Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic syndrome followed by transient palmoplantar keratoderma-like eruption

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Letter to the Editor

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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 complecations.[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/μL 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.

68 FIGURE LEGEND

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

90

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 × 10^9/L)	**Yes (day 13)**
- b. Atypical lymphocytes (> 5%)	**No**
- c. Eosinophils (> 1.5 × 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.

94

95 Table S2. Scoring on a DRESS system

Score	-1	0	1	2	Min	Max	**Our case**
Fever ≥ 38.5˚C	No/U	**Yes**			-1	0	**0**
Enlarged lymph nodes		**No**/U	Yes		0	1	**0**
Eosinophilia		No/U			0	2	**2**
- Eosinophils			≥ 0.7 × 10^9/L	**≥ 1.5 × 10^9/L**			
- Eosinophils, if leucocytes < 4.0 × 10^9/L			≥ 10%	≥ 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.

100

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