Keratosis pilaris atrophicans faciei: An observational, descriptive, retrospective clinical study

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Abstract. Keratosis pilaris atrophicans faciei (KPAF) is a hereditary follicular disorder, an atrophicans subtype of keratosis pilaris (KP) with a highly elusive diagnosis. Clinically, it presents with follicular, horny papules surrounded by an erythematous halo of the cheeks, forehead, chin and eyebrows, and it is followed by a gradual hair loss on the lateral margins of the eyebrows. The onset is as early as a few months after birth, but it is mainly diagnosed in children and adolescents and it can persist through adulthood. At present, the natural progression of the disease is poorly understood, which makes a correct diagnosis highly unlikely. The aim of the present study was to describe the clinical characteristics of KPAF in patients encountered in daily practice, in order to find common characteristics that may aid in the earlier recognition of the disease. An observational, descriptive, retrospective study was performed on 14 patients diagnosed with KPAF between January 2000 and December 2020. The mean age at diagnosis was 17.04 years and the onset of clinical symptoms appeared at a mean age of 4.85 years. The first clinical symptom was KP involving either the upper or lower limbs, or both. Then, erythema of the face appeared at a mean age of 7.21 years, keratotic papules on the face at a mean age of 8.35 years and, finally, loss of hair on the lateral margins of the eyebrows at a mean age of 14 years. The patients also had concomitant xerosis cutis, multiple mole syndrome, acne, contact dermatitis and Laugier-Hunziker syndrome. Evidence of disease progression, associations, as well as efficacious treatment measures are lacking. An earlier diagnosis potentially allows for a more efficacious, targeted treatment option. Either topical emollients, systemic retinoids or laser therapy may prove effective for each patient individually.

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Abbreviations: KPAF, keratosis pilaris atrophicans faciei; KP, keratosis pilaris

Key words: keratosis pilaris atrophicans faciei, keratosis pilaris, eyebrow loss, erythema of the face

Introduction

Keratosis pilaris (KP) is a common skin disorder that can also be associated with less common variants and rare subtypes, including keratosis pilaris rubra, erythromelanosis follicularis faciei et colli and the spectrum of keratosis pilaris atrophicans (1). The atrophicans subtypes, which are even more uncommon, include keratosis pilaris atrophicans faciei (KPAF), atrophoderma vermiculatum, and keratosis follicularis spinulosa decalvans (1). KPAF, also known as ulerythema ophryogenes, is a hereditary disorder characterized by altered follicular keratinization and inflammation, which leads to subsequent atrophy (2). Clinically, it presents with follicular, horny papules surrounded by an erythematous halo of the cheeks, forehead, chin and eyebrows, and it is followed by a gradual loss of hair. These cutaneous manifestations appear sequentially: Erythematous follicular papules of the face are usually the first sign, followed by a gradual hair loss on the lateral part of the eyebrows and finally follicular scar-like follicular atrophy (3). KPAF occurs sporadically; however, autosomal dominant and autosomal recessive inheritance have been described (3). In some cases, an autosomal recessive mutation in the desmoglein 4 (*DSG4*) gene, as well as the LDL receptor related protein 1 (*LRP1)* gene, have been involved (4,5). The onset is as early as a few months after birth, with erythema and

keratotic follicular papules affecting the lateral third of the eyebrows (6); however, KPAF is mainly diagnosed in children and adolescents, and it can persist through adulthood. Most of the subjects have concomitant KP of the extremities and trunk. Given the clinical variability of the particular cutaneous signs, insufficient diagnosis and misdiagnosis are frequent. In the majority of cases, the first clinical signs appeared on the face and are attributed to other diseases, thus making the real incidence of the disease unknown (7).

KPAF is a rare hereditary disorder with well-defined clinical features, but with variable evolution. At present, the natural progression of the disease is poorly understood, which makes a correct diagnosis highly unlikely. Thus, the aim of this observational, descriptive, retrospective study was to describe the clinical characteristics of KPAF in patients encountered in daily practice, in order to find common characteristics that may aid in the earlier recognition of the disease.

Patients and methods

Cases. To identify common characteristics that may aid in the earlier recognition of KPAF, an observational, descriptive, retrospective clinical case series study on 14 patients with KPAF was performed at the Dermatology Clinic of Târgu-Mures, Romania, between January 2000 and December 2020. In this 20-year period, 14 out of 76,440 patients were diagnosed with KPAF. Mean age at diagnosis was 17.04 years, with the youngest patient being diagnosed at the age of 3 years and the eldest at the age of 22 years. The sex ratio was M/F=4/1. The diagnosis was established through clinical examination. Patients were residents of the urban area and were members of wealthy families.

One investigator evaluated the patients and collected data and another investigator, who was blinded to clinical cases and treatment choices, performed outcome assessment. Data acquisition was performed by clinical examination and telephone interview. The patients were followed-up for four years after KPAF diagnosis. Limitations of the current study lie in the relatively low number of patients and in confirmation bias in reporting, since clinical assessment, diagnosis and treatment were performed by a single investigator. Mild form of facial erythema was defined as few papules and mild erythema, whereas severe form was defined as predominant papules and severe erythema.

Results

In this 20-year period, 14 out of 76,440 patients were diagnosed with KPAF. Mean age at diagnosis was 17.04 years, with the youngest patient being diagnosed at the age of 3 years and the eldest at the age of 22 years. The sex ratio was M/F=4/1. The onset of clinical symptoms appeared at a mean age of 4.85 years (2-12 years) and the time between the appearance of the first clinical symptoms to KPAF diagnosis was 9.21 years (1-16 years).

The majority of the 14 patients (71.43%) presented with keratosis pilaris (KP) involving only the upper limb as the first clinical sign; the remaining 28.57% had both upper and lower limb involvement. The second clinical manifestation, erythema of the face, appeared at a mean age of 7.21 years (2-16 years), after a mean period of 3.66 years (1-7 years) since the onset of KP of the extremities, in 9 out of 14 patients; for the remaining 5 patients, both KP and facial erythema appeared concomitantly. Of the 14 patients, 7 patients had mild forms and 7 had severe forms. The third clinical manifestation, keratotic papules on the face, appeared at a mean age of 8.35 years (3-14 years), after a mean period of 1.75 years (1-5 years) after facial erythema and 3.69 years (1-8 years) after KP of the extremities, in 13 out of 14 cases. In one case, though, keratotic papules on the face appeared concomitantly with KP and preceded the appearance of facial erythema. In addition, 8 patients presented skin atrophy. Loss of hair in the lateral margins of the eyebrows appeared at a mean age of 14 years (3-22 years), after a mean period of 9.14 years (1-16 years) since the onset of the first symptom, KP of the extremities, 6.78 years (1-16 years) after facial erythema and 6.07 years (1-15 years) after keratotic papules on the face, for 13 out of 14 patients. For one of the patients, loss of hair in the lateral margins of the eyebrows was concomitant with the appearance of keratotic papules on the face and these symptoms appeared one year after the onset of KP and facial erythema; this case was diagnosed as KPAF at the age of 3 years (Fig. 1). In all of these cases, KPAF was not the first diagnosis. Habitual erythema, keratosis pilaris, contact dermatitis, comedonal acne, infantile acne and atopic dermatitis were the misdiagnoses. Furthermore, 78.57% of the patients had associated xerosis cutis, 35.71% also had multiple mole syndrome, 14.28% had acne, 7.14% had contact dermatitis and 7.14% had Laugier-Hunziker syndrome (Table I). Topical treatments were recommended: emollients, keratolytics (containing lactic acid, salicylic acid, or urea), benzoyl peroxide, with mild, temporary improvement.

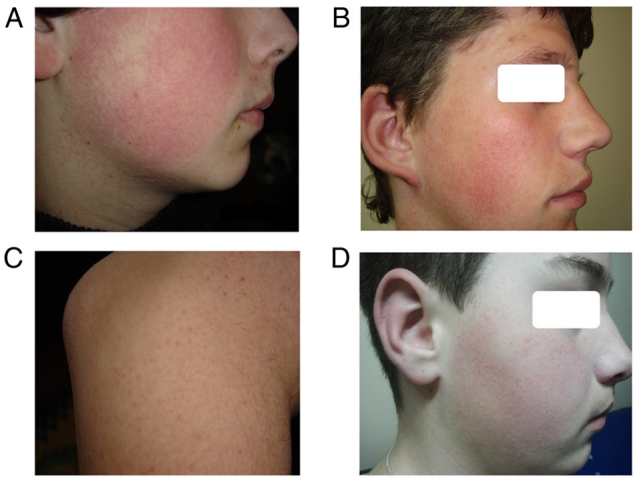

Figure 1. Clinical aspects of KPAF. (A) Follicular, horny papules surrounded by an erythematous halo, on a large surface of the cheeks. (B and D) Follicular, horny papules surrounded by an erythematous halo on the cheeks; partial hair loss in the lateral margins of the eyebrows. (C) Erythematous follicular, horny papules involving the lower extremities.

Discussion

Keratosis pilaris atrophicans faciei (KPAF) is an early-onset disease with an elusive diagnosis, due to the long-term

Table I. Anamnestic and clinical findings.

Case	Age at diagnosis (years)	Sex	Onset of clinical signs (age); KP/location	Onset of clinical signs (age); erythema of the face/severity	Onset of clinical signs (age); keratotic papules on the face	Onset of clinical signs (age); loss of hair on eyebrow area/atrophy yes/no	Previous diagnosis	Associated diseases
1	16	Male	6 years; Upper and lower limbs	10 years; Severe	11 years	16 years; No	Habitual erythema; KP; Contact dermatitis; Comedonal acne	Xerosis cutis
2	17	Male	8 years; Upper limb	13 years; Severe	14 years	17 years; Yes	Habitual erythema; KP; Comedonal acne	Xerosis cutis
3	11	Male	7 years; Upper limb	8 years; Mild	10 years	11 years; No	Atopic dermatitis; Comedonal acne	Xerosis cutis Multiple mole syndrome
4	22	Female	8 years; Upper limb	15 years; Mild	14 years	22 years; Yes	Habitual erythema; KP; Contact dermatitis; Comedonal acne	Xerosis cutis
5	19	Female	12 years; Upper limb	16 years; Mild	12 years	19 years; Yes	KPAF (at 18 years); KP	Xerosis cutis, mild acne
6	7	Male	3 years; Upper limb	3 years; Mild	5 years	7 years; No	KP; Habitual erythema; Atopic dermatitis	Xerosis cutis Infantile acne
7	14	Male	4 years; Upper and lower limbs	8 years; Severe	10 years	13 years; No	KP; Habitual erythema; Atopic dermatitis	Xerosis cutis Multiple mole syndrome
8	9	Male	3 years; Upper limb	3 years; Severe	5 years	9 years; No	KP; Atopic dermatitis	Contact dermatitis
9	3	Male	2 years; Upper limb	2 years; Mild	3 years;	3 years; No	Atopic dermatitis; Infantile acne	Xerosis cutis
10	15	Female	4 years; Upper limb	7 years; Mild	12 years	15 years; No	Atopic dermatitis; Comedonal acne	Xerosis cutis Multiple mole syndrome
11	16	Male	3 years; Upper and lower limbs	3 years; Severe	5 years	16 years; Yes	Atopic dermatitis; Comedonal acne; Contact dermatitis	Multiple mole syndrome
12	19	Male	3 years; Upper and lower limbs	4 years; Severe	5 years	19 years; Yes	Habitual erythema; Atopic dermatitis	Xerosis cutis
13	10	Male	2 years; Upper limb	6 years; Mild	7 years	10 years; No	Atopic dermatitis; Infantile acne	Xerosis cutis
14	19	Male	3 years; Upper limb	3 years; Severe	4 years	1 year; Yes	Atopic dermatitis; Comedonal acne	Multiple mole syndrome; Laugier-Hunziker syndrome

KP, keratosis pilaris.

progression of the symptoms. Results of the present study revealed that from the appearance of the first symptom to a correct diagnosis 9.21 years had passed, with a mean age at diagnosis of 17.04 years. Considering that the first clinical signs appeared as early as the age of 1 year, misdiagnosis delayed a correct assessment of the clinical image. The majority of the cases (64.28%) had a sequential progression; first, they presented KP involving the limbs, then, after a mean of 3.66 years facial erythema appeared; the third symptom, keratotic papules on the face, occurred after a mean of 1.75 years and 6.07 years later loss of hair appeared on the lateral margin of the eyebrows. Patients included in the present study also had associated xerosis cutis, multiple mole syndrome, acne, contact dermatitis and Laugier-Hunziker syndrome. In the literature, more severe afflictions have been described in association with KPAF including Noonan syndrome (8), Zouboulis syndrome (2), Cornelia de la Lange syndrome (6), Rubinstein-Taybi syndrome (9), and woolly hair syndrome (10). Furthermore, Wang and Orlow summarized KP associations with various neuro-cardio-facial-cutaneous syndromes, ectodermal dysplasias, and neuro developmental disorders, as well as KP-induced drug reactions (11). Differential diagnosis includes a large spectrum of diseases that affect children and adolescents, and which progresses with facial erythema, from habitual erythema, rosacea, atopic dermatitis, comedonal acne, to KP subtypes, including keratosis pilaris rubra faciei, erythromelanosis follicularis faciei et colli, atrophoderma vermiculatum, Darier-White disease, and pityriasis folliculorum (12-14).

An early diagnosis allows for a targeted treatment option. The patients in the current study were recommended to receive emollients, benzoyl peroxide and keratolytics containing lactic acid, salicylic acid, or urea, with only mild temporary improvement. Other therapies have been described, with encouraging results including pulsed dye laser (PDL) (15) and intense pulsed laser (16). Additionally, Apalla *et al* described a case of atrophoderma vermiculatum which responded to systemic isotretinoin (17). Furthermore, Wang *et al* summarized various topical treatments with reasonably adequate effect in patients with KP. Thiese included lactic acid, salicylic acid, retinoids, aquaphor, fractional prickle coral calcium, spray-on nitrosomonas eutropha mist, chlorine dioxide complex cleanser, as well as various lasers: PDL, 532-nm potassium titanyl phosphate laser (KTPL), alexandrite laser, long-pulsed diode laser, Q-switched Nd:YAG laser, and fractional carbon dioxide laser (11,18,19). There are no available treatments to prevent or reduce the atrophy in KPAF.

Limitations of the current study lie in the relatively low number of patients and in confirmation bias in reporting, since clinical assessment, diagnosis and treatment were performed by a single investigator.

In summary, KP is a very common skin condition, often dismissed as a cosmetic matter, which frequently leads to missed diagnoses of associated diseases, hereditary syndromes or even adverse events of certain medications. Evidence of disease progression, associations, as well as efficacious treatment measures is lacking. Further case series investigating the chronology of symptoms, as well as the efficacy, tolerability and recurrence rates are necessary in deciphering KPAF.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

GLF was responsible for the clinical management of the cases, the evaluation and analysis of data, and writing of the manuscript. LF was responsible for corrections and preparation of the manuscript. NN, MD and BV were responsible for data search and revision of the manuscript. IB contributed to writing the manuscript. The final version of the article has been read and approved by all authors. GLF and NN are responsible for confirming the authenticity of the raw data.

Ethics approval and consent to participate

Written informed consent from the patients was obtained.

Patient consent for publication

Written informed consent from the patients was obtained.

Competing interests

The authors declare that they have no competing interests.

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