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Oxidative Stress and Generalised Pustular Psoriasis: Report of d-ROM Measurements in Nine Cases Including Three of Pustular Psoriasis of Pregnancy

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ABSTRACT

Reactive oxygen species (ROS) are involved in the pathogenesis of generalised pustular psoriasis (GPP), but this involvement has not been fully elucidated. We performed the diacron-reactive oxygen metabolite (d-ROM) test and the biological antioxidant potential (BAP) test on sera from nine patients with active GPP who were hospitalised and treated at our hospital, including three patients with pustular psoriasis of pregnancy (PPP). The serum d-ROM and BAP levels were evaluated before treatment and at 1 month of treatment. We also performed immunostaining of 4-hydroxy-2-nonenal (4-HNE) in skin tissues. In the GPP patients, the average d-ROM levels were significantly reduced at 1 month of treatment (reduced to 343.0 ± 82.1 U. Carr from 423.2 ± 95.0 U.Carr, $p = 0.005$). The Generalised Pustular Psoriasis Area and Severity Index (GPPASI) score correlated with d-ROM levels ($r = 0.57$, $p = 0.10$), suggesting that those levels reflect the disease severity. In normal pregnancy, d-ROM values are known to increase from mid-term to late-term. The d-ROM values increased when GPP worsened in the case of PPP. Immunohistochemical staining of 4-HNE was positive for subcorneal pustules, neutrophils, and for the cytoplasm of epidermal keratinocytes, especially in upper epidermal layers. Our findings indicate that 4-HNE may play an important role in GPP and PPP.

1 | Background

Generalised pustular psoriasis (GPP) is immunologically distinct from psoriasis vulgaris and is characterised by the dysregulation of the innate immune system, particularly the interleukin-36 (IL-36) inflammatory pathway [1–3]. Pustular psoriasis of pregnancy (PPP), also called impetigo herpetiformis, tends to increase or flare up more frequently in the late stages of pregnancy and mostly resolves after parturition; however, the possibility of recurrence during subsequent pregnancies is high [4]. Pregnancy itself is a state of increased oxidative stress that arises from metabolic activity and the production of reactive oxygen species (ROS) in the placental mitochondria to meet the demands of the growing fetus [5, 6]. Normal pregnancy is characterised by mild oxidative stress, which is exaggerated in preeclampsia and fetal growth restriction [7, 8]. Pregnant women with preeclampsia are known to have higher d-ROM values than normal pregnant women have [9]. Gestational diabetes, gestational hypertension, and preeclampsia are higher in women with psoriasis [10–12].

The test for derivatives of reactive oxygen metabolites (d-ROM test) is a widely used assay for measuring oxidative stress in biological samples, particularly in serum or plasma. The test does not directly measure reactive oxygen or free radicals; rather, it evaluates oxidative stress by quantifying metabolite

hydroperoxides [13–16]. The BAP test is used to assess the antioxidant capacity of biological samples, such as blood or serum. It measures the ability of a biological sample to reduce ferric ions to ferrous ions, reflecting the sample's ability to eliminate free radicals and counteract oxidative stress [17]. Although the d-ROM test and the BAP test have been used in many diseases, they have not yet been reported for GPP patients.

With regard to ROS, 4-hydroxy-2-nonenal (4-HNE) is one of the reaction products of lipid hydroperoxide breakdown in response to oxidative stress. Primary oxidation products such as lipid hydroperoxides may decompose and lead to the formation of reactive lipid electrophiles. Lipid hydroperoxides can then break down further to generate secondary products such as 4-HNE [18]. 4-HNE formation is directly linked to, and is dependent on, the initial generation of lipid hydroperoxides from the oxidation of polyunsaturated fatty acids in cellular membranes under oxidative stress [19, 20].

To investigate the contribution of oxidative stress to GPP pathogenesis, we measured the d-ROM and BAP levels before and after treatment. Furthermore, to visualise ROS, we tried to detect oxidative products by using the anti-4-HNE antibody on samples from lesional skin.

2 | Question Address

This study aims to clarify three points [1]. Do d-ROM levels correlate with GPP severity? [2] Do d-ROM levels correlate with GPP severity during pregnancy, given that d-ROM levels are known to increase from the middle to late stages of pregnancy? [3] Is 4-HNE involved in the increase in oxidative stress in GPP?

3 | Experimental Design

We measured the d-ROM levels from the sera of nine patients with active GPP who were hospitalised and treated between 2015 and 2020. The serum d-ROM and BAP levels were evaluated before treatment and at 1 month of treatment. The patients had been diagnosed on management and treatment of Generalised Pustular Psoriasis 2014 of Japanese Guidelines [21]. The d-ROM and BAP levels were measured using a commercial kit and reader (Redoxlibra; Wismerll, Tokyo, Japan) as previously described [14, 17, 22]. The oxidative stress that corresponds to each range of d-ROM values is as follows: normal, 200–300 U.Carr; borderline, 301–320 U.Carr; mild, 321–340 U.Carr; moderate, 341–400 U.Carr; high, 401–500 U.Carr; severe, ≥ 501 U.Carr. BAP antioxidant levels of > 2000 μmol/L were evaluated as normal. The d-ROM test measures metabolites produced by ROS in a sample by the colourimetric change of a chromogen. The serum d-ROM and BAP levels were evaluated before treatment and at 1 month of treatment (Table 1). We biopsied skin lesions and performed haematoxylin and eosin (HE) staining on paraffin sections. From the patients' medical records, we obtained peripheral blood counts (white blood cells, neutrophils, lymphocytes, and platelets). The patients included cases reported by Mizutani et al. [23] Please refer to the Supporting Information.

4 | Results

4.1 | In Patients With GPP, the d-ROM Levels Increased Before Treatment and Decreased With Treatment

The average d-ROM levels were found to be significantly reduced at 1 month of treatment (reduced to 343.0 ± 82.1 U.Carr from 423.2 ± 95.0 U.Carr, $p = 0.005$, paired t-test) (Figure 1a). The average GPPASI score was also found to be significantly reduced at 1 month of treatment (reduced to 12.8 ± 4.0 from 21.6 ± 2.7, $p = 0.0006$, paired t-test) (Table 1). The BAP levels were within normal limits in four of the nine patients and were reduced at 1 month of treatment (reduced to 2221.3 ± 450.0 μmol/L from 2088.1 ± 492.2 μmol/L) (Figure 1b).

4.2 | In Patients With GPP, the d-ROM Levels Correlated Moderately With GPPASI ($r = 0.57$, $p = 0.10$)

Because high levels of ROS in GPP may play a role in disease activity, we next examined the d-ROM level as measured by the GGPASI. We retrospectively scored the GPPASI before treatment and at 1 month of treatment. As shown in Figure 1c, a moderately positive correlation was found between the d-ROM levels before treatment and the total GPPASI score ($r = 0.57$, $p = 0.10$). The GPP patients had elevated average white blood cell counts (mean 12826.6/μL; normal: 3300–8600/μL). The d-ROM levels showed no correlation with the overall number of neutrophils ($r = -0.22$, $p = 0.67$). In contrast, the d-ROM levels correlated moderately with lymphocyte percentage ($r = 0.44$, $p = 0.22$) (Table 1). Figure 1d–f show the clinical course of PPP (Cases 1–3). For each patient, we checked for variants in the genes for interleukin-36 receptor antagonist (*IL36RN*), caspase recruitment domain-containing protein 14 (*CARD14*), and adaptor-related protein complex 1 subunit sigma 3 (*AP1S3*) (Figure 2a).

4.3 | In GPP patients' Skin Lesions, 4-HNE Stained for Neutrophils in the Subcorneal Pustules and for the Cytoplasm of Epidermal Keratinocytes

To visualise ROS, we tried to detect oxidative products by using the anti-4-HNE antibody on lesional skin in GPP. 4-HNE stained for neutrophils in the subcorneal pustules and for the cytoplasm of epidermal keratinocytes. Staining was particularly strong in the upper epidermal layers (Figure 2b–k). Eight of nine (88.9%) patients were positive for 4-HNE in neutrophils in the subcorneal pustules, and all nine (100%) patients were positive for 4-HNE in the cytoplasm of epidermal keratinocytes. Immunohistochemical staining with 3,5-dibromotyrosine of paraffin sections was negative (data not shown). Immunohistochemical staining with NF-kB p65 and IL-36Ra was positive (data not shown).

TABLE 1 | Summary of the nine GPP patients.

				d-ROM test		BAP test		Peripheral blood				GPPASI			
Case	Age	Sex	Pregnancy	Before	After	Before	After	WBC	Neut	Lymp	NLR	Before	After	Rate of change (%)	Treatment
1	29	F	Yes	527	474	2033	1757	9360	8096	936	8.6	44.4	12.9	70.9	GMA, PSL
2	35	F	Yes	494	376	1459	1574	14960	12641	1571	8.0	25.2	0.4	98.4	Infliximab
3	28	F	Yes	340	321	1736	2265	13350	8392	1351	6.2	8	1.2	85	GMA
4	41	M	No	560	340	2920	2660	5690	3470	1570	2.2	15.2	2.1	86.1	GMA
5	42	M	No	431	323	2551	2593	15810	13597	632	21.5	39.2	1.8	95.4	GMA, apremilast
6	83	F	No	423	364	1968	1807	17060	15695	1280	12.3	21.3	0	100	GMA, etretinate
7	73	M	No	394	384	2121	2507	7080	5900	843	7.0	13.4	1.6	88	Secukinumab
8	80	M	No	386	343	2492	2818	23080	21793	570	38.2	20	4.5	77.5	PSL, etretinate
9	79	F	No	254	162	1513	2011	9050	7893	815	9.7	8.1	0	100	GMA, PSL, etretinate
Avg	54.4	—	—	423.2	343.0	2088.1	2221.3	12827	10831	1063.1	12.6	21.6	2.7	89	
SD	23.7	—	—	95.0	82.1	492.2	450.0	5557	5649	387.2	10.9	12.8	4	10.3	
r	—	—	—	—	—	—	—	−0.18	−0.16	0.44	0.22	0.57	—	—	
p	—	—	—	—	—	—	—	0.63	0.67	0.22	0.56	0.10	—	—	
t-test	—	—	—	$p=0.005$		$p=0.24$		—	—	—	—	$p<0.001$		—	

Note: The d-ROM and BAP test results and the GPPASI scores before treatment and at 1 month of treatment are summarised. The results of the peripheral blood test are before treatment. The *t*-test compares the d-ROM or BAP levels before treatment versus at 1 month of treatment, using a paired *t*-test. R shows the Pearson's correlation coefficient between d-ROM levels before treatment and each item.

Abbreviations: Avg, average; BAP, biological antioxidant potential (normal > 2000 μmol/L); d-ROM, diacron-reactive oxygen metabolite level (normal range: 200–300 U.Carr); F, female; GMA, granulocyte and monocyte adsorption apheresis; GPPASI, Generalised Pustular Psoriasis Area and Severity Index; Lymp, lymphocytes; M, male; Neut, neutrophils; NLR, neutrophil/lymphocyte ratio; *p*, *p* value of *r*; PSL, prednisolone; *r*, correlation coefficient; SD, standard deviation; U.Carr, Carratelli units; WBC, white blood cells (normal range: 3300–8600/μL).

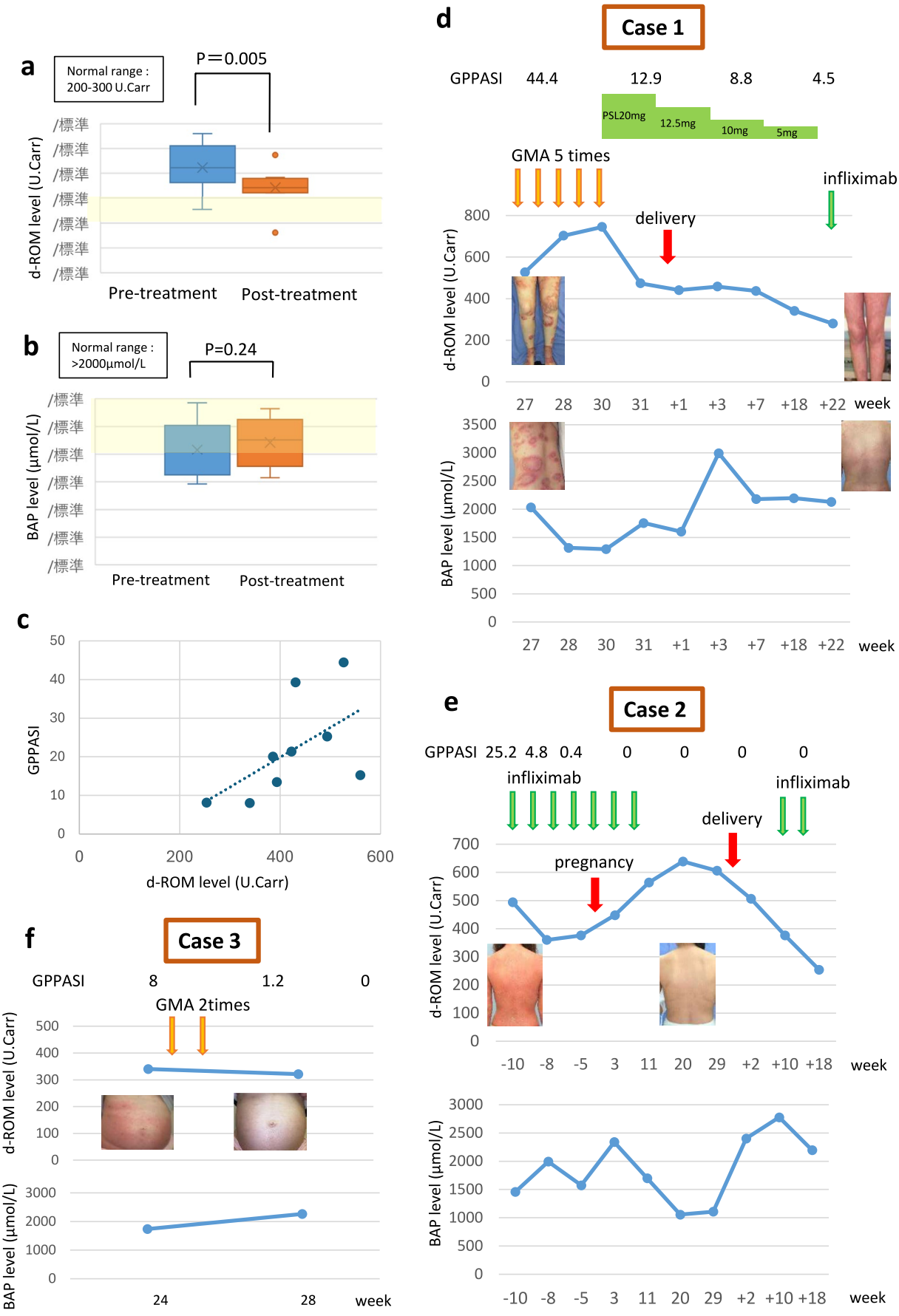

FIGURE 1 | Legend on next page.

FIGURE 1 | Oxidative stress in GPP patients. (a) Box plot of d-ROM levels for nine GPP patients. The d-ROM levels are for before treatment and at 1 month of treatment (reduced to 343.0 ± 82.1 U.Carr from 423.2 ± 95.0 U.Carr, $p = 0.005$, paired *t*-test). (b) Box plot of BAP levels for the nine GPP patients before treatment and at 1 month of treatment (reduced to 2221.3 ± 450.0 μmol/L from 2088.1 ± 492.2 μmol/L, $p = 0.24$, paired *t*-test). The box shows the first and third quartiles, the median (line), and the arithmetic mean (*x*-mark). The whiskers represent values below the first quartile and above the third quartile within the 1.5-fold inter-quartile range, respectively. Outliers beyond the whiskers are shown as squares. (c) Scatterplot of GPPASI scores and d-ROM levels. Scatterplot showing a moderately positive correlation ($r = 0.57$, $p = 0.10$; Pearson's correlation coefficient). The dotted line is the trend line. (d) Clinical course of Case 1. (e) Clinical course of Case 2. The horizontal axis of the graph indicates the number of weeks of pregnancy. In (e), negative values on the *x* axis are the number of weeks before conception and positive values are the number of weeks after delivery. (f) Clinical course of Case 3. GMA, granulocyte and monocyte adsorption apheresis; PSL, prednisolone; U.Carr, Carratelli units.

4.4 | D-ROM Levels Were Elevated in Late Pregnancy, and They Reflected the Skin Symptoms

Case 1 is a 29-year-old female. She has two heterozygous mutations in *IL36RN*: c.28C>T (p.R10X) on exon2 and c.368C>T (p.T123M) on exon5. Her psoriasis onset was at age 3, and her pustular psoriasis onset was at age 16. Cyclosporine introduced at her previous hospital achieved moderate improvements. She visited our hospital in the 26th week of her first pregnancy. She had erythema on the face, trunk, extremities and inguinal areas, with small pustules. We performed granulocyte–monocyte apheresis (GMA) five times, but fever, fatigue, pustules and erythema flared up. So, we added prednisolone at 20 mg/day and cyclosporine at 150 mg/day. She gave birth at 33 weeks gestation. A live female infant weighing 1458 g (8.5th percentile) was delivered vaginally. Figure 1d shows the results of the d-ROM and BAP tests for Case 1. The d-ROM levels increased with skin rash exacerbation and decreased with PSL treatment (20 mg). After delivery, the d-ROM levels returned to normal. The BAP levels decreased from mid to late pregnancy. They returned to normal after delivery.

Case 2 is a 35-year-old primigravida. She has no mutations in *IL36RN*, *CARD14* or *AP1S3*. Her skin symptoms flared up when she was 35 years old, and she was hospitalised. She had been taking cyclosporine for 6 months but stopped when she started fertility treatment and switched to intravenous infliximab. At the fourth administration of infliximab, we found out she was pregnant. The infliximab was readministered every 2 months until 30 weeks. At 41 weeks, she gave birth by caesarean section. Now, at 8 years after that birth, her skin rash is under control with the continued administration of infliximab. Figure 1e shows the results of the d-ROM and BAP tests for Case 2. Before infliximab was started, the skin symptoms worsened and the d-ROM level increased. After the start of infliximab, the d-ROM levels decreased. From mid-pregnancy, the d-ROM level increased. After delivery, the d-ROM levels decreased to normal.

5 | Conclusion and Perspectives

This study found a moderately positive correlation between GPPASI scores and d-ROM values. So, d-ROM levels correlate with GPP severity. Both of these improved with 1 month of treatment ($p = 0.05$ and $p = 0.0006$, respectively). Therefore, the d-ROM value may be a biomarker of GPP severity and of response to GPP treatment. In this study, three of the nine GPP patients were gravida. In GPP during pregnancy, d-ROM values tend to increase as the skin symptoms exacerbate. But d-ROM values tend to increase even in normal pregnancies from the mid-term to the late-term, so we must take that into account when evaluating such values. Increased progesterone levels during pregnancy, especially in the last trimester, are considered to be a potential trigger for the development of PPP [12, 24]. A previous paper reported that NF-κB regulates inflammation, hypoxia, angiogenesis, and oxidative stress, all of which are associated with placental development [25–27]. Pregnancy has been shown to involve two interactions, inflammatory and anti-inflammatory, with NF-κB activity being regulated by the required balance between these interactions [28–30].

In our study, all the patients with GPP skin lesions were positive for 4-HNE. 4-HNE staining was negative in normal skin, suggesting that 4-HNE is associated with increased oxidative stress. This is an α,β-unsaturated hydroxyalkenal (chemical formula: $C_9H_{16}O_2$) that is produced by lipid peroxidation in cells. It is a major end product of lipid peroxidation and is widely recognised as an inducer of oxidative stress [31–33]. 4-HNE is known to express proinflammatory cytokines by the regulation of NF-κB, MCP-1, TNF-α, and TGF-β1 [18, 32, 34]. 4-HNE concentrations below 2 μM are conducive to cell survival and proliferation. However, concentrations exceeding 10 μM are detrimental to the cell, leading to genotoxicity and cell death [18, 19]. 4-HNE activates NF-κB through the formation of protein adducts, the activation of Src kinase, and the activation of the IKK/NIK pathway, leading to the transcription of pro-inflammatory genes [18, 32, 34].

IL-36 cytokines play a central role in recruiting and activating neutrophils, leading to increased ROS production in GPP. IL-36 can create an autocrine amplification loop by promoting the expression of IL-36 itself and its receptor (IL-36R) in immune cells, which in turn increases T cell proliferation and Th1 polarisation. IL-36 is strongly expressed in the nuclei of suprabasal epidermal keratinocytes, and its expression is associated with disease severity [35]. Moreover, IL-36 signalling activates the NF-κB pathway and other pathways, contributing to the production of pro-inflammatory cytokines. The binding of IL-36 cytokines to IL-36R recruits IL-1 receptor accessory protein (IL-1RAcP), leading to the activation of NF-κB and mitogen-activated protein kinases (MAPKs), which are critical for the inflammatory response [2, 36, 37]. IL-36 also plays a role in regulating the inflammatory/anti-inflammatory balance during pregnancy, similar to NF-κB [12, 29]. Elevated levels of IL-36 and NF-κB can contribute to an increased incidence of GPP during pregnancy. It could be interpreted that in GPP, the IL-36/IL-1 axis primarily elevates neutrophil migration and ROS production, leading to the generation of 4-HNE from hydroperoxides. 4-HNE activates

a

Case	Gene mutation
1	*IL36RN*, c.28C>T, heterozygous; *IL36RN*, c.368C>T, heterozygous
2	none
3	*CARD14*, c.236C>T, homozygous
4	none
5	none
6	*IL36RN*, c.115+6T>C, heterozygous
7	none
8	none
9	*IL36RN*, c.115+6T>C, homozygous

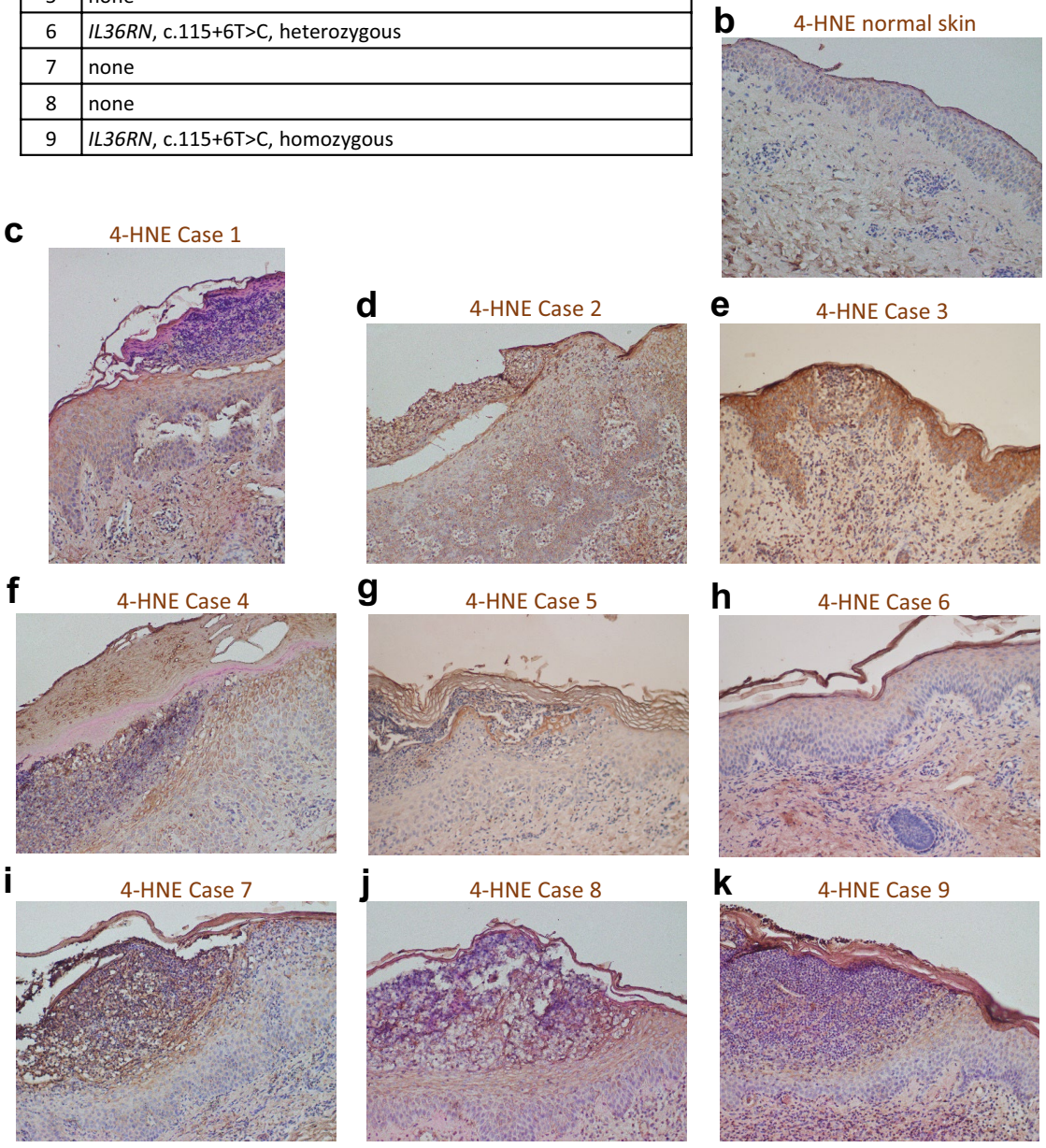

FIGURE 2 | Oxidative stress in GPP patients. (a) Gene mutations for the nine GPP patents. We checked for gene variants in *IL36RN*, *CARD14*, and *AP1S3*. *AP1S3*; adaptor related protein complex 1 subunit sigma 3, *CARD14*; caspase recruitment domain-containing protein 14, *IL36RN*; interleukin-36 receptor antagonist. (b–k) Immunohistochemical staining of 4-HNE. A magnification of the area of small pustules (original magnification × 200). (b) Normal human skin with 4-HNE staining (original magnification × 200).

NF-κB, which further increases inflammation. IL-36 also enhances NF-κB transcription and promotes the migration of neutrophils and other lymphocytes.

d-ROM levels represent the amount of oxidative stress, and their measurement is useful because it reflects clinical severity. The d-ROM test should be considered with this physiological phenomenon in mind, since oxidative stress has been shown to increase from mid to late pregnancy. Because we measured d-ROM levels in only nine GPP cases, our study has limited clinical significance. However, it may have research significance. If future research reveals more about the relationship between oxidative stress and GPP, our understanding of its significance could change. Potential limitations include the retrospective

nature of the data, the single-centre nature, and the small sample size. Also, d-ROM levels have already been known to increase as a result of various factors, such as aging, diabetes, cardiovascular disease, and cancer [13, 38]. Although the d-ROM test is not a specific indicator, when it is elevated, we must check the patient's status carefully.

Author Contributions

Yoko Ueda and Chisato Tawada conceptualised and designed the study. Materials were prepared and data were collected by Yoko Mizutani and Kayoko Tanaka and Xiaoyu Zang. Data were analysed and interpreted by Yoko Ueda and Chisato Tawada. The manuscript was written by Chisato Tawada and Hiroaki Iwata. All authors approved the final article as submitted.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.