Multiple Follicular Pustules as an Atypical Cutaneous Manifestation of Drug-induced Hypersensitivity Syndrome

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Drug-induced hypersensitivity syndrome (DIHS), also known as drug rash with eosinophilia and systemic symptoms (DRESS), is a severe drug reaction presenting with generalized skin eruption, organ failure and haematological abnormality (1, 2). Typical cutaneous manifestations include maculopapular, lichenoid, purpuriform, target-like and possibly also other types of lesions. Erythroderma with or without exfoliation or desquamation may sometimes be observed. We report here a case of DIHS/DRESS presenting with multiple diffuse follicular pustules on the trunk and extremities.

CASE REPORT

A 15-year-old Japanese male student was admitted to our hospital with generalized pruritic rash and high fever after treatment with carbamazepine for epilepsy over 5 weeks. The patient exhibited marked oedema on the face (Fig. 1A), cervical lymphadenopathy, and small follicular pustules diffusely distributed on his trunk and extremities (Fig. 1B). Bacterial cultures of both blood and pustules were negative. A skin biopsy from the back revealed a spongiotic pustule in the follicular infundibulum with moderate upper-dermal perivascular infiltrations of lymphocytes, neutrophils and a few eosinophils (Fig. 1C). A blood test indicated leukocytosis (white blood cell count, 12,000/ml) containing up to 5% atypical lymphocytes, marked eosinophilia (2,280/ml), elevated levels of liver enzymes (aspartate aminotransferase (AST) 367 IU/l and alanine aminotranferase (ALT) 1,637 IU/l), and positivity for human herpes virus (HHV)-6 DNA. Treatment with 30 mg oral prednisone resulted in improvement in the patient's general condition and skin eruptions.

DISCUSSION

This case fulfils the criteria for both DIHS (7/7 of the Japanese consensus group criteria) and DRESS (8/9 of the Kardaun et al. criteria (7)) (Table I). The mechanism of DIHS/DRESS has not been fully elucidated. Immune responses by drug-reactive T cells, plasmacytoid dendritic cells, and activation of herpes viruses have been proposed (2, 3).

Before the concept of DIHS/DRESS was established, anticonvulsant hypersensitivity syndrome was recognized as a severe adverse drug reaction induced by anticonvulsants such as carbamazepine, phenytoin,

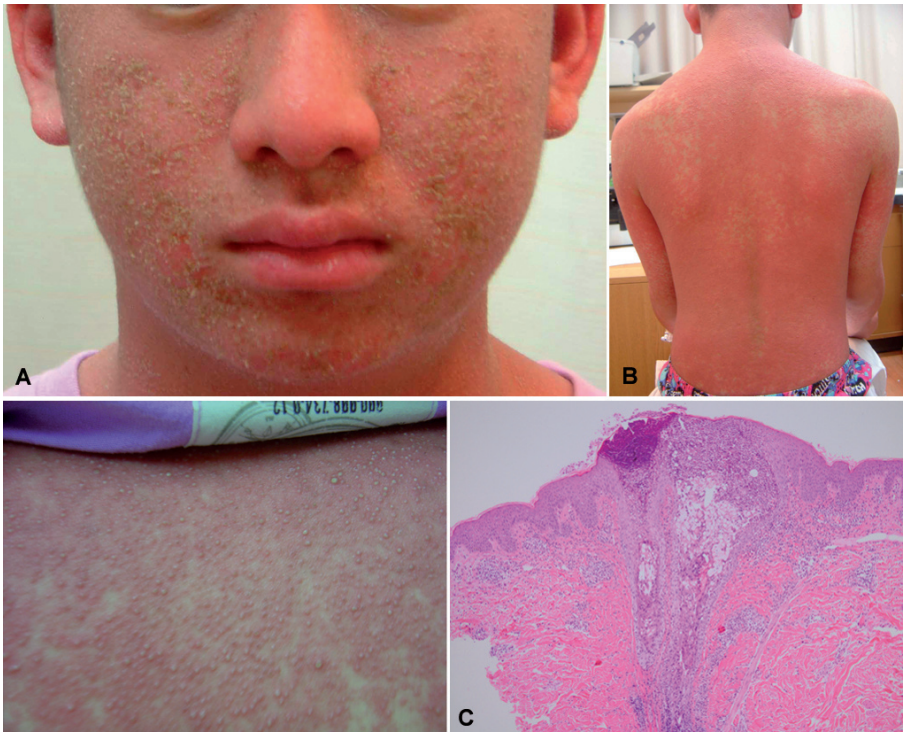

Fig. 1. Clinical and histological findings in a patient with drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms. (A and B) Clinical manifestations. The patient had marked oedema of the face and small, diffusely distributed, follicular pustules. (C) Histological examination revealed a spongiotic pustule in the follicular infundibulum with moderate upper-dermal perivascular infiltrations.

Table I. *Criteria for drug-induced hypersensitivity syndrome (DIHS; top) and drug rash with eosinophilia and systemic symptoms (DRESS; bottom). The patient met the criteria for DIHS (7/7) and DRESS (8/9)*

Criteria for typical DIHS (presence of all 7 criteria) (ref. 6)

1. HHV-6 reactivation
2. Prolonged clinical symptoms 2 weeks after discontinuation of causative drug
3. Maculopapular rash developing > 3 weeks after starting with limited number of drugs
4. Fever > 38ºC
5. Lymphadenopathy
6. Liver abnormalities (alanine aminotransferase > 100 U/l) or other organ involvement, e.g. renal involvement
7. Leukocyte abnormalities (at least one present)
   - Leukocytosis ($> 11 \times 10^9$/l)
   - Atypical lymphocytosis (> 5%)
   - Eosinophilia ($> 1.5 \times 10^9$/l)

	Score –1	Score 0	Score 1	Score 2
*Scoring system for classifying DRESS cases as definite, probable, possible, or no case[a] (applicable items in **bold**) (ref. 7)*				
Fever ≥ 38.5ºC	No/U	**Yes**		
Enlarged lymph node		No/U	**Yes**	
Eosinophilia		No/U		
Eosinophils			$0.7–1.499 \times 10^9 l^{-1}$	**$\geq 1.5 \times 10^9 l^{-1}$**
Eosinophils, if leucocytes $< 4.0 \times 10^9 l^{-1}$			10–19.9%	≥ 20%
Atypical lymphocytes		No/U	**Yes**	
Skin involvement				
Skin rash extent (% body surface area)		No/U	**≥ 50%**	
Skin rash suggesting DRESS	No	U	**Yes**	
Biopsy suggesting DRESS	No	Yes/U		
Organ involvement				
Liver, kidney, lung, muscle/heart, pancreas, other organ			**One organ**	Two or more organ
Resolution ≥ 15 days	No/U	**Yes**		
Evaluation of other potential causes				
Antinuclear antibody				
Blood culture				
Serology for HAV/HBV/HCV				
Chlamydia/mycoplasma				
If none positive and ≥ 3 of above negative			**Yes**	

[a]Total score < 2: no case; 2–3; possible case; 4–5: probable case; > 5: definite case.
U: unknown/unclassifiable; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HHV-6: human herpes virus 6.

and phenobarbital sodium (4). Several cases of acute generalized exanthematous pustulosis (AGEP) induced by anticonvulsants have been reported (5), but isolated pustules in the follicular infundibulum, as seen in our case, are a clear contrast to AGEP, which usually manifests histopathologically as confluent, flaccid pustules with non-follicular, subcorneal or upper-epidermal pustules.

We diagnosed the patient as typical DIHS, since we observed the reactivation of HHV-6 in addition to the clinical manifestations seen in DRESS. The case was diagnosed as DIHS/DRESS with reactivation of HHV-6. We describe here an atypical case of DIHS presenting with diffuse follicular pustules on the trunk and extremities, which was reasonably well controlled by conventional therapy with an oral steroid.

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