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SHORT COMMUNICATION

Elevated Serum Levels of BP180 Antibodies in the First Trimester of Pregnancy Precede Gestational Pemphigoid and Remain Elevated for a Long Time After Remission of the Disease

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Gestational pemphigoid (pemphigoid gestationis; PG) is a rare auto-immune dermatosis of pregnancy, typically occurring in the second or third trimester, with highly pruritic urticarial lesions followed by blistering within weeks (1–3). An allogeneic autoimmune reaction arises against collagen XVII (BP180), an important constituent of skin basement membrane (4). This reaction is detectable in the placenta as early as the first trimester (5). In PG, auto-antibodies mostly target 2 epitopes within the largest non-collagenous 16A (NC16A) domain of collagen XVII, similarly to the mechanism in bullous pemphigoid (6, 7). Diagnosis of PG is based on clinical features and linear complement 3 (C3) deposition in direct immunofluorescence (IF) analysis of perilesional skin biopsy (8). In addition, serum levels of auto-antibodies against collagen XVII (BP180) can be detected and used in patient follow-up, since they parallel the disease activity (9, 10).

There are no data available on BP180 antibodies (BP180ab) in PG prior to the onset of symptoms and diagnosis. The aim of this study was to determine BP180ab levels in the early weeks of pregnancy and to compare the levels in healthy pregnant women with those in patients subsequently diagnosed with PG. Following a diagnosis of PG the levels of BP180ab in subsequent pregnancies was also analysed.

MATERIALS AND METHODS

Eleven Finnish (Caucasian) patients with 13 pregnancies with PG were recruited (Table SI[1], as described in detail in (11)). Inclusion criteria included cutaneous lesions typical for PG and C3 positivity in direct IF analysis of perilesional skin. Clinical data were obtained from the patient records. The study was approved by the ethics committee of Northern Ostrobothnia Hospital District (ref. 61/2004) and performed according to the principles of the Declaration of Helsinki 1983. In addition, all participating women provided informed consent for the use of their medical data for research purposes.

After providing informed consent, approximately 99% of pregnant Finnish women participate in serological screening for HIV, hepatitis B and syphilis at municipal maternity care units during the first trimester of pregnancy. After the screening, 1–3 ml serum is stored at –25°C in the Finnish Maternity Cohort (FMC) serum bank, which is a nationwide biorepository of serum samples established by the National Institute of Health and Welfare (12).

Serum samples of patients with PG later in pregnancy ($n = 13$, index pregnancies), their individually time- and age-matched pregnant controls ($n = 24$, 2 controls per case, except for one with only one control), and serum samples taken in the first trimester of other pregnancies of these women having had PG ($n = 27$) were obtained from the FMC serum bank for the years 1999–2012. Circulating antibodies against collagen XVII (BP180, BP180ab) were analysed with a commercially available enzyme-linked immunoassay (ELISA)-Mesacup BP180 test (Medical and Biological Laboratories Co. Ltd, Nagoya, Japan) according to the manufacturer's instructions.

A Mann-Whitney *U* test was used to compare the levels of BP180ab in PG patients with those in the control group. The odds ratio (OR) and its 95% confidence interval (95% CI) were estimated by conditional logistic regression. Prior to analysis, the variable representing BP180 level was $\log_2$-transformed because of its skewed distribution. IBM SPSS Statistics version 21.0 (SPSS Inc., Chicago, IL, USA) and Stata 5.0 statistical software (Stata Corporation, College Station, TX, USA) were used for data analysis.

RESULTS

The study material consisted of 64 serum samples from 37 women. Thirteen samples were obtained in the first trimester (mean gestational age 9.9 ± 1.9 weeks) of pregnancies in which PG was diagnosed at a later stage (median 23 weeks later, range 0–32 weeks) (index pregnancy, Table SI[1]) while 24 control samples came from pregnant women matched by age and sampling time. In addition, samples prior to ($n = 17$), subsequent to ($n = 9$), or between 2 ($n = 1$) index pregnancies were included in the laboratory analyses. Two mothers had 2 index pregnancies.

To study the longevity of BP180ab, the serum samples of mothers with subsequent pregnancies were analysed. Five patients had subsequent pregnancies after the index pregnancy, and their BP180ab levels were analysed in the first trimester of all these pregnancies. Mean time between delivery of index pregnancy and a new pregnancy was 27 months (range 13–62 months). BP180ab remained elevated in 80% ($n = 4/5$) of subsequent pregnancies compared with the BP180ab in the early weeks of the index pregnancy (Table SI[1], patients 1–3 and 5). However, the mothers had no further skin symptoms.

In addition, we analysed the BP180ab in the first trimester of the index pregnancies (Table SI[1]). Due to constantly elevated BP180ab after an index pregnancy, the second PG pregnancies of the same mother and their

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controls were excluded from analysis. When BP180ab levels in PG pregnancies were compared with those in control pregnancies, the median BP180ab (median 3.10 IU/ml, range 1.9–27.0 IU/ml) was slightly higher in the 11 index samples than in the 20 controls (median 1.55 IU/ml, range 0.7–6.7 IU/ml) with $p = 0.007$. Moreover, the increasing log-transformed BP180ab levels were statistically significantly associated with PG pregnancies, the OR for 1 unit increase on the $\log_2$ scale being 2.6 (95% CI 1.1–6.5, $p = 0.038$).

DISCUSSION

The aim of this study was to determine whether elevated BP180ab levels are detectable in the first trimester even though PG is typically diagnosed much later in pregnancy. In PG pregnancies the median BP180ab level in the first trimester was higher (3.10 vs. 1.55 IU/ml, $p = 0.007$) than in control pregnancies. Since 2 mothers had multiple PG pregnancies, the first trimester samples of their second PG pregnancies were excluded from analysis due to constantly elevated BP180ab. In controls, median BP180ab level in the first trimester of pregnancy was 1.55, corresponding to an earlier study of pregnant patients with polymorphic eruption of pregnancy in which the mean BP180ab level was 2.6 (9). In both control and PG pregnancies first trimester BP180ab levels were below the cut-off value, which was set at 9 IU/ml in the ELISA kit used. However, BP180ab levels were significantly ($p = 0.007$) more elevated in pregnancies where PG was subsequently diagnosed.

Interestingly, after a pregnancy with PG, BP180ab remained elevated for up to one year. However, the patients did not have any symptoms of PG. In bullous pemphigoid, high (>27 IU/ml) BP180ab is a good indicator for a relapse within one year (13), but it seems that in PG, the disease does not re-occur as a rule in subsequent pregnancies even though BP180ab remains clearly elevated, as in our patient 2 (Table SI[1]).

In the controls, BP180ab varied between 0.7 and 6.7 IU/ml, which is within the reference range (<9 IU/ml) of the ELISA analysis used. There were 2 mothers with PG who had surprisingly high levels of BP180ab (19 and 37 IU/ml) in the early weeks of their previous pregnancy prior to a pregnancy with PG. The patient records were reviewed carefully, revealing that both women had had pruritic skin symptoms during the last trimester of those pregnancies, but the diagnosis of PG was unfortunately not confirmed. Since BP180ab are highly specific (9) and the mothers had a pruritic dermatosis, we speculate that they might already have had symptoms of PG in those pregnancies. However, since they did not have a confirmed diagnosis of PG, their index pregnancy was included when analysing BP180ab in the first trimester.

BP180ab are highly specific and have therefore even been suggested as a diagnostic test for PG (9, 10). Our results show for the first time that slightly elevated BP180ab in the first trimester of a pregnancy precedes PG later in pregnancy. However, in differential diagnostics of pruritic pregnancy-associated dermatoses, especially in patients with previous PG, BP180ab levels should be interpreted with care and not used for PG screening in these patients since their BP180ab levels remain constantly elevated.

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