

Dermatologic manifestations of acromegaly: A case in point and a focused review

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Abstract

Acromegaly is a systemic syndrome caused by overproduction of growth hormone. Cutaneous, endocrine, cardiovascular, skeletal, and respiratory systems are affected. Cutaneous changes in acromegaly relate to overexpression of growth hormone and insulin-like growth factor 1 on skin cells and adnexa. Dermal glycosaminoglycan accumulation and edema cause skin distention that is most prominent in the face, hands, and feet. Oily skin with large pores, hypertrichosis, and excessive sweating are common features. Pigmented skin tags, acanthosis nigricans, and psoriasis are also encountered. Cutaneous manifestations of acromegaly are various and prominent, and are an important clue for the early diagnosis and treatment of this high-morbidity disorder.

Keywords: acromegaly, cutaneous changes, growth hormone

Introduction

Acromegaly is a systemic syndrome resulting from an excess of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) in adulthood after or around the time that epiphyses close [1, 2]. Gigantism accounts for up to 5% of cases and occurs when the excess of GH and IGF-1 becomes manifest in the young, before the epiphyseal plates close. Gigantism can also be familial but it is extremely rare [3]. The biological activity of GH (also known as somatotropin) is mediated by IGF-1. The annual incidence is about 11 cases per

million, with an estimated prevalence of 78 cases per million [4]. Acromegaly affects both genders equally [5]. The mean age of diagnosis ranges from 40 to 50 years [6]. In more than 95% of cases, the underlying pathology is a GH-secreting pituitary adenoma (somatotropinoma) arising from somatotroph cells, causing GH and IGF-1 hypersecretion [7]. In less than 5% of cases, excess growth hormone releasing hormone (GHRH) secretion from a hypothalamic tumor or neuroendocrine tumor may lead to somatotroph hyperplasia and acromegaly [3]. Over 90-95% of GH-secreting pituitary adenomas are sporadic and occur as an isolated disorder. However, acromegaly can also occur in a familial setting [3, 8]. An activating mutation of the alpha subunit of the guanine nucleotide stimulatory protein G, the pituitary tumor transforming gene, microduplications on chromosome Xq26.3, and recurrent mutations in *GPR101* (G protein-coupled receptor 101) have been associated with pituitary lesions [9-11]. Familial GH-secreting tumors are seen in association with three separate hereditary clinical syndromes: (1) multiple endocrine neoplasia type 1 (MEN1), (2) Carney complex (CNC), and (3) familial isolated pituitary adenomas (FIPA), [3].

The diagnosis of acromegaly is confirmed by the detection of high GH levels after an oral glucose tolerance test (OGTT) and by increased levels of IGF-1. After a hormonal diagnosis, MRI of the brain is done to show the presence and size of the adenoma and any invasion into the adjacent tissues. High levels of GH and IGF1 are associated with high morbidity and mortality rates [12]. The syndrome affects almost every organ system, mainly cutaneous, endocrine,

cardiovascular, respiratory, and skeletal systems, owing to increased levels of GH and IGF-1. Early and apparent manifestations involve skin and soft tissue, especially the face (marked facial lines, large pores, eyelid edema, widened and thickened nose, thick lips, prognathism, tooth separation) and extremities (hand and foot enlargement, heel pads, hard and thick nails), [6]. Cutaneous changes that accompany acromegaly are classical features of the disorder and an important clue for early diagnosis and treatment of this high morbidity disorder [2]. Thus, suspicion and careful evaluation of the skin findings are crucial for an early and accurate diagnosis. Herein we present a case of acromegaly, which was diagnosed by the cutaneous manifestations at our dermatology clinic. We also present a brief review of the skin manifestations of acromegaly.

Case Synopsis

A 37-year-old man was referred to our clinic with a complaint of enlargement of hands and feet and asymptomatic hyperpigmented patches on the phalangeal and metacarpophalangeal joints for about 3 months prior to his presentation. Symmetric dark-brown patches and papillomatous hypertrophy overlying the phalangeal and metacarpophalangeal joints on the dorsum of both hands were observed (**Figure 1**). Clinical examination revealed other significant findings including velvety brownish-dark plaques and soft, brown hyperpigmented polypoid growths on the neck, groin, and bilateral axillae. Also distributed in these areas were erythematous sinus



Figure 1. Symmetric dark-brown patches and papillomatous hypertrophy in the phalangeal and metacarpophalangeal joints on the dorsum of both hands.

tracts and scarring. Additionally, the patient had thickening of scalp and multiple gyriform oblong skin folds in the occipital region (**Figures 2 and 3**). He was otherwise healthy and had no family history of similar findings. Based on the above described findings, the clinical diagnoses of atypical acanthosis nigricans, hidradenitis suppurativa, and cutis verticis gyrata were made. Because of the extent and rapid progression of the above-mentioned changes, further investigations were initiated. A skin biopsy from the dorsum of the hand revealed the presence of hyperkeratosis, papillomatosis, and increased melanin pigmentation along the rete ridges with digitated protrusion of the dermal papilla, which were compatible with acanthosis nigricans (**Figure 4**). Laboratory tests revealed an erythrocyte sedimentation rate of 12 (reference range: 0-15) mm/h and the C reactive protein concentration of 3.28 (reference range: 0-5) mg/l, plasma glucose of 111 mg/dl and hemoglobin A1C of 5.7%. Laboratory tests also revealed a high serum IGF-1 level of 757 (reference range: 109-284) ng/mL and a serum GH level of 2.65 (reference range: 0-5) ng/mL, which was not suppressed following an oral glucose tolerance



Figure 2. Velvety dark brown plaques and multiple, soft, brown hyperpigmented polypoid lesions and erythematous sinus tracts on axillae.



Figure 3. Thickening of scalp and multiple gyriform oblong skin folds in the occipital region, as well as hyperpigmented folds and multiple soft pedunculated papules on the back of the neck area.

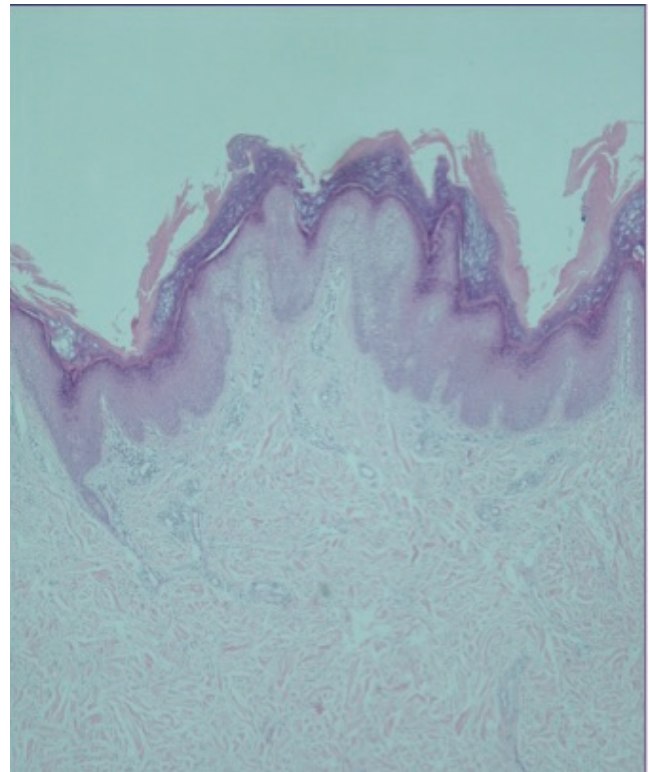


Figure 4. Hyperkeratosis, papillomatosis, increased melanin pigmentation along the tips of rete ridges, (H&E, 40x).

test (OGTT). These laboratory findings confirmed the diagnosis of acromegaly. MRI of the head and neck areas revealed a pituitary mass measuring 11x7.5x5 mm (**Figure 5**). The patient underwent transphenoidal resection of the tumor and was started on lanreotide, a somatostatin inhibitor. During follow up, the patient lost weight and his acanthosis nigricans lesions resolved (**Figure 6**). He continues follow up in the endocrinology department.

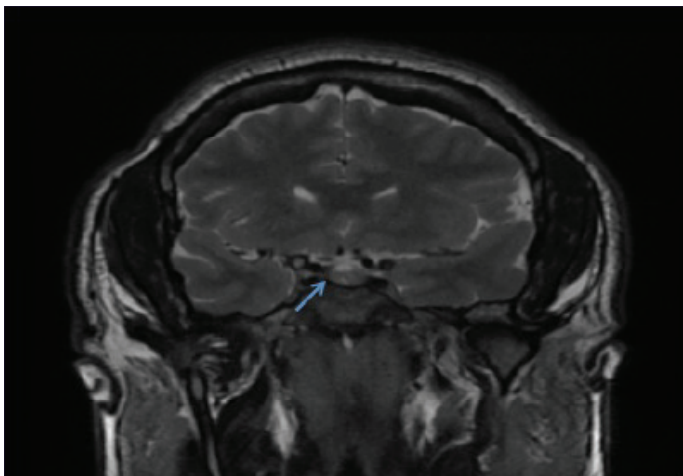


Figure 5. MRI of the head and neck area showing a pituitary mass measuring 11x7.5x5 mm corresponding to a pituitary adenoma.

Review of Mechanisms and Clinical Presentations of Cutaneous Findings in Acromegaly:

Increased production of GH and IGF-1 often results in morphological changes in the skin and other organ systems. Excess GH stimulates oversecretion of IGF-1, and IGF-1 in turn acts as the primary mediator of the growth promoting effects of GH [6]. After binding to IGF-1 receptors (IGFRs), cells such as keratinocytes, fibroblasts, pilar unit cells, Schwann cells, muscle cells, and medial and endothelial cells of arteries are stimulated [2]. The most early and apparent manifestations of acromegaly are in the skin and soft



Figure 6. Resolution of acanthosis nigricans after losing weight.

tissue, particularly notable on the face and extremities. The skin in acromegaly is more elastic than normal skin resulting in deepening of skin folds. Increased proliferation of keratinocytes and fibroblasts causes skin thickening and edema owing to accumulation and infiltration of glycosaminoglycan (GAG) deposits [12]. Similarly, increased skeletal growth is caused by periosteal proliferation and cartilage formation. Findings on the face include prominent nasolabial folds, forehead creases, eyelid edema, increased sebaceous gland proliferation and sebum production

of the skin, large pores, hypertrichosis, widened and thickened nose, thick lips, prognathism, and tooth separation [4, 5, 12]. In the extremities, one can see hand and foot enlargement, heel pads, and hard and thickened nails [6, 12]. Excess sweating is also prominent in patients with acromegaly [14].

A significant number of pigmented skin tags on the trunk is a common finding in patients with acromegaly [15]. In the general population, skin tags are usually associated with diabetes mellitus,

Table 1: Cutaneous findings in patients with acromegaly.

Acral enlargements
Course face
Large triangular nose
Prognathism
Thickened lower lip
Macroglossia
Acrochordons
Widened skin pores
Oily skin
Hypertrichosis
Hyperhidrosis
Thickened heel pads
Thickened nails
Eyelid edema
Cutis verticis gyrate
Cherry angiomas
Seborrheic keratosis
Acneiform lesions
Acanthosis nigricans
Soft fibromas
Varicose veins
Psoriasis
Increased size of external ear
Onychodystrophy
Clubbing

This table with information included in it was adapted from articles in reference list 5, 8, 10.

insulin resistance, and dyslipidemia [14]. It is not clear whether GH/IGF-1 overproduction causes skin tags directly or whether they arise as a result of insulin resistance and dyslipidemia.

Acanthosis nigricans is another cutaneous manifestation that develops in both male and female patients with severe acromegaly. The skin in the axillae and back of the neck becomes dark, soft, and velvet-like with delicate folds and papillae [15]. These acanthosis nigricans changes can also be localized to the knee, ankle, and proximal and distal phalangeal and metocarpophalangeal joints [15]. Increased amounts of skin extracellular matrix, accompanied by edema, and alteration in the GAG quality cause these clinical findings [14, 16].

IGF-1 is one of the growth factors involved in the pathogenesis of psoriasis. Proliferation of epidermal keratinocytes, epidermal hyperplasia, and cell division are induced by IGF-1 [14].

Cutis verticis gyrata is one of the least frequent skin signs reported in acromegaly and it is characterized by deep scalp furrows caused by soft tissue thickening [13].

Hidradenitis suppurativa is a very rare manifestation of acromegaly and is a disorder of the terminal follicular epithelium in the apocrine gland-bearing skin [17].

Besides the typical cutaneous manifestations, multiple cherry angiomas and varicose veins are also observed in patients with acromegaly [13]. A comprehensive list of dermatological findings in patients with acromegaly is listed in **Table 1**.

The definitive test for the diagnosis of acromegaly is the OGTT. After oral administration of 50 to 100 g of glucose, the evaluation of GH serum level response is a reliable test. GH levels will be suppressed after 1 to 2 hours to less than 1 ng/mL, and often will be undetectable. Yet patients with acromegaly do not suppress GH levels after the test. In addition, age and sex matched IGF-1 serum levels are elevated. Some of the cases with acromegaly referred as 'micromegaly' have normal GH levels with elevated IGF-1 as in our patient. This finding strengthens the growing body

of evidence which supports the leading role of IGF-1 levels in diagnostic evaluation [18]. Patients must undergo a pituitary MRI after hormonal diagnosis to determine the presence of a pituitary tumor and detect its size and degree of invasion [6].

Controlling GH and IGF-1 oversecretion moderates most cutaneous manifestations of acromegaly. Treatment protocols include tumor resection with possible adjuvant radiotherapy and/or pharmacotherapy with somatostatin analogs, GH receptor antagonists, or dopamine agonists [6].

Conclusion

In summary familiarity with cutaneous changes that accompany acromegaly are important for early diagnosis and treatment of this high morbidity disorder.

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