

COMMENTS AND OPINIONS

Human Herpesvirus 8 DNA Sequences in Pemphigus: The Role of the Virus in Oncogenic and Autoimmune Manifestations

We read with interest the recent article by Memar et al.¹ Although the polymerase chain reaction studies on the biopsy material were convincing, polymerase chain reaction studies of peripheral blood and serologic test results need to be confirmed. In addition, in situ polymerase chain reaction might define which cell populations contain the virus in the skin.

The authors point out that some of the diseases associated with human herpesvirus 8 (HHV-8) are increased in patients with pemphigus, including Kaposi sarcoma, lymphoma, and benign giant lymph node hyperplasia.² They did not study patients with paraneoplastic pemphigus. Patients with paraneoplastic pemphigus have a much higher association with non-Hodgkin lymphoma, chronic lymphocytic leukemia, and benign giant lymph node hyperplasia (82%) than patients with pemphigus vulgaris and pemphigus foliaceus.³ Most of these neoplasms have been associated with other oncogenic viruses, usually Epstein-Barr virus, but also HHV-8 in some patients with benign giant lymph node hyperplasia.^{2,4-6}

The role of HHV-8 in the augmentation of autoimmune disease, as well as malignancies, may be related to the presence of homologs in cellular genes that are contained within the HHV-8 genome.² In addition to a G protein-coupled receptor and a viral cyclin similar to the type D cyclins, which could function as an oncoprotein increasing cellular proliferation, HHV-8 encodes homologs to *bcl2*, which could increase the resistance of infected cells to some forms of apoptotic cell death, as well as 2 macrophage inflammatory proteins, dihydrofolate reductase, interferon regulatory factors, and interleukin 6.²

Interleukin 6 has been implicated in autoimmune disease and promotes the later stages of B-cell differentiation into plasma cells.⁷ Interleukin 6 also supports the growth of B-cell hybridomas and plasmacytomas in culture and has been implicated in the development of neoplasms that produce excess proteins.⁷ Interleukin 6 can promote immunoglobulin production with Epstein-Barr virus-transformed B cells, particularly enhancing the production of IgG and IgM isotypes.⁷

The origins of autoimmune diseases and malignancies associated with HHV-8 are probably multifactorial. However, these different manifestations may depend in part on whether there is active systemic infection, coinfection of a specific cell population, or transformation of a specific cell population by HHV-8, as well as by another virus, such as Epstein-Barr virus or a retrovirus.³

Because there is a close association of conditions containing human oncogenic viruses with paraneoplastic pem-

phigus, we would be interested in any current or future studies of paraneoplastic pemphigus by Memar et al. In addition, while individuals with paraneoplastic pemphigus associated with benign thymomas or solitary lesions of benign giant lymph node hyperplasia may respond to surgical excision, most patients with paraneoplastic pemphigus respond poorly to present therapies. If underlying etiologic agents were identified, perhaps better strategies for therapy could be determined.

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The views expressed herein are those of the authors and do not necessarily reflect the views of the US Army, the US Navy, or the US Department of Defense.

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In reply

We wish to thank Smith and Skelton for their comments. In fact, serologic studies and polymerase chain reaction studies of peripheral blood are ongoing, as are in situ polymerase chain reaction investigations with tissue from patients with pemphigus vulgaris and pemphigus foliaceus. Furthermore, we agree that the relationship of paraneoplastic pemphigus with certain malignancies associated with human oncogenic viruses proves the need for serologic and virological studies with specimens from patients with paraneoplastic pemphigus. These investigations are being conducted in our laboratory, and we hope to present the data in the near future.

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Therapeutic Options for Superficial Basal Cell Carcinoma: The Role of Radiation Therapy

Using photodynamic therapy in conjunction with the intralesional instillation of δ -aminolevulinic acid, as reported by Fink-Puches and colleagues,¹ was certainly a novel and ultimately successful solution to the therapeutic challenge posed by a patient with a large superficial basal cell carcinoma who refused surgical intervention. What I found surprising, though, was that this case was felt to be particularly challenging since radiation therapy was an obvious nonsurgical alternative therapeutic option. As noted by Goldschmidt et al² in their recent comprehensive review of the use of ionizing radiation in dermatology, radiation therapy is an effective treatment for epithelial skin cancers, particularly for lesions measuring less than 5 cm in diameter. I believe that it is important to realize that although the treatment reported by Fink-Puches and colleagues may have been of interest because of its novelty and ultimate success, radiation therapy remains the established nonsurgical modality for the treatment of superficial basal cell skin carcinoma.

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In reply

We appreciate the interest of Sherr in our article on photodynamic therapy (PDT) of superficial basal cell carcinoma by instillation of δ -aminolevulinic acid (ALA) and irradiation with visible light.¹ We agree with him that the use of ionizing radiation therapy is an effective treatment for epithelial skin cancers. However, it is well recognized that ionizing radiation therapy can sometimes lead to chronic radiodermatitis, which tends to worsen in its appearance over time.² In contrast, the short- and long-term cosmetic results after ALA-PDT always seem to be excellent.³⁻⁵ Whereas the long-term recurrence rate with topical ALA-PDT after epicutaneous drug application is under current investigation,⁴ this rate is completely unknown for ALA-PDT after intralesional drug instillation. However, for ionizing radiation therapy of basal cell carcinoma, the recurrence rate may be considerably higher than that generally assumed by dermatologists. After a 10-year follow-up, it seems to be realistic to count on a recurrence rate of at least 10% to 12%.⁶

Finally, the carcinogenic potential of ionizing radiation therapy is still under debate; thus, its use in otherwise healthy patients is discouraged.² On the contrary, ALA-PDT does not damage DNA directly and does not seem to be mutagenic and carcinogenic because the main target of PDT is cell membranes rather than DNA.⁷ However, fur-

ther studies are necessary to determine the advantages and disadvantages of PDT by instillation of ALA and irradiation with visible light.

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Conservative Clinical Diagnoses in Seborrheic Keratosis

The recent study by Eads et al¹ determined a 6.4% error rate in the clinical differential diagnosis of seborrheic keratosis vs malignancy. During the 30-month period beginning April 1, 1995, and ending September 30, 1997, my laboratory processed approximately 18 000 specimens of all types. Of this number, 390 specimens were submitted by dermatologists with a clinical diagnosis of seborrheic keratosis. Among these, only 8 (2.03%) were diagnosed histologically as malignant and none were malignant melanomas. This rate (2.03%) is less than the 6.4% rate reported by Eads et al.¹

Of interest was the examination of an additional 493 specimens submitted with clinical diagnoses other than seborrheic keratosis, but which yielded a histological diagnosis of seborrheic keratosis. Of these, 415 were from dermatologists and 78 were from nondermatologists. The following specialties were represented among these 78: general surgery, otolaryngology, ophthalmology, podiatry, plastic surgery, family practice, and gynecology. Among the 415 specimens received from dermatologists, 130 had no clinical diagnosis, and 50 had rule-out squamous cell carcinoma or basal cell carcinoma. Fifty-four were nevi and 218 had the generic diagnosis of keratosis. Among the 78 specimens received from nondermatologists, only 8 had clinical diagnoses.

It appears that an aura of clinical diagnostic conservatism prevails. When dermatologists make a clinical diagnosis of seborrheic keratosis, they are correct more than

90% of the time. However, among the cases I have seen, in which a total of 875 were diagnosed histologically as seborrheic keratosis, a clinical diagnosis of seborrheic keratosis was submitted in only 382 cases. Thus, the data indicate that dermatologists make the diagnosis of seborrheic keratosis in only 44.1% of all cases in which seborrheic keratosis is either clinically or histologically possible. Although 78 cases is a small base, it appears that non-dermatologists never make the clinical diagnosis of seborrheic keratosis and are completely dependent on histological examinations to make that diagnosis.

On the issue of sending seborrheic keratoses for pathological examination, the feedback obtained by receiving pathological data to correlate with clinical impressions may be the driving force giving rise to the conservative clinical diagnoses seen in my sample. The 6.4% rate in the sample reported by Eads et al¹ and my 2.03% rate does not leave much room for improvement. Refraining from sending tissue for pathological examination seems unlikely to improve these low error rates, but could instead worsen the rates due to lack of feedback. Although there may be an immediate cost savings, lack of pathological correlation could be penny wise and dime foolish in the long run.

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VIGNETTES

Further Evidence That Syringolymphoid Hyperplasia With Alopecia Is a Cutaneous T-Cell Lymphoma

Syringolymphoid hyperplasia with alopecia (SLHA) is a rare disease, which was first reported by Sarkany in 1969.¹ Clinical features of SLHA include hairless patches with follicular papules. Histopathologic characteristics include a dense lymphohistiocytic infiltrate surrounding hyperplastic eccrine sweat glands and ducts. We report the ninth case of SLHA. Genotypical analysis revealed a biallelic monoclonal rearrangement of the T-cell receptor γ chain gene. This rearrangement provides further evidence that SLHA represents a cutaneous T-cell lymphoma.

Report of a Case. A 52-year-old man with a 5-year history of an undetermined skin disease presented to the Department of Dermatology, Heinrich-Heine University, Düsseldorf, Germany. Results of a physical examination revealed multiple, disseminated, brownish scaly papules, giving the patient's feet a dyshidrosiform aspect (**Figure 1**). Additionally, he had erythematous le-



Figure 1. Multiple papules giving the patient's feet a dyshidrosiform aspect.

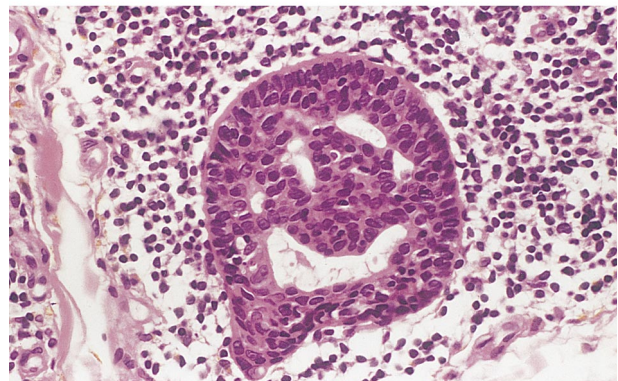
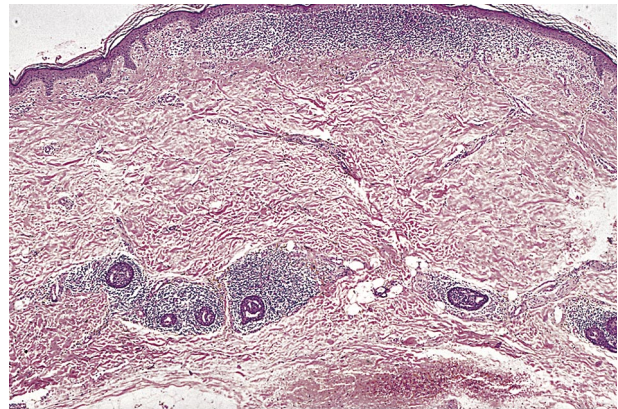


Figure 2. Syringolymphoid hyperplasia. Top, Superficial and deep dense lymphocytic infiltrate with typical epidermotropism of relatively large lymphocytes (hematoxylin-eosin, original magnification $\times 20$). Bottom, Dense epidermotropic infiltrate (syringotropism) around an eccrine duct (hematoxylin-eosin, original magnification $\times 400$).

sions with papules on the lower part of his legs that showed complete alopecia. Biopsy specimens taken from the sole of his right foot and the lower part of his leg showed identical features: a bandlike lymphohistiocytic infiltrate located subepidermally and a large number of lymphocytes that displayed nuclear atypia (**Figure 2**). Epidermotropism was noted. Sweat glands and ducts located in the lower dermis were hypertrophic and surrounded or infiltrated by a dense lymphohistiocytic infiltrate. Additionally, sweat glands were infiltrated by lymphocytes. There were no hair follicles present in the biopsy specimen excised from the lower part of his leg. Immunophenotypic analysis revealed a T-cell immunophenotype: positivity for CD45RO (UCHL1, Dako,

Carpinteria, Calif) and MT1 (Eurodiagnostika BV, Arnheim, the Netherlands) and negativity for L26 (Dako), CD45R 4KB5 (Dako), and MAC387 (Dako). Genotypical studies showed a biclonal rearrangement of the T-cell receptor γ chain gene using the polymerase chain reaction. Results of a complete blood cell count and bone marrow biopsy were normal. Results of radiological studies of the thorax and ultrasonography of the abdomen were unremarkable. The outcome of psoralen–UV-A bath therapy was disappointing.

Comment. Our case extends the series of 8 patients with SLHA who have been described in the medical literature.¹⁻⁸ The distribution of lesions on the soles of both feet as described herein has not been reported previously. The clinical picture was somewhat identical to dyshidrotic eczema, and the possibility of dyshidrotic cutaneous T-cell lymphoma or psoriasis was also considered. However, histological features were consistent with SLHA. The classification of SLHA has yet to be determined. Some authors claim that SLHA is a cutaneous T-cell lymphoma and a variant of mycosis fungoides.⁶⁻⁸ In the years since the first description of this disease, new techniques, such as immunophenotypic and genotypical analysis, have evolved as important tools for the diagnosis and classification of lymphoproliferative disease. Genotypical studies have been inadequately addressed in previous reports. Zelger et al⁷ and Tomaszewski et al⁸ described 2 cases with rearrangement of the T-cell receptor β chain gene. In the current case we had evidence for a clonal biallelic rearrangement of the T-cell receptor γ chain gene. Aside from some exceptions, clonality serves as an excellent marker to prove the neoplastic nature of disease. Taken together, the immunophenotypic and genotypical results in this case suggest a cutaneous T-cell lymphoma. In support of this view, evaluation of the hematoxylin–eosin–stained slides demonstrated typical features of mycosis fungoides, such as bandlike infiltrate, nuclear atypia, and epidermotropism. In this context, we conclude that SLHA may be a cutaneous T-cell lymphoma and extend the spectrum of mycosis fungoides.

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Hypopigmented Common Blue Nevi

Blue nevi are classically divided into 2 major types: common and cellular.¹ However, there is significant overlap between these 2 types of lesions. Both represent benign proliferations of dermal melanocytes, and both occur most commonly in sites where dermal melanocytes are still present at birth, ie, the scalp, lumbosacral region, and dorsum of the hand and foot.

Report of Cases. *Case 1.* A 29-year-old healthy white woman presented for a skin cancer screening examination. A lesion on the dorsum of her right hand had been present for as long as she could remember. For the past several months, its central portion had lightened in color. A firm gray-colored papule on the dorsum of her right hand measured 4 mm in diameter. At the periphery of the lesion, a discontinuous thin rim of blue coloration was noted.

The results of a histological examination revealed a symmetrical wedge-shaped proliferation of spindled cells with prominent pigmentation within the superficial and midreticular dermis. At low power, prominent pigmentation was easily identified at the periphery of the lesion (**Figure 1**). This pigmentation was highlighted using a Fontana-Masson stain. High-power examination revealed uniform spindled and dendritic melanocytes with uniform oval to spindle-shaped nuclei. Finely divided melanin pigment was identified within the melanocytes and within scattered melanophages, especially at the periphery of the lesion.

A tendency for clustering of pigmented melanocytes around adnexal structures was identified; however, prominent pigmentation also was identified in regions without appendages. Toward the center of the lesion, dendritic melanocytes were diminished in number and showed less prominent pigmentation (Figure 1). In this region, small spindle-shaped cells with oval nuclei were associated with thickened collagen bundles. Although the thickened bundles were arranged predominantly in a haphazard pattern, a focal laminar pattern was noted. There was strong labeling of dendritic melanocytes with HMB-45 and Mel-5 immunohistochemical stains (Figure 1).² The labeling was most prominent at the periphery of the lesion. Centrally, the staining was mildly diminished.

Case 2. A 23-year-old healthy man with multiple atypical melanocytic nevi and a family history of melanoma was seen for longitudinal care. On initial physical examination, he was noted to have more than 100 me-

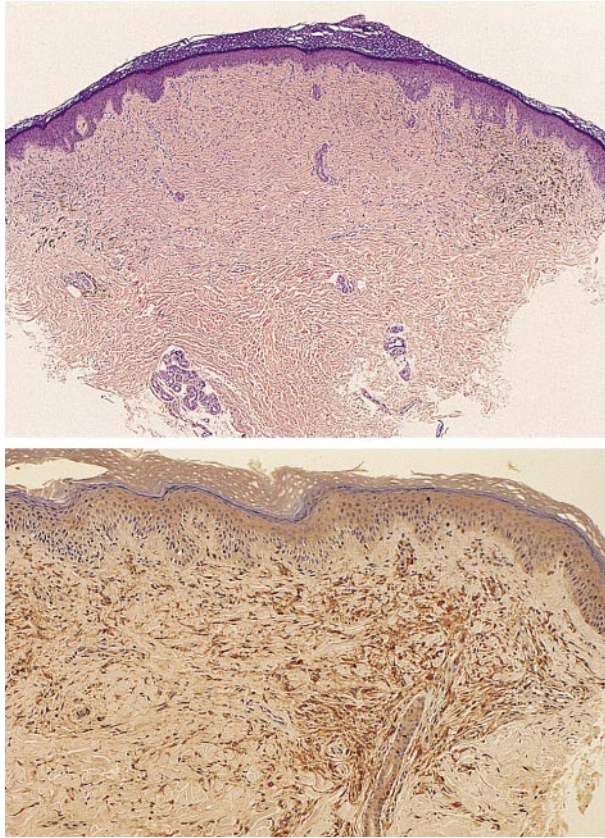


Figure 1. Top, Hypopigmented common blue nevus with central sclerosis and prominent peripheral pigmentation from case 1 (hematoxylin-eosin, original magnification $\times 27$). Bottom, Slightly decreased labeling of melanocytes centrally (left) and prominent labeling of melanocytes at the periphery of the lesion (Mel-5, original magnification $\times 66$).

lanocytic nevi and approximately 10 atypical nevi. The results of histological examination of his most atypical nevus showed architectural disorder and mild cytologic atypia.

During a follow-up examination, a 5-mm gray-white to skin-colored firm papule was noted on the distal portion of his right shin (**Figure 2**). The patient had been unaware of the lesion. Peripherally, at the 3-o'clock and 10-o'clock positions, there were 2 small (<1 -mm) areas of blue coloration. Two years later there had been no interval change and, at the patient's request, a partial biopsy was performed that included one half of the lesion (6-o'clock to the 12-o'clock position).

The results of a histological examination showed prominent dendritic melanocytes at the periphery of the lesion (**Figure 2**). Toward the center of the nevus there were thickened, haphazardly oriented collagen bundles. Pigmentation was nearly absent in this central region (**Figure 2**). There was no inflammation, atypia, or mitotic activity. Immunohistochemical labeling with HMB-45, Mel-5, and S100 protein was similar to that in case 1, with prominent labeling toward the edge of the nevus and slightly diminished staining at its center.

Comment. Although multiple shades of color have been described for the common blue nevus, we were unable

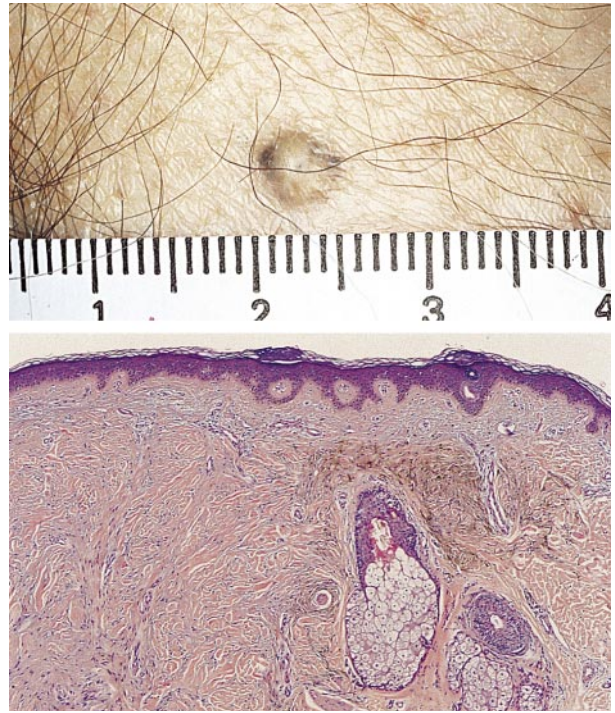


Figure 2. Top, Patient 2 with a hypopigmented common blue nevus measuring 0.5 cm on the distal right shin (centimeter ruler shown in picture). Note the 2 small (<1 -mm) areas of blue coloration at the periphery. Bottom, Sclerosis with markedly diminished pigmentation in the center of the lesion and prominent peripheral pigmentation (hematoxylin-eosin, original magnification $\times 43$).

to document a hypopigmented variant in our review of the literature^{1,3} and standard textbooks of dermatology. In 1954, Dorsey and Montgomery¹ described the colors of blue nevi, including cellular blue nevi. Of a total of 79 blue nevi, there were 21 blue, 33 blue-black, and 11 steel blue nevi. Although no specific numbers were provided, the authors observed several additional nevi, including blue-gray, gray-black, brown, brown-blue, and yellow. The latter was characterized as "capped by a nevoid hyperkeratotic overgrowth of the stratum corneum." Rodriguez and Ackerman³ stated that in their series of 45 cases of cellular blue nevi, there was 1 case in which the overlying skin was not pigmented.

In 1983, Bondi et al⁴ described 2 target blue nevi with a gray-black or blue-black center surrounded by a flesh-colored area that then merged with an outer macular rim of blue-black pigmentation. The central pigmented portion was prominent and occupied approximately 50% of the surface area of the nevus. The histological changes in our cases were similar to those described for the periphery of the target blue nevi, but no central focus of prominent pigmentation was seen in our cases. One explanation for the skin-colored annulus was a regression (or reduction in the number) of the pigmented dermal melanocytes and replacement by collagen.²

The histological correlation for the lack of blue color within the common blue nevi described herein was a marked decrease in the amount of dermal melanin in association with a less prominent decrease in the density

of dermal melanocytes. The relative contribution of dermal fibrosis to the lighter color remains speculative. Telang and Speilvogel⁷ commented that although blue nevi usually remain static throughout life, they may “undergo fibrosis with subsequent flattening, lightening of color, and gradual involution.” The possibility exists that the fibrosis, as well as the desmoplastic response within the nevi described herein, represents an aging or regressive change. One of us (E.J.G.) has noted similar although less prominent histological changes in other blue nevi that were not clinically hypopigmented. We speculate that our reported cases represent a change in blue nevi, which is not uncommon, but had progressed to such an extent that the characteristic blue color was lost.

Since the submission of this article, Carr et al⁶ published histological findings of 9 cases of patients with common blue nevi that were noted to be hypopigmented via histological examination.

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Oral Mucosa Is Frequently Affected in Patients With Dermatitis Herpetiformis

Dermatitis herpetiformis (DH) is a lifelong itching, blistering skin disease. Most patients have an associated gluten-sensitive enteropathy or coeliac disease (CDL)¹ characterized histologically by duodenal and jejunal atrophy. It is well established that DH may affect the oral mucosa as well.^{2,3} According to previous reports,^{1,3} oral lesions are found in 1% to 10% of patients with DH, but Fraser and coworkers³ reported oral lesions in 70% of patients. In the present study, oral changes in DH were assessed.

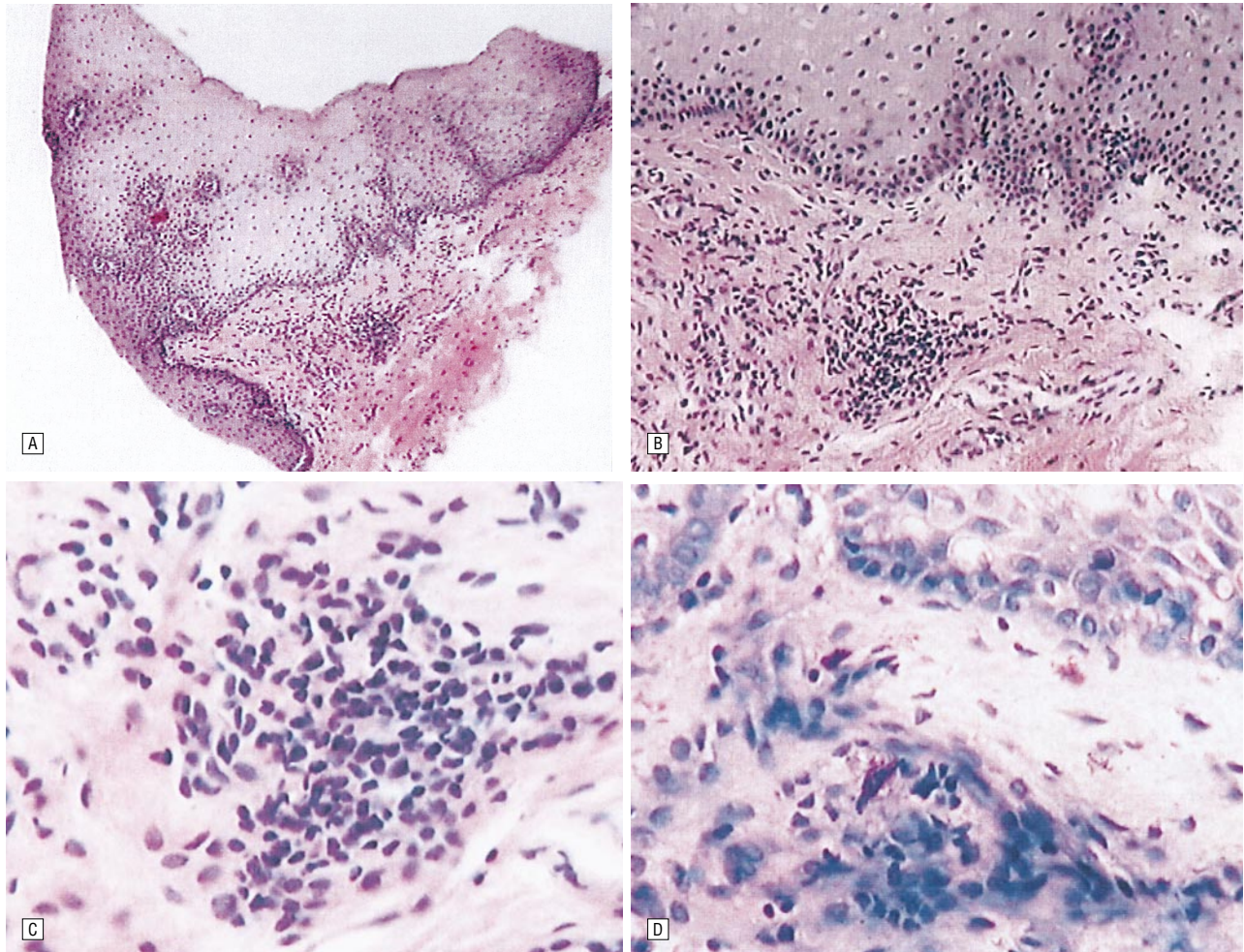
Patients and Methods. A total of 27 patients with DH and 30 patients with CD (the diagnosis confirmed via small intestine biopsy) as a control group were enrolled in the study through the Coeliac Association of Turku, Finland. A second control group comprised 30 healthy subjects. The diagnosis of DH was confirmed by the presence of characteristic histological features of the skin and cutaneous deposits of IgA (**Figure**). All patients with DH underwent gastroduodenoscopy at the time of the diag-

nosis, and CD (a subtotal or partial villous atrophy found via small intestine biopsy) was confirmed in 9 (33%) of the 27 patients. The age and sex distribution of the subjects is given in the **Table**. The study protocol was approved by the Ethical Committee of the Faculty of Medicine, University of Turku. At their examination on study entry, all patients filled in a questionnaire about their medical history as well as oral changes and other manifestations. A biopsy was performed on the uninvolved buccal mucosa with the patients under local anesthesia (Xylocaine, Astra, Södertälje, Sweden). The biopsy sample was submitted for routine histopathological examination, and the inflammation was graded as not present (0), low (1), moderate (2), or severe (3). Mast cells were stained with toluidine blue. The following blood parameters were analyzed: hemoglobin, serum ferritin, serum vitamin B₁₂, red cell folate, and serum IgA, IgG, and IgM levels using the standard laboratory procedures. Antibodies to gliadin (AGA) were studied using a solid-phase enzyme-linked immunosorbent assay method. Serum IgA and IgG antibodies against reticulin (ARA) were measured using an indirect immunofluorescence test and serum antiendomysium antibodies (EmA) via an indirect immunofluorescence test (BioSystems, Barcelona, Spain).⁴ A χ^2 test was used to compare the differences in findings between the DH and control groups.

Results. A total of 21 (78%) of 27 patients with DH had the disease for more than 5 years, 6 (22%) of 27 patients for less than 5 years, and 1 patient (3%) had newly diagnosed DH. Thirteen (48%) of 27 patients followed a gluten-free diet strictly, whereas 3 patients (11%) did not follow it. Twelve (44%) of 27 patients with DH had other diseases (3 had lactose intolerance, 3 had hypertension, 2 had thrombocytopenia, 2 had pernicious anemia, 2 had coronary disease, and 1 had asthma). Fourteen patients received no medication. Ten patients were receiving dapsone treatment for DH. Four of the patients were smokers. None was a heavy drinker. Associated diseases were found in the patients with CD as follows: 2 had asthma, 7 had allergies, 3 had hypertension, 3 had anemia, and 2 had fibromyalgia. In the control group, 2 patients had hypertension, 1 had asthma, 4 had allergies, and 3 had hypothyroidism.

The prevalence of oral symptoms and mucosal changes of the subjects is described in the Table. According to the questionnaire, 6 patients (22%) with DH, 10 patients (33%) with CD, but none of the controls (0%) had recurrent aphthous ulceration. Oral ulceration (other than aphthous ulceration) was the most frequent oral mucosal change. Of 10 patients with DH with oral ulceration, 7 (70%) had CD. Only 1 (11%) of the 9 patients who had DH with associated CD was totally free of symptoms. Oral dryness ($P = .001$) and mucosal ulceration ($P = .001$) were the only symptoms and/or changes for which a statistically significant difference was found between the groups analyzed.

Three patients with DH, 1 patient with CD, and 2 controls had a low hemoglobin level. Serum B₁₂ vitamin level was normal in all subjects studied. Two patients with DH and 3 patients with CD were receiving current medication for pernicious anemia. Results of histopathologi-



A buccal biopsy sample from a patient with dermatitis herpetiformis. With hematoxylin-eosin staining, lymphocytes are present in both the epithelium and lamina propria (A, original magnification $\times 100$; B, original magnification $\times 40$; and D, original magnification $\times 250$). With the toluidine blue staining, mast cells are detected in the lamina propria (C, original magnification $\times 250$).

cal workup of inflammatory cell infiltration include a level of significance in which $P = .12$ and are summarized as follows:

Population and Degree of Grading	No. of Biopsy Samples
Patients with DH (n = 27)*	
None	8
Mild	8
Moderate	9
Intense	0
Patients with CD (n = 30)	
None	11
Mild	13
Moderate	3
Intense	3
Controls (n = 30)	
None	8
Mild	18
Moderate	3
Intense	1

*Two specimens are not representative.

Moderate to severe inflammatory cell infiltration was detected in 9 (36%) of the 25 oral mucosal biopsy samples of patients with DH, in 6 (20%) of the 30 samples of patients with CD, and in 4 (13%) of the 30 samples of con-

trols. The difference between the groups was not statistically significant ($P = .12$). Interestingly, mast cells were present (grades 2 and 3) in biopsy specimens of all 3 groups as follows: in 12 (44%) of 27 patients with DH, in 14 (46%) of 30 patients with CD, and in 8 (26%) of 30 controls.

Oral symptoms were significantly more common in patients with DH with a manifestation of CD than in those with DH only ($P = .006$). The age and sex of the patient, other associated diseases, medication (other than that used for DH), smoking, and alcohol consumption could not be associated either with oral mucosal changes or symptoms in any of the study groups.

In the present study, no statistically significant association was found between ARA, AGA, and EmA and the presence of oral subjective symptoms or changes in the patients with DH or those with CD ($P = .20-.81$). In the DH group, 1 patient with associated CD detected just 1 month earlier was positive for IgA-ARA and IgA-EmA, but IgA and IgG antibody titers to AGA were normal. He described having both oral soreness and dryness and also oral ulceration. Another patient had positive serum IgA values for ARA and EmA. Serum IgA-AGA values were normal but the IgG-AGA level was higher than normal,

Characterization of the Subjects Studied*

Features	Patients With DH (n = 27)	Patients With CD (n = 30)	Controls (n = 30)	P
Sex, F/M	13:14	15:15	19:11	NA
Mean ± SD age, y	47.1 ± 13.8	46.9 ± 9.8	47.9 ± 14.3	NA
Small intestine biopsy				
Normal	18	0	0	.001†
Partial/total villous atrophy	9	30	0	.001†
Gluten-free diet				
Strictly holding	13	21	0	.085†
Rather holding	11	9	0	.085†
Do not follow	3	0	0	.085†
Symptom				
Soreness or burning sensation in tongue	5	6	3	.53
Soreness or dryness in lips	5	6	2	.29
Dryness of the mouth	15	3	7	.001
Soreness of the mouth	6	12	5	.10
Change				
Mucosal redness	5	7	5	.80
Mucosal ulceration	10	12	0	.001
Erythematous tongue	3	3	1	.42
Atrophy in tongue	1	4	1	.23
Aphthous ulcer	0	1	0	.38
Total No. (%) of patients with symptoms	17 (63)	13 (43)	10 (33)	.12
Total No. (%) of patients with oral mucosal changes	15 (56)	19 (65)	7 (23)	.001

*DH indicates dermatitis herpetiformis; CD, gluten-sensitive enteropathy; and NA, not applicable.

†Patients with DH vs patients with CD.

at 9.02 EU/mL (normal, <5.0 EU/mL). Yet another patient had elevated IgG antibody titers to AGA, at 10.1 EU/mL. Moderate to intense inflammatory cell infiltration was seen in both of these patients. Levels of serum IgA-AGA, IgA-ARA, and IgA-EmA were elevated in 3, 2, and 2 patients with CD, respectively. One patient with CD and anemia had IgA antibodies to AGA, ARA (titer, 1:640 EU/mL), and EmA (titer, 1:640 EU/mL). She had recurrent buccal soreness but had no oral changes on clinical examination.

Comment. According to most authors, DH rarely affects the oral mucosa, and there has been no report of DH with oral lesions as the sole manifestation.^{3,5} However, Fraser and coworkers³ report oral lesions in more than 70% of their patients with active DH.

Despite that in our study the patients with DH (except 3) followed a strict or nearly strict gluten-free diet, 17 patients (63%) had oral symptoms and 15 (56%) had oral mucosal lesions as well. Oral symptoms were found in 13 patients (43%) with CD and in 10 controls (33%); mucosal changes were found in 19 patients (65%) with CD and in 7 controls (23%). Our results indicate that oral symptoms and lesions are common in patients with DH and CD but are also detected in the controls. However, oral mucosal ulcerations were not present in the controls and therefore might be more specific to DH and CD. Five of the 7 mucosal lesions found in the controls were

red, which might be caused by mechanical irritation. Three of these subjects were also smokers and used alcohol, which might explain the mucosal redness as well. The high prevalence of oral symptoms found in the patients with DH in the present study is contradictory to that reported by Pindborg⁶ but supports the results of Fraser and coworkers.³

Oral dryness was reported in 15 (56%) of the patients with DH, in 7 (23%) of the controls, and surprisingly in only 3 patients (10%) with CD. Our results are consistent with those published by Hietanen and Reunala.² It is important to observe the association between oral dryness and DH. However, further studies are needed to find how many of the criteria of Sjögren syndrome can be met in patients with DH. In the study by Hietanen and Reunala² none of the 7 patients with DH had oral lesions such as blisters, crusts, or scarring. Oral symptoms in patients with DH, such as soreness, burning sensations, and lesions, are often localized in buccal mucosa close to linea alba. Located at the occlusal level of the teeth, this area is prone to trauma and might be the "locus of minor resistance" of oral mucosa.³

The patients with DH and CD had symptoms significantly more often than patients with DH without CD ($P = .006$). Histopathological findings were more common in biopsy specimens taken from the patients with an associated CD than those without this disease. Because the mouth is a part of the gut-associated lymphoid tissue, CD might be responsible for the more frequent oral symptoms and oral mucosal lesions.

Oral symptoms and lesions are common in patients with DH, as well as in patients with CD. The only significant factor associated with oral symptoms is an associated CD.

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Human Herpesvirus 6 Infection in Patients With Exanthema After Allogeneic Bone Marrow Transplantation

Frequent reactivation of human herpesvirus 6 (HHV-6) has been demonstrated in immunocompromised patients after renal or bone marrow transplantation (BMT). Using polymerase chain reaction (PCR), HHV-6 DNA has been detected in exanthematous skin after BMT,¹ as well as in skin and/or rectal biopsy specimens of patients without exanthema prior to undergoing BMT.² One study showed that after allogeneic BMT there is an increased risk of developing graft-vs-host disease, in which HHV-6 DNA is found in rectal and/or skin biopsy specimens.² To investigate a pathogenic role of HHV-6 reactivation during cutaneous exanthema after allogeneic BMT, we determined HHV-6 DNA levels using quantitative PCR in blood and simultaneously in both erythematous and normal skin biopsy specimens.

Thirteen patients presenting with cutaneous exanthema following allogeneic BMT were studied prospectively. Patients found to have cytomegalovirus viremia via a cell culture were excluded. No patient was infected with human immunodeficiency virus 1 or human immunodeficiency virus 2 before undergoing BMT. Skin biopsy specimens (2 lesional and 1 normal) and blood samples were taken from each patient at inclusion (day 0) and between 1 and 8 days (mean, 2.9 days) after the onset of exanthema. Blood samples for monitoring viral infections were also taken before patients underwent BMT and 30 days after inclusion.

Human herpesvirus 6 antibodies were detected and titered using the anticomplement immunofluorescent assay, as previously described.³ For virus detection in skin, peripheral blood mononuclear cells (PBMCs) and plasma, 3 distinct HHV-6 amplification assays with different primer pairs, and 1 cytomegalovirus amplification assay were used. The quantitative analysis of HHV-6 was done using end point dilution PCR with 5-fold serial dilutions of DNA samples.⁴ Immunohistochemical tests were performed as described previously.⁵

Characteristics, conditioning regimens, and evolution of the exanthema of the 13 patients are shown in **Table 1**. The onset of exanthema occurred 4 to 45 days after patients underwent BMT (median, 24 days). Twelve patients exhibited histological features consisting of a vacuolated basal layer, preneurotic keratinocytes, and lymphohistiocytic infiltration of the upper dermis. The last patient exhibited only mild spongiosis.

The results of the HHV-6 serologic test and PCR in skin, plasma, and PBMCs are shown in **Table 2**. No acute cytomegalovirus, Epstein-Barr virus, or hepatitis A or B infections were detected via serologic monitoring.

In patient 4, the PCR test results were positive for HHV-6 in normal and erythematous skin with a level of 10⁴ to 10⁵ higher in erythematous than in normal skin. In patient 5, the PCR test result was positive only in erythematous skin. In patient 7, PCR results were positive,

Table 1. Clinical Features*

Patient No./Sex/ Age, y	Hematologic Disease	Fever	GVH	Outcome of Exanthema
1/F/44	CML	No	Intestinal	Favorable with C
2/M/27	AML	Yes	No	Stable
3/F/45	Multiple myeloma	No	No	Favorable without C
4/F/42	AML	Yes	No	Favorable with C
5/M/44	Multiple myeloma†	Yes	No	TEN
6/F/43	NHL	No	No	Favorable without C
7/M/28	CML	Yes	Hepatic	Favorable without C
8/F/55	CML†	Yes	No	Favorable with C
9/M/42	AML	No	Intestinal and hepatic	Favorable with C
10/M/57	AML	Yes	No	Favorable with C
11/43/F	AML	No	No	Favorable without C
12/F/22	AML†	No	Intestinal and hepatic	Favorable with C
13/F/46	CML	No	No	Favorable with C

*GVH indicates graft-vs-host disease; CML, chronic myeloid leukemia; C, systemic corticosteroid therapy; AML, acute myeloid leukemia; TEN, toxic epidermal necrolysis; and NHL, non-Hodgkin lymphoma.
†Patient underwent total body irradiation.

Table 2. HHV-6 and CMV Detection in 4 of 13 Patients With Positive PCR Results*

Patient No.	PCR CMV				PCR				Antibody Titer		
	NS	LS	PBMC	P	NS	LS	PBMC	P	Before		
									BMT	D ₀	D ₃₀
4	-	-	-	-	+	+	-	-	10/20	10/20	10
5	-	-	-	-	-	+	-	-	5/10	80	ND
7	-	-	-	-	+	+	+	+	80	80	80
9	+	+	+	-	-	-	-	-	320	160	5

*HHV-6 indicates human herpesvirus 6; CMV, cytomegalovirus; PCR, polymerase chain reaction; NS, normal or nonerythematous skin; LS, lesional or erythematous skin; PBMC; peripheral blood mononuclear cells; P, plasma; BMT, bone marrow transplantation; D₀, day of inclusion; D₃₀, 30 days after inclusion; minus sign, negative; plus sign, positive; and ND, not determined.

with similar levels of HHV-6 DNA in normal and erythematous skin, plasma, and PBMCs (**Table 3**).

Tissue sections from 3 patients with PCR results positive for HHV-6 were also studied immunohistochemically for the presence of HHV-6 antigen. The results of the HHV-6 antigen test were negative.

In 2 of the 13 patients (patient 4 and patient 5), we found the levels of HHV-6 DNA to be either much lower or absent in normal skin compared with erythematous skin. Polymerase chain reaction results were negative for HHV-6 in the PBMCs and plasma in both cases. Therefore, we considered that HHV-6 DNA found in the skin was not the result of blood contamination. In patient 7, HHV-6 DNA was found not only in skin but also in plasma and PBMCs. The HHV-6 sero-

Table 3. HHV-6 Quantification Using PCR With 3 Distinct Primer Sets*

Patient No.	Primers																			
	010				015				023				025				LP1		LP2	
	NS	LS	PBMC	P	NS	LS	PBMC	P	NS	LS	PBMC	P	NS	LS	PBMC	P	NS	LS	PBMC	P
4	-	2	7	-	-	3	7	-	4	-	-	3	6	-	-	-	-	-	-	-
5	-	0	2	-	-	-	2	-	-	-	-	-	2	-	-	-	-	-	-	-
7	-	3	3	-	-	4	3	-	3	-	3	-	3	-	2	-	0	-	-	-

*HHV-6 indicates human herpesvirus 6; PCR, polymerase chain reaction; NS, normal or nonerythematous skin; LS, lesional or erythematous skin; PBMC, peripheral blood mononuclear cells; and P, plasma. The results are the end point DNA dilutions with positive PCR results and are expressed as the exponential of the dilution 5×10^{-x} .

logic test results were discordant, showing the difficulty of interpreting such results in severely immunosuppressed patients.

The results in patients 4 and 5 suggest a role for HHV-6 in exanthema after BMT. However, because only immunohistochemical tests are able to detect viral proteins, we could not formally come to a conclusion, which prompted us to conduct these tests with a more sensitive method. Because graft-vs-host disease, adverse drug reaction, and HHV-6 infection are indistinguishable and share the same pathogenic pathways,⁶ interrelation among these entities has to be explored further.

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Clustered Angiofibromas on the Ear of a Patient With Neurofibromatosis Type 2

Neurofibromatosis type 2 (NF2) is an autosomal dominant disorder associated with bilateral vestibular schwannomas, schwannomas of other central and peripheral nerves, meningiomas, ependymomas, and opacities of the posterior capsular lens.¹ This disorder results from the inactivation of a tumor suppressor gene (*MERLIN*) on chromosome 22q.² Skin abnormalities associated with NF2 but more commonly seen in NF1 (von Recklinghausen disease) include neurofibromas and café au lait spots.

Angiofibromas are firm, dome-shaped, skin-colored or pink-red, small papules (approximately 5 mm); they may be solitary or multiple. Solitary lesions on the dorsal aspect of the distal part of the nose in mature adults are called *fibrous papules*. However, multiple angiofibromas of the face, especially in a malar distribution, are typically associated with the tuberous sclerosis complex (TSC). Genetic linkage analysis has localized the defect in about one half of the cases to chromosome 9q (*TSC1*) and in the other half to chromosome 16q (*TSC2*) without any apparent clinical differences.³ The *TSC1* and *TSC2* genes were recently identified and also seem to function as tumor suppressor genes.^{4,5} Recently, multiple facial angiofibromas were also noted in most patients with multiple endocrine neoplasia type 1 (MEN 1).⁶

We present the first reported case of a patient with NF2 and multiple angiofibromas distributed in a cluster on the external ear.

Report of a Case. A 30-year-old Hispanic man with a history of NF2 presented to our Genetic Skin Clinic, Cooper Health System, Voorhees, NJ, for prenatal genetic counseling related to this diagnosis. The patient's medical history was significant for 2 facial neurofibromas and a right-sided acoustic neuroma (vestibular schwannoma).

His family history was significant for other members with NF2 including the patient's father, 5 paternal uncles, and 3 cousins. His brother had surgery for a tumor of the spine, while his sister was reported to have a café au lait spot as well as a neurofibroma. There was no history of epilepsy or mental retardation.

The results of a physical examination revealed 3 irregularly shaped café au lait spots on the left side of the patient's trunk that were enhanced with an examination using a Wood lamp. No hypopigmented maculae were observed. Two minimally raised, soft, flesh-colored plaques of approximately 1.5 cm were noted on the left side of the abdomen; these were clinically suggestive of neurofibromas. The left antihelix demonstrated a cluster of pink-red, firm papules ranging in size from 2 to 3 mm.

The results of histological examination of the papule from the patient's left ear revealed an increased number of vessels lined by unremarkable endothelium with surrounding fibrosis and plump and stellate fibroblasts consistent with an angiofibroma. Reevaluation of the patient's magnetic resonance imaging scan revealed no intracranial lesions associated with TSC.

Comment. Angiofibromas in a cluster on the external ear were reported in a 28-year-old French woman more than 30 years ago.⁷ No examination for TSC or any other systemic disease was performed. Patients who had overlapping features of different neurocutaneous syndromes have been reported. For example, acoustic neuromas have been found in association with TSC.⁸ Cafe au lait spots and NF1 have also been reported in patients with TSC.⁹ Although these may be coincidental associations, our case demonstrates another example of the phenotypic overlap between these disorders.

While our patient did not have TSC, the angiofibromas of the external ear likely represent another manifestation of his NF2 mutation. An explanation for the occurrence of overlapping features in TSC, MEN1, NF1, and NF2, aside from coincidence, may be that their respective genes function as tumor suppressors in a common pathway. Neurofibromin and tuberin, the products of the *NF1* gene and *TSC2* gene, respectively, have been shown to act in the Ras signal transduction cascade. Ras proteins are a group of homologous guanine triphosphatases involved in regulation of cell proliferation and differentiation.⁴ The NF2 gene protein, MERLIN, appears to play a role in connecting the cytoskeleton to components of the plasma membrane, thereby affecting cell shape, motility, and growth.¹⁰ Recently, 32 patients with MEN1 were found to have several cutaneous symptoms commonly associated with TSC; however, these patients were not tested for systemic symptoms of TSC.⁶ The *MEN1* gene was recently identified and encodes a protein called menin.^{11,12} Although the function of menin has not been verified, the protein localizes to the cell nucleus and is presumed to act as a tumor suppressor.¹³

Our report associates angiofibromas, albeit an unusual distribution (clustered on the ear), with yet another tumor suppressor gene, *NF2*. This case adds further support to the concept of common phenotypic end points that result from shared signaling pathways. Our case also suggests that a workup for NF2 may be war-

ranted for any patient in whom clustered auricular angiofibromas are noted.

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