Parameters of Cellular Immunity in Perimenopausal Patients with Glandular and Adenomatous Endometrial Hyperplasia

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No appreciable disorders of cellular immunity were detected in patients with glandular cystic endometrial hyperplasia. Atypical endometrial hyperplasia was associated with quantitative changes in T lymphocytes and their subpopulations, decreased level of lymphocytes carrying activation antigens, and increased count of natural killers. These changes can be characterized as immunocompensation.

Key Words: *T lymphocytes; B lymphocytes; T lymphocytes subpopulations; endometrium; hyperplasia*

Evaluation of general immune mechanisms in various benign pathologies of the endometrium helps to determine effective approaches to differential diagnosis and treatment strategy.

For a long time, characteristic changes in the cellular and humoral immunity were believed to be an obligatory component of all hyperplastic processes in the endometrium. Now this viewpoint is gradually replaced by an opinion that the general immune mechanisms are preserved and only local immunity is changed in these patients [3].

Further researches in this field were stimulated by the data on a direct correlation between the expression of Fas/APO-1 antigen on peripheral blood lymphocytes and tumor cells in patients with benign and malignant prostatic tumors [2]. The existence of similar parallels in proliferative processes in the mucosa of the corpus uteri was hypothesized.

Here we analyzed the expression of antigen markers on peripheral blood lymphocytes in patients with glandular (GEH) and adenomatous endometrial hyperplasia (AEH).

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MATERIALS AND METHODS

Experimental group consisted of 44 women aged 40-53 years with hyperplastic processes in the endometrium: 24 with GEH and 20 with AEH (9 with slightly manifest and 11 with pronounced forms). The diagnosis was made after histological examination of the endometrium obtained by total curettage with hysteroscopy in all the cases. Fifteen (35%) patients were hospitalized for metrorrhagia, 29 (65%) for menstrual cycle disorders (oligomenorrhea and menometrorrhagia).

Evaluation of body weight and fatty tissue distribution revealed body weight index >25 in 32 (72.7%) patients, abdominal visceral obesity (waist/hip index >0.85) in 17 (38.6%) patients. Compensated glycemia after overnight fasting (4.4-6.1 mmol/liter) was observed in 34 (77.2%) and subcompensated (6.1-7.8) in 6 (13.6%) patients.

The most frequent concomitant extragenital diseases were gastrointestinal and hepatobiliary disorders without organ dysfunctions, which were detected in 12 (27%) patients.

Control group consisted of 15 healthy women aged 40-52 years after curettage for dysfunctional uterine bleeding (DUB). Pathomorphological study showed endometrium at the proliferation stage in all cases.

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The immune status was evaluated immediately after histological examination of the uterine mucosa on days 4-5 after the intervention. The expression of surface lymphocyte antigens was evaluated in indirect surface immunofluorescence with ICO monoclonal antibodies (N. N. Blokhin Cancer Research Center) to differentiation antigens of human leukocytes: CD3, CD5, CD7 (T lymphocyte markers), CD4 (helper/inductor marker), CD8, (suppressor/cytotoxic T lymphocyte marker), CD20 (B lymphocyte marker), HLA-DR (B lymphocyte and activated T lymphocyte marker), CD38 activated lymphocyte marker), CD11b (C3 complement C3bi receptor), CD16 (natural killer marker), CD25 (interleukin-2 receptor α-chain), CD71 (transferrin receptor), CD45RA (naive T and B lymphocytes and 40% of natural killer cells marker), CD50 (adhesion molecule), and CD95 (apoptosis-mediating FAS/APO-1 antigen) [1]. The percentage of antigen-positive cells expressing differentiation antigens was evaluated by flow cytofluorometry on a FACScan cytofluorometer (Becton Dickinson). At least 10,000 events were accumulated in each sample.

The results were analyzed using Consort 32 Lysis II (version 1.02) software. Group data were compared

TABLE 1. Immunological Phenotype of Lymphocytes in Patients with AEH (*n*=20)

Antigen	Group of patients	Distribution of patients depending on expression of antigen markers in lymphocytes			Donors (baseline level)
		below baseline	baseline	above baseline	
CD3	AEH	6 (30)	9 (45)	5 (25)**	60-75
	DUB (*n*=15)	4 (27)	11 (73)	0	
CD4	AEH	10 (50)	5 (25)**	5 (25)	35-46
	DUB	3 (20)	10 (67)	2 (13)	
CD8	AEH	10 (50)	3 (15)**	7 (35)	25-30
	DUB	4 (27)	7 (47)	4 (27)	
CD20	AEH	2 (10)	16 (80)	2 (10)	5-15
	DUB	2 (13)	10 (67)	3 (20)	
HLA-DR	AEH	2 (10)	9 (45)	9 (45)	7-15
	DUB	1 (7)	10 (67)	4 (27)	
CD38	AEH	7 (35)**	10 (50)	3 (15)	24-40
	DUB	1 (7)	12 (80)	2 (13)	
CD25	AEH	—	19 (95)	1 (5)	0-5
	DUB	—	12 (80)	3 (20)	
CD16	AEH	5 (25)	7 (35)	8 (40)**	10-20
	DUB	2 (13)	12 (80)	1 (7)	
CD11b	AEH	2 (10)*	17 (85)	1 (5)	10-35
	DUB	0 (0)	11 (73)	4 (27)	
CD50	AEH	2 (10)	18 (90)	0	85-100
	DUB	2 (13)	13 (87)	0	
CD45RA	AEH	3 (15)	15 (75)	2 (10)	45-65
	DUB	2 (13)	10 (67)	3 (20)	
CD5	AEH	10 (50)*	9 (45)	1 (5)	60-80
	DUB	3 (20)	12 (80)	0	
CD7	AEH	6 (30)	13 (65)	1 (5)	60-80
	DUB	2 (13)	11 (73)	2 (13)	
CD71	AEH	—	15 (75)	5 (25)	0-5
	DUB	—	12 (80)	3 (20)	
CD95	AEH	9(45)***	10 (50)	1 (5)	23-60
	DUB	0	14 (93)	1 (7)	

Note. *p<0.01, **p<0.05 compared to patients with DUB. Here and in Table 2: the percentage is shown in parentheses.

using Fisher's precise test (a nonparametrical test not depending on the distribution pattern).

RESULTS

Changes in the studied immunological parameters were detected mainly in patients with AEH. AEH was associated primarily with quantitative changes in T lymphocytes and their subpopulations (Table 1). The number of patients with high count of lymphocytes expressing $CD3^+$ antigen increased and the number of patients with baseline levels of $CD4^+$ and $CD8^+$ lymphocytes decreased in endometrial precancer in comparison with the control group and patients with GEH (Table 2). The content of $CD5^+$ lymphocytes in the group tended to decrease.

GEH was associated by increased number of patients with low content of $CD8^+$ effector T cells.

Evaluation of the number of lymphocytes expressing activation antigens showed low levels of $CD38^+$ lymphocytes in one third of patients with AEH, which 5-fold surpassed the corresponding parameter in the control group. Changes in this parameter were characteristic mainly of patients with pronounced AEH

TABLE 2. Immunological Phenotypes of Lymphocytes in Patients with GEH (n=24)

Antigen	Group of patients	Distribution of patients depending on expression of antigen markers in lymphocytes			Donors (baseline level)
		below baseline	baseline	above baseline	
CD3	GEH	8 (35)	15 (65)	0 (0)	60-75
	DUB (n=15)	4 (27)	11 (73)	0 (0)	
CD4	GEH	10 (42)	8 (33)	6 (25)	35-46
	DUB	3 (20)	10 (67)	2 (13)	
CD8	GEH	16 (67)**	4 (17)**	4 (16)	25-30
	DUB	4 (27)	7 (47)	4 (27)	
CD20	GEH	4 (17)	16 (67)	4 (6)	5-15
	DUB	2 (13)	10 (67)	3 (20)	
HLA-DR	GEH	2 (8)	15 (63)	7 (29)	7-15
	DUB	1 (7)	10 (67)	4 (27)	
CD38	GEH	8 (42)**	6 (32)	5 (26)	24-40
	DUB	1 (7)	12 (80)	2 (13)	
CD25	GEH	—	13 (68)	6 (32)	0-5
	DUB	—	12 (80)	3 (20)	
CD16	GEH	3 (13)	14 (58)	7 (29)*	10-20
	DUB	2 (13)	12 (80)	1 (7)	
CD11b	GEH	0 (0)	15 (79)	4 (21)	10-35
	DUB	0 (0)	11 (73)	4 (27)	
CD50	GEH	4 (21)	15 (79)	0 (0)	85-100
	DUB	2 (13)	13 (87)	0 (0)	
CD45RA	GEH	2 (10)	14 (74)	3 (16)	45-65
	DUB	2 (13)	10 (67)	3 (20)	
CD5	GEH	6 (32)	13 (68)	0 (0)	60-80
	DUB	3 (20)	12 (80)	0 (0)	
CD7	GEH	4 (21)	14 (74)	1 (5)	60-80
	DUB	2 (13)	11 (73)	2 (14)	
CD71	GEH	—	15 (79)	4 (21)	0-5
	DUB	—	12 (80)	3 (20)	
CD95	GEH	4 (21)*	14 (74)	1 (5)	23-60
	DUB	0 (0)	14 (93)	1 (7)	

Note. *p<0.05 compared to the control.

(50% patients). The number of patients with low content of $CD11b^+$ lymphocytes increased significantly in this group. The number of $CD25^+$ lymphocytes remained at the baseline level in AEH, and increased in GEH. On the other hand, the percentage of patients with low content of $CD38^+$ lymphocytes was similar in GEH and AEH.

The detected imbalance in T lymphocytes and their subpopulations and quantitative redistribution of lymphocytes carrying activation antigens can reflect aggravation of immunosuppression in the system of specific immunity accompanying progression of pathomorphological changes in the endometrium.

By contrast, high counts of natural killers observed in almost 50% patients with AEH were significantly higher than in DUB patients, mainly at the expense of increase of this parameter in patients with pronounced AEH (patients with GEH developed just a trend to an increase of this parameter).

The number of lymphocytes expressing CD95 antigen (Fas/APO-1) was increased in only 1 patient with AEH, in 10 patients the count of these lymphocytes did not differ from the baseline, and 9 patients had less than 23% antigen-positive lymphocytes.

Low level of lymphocytes expressing this marker was not characteristic of women without endometrial abnormalities and was found in only 4 patients with GEH.

High level of natural killer cells in patients with uterine mucosa precancer, on the one hand, indicates preserved capacity to mobilization of natural immunity and, on the other hand, attests to a strain of these mechanisms. This acquires special importance in light of decreased level of activation antigens and relative insufficiency of the Fas system, which can participate in induction of apoptosis in tumor cells [4], if we suggest that this marker is universally distributed at least among lymphoid and epithelial cells [2], including the endometrium [5].

The detected shifts in parameters of cellular immunity in GEH patients can be hardly considered pathologically significant.

At the same time, changes in the studied parameters in AEH patients can attest to involvement of the immunity mechanisms in the pathological process in precancer. Opposite changes (decreased level of lymphocytes carrying activation and Fas/APO-1 antigens and increased count of natural killers) can be characterized as immunocompensation status. However, it is difficult to evaluate stability of this equilibrium in each case. Imbalance in this system can lead to defects in immunocompetent cells with possible impairment of mechanisms of antitumor immune control, which provides conditions for reproduction of the tumor clone.

Thus, even though immunocorrection is undesirable in GEH and its efficiency is doubtful in AEH, the need of laboratory monitoring of immune defense parameters in perimenopausal patients with endometrial precancer is obvious.

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