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Familial seborrhoeic keratosis associated with multiple 'pure reticulated acanthomas' and infundibulocystic basal cell carcinomas*

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Summary

Background A variety of genodermatoses with multiple cutaneous tumours and germline genetic alterations, such as *PTCH1* mutations, have been described. Other cutaneous syndromes have been associated with somatic gene mutations, such as *FGFR3* in familial seborrhoeic keratosis.

Objectives To describe the clinical, dermoscopic and histopathological features of multiple cutaneous lesions, mostly infundibulocystic basal cell carcinomas (ICBCCs) and pure reticulated acanthomas, present in a family affected by familial seborrhoeic keratosis. In addition, we tested for possible germline alterations in *FGFR3* and *PTCH1*.

Methods Ten members of one family were clinically examined and 92 skin biopsy specimens were evaluated. Blood samples from six individuals were analysed for *FGFR3* and *PTCH1* germline alterations. We reviewed the literature concerning genetic *FGFR3* alterations in seborrhoeic keratosis.

Results Individuals of all generations affected by familial seborrhoeic keratosis also presented other skin tumours that corresponded histologically to reticulated acanthomas without apocrine or sebaceous differentiation, as well as ICBCCs. In addition, two novel germline variants, p.Pro449Ser (c.1345C>T) in *FGFR3* and p.Pro725Ser (c.2173C>T) in exon 14 of *PTCH1* were identified in five participants.

Conclusions We characterize for the first time the clinical, dermoscopic and histopathological features of multiple reticulated acanthomas without apocrine or sebaceous differentiation, for which we propose the term 'pure reticulated acanthoma', and ICBCCs associated with familial seborrhoeic keratosis. We identified *FGFR3* and *PTCH1* germline polymorphisms whose influence in the development of reticulated acanthomas is unknown.

What's already known about this topic?

- Rare cases of familial seborrhoeic keratosis have been reported in the literature, including presentation of high numbers of seborrhoeic keratosis at a young age, supporting a hereditary background.
- Somatic activating mutations of *FGFR3* have been identified in human seborrhoeic keratosis.
- To date, no germline *FGFR3* alterations have been found related to familial seborrhoeic keratosis in patients without skeletal dysplasias.

What does this study add?

- This is the first report of multiple reticulated acanthomas without apocrine or sebaceous differentiation, for which we propose the term 'pure reticulated acanthomas' in a family with familial seborrhoeic keratosis.
- Germline *FGFR3* or *PTCH1* variants were identified in five members of the same family.

What is the translational message?

- Recognizing multiple pure reticulated acanthomas would avoid an unnecessary excisional approach.
- *FGFR3* and *PTCH1* germline polymorphisms may potentially be involved in an undetermined, complex pathway influencing the development of multiple pure reticulated acanthomas, seborrhoeic keratoses and infundibulocystic basal cell carcinomas.

Several types of genodermatosis with multiple cutaneous tumours with adnexal differentiation have been described,[1,2] such as naevoid basal cell carcinoma syndrome (NBCCS, Gorlin syndrome), multiple hereditary infundibulocystic basal cell carcinoma (ICBCC), generalized basaloid follicular hamartoma syndrome, Bazex–Dupé–Christol syndrome, Brown–Crounse syndrome and Rombo syndrome, as well as multiple hereditary trichoepithelioma or seborrhoeic keratoses.[2–5] In some of these conditions, gene alterations such as mutations in *PTCH1* in Gorlin syndrome,[6,7] silent polymorphism in exon 5 of *PTCH1* or common haplotype at the NBCCS locus on chromosome 9 of *PTCH1* in multiple hereditary ICBCC,[2,8] multiple hereditary trichoepithelioma or generalized basaloid follicular hamartoma syndrome have been identified.[1,2]

Seborrhoeic keratosis is one of the most common benign human skin tumours.[9] Its prevalence increases with age, and although seborrhoeic keratoses do not usually develop before the third or fourth decade of life,[1] they are found in 80–100% of people aged 50 years or older.[9–11] In addition to age, sun exposure has also been reported as an independent risk factor for the occurrence of seborrhoeic keratosis.[10,11] However, Kennedy *et al.* found no correlation between lifetime sun exposure or painful sunburns and increased risk of seborrhoeic keratosis.[12]

Rare cases of familial seborrhoeic keratosis have been reported in the literature, including presentation of high numbers of seborrhoeic keratosis at a younger age supporting a hereditary background.[3] Somatic activating mutations of *FGFR3* have been identified in human seborrhoeic keratosis.[3,13] These *FGFR3* mutations may be early events in the pathogenesis of a subset of seborrhoeic keratosis, constituting a risk factor independent of age or ultraviolet (UV) radiation exposure.[4] Nevertheless, the underlying genetic alterations in familial seborrhoeic keratosis are still unclear. In contrast, it has been well documented that germline *FGFR3* mutations play an important role in skeletal dysplasias, such as achondroplasia, hypochondroplasia, thanatophoric dysplasia, Crouzon syndrome or severe achondroplasia with developmental delay and acanthosis nigricans syndrome among others.[5,14,15] These patients develop epidermal thickening and only one patient in the literature presented associated multiple seborrhoeic keratosis.[16] However, to date no germline *FGFR3* alterations have been found related to familial seborrhoeic keratosis in patients without skeletal dysplasias.[3,9,13,17]

We report a family with familial seborrhoeic keratosis and numerous ICBCCs, as well as multiple reticulated acanthomas without apocrine or sebaceous differentiation, which we labelled 'pure reticulated acanthomas' (PRAs).

Materials and methods

We studied 10 members of a white Spanish family from Jaen, including a first generation of four patients, all women, and a second generation of six patients (two women and four men; Fig. 1).

Members of the first generation presented with the highest number of lesions. These four women, aged 61–78 years, presented at the dermatology service with similar cutaneous tumours, located predominantly on the trunk. These lesions appeared progressively after the age of 20 years in all the patients, with up to 100 tumours in a single individual (Fig. 2, Table 1).

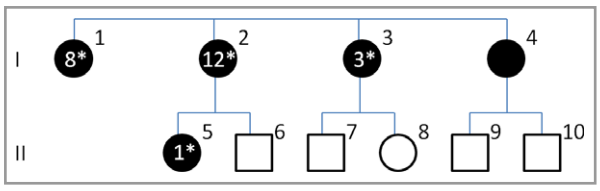

Fig 1. Detailed pedigree of family. Patients affected by familial seborrhoeic keratosis (black symbols). Number of unusual pure reticulated acanthomas indicated by asterisk.

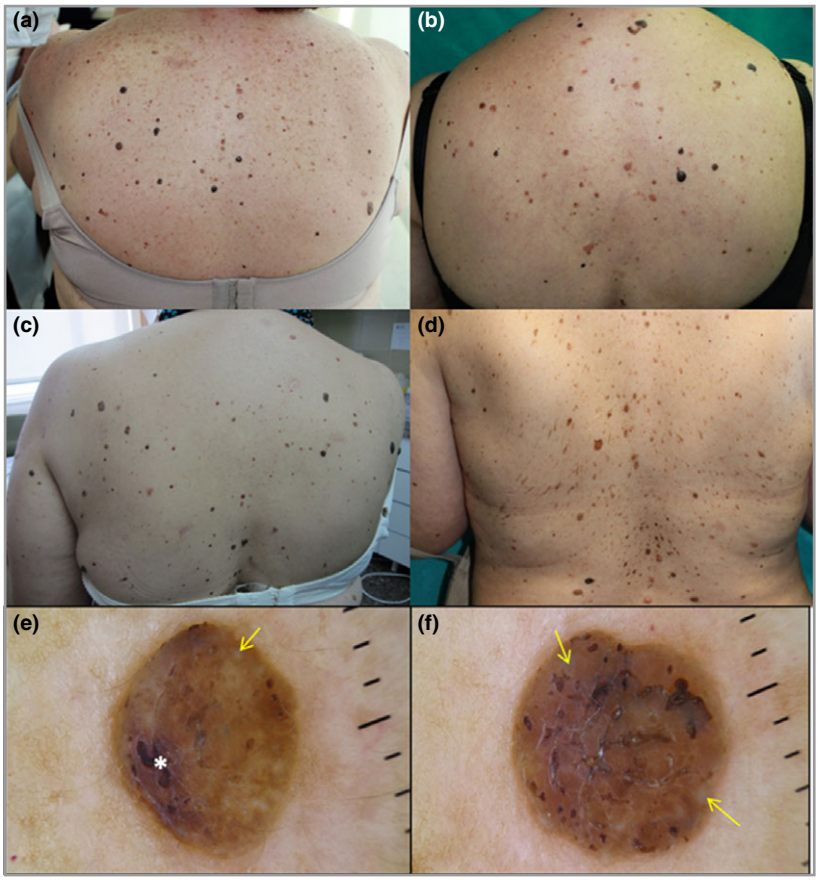

Fig 2. Familial seborrhoeic keratosis. (a–d) Clinical images of the back of first-generation patients: (a) patient 1; (b) patient 2; (c) patient 3; (d) patient 4, showing multiple lesions dispersed all over the surface, predominantly of brownish colour. (e–f) Dermoscopy of typical seborrhoeic keratosis showing sharply demarcated lesions with multiple milia-like cysts (asterisk) and comedo-like openings (arrows).

Table 1 Summary of clinical and genetic findings

	Patients									
	First generation				Second generation					
	1	2	3	4	5	6	7	8	9	10
Seborrhoeic keratosis										
Number	> 100	> 100	> 100	35	40	4	5	7	2	5
Location	Trunk	Trunk	Trunk	Trunk	Trunk	Trunk	Trunk	Trunk	Trunk	Trunk
Starting age (years)	28	27	29	35	30	35	33	35	38	36
Pure reticulated acanthoma										
Number	8	12	3	0	1	0	0	0	0	0
Location	Trunk	Trunk	Trunk	–	Trunk	–	–	–	–	–
Starting age (years)	40	42	46	–	30	–	–	–	–	–
Infundibulocystic basal cell carcinomas										
Number	8	9	0	0	0	0	0	0	0	0
Location	Head and trunk	Head and trunk	–	–	–	–	–	–	–	–
Starting age (years)	> 40	> 40	–	–	–	–	–	–	–	–
FGFR3 variant[a]	No	Yes	Yes	Yes	No	–	–	–	No	–
PTCH1 variant[b]	Yes	No	Yes	Yes	No	–	–	–	Yes	–

[a]*FGFR3* variant: germline p.Pro449Ser (c.1345C>T) in *FGFR3*; [b]*PTCH1* variant: germline p.Pro725Ser (c.2173C>T) in exon 14 of *PTCH1*.

Monitoring of the patients started in 1988 and ended in 2015. Apart from the above lesions there were no other abnormal clinical findings, and none of the patients presented with systemic disorders. The results of laboratory tests, including complete blood cell count, serum chemistry and immunity, were within normal limits. There was no evidence of myasthenia gravis, palmar or plantar pits, hypotrichosis or hypohidrosis. Orthopantomography did not show jaw cysts or any other features of Gorlin syndrome or generalized basaloid follicular hamartoma syndrome,[1,2,18] and no skeletal dysplasias

were present. Therefore, Gorlin syndrome could be clinically excluded.

We obtained peripheral blood samples from patients 1 and 2 (Fig. 1), the two sisters with the highest number of PRAs, according to standard procedures after obtaining informed consent. Exons 7, 13–15, 17 and 19 of *FGFR3* and exons 2–23 of *PTCH1* were analysed and subsequently amplified by polymerase chain reaction. The amplified products were used for direct sequencing by BigDye Terminators (Thermo Fisher Scientific, Waltham, MA, U.S.A.) in an ABI 3100 genetic analyser (Thermo Fisher Scientific) in accordance with the manufacturer's instructions. Following the genetic study of these two patients (see below), the variants detected in *FGFR3* and *PTCH1* were subsequently tested for in blood samples from patients 3, 4, 5 and 9.

Results

Clinical findings

The predominant lesions were hyperkeratotic plaques and papules, without skin infiltration and with variable shape, contour and colour (brown to black), a waxy satin surface and comedo-like openings. Dermoscopic examination evidenced the presence of brain-like figures, sharp demarcation and comedo-like openings, all typical criteria for seborrhoeic keratosis (Fig. 2).[19]

However, these patients also had numerous clearly contoured, asymptomatic erythematous papules of variable size, which clinically suggested basal cell carcinoma (BCC). These lesions presented slow and progressive growth, as well as flat and translucent surfaces. Some individuals presented microulcerations covered by scabs that complicated their differentiation. Nevertheless, dermoscopy showed an undefined pattern, with pigment remnants with no clear melanocytic pattern and an evident predominant vascular component revealing several vascular polymorphisms. The predominant vascular morphology consisted of hairpin blood vessels next to thin 'microarborizing' vessels extending to the centre of the lesion, similar to superficial BCC.[20–22]

The characteristics of these two predominant vascular patterns were primary vessels, mainly found in the periphery of the lesions, and which corresponded to hairpin blood vessels commonly seen in keratinizing tumours.[20] The vessels formed long capillary loops, and in most cases had a whitish halo that gave them a 'grapelike' appearance with fine 'microarborizing' secondary vessels as in superficial BCC.[19] Nonetheless, the predominant presence of hairpin vessels and the absence of other typical BCC criteria indicated a squamous lesion rather than basaloid tumour.[23,24] Many of these lesions were associated with remnants of melanocytic pigment forming short, brown, elongated and oval structures that could indicate the 'fat fingers' typically seen in lesions with a brain-like surface.[25]

In the literature we found two acanthomatous lesions: a clear cell acanthoma and a 'reticulated acanthoma with apocrine or sebaceous differentiation', both revealing a particular dermatoscopic pattern with dotted vessels following a linear pearl-like distribution and overall reticular appearance.[26,27] Nonetheless, the lesions in our patients did not match that description, and could therefore be considered a new distinctive dermoscopic pattern, corresponding histologically to reticulated acanthoma without apocrine or sebaceous differentiation (Fig. 3). In addition to these two major cutaneous lesions, we found classical BCCs and diverse tumours with follicular differentiation, with no remarkable clinical peculiarities.

The second generation of the family consisted of six participants, aged 34–42 years, with a lower number of eruptive lesions that started at similar ages as those in the first generation. Typical seborrhoeic keratosis lesions were predominant in this group, with one of the participants presenting clinical and dermatoscopic lesions with characteristics identical to the first-generation participants (Table 1).

Histopathological findings

In total, 92 biopsy specimens from six of the 10 family members were histopathologically evaluated; most of the specimens were obtained from patients 1, 2, 3 and 5 (Table 2). The microscopic analyses revealed 92 distinct lesions. There were 24 unusual lesions that were interpreted as PRA, and which affected the three sisters of the first generation (patients 1, 2 and 3) and one woman in the second generation (patient 5); 17 ICBCCs (according to the diagnostic criteria of Requena *et al.*);[8] four basaloid follicular hamartomas (according to the criteria of Saxena *et al.*);[18] three sebaceous epitheliomas [all without loss of mutL homolog 1 (MLH1), PMS1 homolog 2 (PMS2), mutS homolog (MSH) 2 or MSH6 immunoreactivity, supporting the absence of microsatellite instability]; 42 seborrhoeic keratoses (predominantly pigmented, acanthotic and hyperkeratotic subtypes); one superficial, spreading, *in situ* melanoma (patient 4); and one nodular BCC.

The 24 clinically and histologically unusual lesions interpreted as PRA were characterized by an acanthotic plate-like epidermal and/or infundibular squamous hyperplasia with bundles of keratinocytes with horizontal and parallel orientation to the skin surface, adopting a reticular pattern and only exceptionally showing some lumina also parallel to the surface (Fig. 4a, b). The basal layer of this reticular acanthosis showed many foci of nuclear palisading, frequently associated with retraction of the stroma around the tumour with or without mucinous material (Fig. 4c, d). Tumour cells were predominantly spindle with dense cytoplasm. Nuclear atypia was not present and no mitoses were identified. Immunohistochemistry was performed and revealed diffuse and intense immunostaining for cytokeratin (CK)14, weak and heterogeneous immunoreactivity for pleckstrin homology like domain family A member 1 (PHLDA1) in some lesions, and absence of CK7, CK19 and Ber-EP4 immunoreactivity.

Moreover, some of these lesions showed other unusual features: one lesion from patient 2 showed extensive poroid areas and parallel ducts with positive immunostaining for CK7

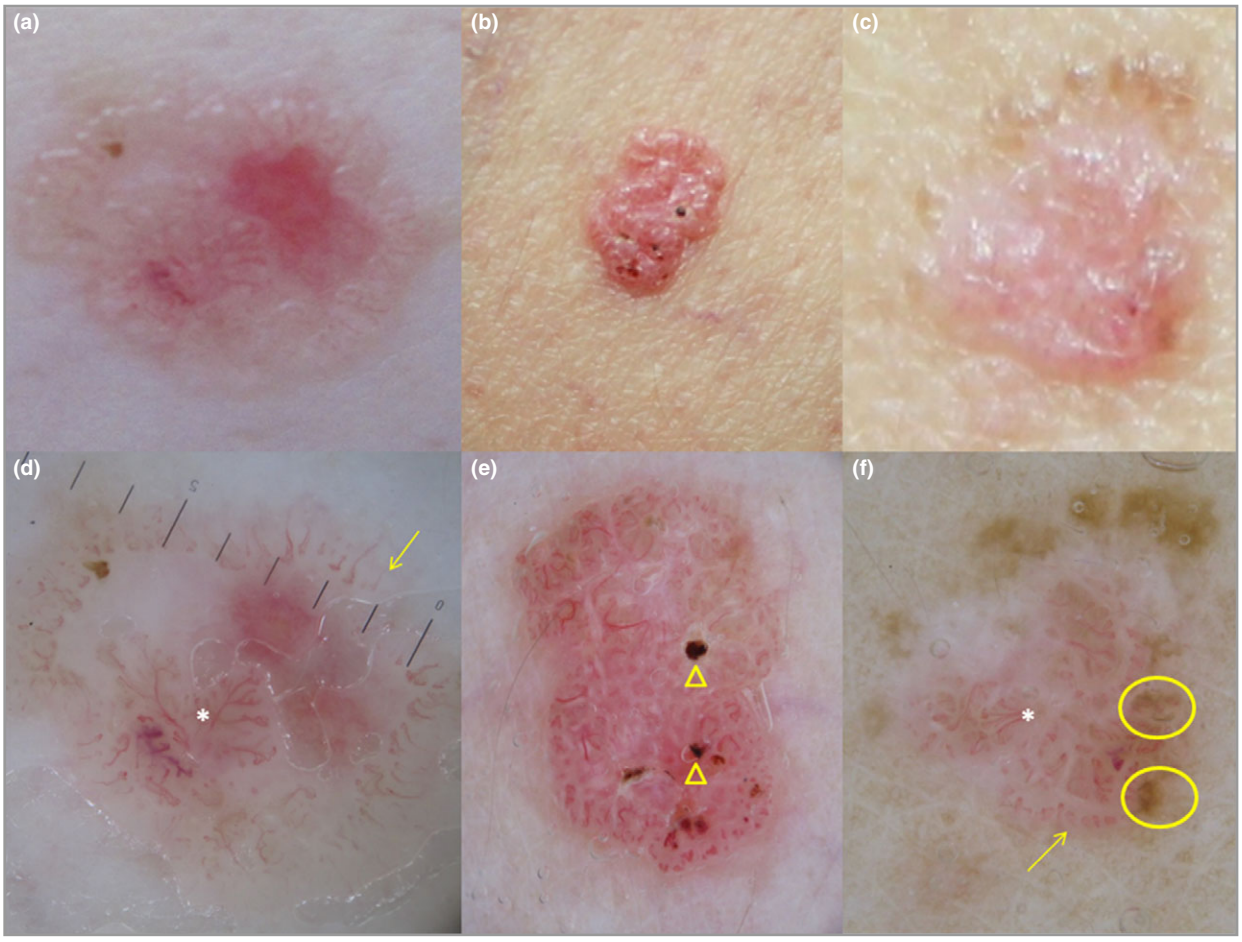

Fig 3. Reticulated acanthoma. (a–c) Macroscopic photography showing erythematous papules of variable size with translucent surface. (d–f) Dermoscopic images showing hypomelanotic lesions with an evident predominance of vascular components: hairpin blood vessels (arrows) and thin microarborizing vessels (asterisks), lesion presenting microulceration (triangles) and (e) vascular polymorphisms, and (f) traces of light brown pigmentation like 'fat fingers' (circles).

Table 2 Summary of histopathological findings

	Patients									
	First generation				Second generation					
Lesion	1	2	3	4	5	6	7	8	9	10
Pure reticulated acanthoma	8	12	3	–	1	–	–	–	–	–
Infundibulocystic basal cell carcinoma	8	9	–	–	–	–	–	–	–	–
Basaloid follicular hamartoma	2	2	–	–	–	–	–	–	–	–
Sebaceous epithelioma	3	–	–	–	–	–	–	–	–	–
Seborrhoeic keratosis	–	12	2	–	28	–	–	–	–	–
Nodular basal cell carcinoma	–	–	–	–	–	–	–	1	–	–
Superficial spreading *in situ* melanoma	–	–	–	1	–	–	–	–	–	–

(Fig. 5a, b), supporting focal sweat gland duct differentiation. One lesion from patient 3 showed thin cords of follicular germinative cells associated with collagen fibres radiating in a fibrofolliculoma-like pattern (Fig. 5c, d). One lesion from patient 2 presented a solitary nest of BCC (severe atypia, numerous mitoses, Ber-EP4 immunoreactivity, peripheral palisading and retraction from the stroma) arising within the lesion, with a gradual transition between the PRA and the BCC, which was highlighted by Ber-EP4 immunostaining (Fig. 5e, f). These histopathological features showed similarities to reticulated acanthoma with sebaceous or apocrine differentiation,[28–30] whereas no morphological or immunohistochemical evidence of sebaceous or apocrine differentiation was found in most cases. These lesions were also reminiscent of seborrhoeic keratosis owing to the acanthotic and reticulated pattern.

Shuweiter and Böer have discussed the controversy regarding the differential diagnosis between reticulated acanthoma with sebaceous differentiation and seborrhoeic keratosis with sebaceous differentiation.[31] Although our lesions could be

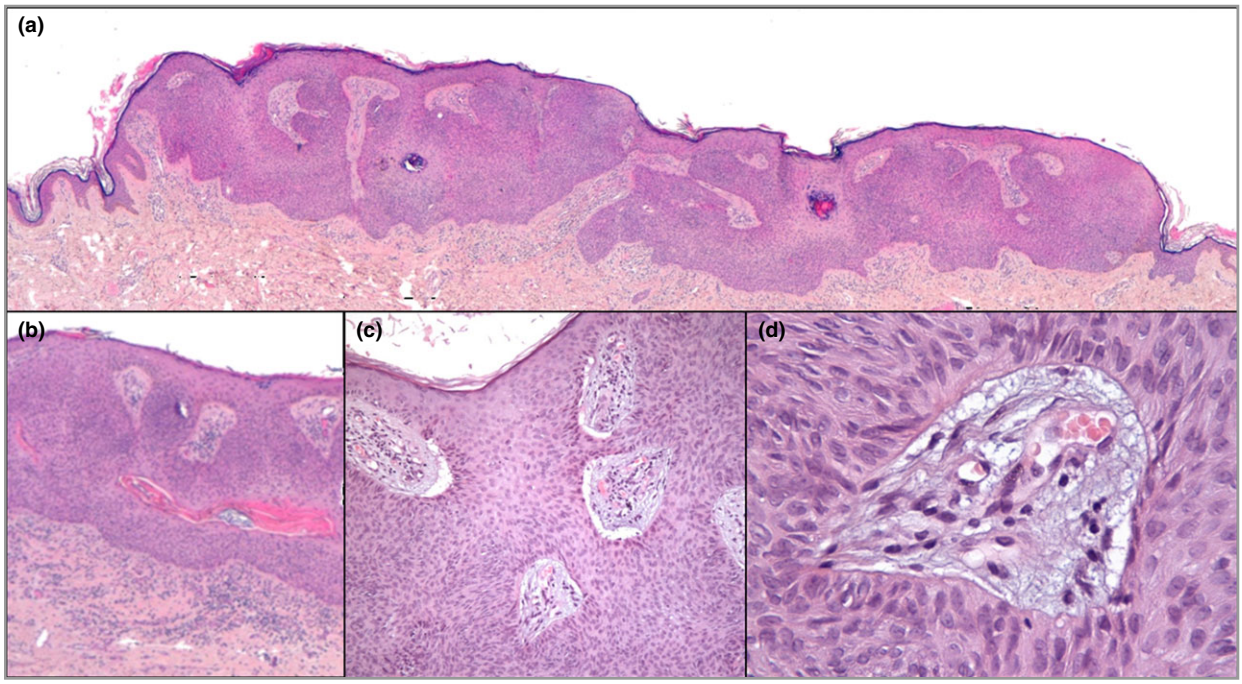

Fig 4. Reticulated acanthoma. (a) Scanning view showing a plate-like lesion with reticular acanthotic pattern [haematoxylin and eosin (H&E) × 10]. (b) Example of a lumen parallel to the surface present in some lesions (H&E × 40). (c) Spindle-shaped cells with reticular pattern and retraction between stroma and tumour buds (H&E × 100). (d) Peripheral palisading and myxoid features of the stroma (H&E × 200).

considered rare examples of seborrhoeic keratosis, the characteristic reticular and parallel spindle-cell bundles, focal peripheral palisading and retraction, focal follicular or sweat gland differentiation and the similarities to the tumour of follicular infundibulum (TFI) suggest an adnexal, probably infundibular, differentiation, although no significant immunoreactivity for PHLDA1 (a follicular germ cell marker) was found.[31–35] However, TFI is a well-characterized entity that shows a horizontal plate-like organization with a dense elastic network beneath, connecting follicular infundibula and overlying epidermis and extensive clear cell changes.[36–39] We excluded TFI in our cases as they did not include the latter features. As a result of the difficulty in categorizing these lesions and the extreme similarity with reticulated acanthoma with apocrine or sebaceous differentiation but without evidence of apocrine or sebaceous differentiation in most cases (Fig. 6), we propose the term 'pure reticulated acanthoma' to label this lesion with particular clinical, dermatoscopic and histopathological features.

Genetic findings

We identified two gene variants: a heterozygotic substitution C>T at nucleotide 1345 (c.1345C>T) in *FGFR3* causing variant p.Pro449Ser in patients 2, 3 and 4; and a heterozygotic substitution C>T at nucleotide 2173 (c.2173C>T) in exon 14 of *PTCH1* causing variant p.Pro725Ser in patients 1, 3, 4 and 9. Patient 5 did not present either of these two gene variants (Table 1).

In order to confirm the relevance of the *PTCH1* germline variant, it was tested for in human blood samples from 200 healthy individuals. The variant was not found in any of these samples. The *in silico* approach of this mutation was analysed by different bioinformatics programmes concluding that p.Pro725Ser of *PTCH1* may be a neutral form, and probably a low prevalence (0·00069) polymorphism.[40]

Discussion

Somatic mutations in *FGFR3* have been reported in sporadic and familial seborrhoeic keratosis.[3,9,13,17] Hafner *et al.* hypothesized that the development of benign acanthotic skin tumours requires a strong degree of *FGFR3* activation.[4] Some studies indicate the strong implication of environmental risk factors, mainly sun exposure, in *FGFR3* mutations, a fact that would explain the influence of UV exposure in the pathogenesis of seborrhoeic keratosis.[4] Nevertheless, although the special features of familial seborrhoeic keratosis suggest an underlying genetic alteration, with the exception of one patient affected by thanatophoric dysplasia and multiple seborrhoeic keratosis,[16] *FGFR3* germline mutations have not so far been described in the literature.[3]

The variant c.1345C>T (p.Pro449Ser) of *FGFR3* we identified is the first *FGFR3* germline variant reported in familial seborrhoeic keratosis unrelated to skeletal dysplasias. This germline polymorphism may be a predisposing factor that may determine the number and age of appearance of seborrhoeic keratosis and, in addition, may play a still unclear role

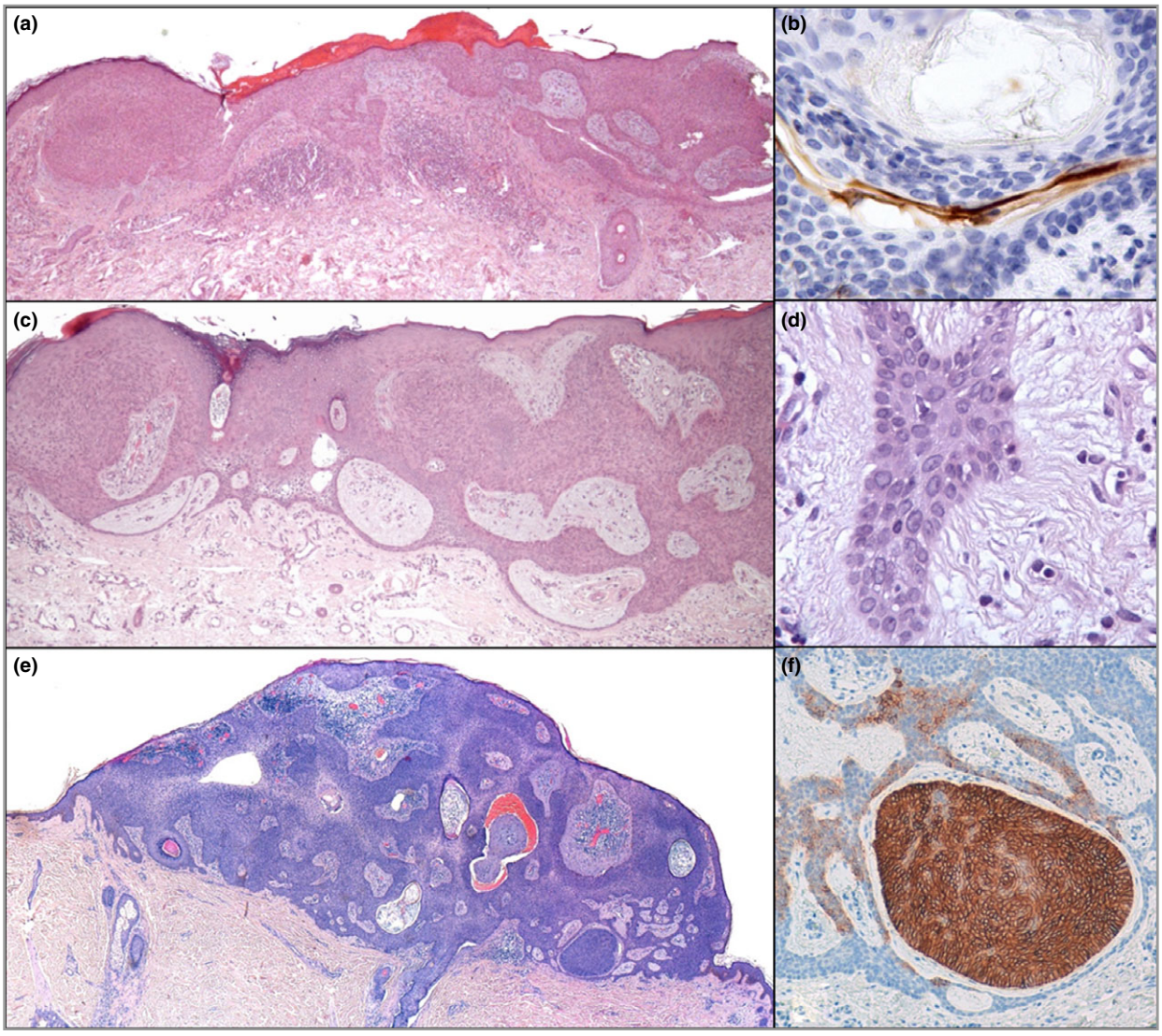

Fig 5. Reticulated acanthoma with particular features. (a, b) Only one case showed sweat gland duct differentiation [highlighted with cytokeratin 7 (CK7 × 200) immunoreactivity in (b); (a) haematoxylin and eosin (H&E) × 10]. (c, d) Reticulated acanthoma with follicular differentiation, showing (c) follicular germinative cords (H&E × 10) and (d) characteristic collagen fibres (H&E × 200). (e, f) Nest of nodular basal cell carcinoma arising within reticulated acanthoma [(e) H&E × 10; (f) Ber-EP4 × 40].

in the development of PRA. However, we only found this variant in three of the five family members affected by familial seborrhoeic keratosis and in two of the four family members who presented PRAs. In addition, genetic resources consider this particular mutation to be of benign clinical significance.[41]

Our results support the proposal by Hafner *et al.* of the existence of a possible continuous spectrum of germline variants modifying the risk of seborrhoeic keratosis development in concert with potential exogenous risk factors,[3] and that familial seborrhoeic keratoses may represent only one prominent end of this spectrum rather than a strongly autosomal dominant inherited disease. In this regard, several skeletal dysplastic syndromes in which *FGFR3* germline mutations are implicated include increased epidermal thickness,[14,15] and lack hallmark features of typical seborrhoeic keratoses.[17] The morphological similarities between PRA and these 'atypical epidermal hyperplasias' described by Duperret *et al.*,[17] along with the familial presentation of PRAs and seborrhoeic keratoses in our patients, lead us to believe that the Pro449Ser *FGFR3* variant may play a more or less relevant role in the development of PRA. Nevertheless, the small difference in number of PRAs between patients with and without the *FGFR3* germline variant and the presence of this variant in the only patient without PRA in the first generation support other unknown environmental or genetic factors as the main players in the development of PRA and seborrhoeic keratoses in these family members.

Furthermore, this family also presented multiple ICBCCs. Syndromes with multiple ICBCCs, such as Gorlin syndrome or multiple hereditary ICBCC,[6,7] have been causally related to *PTCH1* alterations. In this regard, we identified a germline variant p.Pro725Ser in *PTCH1*. Although this variant is

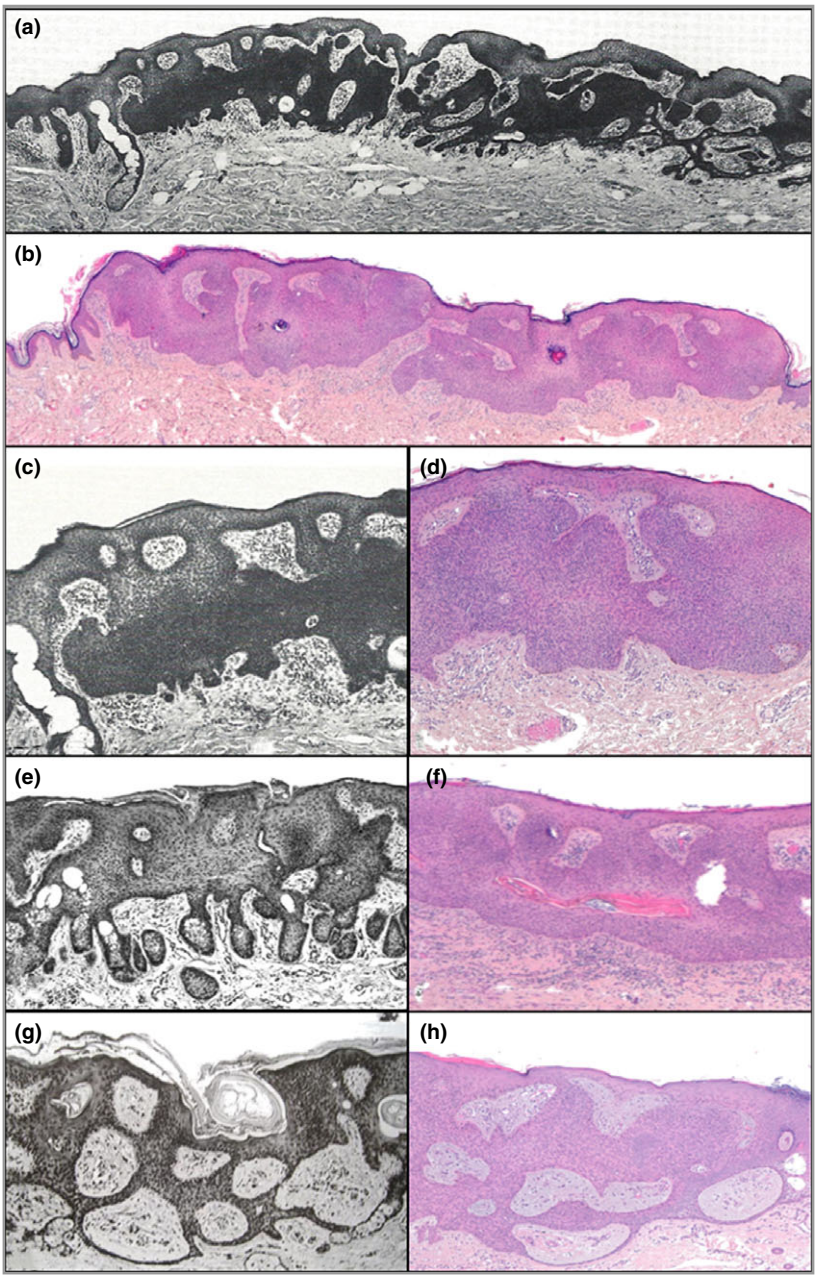

Fig 6. Comparative chart between (a, c) reticulated acanthoma with apocrine differentiation and (b, d) one of our pure reticulated acanthomas.[29] Comparative chart between (e, g) reticulated acanthoma with sebaceous differentiation and (f, h) one of our pure reticulated acanthomas.[28]

considered of uncertain clinical significance,[40] the fact that it is present in only one of the two family members affected by numerous ICBCCs and in several members who did not present ICBCCs led us to conclude that its role in the development of ICBCCs is questionable.

Whether or not the three types of lesions described in this report are pathogenetically related is beyond the scope of this study. However, the presence of rare germline variants in two genes that are linked to seborrhoeic keratosis and ICBCC may be indicative of a genetic predisposition to both. And the similarities between the epidermal hyperplasia described in *FGFR3* germline skeletal dysplasias and PRA also suggest a potential role for this *FGFR3* polymorphism in multiple PRA development.

In conclusion, we propose the term 'pure reticulated acanthoma' as a new cutaneous entity with distinct clinical, dermoscopic and histopathological characteristics. We believe that recognizing multiple PRAs will make it possible to avoid an unnecessary excisional approach. We also report the first combination of multiple PRAs and ICBCCs associated with familial seborrhoeic keratosis, and identify *FGFR3* and *PTCH1* germline polymorphisms that may potentially be involved in an undetermined, complex pathway influencing the development of multiple PRAs, seborrhoeic keratoses and ICBCCs.

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