Absence of serum autoantibodies to desmoglein 1 and 3 in Hailey-Hailey disease (familial benign pemphigus)

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Summary

Hailey-Hailey disease is caused by germline mutations in the ATP2C1 gene. This gene encodes an adenosine triphosphate-powered calcium and manganese channel pump. Mutations in ATP2C1 affect Ca2+ signalling in keratinocytes determining abnormalities of desmosomal proteins which are in turn responsible of the epidermal defects observed in the skin lesions. Recently, anti-desmoglein antibodies were observed in a patient with Hailey-Hailey disease and there are no other data on the presence of autoantibodies against desmogleins in Hailey-Hailey disease. The purpose of the present study was to determine the presence of circulating autoantibodies against desmogleins in patients with this disorder. The study comprised 6 patients with Hailey-Hailey disease. The diagnosis was made on the basis of clinical, histologic and immunopathologic criteria. We performed skin biopsies and collected serum from these subjects. Hematoxylin-eosin stain and direct immunofluorescence were performed in each case. For the detection of autoantibodies by ELISA we used the recombinant proteins expressing overlapping sequences with the entire extracellular DSG1 and DSG3 domains. In all patients a DSG1/DSG3 double negative profile of autoantibodies was observed indicating that an epitope spreading-like mechanism is probably not operative in Hailey-Hailey disease.

KEY WORDS: Hailey-Hailey disease; autoantibodies; desmogleins; ELISA.

Introduction

Cadherins are a family of Ca2+-dependent cell adhesion molecules. Abnormal expression of cadherins caused by altered Ca2+ concentration is suggested to be involved in mechanisms of acantholysis of both inherited blistering disease and acquired autoimmune acantholytic dermatoses (1). Pemphigus vulgaris and pemphigus foliaceus are known to be caused by binding of autoantibodies to the desmosomal cadherins, desmoglein 1 (DSG1) and desmoglein 3 (DSG3), whereas the inherited blistering disease, Hailey-Hailey disease (also known as familial benign pemphigus) is caused by germline mutations in the ATP2C1 gene (2). This gene encodes an adenosine triphosphate-powered calcium and manganese channel pump. Mutations in ATP2C1 affect Ca2+ signalling in keratinocytes determining abnormalities of desmosomal proteins which are in turn responsible of the epidermal defects observed in the skin lesions (3). Hailey-Hailey disease usually becomes manifest in the third or fourth decade, although it can occur at any age. The disorder is characterized by recurrent erythema, vesicles, and crusted erosions in the fold areas exposed to friction, particularly the groin and axillary regions. Lesions are aggravated by external factors, notably sweating and cutaneous infections. Burning and itching may also be associated (4).

In Hailey-Hailey disease, intracellular Ca2+ concentration is dysregulated by mutation in the Ca2+ pump which is responsible of alterations in cadherin expression and function. Alteration of these proteins induce loss of the normal epithelial cell-to-cell adhesion (3). It is hypothesizable that acantholysis may determine the release of sequestered antigens to the systemic immune determining the induction of autoantibodies which in turn may aggravate the adhesion defect. There are no data on the presence of autoantibodies against desmosomal cadherins in Hailey-Hailey disease. The purpose of the present study was to determine the presence of circulating autoantibodies against DSG1 and DSG3 in patients with this disorder.

Material and methods

The study comprised 6 patients with Hailey-Hailey disease. The diagnosis was made on the basis of clinical, histologic and immunopathologic criteria. We performed skin biopsies and collected serum from these subjects. Hematoxylin-eosin stain and direct immunofluorescence were performed in each case. For the
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detection of autoantibodies by ELISA we used the recombinant proteins expressing overlapping sequences with the entire extracellular DSG1 and DSG3 domains. These antigens have been provided (Medical & Biological Laboratories, Nagoya, Japan) as fusion proteins produced by baculovirus in “High Five insect cell line”. Positive controls for DSG1 and DSG3 were a diluted standard pemphigus foliaceus and pemphigus vulgaris serum, respectively. Negative control was diluted standard serum obtained from normal individuals.

Results and Discussion

All the 6 patients with Hailey-Hailey disease showed a double negative DSG3/DSG1- phenotype indicating lack of circulating autoantibodies against these desmosomal cadherins. Recently, IgG accumulation has been detected between the cells of the multi-layered epithelium in 17 of 19 biopsies from patients with Hailey-Hailey disease (5). Furthermore, this condition can be responsive to treatment with immunsuppressive drugs (6). Recently, antidesmoglein antibodies were observed in a patient with Hailey-Hailey disease (7). Taken together, these data may suggest that Hailey-Hailey disease could be exacerbate by an autoimmune response. On the other hand, the presence of anti-desmoglein antibodies in a patient with Hailey-Hailey disease (7) is not necessarily associated with a clinically relevant autoimmune process since positive anti DSG1 and DSG3 antibodies can be also detected in unaffected relatives of pemphigus patients and, more rarely, also in the general population (8).

In conclusion, we analysed the presence of autoantibodies against the desmosomal cadherins DSG1 and DSG3 possibly determined by the exposure of desmosomal antigens. In all patients a DSG1/DSG3 double negative profile of autoantibodies was observed indicating that an epitope spreading-like mechanism is probably not operative in Hailey-Hailey disease.

References

Self-involution of a nasal giant keratoacanthoma in a young female patient

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Summary

Keratoacanthomas are epithelial skin tumors with a characteristic rapid growth within a few weeks. We present the case of a 32-year-old female patient who developed six months postpartum fast-growing coalescing erythematos to yellowish nodules on her nose. Several repeatedly performed skin biopsies showed characteristics of a keratoacanthoma-like squamous cell carcinoma. Because of the extraordinary clinical appearance, the young age of the patient and the rapid growth, skin biopsies were evaluated by histopathologists from several different histopathological reference centers. Based on clinical behavior and histopathological findings our final diagnosis was that of a giant keratoacanthoma. The patient refused any surgical treatment or radiotherapy, despite further growth of the lesion. After three months of continuous growth the lesion started to involute spontaneously and resolved almost completely. Taken together, the present case underscores the importance of a clinical-histopathological correlation before invasive therapeutic measures as used in squamous cell carcinoma are initiated. We emphasize that surgical intervention is also the treatment of choice for giant keratoacanthomas. The subsequent active surveillance strategy with almost completed clearing of the lesion may add to the ongoing discussion on the treatment of giant keratoacanthomas in centro-facial localizations, in particular when the patient refuses surgery. However, careful follow-up examinations are mandatory.

KEY WORDS: giant keratoacanthoma; self-involution; keratoacanthoma; epithelial skin tumor.

Introduction

Keratoacanthomas are epithelial skin tumors with a characteristic rapid growth within a few weeks (1-3). Giant keratoacanthomas are a rare variant of keratoacanthomas with a size exceeding 2 cm (4, 5). Like other forms of keratoacanthomas, they are fast growing and have a tendency to spontaneously regress, however can cause significant anatomic damage. Giant keratoacanthomas are mostly treated by surgery or by a combination of surgery and radiotherapy. Even deeply infiltrative giant keratoacanthomas may have the potential for spontaneous involution. The present case may add to the ongoing discussion on the treatment strategy of larger keratoacanthomas in difficult facial localizations.

Case report

Six months postpartum a 32-year-old breastfeeding female developed progressively growing erythematous to yellowish nodules on her nose (Figure 1 a). With the initial diagnosis of a carbuncle the patient was admitted to our department for intravenous antibiotic treatment. After increasing erythema and further expansion, systemic treatment was changed to doxycycline and a short course methylprednisolone, under the assumption of a localized rosacea fulminans. Treatment with oral retinoids was refused by the patient. A punch biopsy revealed a huge proliferation of epithelial strands with massive keratinization accompanied by a dense lymphocytic infiltrate (Figure 2 a-d). Focally perineural infiltration was observed. Apart from a well differentiated squamous cell carcinoma of the keratoacanthoma type, initially also a pseudocarcinomatous proliferation as for example
known from halogenodermas or a hypertrophic variant of lupus erythematosus was discussed. Because of the unusual medical history and the clinical presentation clinical pictures as well as biopsy material were also evaluated by several dermatopathologists. The histopathological findings were interpreted as a well-
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differentiated keratoacanthoma-like squamous cell carcinoma. Two weeks after discharge from our department the patient presented with further enlargement of the tumorous lesion on the nose (Figure 1 b). Three additional skin biopsies (Figure 1 c) were taken with similar histopathological findings compared to the first biopsy. Consultations of further (dermatopathologists confirmed the diagnosis of a well-differentiated squamous cell neoplasm and in the context with the clinical presentation the diagnosis of a giant keratoacanthoma was made (3). Further diagnostic examinations including ultrasound of the local lymph nodes, a cerebral MRI and a whole-body CT-scan were normal. The patient's findings were discussed in our interdisciplinary tumor board. Due to an erythematous streak along the vena angularis suggestive for lymphangiosis as an initial sign of further tumor spread, a biopsy and ligation of the vessel were performed. Histological examination showed no signs of malignancy. Any further surgical interventions as well as radiotherapy were refused by the patient. Six weeks later the patient presented again to our department with beginning spontaneous involution of the lesion. After another six weeks a nearly complete resolution of the lesion was observed (Figure 1 d). Further biopsies were refused by the patient. Instead we chose an active surveillance strategy with regular close follow-ups.

Discussion

Keratoacanthomas were first described in 1889 by Sir Jonathan Hutchinson as “the crateriform ulcer of the face, a form of acute epithelial cancer” (1). Indeed keratoacanthomas are epithelial neoplasms of the skin with a characteristic rapid growth within a few weeks. Their maximal size is normally reached after 6 weeks. The etiology of keratoacanthomas is unknown, but an association with chronic UV-exposure, defects in DNA repair genes, genetic alterations and human papilloma viruses has been described (2). Moreover, keratoacanthomas appear with higher frequency in immunodeficient patients (6). In our case postpartal hormonal changes in a breastfeeding woman might be discussed as a kind of immunomodulation. Keratoacanthomas are thought to represent a special variant of well differentiated squamous cell carcinomas. Untreated keratoacanthomas tend to involute passing three stages: proliferative stage with rapid growth, maturing stage with development of a central keratinous plug and involution with necrosis (7). Keratoacanthomas that exceed a size of 20 mm in diameter are defined as giant keratoacanthomas (5). Giant keratoacanthomas may result in severe destruction of the surrounding tissue and tend to leave a scar after self-involution. In the majority of cases keratoacanthomas are removed surgically, but successful treatments with radiotherapy, systemic retinoids or intralesional drug therapy such as 5-fluorouracil, methotrexate, bleomycin and interferon have been described. In a small number of five published cases giant keratoacanthomas on the face spontaneously involuted without any therapeutic intervention (4, 8-11). Lucente described in 1985 the involution of a giant keratoacanthoma of the size of 8 cm (10). Nevertheless, due to the often exposed localization of keratoacanthomas and the unpredictable course most patients and physicians are concerned about these tumors, and tumors are therefore rarely left untreated.

In summary, clinical-pathological correlation is essential for the diagnosis of giant keratoacanthoma, and its differentiation from squamous cell carcinoma impacts on treatment recommendations. Recommended treatments for giant keratoacanthoma are surgery or radiotherapy. However, although rarely described, a successful active surveillance strategy, may add to the ongoing discussion on treatment strategies for individual patients.

References