Natural killer cells and Tac antigen in the hypertension of pregnancy

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Summary: Of the immunological alterations in pregnancy hypertension were studied peripheral blood lymphocyte subpopulation in normal and hypertensive pregnancies by means of monoclonal antibodies.

In pregnant women with hypertension an increase was found in NK activity. It was also shown that an increase in circulating T cells expressing Tac antigen occurred in women with pregnancy hypertension. These preliminary data on Tac antigen suggest that there is an activation of Leu 3 cells; which may introduce the concept of Leu 3 activity like NK activity. Further studies on this subject could explain that the concept of Leu 3 activity is correct.

Key words: hypertension; NK activity; Tac antigen.

INTRODUCTION

Pregnancy is a state similar to that of the tumor-host interrelationship, being characterized by the non rejection of an antigenically different graft. The immunologic concept of pregnancy hypertension has been reconsidered recently. Pregnancy hypertension might be interpreted as either a partial or total malfunction of the fetal or the maternal immune system (1). Pregnancy hypertension could thus represent a mechanism of partial rejection of the fetal allograft. Several investigations have attempted to demonstrate quantitative changes in the functioning of the maternal immune system in association with pregnancy hypertension, and a large number of investigations have been made on the correlation between pregnancy hypertension and the immunoglobulin and complement levels. It could be stated that at present no clear association between immunoglobulin and complement levels and pregnancy hypertension exists (2). The presence of immune complexes in normal and abnormal pregnancy has been discussed elsewere. Immune-complexes have a known ability to affect the immuno-response. This effect may be on either the humoral or cellular immunoresponse, and may be suppressive or enhancing. From this point of view, pregnancy hypertension may represent rejection induced by the immune complex, and the presence of immune complexes in graft rejection has actually been reported in allograft systems other than pregnancy (3).

Renal deposits of immune complexes can induce a number of events which may result in the hypertensive disease, protei-

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nuria and proteinuria related edema. The renal mechanism, by which these processes may be instigated are poorly understood. From the studies on the circulating soluble immune complexes, it is evident that the presence of immune complexes in association with pregnancy hypertension has not yet been determined [4, 5].

Studies of lymphocyte subpopulations in pregnancy hypertension have given controversial results [6, 7].

Moore [8] reported an increase of T helper cells, Toder [6] an increase of NK cells, which was confirmed by Okamura [7]. We aimed to study whether the lymphocyte subpopulations were an expression of immunological alterations in pregnancy hypertension.

MATERIAL AND METHODS

Patients

Ten primigravid patients with hypertension and ten normotensive pregnant women in the third trimester of gestation were studied. The patients were considered to be pregnancy induced hypertensive according to the following criteria: one measurement of diastolic blood pressure >110 mmHg on a single occasion, or two consecutive measurements of DBP >90 mmHg four or more hours apart, after the 20th of week gestation, in previously normotensive, and non-proteinuric women. The patients in the two groups were pair-matched for age, parity and duration of pregnancy.

Methods

Peripheral mononuclear cells were isolated by Ficoll-Hypaque density gradient centrifugation of 10-15 ml of blood collected into heparinized containers. The cells were washed once in phosphate-buffered saline and any contaminating erytrocytes lysed in an ammonium chloride buffer. The cells were washed twice at 4C in RPMI 1640 with 25 mM-Hepes and L-Glutamine and supplemented with 5% heat-inactivated fetal calf serum. The cells were finally resuspended in this medium at 5×10/ml and 200 microliters of each of the monoclonal antibodies Leu 4, Leu 3, Leu 3, Leu 7. In 4 women studied monoclonal antibodies anti-Tac. Results were expressed as a mean, and were tested for statistical significance by the Student's t test.

Natural killer cell activity was assayed against the target cell line K 562. The target cells were labelled with 100 microliters of Cr 51 by incubation at 39 °C for 30 minutes. The labelled target cells were placed in the round bottom wall of a microplate in triplicate, followed by the addition concentration. Target cells were also placed as controls, in walls that contained RPMI only, to determine spontaneous release of Cr 51. The plates were incubated at 37 °C for 5 hours in a 5% carbon dioxide humidified atmosphere. The proportion of the total lymphocyte population capable of lysing K 562 was calculated as:

$$\frac{\text{Cr release - Spontaneous Cr release}}{\text{Total Cr release - Spontaneous Cr release}} \times 100$$

RESULTS

Comparing the hypertensive pregnant group with the normotensive pregnant control group, T helper (Leu 3) and NK cells were slightly increased but the difference was statistically significant only for the NK cells. The total number of T suppressor (Leu 2) showed no statistical difference (Table 1).

Table 1.

Subset	Normotensive	Hypertensive	t Student
Leu 4	1256±340	1331±316	ns
Leu 3	925±290	1090±210	ns
Leu 2	485±160	525±145	ns
Leu 7	286±141	512±175	$p < 0.05$

In the hypertensive pregnant group the NK activity was significantly higher as to the control group (35 - 6 vs. 15 - 4% lysis). Tac antigen was expressed only on the Leu 3 inducer subset, but not on the Leu 2 inducer cells.

DISCUSSION

A change in the balance of maternal immunoregulatory cells towards greater suppression of immune responses could con-

tribute to the immunoregulation of normal pregnancy. A decrease of NK cells has been observed in normal pregnancy and this represents a protection against early abortion.

In pregnancy hypertension we reported an increase of Leu 3 (T helper cells) and Leu 7 (NK cells). The increase in Leu 3 cells in pregnant hypertension with respect to the controls is not statistically significant; however, the number and the activity of the NK cells is significantly increased, and this suggests that the NK cells could play a role in the immunological response of pregnant women with hypertension. Recent studies have indicated that a monoclonal antibody, termed anti-TAC, may recognize the receptor sites or closely associated structures for interleukin 2 on activated human T cells ([9]). The Tac antigen, definable by anti-Tac antibody and usually found on mitogen or alloantigen stimulated T cells, was not expressed to any appreciable extent on normal circulating T cells. In the present study we showed that an increase in circulating T cells expressing Tac antigen occurred in women with pregnancy hypertension.

These Tac-positive T cells were generated only on the Leu 3 subset ([10]). These preliminary data on only 4 patients regarding Tac antigen suggest that there is an activation of Leu 3 cells; that may introduce the concept of Leu 3 activity like NK activity. Further studies on this subject could explain that the concept of Leu 3 activity is correct.

It still has to be demonstrated whether the immunologic alterations in pregnancy-induced hypertension could be related to the genesis of this disease syndrome, or if it only reflects a secondary response of the immune system to this disease. If pregnancy-induced hypertension represents a subclinical rejection mechanism, it would seem more logical that the increase of NK and Leu 3 cells occurs because of the "failure" of the maternal immune system as a response to the exposure to fetal antigenicity.

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