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SHORT COMMUNICATION

Case report

Herpes simplex virus acute retinal necrosis during pregnancy

C. CHIQUET[1], G. THURET[2], F. POITEVIN-LATER[3], P. GAIN[2], F. NAJIOULLAH[4], P. DENIS[1]

[1]Department of Ophthalmology, Edouard Herriot Hospital, Lyon
[2]Department of Ophthalmology, Bellevue Hospital, Saint-Etienne
[3]Department of Neuro-Immunology, Neurological Hospital, Lyon
[4]Department of Virology, Rockefeller Faculty, Claude-Bernard University, Lyon - France

PURPOSE. *As pregnancy is liable to modify immune response, the authors explored the immune functions of a pregnant patient with acute retinal necrosis (ARN) to ascertain whether pregnancy may promote the onset of infection.*
METHODS. *Polymerase chain reaction (PCR) was used for the detection of herpes simplex virus (HSV) DNA in ocular, uterus cervix, and cerebrospinal fluid samples. Peripheral blood mononuclear cells were cultured for 72 hours with mitogens and cellular proliferation was assessed using (methyl-3H) thymidine incorporation. Flow cytometry was performed for T, B, and NK cell count using CD2, CD3, CD4, CD8 (T cells), CD19, CD20 (B cells), and a combination of CD3-CD16 and CD56 monoclonal antibodies (NK cells).*
RESULTS. *Unilateral ARN, with a confluent peripheral necrotizing retinitis extending throughout the entire retina, was diagnosed clinically. The herpetic infection (herpes simplex virus 1) was confirmed using PCR of aqueous humor specimen. The immunologic study performed during and after pregnancy showed that T and B lymphocytes were quantitatively normal and responses to concanavalin A, phytohemagglutinin, and pokeweed mitogens were weaker during pregnancy.*
CONCLUSIONS. *A reduced response to mitogens, with postdelivery normalization, was noted in a pregnant woman with an ARN syndrome. Further studies are needed to explore the antigen-specific immune deviation in pregnant patients with ARN. (Eur J Ophthalmol 2003; 13: 662-5)*

KEY WORDS. *Herpes simplex virus, Pregnancy, Acute retinal necrosis, Immune function, Polymerase chain reaction*

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Herpes simplex virus type 1 (HSV-1) is implicated in acute retinal necrosis (ARN) in both immunocompetent and immunocompromised patients. The physiopathology of ARN is not yet fully understood. Immune dysfunction has been described in patients with ARN syndrome. We explored the immune functions of a pregnant woman to ascertain whether changes described in immune system during pregnancy (1) could be correlated with the development of ARN.

Case report

A 34-year-old woman, 5.5 months pregnant, was admitted to the ophthalmology department in Janu-

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ary 1999 with a 4-day history of gradual progressive profound diminution of vision in the left eye (20/30). The patient's medical history included two full-term pregnancies and two spontaneous abortions. Systemic examination did not reveal presence of any cutaneous labial or genital ulceration. The current pregnancy was uneventful. On examination, the visual acuity in the left eye was light perception. Slit-lamp examination revealed a moderate anterior uveitis with granulomatous keratic precipitates, and an intraocular pressure of 18 mm Hg. Funduscopic examination revealed marked vitritis, scattered perivascular areas of intraretinal hemorrhages, retinal vasculitis, and a peripheral retinal detachment. A diagnosis of unilateral ARN, with a confluent peripheral necrotizing retinitis extending to the entire retina, was considered at this point.

Routine laboratory and screening tests for uveitis, including complete blood count, sedimentation rate, antinuclear antibody, rheumatoid factor, fluorescent treponemal antibody absorption test, renal and hepatic function, serologic testing for cytomegalovirus (CMV), human immunodeficiency virus type 1 and 2 (HIV-1 and -2), human T-cell lymphotrophic virus type 1 and 2 (HTLV-1 and -2), Lyme disease, and toxoplasmosis, were negative or within normal limits. Polymerase chain reaction (PCR) of the aqueous humor detected HSV-1 DNA. Other herpesviruses (HSV-2, varicella zoster virus [VZV], CMV) were not detected by PCR in this sample. The gyneco-obstetric examination had normal results, confirming in particular the absence of any lesion of the uterus cervix (PCR sample for HSV-1 tested negative) and a normal fetus (ultrasound scan and monitoring). Neurologic examination and magnetic resonance imaging of the brain were normal at admission. Biochemistry, PCR for HSV-1 and 2, Gram stain, and culture of cerebrospinal fluid samples were negative.

A detailed study of the immune status was performed. The results of the immunologic study at the time of presentation (before steroid therapy) and 1 year after delivery (without steroid therapy) are listed in Table I. In order to quantify the proliferative capacity of lymphocytes, peripheral blood mononuclear cells were obtained from heparinized venous blood and cultured

TABLE I - IMMUNOLOGIC FINDINGS DURING AND AFTER PREGNANCY

Cells (normal values*)	**At the time of ARN syndrome (during pregnancy)**	**1 year after pregnancy**
Lymphocytes/μL (1600-2400)	1690	1990
T lymphocytes/μL		
CD3 cells (800-2800)	1423	1650
CD4 cells (500-1700)	830	855
CD8 cells (240-1040)	559	755
B lymphocytes/μL		
CD19 cells (30-500)	203	199
Natural killer cells/μL (<600)	51	139
Lymphocyte transformation tests performed with:		
Concanavalin A	8990 ±703 (SD) cpm	14,580 ±1708 (SD) cpm (p = 0.042)**
(15,000 cpm, SI = 300)	SI = 66	SI = 384
Phytohemagglutinin	25,790 ± 1129 cpm	30,790 ± 894 cpm (p = 0.047)**
(15,000 cpm, SI = 200)	SI = 190	SI = 810
Pokeweed mitogen	2910 ± 135 cpm	3410 ± 274 cpm (p = 0.035)**
(4000 cpm, SI = 60)	SI = 22	SI = 90

*Normal values of the laboratory (controls)
**p Value of statistical comparison (paired t-test): 1 year after pregnancy vs during pregnancy
cpm = Count per minute; SI = Stimulation index

for 72 hours with mitogens. Responses to mitogens concanavalin A, phytohemagglutinin, and pokeweed mitogen were significantly reduced during pregnancy at the time of ARN syndrome as compared with values 1 year after pregnancy (t-test for paired samples, p=0.042, 0.047, and 0.035, respectively). Cellular proliferation was assessed using (methyl-3H) thymidine incorporation and results were expressed in count per minute (cpm) as the mean value of the triplicate culture wells. For lymphocyte immunophenotyping, a whole blood direct triple or quadruple immunofluorescent staining technique was used with CD45 monoclonal antibody. Flow cytometry was performed for T, B, and NK cell counting using CD2, CD3, CD4, CD8 (T cells), CD19, CD20 (B cells), and a combination of CD3-CD16 and CD56 monoclonal antibodies (NK cells). Results were expressed as percentages of stained cells in the lymphocyte gate and as absolute values using the Tetraone system (Beckman Coulter).

Antiviral treatment was immediately started with induction doses of intravenous acyclovir (30 mg/kg/d) continued for 10 days along with aspirin (125 mg/d) and oral prednisolone acetate (1 mg/kg/d). Topical steroids and cycloplegic therapy were also prescribed.

Three months later, the poor visual outcome (poor light perception) was related to optic nerve atrophy and an extensive retinal detachment. The patient delivered a healthy baby without any evidence of neonatal herpetic infection. Antiviral therapy was stopped after 12 months. Up to December 2002, no contralateral involvement was observed.

DISCUSSION

This report describes a case of ARN syndrome in a pregnant woman and its association with a temporary qualitative anomaly of the immune system. An HSV-ARN syndrome during pregnancy has only been documented once before (2). No study of immune function has been carried out in pregnant women presenting with a retinitis by HSV or VZV. In immunocompetent patients, host factors are likely to predispose to the development of ARN syndrome. Several studies have emphasized the role of an immunogenetic predisposition to the disease, such as an association with human leukocyte antigen (HLA) phenotypes DQw7 and DR4. Our patient did not present these HLA antigens.

Two previous studies have demonstrated immune dysfunction (cutaneous anergy, increase of B lymphocytes, reduced lymphocytic proliferation) in patients with ARN (3, 4). Classic ARN was associated with discrete immune dysfunction, including cutaneous anergy (6/6 cases, and 1 case not determined), impaired in vitro lymphocyte stimulation (4/5 cases, and 2 cases not determined), and increase of B lymphocytes (5/5 cases, and 2 cases not determined). Impaired immune function was defined by comparison with a control group. Signs of impaired cellular immunity were found in 16% of patients in an exhaustive review of 216 ARN cases published in the literature. (5) The severity and the type of disease seem to depend on the immune impairment (4).

In our case report, we compared immune dysfunction in our patient at the onset of ARN versus 1 year later. Data obtained in our patient are consistent with previous studies in pregnant women. The immunologic study of our patient performed during and after pregnancy showed that T and B lymphocytes were quantitatively normal (6) and that responses to Con A and PWM mitogens were weaker during pregnancy (1). Published data (1, 6) have shown that there are small variable reductions in circulating T lymphocytes and little or no change in helper-to-suppressor ratios.

The weaker response to mitogens noted during normal pregnancy and reported in our patient, with postdelivery normalization, was also described in a subpopulation of nonpregnant patients presenting an ARN (4). In contrast with previous studies (3, 4), we did not find any increase of B lymphocytes in our patient. The impaired cellular immunity described in our patient (without concomitant steroid therapy) and in pregnant women is consistent with that found in some patients with ARN. More recently, a temporary deficit in delayed hypersensitivity limited to VZV antigens was positively correlated with the severity of VZV-induced ARN (7). This recent study showed that some patients had a selective deficit of delayed hypersensitivity to VZV antigens and not a global nonspecific inability to display delayed hypersensitivity reactivity, as described by Rochat et al (3). Discrepancies between these two studies could be related to the timing of skin tests and treatment with steroids. Further studies are needed to explore the antigen-specific immune deviation in pregnant women and in pregnant patients with ARN.

In conclusion, during pregnancy, dysfunction of cellular immunity, such as a temporary fall in lymphocyte response to mitogens, has been demonstrated and shares some similarities with that found in patients with ARN syndrome. In the future, in pregnant women presenting with ARN syndrome, investigations should be performed to explore qualitative and quantitative abnormalities of the immune system to confirm these preliminary data.

Reprint requests to:
Christophe Chiquet, MD
Department of Ophthalmology
Edouard Herriot Hospital
Place d'Arsonval
69437 Lyon cedex 3, France
chiquet@lyon.inserm.fr

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