LEUKOCYTE MIGRATION INHIBITION TEST IN PATIENTS WITH TROPHOBLASTIC TUMORS

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UDC 618.14-006.882-097.3-078

Inhibition of leukocyte migration under the influence of protein extract from a chorionepithelioma was investigated in 40 patients with trophoblastic tumors. Marked inhibition of leukocyte migration was found in patients with evidence of active tumor growth before and in the course of treatment. The exception was four patients in whom no inhibition was found either before or during treatment. The inhibition effect was absent in most patients when the clinical course was favorable as a result of surgery and chemotherapy or of chemotherapy alone. Leukocytes of healthy donors did not react to the tumor extract in any of 24 cases.

KEY WORDS: *trophoblastic tumors*; *inhibition of leukocyte migration.*

One indicator of the patient's immunologic activity is the leukocyte migration inhibition test (LMIT) [1, 3, 4]. In a previous investigation correlation was found between this index and the degree of spread and the course of the tumor process in patients with melanoma [1].

In this investigation the LMIT was studied in patients with trophoblastic tumors admitted to the Department of Gynecology, Oncologic Scientific Center, Academy of Medical Sciences of the USSR, under the care of Dr. T. M. Grigor'eva.

EXPERIMENTAL METHODS

The LMIT was performed in E. P. Troshanov's 5-channel migration capillary tubes by the method of A. G. Artemova and V. I. Ioffe, in the writers' modification described previously [1]. Instead of human embryonic serum, bovine serum was used in this investigation.

As antigen the same protein extract obtained from a chorionepithelioma of patient K. by Gerszynski's method [2] was used throughout the period of observation. The protein concentration in the extract, determined by Lowry's method, was 22.6 mg/ml. The extract was frozen and kept at −20°C. Before the test the extract was thawed and diluted with medium 199 to obtain the necessary final protein concentration of 700 μg/ml. Neither this nor a much higher protein concentration (about 2 mg/ml), incidentally, gave a toxic effect.

The ratio between the mean length of the column of leukocytes (in 10 capillary tubes) after incubation and its length before incubation was used as the index of the intensity of leukocyte migration. The migration index (MI) was calculated as the ratio between this index in the experiment (incubation with antigen) and its value in the control (incubation with medium). Student's t test was used for the statistical analysis of the results. If MI was less than 1 it indicated the presence of inhibition, if greater than 1 it indicated stimulation of migration. Values of MI not significantly differing from unity indicated the absence of either effect.

Forty pateints with trophoblastic tumors, aged from 21 to 55 years, were under observation. They included 18 patients with chorionepithelioma (6 without metastases, 12 with metastases in the internal organs), malignant hydatidiform mole (5 without metastases, 1 with metastases), and 16 with trophoblastic tumors not confirmed histologically (13 without metastases, 3 with metastases). The control group consisted of 24 healthy donors of both sexes aged 20-40 years.

Group for Combined Methods of Treatment, Department of Gynecology, Oncologic Scientific Center, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR L. M. Shabad.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 85, No. 5, pp. 580-582, May, 1978. Original article submitted July 11, 1977.

0007-4888/78/8505-0635$07.50

TABLE 1. MI in Patients with Trophoblastic Tumors before Treatment

Patients	Diagnosis	Metastases	MI	P
K.	Che	—	0,74	<0,01
Z	Che	In lungs	0.62	<0,01
A.	Che	Ditto	0,54	<0,01
V.	Che	» »	0,67	<0,01
B.	Che	» »	0,57	<0,01
G.	Che	» »	0,76	<0,01
M.	Che	» »	0,67	<0,01
P.	Tr. t	» »	0,78	<0,05
L.	Tr. t	» »	0,60	<0,01
N.	Tr. t	» »	0,62	<0,01
S.	Tr. t	» »	0,49	<0,01
G-Ko	Tr. t	» »	0,78	<0,05
R.	Tr. t	» »	0,56	<0,01
Z-va	D. h. m.	» »	0,35	<0,001
O.	D. h. m.	» »	0,70	<0,05
K-yan	D. h. m.	» »	0,40	<0,001

Note. Che) Chorionepithelioma; Tr. t) trophoblastic tumor; D. h. m) destructive hydatidiform mole.

EXPERIMENTAL RESULTS

In 16 patients with marked symptoms of tumor growth, the investigations carried out before the beginning of treatment revealed significant inhibition of migration (MI between 0.35 and 0.78; see Table 1 and Fig. 1).

Repeated performance of the LMIT in 10 patients from this group in the course of treatment gave inconsistent results. In two patients with metastases of a chorionepithelioma in the internal organs, in whom chemotherapy gave only a transient effect, marked inhibition of migration was observed for 5 months. Later, however, during an investigation 1 month after surgical removal of the primary focus, no inhibition was discovered (Fig. 2). Inhibition of migration also remained stable for 4 months in one patient who received several courses of methotrexate for a destructive hydatidiform mole. Four months later, however, at a time of complete clinical absence of symptoms, no inhibition could be found.

In four other patients of this group with a rapid and lasting effect of chemotherapy, no inhibition of migration could be found 1-2 months after the beginning of treatment or during subsequent reinvestigations in the course of 4-8 months. In the remaining three patients repeated investigations at a time of complete absence of clinical symptoms only 5-7 months after the first investigation, undertaken before treatment, likewise revealed no inhibition.

Significant inhibition of migration was found in three more patients reinvestigated during treatment and showing signs of active growth of the tumor at the time of the LMIT (Fig. 1).

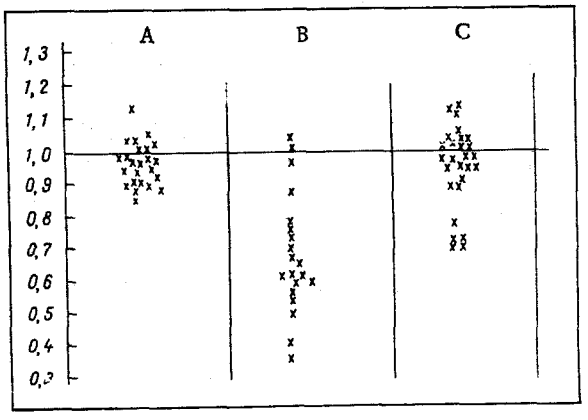

Fig. 1. LMIT on patients with trophoblastic tumors. A) Healthy donors; B) patients with signs of active tumor growth; C) patients without clinical signs of disease. Ordinate, MI.

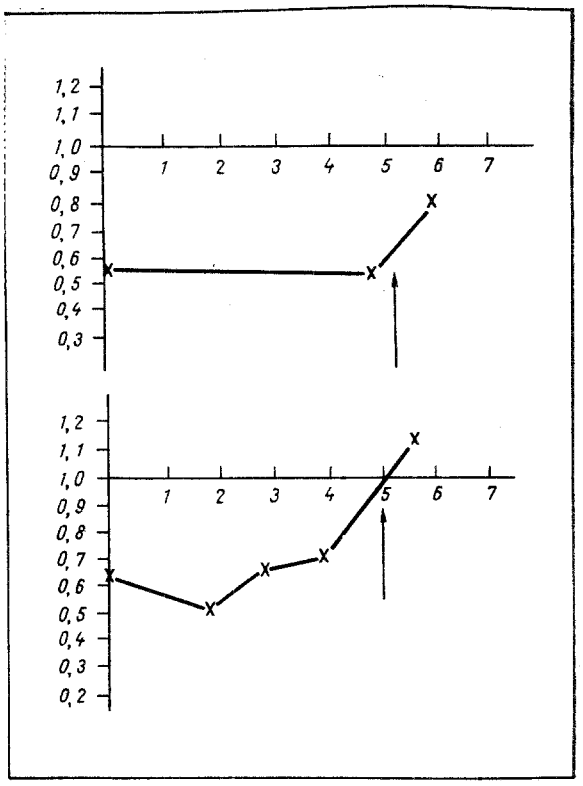

Fig. 2. Dynamics of LMIT in patients with chorionepithelioma during treatment. Abscissa) time of first measurement of MI (in months); ordinate) MI. Arrows indicate extirpation of uterus.

However, not in all patients was the result of the test positive before the beginning of treatment: In 4 cases (3 with chorionepithelioma with metastases in internal organs, 1 with a trophoblastic tumor) inhibition could not be detected either before treatment or on retesting during the 3-4 months of treatment, accompanied by a short-term effect (MI from 0.88 to 1.05).

Some patients were investigated for the first time after 1 or 2 courses of effective chemotherapy, and then again a few months after the first test. In 10 of 15 patients in whom no signs of growth of the tumor could be discovered during observation for 3-8 months, inhibition of migration could not be detected during this period either, and only in 5 patients was slight inhibition observed (MI from 0.70 to 0.76; $P < 0.05$); moreover, in 2 of 5 cases when repeated testing (5-6 times) was possible, this inhibition continued to be stable for 4 and 8 months of observation respectively.

The absence of inhibition (MI from 0.94 to 1.02) was observed in a further two patients in whom chemotherapy was ineffective and who died with metastases in the brain. These results are in agreement with the writers' previous observations on patients with melanoma in the stage of dissemination [1].

Leukocytes of healthy donors did not react to the tumor extract in any of 24 cases (MI from 0.86 to 1.17; $P > 0.05$; see Fig. 1).

The results of this investigation can be briefly summarized as follows. Inhibition of migration discovered in patients with trophoblastic tumors before treatment and also in the case of insufficiently effective chemotherapy can be regarded, on the one hand, as an indicator of an active tumor process and, on the other hand, of the preservation of immunologic reactivity. The absence of inhibition of migration in patients with no clinical signs of the desease as a result of effective treatment is evidently an indicator of irradication of the tumor focus as the source of tumor antigens. Similar conclusions were drawn by Rieche et al. [5], who observed an effect of inhibition in patients with breast cancer before operative treatment and the absence of this effect after the operation, which remained stable for a further year.

The absence of inhibition observed in cases of insufficiently effective or ineffective treatment evidently indicates the suppression of the patient's immunologic reactivity and must be regarded as an unfavorable prognostic sign.

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MECHANISM OF REGRESSION OF MAMMARY GLAND CARCINOMA IN LACTATING RATS

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UDC 618.19-006.6-092.9-007.16

The effect of the conditions of lactation on the frequency of regression of a transplantable mammary gland carcinoma RMK-1 was studied in albino rats. In rats feeding 8±1 young the tumor underwent regression in 47% of cases. After ovariectomy and administration of cortisone and oxytocin, which have an indirect inhibitory action on the secretion of FSH by the pituitary, the frequency of regression of tumors in rats feeding the same number of young rose to 71-81%. In rats with prolonged lactation, feeding 8±1 young for 2-2.5 months, and in rats with intensive lactation feeding litters of 13±2 young, regression of the tumors did not increase. The results confirm the validity of the hypothesis that, besides high secretion of pituitary FSH, a decrease in the secretion of pituitary LH plays a role in the regression of mammary gland carcinoma in the course of lactation.

KEY WORDS: *carcinoma; regression; lactation.*

The view is held that lactation, like pregnancy, stimulates growth of breast cancer and is categorically contraindicated during the treatment of this form of tumor. However, there have been isolated reports that regression of spontaneous, induced, and transplanted mammary gland carcinomas may be observed in lactating animals. Regression of tumors in such cases has been shown to depend on the intensity of lactation and on the number of young in the litter [8]. The present writer also found the same relationship during a study of the effect of lactation on growth of transplantable mammary gland carcinoma RMK-1 in rats [4]. Regression of the tumors took place in 53% of cases in properly lactating rats feeding seven to nine young, but was not observed in weakly lactating rats with only two to four young in the litter. Data on the importance of the intensity of lactation in the regression of mammary gland carcinoma suggested that an important role in the mechanism of tumor regression is played by intrinsic luteinizing hormone (LH) of the pituitary, the production of which during lactation depends on the number of young in the litter [9, 4]. However, there are observations to show that regression of tumors, even in properly lactating rats, is observed only in half of the animals and, moreover, at the end of the period of lactation, although LH secretion reaches the optimal level during the first half of lactation [10]. Hence it follows that regression of tumors is due not only to the action of pituitary LH.

In the course of lactation, the increase in pituitary LH secretion is accompanied by a decrease in the secretion of pituitary follicle-stimulating hormone (FSH), as a result of the stimulation connected with the act of suckling [1, 11]. According to the results of the writer's investigations inhibition of pituitary FSH production is a leading factor in the mechanism of the antitumor action of certain hormones on mammary gland cancer [2, 6]. In particular, the LH preparation prolactin, isolated from bovine pituitary glands, induces regression of mammary gland carcinoma in rats because one of its properties is to inhibit the secretion of pituitary FSH [3]. Consequently, it can be tentatively suggested that for the regression of mammary gland carcinoma during lactation, besides high pituitary LH secretion,

Oncologic Scientific Center, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR L. M. Shabad.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 85, No. 5, pp. 582-585, May, 1978. Original article submitted February 22, 1977.

 0007-4888/78/8505-0638$07.50