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Homozygous missense mutation in IL36RN in generalized pustular dermatosis compatible with both AGEP and generalized pustular psoriasis

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Abstract

Acute generalized pustular eruptions (AGEP) and generalized pustular psoriasis (GPP) show many overlapping clinical features. Here we report a 40 years old man who initially presented with generalized pustules and systemic inflammatory response syndrome 5 days after intake of amoxicillin, suggesting a diagnosis of AGEP due to amoxicillin. Nine months later, a throat infection was followed by a generalized pustular skin reaction with systemic symptoms without prior drug intake. Clinical presentation and histology was compatible with the diagnosis of GPP, and the patient recalled a similar episode 20 years before. Retrospectively, our initial diagnosis of AGEP was therefore called into question, as drug-triggered GPP was now the likely diagnosis. However, based on current classification systems, it remains unclear whether such cases should be diagnosed as AGEP or drug-elicited GPP.

Genetic analysis of this patient identified a homozygous mutation in exon 5 (c.C338T:p.S113L) of the *IL36RN* gene. The *IL36RN* gene encodes the anti-inflammatory IL-36-receptor antagonist, IL-36Ra, which blocks the pro-inflammatory cytokine IL-36. *IL36RN* mutations can lead to uncontrolled IL-36 signaling and enhanced production of IL-6, IL-8, and IL-1 which give rise to pustular eruptions. Recent findings show that *IL36RN* variants are common in GPP without plaque psoriasis and that they can be found in a subset of AGEP.

In this case, the *IL36RN* mutation therefore underlies the generalized pustular eruptions and provides the pathogenetic link between the clinically overlapping presentation of AGEP and GPP. It is likely that in our patient stimulation of the immune system, be it by drug hypersensitivity to amoxicillin or throat infection, led to uncontrolled neutrophilic skin inflammation because of deficiency in IL-36RA. Moreover, our case supports the emerging concept that the disease taxonomy of pustular skin eruptions could in future be based on genetic profiling.