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Additional Contributions: Eunice Lee, BS, provided technical assistance.

1. Bork K, Böckers M, Pfeifle J. Pathogenesis of paraneoplastic follicular hyperkeratotic spicules in multiple myeloma: follicular and epidermal accumulation of IgG dysprotein and cryoglobulin. *Arch Dermatol*. 1990;126(4):509-513.

2. Matthews MR, Wang RC, Reddick RL, Saldivar VA, Browning JC. Viral-associated trichodysplasia spinulosa: a case with electron microscopic and molecular detection of the trichodysplasia spinulosa-associated human polyomavirus. *J Cutan Pathol*. 2011;38(5):420-431.

3. Kazem S, van der Meijden E, Kooijman S, et al. Trichodysplasia spinulosa is characterized by active polyomavirus infection. *J Clin Virol*. 2012;53(3):225-230.

4. van Boheemen S, Jones T, Muhlemann B, Feltkamp MC, Fouchier RA, Hajdarbegovic E. Cidofovir gel as treatment of follicular spicules in multiple myeloma [published online September 3, 2014]. *JAMA Dermatol*. 2014;Sep 3.

5. Weibel L, Berger M, Regenass S, Kamarashev J, Hafner J, French LE. Follicular spicules of the nose and ears: quiz case. *Arch Dermatol*. 2009;145(4):479-484.

In Reply We are grateful to our colleagues for their contribution in consolidating the available knowledge on follicular spicules in multiple myeloma (FSMM). Gathering evidence on rare disorders is hampered by nonuniform terminology and variations in methodology in addition to the limited number of cases. The great similarity between the clinical pictures of FSMM and trichodysplasia spinulosa (TS) has led to clinicians mistaking the 2 diagnoses.[1] Our article[2] describes the first exhaustive, robust, and modern method of virologic analysis, which enabled us to exclude the presence, and therefore direct involvement, of TS polyomavirus (TSPyV) in FSMM. It is surprising that this had not been attempted before, given the similarities between TS and FSMM.

We agree that current scientific insights favor an immunoglobulin-mediated cause of FSMM. It is statistically more probable that the detection of the Merkel cell polyomavirus (MCPyV) genome in the spicules of our patient represented asymptomatic carriage rather than MCPyV involvement in his dermatosis. However, there are some important considerations to be taken into account.

Though viral cause is unlikely, it cannot be ruled out. Low copy numbers may point to clonal genome integration into host cells and hijacking of the cellular machinery producing the outgrowths as seen in Merkel cell carcinoma.[3] This is supported by the recovery of an incomplete MCPyV genome in our case. We must also emphasize that the observed effect of cidofovir in our study was treatment site specific, although no agent with a viral polymerase was detected. The evidence implicating keratolytic agents in this condition is also anecdotal; their low cost is the best argument for their use in place of cidofovir. Of course, systemic treatment of multiple myeloma should always be pursued when indicated.

Most of the skin phenomena seen in multiple myeloma are associated with deposition of dysproteins. The presence of immunoglobulin fragments around follicles in FSMM has been well established and is probably universal.[4,5] Nevertheless, association does not preclude cause, which we agreed to apply to the presence of MCPyV. It is interesting to see that TSPyV, as well as immunoglobulins in multiple myeloma, can induce the follicles to produce spicules. As far as we know, no research has focused on a possible role of immunoglobulins in TS. We understand that the puzzle of FSMM is far from solved, and we have decided to share our findings with other researchers and clinicians to stimulate further research into the cause and ultimately the treatment of this enigmatic rare disorder.

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Conflict of Interest Disclosures: None reported.

1. Linke M, Géraud C, Sauer C, Marx A, Goerdt S, Peitsch WK. Follicular erythematous papules with keratotic spicules: a quiz: trichodysplasia spinulosa. *Acta Derm Venereol*. 2014;94(4):492-496.

2. van Boheemen S, Jones T, Muhlemann B, Feltkamp MC, Fouchier RA, Hajdarbegovic E. Cidofovir gel as treatment of follicular spicules in multiple myeloma [published online September 3, 2014]. *JAMA Dermatol*. 2014;Sep 3.

3. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science*. 2008;319(5866):1096-1100.

4. Satta R, Casu G, Dore F, Longinotti M, Cottoni F. Follicular spicules and multiple ulcers: cutaneous manifestations of multiple myeloma. *J Am Acad Dermatol*. 2003;49(4):736-740.

5. Bork K, Böckers M, Pfeifle J. Pathogenesis of paraneoplastic follicular hyperkeratotic spicules in multiple myeloma: follicular and epidermal accumulation of IgG dysprotein and cryoglobulin. *Arch Dermatol*. 1990;126(4):509-513.

Trichodysplasia Spinulosa in Gorlin Syndrome Treated With Vismodegib

To the Editor We read with interest the article by Richey and colleagues[1] that described a patient treated with vismodegib who developed multiple erythematous, pruritic perioral papules with white spicules. A diagnosis of trichodysplasia spinulosa (TS) was established exclusively by clinical and histopathologic findings. This diagnosis should be confirmed by electron microscopy or polymerase chain reaction analysis. As noted,[1] TS is associated with TS polyomavirus (TSPyV) infection and has only been reported in immunosuppressed patients.[2] In the present case,[1] the patient's medical history was negative for immunosuppression, and when vismodegib therapy was restarted, the papules recurred. Therefore, it is reasonable to consider this cutaneous reaction as an adverse effect of vismodegib therapy but not necessarily linked with TSPyV.

Benign and malignant proliferative processes as cutaneous adverse drug effects are increasingly being reported in patients treated with targeted therapies (eg, development of squamous cell carcinomas during vismodegib therapy),[3] and especially with BRAF inhibitors. Of note, patients taking in-

hibitors targeting the *BRAF*^{V600E} mutation exhibited a variety of cutaneous reactions including spiny follicular papules.[4,5] Given the similarity of findings in patients taking these small-molecule drugs (namely vemurafenib, sorafenib, and vismodegib), *spiny hyperkeratosis* could be the suggested term for this adverse effect and may represent a distinct entity. The term *trichodysplasia spinulosa* should be reserved for immunocompromised individuals with proven TSPyV infection. Studies seeking the pathophysiology of this nonmalignant cutaneous adverse effect are warranted.

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1. Richey JD, Graham TA, Katona T, Travers JB. Development of trichodysplasia spinulosa: case report of a patient with Gorlin syndrome treated with vismodegib. *JAMA Dermatol*. 2014;150(9):1016-1018.

2. Kazem S, van der Meijden E, Feltkamp MC. The trichodysplasia spinulosa-associated polyomavirus: virological background and clinical implications. *APMIS*. 2013;121(8):770-782.

3. Zhu GA, Sundram U, Chang AL. Two different scenarios of squamous cell carcinoma within advanced basal cell carcinomas: cases illustrating the importance of serial biopsy during vismodegib usage. *JAMA Dermatol*. 2014;150(9):970-973.

4. Franck N, Barete S, Moguelet P, et al. Spiny follicular hyperkeratosis eruption: a new cutaneous adverse effect of sorafenib. *J Clin Oncol*. 2010;28(31):e640-e642.

5. Boyd KP, Vincent B, Andea A, Conry RM, Hughey LC. Nonmalignant cutaneous findings associated with vemurafenib use in patients with metastatic melanoma. *J Am Acad Dermatol*. 2012;67(6):1375-1379.

In Reply We appreciate the letter in response to our case report. We acknowledge the limitations in making a diagnosis of trichodysplasia spinulosa (TS) using only clinical and histologic findings.

Electron microscopy (EM) was attempted in our case, but the diagnostic area was exhausted. We want to emphasize that owing to our patient's syndrome, he had undergone a multitude of procedures and imaging studies. Therefore, from a compassionate standpoint, and at the patient's request, additional biopsies of the spiny facial lesions were not performed. Although virus was not confirmed, we believe that the clinical (central face, folliculocentric) and histologic (trichohyalin debris in inner root sheath cells) features of this case are very similar to those of virus-proven cases of TS, both in publication and presented at a recent American Society of Dermatopathology meeting.[1,2] Other cases of targeted therapy-induced follicular hyperkeratosis do not demonstrate the same trichohyalin debris or inclusions.[3]

We agree that the diagnosis of TS should only refer to lesions associated with viral infection of TS polyomavirus. Our understanding from histologic findings in our case is that pathologic accumulation of the virus occurred. While this accumulation did not appear to occur because of a detectable compromise in the patient's immune system, a drug-induced susceptibility is possible. Hedgehog inhibitors have been shown to decrease activation of natural killer cells, important cells in the response to viral infection.[4,5]

If EM or polymerase chain reaction is required before making the diagnosis, perhaps the term *trichodysplasia spinulosa-like hyperkeratosis* or *trichodysplasia spinulosa-unconfirmed* can be used.

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1. Osswald SS, Kulick KB, Tomaszewski MM, Sperling LC. Viral-associated trichodysplasia in a patient with lymphoma: a case report and review. *J Cutan Pathol*. 2007;34(9):721-725.

2. Lori D, Prok M. *Pediatric dermatopathology: how may I help you?* American Society of Dermatopathology Annual Meeting; October 10-13, 2013; Washington, DC.

3. Franck N, Barete S, Moguelet P, et al. Spiny follicular hyperkeratosis eruption: a new cutaneous adverse effect of sorafenib. *J Clin Oncol*. 2010;28(31):e640-e642.

4. de la Roche M, Ritter AT, Angus KL, et al. Hedgehog signaling controls T cell killing at the immunological synapse. *Science*. 2013;342(6163):1247-1250.

5. Onishi H, Morisaki T, Kiyota A, et al. The Hedgehog inhibitor cyclopamine impairs the benefits of immunotherapy with activated T and NK lymphocytes derived from patients with advanced cancer. *Cancer Immunol Immunother*. 2013;62(6):1029-1039.