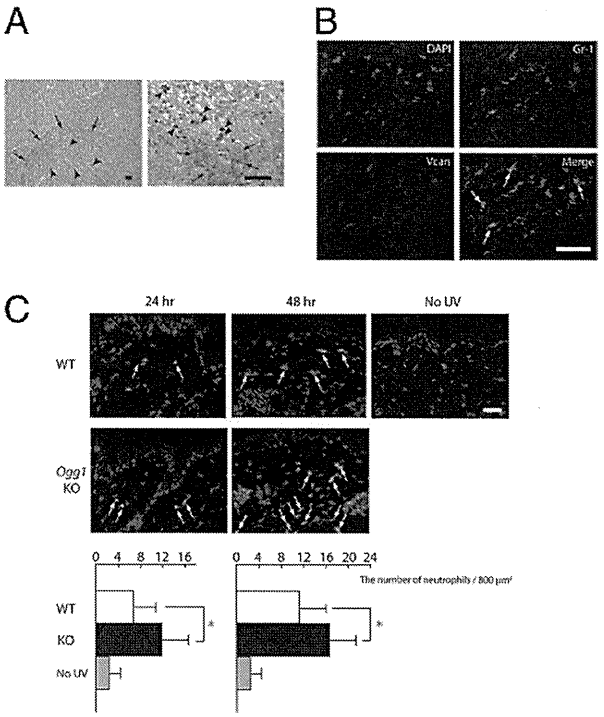

Figure 6. Versican expression and neutrophil localization in human and murine skin tumors. **A:** Versican expression and inflammatory cells in human squamous cell carcinoma. Versican is strongly expressed in the dermal components (**arrows**) and inflammatory cells (**arrowheads**), seen at low magnification (**left**) and high magnification (**right**). Two focused areas are taken from different part of sections. Inflammatory cells, especially segmented leukocytes (neutrophils) (**arrowheads**), were strongly positive for versican. Scale bars = 30 μm. **B:** Versican expression and neutrophils in mouse skin. In the merged iamge, neutrophils with versican expression (**arrows**) appear yellow. Scale bar = 30 μm. **C:** Neutrophil infiltration after UVB irradiation in wild-type and *Ogg1* knockout mice. **Arrows** indicate Gr-1-positive cells (green) in the dermis at 24 and 48 hours after UVB exposure in the wild-type and *Ogg1* knockout mice. Scale bar = 30 μm. The accompanying graphs show the average number of neutrophils per 800 μm^2 at each time point. $^*P < 0.02$.

tumors than their wild-type counterparts.[7] Although several gene profiling studies have addressed the UVB response using primary human keratinocytes[21] or human skin xenografts[22] or the radiation effects using *Ogg1*-deficient human leukemia cell lines,[23] the gene pathways in the *Ogg1*-mediated UVB response remain to be elucidated. We found that the most affected pathway in *Ogg1* knockout mice is the inflammatory response pathway. Although the accumulation of DNA damage does not seem to directly influence the inflammatory response, persistent DNA damage response might allow the damaged cells to compromise the biological state of the surrounding tissue, which then secretes inflammatory cytokines. This altered inflammatory state will create a permissive microenvironment that allows the proliferation and metastasis of tumor cells.[24,25] Rodier et al[26] reported that irreparably large radiation doses induce DNA double-strand breaks and increase IL-6 secretion. We compared *IL-6* levels after 250 mJ/cm^2 of UVB irradiation (approximately 1 minimal erythema dose) between the wild-type and *Ogg1* knockout mice by real-time PCR and found that *Ogg1* knockout mice express significantly higher levels of IL-6 at 3 and 24 hours after UVB exposure than do wild-type mice (see Supplemental Figure S2 at *http://ajp.amjpathol.org*). We also performed RT-PCR for inflammatory *Mmp2* and *Tnf*, but found no significant difference between the two *Ogg1* genotypes (data not shown).

The present data indicate that IL-1β and IL-6 are the most important candidate cytokines to induce inflammatory conditions associated with 8-oxoG accumulation after UVB exposure. However, the exact inflammatory pathway genes that are involved in 8-oxoG-induced skin tumorigenesis still remain to be fully elucidated.

Role of Versican in UVB/8-OxoG-Induced Skin Tumorigenesis in Mice and Humans

Versican is a large chondroitin sulfate proteoglycan.[27] In the skin, versican is expressed not only in the associated elastic fibers in the dermis but also in the epidermis, hair follicles, and sweat glands.[18,28] Versican is also known to be expressed in photoaged skin,[29] which is consistent with our immunohistochemical finding that chronically sun-exposed skin tumors of *Ogg1* knockout mice expressed high levels of versican, thus implying that continuous accumulation of 8-oxoG induced by UV leads to versican overexpression and photoaged skin. Versican has also been reported in a wide variety of cancers.[16,19] Elevated expression of stromal versican predicted increased risk and rate of relapse.[30] Moreover, versican is highly expressed in the metastatic lesions of pharyngeal

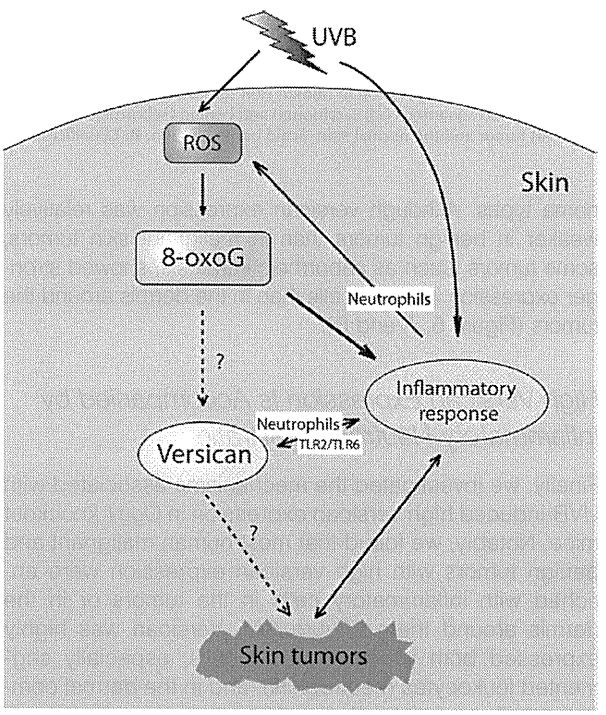

Figure 7. Proposed relationships of versican in the inflammatory response leading to the development of skin tumors in terms of UVB-induced 8-oxoG accumulation. The accumulation of UVB/ROS-induced 8-oxoG in the skin leads to inflammatory reactions. High versican expression is induced by a highly inflammatory microenvironment with high numbers of infiltrated neutrophils; conversely, neutrophil infiltration induces versican overexpression. More ROS will be generated at the inflammatory sites by neutrophils.

squamous cell carcinoma.[31] Our immunohistochemistry studies revealed that versican expression is significantly higher in UVB-exposed *Ogg1* knockout mice than in the wild-type counterparts. Versican overexpression induces skin tumor development, especially malignant tumors in *Ogg1* knockout mice exposed to long-term UVB irradiation. In mouse skin tumors, versican is expressed in not only the dermal stroma but also intracellular components of the epidermis. These observations are in agreement with the results from immunohistochemical studies in the skin at 24 hours after UVB irradiation (Figure 3B). Furthermore, we evaluated human skin tumors related to long-term UV exposure and found that several skin tumors, including malignant melanomas, exhibit high versican expression. These data suggest that human UV-related skin tumors are associated with UV-induced 8-oxoG generation, as well as other DNA damage products previously reported to cause mutation-prone DNA damages by UV,[2] such as cyclobutane pyrimidine dimers and (6-4) photoproducts.

Among the various types of benign and malignant tumors analyzed in the present study, malignant melanomas exhibited a distinct expression pattern for versican. Of the four malignant melanoma types analyzed (ie, lentigo maligna melanoma, superficial spreading melanoma, acral lentiginous melanoma, and nodular melanoma), lentigo maligna melanoma, which is thought to be strongly associated with chronic UV exposure, showed the strongest versican expression. These results indicate that these four subtypes of malignant melanoma have different pathogenesis in terms of UV induction and 8-oxoG accumulation. Versican was significantly and strongly expressed in basal cell carcinoma, another UV-related skin tumor, especially in the stromal components surrounding the tumors. Although strong versican expression in basal cell carcinoma could be attributed to 8-oxoG accumulation after long-term UV exposure, we consider the possibility that development of basal cell carcinoma is associated with versican up-regulation through epithelial and mesenchymal interactions that occur during hair follicle development. In fact, basal cell carcinoma is a hair follicle-oriented tumor, and the versican promoter is activated during hair follicle development.[32]

Interaction between 8-OxoG and Versican in the Development of Skin Tumors

Gene profiling of UVB-irradiated *Ogg1* knockout mouse skin showed that 8-oxoG accumulation in the skin leads to high inflammatory responses. Furthermore, the highly inflammatory state in *Ogg1* knockout mice is accompanied by neutrophil infiltration. Neutrophil infiltration might increase the susceptibility of the epidermal and dermal microenvironment to the development of versican-positive skin cancers, which might be one of the mechanisms for high 8-oxoG accumulation leading to high versican expression in skin tumors (Figure 6). These data are consistent with a previous report showing that a chondroitin sulfate proteoglycan such as versican has a specific receptor for platelet factor 4 (PL-4), a member of the α-chemokine subfamily of cytokines on human neutrophils[33] (Table 2). Versican carries many strong negatively charged glycosaminoglycans. One of the main glycosaminoglycans, chondroitin sulfate, establishes the interaction between versican and various cytokines and chemokines,[34] modulating their function.[10] The interaction of L- and P-selectins and the CD44-expressing leukocytes, fibroblasts, and epithelial cells with versican also suggests a role of versican in leukocyte infiltration into the ECM.[35] In addition, P-selectin glycoprotein ligand-1 (PSGL-1), a glycoprotein expressed on the cell surface of neutrophils, binds to the G3 domain of the extracellular proteoglycan versican and mediates leukocyte aggregation, which might be another implication of association between versican and neutrophils.[36,37]

In the present study, the levels of IL-6, a key cytokine triggered by persistent DNA damage,[26] were significantly up-regulated in *Ogg1* knockout mouse skin at both 3 and 24 hours after UVB exposure (see Supplemental Figure S2 at *http://ajp.amjpathol.org*). Previously, we showed that *Cxcl1/KC*, a chemoreactant gene, is associated with neutrophils during skin inflammation and is more up-regulated when UVB is irradiated.[38] In the present study, we found no differences in *Cxcl1/KC* expression in the skin of UVB-exposed wild-type and *Ogg1* knockout mice, as determined by real-time PCR (data not shown). Recently, it was reported that versican functions as a macrophage activator via the Toll-like receptor family members TLR2 and TLR6, leading to a more inflammatory microenvironment in which cancer cells can be easily grown.[25,39] Kim et al[25] reported the up-regulation of *Il1b* in metastatic Lewis lung carcinoma and showed that versican functions as a macrophage activator. Our present data indicate that IL-1β and IL-6 are the most important candidate cytokines in inducing inflammation associated with 8-oxoG accumulation after UVB exposure. Versican and the inflammatory response might be reciprocally up-regulated in the skin after UVB exposure. A highly inflammatory microenvironment that is rich in neutrophils will produce more ROS by positive feedback[40] (Figure 7). Although our present data clearly suggest that high versican expression colocalizes with neutrophil infiltrated in UVB-exposed *Ogg1* knockout mice skin, the exact cytokine profile associated with those interactions, and whether the accumulation of 8-oxoG up-regulates versican directly after UVB exposure, remain to be elucidated.

In conclusion, the accumulation of UVB/ROS-induced 8-oxoG in the skin leads to inflammatory reactions. A highly inflammatory microenvironment characterized by neutrophil infiltration up-regulates versican expression. Versican overexpression contributes to more aggravated skin inflammation, ultimately leading to the development of skin tumors. The present study provides new clues for understanding the mechanism underlying ROS-induced skin tumorigenesis after UV irradiation.

Acknowledgment

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An Erythematous Plaque With Overlying Alopecia on the Scalp of a Child

Mohammad Kazem Fallahzadeh, MD; Fatemeh Sari-Aslani, MD; Reza Khelat, MD; Mohammad Reza Namazi, MD; Shiraz Skin Research Center, Shiraz, Iran

REPORT OF A CASE

A 4-year-old boy presented with a slightly pruritic, erythematous, ill-defined, 3×3-cm plaque on his scalp associated with overlying alopecia developing 4 months before presentation (**Figure 1**). Findings from physical examination were otherwise unremarkable. Potassium hydroxide smear for dermatophytes was negative. A punch biopsy was obtained from the lesion and submitted for dermatopathologic study (**Figure 2** and **Figure 3**).

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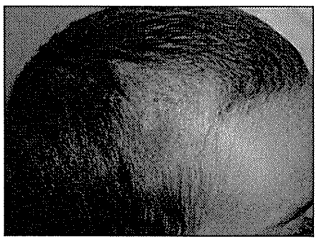

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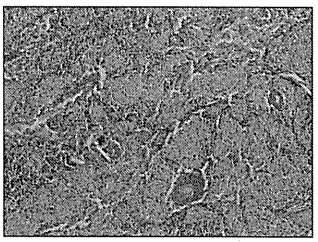

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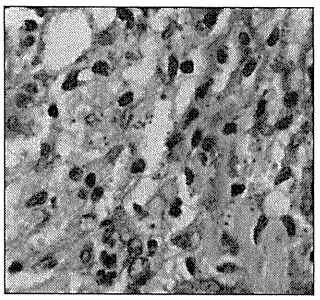

Figure 3.

Grayish Brown Macules on the Axillae, Lower Abdomen, and Groin

Hiroshi Nagai, MD, PhD; Masanobu Sakaguchi, MD; Tetsuya Ikeda, MD; Chikako Nishigori, MD, PhD; Kobe University Graduate School of Medicine, Kobe, Japan

REPORT OF A CASE

A 58-year-old man presented with a 1-month history of slightly pruritic, grayish brown macular lesions symmetrically located on his axillae, lower abdomen, and groin (**Figure 1** and **Figure 2**). He had neither taken medicines nor applied any cosmetics to his body. On physical examination, the lesions were found to comprise mainly grayish brown macules or papules along with a few violet-gray plaques. The lower abdomen lesion was broadly located at the intertriginous zone, created by the waistband of his clothing. His mucous membranes, nails, palms, and soles were not affected. A skin biopsy specimen was obtained from the violet-gray plaques on the right lower abdomen, and hematoxylin-eosin staining was performed (**Figure 3**).

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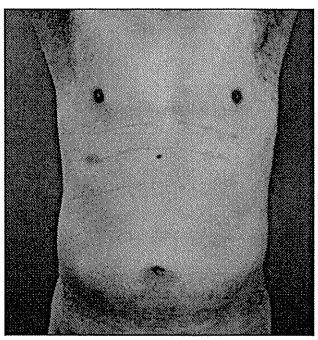

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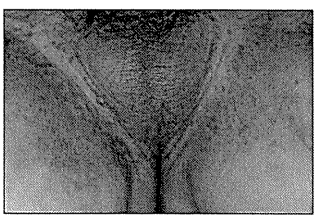

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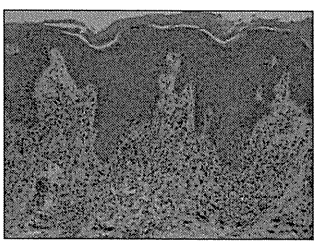

Figure 3.

Long-term Progression Facial Plaque

Alicia Lapresta, MD; Ana Isabel Sánchez Moya, MD; Rebeca de Miguel, MD, PhD; Rocío Juárez, MD; Domingo García-Almagro, MD, PhD; Virgen de la Salud Hospital, Toledo, Spain

REPORT OF A CASE

A 37-year-old woman from Morocco presented with a 10-year history of pruritic facial plaques. The lesions appeared gradually and grew progressively with no previous trauma or scar. The patient did not report a family history of similar lesions. Physical examination showed a 13-mm erythematous annular plaque on the upper lip, with a well-demarcated raised keratotic border and central atrophy (**Figure 1**). In addition, we observed another 2 small but similar lesions at the right nasal ala (**Figure 2**). A complete skin examination failed to reveal additional lesions elsewhere. A punch biopsy specimen from the margin of an upper lip lesion was examined microscopically (**Figure 3**).

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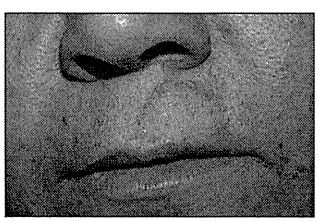

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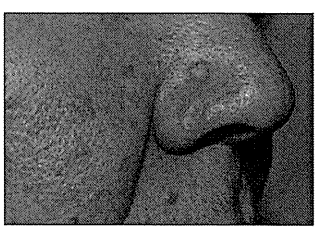

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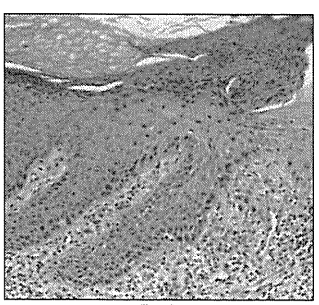


Figure 3.

Pruritic Urticarial Skin Lesions

Paula Davila Seijo, MD; Aranzazu García-Cruz, MD; Ignacio García-Doval, PhD; Complexo Hospitalario de Pontevedra, Pontevedra, Spain (Drs Seijo and García-Doval), and Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Spain (Dr Cruz)

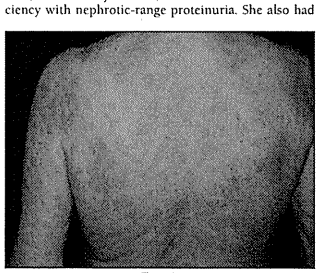
REPORT OF A CASE

A 65-year-old woman presented with mildly pruritic urticarial skin lesions that did not respond to treatment with antihistamines. Her medical history revealed that she had had chronic urticaria since 2001; restrictive myocardiopathy, probably due to a nonconfirmed deposit disease, such as amyloidosis; and chronic renal insufficiency with nephrotic-range proteinuria. She also had self-limited febrile episodes with temperatures up to 39°C, which occurred during the urticarial rash events.

Physical examination revealed numerous confluent wheals on the trunk (**Figure 1**) and the proximal aspect of the limbs, sparing the head, palms, and soles. The lesions disappeared within 24 to 48 hours, without sequelae. Hepatomegaly and axillary lymph nodes were present. A biopsy specimen was obtained from a lesion on the left thigh (**Figure 2** and **Figure 3**).

Laboratory investigations showed leukocytosis with neutrophilia, microcytic anemia, an elevated erythocyte sedimentation rate, and elevated C-reactive protein levels. Immunoelectrophoresis provided evidence of a monoclonal gammopathy-type IgM-κ. Urinary Bence-Jones protein was absent. Computed tomography revealed bone sclerosis in some vertebral bodies as well as axillary and inguinal lymphadenopathy.

What is your diagnosis?



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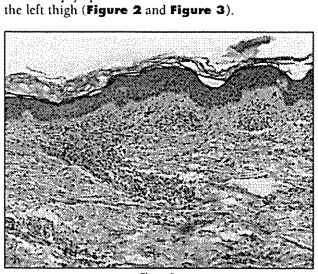

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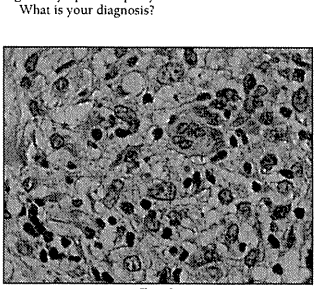


Figure 3.

Tender Ulceronecrotic Nodules in a Patient With Leukemia

Sarah N. Gee, MD; Brian Rothschild, MD; James Click, MD; Vaneeta Sheth, MD; Arturo Saavedra, MD, PhD, MBA; Mei-Yu Hsu, MD, PhD; Brigham and Women's Hospital, Boston (Drs Gee, Rothschild, Click, Sheth, Saavedra, and Hsu), and Caris-Cohen Dermatopathology, Newton (Dr Hsu), Massachusetts

REPORT OF A CASE

A 64-year-old woman with chronic lymphocytic leukemia presented with a 2-week history of burning and painful nodules on her legs, abdomen, and arms. Her eruption started 4 days after she began taking the clinical trial drug navitoclax, a targeted small-molecule antagonist of the antiapoptotic lymphocytic protein Bcl-2. Otherwise, she felt well and denied recent travel.

Physical examination revealed numerous tender, erythematous to ulceronecrotic, 1- to 3-cm nodules onher arms, abdomen, and thighs (**Figure 1**). The early lesions were slightly erythematous indurated plaques. The later lesions were necrotic and purulent nodules.

Six biopsy specimens were obtained from the necrotic lesions, 3 for histologic examination and 3 for culture. Histologic examination showed suppurative inflammation with tissue necrosis, with no organisms identified on special stains. All tissue cultures were negative for organisms. Based on this information, a 3-week regimen of empirical coverage for atypical mycobacteria with doxycycline hydrochloride, ciprofloxacin, and clarithromycin was initiated. The therapy was discontinued when the patient showed no improvement. Subsequently, oral prednisone therapy (60 mg/d) for a presumed neutrophilic dermatosis was initiated; however, it was discontinued 3 days later because of clinical deterioration. Another biopsy was performed on a new early lesion on the right side of the patient's back (**Figure 2** and **Figure 3**).

What is your diagnosis?

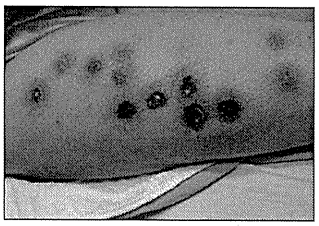
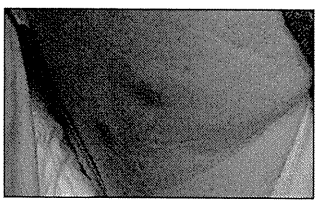


Figure 1.



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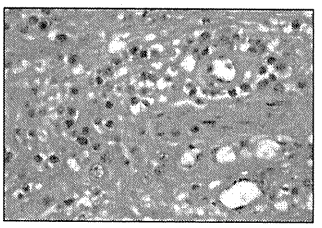


Figure 3.

Double-Headed Nodules on the Abdomen

Makoto Kunisada, MD, PhD; Hiroshi Nagai, MD, PhD; Hidehi Shimizu, MD; Flandiana Yogianti, MD; Satoshi Nishiyama, MD; Chikako Nishigori, MD, PhD; Kobe University Graduate School of Medicine, Kobe, Japan

REPORT OF A CASE

A 69-year-old man presented with an 8-month history of nodules growing on his abdomen. The nodules were tender, but otherwise he was healthy. Physical examination revealed 50×45-mm and 35×30-mm hard polypoidal nodules that occurred as an irregularly shaped single hard brown plaque on his abdomen (**Figure 1**).

A skin biopsy was performed, and the specimen was analyzed under hematoxylin-eosin staining (**Figure 2**). A genetic study was also carried out (**Figure 3**).

What is your diagnosis?

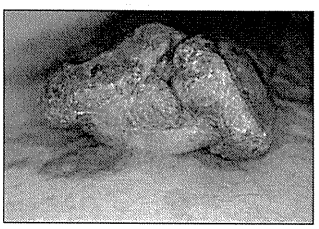


Figure 1.

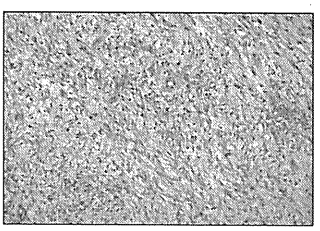


Figure 2.

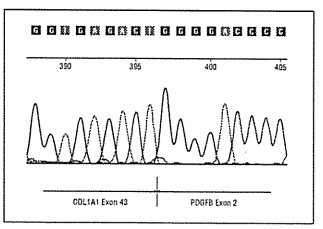


Figure 3.

Widespread Papules and Indurated Plaques on a 43-Year-Old Man

Joaquín Sola-Ortigosa, MD; Montserrat Salleras-Redonnet, MD; Pablo Umbert-Millet, MD; Hospital Universitari Sagrat Cor, Barcelona, Spain

REPORT OF A CASE

A 43-year-old man presented with a history of hoarseness of voice since he was 3 years of age and a progressive development of asymptomatic, multiple pebbly and infiltrated warty skin lesions over his hands (**Figure 1**), feet, elbows, eyelids, and gluteal region. His face revealed poxlike and acneiform scars on the cheeks, giving him a wrinkled appearance. Pearly beaded papules were present on the upper and lower eyelids. The lowerlabial mucosa showed a yellowish papillary growth. The tongue was woody, with small white papules and fissures (**Figure 2**). The frenulum was thickened, causing an inability to protrude the tongue. The patient remembered a stage with vesicles and erosions with scarring when he was 10 years old. Laryngeal examination revealed nodular thickening of vocal cords. Results from complete laboratory tests were within reference range. Some histologic changes are shown in **Figure 3**.

What is your diagnosis?

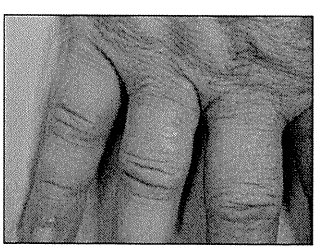


Figure 1.

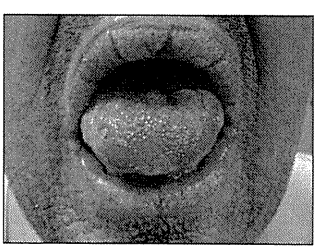


Figure 2.

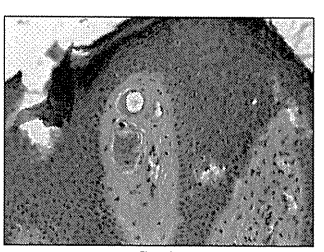


Figure 3.

Perifollicular Papules and Hyperkeratotic Plaques on the Back in a Blaschkoid Distribution

Larissa Stewart, BS; Anthony Nuara, MD, PhD; Dipti Anand, MD; Kevin Kia, MD; Clay J. Cockerell, MD; University of Texas Southwestern School of Medicine (Drs Nuara and Kia) and Dermpath Diagnostics (Drs Anand and Cockerell), Dallas. Ms Stewart is a visiting medical student, University of Texas Southwestern School of Medicine, from Baylor College of Medicine, Houston, Texas

REPORT OF A CASE

A 28-year-old African American man presented with a history of asymptomatic scaly areas on his back. He stated that the lesions started in his axilla and slowly expanded toward his back over the past 6 months. His medical history was remarkable only for urticaria controlled with daily use of cetirizine hydrochloride. Physical examination revealed perifollicular hyperkeratotic papules coalescing into well-demarcated plaques with fine scale and a slightly raised erythematous border in a blaschkoid distribution from his right axilla to his upper back (**Figure 1**). A biopsy specimen was obtained from his right posterior shoulder (**Figure 2** and **Figure 3**).

What is your diagnosis?

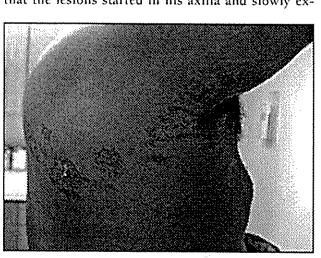
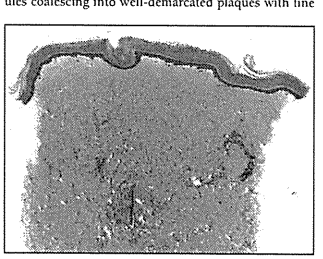


Figure 1.



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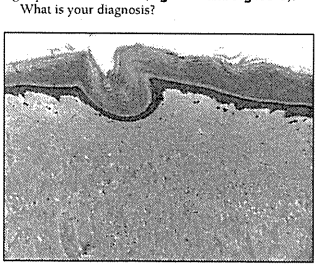

Figure 3.