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FOXP3-positive cell infiltration in the chorionic villi is increased in the placenta accreta and decreased in the placental abruption

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Short title: **Treg cells in abnormal placentation**

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ABSTRACT

Objectives: Growing data suggest a role of Treg cells in placentation. The aim of the study was to evaluate Treg cells (FOXP3-positive cells) placental bed infiltration in patients with placenta accrete syndrome (PAS) and patients who experienced placental abruption.

Material and methods: The study group included 13 patients with PAS and the control group consisted of 66 women who had caesarean (CD) delivery of whom, 44 patients with elective caesarean (EC) delivery, and 22 patients with urgent caesarean (UC) delivery due to placental abruption. FOXP3 cell infiltration was assessed by means of immunohistochemistry in

placental chorionic villous (CV) and in the decidua (D) and cumulatively in the placental bed (PB).

Results: We observed significant difference in the degree of FOXP3-positive cell CV infiltration between studied groups ($p = 0.04$). FOXP3-positive cells were the most commonly observed in PAS patients, while, they were the least frequently presented in patients after UC. The immunoreactivity for FOXP3-positive cells in CV were as follows: PAS 5 (38%), urgent CS 1 (5%) and elective CS 8 (18%) subjects. We found no difference in the presence of FOXP3-positive cells in the D ($p = 0.35$) and in the PB ($p = 0.23$) of analyzed groups. FOXP3-cell infiltration was not related with patient age, BMI, gestational age and neonatal birth weight.

Conclusions: Our study provides further evidence that abnormal invasive placentation is an associated disturbance of the maternal immune response. Accordingly, we have theorized that alteration of the FOXP3-positive Treg cell infiltration into the placental bed allows trophoblast cell invasion.

Key words: placenta accreta spectrum; placental abruption; T regulatory cells; FOXP3

INTRODUCTION

Maternal immune tolerance against fetal antigen is a well-known phenomenon. The recruitment of T regulatory (Treg) cells in placental bed is one of the main molecular mechanisms that enable trophoblast fetal cells to escape from maternal immune surveillance [1]. T-regulatory lymphocytes are a subtype of T cell characterized by strong immunosuppressive qualities. They can be identified by the presence of CD4, CD25, and FOXP3 (forkhead box protein 3) antigens. FOXP3 transcription factor is widely accepted as a master regulator gene connected to the suppressive function of these cells. Tregs suppress other immune system cells through cell-cell interactions by receptors, including CTLA-4, PD-1, LAG-3, and Tim-3, and by the production of such cytokines as Il-10, IL-6, TGFβ, and Il-35 [2, 3]. Dysfunction in Tregs has been extensively studied not only in cases of preterm birth and miscarriage [4, 5], but also in cases of preeclampsia [6, 7].

It has been well established that Treg cells as suppressory lymphocytes participate in the maintenance of maternal immune tolerance and are essential for implantation and pregnancy development. Not only is pregnancy development linked with the suppression of the maternal immune response, but both implantation and the spontaneous beginning of labor depend on an adequate maternal immune cytotoxic response [1, 8]. Proper immune response regulation forms the background for normal placentation and depends upon the immune

regulating activities of fetal cells, decidual cells, and maternal immune cells. When such regulation is disturbed, abnormal invasive placentation may occur. These functional mechanisms are also influenced by the morphological condition-localization of the placental bed, which may be observed during placentation within the uterine scar. The risk of abnormal adherence of the placenta trophoblast to the uterine scar increases in relation to the number of previous cesarean sections and may result in development of the placenta accreta spectrum (PAS) [9]. It has been suggested that accreta placentation is secondary to the scar defect and lack of decidua. When the tissue within the placental bed is harvested at the time of cesarean section, trophoblast invasion during the development of a subsequent pregnancy is associated with the failure of normal decidualization and the loss of the subdecidual myometrium [10]. However, in recent studies, aberrant immune cell infiltration, including Treg cells, was observed in patients with PAS [11, 12]. These results suggest, that Tregs may participate in the regulation of placentation and therefore, the disturbance in Treg placenta infiltration may be observed in patients with abnormal placentation related with PAS.

Since abnormal invasive placentation results in an elevated risk of peripartum hemorrhage, particularly in patients following cesarean section, it is important from a clinical standpoint to recognize the molecular mechanisms influencing trophoblast invasiveness limitation. The potential role in the regulation of these processes of Treg cells that infiltrate decidua locally has yet to be precisely described. The current understanding is that the incidence of PAS has risen because in recent years an increasing number of Cesarean section has been observed. For this reason, we have decided to analyze FOXP3 immunoreactivity in the decidual and placental samples derived from groups of patients with placenta accreta and placental abruption.

MATERIAL AND METHODS

Patients

The study was performed retrospectively on archival data and tissue samples from (-). We divided the patients into two groups: study group: patients with PAS, and a reference group: patients who had cesarean section. Subsequently, the reference group was divided into two subgroups: 1) elective cesarean delivery; 2) urgent cesarean delivery performed due to placental abruption.

The first 13 patients had a diagnosis of PAS and underwent elective cesarean section and peripartum hysterectomy due to severe postpartum hemorrhage risk. Patients were diagnosed based on ultrasound examination and magnetic resonance imaging prior to labor

and the diagnosed was confirmed by an experienced gynecologist (–). After cesarean section followed by hysterectomy, paraffin-embedded specimens were checked by an experienced pathologist (–). Placenta accreta was histologically diagnosed when the placental villi invaded the myometrium and the local absence of decidua was proven. Only patients with true placenta accreta (4 cases) and increta (9 cases) who required hysterectomy were included. Patients with placenta percreta were excluded.

The control group consisted of 66 women who had caesarean delivery, and the placenta was sent for histopatological evaluation. Among these patients, we distinguish 44 patients with elective caesarean delivery, and 22 patients with urgent caesarean delivery. The subgroup of patients after elective caesarean delivery included healthy pregnant women who then underwent elective cesarean deliveries performed with an unripe cervix and in the absence of uterine contractions. Cesarean section was performed due to either breech presentation at term or absolute disproportion prior to the beginning of spontaneous labor. The second subgroup included 22 women on whom emergency cesarean section was performed due to placental abruption during the first stage of labor. In all cases, a retroplacental clot was confirmed following the surgical procedure.

Tissue samples were derived from the pathomorphological archives of (–). Based on the documentation, paraffin embedded placental chorionic villous, and decidual basalis tissue samples were collected. The protocol for our study was approved by the institutional Bioethical Committee of the (-). Written consent was obtained from all patients participating in the study. Patients and controls who had had multiple pregnancies or who had existing pregnancy complications such as preterm deliveries, hypertension, diabetes mellitus, as well as cases of fetal demise, were excluded from our study.

Immunohistochemistry

Immunohistochemical analysis was performed manually in the (-) with the application of the Ultravision LPValue Detection System (Thermo Scientific Lab Vision Corporation, Fremont, CA, USA). For visualization of reaction products, DAB+chromogen (DAKO, Carpinteria, CA, USA) (gold-brown color of the final product) was used for 10 minutes at room temperature. Sections were then counterstained with Meyer's hematoxylin and mounted in glycer gel. A ductal breast cancer specimen was used as a positive control for FOXP3.

The slides were washed in TBS plus 0.025% Triton X-100 and blocked in 10% normal serum with 1% BSA in TBS for 2 hours at room temperature. They were then drained and the primary antibody, FOXP3 antibody, rabbit monoclonal (abcam; Cambridge Biomedical

Campus, Cambridge, UK, Catalog No. EPR20236), applied in dilution 1:100 in TBS with 1% BSA. Next, the slides were incubated with the primary monoclonal antibody in a humidified chamber overnight at 4 degrees Celsius. Afterwards, they were rinsed twice for 5 minutes with TBS plus 0.025% Triton and submitted to 0.3% H_2O_2 in TBS for 15 minutes. Enzyme-conjugated secondary antibody was applied to each slide, diluted in TBS with 1% BSA, and incubated for 1 hour at room temperature. The slides were then developed with chromogen for 10 minutes at room temperature and rinsed in running tap water. Finally, they were counterstained with hematoxylin.

A quantitative interpretation of the immunohistochemical results was carried out by two independent pathologists. When reviewing slides, the pathologists were blinded to the cohort status of the subjects. The average number of FOXP3-positive placental chorionic villous and of decidual basalis cells per 50HPF (high power field-objective magnification ×40, Nikon Eclipse 50i Microscope; Nikon Corporation, Tokyo, Japan) were calculated. The cells were evaluated on entire slides. We assessed FOXP3-positive cells separately (in placental chorionic villous and in the decidua) and cumulatively in the placental bed (as a sum of chorionic villous and decidual immunoreactivity). Finally, we evaluated the presence or absence or FOXP3 cells in tissue specimen, regardless the number of cells.

Statistical analysis

The distribution of variables in the study groups was verified using the Shapiro-Wilk test. Non-parametric tests (Mann-Whitney or Kruskal-Wallis) were used for evaluation of median between analyzed groups. To compare categorical data between analyzed groups we used Fisher exact test (for 2 × 2 table). Statistical analysis was conducted using MedCalc 11.4.2.0., MedCalc Software, Seoul, Republic of Korea, and GraphPad In Stat 3.06, GraphPad Software Inc., San Diego, CA, USA. The evaluation categorical data of 2 × 3 table was conducted using with Fisher exact test with the Freeman-Halton extension (VassarStats; http://vassarstats.net/fisher2x3.html).

RESULTS

Patient characteristics

We found no difference in patient age and patient BMI between analyzed groups. However, PAS patients had significantly lower neonatal birth weight and delivered prematurely. The results are summarized in the Table 1.

Table 1. Clinical and demographic data recorded from all patients in the study

	PAS (n = 13)	Urgent CS due to placental abruption (n = 22)	Elective CS (n = 44)	p value
Age [years] Median (range)	29 (20–40)	29.5 (20–38)	29 (15–38)	0.60
BMI [kg/m^2] Median (range)	22 (18–30)	23 (16–32)	22.5 (16–33)	0.97
Gestational age at delivery [week] Median (range)	35 (33–37)	39 (37–41)	39 (37–41)	< 0.01
Neonatal birth weight [grams] Median (range)	2480 (1780–3130)	3195 (2800–3930)	3265 (2680–3930)	< 0.01

PAS — placenta accreta spectrum; CS — caesarean section; N — number of patients; SD — standard deviation; BMI — body mass index

FOXP3 immunoreactivity

Immunohistochemical evaluation of obtained samples revealed immunoreactivity for FOXP3 both in chorionic villi and in the decidua. In the case of PAS patients, we found similar FOXP3-positive immunoreactivity in the chorionic villi and in the deciduas. In the case of chorionic villi, FOXP-3 immunoreactivity was observed in 5 (38%) patients, and in the deciduas in 7 (54%) patients (p = 0.70). However, in the case of patients after CS, we found significantly higher percentage of FOXP3 cells in the decidua (23 patients, 35%) when compared to the chorionic villi (8 patients, 14%; p = 0.003). When we evaluated the amount of FOXP3-cells, in general, we found low quantity of FOXP3-cells both in the chorionic villi and in the decidua. In the case of PAS patients, there was no difference between median number of FOXP3-positive cells per HPF within the chorionic villi (0, range 0–4), and, within the decidua (0–5; p = 0.48). We observed significant difference in number of FOXP3 per HPF in CS group (chorionic villi median 0, range 0–10 and decidua: median 0, range 0–50; p = 0.009). However, due to generally low number of FOXP3-positive cells within analyzed samples, further analysis was based on the qualitative analysis (presence or absence) of

FOXP3-cells. Representative images of FOXP3 immunoreativity are presented in the Figure 1.

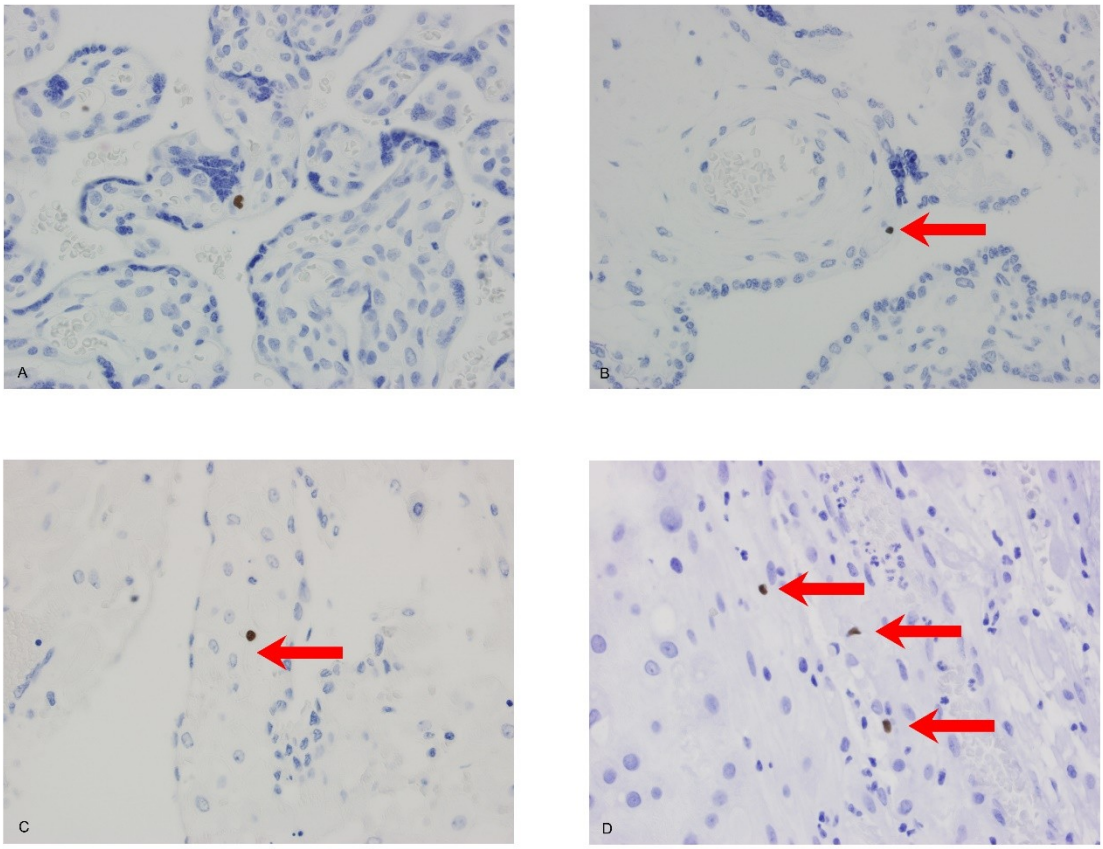

Figure 1. FOXP3 immunoreactivity within decidua and chorionic villi samples; **A, B.** Chorionic villi; **C, D.** Decidua. Red arrows indicate FOXP3-positive cells

We found FOXP3-positive cell infiltration in the chorionic villi of 5 (38%) tissue samples derived from the PAS group, and in 9 (14%) tissue samples obtained of patients after cesarean section ($p = 0.04$). The difference was also significant, when the control group was divided into elective and urgent CS. Then the presence of FOXP3-positive cells was as follows: PAS 5 (38%) subjects, urgent CS 1 (5%) and elective CS 8 (18%), $p = 0.04$.

We found no difference in the presence of FOXP-3-positive cells in decidua both when the percentage of FOXP3-positive cell were compared between PAS-patients and patients after CS ($p = 0.35$), as well as, when the group of cesarean section was divided into subgroups ($p = 0.42$). FOXP3-positive cells were found in 7 (54%), 9 (41%) and 15 (34%) tissue samples obtained from patients with PAS, urgent CS and elective CS respectively.

Similarly, there were no difference in the presence of FOXP3-positive cells in placental bed (when chorionic villii and decidual immunoreactivity was assessed simultaneously). FOXP3-positive cells were found in 7 (54%) cases of patients with PAS and in 27 (55%) of patients after CS (p = 0.23). The difference was also no significant (p = 0.36), when patients after CS were divided into subgroup of urgent CS (10 patients, 45% cases with FOXP3-positive cells) and elective CS (17 patients, 39% cases with FOXP3-positive cells). The results were summarized in the Figure 2.

Figure 2. Immunoreactivity of FOXP3 in chorionic villi, decidua and placental bed of patients with placenta accreta spectrum (PAS), urgent caesarean section (CS) performed due to placental abruption and elective CS. Placental bed refer to simultaneous evaluation of FOXP3 immunoreactivity both in chorionic villi and deciduas

We found no difference in patients age, BMI, gestational age and neonatal birth weight regarding presence of FOXP3-cells in chorionic villi and decidua o analyzed groups. Detailed data is presented in the Table 2.

Table 2. The presence of the infiltration of FOXP3-positive cells within chorionic villi and decidua derived from patients with placenta accreta spectrum (PAS) and those with cesarean section (CS)

Chorionic villi									
		Age Median (range)		BMI Median (range)		Gestational Age Median (range)		Neonatal birth weight Median	

								(range)	
PAS	FOX3P+ (n = 5)	30 (20–37)	p = 0.77	23 (19–30)	p = 0.71	35 (34–37)	p = 0.99	2480 (1780–3130)	0.88
	FOX3P- (n = 8)	27 (22–40)		22 (18–27)		35 (34–36)		2490 (2310–3020)	
CS	FOX3P+ (n = 9)	32 (15–38)	0.29	24 (16–28)	0.91	39 (37–41)	0.19	3300 (3089–3500)	0.90
	FOX3P- (n = 57)	29 (20–38)		23 (16–33)		39 (37–41)		3200 (2680–3930)	
Decidua									
PAS	FOX3P+ (n = 7)	26 (20–37)	0.39	22 (19–27)	0.57	35 (34 -37)	0.22	2480 (1780–3130)	0.73
	FOX3P- (n = 6)	30 (24-40)		23 (18-30)		35 (34 -36)		2425 (2140–3020)	
CS	FOX3P+ (n = 24)	27.5 (15–37)	0.22	23.5 (19–33)	0.48	39 (37–41)	0.37	3265 (2930–3780)	0.99
	FOX3P- (n = 42)	30 (20–38)		22 (16–30)		39 (37–41)		3210 (2680–3930)	
Placental bed									
PAS	FOX3P+ (n = 8)	27 (20–37)	0.30	22 (18 0 27)	0.88	39 (38–41)	0.65	2480 (1780–3130)	0.83
	FOX3P- (n = 5)	31 (24–40)		22.5 (19–30)		39 (37–41)		2500 (2310–3020)	
CS	FOX3P+ (n = 38)	29 (15–38)	0.98	23.5 (16–33)	0.55	39 (37–41)	0.22	3280 (2920 -3780)	0.97
	FOX3P- (n = 28)	29 (20–		22 (16–		39 (37–41)		3200 (2680–	

		39)		30)				3930)	

FOX3P+ — presence of FOXP3-positive cell infiltration; FOXP- — absence of FOXP3-positive cell infiltration. “Placental bed” refers to simultaneous evaluation of FOXP3 immunoreactivity both in chorionic villi and deciduas

DISCUSSION

Placenta accrete syndrome is clearly linked to surgical intervention within the uterine cavity, particularly cesarean delivery [10, 13]. The decidualization process fails in the area surrounding the uterine scar, triggering exaggerated trophoblast invasion. This invasion then leads to heightened maternal immune system suppression due to the constant exposure of the system to fetal antigens. Wynn referred to the placental bed area as a battleground and indicated the crucial role of the maternal component of the placenta in the local regulation of pregnancy development [14, 15]. Furthermore, PAS seems to be caused not only by the abnormal invasiveness of extravillous trophoblasts that migrate close to the serosal surface of the uterus, but also by the disturbance of the implantation microenvironment (placental bed microenvironment). Deep villous attachment in women with severe cases of PAS occurs when the anchoring villi develop in the microscopic gaps within the myometrium that are secondary to previous injury (*e.g.*, a cesarean section scar) [16].

Treg cell levels were found to be elevated in the pregnant women compared to the levels in nonpregnant controls [17]. A lack of Tregs leads to miscarriage and preterm birth [18, 19].

In our study, we observed an increased infiltration of FOXP3-positive cells in the chorionic villi of patients with PAS compared to patients after cesarean delivery without PAS. Similar results were obtained by Hecht et al. [11], who identified FOXP3-positive cells in the vessels adjacent to the placenta, when chorionic villous develops within the uterine scar in patients with PAS. Similarly, Schwede et al. [12], observed FOXP3-positive Treg cell infiltration into the decidua and a corresponding increase in the incidence of placenta accreta. In our study, we found FOXP3-positive cells in both the decidua and chorionic villi derived from patients with PAS. However, when compared to normal pregrancy, FOXP3-positive infiltration was increased only in the case of chorionic villi. Cross of the decidua by chorionic villous is associated not only with an increasing number of Treg cells but also with alteration in the microenvironment of the placental bed. A decrease in other regulatory and effector cells (*e.g.*, CD209-positive DC cell and CD56+ NK cell) tinfiltrations was observed in patients with PAS [12]. In the study by Khamoushi et al. [20], The profile of the cytokines, including TGFb1

(transforming growth factor-beta 1) and IL-35 (interleukin-35), was also altered in PAS patients. These results suggest that PAS is associated with the disturbance of the maternal immune response, propably due to the lack of the immunomodulating activity within decidua.

Placental abruption is a clinical syndrome defined by premature placental separation, a condition that is correlated with a serious risk of perinatal death [21]. HLA-G is expressed on the surface of Treg cells [22]. The pregnant women who demonstrated placenta abruption in the first trimester had sHLA-G concentration levels that were more than three times lower than the levels found in the women with normal pregnancies [23]. Steinborn et al. observed significantly lower levels of sHLA-G in the patients with placental abruption compared to the levels observed in controls [24], what may lead to increased maternal activation against trophoblast cells. Moreover, placental abruption has been associated with increased fetal monocyte activation [25] and with an alteration in the levels of such suppressive factors as B7H4 and RCAS1 within the feto-maternal interface [26, 27]. In our study, the levels of FOXP3-positive lymphocyte infiltration were lower in the chorionic villi derived from the women in the placental abruption group compared to patients after elective CS and patients with PAS. This observation also supports the concept, that disturbance of immune system cells inhibition may lead to placental abruption.

The main limitation of this study is the small series analysed; however, PAS is relative rare disorder. Another limitation is the retrospective character of the study, as it is based on data obtained from medical reports and archival materials. Furthermore, due to limited number of cases, we did not analyzed the FOXP3-positive cells infiltration in relation to degree of placental invasion. However, our study group was homogenous, while percreta cases were excluded and all patients required hysterectomy. In addition, we provided appropriate control group and immunohistochemical studies were evaluated independently by two expert pathologists. Therefore, despite the limitations, this report provides further data on the role of FOXP3-positive cells in PAS.

CONCLUSIONS

Our study provides further evidence that abnormal invasive placentation is an associated disturbance of the maternal immune response. Accordingly, we have theorized that alteration of the FOXP3-positive Treg cell infiltration into the placental bed allows trophoblast cell invasion.

Article informations and declarations

Data availability statement

Data is avalaible on request.

Ethics statement

The protocol for our study was approved by the institutional Bioethical Committee of the Centre for Postgraduate Medical Education (resolution of 15 Jan 2020, number 6/PB/2020).

Author contributions

Magdalena Dutsch-Wicherek — concept, article writing;

Błażej Nowakowski — article writing, concept;

Jan Faryna — IHC analysis, article revision;

Krystyna Gałązka — IHC analysis, article revision;

Michał Lew-Starowicz — article revision, concept, supervision;

Sebastian Szubert — correspondence, statistical analysis.

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Conflict of interest

All authors declare no conflict of interest.

Supplementary material

None.

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