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CLINICAL REPORT

Eosinophilic Pustular Folliculitis in Association with Nevoid Basal Cell Carcinoma Syndrome

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This study reports on the clinical and light microscopic features of a nevoid basal cell carcinoma syndrome with the complication of eosinophilic pustular folliculitis. To the authors' knowledge, this is the first report of such an association, which is possibly due to immune dysregulation. Moreover, the patient experienced remission of eosinophilic pustular folliculitis after removal of the jaw cyst. One possible explanation for the remission is that a long-lasting TH_1 type inflammatory response as a result of the bone defect produces effective cytokines such as interferon-γ. ***Key words: basal cell carcinoma; jaw cyst; pitting; clinical picture.***

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The nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome or the basal cell nevus syndrome, is an autosomal dominant disorder characterized by multiple basal cell carcinomas, pits of the palms and soles, jaw keratocysts, a variety of other tumors and developmental abnormalities (1). This study reports a case of NBCCS in association with eosinophilic pustular folliculitis that resolved after removal of the jaw cyst.

CASE REPORT

A 29-year-old Japanese woman presented with a 10-year history of a blackish nodule on her right lower eyelid. This nodule had gradually increased in size and elevated 1 year earlier. There had been occasional bleeding and ulceration associated with the growth. She was also seen for evaluation of pruritic pustular erythemas on both her flanks that had been present for 8 months. These erythemas spontaneously regressed, leaving pigmented areas, but recurred within these pigmented lesions. The patient's past history included skin grafts for burn ulcers 4 times during her elementary school period. The family history was unremarkable. The results of preoperative laboratory tests, including serological test for syphilis (STS), hepatitis C and B viruses (HCV, HBV) and the human immunodeficiency virus (HIV), were normal on the first visit.

Examination revealed a characteristic face with a broad nasal root and ocular hypertelorism, and a brownish-black exophytic nodule measuring $8 \times 8 \times 6$ mm with partial ulceration on the right lower eyelid (Fig. 1). Furthermore, 2 miliary sized black spots, which could not be differentiated from basal cell carcinoma, were detected on the central portion of the forehead. Examination of the trunk revealed many annular or arch-like erythemas littered in the base of the pigmentation on both flanks, which were up to the size of a hen's egg (Fig. 2). These erythemas had pustules on their rims as well as central pigmentation with or without scales. Examination of the palms and soles revealed a small number of pits. The clinical features were suggestive of NBCCS. Radiography showed a cystic lesion in the left mandibular bone. This lesion was demonstrated to be 5.5 cm in diameter by computed tomography. There were no other skeletal anomalies.

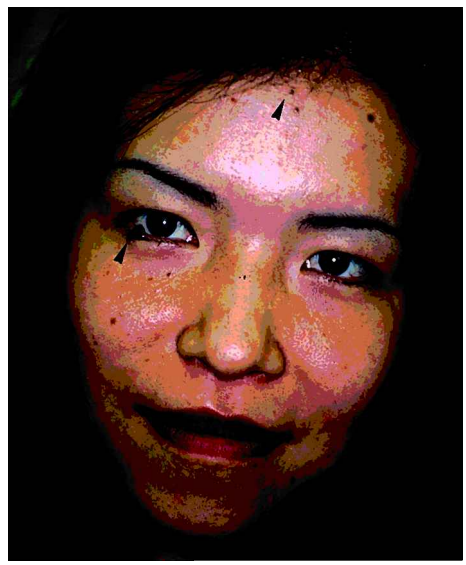

Fig. 1. Characteristic face with a broad nasal root and ocular hypertelorism and a brownish-black exophytic nodule on the right lower eyelid. *Arrowheads*: lesions of the basal cell carcinoma. (The patient agreed that the photograph could be published without masking.)

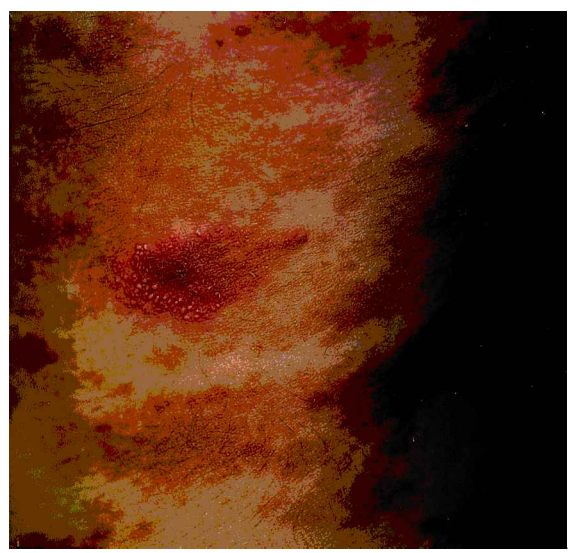

Fig. 2. Annular or arch-like erythemas with pustules on the rim are detected in the base of pigmented lesions on both flanks.

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Three pigmented lesions on the face were excised and a pustule on the patient's flank was biopsied under local anesthesia. On histological examination, the right-lower eyelid and upper–central forehead lesions showed the typical characteristics of basal cell carcinoma, solid type (Fig. 3a). The lower–central forehead lesion was compatible with melanocytic nevus, junctional type. These findings were highly suggestive of NBCCS.

The specimens from her flank were processed for light microscopy and direct immunofluorescence. Histological examination demonstrated a large subcorneal pustule with a moderate number of eosinophils that depressed the epidermis downwards. The epidermis showed slight acanthosis, but no elongation of rete ridges or granular layers (Fig. 4a). Neutrophilic and eosinophilic spongioses were detected in the spinous layer (Fig. 4b). In the vicinity of a large pustule, Munro microabscesses were detected in the horny layer. A moderately dense perivascular infiltrate of many neutrophils and a few eosinophils was observed in the upper dermis. A few acantholytic keratinocytes were found in the deep portion of the large pustules. There were no positive findings for immunoglobulin G (IgG), IgA, IgM or complement components by direct immunofluorescence. The authors conceived of some differential diagnoses of this lesion such as eosinophilic pustular folliculitis and annular pustular psoriasis. Neutrophilic spongiosis is not specific for annular pustular psoriasis and the eosinophil infiltrate is rare in psoriasis. Clinical recurrence occurred in the pigmented areas of the previous lesions. Based on these findings, the pustular lesions were considered to represent an eosinophilic pustular folliculitis despite their lacking follicular lesions. Thereafter, the patient was treated with topical applications of steroid ointment and systemic minocycline (200 mg/day) and nicotinamide (900 mg/day). This therapeutic regimen was moderately effective, but remission was still not achieved even 5 months after beginning the medication.

It has been proposed that the eosinophilic pustular follicular reaction represents an expression of an excessive immediate or delayed-type hypersensitivity reaction to various autostimuli, epicutaneous or ingested stimuli (2). Therefore, the patient decided to have the mandibular cyst removed. At that time, unlike at the previous examination, the results of the preoperative examination showed a biological false-positive result for STS. Histological examination revealed an epidermoid cyst without the granular layer and an inflammatory reaction, which are typical characteristics of odontogenic keratocysts (Fig. 3b). The defect in the bone was spontaneously refilled with surrounding connective tissues. Finally, the patient was diagnosed as suffering from NBCCS in association with eosinophilic pustular folliculitis.

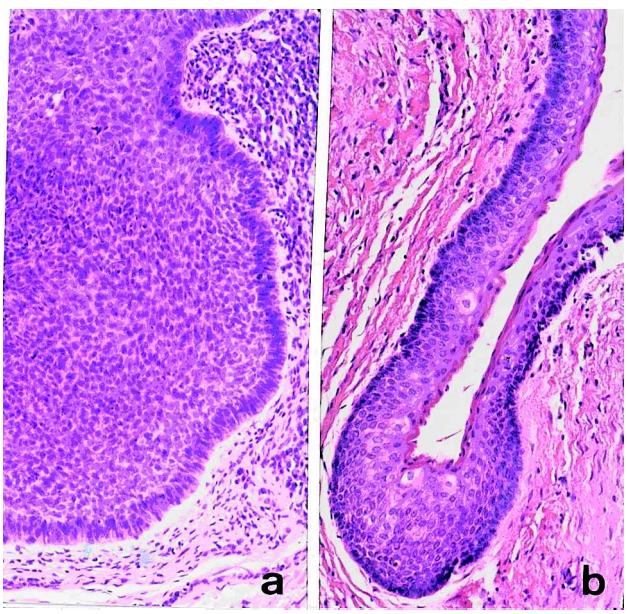

Fig. 3. Typical features for basal cell carcinoma on the lower eyelid (*a*) and for odontogenic keratocyst in the jawbone (*b*). (Original magnification *a* and *b*: ×33.)

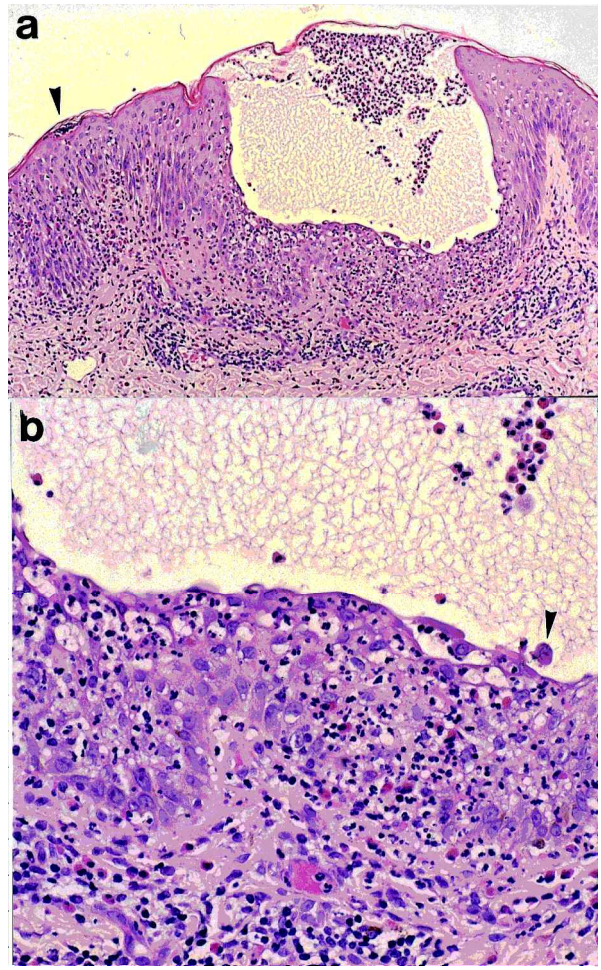

Fig. 4. (*a*) Large subcorneal pustule in the epidermis. In the vicinity of the pustule, a Munro microabscess (*arrowhead*) is detected. (Original magnification ×33). (*b*) Neutrophilic and eosinophilic spongiosis detected at the base of the pustule. A few acantholytic keratinocytes (*arrowhead*) are found. (Original magnification ×70).

Although she continued to be treated with same medication, the rate of recurrence of pustular lesions gradually reduced after removal of the cyst. Remission was achieved 2 months after removal and there has been no recurrence during 10 months of follow-up after stopping the medication.

DISCUSSION

The target gene of NBCCS maps to chromosome 9q22.3. Familial and sporadic basal cell carcinomas display loss of heterozygosity in this region, consistent with the gene being a tumor suppressor. The mutation of the patched gene was shown in NBCCS patients and in the tumors. Therefore, a reduction in the expression of the patched gene can lead to the developmental abnormalities observed in the syndrome, and the complete loss of patched function contributes to the transformation of certain cell types (3, 4).

Unfortunately, in this patient, a linkage analysis of the patched gene was not possible, but she fulfilled the clinical diagnostic criteria for NBCCS (5). Many potential complications have been reported in association with NBCCS. In a study of 84 cases in the north-west of England, the major complications of basal cell carcinomas and jaw cysts occurred

in over 90% of patients by 40 years of age, but also occurred before 10 years of age. Less well-described complications were ovarian calcification or fibroma (24%), medulloblastoma (5%), cardiac fibroma (3%), cleft palate (5%) and ophthalmic abnormalities such as squints or cataracts (26%) (5).

In addition to typical manifestations of NBCCS, this patient had relapsed erythemas with pustules on her flank. The main histological findings were a large pustule with neutrophilic and eosinophilic spongioses. The histological differential diagnosis of neutrophils in the epidermis included annular pustular psoriasis, subcorneal pustular dermatosis, dermatitis herpetiformis, and new pemphigus such as pemphigus herpetiformis and IgA pemphigus (6–8). Neutrophilic spongiosis is not specific for annular pustular psoriasis and eosinophilic infiltrate is rare in psoriasis. Clinically, the site of recurrence was limited to pigmented areas of the previous lesions. Based on these findings and the negativity of direct immunofluorescence, in spite of a lack of follicular lesions, an eosinophilic pustular folliculitis was diagnosed.

Eosinophilic pustular folliculitis was first described by Ofuji et al. in 1970 (9). They characterized the disease as follows: recurrent crops of pruritic, follicular, sterile papulopustules in fairly well-defined areas; peripheral extension with central clearing; resolution with residual pigmentation; subsequent appearance of new lesions in the areas of pigmentation of the old lesions; sparing of the hands, feet and mucosal membranes; absence of systemic symptoms; unpredictable response to therapeutic agents; and chronicity. The major distinguishing histological feature is the presence of abundant eosinophils that invade sebaceous glands and the outer root sheath of hair follicles. This is accompanied by nuclear fragmentation, dermal perivascular infiltrate composed predominantly of eosinophils, and intraepidermal microabscess formation (9–11). Furthermore, in 18% of patients with eosinophilic pustular folliculitis, lesions are also present on the palms and soles (12). Therefore, the presence of follicular lesions is not always necessary to make a diagnosis. The etiology of this disease is unknown, but dysfunctional immune mechanisms and infectious mechanisms have been proposed (2, 13). The former mechanism seems likely because of the association between the disease and atopy, diabetes, HIV infection and anticonvulsant drug therapy (2). These patients have a TH_1/TH_2 imbalance due to a specific T-cell dysfunction (2). The present patient had NBCCS with a biological false-positive reaction for STS. Therefore, this case also supports the former, immunological, mechanism. To the authors' knowledge, this is the first reported case of NBCCS in association with an eosinophilic pustular folliculitis.

Recent evidence has indicated that remission of eosinophilic pustular folliculitis may be associated with increased serum concentrations of interferon-γ (14, 15). The patient studied here experienced a gradually decreasing recurrence rate of relapsing eosinophilic pustular folliculitis, with eruptions finally ceasing 2 months after the removal of the jaw cyst. One possible explanation is that the long-lasting inflammation refilling the bone defect, probably a TH_1-type reaction, may produce effective cytokines such as interferon-γ.

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