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Received: 23 January 2024 | Revised: 22 April 2024 | Accepted: 27 April 2024

DOI: 10.1111/cen.15071

ORIGINAL ARTICLE

Pituitary/Neuroendocrinology

WILEY

Cutaneous findings in patients with acromegaly and its relationship with concomitant endocrinopathies

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Abstract

Objectives: Skin changes in acromegaly are often the first sign of the disease. The aim of this study was to describe the cutaneous findings in patients with acromegaly. In addition, a secondary aim was to investigate the possible association of these findings with remission status and concomitant endocrinopathies.

Design, Patients, and Measurements: In this prospective multicenter study, 278 patients over the age of 18 years with acromegaly who were followed up in 14 different tertiary healthcare institutions were included. These patients, who were followed up by the Endocrinology Department, were then referred to a dermatologist for dermatological examination. The frequency of skin lesions was investigated by detailed dermatologic examination. Dermatological diagnosis is reached by clinical, dermatological and/or dermoscopic examination, and rarely skin punch biopsy examinations in suspicious cases. The possible association of the skin findings between remitted and nonremitted patients and with concomitant endocrinopathies were evaluated.

Results: The most common skin findings in patients with acromegaly in our study were skin tags (52.5%), cherry angiomas (47.4%), seborrhoea (37%), varicose veins (33%), acneiform lesions (28.8%), hyperhidrosis (26.9%) and hypertrichosis (18.3%). Hypertrichosis was significantly more prevalent in patients nonremitted (p: .001), while xerosis cutis was significantly more prevalent in patients remitted (p: .001). The frequency of diabetes mellitus and hypothyroidism was significantly higher in patients with varicose veins and seborrhoeic keratosis than those without. Additionally, the coexistence of hypothyroidism, hyperthyroidism and galactorrhea was significantly higher in

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patients with Cherry angioma than in those without Cherry angioma (*p*-values: .024, .034 and .027, respectively). The frequency of hypogonadism in those with xerosis cutis was significantly higher than in those without (*p*: .035).

Conclusions: Cutaneous androgenization findings such as skin tag, seborrhoea, acne and acanthosis nigricans are common in patients with acromegaly. Clinicians should be aware that skin findings associated with insulin resistance may develop in these patients. It can be said that the remission state in acromegaly has no curative effect on cutaneous findings. Only patients in remission were less likely to have hypertrichosis. This may allow earlier review of the follow-up and treatment of acromegaly patients presenting with complaints of hypertrichosis. Additionally, it can be said that patients with skin findings such as cherry angioma may be predisposed to a second endocrinopathy, especially hypothyroidism. Including dermatology in a multidisciplinary perspective in acromegaly patient management would be beneficial to detect cutaneous findings earlier.

KEYWORDS
acromegaly, cherry angioma, endocrinopathy, skin, skin tag

1 | INTRODUCTION

Acromegaly is a rare systemic disorder that leads to excessive secretion of growth hormone (GH) and excessive production of insulin-like growth factor-1 (IGF-1) after the epiphyses close.[1] IGF-1 causes the characteristic proliferation of many tissues such as cartilage, bone and connective tissue, resulting in the classic clinical features of acromegaly.[2–4] Similarly, skin changes in acromegaly are the result of increased proliferation of keratinocytes and fibroblasts and deposition of dermal glycosaminoglycans stimulated by excessive GH and IGF-1. As a result, the skin thickens; coarsening is especially pronounced on the face and acral parts.[1,5] In acromegaly, the time from the onset of clinical symptoms to diagnosis can be up to 12 years.[5] Since skin changes in the disease are usually the first sign of the disease, they can be an important clue for early diagnosis.[6] There are a limited number of studies in the literature evaluating cutaneous findings in patients with acromegaly; however, these studies were small-scale studies that did not evaluate the frequency of skin findings depending on whether the patients were in remission and the relationship of this condition with other endocrinopathies.[2,3,7,8] With this study, we aimed to determine cutaneous findings in patients with acromegaly and to investigate the possible relationship of these findings with remission status and concomitant endocrinopathies.

2 | METHODS

2.1 | Study design and participants

We conducted a nationwide, multicenter, prospective, observational study. Ethical approval for this study was obtained from Harran University Faculty of Medicine Ethics Committee (Date: 24/05/2021, Number: HRU/21.10.05).

The study group included 278 patients over the age of 18 who were diagnosed with acromegaly by the department, followed up and referred to the dermatology outpatient clinic between 15 May 2021 and 15 February 2022. The study included patients from 14 centres covering different regions of Turkey.

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2.2 | Data collection

Informed consent was obtained from all participants. Patients diagnosed with acromegaly were first evaluated by the endocrinologist. Age, gender, body mass index (BMI), concomitant endocrinopathies (diabetes mellitus [DM], hypothyroidism, hyperthyroidism, hypogonadism, adrenal insufficiency, hyperparathyroidism, galactorrhea), comorbidity status (cardiac [arrhythmia, coronary disease, hypertension], cerebrovascular accident, sleep apnoea syndrome, anaemia, sexual dysfunction, osteoporosis, arthritis, carpal tunnel syndrome, visual impairment) was recorded by the endocrinologist. Patients were judged to be in remission and nonremission by the endocrinologist according to the following criteria.

Remission criteria: No clinical signs, random GH < 1 μg/L or nadir GH after 75 g oral glucose tolerance test (OGTT) < 0.4 μg/L, age-sex normalised IGF-I.[9]

Nonremission criteria: Active clinical signs, random GH > 1 μg/L and nadir GH after 75 g OGTT ≥ 0.4 μg/L, elevated IGF-1 (for age and sex).[9]

Serum GH was assessed by electrochemiluminescence immunoassay (human GH kit, Architect c8000 Chemistry Analyser; Abbott Diagnostics). Serum total IGF-1 was assessed by immunometric chemiluminescence assay (IMMULITE 2000; Siemens).

These patients, who were followed up by the Endocrinology Department, were then referred to a dermatologist for dermatological examination. Dermatological diagnosis is reached by clinical, dermatological and/or dermoscopic examination, and rarely skin punch biopsy examinations in suspicious cases such as epidermal cyst, lipoma, trichilemmal cyst.

2.3 | Statistical analysis

The Kolmogorov–Smirnov test was used to determine whether the data fit the normal distribution. Normally distributed continuous variables were expressed as mean and standard deviation (mean ± SD) and compared by Student's *t*-test. Since age was not normally distributed, it was expressed as median (interqurtile range) and evaluated with the Mann–Whitney *U*-test. Categorical variables were expressed as absolute (*n*) and relative (%) frequencies and compared with the chi-square and Fisher's tests.

The association between skin findings in patients with and without remission and in patients with and without comorbidities was evaluated with. $p < .05$ was considered to be statistically significant. SPSS 25.0 (SPSS Inc., PASW Statistics for Windows, Version 25.0) was used for statistical analysis.

3 | RESULTS

Of the patients, 119 (43%) were male, 159 (57%) were female and the mean age was 50.0 ± 16.2 years. The mean age at onset of acromegaly was 37.4 ± 11.5 years. The mean height, weight and BMI of patients with acromegaly were 167.4 ± 9.8 cm, 81.1 ± 11.6 kg and 29.5 ± 8.4, respectively. The most common phenotypic features typical of acromegaly patients were acral growth (83.8%), large triangular nose (77.6%), coarse facial appearance (64%) and prognathism (56.1%). All phenotypic characteristics of the patients are shown in Table 1. The most common endocrinopathies in patients with acromegaly were DM (39.9%),

TABLE 1 Phenotypic characteristics seen in patients with acromegaly.

Phenotypic characteristics	*n*: 278	%
Acral enlargement and thickening of the skin of the hands	233	83.8
Large triangular nose	216	77.6
Course face	178	64
Prognathism	156	56.1
Increased tooth spacing	151	54.3
Macroglossia	149	53.5
Thickened lower lip	146	52.5
Widened skin pores	115	41.3
Thickened heel pads	109	39.2
Increased size of external ear	94	33.8
Thickened oedematous eyelids	94	33.8

TABLE 2 Comorbidities seen in patients with acromegaly.

Comorbidities	*n*: 278	%
Endocrinopathies	180	64.6
Diabetes mellitus	111	39.9
Hypothyroidism	99	35.6
Hypogonadism	36	12.9
Adrenal insufficiency	23	8.2
Hyperthyroidism	7	2.5
Galactorrhea	5	1.7
Hyperparathyroidism	3	1.1
Cardiac comorbidities	130	46.7
Hypertension	102	36.6
Arrhythmia	26	9.3
Coronary artery disease	2	0.7
Defect of vision	64	23
Sleep apnoea syndrome	53	19
Anaemia	40	14.3
Sexual dysfunction	37	13.3
Osteoporosis	21	7.5
Arthritis	20	7.1
Carpal tunnel syndrome	19	6.8
Cerebrovascular event	5	1.7

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hypothyroidism (35.6%), hypogonadism (12.9%) and adrenal insufficiency (8.2%). Cardiac comorbidities were present in 130 (46.7%) patients. All comorbidities are shown in Table 2. In addition, two acromegaly patients were diagnosed with McCune-Albright Syndrome.

The most common skin findings in patients with acromegaly in our study were skin tags (52.5%), cherry angiomas (47.4%), seborrhoea (37%), varicose veins (33%), acneiform lesions (28.8%), hyperhidrosis (26.9%) and hypertrichosis (18.3%). All skin findings detected in the patients are shown in Table 3. Figure 1 shows the skin findings in some patients.

Demographic characteristics, the top 10 most common skin lesions, and accompanying endocrinopathy status of patients in remission and those not in remission are shown in Table 4. While 157 (56%) patients (male: 61, female: 96) with acromegaly were in clinical remission, 121 (44%) patients (male: 58, female: 63) were not. The mean age of patients in remission and those not in remission was 51.44 ± 11.59 and 50.06 ± 12.32 years, respectively. There was no difference between patients remitted and non-remitted in terms of gender and age (p-values: .129, .336, respectively). When patients remitted and nonremitted were compared in terms of accompanying skin findings, xerosis cutis was significantly higher in patients in remission (p: .001), while hypertrichosis was significantly higher in patients without remission (p: .001). When the relationship between remission status and endocrinopathies was analysed, hyperthyroidism was found to be significantly higher in patients remitted (p: .019), while no difference was found between other endocrinopathies and remission status ($p > .05$).

TABLE 3 Skin manifestations seen in patients with acromegaly.

Skin findings	*n*: 278	%	Skin findings	*n*: 278	%
Skin tags	146	52.5	Vitiligo	4	1.6
Cherry angiomas	132	47.4	Callus	3	1.2
Seborrhoea	103	37	Pityriasis versicolor	3	1.2
Varicose vein	92	33	Ephelides	3	1.2
Acneiform lesion	80	28.8	Cafe au lait	2	0.8
Hyperhidrosis	75	26.9	Verruca vulgaris	2	0.8
Hypertrichosis	51	18.3	Herpes labialis	2	0.8
Xerosis cutis	48	17.2	Striae	2	0.8
Seborrhoeic keratosis	27	9.7	Hemangioma	2	0.8
Acanthosis nigricans	21	7.5	Xanthelasma	2	0.8
Tinea pedis	19	6.8	Atopic dermatitis	2	0.8
Cutis vertisis gyrata	18	6.4	Hidradenitis suppurativa	2	0.8
Epidermal cyst	16	5.8	Keloid	1	0.4
Benign melanocytic naevus	16	5.8	Lichen planus	1	0.4
Pruritus	12	4.8	Prurigo nodülaris	1	0.4
Irritant/allergic contact dermatitis	10	3.6	Rosacea	1	0.4
Seborrhoeic dermatitis	10	3.6	Erythema annulare centrifugum	1	0.4
Keratosis pilaris	8	3.2	Sebase hyperplasia	1	0.4
Postinflammatory hyperpigmentation	8	3.2	Syringoma	1	0.4
Milium	7	2.8	Dermatofibroma	1	0.4
Melasma	7	2.8	Erythrasma	1	0.4
Lipoma	7	2.8	Herpes zoster	1	0.4
Trichilemmal cyst	6	2.1	Becker's naevus	1	0.4
Palmoplantar keratoderma	5	1.8	Naevus flammeus	1	0.4

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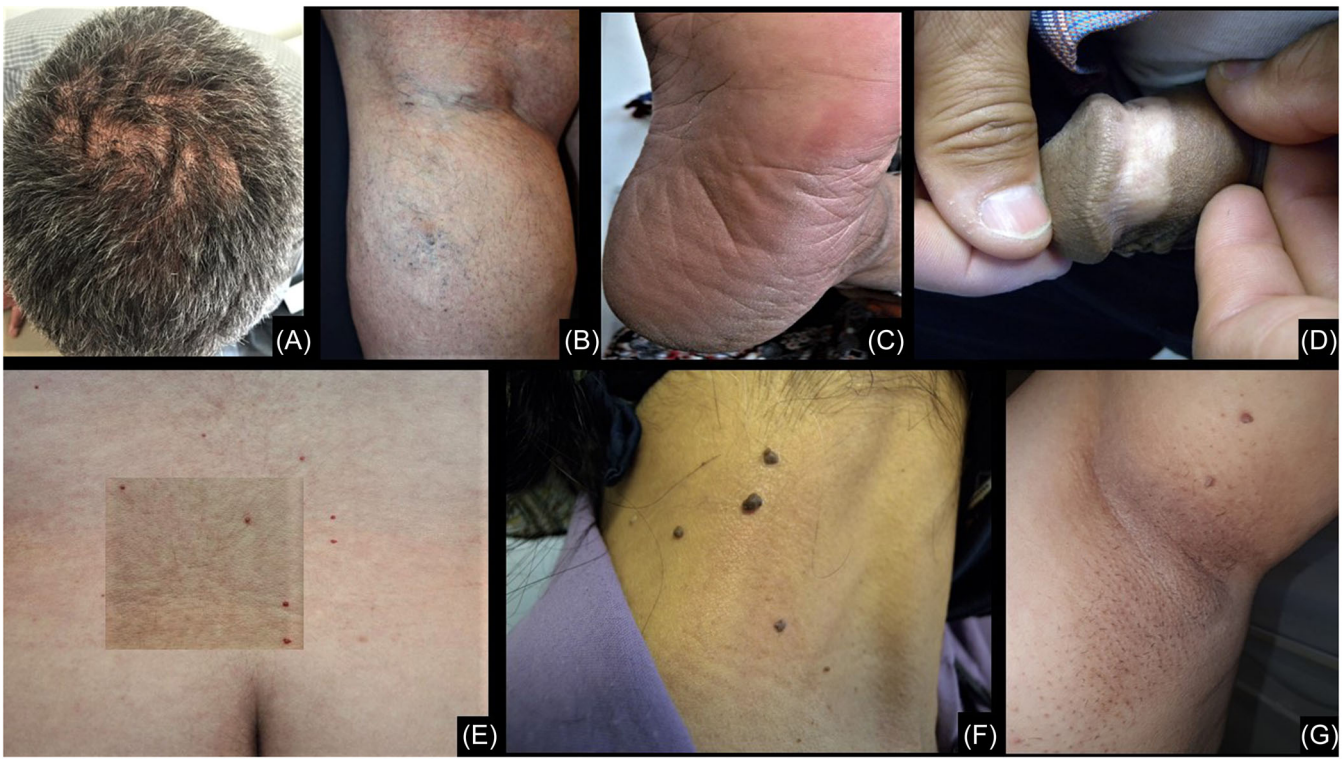


FIGURE 1 Some examples of skin findings of acromegaly (A: cutis verticis gyrata, B: varicose veins, C: xerosis cutis, D: vitiligo, E: cherry angioma, F: skin tags, G: acanthosis nigricans). [Color figure can be viewed at wileyonlinelibrary.com]

When acromegaly patients with and without endocrinopathy were compared in terms of skin manifestations: the incidence of hypothyroidism was significantly higher in patients with cherry angiomas compared to those without (*p*: .024), while the incidence of hyperthyroidism (*p*: .034) and galactorrhea (*p*: .027) was significantly lower. The frequency of DM and hypothyroidism was significantly higher in patients with varicose veins compared to those without (*p*-values: .001, .017, respectively). The frequency of DM (*p*: .001) and hypothyroidism (*p*: .001) was significantly higher in patients with seborrhoeic keratosis than in those without. The incidence of hypogonadism was significantly higher in patients with xerosis cutis (*p*: .035).

4 | DISCUSSION

The skin serves as a window for clinicians to understand and diagnose endocrine diseases.[10] Although cutaneous manifestations of endocrinopathies such as DM and hypothyroidism seem to be well established, there is limited data on the relationship between acromegaly and the skin.[2,3,7,8] In addition to the typical acromegaly phenotypic features, it had been demonstrated that the majority of these patients have some degree of skin involvement at disease onset, most typically on the face, hands and feet. Facial thickening and oedema usually manifest as macroglossia, macrocheilia and gingival hyperplasia, in addition to prognathism of the chin, nose and supraorbital protrusion. In addition to a prominent nasolabial groove, increased size, redness and wrinkling of the forehead have been reported to cause a melancholic expression in patients. Acromegalic skin thickening is primarily attributed to glycosaminoglycan deposition in the papillary dermis, reticular dermis and sweat glands. This deposition consists of hyaluronic acid (as in normal skin), chondroitin-4 and 6-sulphate, and dermatan sulphate.[2,3,7,8] We found phenotypic features such as acral growth and thickening of the skin of the hands, large triangular nose, coarse facial appearance, prognathism, increased tooth spacing and thickened lower lip in more than half of our patients. In our study, large skin pores were 41% and thickened heel pads were 39% in patients with acromegaly. In the literature, large skin pores were reported in 67.3% and thickened heel pads in 46.9% of patients with acromegaly.[2]

Regarding the accompanying skin lesions, we found skin tags (soft, skin-coloured growths on the skin) and cherry angiomas (small bright red dome-shaped bump on the skin) in almost half of the patients with acromegaly in our study. In the literature, skin tags have been reported with a rate of 5.9%–45%[2,3,7,8] and cherry angiomas with a rate of 13%[8] to 28.6%[2] in patients with acromegaly. The induction of cutaneous angiogenesis by the IGF-1/Insulin-like growth factor 1 signalling pathway has been implicated in the development of cherry angiomas in these patients.[2] In our study, we found cherry angiomas with a rate of 47% and the incidence of hypothyroidism was higher in these patients. Since hormonal factors such as pregnancy have also been involved in the aetiology of cherry

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TABLE 4 Demographic characteristics, top 10 most common skin lesions and accompanying endocrinopathy status of remitted and nonremitted patients.

Parameters	All patients (*n*: 278)	Remitted (*n*: 157)	Nonremitted (*n*: 121)	*p* Value
Sex	278	157 (56.4%)	121 (43.6%)	.129
Male	119	61 (51.2%)	58 (48.8%)	.315
Female	159	96 (60.3%)	63 (39.7%)	.108
Age (years)	50.00 (16.25)	50.00 (16.50)	49.00 (16.50)	.538
Skin findings				
Skin tags	146	77 (52.7%)	69 (47.3%)	.154
Cherry anjiomas	132	75 (56.8%)	57 (43.2%)	.913
Seborrhoea	103	51 (49.5%)	52 (50.5%)	.073
Varicose vein	92	56 (60.8%)	36 (39.2%)	.299
Acneiform lesion	80	39 (48.7%)	41 (51.3%)	.226
Hyperhidrosis	75	37 (49.3%)	38 (50.7%)	.085
Hypertrichosis	51	18 (35.2%)	33 (64.8%)	.001*
Xerosis cutis	48	34 (70.8%)	14 (29.2%)	.001*
Seborrhoeic keratosis	27	15 (55.5%)	12 (44.5%)	.124
Acanthosis nigricans	21	14 (66.6%)	7 (33.4%)	.327
Endocrinopathies	180	73 (40.5%)	107 (59.5%)	.134
Diabetes mellitus	111	65 (58.5%)	46 (41.5%)	.568
Hypothyroidism	99	56 (56.5%)	43 (43.5%)	.982
Hypogonadism	36	24 (66.6%)	12 (33.4%)	.123
Adrenal insufficiency	23	12 (52.1%)	11 (47.9%)	.664
Hyperthyroidism	7	7 (100%)	0 (0%)	.019*
Galactorrhea	5	4 (80%)	1 (20%)	.286
Hyperparathyroidism	3	2 (66.6%)	1 (33.4%)	.724

*Statistically significant values.

angiomas,[11] we thought that the frequency of accompanying hypothyroidism might be responsible for the high frequency of cherry angiomas in our study.

Seborrhoea (oily skin) and acne, which may also be associated with hyperandrogenism, had remarkable rates of 37% and 29%, respectively, in this prospective study. Although it has been reported in the literature that large pore oily skin is frequently observed in patients with acromegaly, the incidence of acne vulgaris is not common,[1,12] it has been stated that especially androgens, less frequently GH and IGF-1, may increase sebum production and rarely cause development of acne.[1,13] In one study, the presence of seborrhoea was remarkable in 79% of cases of acromegaly.[3] When cases of acromegaly were compared with the control group, it was concluded that there was no significant change in the number of sebaceous glands and that sebum secretion was responsible for the presence of increased seborrhoea in these patients.[1,7] In another study, the frequency of seborrhoea and acneiform lesions in patients with acromegaly was found to be 34.7% and 14.3%, respectively.[2] Considering the importance of increased sebum in the etiopathogenesis of acne, we can say that the presence of increased sebum in acromegaly patients may predispose these patients to develop acne.

In our study, we found the rate of acanthosis nigricans (a velvety, darkening of the skin that usually occurs in intertriginous areas) to be 8% in patients with acromegaly. Acanthosis nigricans, which is closely related to hyperandrogenism and insulin resistance, has been observed in 10%–42% of patients with acromegaly.[2,3,7,8] It is still unclear whether acanthosis nigricans and skin tags are the result of an excess of the GH/IGF-1 axis or metabolic dysregulation.[7,8,14]

Another unexpected finding in our study was that varicose veins were observed in 33% of patients. In our study, the incidence of DM and hypothyroidism was significantly higher in patients with varicose veins compared to patients without varicose veins. In the literature, the prevalence of varicose veins was found to be 10.2% in patients with acromegaly, increased matrix metalloproteinase (MMP) levels were shown in these patients, and it was reported that vessel wall

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damage due to MMP activation leads to varicose vein formation.[2,14] It is well known that DM and hypothyroidism lead to endothelial dysfunction.[15,16] Accordingly, we found a higher prevalence of varicose veins in our study compared to the literature, which we explained by the higher prevalence of endocrinopathies such as DM and hypothyroidism in these patients.

While the incidence of hyperhidrosis was 27% in our study, it has been reported in the literature that hyperhidrosis develops in 50%–88% due to hyperfunction of eccrine sweat glands.[2,3,7,8] The detection of IGF-1 immunoreactivity in the outer root sheath, sebaceous gland and myoepithelial cells of the secretory portion of eccrine sweat glands in these patients suggests that hyperhidrosis is induced by high IGF-1 levels.[2,17]

In our study, hypertrichosis was found in 18% of the patients, while no patient had hirsutism. IGF-1 also has an effect on the hair cycle by strongly stimulating the growth of hair follicles and preventing them from entering the catagen phase.[17] In the literature, it is stated that hypertrichosis is a common finding in patients with acromegaly and the IGF/Insulin-like growth factor IGFR interaction is responsible for the pathogenesis of hypertrichosis in these patients.[6,14] However, it is accepted that hirsutism is seen at a higher rate in these patients due to the decrease in sex hormone-binding globulin levels caused by excessive GH production.[18] In the literature, hypertrichosis was observed in 22.4% of patients with acromegaly.

In our study, xerosis (excessively dry skin), seborrhoeic keratosis (benign [noncancerous] skin growth), cutis vertisis gyrate (CVG) (overgrowth of the scalp skin resulting in convoluted folds and deep furrows of skin that resemble the surface of the brain) were observed at considerable rates. It has been reported that IGF may increase the incidence of seborrhoeic keratosis in patients with DM by causing keratinocyte and dermal fibroblast proliferation.[19] While seborrhoeic keratosis was found in 18% of patients with acromegaly in one study,[2] this rate was 10% in our study. In fact, this suggests the existence of a common pathway, such as IGF, in the pathogenesis of skin diseases in patients with DM and acromegaly. CVG rates of 1.6%[6] and 24.5%[2] have been reported in the literature, and it has been stated that the actual frequency of CVG may be higher than the rate reported in the literature due to the appearance of the lesion under the hair that prevents it from being recognised until it becomes prominent.[2] This rate was 6% in our study.

As for other skin lesions, generalised hyperpigmentation,[20] melasma (skin condition characterised by brown or blue-grey patches or freckle-like spots),[8] poikiloderma of Civatte (noncancerous skin condition that appears as reddish-brown spots usually on your neck and cheeks),[20] hidradenitis suppurativa (painful, long-term skin condition that causes skin abscesses and scarring on the skin),[13,21,22] psoriasis (skin disease that causes a rash with itchy, scaly patches, most commonly on the knees, elbows, trunk and scalp)[8,23] have been other skin lesions for which an association with acromegaly has been sought in the literature. IGF-1 is one of the growth factors that induce cell division, and epidermal keratinocyte proliferation. In fact, epidermal hyperplasia plays an important role in the pathogenesis of psoriasis.[5,23] A potential increased risk of developing psoriasis in patients with acromegaly has been suggested.[8,14] Acromegalic patients with psoriasis have been reported to benefit from pituitary tumour excision[23] or treatment with somatostatin analogues.[24] In summary, based on literature data, hypersecretion of GH and IGF-1 leads to differentiation of the skin and adnexa and this common pathway seems to be responsible for the development of almost all skin lesions.

As a result of hypersecretion of GH and IGF-1 and this differentiation in the skin and adnexa, we would like to draw attention to the frequency of insulin resistance and cutaneous androgenization findings in these patients. In our study, we found DM, hypothyroidism and hypogonadism to be the most common endocrinopathies among patients with acromegaly who exhibit skin lesions. It has also been reported in the literature that some endocrinopathies similar to our study are more common in patients with acromegaly.[2,3,7,8] In our study, the more common endocrinopathy in acromegaly patients in remission was hyperthyroidism.

Cases of xanthelasma (painless, yellowish bumps that typically form near the eye or on the eyelid), sebaceous hyperplasia (common, benign condition of sebaceous glands in adults of middle age or older), lipoma (lump of fatty tissue that grows just under the skin), epidermal cyst (benign encapsulated, subepidermal nodule filled with keratin material), lentiginous naevus (lentiginous epidermal hyperplasia) and melanocytic naevus (noncancerous condition of pigment-producing skin cells) have also been reported in patients with acromegaly; however, a direct relationship between these findings and acromegaly has not been established.[8,25,26] We think that studies involving larger patient groups are needed to understand whether these similar benign tumours are incidental or related to angiogenesis, cell division and epidermal hyperplasia associated with acromegaly. We also found palmoplantar keratoderma (abnormal thickening of the stratum corneum of the palms and soles), vitiligo (chronic autoimmune disorder that causes patches of skin to lose pigment or colour), lichen planus (recurrent, pruritic, inflammatory eruption characterised by small, discrete, polygonal, violaceous papules that may coalesce into rough scaly plaques, often accompanied by oral and/or genital lesions), prurigo nodularis (chronic disorder of the skin that is classically seen as multiple, firm, flesh to pink coloured papules, plaques and nodules commonly located on the extensor surfaces of the extremities), erythema annulare centrifigum (annular, erythematous lesion that appears as urticarial-like papules and enlarges centrifugally, then clears centrally), syringoma (noncancerous growth in the sweat glands), dermatofibroma (common benign fibrous nodule usually found on the skin of the lower legs), Becker naevus (cutaneous hamartoma characterised by circumscribed hyperpigmentation with hypertrichosis) and naevus flammeus (permanent pink or purple birthmark that usually appears on the face), which have not been previously reported in patients with acromegaly.

A limitation of this study is the lack of a control group. Another limitation of this study was the possibility of encountering a margin of error when comparing these findings according to the patients' remission status since many skin findings were detected. When the

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disease and remission findings of the patients were compared, there was a significant difference only in patients with xerosis cutis and hypertrichosis. Perhaps for this reason, xerosis cutis may have been observed more frequently in patients in remission. However, the fact that hypertrichosis was observed more frequently in patients who were not in remission was an understandable and important finding. Finally, we investigated skin findings and their relationship with other accompanying endocrinopathies in a large series of patients with remitted and nonremitted acromegaly. Cutaneous androgenization findings such as skin tag, seborrhoea, acne and acanthosis nigricans are common in patients with acromegaly. Clinicians should be aware that skin findings associated with insulin resistance may develop in these patients.

5 | CONCLUSION

It can be said that the remission state in acromegaly has no curative effect on cutaneous findings. Only patients in remission were less likely to have hypertrichosis. This may allow earlier review of the follow-up and treatment of acromegaly patients presenting with complaints of hypertrichosis. Additionally, it can be said that patients with skin findings such as cherry angioma may be predisposed to a second endocrinopathy, especially hypothyroidism. Dermatology examinations can also be included in acromegaly patient management to detect these cutaneous findings earlier.

ACKNOWLEDGEMENTS

There is no financial support.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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REFERENCES

1. Molitch ME. Clinical manifestations of acromegaly. *Endocrinol Metab Clin North Am*. 1992;21:597-614.
2. Akoglu G, Metin A, Emre S, Ersoy R, Cakir B. Cutaneous findings in patients with acromegaly. *Acta Dermatovenerol Croat*. 2013;21:224-229.
3. Dahbar M, Danilowicz K, Malavela M, et al. Cutaneous manifestations of acromegaly. *Dermatol Argent*. 2009;15:186-190.
4. Vila G, Jørgensen JOL, Luger A, Stalla GK. Insulin resistance in patients with acromegaly. *Front Endocrinol*. 2019;10:509.
5. Centurión SA, Schwartz RA. Cutaneous signs of acromegaly. *Int J Dermatol*. 2002;41:631-634.
6. Nabarro JDN. Acromegaly. *Clin Endocrinol*. 1987;26:481-512.
7. Arya KR, Krishna K, Chadda M. Skin manifestations of acromegaly – a study of 34 cases. *Indian J Dermatol Venereol Leprol*. 1997;63:178-180.
8. Resende M, Bolfi F, Nunes VS, Miot HA. Prevalence of dermatologic disorders in 15 patients with acromegaly. *An Bras Dermatol*. 2012;87:166-168.
9. Cordido F, García Arnés JA, Marazuela Aspiroz M, Torres Vela E. grupo de Neuroendocrinología de la Sociedad Española de Endocrinología y Nutrición. Guía práctica de diagnóstico y tratamiento de la acromegalia. [Practical guidelines for diagnosis and treatment of acromegaly. Grupo de Neuroendocrinología de la Sociedad Española de Endocrinología y Nutrición]. *Endocrinol Nutr*. 2013;60:457.e1-457.e15.
10. Lause M, Kamboj A, Fernandez Faith E. Dermatologic manifestations of endocrine disorders. *Transl Pediatr*. 2017;6:300-312.
11. Nakashima T, Jinnin M, Etoh T, et al. Down-regulation of mir-424 contributes to the abnormal angiogenesis via MEK1 and cyclin E1 in senile hemangioma: its implications to therapy. *PLoS One*. 2010;5:e14334.
12. Ben-Shlomo A, Melmed S. Skin manifestations in acromegaly. *Clin Dermatol*. 2006;24:256-259.
13. Chalmers RJ, Ead RD, Beck MH, Dewis P, Anderson DC. Acne vulgaris and hidradenitis suppurativa as presenting features of acromegaly. *Br Med J (Clin Res Ed)*. 1983;287:1346-1347.
14. Sandru F, Popa A, Paduraru D, Filipescu A, Carsote M, Ghemigian A. Skin anomalies in acromegalic patients (review of the practical aspects). *Exp Ther Med*. 2021;22:1330.
15. Hadi HA, Suwaidi JA. Endothelial dysfunction in diabetes mellitus. *Vasc Health Risk Manag*. 2007;3:853-876.
16. Niknam N, Khalili N, Khosravi E, Nourbakhsh M. Endothelial dysfunction in patients with subclinical hypothyroidism and the effects of treatment with levothyroxine. *Adv Biomed Res*. 2016;5:38.
17. Lange M, Thulesen J, Feldt-Rasmussen U, et al. Skin morphological changes in growth hormone deficiency and acromegaly. *Eur J Endocrinol*. 2001;145:147-153.
18. Jain R, Dutta D, Shivaprasad K, et al. Acromegaly presenting as hirsuitism: uncommon sinister aetiology of a common clinical sign. *Indian J Endocrinol Metab*. 2012;16:297.
19. Girisha B, Viswanathan N. Comparison of cutaneous manifestations of diabetic with nondiabetic patients: a case-control study. *Clin Dermatol Rev*. 2017;1:9-14.
20. Kaltsas GA, Mukherjee JJ, Jenkins PJ, et al. Menstrual irregularity in women with acromegaly. *J Clin Endocrinol Metab*. 1999;84:2731-2735.
21. Degirmentepe EN, Gungor S, Kocaturk E, et al. Dermatologic manifestations of acromegaly: a case in point and a focused review. *Dermatol Online J*. 2017;23:4.
22. Scheinfeld N. Diseases associated with hidranitis suppurativa: part 2 of a series on hidradenitis. *Dermatol Online J*. 2013;19:18558.
23. Todd DJ, Eedy DJ, McMillan JC. Acromegaly and psoriasis. *Clin Exp Dermatol*. 1991;16:222-223.
24. Weber G, Klughardt G, Neidhardt M, Galle K, Frey H, Geiger A. Treatment of psoriasis with somatostatin. *Arch Dermatol Res*. 1981;272:31-36.
25. Zanini M, Oshiro RR, Paschoal LHC, Paschoal FM, Timoner FR. Aspectos dermatológicos da acromegalia. *An Bras Dermatol*. 2004;79:491-494.
26. Billon C, Beylot-Barry M, Doutre MS, Latapie JL, Roger P, Beylot C. Cutaneous manifestations of acromegaly: 4 cases. *Ann Dermatol Venereol*. 1996;123:821-823.

How to cite this article: An i, Kahraman FC, Bilgiç A, et al. Cutaneous findings in patients with acromegaly and its relationship with concomitant endocrinopathies. *Clin Endocrinol*. 2024;1-8. doi:10.1111/cen.15071

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