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.

Since recent findings have shown that pustular forms of psoriasis are related to genetic defects involving IL-36Ra, we carried out genetic analysis and identified a homozygous mutation in exon 5 (c.C338T:p.S113L) of the IL36RN gene. 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 cytokine IL-36. Thus, intraoral involvement in cases of AGEP and drug-elicited GPP 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 DIETRA (deficiency of IL-36 receptor antagonist) and in 2 of 4 patients with IL-36RN-dependent AGEP. 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 or metastatic melanoma harboring the BRAF V600 mutation. Recently, vemurafenib-associated renal toxic effects have been reported. 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/1.73 m², and so a kidney biopsy was not per-
formed. The exanthema and the eosinophilia decreased gradually until normalization was achieved on day 16.

On day 19, vemurafenib therapy was discontinued, and within 7 days thereafter, the fever had improved, and the electrolyte profile had normalized. Tumor assessment showed a major tumor response.

On day 29, vemurafenib treatment was restarted at half dose, leading within 21 days (day 50) to a relapse of hypokalemia and hypouricemia with acute urinary loss but without relapse of fever, exanthema, or eosinophilia. Vemurafenib treatment was then definitively stopped, followed by normalization of electrolytic findings within 5 days. At that time, treatment with dabrafenib, another BRAF inhibitor, was started. At last follow-up 5 months later, no adverse event had occurred.

Discussion
To our knowledge, this is the first case of Fanconi syndrome associated with vemurafenib. Fanconi syndrome is characterized by a generalized transport defect in the proximal tubules leading to renal losses of potassium, phosphate, uric acid, glucose, amino acids, bicarbonates, and/or low-molecular-weight proteins. Not all of these losses occurred in our case, as they do not in most cases, but we did observe abnormal losses of potassium, phosphate, and uric acid.

Three recent studies2-4 have reported vemurafenib-induced nephrotoxic effects in 27 cases, most of these showing a moderate decrease in GFR (30%-35%) within the first month of treatment. Mild proteinuria occurred in 10 of 24 cases,2-4 and various cutaneous toxic effects in 7 of 12 cases.3,4

A kidney biopsy was performed in only 1 case of severe renal dysfunction, revealing acute tubular necrosis. Mechanisms remain unclear; specific tubular toxic effects2 and acute immunologic interstitial nephritis3 are possible explanations.

In our case, there was no decrease in GFR, but Fanconi syndrome occurred, which suggests that vemurafenib exerts tubular toxic effects. The chronologic sequence from initiation of vemurafenib treatment to the onset of Fanconi syndrome (Figure) and the absence of other evidence of tubular defects strongly suggest a drug-induced mechanism, as has been reported with other toxic effects.5

Our patient also presented some features of DRESS (drug reaction with eosinophilia and systemic symptoms): fever, eosinophilia, and atypical lymphocytes. However, evaluating according to the Kardaun criteria established by the European Regiscar group,6 we found a score of 2. To our knowledge, Fanconi syndrome has never been associated with these clinical features. Moreover, only the biological anomalies relapsed when vemurafenib was reintroduced. This may suggest that the 2 manifestations are not related and should be considered different sets of adverse effects.

We recommend regular monitoring of blood electrolyte profiles in vemurafenib-treated patients. If Fanconi syndrome occurs, discontinuation of vemurafenib treatment and initiation of treatment with a different BRAF inhibitor should be considered.

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Moon Jellyfish Stings

Envenomation by jellyfish is a common occurrence affecting millions of individuals yearly. Little literature exists on jellyfish stings caused by the “moon jellyfish,” Aurelia aurita. The main objective of the present report is to illustrate that A aurita stings are not as benign as once thought and to propose a treatment sequence for jellyfish stings to address the local cutaneous reactions that these stings can cause.