Acute generalized exanthematous pustulosis (AGEP) and toxic epidermal necrolysis (TEN) are adverse severe cutaneous reactions usually induced by drugs. The more severe AGEP becomes, the more it clinically resembles TEN (1–3). A few overlapping cases of AGEP and TEN have been reported (4–6). However, these reports are questionable because sufficient histological evidence worthy of TEN has not been shown.

CASE REPORT
A 37-year-old man presented with vesicles and pustules on the hands and feet, redness of the face, congestion and erosion of bulbar conjunctiva and oral mucosa, general fatigue, and a fever of 39.0°C. He had taken lamotrigine for approximately 2 weeks for epilepsy and estazolam for 4 days for insomnia. After a few days, non-follicular vesicles and pustules spread to his face, trunk, and extremities in spite of discontinuing both medicines (Fig. 1a). Non-follicular vesicles and pustules expanded into confluent bullae on the erythematous base (Fig. 1b). Flat atypical targets could be partially seen. Nikolsky’s sign was positive. Body surface area (BSA) of the detached and detachable epidermis was 30–40% at the worst stage of the disease. Bacterial samples from pustules, repeated 3 times, were all negative. Total white blood cell count was 13,100/mm$^3$ (normal 3,400–9,600), accompanied by a high neutrophil count of 8,750/mm$^3$. Only alanine aminotransferase (ALT) was slightly elevated (44 U/l (normal 8–37)) among liver enzymes and C-reactive protein was 8.23 mg/dl (normal 0–0.32).

Histological examination of the pustules demonstrated subcorneal pustules, which consisted of high levels of neutrophils and eosinophils (Fig. 2a). There were spongiform pustules at the edge of the subcorneal pustules (Fig. 2b). At the periphery of the spongiform pustules, there were superficial perivascular and interface dermatitis. Many apoptotic keratinocytes were seen in the lower epidermis, becoming confluent necrosis (Fig. 2c). Dermal infiltrate below the necrotic epidermis mainly comprised lymphocytes and histiocytes. Histological examination of confluent bulla demonstrated full-thickness epidermal necrosis and subepidermal blistering (Fig. 3a). Furthermore, high levels of neutrophils and eosinophils infiltrated the blister cavity and papillary dermis (Fig. 3b).

Oral prednisolone was administered at 50 mg/day, and tape-red gradually. The patient’s skin detachment resolved quickly. Duration from onset to resolution was approximately 10 days. A formal calculation of AGEP score was 4, which was consistent with a possible diagnosis (7).

DISCUSSION
AGEP is an adverse and potentially severe cutaneous reaction that usually occurs in response to drugs, but has also been reported to develop after viral infections, ultraviolet (UV) radiation, and heavy metal exposure (5, 7). It is usually characterized by sterile pinhead-sized non-follicular pustules, erythema, oedema, fever, and leukocytosis with neutrophilia (8). In addition to subcorneal or intraepidermal pustules, AGEP may show spongiform pustules of Kogoj and perivascular inflammatory infiltrate accompanied by neutrophils and eosinophils. Furthermore, scattered necrotic keratinocytes and papillary dermal oedema may be seen. The onset of drug-induced AGEP is rapid, often occurring hours to days after drug exposure (8, 9). AGEP usually resolves once the causative drug is no longer used. However, AGEP is sometimes persistent and mimics TEN (1–3).

TEN is a severe cutaneous reaction characterized by large, flaccid bullae and epidermal detachment in sheets, involving more than 10% of the BSA. Histological characteristics are full-thickness epidermal necrosis and subepidermal blistering. There is slight lymphocytic infiltrate with sparse eosinophils. Leukopaenia sometimes occurs and is different from AGEP. The latent period between intake of the drug and the onset of TEN symptoms is usually 2–3 weeks, which is longer than that of AGEP (7). While the use of corticosteroids in

![Fig. 1.](a) Many non-follicular pustules on the face, and (b) confluent bullae on the back (clinical view of a 37-year-old man). Permission to publish this photo is given from the patient.
TEN is controversial, current data are not sufficient to suggest that steroids are necessary in the treatment of AGEP (7). Thus, it is very important for dermatologists to distinguish between AGEP and TEN.

There are 3 reports that report overlapping AGEP and TEN (4–6). However, these reports are all questionable because neither full-thickness epidermal necrosis nor subepidermal blistering characteristic of TEN was shown. Meiss et al. (4) described 3 cases with subcorneal pustules and scattered necrotic basal keratinocytes, both of which were not characteristic of TEN. Goh et al. (5) described subcorneal pustules and full-thickness epidermal necrosis. However, the illustrations provided did not show full-thickness epidermal necrosis, only spongiform epidermis at the edge of subcorneal pustules. Lateef et al. (6) described a case with neutrophilic spongiosis, which is a characteristic of AGEP. Although all of these cases were reported to be clinically accompanied by TEN, they could all also be interpreted as severe AGEP clinically mimicking TEN.

In the present case, histological findings from the pustules demonstrated subcorneal and spongiform pustules, consistent with AGEP. Many apoptotic keratinocytes in the lower epidermis of the periphery of spongiform pustules are suggestive of Stevens-Johnson syndrome/TEN, not AGEP. Furthermore, histological findings of confluent bulla demonstrated full-thickness epidermal necrosis and subepidermal blistering characteristic of TEN. In addition, there were high levels of neutrophils and eosinophils in the blister cavity and papillary dermis, indicative of AGEP. Both specimens showed intermingled histological characteristics of AGEP and TEN. Although a formal calculation score is consistent with a possible diagnosis of AGEP, lamotrigine is a well-demonstrated inducer of Stevens-Johnson syndrome, with a time latency that matches that observed in the present case. Furthermore, TEN is sometimes accompanied by superficial pustules, to which the prognosis is not linked. In conclusion, the present case was diagnosed as TEN with some features of AGEP.

REFERENCES


Fig. 2. Histological examination of pustules demonstrated (a) subcorneal pustules and (b) spongiform pustules at the edge of subcorneal pustules. (c) Many apoptotic keratinocytes in the lower epidermis of the periphery of spongiform pustules. (Haematoxylin & eosin staining, original magnification (a) × 40, (b) × 200, (c) × 200).

Fig. 3. Histological examination of confluent bullae demonstrated: (a) full-thickness epidermal necrosis and subepidermal blistering; (b) high levels of neutrophils and eosinophils in the blister cavity and papillary dermis. (Haematoxylin & eosin staining, original magnification (a) × 40, (b) × 400).


