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Are naïve T cells and class-switched memory (IgD^- $CD27^+$) B cells not essential for establishment and maintenance of pregnancy? Insights from a case of common variable immunodeficiency with pregnancy

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ABSTRACT

The disruption of adaptive immune response has adverse effects on the establishment and maintenance of pregnancy. The adaptive immune system is regulated by several types of immune cells. However, there is limited information about cell hierarchy in the adaptive immune response to the establishment and maintenance of pregnancy in women. The assessment of the outcome of pregnancy in primary immunodeficiency diseases could help in understanding the cell hierarchy in the adaptive immune system during pregnancy. Common variable immunodeficiency (CVID) is a heterogeneous adaptive immune system disorder characterized by primary hypogammaglobulinemia. A few studies have previously reported the assessment of the T and B cell subpopulations in CVID patients. However, an assessment of the subpopulations of T and B cells and the outcome of pregnancy in women with CVID has not been reported till date. Most CVID patients show a general decrease in the expression of CD27 in B cells. The assessment of pregnancy and the subpopulations of T and B cells in CVID women with severe reduction in the naïve T and switched B cells could help understand whether these cells are essential for the establishment and maintenance of pregnancy in women.

Introduction

It has been a long-standing question as to why fetus, as a semi-allograft, is not rejected by the maternal immune system. Moreover, the question, whether the maternal immune system is a friend or foe of pregnancy, remains to be answered [1]. Appropriate adaptive immune response is important for the establishment and maintenance of pregnancy [2]. The adaptive immune system is regulated by T and B lymphocytes. Several studies suggest that $CD4^+$ T cells and regulatory T (Treg) cells play key roles in adaptive immunity and the disruption of Th1/Th2/Th17 and Treg paradigm could lead to adverse effects on the establishment and maintenance of pregnancy [3–5]. The effector T cells including the major $CD4^+$ T cell subsets, Th1, Th2, and Th17 cells, and Treg cells, are differentiated from naïve $CD4^+$ T cells upon ligation of their T cell receptors with antigens, depending on the cytokines [6–8].

There is limited information on the sub-populations of B cells during pregnancy compared to that on the sub-populations of T cells. B cells are involved in humoral immunity of the adaptive immune system. It has been considered that maternal B cells, which express autoantibodies specific for fetal antigens, are depleted during pregnancy and the increase in B cell activation markers and functions were reported in the complications during pregnancy, such as in anti-phospholipid syndrome, recurrent spontaneous abortion (RSA), preeclampsia, preterm birth, fetal growth restriction (FGR), and hypertensive disorders of pregnancy [9]. Recently, in malaria-naive cohorts, it was observed that pregnancy was associated with a significant expansion of all the switched (IgD^-) memory B cells and a decrease in the number of naïve B cells [10]. On the other hand, the animal studies revealed the normal litter size of offspring in B cell deficient mice [11], and normal pregnancy phenotype after treatment with B cell-depleting agents in mice [12] and cynomolgus monkeys [13,14].

It is not fully understood as to how the adaptive immune system is regulated for the establishment and maintenance of pregnancy. Sometimes the mice models showed different phenotype from human. It

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is not easy to investigate the role of each immune cell involved in the establishment and maintenance of pregnancy in women. Moreover, the assessment of the outcome of pregnancy, including the complications during pregnancy in the primary immunodeficiency diseases (PIDs), could help in understanding the role of particular immune cells in the establishment and maintenance of pregnancy in humans. However, some of the PIDs show poor prognosis. Moreover, there are many X-linked PIDs, such as X-linked agammaglobulinemia, X-linked severe combined immunodeficiency, X-linked hyper IgM syndrome, X-linked chronic granulomatous disease, and Wiskott-Aldrich syndrome [15].

Common variable immunodeficiency (CVID)

Common variable immunodeficiency (CVID) is a heterogeneous adaptive immune system disorder characterized by primary hypogammaglobulinemia (with IgG, IgA, and/or IgM, conventionally at least two standard deviations below the reference levels [16]), with reduced or absent specific antibody production [17]. Most patients are diagnosed during the adulthood, at 20–40 years of age, after recurrent upper and/or lower respiratory tract infections. The prevalence rate is about 1 in 25,000–50,000 [18]. However, it is considered that the actual prevalence rate could be higher because many CVID cases are not diagnosed for long time [19]. CVID mainly occurs sporadically, but 20–25% cases are familial. The etiology of the vast majority of cases of CVID is unknown. Some specific molecular defects have been identified in the small population with CVID [19]. The common complications of CVID include infections, granulomatous and autoimmune diseases, and non-Hodgkin's lymphoma [19]. The primary treatment of CVID is antibody replacement with either intravenous or subcutaneous administration of immunoglobulin at an initial dose of 400–600 mg/kg of gammaglobulin per month [17,20,21]. The frequency of respiratory tract infections, which is the most common complication, decreases after initiation of immunoglobulin replacement treatment, however other complications are unaffected [22].

In women with CVID, possible complications of pregnancy including an increased risk of miscarriage and preterm labor have been reported [22–24]. Kralickova and colleagues reported significantly higher frequencies of the threat of preterm labor, vaginal bleeding, eclampsia/preeclampsia, stillbirths, and babies with low birth weight (less than 2500 g) compared to the general populations [25]. On the other hand, Gundlapalli and colleagues reported that the fecundity rate of women with CVID was similar to that of the healthy population [26]. However, their report included not only women with CVID but also women with hypogammaglobulinemia, although CVID is a heterogeneous disorder. Several studies have shown that untreated, symptomatic females with CVID can give birth to healthy newborns [27–30]. However, a connection with miscarriage or abortion in untreated women with CVID was described as well [25,31]. Some studies have reported the assessment of the subpopulations of T and B cells in CVID patients [32–36]. However, not many reports have assessed the subpopulations of T and B cells and the outcome of pregnancy.

Hypothesis

Because CVID is a heterogeneous disorder of PID, assessment of each woman with CVID for the outcome of pregnancy and T and B cell subpopulations could provide some information about the immune cells that are essential for the establishment and maintenance of pregnancy in humans.

We describe our experience of a pregnancy case with CVID where severe reduction of naïve T cells and switched memory B cells was observed. The assessment of the outcome of pregnancy in this case might help in understanding whether naïve T cells and switched memory B cells are essential for the establishment and maintenance of pregnancy.

Evaluation of the hypothesis

This study was approved by the Institutional Ethics Board of Osaka University (No. 708). Written informed consent was obtained from the patient. Peripheral blood samples were collected before pregnancy, at 3rd trimester of pregnancy, postpartum day 1 (PPD1), and postpartum week 7 (PPW7). Peripheral blood mononuclear cells (PBMCs) were obtained by Ficoll® gradient centrifugation. PBMCs were analyzed by multicolor flow cytometry. Treg cells were defined according to the gating strategy described by Miyara et al. [37].

Empirical data

Case

A 34-year-old Asian woman with a history of one miscarriage (gravidity 1, parity 0) was diagnosed with CVID (IgG 112 mg/dl, IgA < 20 mg/dl, IgM 22 mg/dl) after recurrent infections of the respiratory tract. At diagnosis, low proportion of $CD45RO^-$ naïve T cells among $CD4^+$ T cells (8.9%) and IgD^- $CD27^+$ switched memory B cells (0.6%), which produce IgG, IgM, or IgA, among total peripheral B cells were observed. Since the diagnosis, she was receiving immunoglobulin replacement treatment (400 mg/kg of intravenous immunoglobulin: IVIg) every 4 weeks to maintain an IgG level above 500 mg/dl, including the time during pregnancy. She conceived after her 4th intrauterine insemination treatment because of unexplained primary infertility. A healthy female baby weighing 3028 g was delivered at 41 weeks of gestation with no obstetric complications and no episodes of infection during pregnancy or during the postpartum period.

Reduced $CD4^+$ to $CD8^+$ T-lymphocyte (CD4:CD8) ratio and naïve T cells

There was no change in the CD4:CD8 ratio in the peripheral blood T cells before pregnancy (0.7), during pregnancy (at the 3rd trimester of pregnancy; 0.7), and on PPD1 (0.6) (Fig. 1A). At PPW7, the CD4:CD8 ratio was slightly decreased (0.4). As shown in Fig. 1B, the majority of $CD4^+$ T cells were $CD45RO^+$ memory T cells, and there was a severe deficiency of $CD45RO^-$ naïve T cells, although they increased slightly after pregnancy (8.9% before pregnancy, 16.0% during pregnancy, 13.7% at PPD1, 13.0% at PPW7). In contrast, in the umbilical cord blood, the majority of $CD4^+$ T cells were naïve T cells (90.7%), as was previously reported in cord blood from healthy volunteers [37], despite the low proportion of naïve T cells in the maternal peripheral blood (Fig. 1C).

The percentage of $Foxp3^{high}CD45RA^-$ (effector Treg) cells among the $CD4^+$ T cells was reduced after parturition (Fig. 1D, 8.9% during pregnancy, 4.8% at PPD1, 3.4% at PPW7), whereas the percentage of $Foxp3^{low}CD45RA^+$ (naïve Treg) cells was increased after parturition (Fig. 1D, 0.24% during pregnancy, 0.57% at PPD1, 2.49% at PPW7).

Reduced class-switched memory (IgD^-CD27^+) B cells

The patient showed a decrease in the percentage of B cells among the lymphocytes (2.0% before pregnancy), which was ameliorated after pregnancy (27.0% during pregnancy, 13.9% at PPD1, 7.4% at PPW7). We observed low proportions of IgD^-CD27^+ switched memory B cells (0.6% before pregnancy, 0.28% during pregnancy, 0.05% at PPD1, and 0.08% at PPW7), IgD^+CD27^+ non-switched memory B cells, which predominantly produce IgM (9.4% before pregnancy, 4.2% during pregnancy, 4.3% at PPD1, and 3.9% at PPW7), and IgD^-IgM^- switched B cells (2.0% before pregnancy, 0.6% during pregnancy, 0.5% at PPD1, and 0.5% at PPW7) among the total peripheral B cells (Fig. 1E).

Consequences of the hypothesis and discussion

Most CVID patients show a general decrease in the expression of