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Letter to the Editor

Title: Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic syndrome (DIHS/DRESS) followed by transient palmoplantar keratoderma-like eruption

Running head: PPK-like eruption after DIHS/DRESS

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Dear Editor,

Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic syndrome (DIHS/DRESS) is characterized by **maculopapules** developing more than 3 weeks after starting with drug which is **accompanied by various complications**.¹ Here, we describe a DIHS/DRESS case with palmoplantar keratoderma (PPK)-like sequela.

A 44-year-old Japanese woman started Vegetamin B® (chlorpromazine 12.5 mg, promethazine 12.5 mg, and phenobarbital 30 mg) for depression on day -31. She developed a flu-like symptom on day -10. She was hospitalized on day -5 **when the examination revealed** 3,300/ μ L of white blood cells (WBCs; normal range 3,500–9,100) with 1% atypical cells, AST 275 U/L (10–40), ALT 175 U/L (5–45), **alkaline phosphatase 2,159 U/L (110–360)**, γ -GTP 1,173 U/L (≤ 45), **IgG 1707 mg/dl (870–1700)** and **total bilirubin 0.8 mg/dl (0.2–1.1)** (Fig. 1a). Antinuclear antibody and infections were negative for **influenza viruses**, HBV, HCV, HIV, rubella, rubeola, Epstein-Barr virus, and cytomegalovirus. X-ray computed tomography revealed para-aortic lymphadenopathy, splenomegaly, and edematous gall bladder.

On day 0, non-pruritic rash appeared on her arms. On day 3, her face **became** edematous (Fig. 1b) **with icteric sclera (total bilirubin, 4.9 mg/dl)** and **the rash covered 90% of the body** (Fig. 1c and d). Biopsy of her left arm exhibited spongiosis, apoptotic keratinocytes, and vacuolar degeneration with lymphocytic infiltration including perifollicular area (Fig. 1e-f). We discontinued Vegetamin B® and started 60 mg/day (1.0

mg/kg/day) of oral prednisolone. The patient disagreed with testing HHV6 and lymphocyte stimulation for Vegetamin B®. Dermatitis improved on day 7 and we reduced prednisolone to 50 mg/day on day 10. However, a flare-up of dermatitis and a recovery of lymphocytes followed, suggesting the presence of viral reactivation and/or corticosteroid-reduction-associated immune reconstitution inflammatory syndrome. Examination on day 13 revealed WBCs 11,200/μL (eosinophils 2,240/μl) and TARC 3,556 pg/ml (< 450) (Fig. 1a). We increased prednisolone to 60 mg/day from day 14 until day 30 when the eruptions disappeared. On day 18, the palmoplantar area started to become hyperkeratotic without itch and formed thick brick-like scales by day 124 (Fig. 1g-i). Nails were unaffected. There was no family or past history of PPK. Biopsy was disagreed. We started difluprednate and 10% salicylic acid ointments for palmoplantar area on day 116. PPK-like lesion gradually disappeared by day 224. We diagnosed her as atypical DIHS and a definite case of DRESS (Table S1–2).¹⁻³

An unusual aspect of our case was PPK-like eruption. Whether our case shares etiology with a DIHS/DRESS-affected woman who showed palmoplantar desquamation is unclear.⁴ Pompholyx with increased IgG at acute stage of DIHS/DRESS could have caused PPK-like lesion.⁵ However, we did not find such lesion and unfollowed IgG. ~~We did not perform microscopic examination for fungi and scabies, which can cause keratosis.~~ Hand-foot-mouth disease (by the reactivated viruses) and pityriasis rubra pilaris (reminisced by the disseminated folliculocentric erythropapules) were other differential diagnoses, which were not assessed due to the limitation of obtaining informed consent. Accumulation of further cases is required to verify whether PPK-like change is a sequela of DIHS/DRESS.

FIGURE LEGEND

Figure 1. (a) Summary of the disease course. The patient, who started Vegetamin B® (the culprit drug) on day -31, developed a flu-like symptom on day -10. She was hospitalized on day -5 for hepatitis. On day 0, non-pruritic rash started to develop. On day 3, the patient became erythrodermic and was referred to us. We discontinued Vegetamin B® and started oral prednisolone (PSL) at 60 mg daily. As the primary eruption faded away, palmoplantar area started to become hyperkeratotic, resulting in a palmoplantar keratosis (PPK)-like appearance by day 124. The PPK-like lesion disappeared by day 224 by the treatment with difluprednate and 10% salicylic acid ointments. Changes of body temperature (BT), white blood cells (WBC), eosinophils (Eos), lymphocytes (Lym), platelets (PLT), lactate dehydrogenase (LDH), thymus and activation-regulated chemokine (TARC), immunoglobulin G (IgG), C-reactive protein (CRP), bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyltransferase (γ -GTP) are shown. (b) Edematous face with erythema and follicular red papules. Frangible crusts adhered on the nasolabial sulci. Sclera was icteric (not shown). (c) Disseminated erythema intermingled with purpura on the left upper arm. (d) Abdomen presenting scattered folliculocentric erythema and petechiae (inset). (e-f) Histology. The specimen was taken from erythema on the left arm. (e) The epidermis showed spongiosis, apoptotic keratinocytes, vacuolar degeneration of basal keratinocytes, and infiltration of lymphoid cells. (f) Inflammatory cells infiltrated the follicular epithelium at the level of a pilosebaceous unit. (g-i) Palmoplantar keratoderma-like change which became apparent by day 58 (g-h) and pronounced on day 124 (i). Black bars are to redact personal information.

91 Supporting Information

92 Table S1. Scoring on a DIHS system

Features	Our case
No. 1. Maculopapular rash developing > 3 weeks after starting with a limited number of drugs	Yes
No. 2. Prolonged clinical symptoms 2 weeks after discontinuation of the causative drug	Yes
No. 3. Fever > 38°C	Yes (day -10)
No. 4. Liver abnormalities (alanine aminotransferase > 100 U/L) *	Yes (day -5)
No. 5. Leukocyte abnormalities (at least one present)	
- a. Leukocytosis ($> 11 \times 10^9/L$)	Yes (day 13)
- b. Atypical lymphocytes (> 5%)	No
- c. Eosinophils ($> 1.5 \times 10^9/L$)	Yes (day 13)
No. 6. Lymphadenopathy	Yes (deep abdominal)
No. 7. Human herpesvirus 6 reactivation	Not tested
The diagnosis is confirmed by the presence of the seven criteria above (typical) or of the five (No. 1 to No. 5; atypical).	Atypical

93 * This can be replaced by other organ involvement, such as renal involvement.

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95 Table S2. Scoring on a DRESS system

Score	-1	0	1	2	Min	Max	Our case
Fever $\geq 38.5^{\circ}\text{C}$	No/U	Yes			-1	0	0
Enlarged lymph nodes		No/U	Yes		0	1	0
Eosinophilia		No/U			0	2	2
- Eosinophils			$\geq 0.7 \times 10^9/\text{L}$	$\geq 1.5 \times 10^9/\text{L}$			
- Eosinophils, if leucocytes $< 4.0 \times 10^9/\text{L}$			$\geq 10\%$	$\geq 20\%$			
Atypical lymphocytes		No/U	Yes		0	1	1
Skin involvement					-2	2	2
- Skin rash extent (% body surface are)		No/U	> 50%				
- Skin rash suggesting DRESS	No	U	Yes				
- Biopsy suggesting DRESS	No	Yes/U					
Organ involvement					0	2	2
- Liver		No/U	Yes				
- Kidney		No/U	Yes				
- Lung		No/U	Yes				
- Muscle/heart		No/U	Yes				
- Pancreas		No/U	Yes				
- Other organs		No/U	Yes				Gall bladder
Resolution ≥ 15 days	No/U	Yes			-1	0	0
Evaluation of other potential causes							
- Antinuclear antibody							No
- Blood culture							No
- Serology for HAV/HBV/HCV							No
- Chlamydia/mycoplasma							U
- If none positive and ≥ 3 of above negative			Yes		0	1	1
Total Score					-4	9	8

96 U, unknown/unclassifiable; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV,

97 hepatitis C virus;

98 * After exclusion of other explanations: 1, one organ; 2, two or more organs

99 Final score < 2 , no case; 2–3, possible case; 4–5, probable case; > 5 , definite case.

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Figure 1a. Nomura et al.

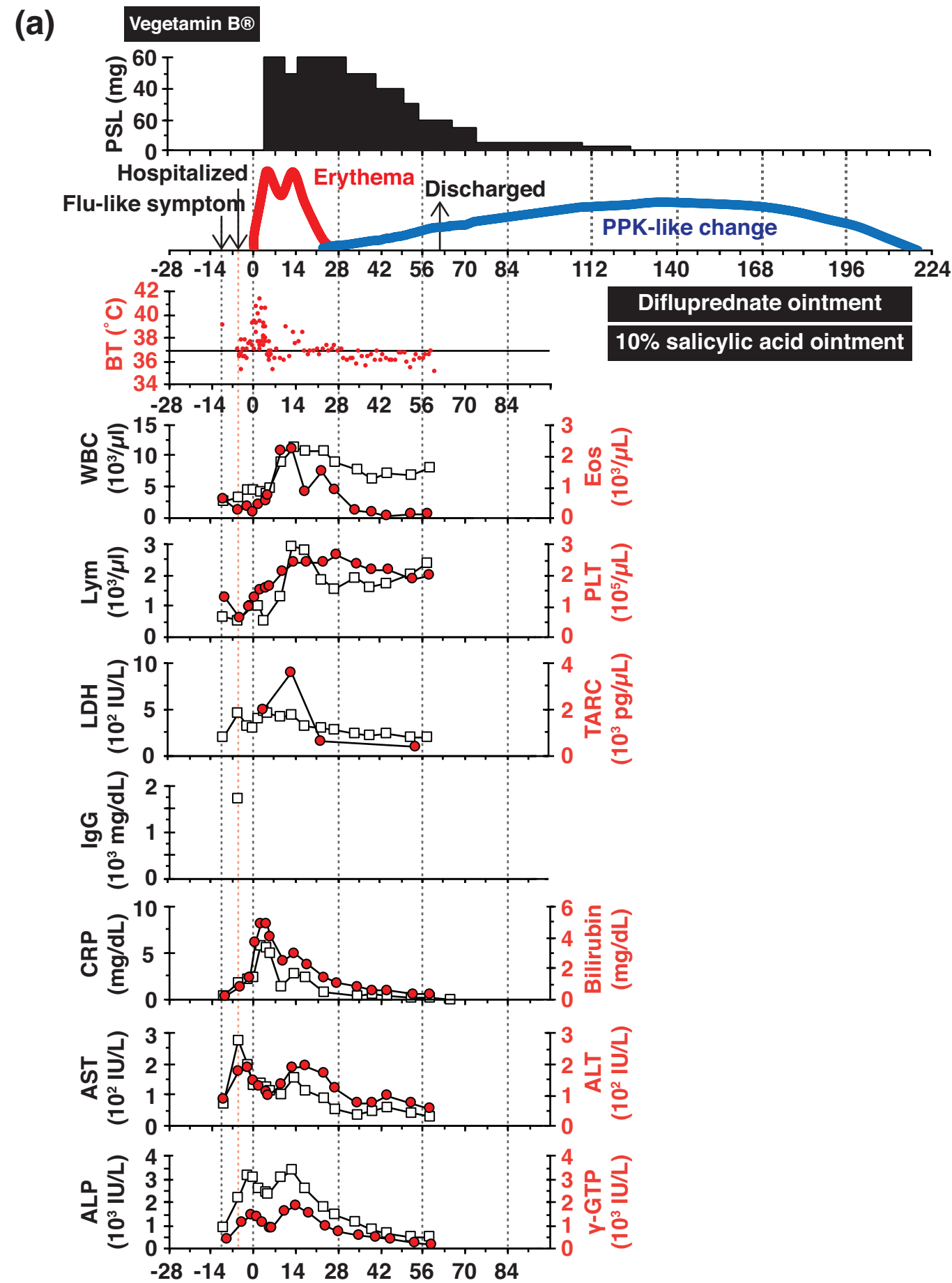


Figure 1b-i. Nomura et al.

