Case Report

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Expanding Phenotypic Spectrum of Familial Comedones

Pawinee Rerknimitr[a, c] Wiwat Korkij[c] Jade Wititsuwannakul[c] Wipa Panmontha[b, d]
Kanya Suphapeetiporn[b, d] Vorasuk Shotelersuk[b, d]

[a]Dermatology Unit, Department of Medicine and [b]Excellence Center for Medical Genetics, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, and [c]Division of Dermatology, Department of Medicine and [d]Center of Excellence for Medical Genetics, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Key Words
Phenotypic spectrum · Familial comedones · Squamous cell carcinoma

Abstract
Familial comedones is a rare autosomal dominant disorder characterized by thousands of comedones developing in teens. Some pits or inflammatory lesions may coexist. Only 32 patients from three families have previously been reported. We report herein 12 cases in two unrelated families with familial comedones. Clinical manifestations among members in the same family vastly vary from scattered comedones on the face, trunk, upper and lower extremities to generalized thousands of open comedones, a large number of skin pits and acneiform inflammatory lesions over the entire body. Additionally, multiple severe purulent nodules and abscesses that leave unsightly scars similar to those of hidradenitis suppurativa are observed. Lesions of long-standing inflammation in two patients had developed into squamous cell carcinoma with a poor prognosis. The phenotypic spectrum of familial comedones varies to a large degree. Most importantly, there is potential for some long-standing inflammatory lesions to develop into squamous cell carcinoma. Extra vigilance in surveillance and prompt treatment for such lesions are recommended.

Introduction

Familial comedones is a rare autosomal dominant disease first described in 1967 [1]. There have been only 32 patients from three families reported to date [1–3]. The phenotype is characterized by the presence of numerous disseminated comedones all over the body, especially on the face, neck, trunk and forearms. Comedo removal leaves pit-like depressions. Histological examination of the skin specimen reveals follicular dilatation filled with keratinous plugs. Importantly, the external sheath of the hair follicle shows a distinctive arborescent branching pattern. No dyskeratotic cells are found.

We herein describe a case series of patients presenting with clinical phenotypes that would fit into the diagnosis of familial comedones with an interesting extended spectrum of clinical manifestations. This varies from mild to severe form of the disease, with a fatal outcome in one case.

Case Reports

Case 1

The 33-year-old propositus (IV-11, fig. 1a) presented with several recurring boils on the face, neck and trunk over 4 years. The skin changes began when he was 8 years old. He first noticed a number of pit-like lesions on the elbows and knees. These gradually extended to involve his arms and legs and his trunk and face. At 15 years of age, some of them developed into discharging nodules and large tender abscesses that healed with unsightly scars. Involvement of the axillae was also seen to a lesser extent.

Physical examination revealed numerous open comedones and skin pits all over the face, neck, entire anterior and posterior trunk and extremities. The palms and soles were spared. A large abscess with multiple draining sinuses was detected on his left upper back. Mutilating scars were observed. Pigmentary changes were not seen (fig. 2c).

Histological examination from the skin pit revealed a shallow epidermal invagination. The invaginated epidermis was mildly acanthotic and had filiform projection of basaloid cells connected to small vellus hair cysts (fig. 3a). Another specimen from the abscess on the back showed fragments of tissue displaying squamous cell proliferation. The cells exhibited enlarged nuclei with prominent nucleoli. Mitoses were present. The findings were consistent with well-differentiated squamous cell carcinoma (SCC).

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Kanya Suphapeetiporn, MD, PhD
Department of Pediatrics, Sor Kor Building 11th floor
Faculty of Medicine, Chulalongkorn University
Bangkok 10330 (Thailand)
E-Mail kanya.su@chula.ac.th

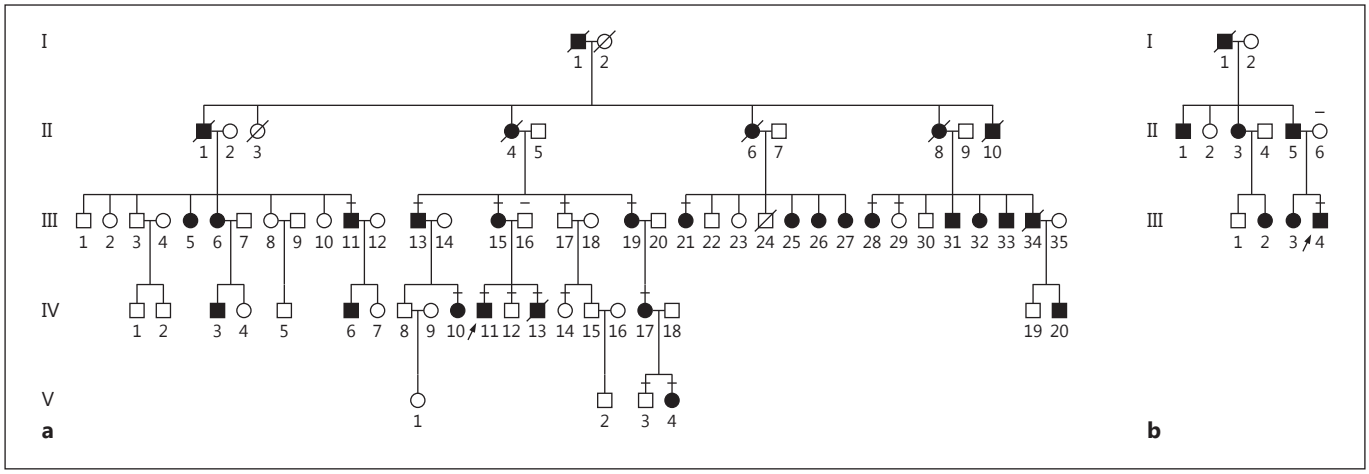

Fig. 1. Pedigrees. **a** Pedigree of family I with IV-11 as the proband. **b** Pedigree of family II with III-4 as the proband. The small horizontal bars above family members denote individuals who were examined.

Table 1. Sex, age of onset, age at last follow-up, distribution of comedones, presence of purulent lesions and scars and development of SCC among 12 patients reported in this case series

Patient	Family	Sex	Age of onset, years	Age at last follow-up, years	Face	Neck	Trunk	Extremities	Purulent lesions and scars	SCC
III-11	I	M	17	54	+	++	++	++	–	–
III-13	I	M	6	63	++	+++	+++	+++	++	–
III-15	I	F	20	61	+	++	+	++	+	–
III-19	I	F	19	53	++	+++	++	+++	–	–
III-21	I	F	30	65	+	++	++	++	++	–
III-28	I	F	15	60	+	++	++	++	+	–
IV-10	I	F	15	21	+	+	+	+	–	–
IV-11*	I	M	8	33	+++	+++	+++	++	+++	+
IV-13	I	M	11	25	+++	+++	+++	++	+++	+
IV-17	I	F	20	33	+	+	+	+	–	–
V-4	I	F	12	13	–	–	–	+	–	–
III-4*	II	M	13	16	++	+	++	+	+	–

* Probands. + = Few, ++ = moderate, +++ = abundant, – = absent.

Case 2

The patient (IV-13 in fig. 1a) was a 25-year-old man. His lesions first started when he was 11 years old as numerous open comedones. They were prominent on the arms and legs, trunk and face and gradually increased in number. When he reached 20 years of age, multiple nodules and abscesses developed.

On examination, a large number of comedones interspersed with pit-like skin depressions were found on the face, back, abdomen, extensor forearms and legs. Few were observed on the antecubital fossa. Multiple inflammatory nodules and cysts were scattered on the back and abdomen. A large tender abscess with marked swelling and draining sinus was present on the nape of the neck extending to the upper back. Many keloids and scars were seen. Multiple firm cervical and supraclavicular lymph nodes with a diameter of up to 4.5 cm were also observed.

Skin biopsy of the pitted lesions revealed mild acanthotic epidermis with proliferation of interconnecting strands of basaloid cells extending to the dermis. Excisional biopsy of the large abscess on the neck showed abnormal squamous epithelium growing in solid sheets pattern. The cells were highly pleomorphic with abnormal mitoses. Islands of neoplastic cells were found among a distinct inflammatory background. A diagnosis of moderately differentiated SCC was made. Moreover,

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fine needle aspiration from the enlarged lymph nodes also demonstrated metastatic SCC.

The patient underwent wide excision of the SCC and received carboplatin-paclitaxel-based chemotherapy and additional radiotherapy. Despite multi-modality treatment, recurrence of SCC of the neck and pulmonary metastasis occurred. Unfortunately, the patient succumbed a year after the diagnosis of SCC had been made.

An additional nine affected family members' clinical manifestations are summarized in table 1. Interestingly, some of them exhibited only non-inflammatory comedonal and pitted lesions (fig. 2a), while others had frequent purulent inflammatory lesions that healed with scars.

Case 3

The propositus was a 16-year-old man (III-4, fig. 1b) who presented with pit-like lesions that developed since he was 13 years old. His affected family members are shown in figure 1b.

Physical examination showed multiple open comedones on the face, upper back and chest interspersed with multiple small crater-like depressions. Inflammatory nodules, cysts and deep-seated abscesses were detected on the back and intergluteal space. Fewer lesions were observed in the axillary area (fig. 2b). Skin biopsy from the comedonal lesion revealed a dilated hair follicle with a filiform projection (fig. 3b).

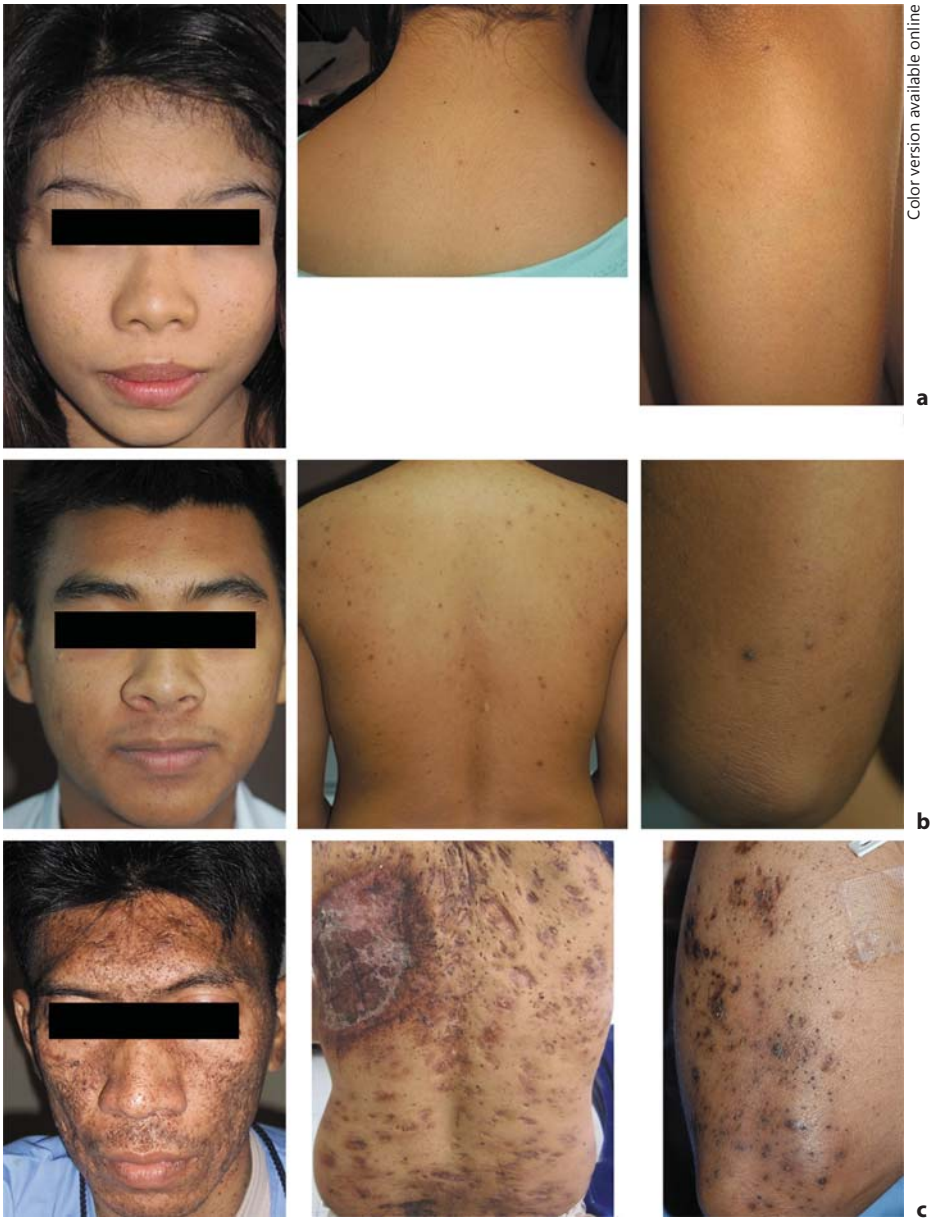

Fig. 2. Variable clinical manifestations among affected patients. **a** Few open comedones and skin pits on the face, neck and forearm in IV-10 of family I. **b** Widespread comedones, pits and inflammatory papules on the face, back and elbow of the proband of family II. **c** Numerous comedones and skin pits with disfiguring scars on the face and back, after removal of SCC, in the proband IV-11 of family I. The lesions on the elbow are much more extensive.

Discussion

Familial comedones is originally characterized by the occurrence of thousands of comedones developing in teens. Male patients have a worse prognosis. The disease gets worse when patients reach puberty and severity increases with age. The face is often the initial site of involvement. The lesions subsequently spread to the neck, thorax, abdomen and extremities. In most patients, some inflammatory lesions coexist with comedones [1–3]. Since there have been only 32 patients reported to date, the knowledge about clinical variability is limited.

In our case series, besides generalized comedones and acneiform inflammatory lesions on the face and body as originally described, we found a number of patients who additionally presented with multiple severe inflammatory lesions and scarring. Moreover, some of the lesions in this long-standing inflammation had a propensity to develop into SCC, resulting in fatality in one of our patients.

Some features of our patients, including painful nodules, abscesses and hypertrophic scars, were similar to those of hidradenitis suppurativa [4]. However, while most of these purulent lesions found in our patients were presented on the back, abdomen, neck and legs, frequent areas of involvement in hidradenitis suppurativa are on the axillae and inguinal, perianal, peri-

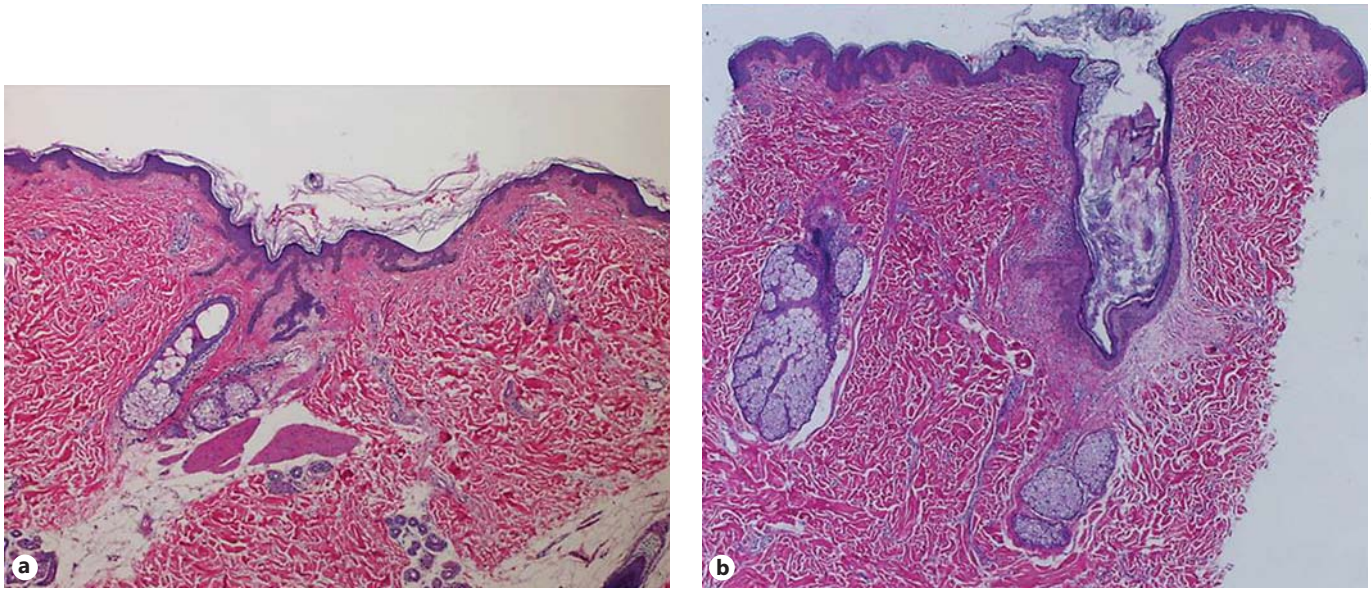

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Fig. 3. Photomicrographs showing an invaginated epidermis with filiform projection of basaloid cells, the skin specimen having been taken from a skin pit of proband IV-11 of family I (hematoxylin and eosin; original magnification ×40) (**a**), and a dilated hair follicle containing abundant keratinous material and arborescent projections of basaloid cells from the wall of the follicle, taken from a comedonal lesion of proband III-4 of family II (hematoxylin and eosin; original magnification ×40) (**b**).

neal, mammary and submammary regions [5]. In addition, numerous widespread comedones and pits were observed in all of our patients. Furthermore, these lesions showed distinctive histological features, such as follicular dilatation that filled with keratinous plug and arborescent branching pattern of basaloid cells in the external sheath of the hair follicles. Notably, five family members (III-11, III-19, IV-10, IV-17 and V-4) of family I solely had diffuse comedonal lesions without development of purulent discharging nodules. The presence of diffuse comedones without purulent nodules in some members, distributions of the purulent lesions in members with inflammation and typical histology would make a diagnosis of familial comedones more favorable than hidradenitis suppurativa.

Familial dyskeratotic comedones is an autosomal dominant disease. Its clinical features consist of scattered comedo-like papules that have a predilection for the trunk, arms and legs. The face, palms, soles, scalp and mucosal surfaces are spared. There is usually no sign of inflammation. Histology shows characteristic findings of crateriform cysts filled with keratinous material lined with dyskeratotic squamous epithelium [6]. Although our patients presented with numerous comedo-like papules, the difference in location, the presence of sign of inflammation and the histological findings would differentiate these two disorders.

A cluster of patients with acneiform lesions raises a diagnosis of metabolizing acquired dioxin-induced skin hamartomas [7], formerly called chloracne. This condition is caused by intoxication with dioxin and its analogs. Dioxin has been used in the production of pesticides and herbicides. Due to its high stability, it is ubiquitous in the environment and accumulates in the human food chain. Clinical presentations include numerous acneiform lesions, open comedones and yellowish cysts on the malar eminences, postauricular areas, ears, neck, trunk and scrotum. Systemic manifestations may ensue [7, 8]. Its characteristic histopathologic findings are mantle-like downgrowths of columnar epithelium of the cyst walls which are stained focally positive for CYP1A1, a major dioxin-metabolizing cytochrome P450 enzyme. Another striking feature is the absence of sebaceous glands in the skin section examined [9].

Our patients lived separately in different areas far apart from one another. Some never met. Moreover, their onsets of this disease spanned over 50 years (the onset of III-13 and V-4 was 56 years apart). Their only common factor was genetic. If it was caused by an environmental factor, some individuals in the same environments should have had some symptoms. In fact, none of their spouses, in-laws or neighbors who lived in the same houses or areas for a long time developed symptoms. Geographically and chronologically, we exclude possibilities of environmental insults. In addition, though skin specimens from the patients showed downward growths of the comedonal wall epithelium, the sebaceous glands were well preserved (fig. 3). Moreover, a specific CYP1A1 expression in two skin biopsies from two of our patients was not observed.

A comedonal variant of Darier's disease presents with numerous comedones and deeply pitted ice-pick scars as well. However, the closed comedonal lesions usually intermingle with typical hyperkeratotic papules of Darier's disease and are classically found on sun-exposed areas. On histology, dilated hair follicles with villi projections, suprabasal epidermal separation, corps ronds and grains are observed [10]. In our patients, the lack of the characteristic warty papules and the difference in histology excluded this diagnosis.

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From a histological point of view, Dowling-Degos disease is an important differential diagnosis [11]. However, the absence of reticulate pigmentation in the flexural area in our patients would exclude this diagnosis.

To our knowledge, this is the largest case series of familial comedones reported to date. In addition, there is no previous report of SCC arising in such a condition. Hence, our cases emphasize a need to be vigilant in screening for SCC in long-standing inflammatory lesions. Early detection and prompt treatment might alleviate morbidity or even avoid mortality in these patients.

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Disclosure Statement

The authors declare no conflicts of interest.

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