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ORIGINAL ARTICLE

CD39 downregulation in chronic intervillositis of unknown etiology

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Abstract

Chronic intervillositis of unknown etiology (CIUE) is a rare placental lesion associated with infiltration of mononuclear inflammatory cells into the intervillous space, poor perinatal outcomes (intrauterine fetal demise or fetal growth restriction), and high rates of recurrence. CD39 is the ectonucleotidase that protects tissues from inflammatory stress and cell injury, which is localized on the surface of villi in normal placentas; however, its expression and role in CIUE are unknown. The aims of this retrospective study were to determine the expression of CD39 in CIUE and its significance in pregnancy outcomes. We compared the number of CD68- and CD3-positive cells, CD39 expression, and complement 4d (C4d) and fibrin deposition in placental tissues from patients with CIUE ($n = 22$) and gestational age-matched controls ($n = 20$), and between CIUE pregnancies with poor and good outcomes. The numbers of CD68- or CD3-positive cells were significantly higher ($P < 0.0001$), whereas CD39 expression on the surface of villi and endothelial cells of the stem villi was significantly lower in the CIUE group than that in controls (45% vs. 95%, $P < 0.0001$ and 77% vs. 96%, $P < 0.001$, respectively). C4d and fibrin deposition were also significantly increased in CIUE compared with those of controls. Furthermore, CD39 downregulation and the number of CD68 cells were strongly associated with poor pregnancy outcomes ($P < 0.01$ and $P < 0.05$, respectively), but other histological parameters (CD3, C4d, and fibrin) did not show this association. Our study suggests that CD39 downregulation is a useful marker of CIUE and is associated with poor pregnancy outcomes in patients with CIUE.

Keywords Chronic intervillositis of unknown etiology · CD39 · CD68 · CD3 · C4d · Abortion · Fetal growth restriction

Introduction

Chronic intervillositis of unknown etiology (CIUE)—also known as chronic histiocytic intervillositis or chronic intervillositis—is a relatively rare pathological lesion of the placenta characterized by mononuclear inflammatory cell infiltration in the intervillous space [1–3]. CIUE has been associated with poor perinatal outcomes, including intrauterine fetal demise (IUFD) and fetal growth restriction (FGR), and typically shows recurrence in subsequent pregnancies [3–6]. Although the etiology is unknown, immunological and/or coagulation disturbances may play a role in the pathophysiology of CIUE. Several histological reports showed that the severity of the intervillous cell infiltrate was associated with poor neonatal outcomes using a semi-quantitative grading system [7, 8], the number of CD68-positive cells [9], fibrin deposition [10], or C4d deposition [11]; however, the etiology or mechanism of CIUE remains unclear.

Extracellular nucleotides, including ATP, induce an inflammatory response that is controlled by surface-located enzymes (ectonucleotidases). CD39 is one such ectonucleotidase that protects against inflammatory stress and cell injury [12, 13]. A previous study [14] demonstrated that CD39 was located on the surface of trophoblasts in normal human placentas, and several mouse model studies showed that CD39 protected against an increase of blood pressure [15], thrombus formation [16], and miscarriages with human antiphospholipid antibody infusion [17]; however, the role of CD39 expression in CIUE has not yet been assessed.

We hypothesized that CD39 expression would be suppressed in placentas with CIUE, which may be associated with

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poor outcomes. Therefore, the aim of the present study was to examine the expression of CD39 in CIUE and its significance in neonatal outcomes.

Material and methods

Study population

Patients with CIUE were retrospectively identified from the Diagnostic Pathology Department of the University of Miyazaki Hospital between 2004 and 2013.

A retrospective review of maternal and infant pair charts was conducted for cases and controls. Maternal findings of interest were age, gestational age, history of hypertensive disorders in pregnancy (HDP), gestational diabetes mellitus, and collagen disease. Neonatal findings of interest were birth weight, IUFD, and FGR. The final study population included 22 cases and 20 matched controls. We defined IUFD or FGR as a poor outcome, and no IUFD or FGR as a good outcome.

Placental findings

Gross findings were recorded from the original pathology reports. Microscopic sections had been submitted on the basis of the Amsterdam Criteria, developed by a group of experts for the submission of placental specimens for pathological examination, and were available for all cases [18]. Placentas were fixed in 10% buffered formalin after gross examination, and three to six samples were randomly taken and systematically analyzed for each case. Serial sections (5 μm) of tissue embedded in paraffin blocks were processed and stained using hematoxylin-eosin (HE). All slides were reviewed by two pathologists (Y.S. and K.M.). The diagnosis of CIUE was based on the presence of the following criteria proposed by Bos et al. [19]: (i) infiltrate in the intervillous space, (ii) approximately 80% of the mononuclear cells in the intervillous space are CD68-positive cells, (iii) at least 5% of the intervillous space is occupied by an infiltrate, and (iv) no clinical and histopathological signs of infection. In addition, we excluded cases with villitis of unknown etiology (VUE, i.e., inflammation of the villous stroma) [2, 3]. We included mild cases of CIUE. Gestational age-matched controls were selected based on the absence of CIUE by routine histopathological examination.

Immunostaining was performed using formalin-fixed and paraffin-embedded tissue sections in all cases with anti-CD68 (Dako, Glostrup, Denmark), anti-CD3 (Dako), anti-CD39 (Japan Clinical Laboratories, Inc., Kyoto, Japan), anti-C4d (Abgent, San Diego, CA, USA), and anti-fibrin (Accurate Chemical & Scientific Corp, Westbury, NY, USA) antibodies. A positive villous CD39 or C4d staining result was defined as circumferential immunostaining around the chorionic villi [20]. The CD39-positive villi signal was quantified as a percentage of the total number of villi in three high-power fields (× 400 magnification). We also evaluated CD39 expression specific to endothelial cells and stromal cells. The CD39-positive vessels or stromal cells were quantified as a percentage of the total number of vessels or stromal cells in three high-power fields. The number of CD68- or CD3-positive cells in the intervillous space was evaluated using the method of Heller [9]. Three counts were performed at × 400 magnification (high-power field) and the mean number was calculated. The fibrin immunoreactive areas were quantified using image analysis (Win Roof, Mitani Corp., Mitani, Fukui, Japan) [21] based on three counts at × 10 magnification, and the mean positive area was calculated.

Statistical analysis

All statistical analyses were performed with JMP version 13.0.0 (SAS, Cary, NC, USA) and GraphPad Prism 7.03 (GraphPad Software, San Diego, CA, USA). Maternal and gestational ages and birth and placental weights are expressed as means ± SD. The non-parametric Mann-Whitney test was used to analyze the differences in CD39- or C4d-positive villi, CD68- or CD3-positive cell numbers, and fibrin-positive areas between the controls and cases. These same parameters were also compared between CIUE pregnancies with good and poor outcomes. Associations between individual variables were calculated using Spearman's correlation method or chi-squared analysis with the raw data. A P value below 0.05 was considered significant.

Results

Twenty-two placentas from 18 patients were diagnosed as having CIUE (Table 1). Three of 18 women (17%) presented with one to three recurrences. The average maternal age was 31.6 years (range 19–40 years). Five cases (23%) had a history of HDP, four (18%) had antiphospholipid syndrome (APS), and two (8.7%) had collagen disease (systemic lupus syndrome or Graves' disease). The average gestational age of the cases was 27 weeks (range 8–39 weeks). Overall, 83% of the cases did not reach 37 weeks of gestation. IUFD or FGR occurred in 15 (68%) cases. The frequencies of IUFD or FGR, and APS were higher in cases than in controls. However, maternal age, birth weight, IUFD, history of HDP, diabetes, and collagen disease were not significantly different between cases and controls.

Gross placental examination did not show any specific abnormalities. The mean placental weight was 280 g (range 120–450 g). Small placentas (< 10th percentile of singleton placental weight) were observed in eight cases (44%, 8/18). Histologically, the lesions were characterized by infiltration of

Table 1 Clinical characteristics of this study population

	Control ($n = 20$)	CIUE ($n = 22$)	P value
Mother age (years)	31.6 ± 0.9	32.3 ± 1.0	n.s.
Gestational age (weeks)	27.0 ± 2.1	27.2 ± 2.1	n.s.
HDP (%)	3 (15)	5 (23)	n.s.
Diabetes (%)	1 (5)	0 (0)	n.s.
Collagen disease (%)	1 (5)	2 (9)	n.s.
APS (%)	0 (0)	4 (18)	0.04
Birth weight (g)	1365 ± 183	1465 ± 943	n.s.
Placental weight(g)	254 ± 35	280 ± 32	n.s.
IUFD or FGR (%)	6 (30)	15 (68)	0.01
IUFD (%)	2 (10)	5 (22)	n.s.
FGR (%)	4 (20)	11 (50)	0.04

CIUE chronic intervillositis of unknown etiology, *HDP* hypertensive disorders in pregnancy, *APS* antiphospholipid syndrome, *IUFD* intrauterine fetal demise, *FGR* fetal growth restriction, *n.s.* not significant. Values are expressed as mean ± SD

chronic inflammatory cells into the intervillous space with or without trophoblast erosion and fibrin deposits of varying degrees (Fig. 1b). These cases showed other pathological findings (infarctions in three, atherosis in two, and fetal vessel thrombosis in one case). We observed chorioamnionitis (CAM, Fig. 1e) in four and VUE (Fig. 1g) in two of the controls.

CD68-positive cell numbers were significantly higher in patients with CIUE than in controls (Fig. 2a, $P < 0.0001$). There was also a greater number of CD3-positive cells in patients with CIUE (mean 18, range 1.3–70) than in controls (mean 0.8, range 0–5) (Fig. 2b, $P < 0.0001$). The majority of chronic inflammatory cells were CD68 positive (86%). Almost all chorionic villi in the controls expressed CD39 of the surface of villi (mean 95%, range 91–100%) (Fig. 1b). In contrast, CD39 expression of the surface of the villi was significantly reduced in CIUE cases (mean 44%, range 4–97%) (Figs. 1d, 2c). This downregulation of CD39 was more frequently observed on villi in areas with a dense infiltrate of chronic inflammatory cells in the intervillous space than on villi in areas with only a sparse chronic inflammatory infiltrate. This reduction in CD39 expression was not present in cases with CAM (Fig. 1f) or VUE (Fig. 1h). In control placentas, CD39 expression of the endothelial cells was also found in the chorionic and stem villi, but not in the capillary vessels in the terminal villi (Fig. 1b). We also could not detect CD39 expression of the endothelial cells in the IUFD cases. The percentage of CD39 expressing vessels was lower in CIUE than in control placentas (Fig. 1d, 77% vs. 96%, $P < 0.001$). CD39 expression of the stromal cells was weak and focal, and there was no significant difference between CIUE and control placentas (16% vs. 16%, $P = 0.72$). C4d deposition was significantly increased at the surface of the chorionic villi in the CIUE group compared with that of controls (Fig. 2d). Fibrin deposition was also higher in patients with CIUE than in controls, but five cases (23%) of CIUE showed only weak fibrin deposition (< 10%) (Fig. 2e).

Next, we compared histological parameters in the CIUE groups with good outcomes ($n = 7$) and poor outcomes ($n = 15$) (Fig. 3). Placentas with poor outcomes showed significantly reduced numbers of CD39-positive cells ($P < 0.01$) and increased numbers of CD68-positive cells ($P < 0.05$), but there were no differences in CD3-positive cells, fibrin deposition, and C4d deposition between these groups. Finally, we examined associations of CD39 expression with other histological findings (i.e., CD68-positive cells, CD3-positive cells, C4d deposition, and fibrin deposition). CD39 downregulation was associated with increased numbers of CD68- or CD3-positive cells and was weakly associated with C4d deposition but was not associated with fibrin deposition (Fig. 4).

Discussion

We compared the expression of CD39 in CIUE and control placentas. A few studies have reported that CD39 expression is present at the syncytiotrophoblasts of the terminal villi and umbilical endothelial cells of full-term healthy pregnancies, although CD39 expression has been observed in placentas of 10-week gestational age [13, 22]. The present results also confirmed strong expression of CD39 on the surface of the villi in controls. Our controls included two placentas at less than 24 weeks gestation (8 weeks and 15 weeks), which both showed high CD39 expression percentages at the syncytiotrophoblasts of the terminal villi (100% and 96%, respectively). In addition, five of the control placentas had CAM, which did not show a difference in CD39 expression of the terminal villi from the other control samples. We also found CD39 expression at the endothelial cells of the chorionic or stem villi, but not in the capillaries of the terminal villi or in IUFD cases. These findings suggest that CD39 expression on endothelial cells is associated with vessel size or differentiation.

The placentas from the CIUE group demonstrated significant decreases in CD39 expression of the syncytiotrophoblasts of the terminal villi and endothelial cells of the stem villi. This downregulation of CD39 was more frequently observed in cases with more chronic inflammatory cells in the intervillous space. This suggested that CD39 can protect against these pathological conditions, and that its downregulation is associated with more advanced disease. Accordingly, CD39 downregulation might be an important histological finding of CIUE, and we hypothesize that CD39 downregulation of the chorionic villi is specifically involved in the CIUE pathogenesis.

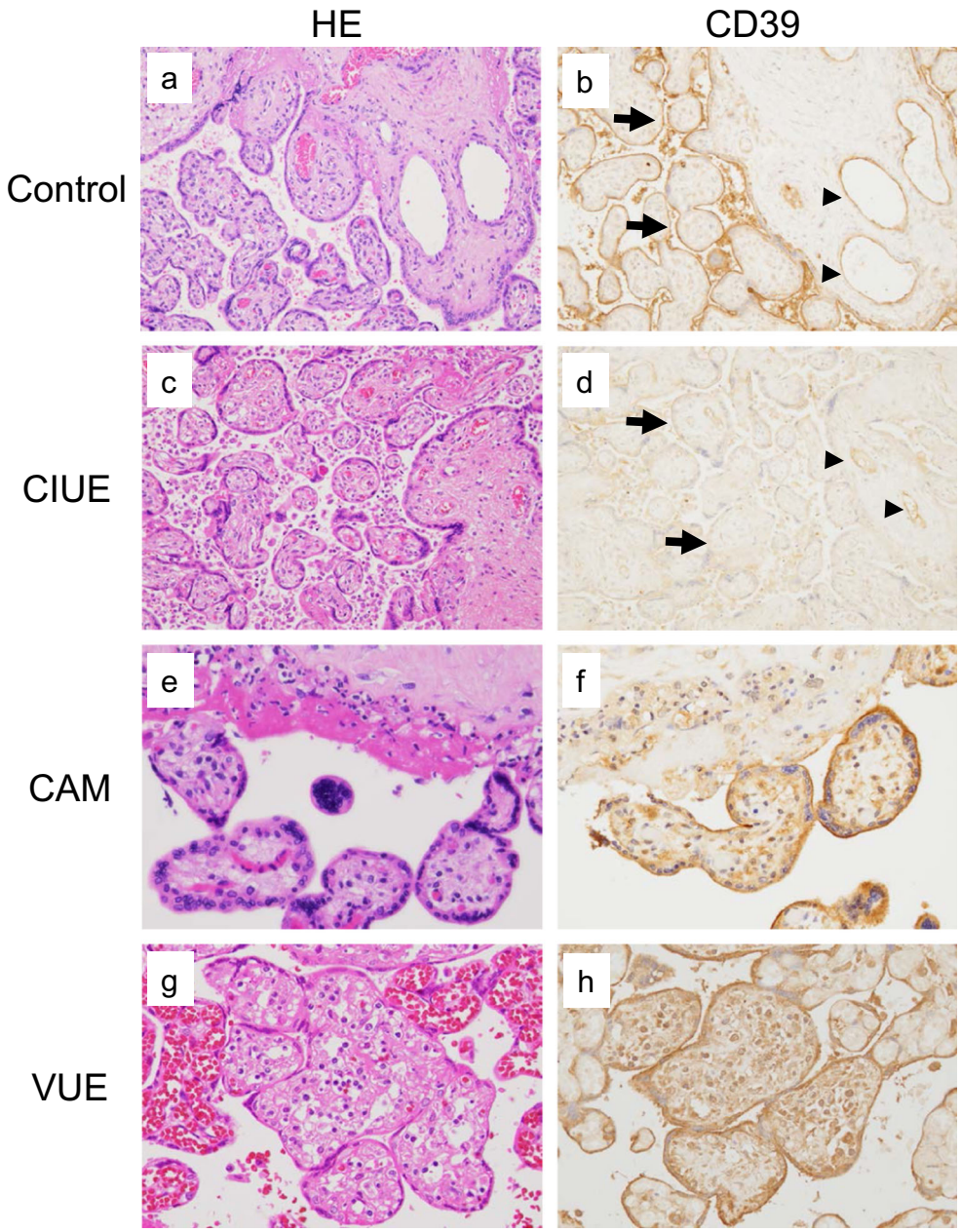

Fig. 1 Pathological findings of control (**a**, **b**), chronic intervillositis of unknown etiology (CIUE) (**c**, **d**) groups, chorioamnionitis (CAM) (**e**, **f**), and villitis of unknown etiology (VUE) (**g**, **h**). **a** Control placental tissue without chronic inflammatory cells in the intervillous space (hematoxylin eosin, HE). **b** CD39 staining in a control sample. Strong and linear CD39 expression is present at the surface of the villi (arrows) and endothelial cells of the stem villi (arrowheads). **c** CIUE placenta with HE stain. Many chronic inflammatory cells are present in the intervillous space. **d** CD39 staining in a CIUE sample. CD39 expression is weak at the surface of the villi (arrows) and endothelial cells of the stem villi (arrowheads). **e** CAM sample with HE stain. Infiltration of neutrophils is noted in the subchorionic lesion. **f** CD39 staining in the CAM sample. CD39 expression is present at the villi. **g** VUE sample with HE stain. Chronic inflammatory cells are present in the villi, and capillaries are reduced. **h** CD39 staining in the VUE sample. CD39 expression is observed at the villi

Chronic inflammation and/or coagulation disturbances may play a role in the pathophysiology of CIUE. A semi-quantitative evaluation of CIUE previously revealed that severe intervillositis with massive fibrin deposition was associated with severe perinatal prognosis, whereas the prognosis of patients with moderate intervillositis was better [7]. Moreover, other microscopic examinations showed that fibrin deposition was significantly associated with abortion and FGR, but not with the severity of intervillositis [10]. In the present study, we found that CD39 downregulation and the number of macrophages and T cells were associated with poor outcomes, whereas fibrin deposition and C4d deposition were not significantly associated with poor outcomes.

Cardiac-specific expression CD39 in mice showed a protective effect against myocardial infarction [23], and systolic blood pressure was not increased in a CD39 transgenic mouse model of eclampsia [15]. Furthermore, CD39 knockout mice with infarctions demonstrated increased infarct sizes and macrophage infiltrations [24], and CD39 knockout mice with human antiphospholipid antibody infusion had an increased rate of miscarriages [17]. In the present study, we determined that CD39 downregulation was associated with poor outcomes. In addition, we found a correlation between CD39 downregulation and increased numbers of CD68- and CD3-positive cells in the intervillous space.

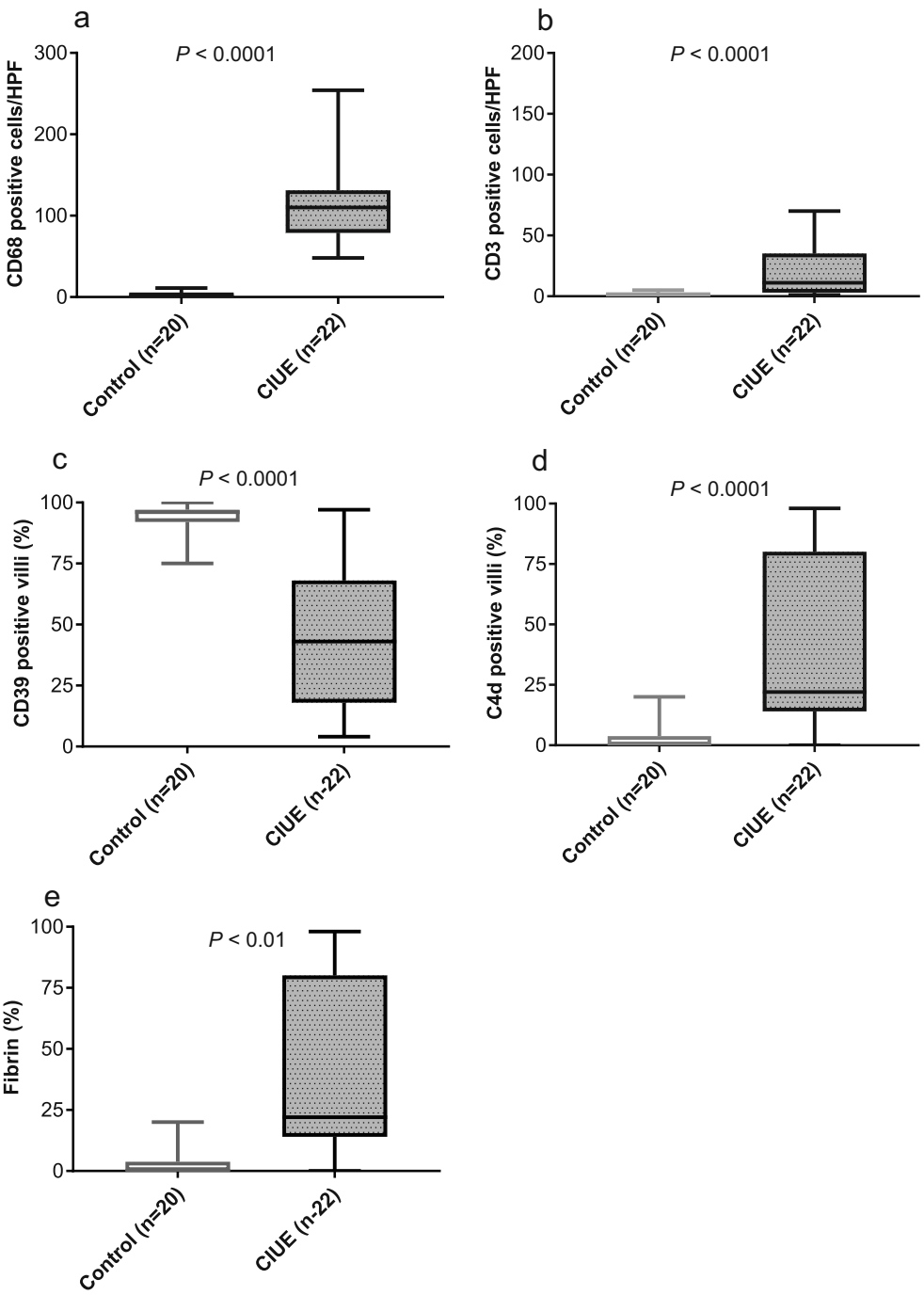

Fig. 2 Mean number of CD68 (**a**), CD3 (**b**), CD39 (**c**), and C4d positive (**d**) cells, and fibrin deposition (**e**) in control and CIUE placentas. CD39 expression was significantly decreased in CIUE compared to that in control samples, whereas increased numbers of CD68, CD3, C4d, and fibrin positive cells were observed in CIUE than in control samples

The definition of CIUE used for diagnosis is currently not clear, and different criteria have been applied in various studies. Labarrere and Mullen [1] first described CIUE as massive chronic intervillositis, histologically characterized as the intervillous infiltration of mononuclear cells in the placenta with fibrin deposition and trophoblast necrosis. Bos et al. [19] recently reviewed the published definitions of CIUE and proposed diagnostic criteria. In the present study, we found that the mean numbers of CD68- and CD3-positive cells per high-power field were much higher for the CIUE group than for controls, in line with a previous study [9]. Approximately 80% of the mononuclear cells in the intervillous space were CD68-positive cells. Thus, our data support the criteria proposed by Bos et al. [19]. In addition, the examination of CD68-positive cells is a simple and useful parameter for the diagnosis of CIUE.

Several limitations of this study should be acknowledged. First, the study included relatively mild cases of CIUE, whereas previous reports analyzed more severe cases [1, 2]. The mean positive number of CD68 was 113/high-power field

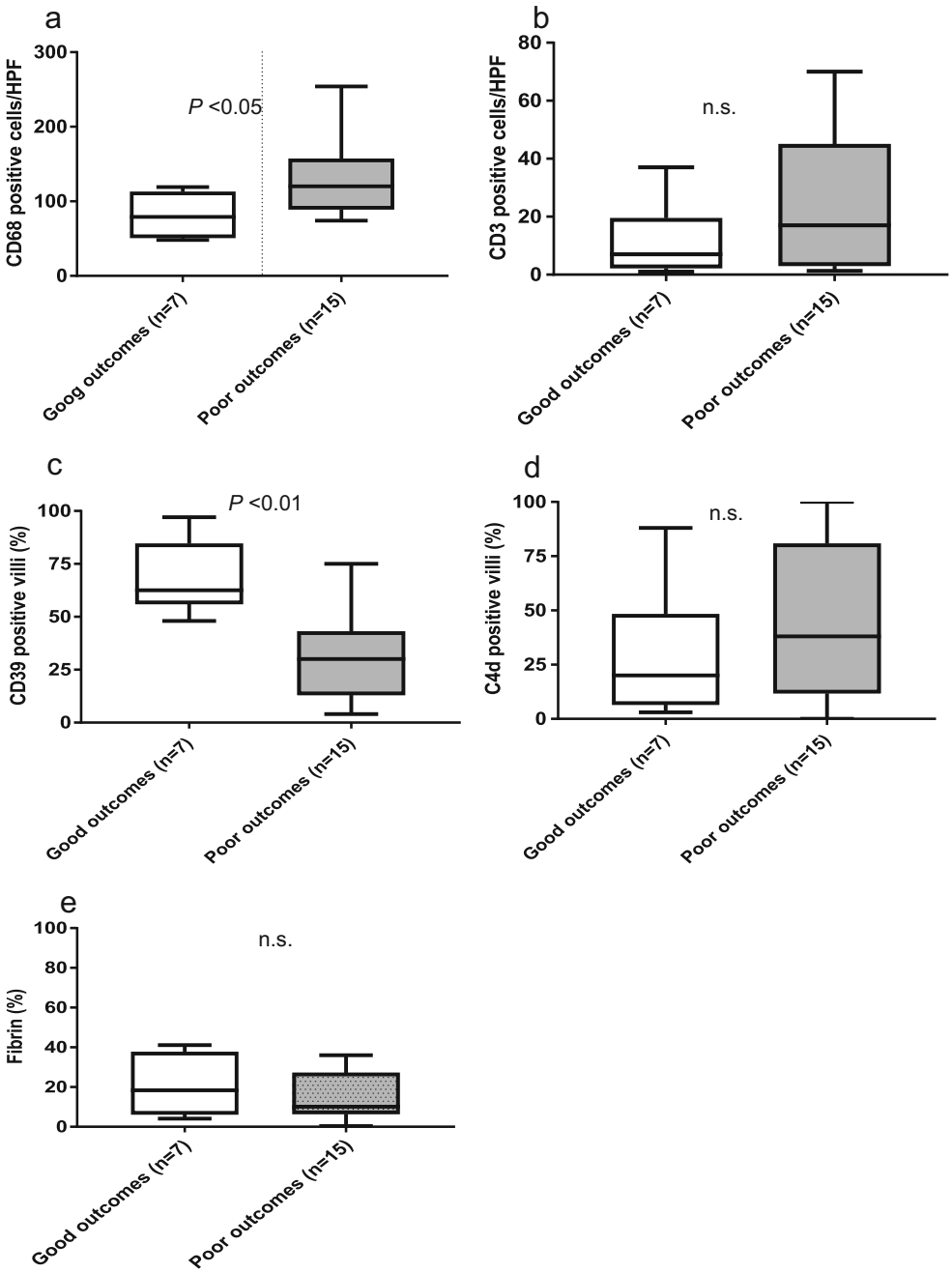

Fig. 3 Mean number of CD68 (**a**), CD3 (**b**), CD39 (**c**), and C4d positive cells (**d**), and fibrin deposition (**e**) in CIUE placentas with good outcomes and poor outcomes. n.s., not significant. CD39 expression was significantly decreased in fetuses with poor outcomes than in those with good outcomes, but CD68 expression showed the opposite pattern; there were no differences of CD3, C4d, and fibrin according to outcome

(range 48–254) in this study but was only 60/high-power field in three cases. In addition, the sample size was quite small, especially for the evaluation of next pregnant placentas, because CIUE is very rare, especially for patients who visit our hospital for subsequent pregnancies. Previous studies reported an overall prevalence of 9.6 per 1000 miscarriages and in 0.6 per 1000 placentas in the second and third trimester [3, 4]. It was difficult to determine the true incidence of CIUE in our sample because of the relatively small sample size. Moreover, we did not investigate the mechanism of CD39 downregulation or CIUE pathology. Infiltrative macrophages, T cells, or C4d deposition may induce the downregulation of CD39 of the chorionic villi, which should be examined in further detailed studies.

In summary, the proportion of the villi with complete circumferential staining of CD39 was decreased in CIUE placentas compared with that of controls. The reduction of CD39 and the high number of cells expressing CD68 were significantly associated with fetal outcomes, but other parameters were not. These findings suggest that the downregulated expression of CD39 is associated with more infiltration of chronic inflammatory cells and a poor fetal outcome. However, future research is needed to elucidate the precise mechanism linking CD39 downregulation and CIUE.

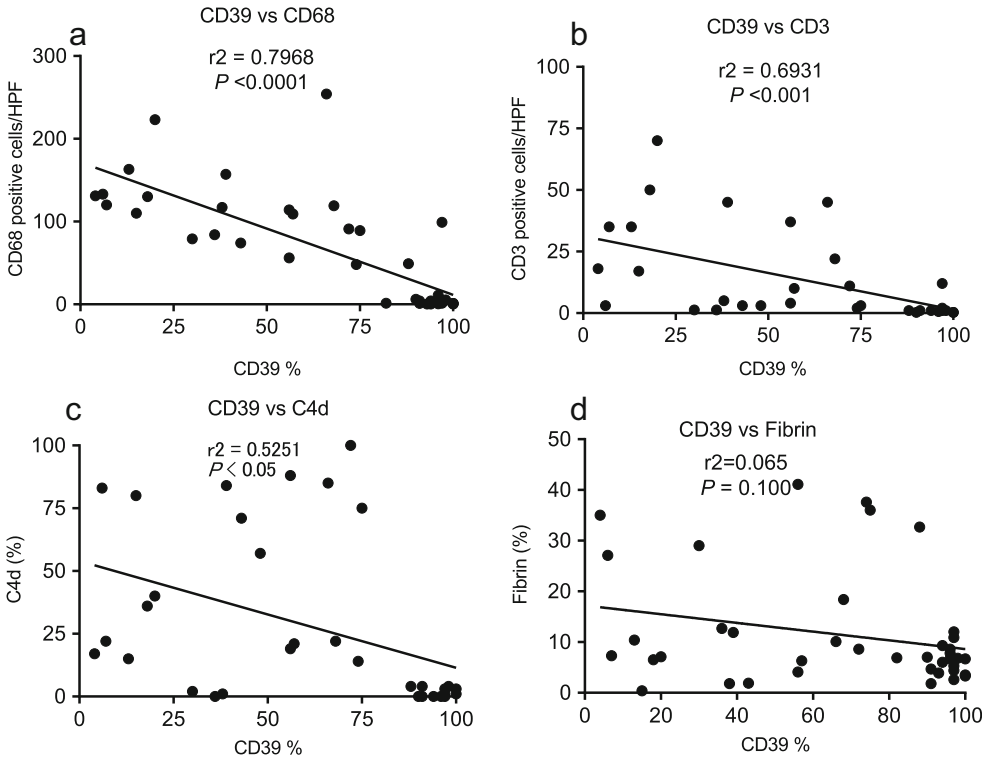

Fig. 4 Correlation between CD39 and CD68 (**a**), CD3 (**b**), C4d (**c**), and fibrin (**d**) expression levels. The plotted values demonstrate that reduced CD39 expression was significantly associated with increased expression of CD68, CD3, and C4d in the intervillous inflammatory infiltrate. The association with fibrin expression did not reach statistical significance

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Author contributions YS, KM, and MA conceived and designed the study and wrote the manuscript. AY, YS, YK, and YM collected and analyzed the data. HS and YA wrote, edited, and reviewed the manuscript. All authors participated in the interpretation of the results and writing of the report and approved the final version submitted. YS takes full responsibility for the work, as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

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Compliance with ethical standards

This study was approved by the Medical Ethics Committee of the Faculty of Medicine at the University of Miyazaki on September 4, 2018 (project number 0-0401).

Conflict of interest The authors declare that they have no conflict of interest.

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