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OBSERVATION

Homozygous Missense Mutation in IL36RN in Generalized Pustular Dermatosis With Intraoral Involvement Compatible With Both AGEP and Generalized Pustular Psoriasis

Acute generalized exanthematous pustulosis (AGEP) and generalized pustular psoriasis (GPP) show multiple overlapping clinical features. Recently, mutations in the IL36RN gene encoding the interleukin (IL)-36 receptor antagonist (IL-36Ra) have been found to cause increased secretion of inflammatory cytokines in GPP and in a subset of AGEP.\(^1\)=\(^2\) In both conditions, half of the patients with IL36RN variants had oral involvement.\(^1\)=\(^2\)

Report of a Case | Herein we report a man in his 40s who initially presented with fever, systemic inflammatory response syndrome, and generalized, sterile, nonfollicular pustules (Figure 1) accentuated in the major flexures and on the palatal mucosa 5 days after intake of amoxicillin, which he took as postoperative prophylaxis after surgery of the thumb. His family history was negative for psoriasis. Medical history and clinicopathologic findings (Figure 2) were consistent with AGEP due to amoxicillin. After obtaining a EuroSCAR AGEP valida-

Figure 1. Clinical Photograph of the Head After the First-Described Acute Generalized Pustular Eruption

Compatible with acute generalized exanthematous pustulosis, nonfollicular pustules on confluent erythematous and edematous plaques are seen on the head.

Figure 2. Right Thoracic Histologic Specimen Taken After the First-Described Generalized Pustular Eruption

Numerous subcorneal pustules, necrotic keratinocytes, edema of the papillary dermis, and perivascular lymphocytic infiltrate consisting mainly of neutrophils and eosinophils (hematoxylin-eosin, original magnification \( \times 100 \)).
lyzing group A streptococci, notably without prior drug intake. Again, intraoral pustules were observed. During this episode, clinical and histologic findings were consistent with GPP. The patient recalled a similar episode 20 years before with a generalized pustular eruption with systemic symptoms without prior drug intake. The patient was given oral clarithromycin (500 mg twice daily) for his throat infection and 2 infusions with infliximab (5 mg/kg of body weight), which resulted in rapid clearance of the lesions.

**Discussion** | Our patient presented with 2 episodes of acute generalized pustular eruptions. While the first episode was consistent with AGEP, the second occurred without a triggering drug and was consistent with GPP. However, current classification systems leave it unclear whether such cases should be diagnosed as AGEP or drug-elicited GPP.4

Since recent findings have shown that pustular forms of psoriasis are related to genetic defects involving IL-36Ra,5 we carried out genetic analysis and identified a homozygous mutation in exon 5 (c.C338T:p.S113L) of the IL36RN gene.2 This gene encodes the anti-inflammatory IL-36Ra, which blocks the proinflammatory cytokine IL-36. Mutations in IL36RN may lead to uncontrolled IL-36 signaling and enhanced production of proinflammatory cytokines IL-6, IL-8, and IL-1, giving rise to pustular eruptions.3

In our patient, the IL36RN mutation may predispose for and drive the generalized pustular reactions and constitutes the pathogenetic link between the overlapping presentation of AGEP and GPP. Stimulation of the immune system by either a drug hypersensitivity to amoxicillin or throat infection may thus result in uncontrolled neutrophilic skin inflammation due to a deficiency in IL-36Ra. Hence, our case supports the emerging concept that the disease taxonomy of pustular skin eruptions could in future be based on genetic profiling.

Intraoral involvement was observed in half of the patients with IL-36RN-dependent DITRA (deficiency of IL-36 receptor antagonist) and in 2 of 4 patients with IL-36RN-dependent AGEP.2 The observation that in our patient intraoral pustules were present during the 2 episodes of AGEP and GPP suggests that intraoral involvement during generalized pustular eruptions is a clinical clue for underlying mutations in IL36RN. Thus, intraoral involvement in cases of either AGEP or GPP should prompt clinicians to perform further testing including genetic analysis, drug-hypersensitivity tests, and detailed medical history. Further studies and review of patients’ data are needed to confirm this potential association.

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**Fanconi Syndrome Induced by Vemurafenib: A New Renal Adverse Event**

Vemurafenib is a BRAF inhibitor approved by the US Food and Drug Administration as treatment for patients with unresectable metastatic melanoma harboring the BRAF V600 mutation.1 Recently, vemurafenib-associated renal toxic effects have been reported.2-4 We describe herein a patient exhibiting Fanconi syndrome as a new renal adverse event while undergoing treatment with vemurafenib.

**Report of a Case** | A man in his 70s began treatment with vemurafenib, 960 mg twice daily, as first-line treatment for a stage IV melanoma (BRAF mutation V600K) with hepatic and lymph node metastasis. On day 9 of treatment, he developed fever (body temperature, 38.6°C [101.5°F]), an erythematous maculopapular eruption with keratosis pilaris on all 4 limbs and trunk involving 30% of the body surface area, and photosensitivity on the face. The dose of vemurafenib was decreased to 720 mg twice daily. Laboratory workup showed a white blood cell count of 12 × 10⁹/L with 12% eosinophils and 2% atypical lymphocytes. The liver enzyme levels remained normal. (To convert white blood cells to number of cells per microliter, divide by 0.001.)

On day 12, blood chemical analysis revealed hypokalemia with excessive kaliuresis persisting despite potassium supplementation. The electrolyte profile showed urinary excretion associating hyperphosphaturia and hyperuricuria. The blood electrolyte profile showed hypophosphatemia and hypouricemia. These findings were consistent with the diagnosis of Fanconi syndrome. The proteinuria measurement was 0 to 27 g/d. The glomerular filtration rate (GFR) remained stable at 101 mL/min/1.7 m², and so a kidney biopsy was not per-