Table II. Quality of life measures by skin cancer group

Scale	1-4 skin cancers (n = 26)	≥5+ skin cancers (n = 43)	*P* value
SF-20			
Physical	81.1	62.0	.04
Role	92.3	72.7	.02
Social	89.2	80.0	.11
Mental health	76.0	79.1	.54
Current health	69.6	63.7	.38
Pain	76.2	67.4	.17
Skindex-16			
Symptoms	16.5	30.0	.03
Emotional	23.9	42.1	.01
Functional	7.9	21.3	.02
Lawton IADL scale	6.9	6.6	.16

Results are presented as means.
IADL, Instrumental Activities of Daily Living; *SF-20*, 20-Item Short Form Health Survey.

strategies improve outcomes. First, however, we must have criteria to define NMSC as a chronic disease, and our data suggest that 5 or more skin cancers can be used to operationalize this distinction.

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Adam Sutton, MD, MBA, Ashley Crew, MD, Shauna Higgins, MD, Andrew Kwong, BS, and Ashley Wysong, MD, MS

From the Department of Dermatology, Keck School of Medicine of University of Southern California, Los Angeles, California

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Correspondence to: Adam Sutton, MD, MBA, Department of Dermatology, University of Nebraska Medical Center 985520 Nebraska Medical Center, Omaha, NE 68198-5645

E-mail: adam.sutton@unmc.edu

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Sirolimus for treatment of verrucous venous malformation: A retrospective cohort study

To the Editor: Verrucous venous malformation (VVM) is a rare, congenital vascular malformation.[1] The treatment for VVM is particularly difficult.[2] Couto et al[3] found a somatic MAP3K3 mutation in patients with VVM. MAP3K3 is an upstream molecule of the mammalian target of rapamycin signaling pathway, and sirolimus is an inhibitor of the mammalian target of rapamycin.

We retrospectively analyzed a cohort of 10 patients with VVM who were treated with sirolimus. Patients who presented with VVM were consecutively enrolled in a study at the Dermatology and Venereology Department of the Capital Institute of Pediatrics in Beijing, China, between 2015 and 2017. Individuals with comorbidities including malignancy, pneumonia combined with serious sepsis, or encephalitis were to be excluded; however, no patients had these comorbidities. Informed consent forms were obtained from all subjects or their family members. According to the International Society for the Study of Vascular Anomalies classification of vascular anomalies and the 10th edition

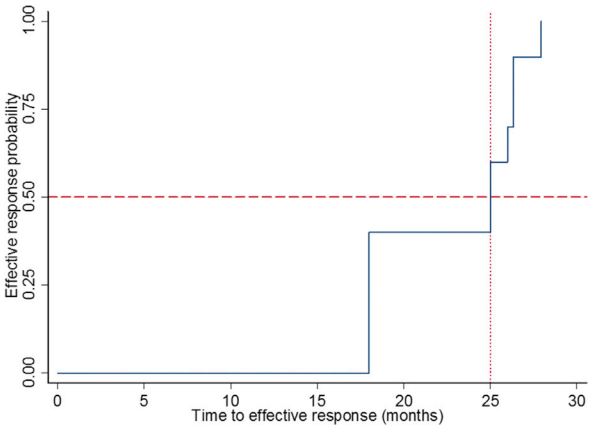

Fig 1. Effective treatment response rate curve for sirolimus in the treatment of verrucous venous malformation.

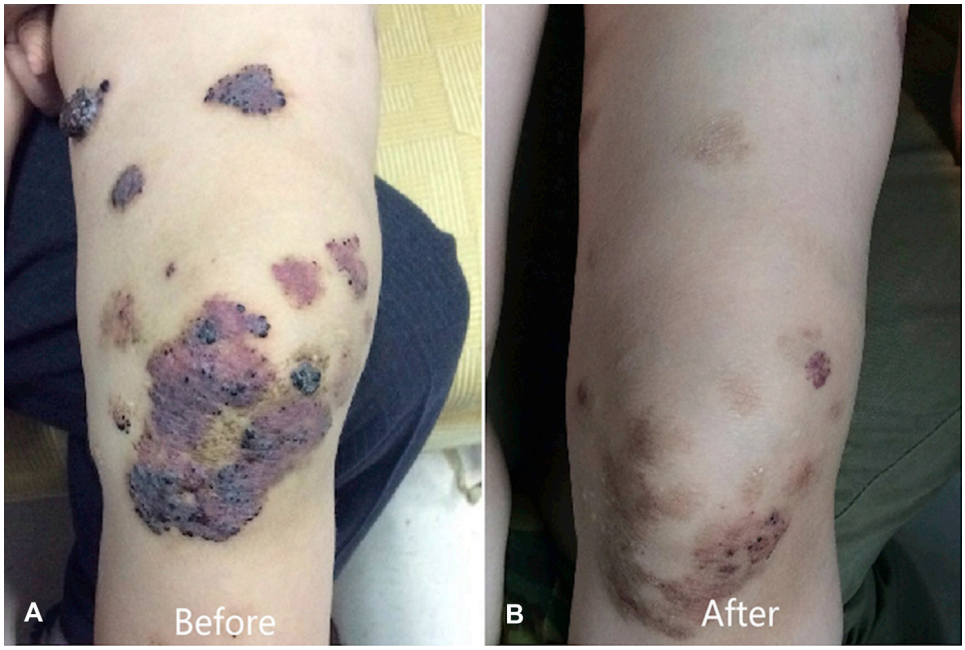

Fig 2. Clinical photographs (**A**) before and (**B**) after treatment with sirolimus.

of the International Statistical Classification of Disease and Related Health Problems, a diagnosis of VVM was made. The initial sirolimus dose was 0.8 mg/m^2 and was administered twice daily.[4] The random serum levels of sirolimus ranged from 6 to 15 ng/mL. To achieve the desired serum level, the weight and serum levels were tested and further consulted with a doctor once a month. All patients were maintained for the treatment course with sirolimus as the single agent. Volume reduction ratio (VRR) was used as indicator to measure an overall treatment response at the moment the data collection was completed. Effective response time (assessed as a VRR ≥90%) of sirolimus was estimated using Kaplan−Meier survival curves. The size was comprehensively measured by clinical and radiographic imaging including magnetic resonance imaging and B-ultrasound.

There were 5 male (50%) and 5 female (50%) patients in this study. The mean age was 17 months (interquartile range [IQR] 14-22 months) after birth for all subjects, 15 months (IQR 14-19 months) after birth for females, and 21 months (IQR 14-37 months) after birth for males. The lesions of 7 patients (70%) were located in the legs, foot and ankle joints, and knee joints, and 3 (30%) in the arms, fingers, and back of the hands. Six patients (60%) previously received prednisone, propranolol, pingyangmycin, laser therapy, or cryotherapy for VVM in their local hospitals, and these patients frequently had relapses. The median effective response time was 25 months (IQR 18-26 months; Fig 1). During the study, all patients had obvious improvement with volume reduction of ≥90% (Fig 2). Gender, age, lesion location, and history of previous treatments were not found to be associated with treatment response rate. No serious adverse drug reactions were found during treatment save for 1 case with mild oral ulcer. In this study, the estimated median effective response time was 25 months when VRR ≥90% was defined as the event of interest. If a response <90% was defined as the event of interest, the median effective response time was shortened.

In conclusion, we found that sirolimus is a reliable targeted treatment regimen for VVM and is effective and well-tolerated.

Gaolei Zhang, MD, PhD,[a] Hongguang Chen, MD, PhD,[b] Zhen Zhen, MD,[c] Jianyou Chen, MD,[a] Sheng Zhang, MMSc,[a] Qin Qin, BMS,[a] and Xiaoyan Liu, MD, PhD[a]

Department of Dermatology and Venereology,[a] Capital Institute of Pediatrics; Peking University Sixth Hospital,[b] Peking University Institute of Mental Health, Key Laboratory of Mental Health, Ministry of Health (Peking University), National Clinical Research Center for Mental Disorders (Peking University Sixth Hospital); and the Department of Otolaryngology,[c] Peking University First Hospital, Beijing, China

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Correspondence to: Gaolei Zhang, MD, PhD, Department of Dermatology and Venereology, Capital Institute of Pediatrics, No 2 YaBao St, ChaoYang District, Beijing 100020, China

E-mail: pkuzhgl@163.com

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Drug reaction with eosinophilia and systemic symptoms syndrome induced by combination of vemurafenib and cobimetinib in melanoma: A series of 11 cases

To the Editor: The combination of B-Raf and mitogen-activated protein kinase kinase (MEK) inhibitors has become the standard of care in metastatic melanomas harboring the $BRAF^{V600E}$ mutation. Four cases of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been previously reported in patients treated with vemurafenib alone[1]; 2 of these cases were treated safely with the dabrafenib.[2]

We report 11 cases of DRESS syndrome induced by vemurafenib and cobimetinib identified in Nantes University Hospital Dermatology Department during July 2015-July 2017. Clinical, biologic, and histologic features of these 11 cases are summarized in Table I. The RegiSCAR score[3] was used to diagnose DRESS syndrome (Table II): 6 cases were definite and 5 were probable DRESS syndrome.

Unusual characteristics were observed in the current series. Mainly, an early onset was found in all our 11 cases: 7-11 days after treatment initiation. A delayed onset of symptoms, ie, 2-6 weeks after the first drug intake is usually described in publications on DRESS syndrome. All patients experienced cheilitis, and 6 of them had buccal erosions or pharynx erythema. For all the cases, symptoms lasted >2 weeks, and the mean time to full recovery with no sequelae was 1 month. None of the patients had a fatal evolution. We observed an unusual Sweet syndrome–like histopathologic pattern in 7 out of the 11 patients that included no epidermal alteration but papillary dermal edema and nuclear dust without vascular necrosis and a superficial perivascular lymphocytic dermatitis.

Skin patch tests with vemurafenib and cobimetinib were performed in 3 patients and results were all negative. Interestingly, initiating a combination of other B-Raf and MEK inhibitors, dabrafenib and trametinib, in 7 cases was associated with no recurrence of symptoms. The 4 other patients did not wish to start another B-Raf + MEK inhibitor treatment.

Regarding the pathogenesis, an Epstein-Barr virus (EBV) reactivation was observed in 7 out of the 11 cases, with positive EBV PCR results. In 1 case, it was associated with a positive parvovirus B19 PCR result. All patients who were previously treated with immunotherapy showed EBV reactivation (5 patients). A recent publication has shown an association between a previous treatment with anti-PD1 and the severity of vemurafenib-induced skin disorders, including hypersensitivity syndrome.[4] Finally, 5 patients carried the human leukocyte antigen B44 allele. A recent publication has shown an association between certain human leukocyte antigen alleles and severe cutaneous reactions, but B44 has not been described in association with DRESS syndrome.[4]

We did not identify predictive factors of this drug-induced toxicity. Because the rash always appeared with the combined use of vemurafenib and cobimetinib, determining whether the reaction is more related to the use of 1 of these 2 drugs or the combination is not possible. In our department, in the previous 2 years, vemurafenib cobimetinib combination treatment was initiated in 68 patients and 11 cases of DRESS syndrome occurred, corresponding to 16% of patients treated.

This series demonstrates that DRESS syndrome induced by the vemurafenib and cobimetinib combination treatment is frequent. The early onset of symptoms must not misguide the diagnosis, and treatment should be rapidly discontinued. Dabrafenib and trametinib were safely initiated without recurrence of symptoms.