Generalized Atrophic Benign Epidermolysis Bullosa in 2 Siblings Complicated by Multiple Squamous Cell Carcinomas

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Background: Generalized atrophic benign epidermolysis bullosa is a form of junctional epidermolysis bullosa characterized by skin fragility; atrophic alopecia; sparse eyebrows, eyelashes, and axillary and pubic hair; dystrophic fingernails and toenails; and enamel defects in decidual and permanent teeth. Substantial progress was recently made elucidating the genetic defects underlying this disorder. In affected persons, pathogenetic mutations were identified in the genes encoding the β3 chain of laminin 5 (LAMB3) or the 180-kd bullous pemphigoid antigen (BPAG2/COL17A1).

Observations: Two brothers, aged 39 and 32 years, had characteristic clinical features of generalized atrophic benign epidermolysis bullosa. By electron microscopy, dermoepidermal separation was seen at the level of the lamina lucida, establishing a diagnosis of junctional epidermolysis bullosa. Lesional and clinically unaffected skin showed basal keratinocytes with hypoplastic hemidesmosomes, possibly indicating a defect of hemidesmosomal or associated proteins. Both patients presented with multiple fungating tumors on atrophic and scarred skin on their lower legs; 2 tumors in the older sibling and 4 tumors in the younger sibling were diagnosed as well-differentiated squamous cell carcinomas. Tumor staging elicited no evidence of regional lymph node involvement or systemic disease. Treatment was by microscopically controlled surgery. All wounds were allowed to heal by secondary intention. In both patients, wound healing was markedly delayed and characterized by the formation of abundant granulation tissue and poor re-epithelialization.

Conclusions: In the absence of other apparent risk factors for the development of squamous cell carcinomas, chronic wounding resulting from recurrent skin blistering probably provided an important prerequisite for tumor promotion in these patients. The 2 cases presented herein provide evidence that the development of malignant skin tumors in patients with epidermolysis bullosa is not confined to the dystrophic forms but also may occur in some variants of junctional epidermolysis bullosa, such as generalized atrophic benign epidermolysis bullosa.

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MATERIALS AND METHODS

SPECIMENS

Two 4-mm punch biopsy specimens were obtained from each patient for diagnostic electron microscopy. One specimen was from a natural blister, the other from nonlesional rubbed skin. Biopsy specimens were taken of all skin lesions suspected of being SCC and the specimens studied by histopathologic methods. Biopsy specimens were obtained of 2 tumors in patient 1 and 4 tumors in patient 2.

TRANSMISSION ELECTRON MICROSCOPY

Specimens were processed for electron microscopy in a standard manner. They were fixed for 4 hours at 4°C in half-strength Karnovsky fixative. Specimens were postfixed in 1.3% osmium tetroxide in distilled water for 2 hours at 4°C. After dehydration in a graded ethanol series, specimens were embedded in epoxy resin (Taab 812, Agar Scientific Ltd, Stansted, Essex, England) via propylene oxide. Semithin sections (0.5 μm) were stained with the Richardson stain. Ultrathin sections were double-stained with 5% uranyl acetate in ethanol and lead citrate. Sections were viewed with an electron microscope (model EM901, Carl Zeiss, Oberkochen, Germany).

The expression of 180-kd bullous pemphigoid antigen (BPAG2/COL17A1) has been shown to be markedly reduced in skin from some patients with GABEB. Similarly, laminin 5 expression has been reported to be reduced in other persons affected with GABEB. McGrath et al studied several families with GABEB and identified distinct genetic defects underlying this condition. Affected persons carried mutations in the genes encoding either the β3 chain of laminin 5 or the 180-kd bullous pemphigoid antigen (BPAG2/COL17A1). Further mutations have been identified in the bullous pemphigoid antigen 2 gene in 5 Austrian families with GABEB.

Herein we report the cases of 2 siblings with characteristic clinical signs of GABEB. At age 39 (patient 1) and 32 years (patient 2), both patients presented with multiple fungating tumors on atrophic and scarred skin of their lower legs. By histopathologic examination, tumors were identified as well-differentiated squamous cell carcinoma (SCC).

REPORT OF PATIENTS

PATIENT 1

This 39-year-old man (Figure 1: II/5) first developed skin blisters in the umbilical area 3 days after birth. Blisters and erosions subsequently developed at various skin sites, including oral and nasal mucosa. Blisters seemed to follow mechanical trauma and preferably occurred on the patient's arms and legs. Wound healing was slow and resulted in patches of atrophic skin. His scalp hair, eye-brows, and eyelashes first grew normally, but later the eyebrows and eyelashes almost completely disappeared. Dentition occurred in time, but decidual and permanent teeth showed pronounced enamel pitting indicative of amelogenesis imperfecta. Fingernails and toenails were present at birth and then became dystrophic; by age 4 years, he had lost almost all his nail plates. At 9 years of age, the patient had postinfectious glomerulonephritis, probably resulting from recurrent episodes of impetigo. Apart from this, he developed normally. Puberty was on time and inconspicuous except for a lack of axillary and pubic hair. The patient is a trained tool-maker. He is married and has 2 sons and 1 daughter (Figure 1) aged 11, 9, and 7 years, respectively, none of whom are affected.

On clinical examination, the patient shows discrete spotty alopecia and sparse eyelashes. His eyebrows and pubic and axillary hair are lacking, and his fingernails and toenails are missing. Skin lesions are widespread, predominantly affecting the extensor aspects of the extremities. Lesional skin shows erythematous and violaceous atrophic patches next to erosions and hemorrhagic crusts. In places, intact vesicles are seen (Figure 2). The patient's face and neck, palms and soles, and oral mucosa seem uninvolved. Exophytic tumors are present on his right calf (−6×5 cm) and on his left shin (−10×9 cm).

PATIENT 2

The 32-year-old brother of patient 1 (Figure 1, II/4) developed severe generalized skin blistering 2 days after birth. Ever since, recurrent skin blistering and mucosal erosions have occurred. When the patient started to walk, blistering occurred on the skin of his arms and legs. Atrophy and scarring were seen after repeated skin wounding. Impetiginization occurred frequently and led to delayed wound healing and pronounced scarring. His hair growth was normal, but blisters and erosions occurring on the scalp led to patches of atrophic alopecia. The involvement of facial skin resulted in a permanent loss of eyebrows and eyelashes. His fingernails and toenails seemed intact at birth, but later became dystrophic. Dentition was normal except for the retention of teeth numbers 38, 47, and 48, which had to be removed surgically. Decidual and permanent teeth showed marked enamel pitting. Mucosal erosions caused severe problems in infancy, but occurred less frequently with age. Many of his permanent teeth were removed because of extensive caries. He is trained in retail sales but currently is unemployed. He is unmarried and has no children.

On clinical examination, the patient's skin lesions are essentially similar to those seen in patient 1, but this patient is more severely affected. He shows severe atrophic alopecia, and his eyebrows and eyelashes are sparse. His facial skin is atrophic and in places covered by numerous milia. Axillary and pubic hair are lacking, and nail plates are missing. Skin lesions are widespread, predominantly affecting his arms and legs. Atrophic scarring is particularly prominent on the legs. Four tumors are noted on his lower legs: 2 are located above the inner ankle (Figure 3), and another is present on
were diagnosed as well-differentiated SCC (Figure 1). The preoperative diagnoses were confirmed histopathologically after the complete removal of all tumors. The differential diagnoses included pseudoepitheliomatous hyperplasia, keratoacanthoma, especially keratoacanthoma marginatum centrifugum, and verrucous carcinoma. In junctional EB, dermoepidermal separation occurs at the level of the lamina lucida (Figure 4), indicative of junctional EB. An intact lamina densa and normal anchoring fibrils were seen at the bottom of the blister. The blister roof contained intact basal cells. Hemidesmosomes of blistered and intact patient skin were conspicuous, showing abnormal variations in size and shape (Figure 3). The hemidesmosomes were hypoplastic and reduced in number. The association between hemidesmosomes and keratin filament bundles seemed reduced. Ultrastructural changes were essentially similar in both patients.

HISTOPATHOLOGIC EXAMINATION OF SKIN TUMORS

Two skin tumors in patient 1 and 4 tumors in patient 2 were diagnosed as well-differentiated SCC (Figure 5, Table 1). The preoperative diagnoses were confirmed histopathologically after the complete removal of all tumors. The differential diagnoses included pseudoepitheliomatous hyperplasia, keratoacanthoma, especially keratoacanthoma marginatum centrifugum, and verrucous carcinoma.

STAGING

Tumor staging included chest radiography, abdominal ultrasonography, computed tomography of the chest and abdomen, and needle-aspiration cytologic examination of suspicious inguinal lymph nodes. There was no evidence of tumor spread. Furthermore, magnetic resonance tomography of the lower legs showed no involvement of skeletal muscles or bones by SCC.

THERAPY AND COURSE

In the absence of regional lymph node involvement and systemic tumor spread, we decided to treat all tumors surgically. Two SCCs in patient 1 and 4 SCCs in patient 2 were removed using microscopically controlled surgery. Because of the location, tumor size, and skin fragility, we refrained from primary wound closure or surgical reconstruction. All wounds were allowed to heal by secondary intention. Granulation tissue formed swiftly (Figure 3, right), but re-epithelialization was poor and resulted in markedly delayed wound healing.

COMMENT

Epidermolysis bullosa is a heterogeneous group of genetically determined blistering skin diseases. According to the level of split formation in the skin, 3 major types of EB are distinguished: simplex, junctional, and dystrophic. In junctional EB, dermoepidermal separation occurs at the level of the lamina lucida. On clinical grounds, 6 types of junctional EB are recognized. Substantial progress has recently been made in identifying the genetic defects underlying the generalized forms of junctional EB, i.e., the Hérlich form and GABEB. The genetic defects identified in patients with GABEB to date include mutations in the gene encoding the β3 chain of laminin 5 (LAMB3) and mutations in the gene encoding the 180-kd bullous pemphigoid antigen (BPAG2/COL17A1).

We describe 2 siblings with the characteristic clinical appearance of GABEB. Electron microscopy of lesional and nonlesional rubbed skin revealed split formation at the level of the lamina lucida (Figure 4, top), confirming the diagnosis of junctional EB. Hemidesmosomes in clinically unaffected skin were markedly hypoplastic and apparently reduced in number (Figure 4, bottom). Both siblings presented with multiple fungating SCCs on their lower legs. Staging investigations gave no indication of regional lymph node involvement or systemic tumor spread. All tumors were removed by radical excision.

To our knowledge, only 2 other cases of junctional EB with concomitant malignant skin tumors have been reported. Pellicano et al described a 43-year-old man with junctional EB in whom 3 keratoacanthomas developed in lesional skin. These tumors were first treated with etretinate and later excised. Parker et al described a 45-year-old Cypriot man with junctional EB in whom 2 SCCs developed. One occurred in previously uninvolved skin on the back of his hand, and the other grew on scarred lesional skin of his lower leg. In addition, the patient had transitional cell carcinoma of the urinary bladder. (In retrospect, it is apparent that this patient had been described previously by Monk and Pembroke as a case of pretribial epidermolysis bullosa.) The occurrence of bladder carcinoma in this patient is noteworthy because the involvement of transitional cell epithelium of the urinary tract is known to occur in patients with junctional EB, and bullae formation and erosions of bladder epithelium have been reported.

In contrast to the patient described by Parker et al, in whom only 1 of the SCCs developed in lesional skin, all tumors occurring in our patients grew in atrophic or scarred lesional skin.

Because neither of our patients had any of the well-established risk factors for the development of SCC, it seemed probable that chronic skin wounding precipitated...
by the genetically determined skin fragility provided the single most important factor for skin carcinogenesis.

Although not understood pathogenetically, the occurrence of carcinomas in chronic wounds and scars is a well-known complication that was mentioned as early as 1828 by the French surgeon Marjolin. Since then, SCC had been observed in various long-standing skin disorders such as chronic osteomyelitis, burn scars, lupus vulgaris, discoid lupus erythematosus, necrobiosis lipoidica, and chronic radiodermatitis. In dystrophic EB, especially in severe generalized dystrophic EB of Hallopeau-Siemens, the development of malignant tumors is a well-known complication. Almost all tumors occurring in this condition are SCCs that most often appear on the extremities and mucous membranes of the mouth, the tongue, and the upper gastrointestinal tract. Most SCCs complicating dystrophic EB show a propensity for metastatic spread and tumor progression, and their
existence carries a grave prognosis.34-45 Mutant p53 protein expression has been observed in a number of poorly differentiated SCCs, suggesting a correlation between p53 mutations and tumor behavior.46 In contrast to dystrophic EB, only 2 cases of junctional EB complicated by malignant skin tumors have been reported to date.35-36 Among patients with generalized junctional EB, only those with the mitis or benign variant survive long enough to allow possible SCCs to develop.

The cases presented here provide further evidence, however, that the development of malignant skin tumors as a complication of EB is not confined to the dystrophic forms but can occur in junctional forms such as GABEB. Whether SCCs occurring in junctional EB carry the same grave prognosis is as yet unclear. With this report, we hope to encourage the early diagnosis and treatment of malignant tumors in these patients.

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REFERENCES