of Inoue et al. (1990) and Imura et al. (1989) who had found the STN-antigen in serous adenocarcinomas, our results indicate that theese neoplasms, regardless to histologic gradus, were STN-negative. The presence of STN in the foci of serous glands in benign and borderline tumors (much less) can be explained by the local differentiation of the gland epithelium into mucinous direction (3,4). The same reason is the cause of mixed tumor (serous-mucinous) appearance. The findings of our study suggest that STN is a good marker for benign mucinous tumors with or without displasia and the best marker for mucinous cystadenocarcinomas. These data and the fact that the normal ovarian tissue does not express STN (except endothelial stromal cells) emphasize the differential-diagnostic importance of this marker for the diagnosis of mucinous ovarian lesions (1,6,11).

CONSCLUSION

Our results indicate that STN is a good marker for mucinous differentiation in cystadenomas, the cystadenomas with displasia and an excellent marker for mucinous cystadenocarcinomas. The absence of this antigen in normal tissue emphasizes a differential-diagnostic significance of this marker.

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Bilateral adenocarcinoma of the fallopian tubes

ABSTRACT

Primary adenocarcinoma of the fallopian tubes is one of the rarest tumors of the female genital tract, and in 20 per cent of all cases it is bilateral. The authors reported a case of a 50-year-old woman with bloody vaginal discharge, pelvic pain and swelling. After an explorative fractional curettage and radical surgical operation, a bilateral adenocarcinoma of the fallopian tubes was diagnosed. The possibility that a tubal occlusion is a risk factor in the development of tubal carcinoma is discussed.

KEYWORDS: Fallopian Tube Neoplasms; Adenocarcinoma

INTRODUCTION

Primary adenocarcinoma of the tube is an uncommon tumor which arises from the cylindrical epithelium. It has been reported in approximately 0,2-0,5 per cent of all malignancies of the female genital tract. It is encountered in women between 40 and 60 years of age, although patients as young as 18 years have been observed as well. The bilateral involvement occurs in about 20 per cent of the cases. The histologic structure of the tumor is mostly similar to that of the serous ovarian adenocarcinoma, and can be well or poorly differantiated, papillary or papillary-alveolar and solid or medullary. Macroscopically, it is divided into papillary and solid tumors.

CASE REPORT

A 50-year-old woman, gravida 1, para 1, noticed an irregular bloody vaginal discharge, pelvic pain and swelling in the lower abdomen. She had been unsuccessfully treated surgically and medicamentously for infertility 22 years before. In April 1998, she visited the Clinic for Obstetrics and Gynecology. The gynecologic and ultrasonographic examination revealed bleeding from the uterus, an egsocervical and endocervical tumor-like mass, enlargement of the uterus, the presence of leiomyomata, as well as a cystic tumor of the left ovary, which looked malignant due to its papillary appearance. The level of the CA-125 antigenic determinant was significantly elevated (four times). After the examination, the fractional explorative curettage and elimination of the cervical egsophytic mass on the vaginal portion of the uterus, cervical canal and the uterus cavity were performed. The material was sent to the Department of Pathology and Histology of the Novi Sad Clinical Centre, where it was prepared by the standard laboratory tehnique, paraffin sectioned and stained with haematoxylin-eosin for pathohistologic analysis.

RESULTS

In all sections, a tissue of adenocarcinoma composed of branching, papillary and cribriform formations with loose fibrovascular cores was found on microscopic examination. The papillae were covered by malignant epithelial cells with enlarged hypochromatic nuclei and a moderate degree of nuclear atypism. The fact that endometrial structure was unchanged and clearly demarcated from the neoplastic areas in the material obtained from the uterus cavity, pointed to a secondary localization of the neoplasm. A total abdominal hysterectomy, bilateral salpingooophorectomy, omentectomy and regional lymphadenectomy were performed. On macroscopic examination, the tubal serosa was smooth on both sides, and both tubes were dilated and filled with a papillary, white, soft substance. The tumor formation was found near the left ovary. A few lymh nodes were found in the adipose tissue. Small islets of white tissue were found in the peritoneum, omentum, right parametrium and uterus (subserosal localization). There were no remarkable histologic changes in the right ovary, endometrium, and cervix, except for the myometrium, where leiomyomata were found. On microscopic examination, the tumorous tissue from the tubes showed the same histologic structure as in the curettage material, described above. The tumorous tissue infiltrated the muscular layer of both tubes, and showed large regions of necrosis. The tumor was found in the left ovary, in the form of a cyst filled with a malignant tissue. The uterus (its subserosal region), right parametrium, peritoneum of the urinary bladder and the Douglas, space, as well as omentum were also the sites of the secondary tumor's depositions, followed by small calcifications. In spite of a detaled examination, a tumorous tissue was not found in the endometrium and cervix. The lymph nodes showed only reactive changes. Finally, the diagnosis was reached: Bilateral adenocarcinoma of the Fallopian tubes, histological grade II, stage III (according to the FIGO classification). After the normal postoperative period, the patient received teletherapy, chemiotherapy (with carbuplatina 450mg. and endoxan 1000mg.), and radiotherapy (in 22 series) in the Institute of Oncology, Sr. Kamenica. The patient was well four month after the operation and the level of CA- 125 antigenic determinant was normal.

DISCUSSION

The etiology of the primary adenocarcinoma of the fallopian tube is still unknown. Chronic inflammatory lesions, tuberculosis and other forms of the specific inflammations of the tube, as well as adenomyosis, are thought by some authors to be frequently associated with carcinoma, but those lesions of the tube are very frequent and carcinoma is equally rare. Adenomatous hyperplasia of the tube and estrogen-producing ovarian tumors have been discussed as possible couses of the bilateral carcinoma (2). Hyperplastic and atypical changes of the tubal epithelium have also been considered as potential premalignant lesions of the ffallopian tubes (3). A case of a primary fallopian tube adenocarcinoma after antiestrogen therapy for brest carcinoma was also reported (4). The bilateral involvement frequently occurs, its reason being unknown though. The question as to whether these two tumors arose independently because of the simultaneous carcinogenic stimulus or one tumor metastazed to the contralateral tube is difficult to answer (1,3). It is possible that some carcinogenic chemicals migrate to the ovarian surface and the peritoneal cavity from the vagina through the uterus and normal tubes, pass through them and stimulate the ovarian surface epithelium to develop an ovarian carcinoma. If the tubes are occluded for any reason carcinogens could not be transported and those chemicals might be accumulated within the tubes and act as a stimulus for the development of a tubal bilateral adenocarcinoma. A case of bilateral tubal adenocarcinoma occuring 22 years after the tubal

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sterilization contributes to this hypothesis, as well as the case we described (3). A search for similar cases is necessary for a better understanding of the relatioship between the tubal occlusion and carcinoma. The clinical signs of this neoplasm are not characteristical. Vaginal discharge, presence of an adnexal mass and pelvic pain (5) are the most common signs, but the presence of the Meigís syndroma was reported as well (6). The diagnosis of this neoplasm is very difficult to make and it is usualy reached intraoperatively. Only 6,5 per cent of the correct diagnoses were made preoperatively (2). Ultrasonographic examination and magnetic resonance imaging could be used as the diagnostic methods, as well as the cervicovaginal and endometrial cytology which in our opinion should be emphasized. Fractional explorative curettage was also a very important method in reaching a diagnosis in our case. This higly malignant neoplasm metastasizes locally to the regional lymph nodes, uterus, cervix, ovarium, peritoneal surface, omentum, even into the retroperitoneal cavity (7). Long distant metastazes are rare, but metastatic deposites could be found in the central nervous system (8,9), brest (10), lungs (11), skin (12), and bones (13),as well as in the other organs. In our case, only local metastases were found, including uterus subserosal localisation. The absence of the tumorous tissue in the endometrium and endocervical mucosa could be explained only by the total elimination of the tumorous tissue during the curettage. The prognosis of this rare tumor depends of the disease stage and histologic grade. According to some authors, the 5-year survival rate is 40 per cent (14), but according to the others it is 60 per cent (15). The 5-year survival rates for stage I/II and stage III/IV are 88,9 per cent and 16,7 per cent, respectively (15). The differences between the results are due to the therapy after the radical operation. The rules are not established, so the therapy is empirical and includes radiotherapy (16) or chemiotherapy (like the treatment with polychemiotherapy containing platinum which gives the best results (17). The CA-125 antigenic determinant is very useful in the patient's, follow-up.

In conclusion, the case reported still keeps open the questions of the diagnosis and possible couse of this rare disease, although the tubal occlusion could be the risk factor of the growth of this tumor.

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Metastatic sites of ovarian cancer

ABSTRACT

The patient was a 56-year old woman who had liver metastasis at the time of initial diagnosis of ovarian cancer. With operative and cytostatic therapy we achieved the DFS of 22 months. Relapses were diagnosed three times, and with combined debulking surgery, chemotherapy and palliative radiotherapy, new DFS intervals of 18 and 2 months were achieved. Overall survival was almost 5 years. The case is representative not only because of the long-term survival, but on the account of unusual metastatic sites (appendix, spleen) for ovarian cancer.

KEYWORDS: Ovarian Neoplasms; Neoplasm Metastasis; Splenic Neoplasms; Apendiceal Neoplasms

INTRODUCTION

Ovarian cancer is the fifth commonest type of cancer in females, the fourth leading couse of death in women and the leading cause of death from gynecologic cancers (1). It is usually presented at an advanced stage due to the lack of symptoms and our current inability to detect early stage disease. Over 70% of ovarian cancer patients are initialy diagnosed with International Federation of Gynecology and Obstetrics (FIGO) at stage III or IV disease (2), and while the intraabdominal disease is often widespread, parenchymatous metastases at initial presentation are rare. The most common presenting symptoms include abdominal pain, distension and early satiety, and the most significant sign present at initial examination is a pelvic mass. Refined surgical techniques and platinum based chemotherapy have increased the number of patients achieving complete remission and a prolonged progression-free survival, but only around 20% will survive in the long run (3). Second look laparotomy has been performed for evaluation of the response to therapy in patients who are clinically free of the disease or for secondary cytoreduction after chemotherapy in patients with residual tumor, as well as for resection of the new secondary deposits.

CASE REPORT

A 56-year old woman, postmenopausal for 1 year, gravida 2, para 2, presented to her internist in September 1990 for abdominal pain and distension. Other history was unremarkable. On physical examination, ascites was noted as well as a palpable abdominal mass. Ultrasound of the abdomen and pelvis revealed a significant omental disease, solitary liver metastasis, 40x36 mm in diameter, marked ascites and adnexal tumor. Chest x-ray was normal. The patient was referred to the gynecologists two weeks later and then underwent laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy and partial omentectomy. Surgicopathologic assessment revealed stage IV, grade 2 papillary serous ovarian adenocarcinoma, with involved liver parenchyma, ascending colon, omentum, right ureter and bilateral tubes and ovaries, as well as positive peritoneal washing. The largest diameter of the largest residual mass was 2 cm or less which was considered an optimal cytoreduction. Postoperatively, the patient received eight courses of cisplatin-based chemotherapy. After three cycles of the therapy liver CT scan showed no evidence of the disease and her CA-125 became normal (13 U/ml). Chemotherapy was completed in August 1991 and the patient was followed-up in two month intervals. The patient continued without complaints until February 1993 when she got pelvic pain due to developing local recurrence after 22 months DFS. Physical examination and imaging techniques suggested no other sites of relapse. Serum CA-125 level was elevated at the time of local recurrence (147 U/ml). From March 1993 to April 1993 palliative irradiation was performed (external beam therapy with 40 Gy pelvic dose and 36 Gy brachytherapy on vaginal vault). Because of the patientÌs socioeconomic status, we werenÌt able to introduce taxanes as the second line chemotherapy, so we started with Melphalan ending it in June 1994 after twelve cycles. A complete response was documented after palliative radiotherapy and two courses of chemotherapy. The disease progression was observed in December 1994 after 18 months DFS. CT scan revealed spleen metastases and the patient underwent relaparotomy, spleenectomy and appendectomy. Pathologic assessment revealed secondary deposits in these organs. In May 1995 palliative pelvic re-irradiation was performed with 30 Gy external beam radiotherapy. The patient died in July 1995, 4 years and 10 months after the diagnosis of stage IV ovarian cancer.

DISCUSSION

Early-stage ovarian cancer is usually asymptomatic and it is the intraperitoneal spread of disease that produces the symptoms and signs most often observed. Patients frequently complained on vague abdominal pain, decreased appetite or early satiety, or abdominal distension. On physical examination, the presence of ascites or an abdominal/pelvic mass is most consistent with ovarian cancer. Ovarian cancer primarily disseminates by direct exfoliation of malignant cells within the peritoneal cavity. Once the pelvic and paraaotic lymph nodes have been invaded, lymphatic channels in the diaphragm and retroperitoneum permit dissemination above the diaphragm. The frequency of metastatic spread to the pelvic and paraaotic lymph nodes increases with stage. Chen and Lee found that the incidence of positive paraaortic lymph nodes was 42% and 67% in patients with stage III and IV disease, respectively.Hematogenous spread is the least common route of spread. Fewer than 5% of patients will have parenchymal metastases indicative of hematogenous spread at the time of presentation (4). Despite aggressive surgical and medical therapy, ovarian cancer usually continues to metastasize resulting in death. Dvoretsky et al. found a high frequency of metastatic lesions in an autopsy series of 100 patients treated for ovarian cancer. Visceral parenchimal metastases to the liver (45%), lung (39%), pancreas (21%), spleen (15%), bone (11%), kidney (10%) and brain (6%) were noted (5). Standard therapy remains cytoreductive surgery followed by adjuvant chemotherapy and although median survival was improved over the last decade, the prognosis remains poor with a five-year rate for stages III and IV disease of around 20% and 10% (6,7).

In conclusion, our case suggests that the patient with stage IV epithelial ovarian cancer responded to treatment i.e. induction chemotherapy followed by interval debulking. In spite of the overall poor prognosis, some patients will be long-term survivors, with the extent of surgical debulking as a strong determinant of an outcome.

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Leiomyomatosis peritonealis disseminata. Clinico-pathohistological manifestations

KEYWORDS: Leiomyomatosis; Peritoneal Neoplasms; Diagnosis; Histocytochemistry

Leiomyomatosis peritonealis disseminata (LPD) is very rare lesion in female presented by multiples smooth - muscle nodules subperitonealy located into the abdominal cavity. The autors show a case of pelvic LPD in 32-years old female. Number of tissue specimens from surgicaly removed subperitoneal nodes were fixed in 10% pufered, neutraly formaline, imbibed into the paraffin and cutted by microtome on the 5-7 microne section were stained by standard hematoxyllin-eosin (H&E) metod, following histochemistry metods (PAS,Van Gieson, Masson trichrome) and imunohistochemistry metod (Actin). Pathoanatomical aspect: Number of subperitoneal tumor nodules diameter ranged from 25 to 95 mm, smooth surface, inhomogeneous structure, with number of porous areas, soft-elastic consistence. Histological aspect shows well-differented smooth muscle tumors formed of fusiform, elongated cells associated in knitted fibers, with minimally pleomorphysm and rare mitoses and focal hypercellularity. Particulary hyalinisation and stromal oedema were noted. Multiple tissue analyses and well correlation with gynecological and operative finding are necessary to determine LPD from well-differentiated Leiomyosarcoma.

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