Multiple myeloma (MM) has many cutaneous manifestations. Follicular spicules are relatively rare among them. Previous articles on this dermatosis categorized it as paraneoplastic in origin. No specific treatment is available. The clinical picture is very reminiscent of trichodysplasia spinulosa (TS), which is known to be caused by the TS–associated polyomavirus (TSV). Herein, we describe a case of follicular spicules in a patient with MM. We attempted to identify a possible viral cause and to classify this enigmatic entity.

Report of a Case

A man in his 70s consulted us regarding coarse outgrowths on his face that had been present for several months (Figure 1A). These lesions were asymptomatic, but the patient was concerned about his appearance. He had been treated with mid-potency topical corticosteroids for several weeks with no apparent effect. The patient had no medical history, but he complained of fatigue and malaise. Examination of his skin revealed small, folliculocentric, coarse, yellowish spicules located mainly on his face but also on his chest and lower arms. Ulcerated papules covered with hemorrhagic crusts were also visible on his torso. All his fingernail plates were white (Figure 1B).

We considered the differential diagnosis of facial folliculocentric spicules comprising TS and follicular spicules of MM (FSMM). The first is a well-characterized infection with TSV in immunosuppressed patients. The latter is seen in patients with MM, but its pathophysiologic role is not understood. Conventional hematoxylin-eosin staining of a skin biopsy specimen taken from the forehead showed a widened hair follicle with a protruding spicule with hyperparakeratosis surrounded by multiple eosinophilic bodies (Figure 2A).

Electron microscopy of a follicular keratinocyte revealed multiple round structures of approximately 1 μm in diameter arranged in a colonlike pattern (Figure 2B). Further magnification showed these structures to consist of fibrillar bodies arranged in a paracrystalline configuration. No viral particles could be found. These findings are reminiscent of both TS and FSMM, making differentiation based on these investigations alone impossible. Further serological testing showed an increased serum protein level of 10.1 g/dL (to convert to grams per liter, multiply by 10), which was primarily composed of γ-globulins (5.85 g/dL). No antibodies against the human immunodeficiency virus were found, and leukocyte levels were normal. A bone marrow biopsy revealed 50% infiltration by monoclonal plasmacytoid, CD138-positive, and IgG-producing cells. Fluorescence in situ hybridization revealed an extra copy of chromosome 9 in 41% of the analyzed cells, fitting the diagnosis of MM. With this information, we diagnosed FSMM in this patient.

Because the etiology of FSMM is unknown, specific treatment is lacking. However, the clinical and histopathological findings in FSMM are reminiscent of TS. Identifying TSV in the lesions of our patient could provide a basis for treatment. We therefore endeavored to identify a possible viral causative agent for FSMM. Trichodysplasia spinulosa has been well characterized as a viral dermatosis caused by a polyomavirus, but in the case of FSMM, no publications record attempts to identify the causative agent. A TSV-specific polymerase chain reaction did not reveal TSV in the spicules. To rule out another polyomavirus, rolling circle amplification was undertaken; however, no polyomavirus was detected using this technique.

Having ruled out TSV as the causative agent, we turned to our random amplification virus discovery approach to detect viral sequences. In this protocol, we enriched for virus particles and used a combined random amplification and 454 pyrosequencing approach.
A deep-sequencing approach to search for both RNA and DNA viruses. We used a spicule from a hair follicle to search for viral presence. The protocol for the discovery of RNA viruses and DNA viruses yielded 42,641 and 152,082 reads, respectively. After quality trimming, reads were assembled into contigs. Contigs and reads that were not assembled into contigs (so-called singletons) were submitted to the Basic Local Alignment Search Tool for nucleotides (BLASTn). This algorithm finds regions of local similarity between the submitted sequence and known sequences in a nucleotide database and makes calculations on statistical significance of possible matches. Sequences were classified into viruses, bacteria, and/or eukaryotes based on the taxonomic origin of the best-hit sequence using MEGAN (metagenome analyzer) software. The contigs from both the RNA and DNA virus discovery protocols and the singletons derived from the RNA virus discovery protocol did not result in any viral hits in the nucleotide BLAST. However, the singletons resulting from the DNA virus discovery protocol, showed 10 hits that were assigned to the polyomavirus family. All hits had the highest score to Merkel cell polyomavirus (MCV). A translated protein BLAST search based on the nucleotide sequences did not result in any additional viral hits. Using different BLAST parameters and MCV genome as a reference, another 4 reads were found to be assigned to MCV. The 14 sequence reads ranged in size from 109 to 462 nucleotides. The sequence identity of these hits to MCV ranged from 95% to 100%. Together, the 14 reads covered 1943 nucleotides of the viral genome. However, the reads that aligned to the genome were not equally distributed \( (P > .05) \). Instead, the first approximately 1800 nucleotides of the genome were not cov-
Discussion

Polyomaviruses are ubiquitous viruses capable of infecting humans and many animal species. Sequences from human polyomaviruses have been isolated from stool, respiratory secretions, blood, central nervous fluid, urine, and skin. Because of new technologies, their involvement in various human diseases is easier to establish. Our findings suggest a pathophysiological role for a polyomavirus but not TSV in FSMM.

A recent article reported absence of TSV in a case of follicular spicules in a MM confirming our findings. Satta and colleagues suggested a role for paraprotein deposition in FSMM after finding the same electrophoresis pattern in a patient’s spicules and serum paraprotein, although we found no immunoglobulin deposits in our patients’ skin.

Although MCV cannot be appointed as the etiological agent of FSMM, several aspects suggest a role for this virus in this dermatosis. First, the patient has MM, a disease that predisposes to opportunistic infections. Second, the clinical picture resembled TS, caused by a related polyomavirus TSV. Third, the treatment with cidofovir, a viral DNA-polymerase inhibitor, cleared the spicules. This effect is also seen in TS and human papillomavirus-infected skin, although polyomaviruses are not known to encode any polymerase. Although the patient was started on chemotherapy 1 week before the full clearing of spicules, the confinement of the effect to the treated area is suggestive of some cidofovir effect. In addition, the patient had a notable response to cidofovir within 1 week, which was prior to the initiation of chemotherapy. And finally, MCV was discovered inside the affected tissue. Regarding the latter, and the fact that MCV spread from healthy skin cannot be ruled out because asymptomatic carriage is highly prevalent in older individuals, further study into the observed association between MCV and FSMM as well as why cidofovir would have an effect on the lesions is warranted.

Conclusions

We have found evidence implicating a possible viral etiology instead of a paraneoplastic origin for FSMM. The differential diagnosis of TS was rejected owing to the absence of TSV by polymerase chain reaction. However, further research is necessary to confirm our findings.