

Skin anomalies in acromegalic patients (Review of the practical aspects)

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Abstract. Acromegaly is a hormonal disorder which occurs as the result of growth hormone (GH) and insulin growth factor 1 (IGF-1) over-secretion; both hormones are related to skin anomalies. The skin acts as a large endocrine organ, hosting GH receptors in every cell while IGF-1 receptors are expressed only in keratinocytes. This review is a literature review of skin anomalies found in acromegaly, either related to the disease itself or associated with related complications such as secondary diabetes mellitus, or involving associated conditions such as genetic syndromes. The following clinical points are mentioned as follows. Excessive skin and enlargement of soft tissue are due to glycosaminoglycan deposits, edema, and hyperhidrosis (mostly facial and acral). Acanthosis nigricans, a body fold dermatosis associated with insulin resistance, involves local or diffuse hyperkeratotic plaques with or without hyperpigmentation, caused by growth factors including GH/IGF-1. Other findings include cherry angiomas (due to the effects of lipid anomalies on small vessels); oily skin features with keratosis, epidermoid cysts, crochordons,

pseudo-acanthosis nigricans; a potentially higher prevalence of varicose veins and psoriasis; low level of evidence for basal cell carcinoma, respective hidradenitis suppurativa has been noted. In addition, complicated uncontrolled secondary diabetes mellitus (DM) may result in necrobiosis lipoidica diabetorum, diabetic dermopathy, skin bacterial infections, dermatological complications of diabetic neuropathy, and nephropathy. Finally, associated hereditary syndromes may cause collagenomas, fibromas/angiofibromas, lipomas in multiple endocrine neoplasia type 1 (MEN1) syndrome; café-au-lait macules, early onset neurofibromas, juvenile xanthogranuloma (involving non-Langerhans cell histiocytes), and intertriginous freckling in neurofibromatosis type 1. Clinical findings are differentiated from pseudo-acromegaly such as pachydermoperiostosis. Iatrogenic rash, lipodystrophy (lipoatrophy with/without lipohypertrophy) are rarely reported after pegvisomant/somatostatin analogues or after insulin use for DM. Experiments using human cell lines have shown that GH/IGF-1 over-secretion are prone to epithelial-to-mesenchymal transition (EMT) in melanoma. In non-acromegalic subjects, the exact role of GH/IGF-1 in skin tumorigenesis is yet to be determined. Skin in acromegaly speaks for itself, either as the first step of disease identification or as a complication or part of a complex syndromic context.

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Abbreviations: EMT, epithelial-to-mesenchymal transition; GH, growth hormone; GH-R, growth hormone receptor; HR, hazard ratio; IGF, insulin growth factor; lncRNAs, long noncoding RNAs; MEN1, multiple endocrine neoplasia type 1

Key words: acromegaly, growth hormone, IGF1, skin, dermatologic, diabetes mellitus, angiomas, acanthosis nigricans, melanoma, MEN1 syndrome

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1. Introduction

Acromegaly is caused by a pituitary somatotropinoma in 95% of cases. The complications are due to an excess in growth hormone (GH) or insulin growth factor 1 (IGF-1) or both; females and males are similarly affected; the peak incidence is between 40 and 50 years of age; 5% of cases are gigantism; 10% of tumors co-secrete prolactin; and 5% of cases are detected below the age of 20 years (1). A multitude of complications are related to abnormal imbalance and to the presence of a pituitary mass, overall impacting the quality of life, morbidity and mortality of the patients (2).

Acromegaly occurs as the result of GH and IGF-1 over-secretion; skin anomalies are caused by both hormones (3). Skin, a large endocrine organ, has receptors for GH at all cell types while IGF-1 receptors are only expressed at the level of keratinocytes in the epidermis (4).

Excessive skin and enlargement of soft tissue are due to glycosaminoglycan deposits, edema, hyperhidrosis, mostly at the level of the extremities (acral) and face (5,6).

Facial features and skin changes in addition to bone and joint modifications need to be differentiated from other conditions that are not induced by GH/IGF-1 excess, which are termed 'acromegaloidism' or 'pseudo-acromegaly' (7). In addition, pachydermoperiostosis involves pachyderma, periosteal hypertrophy and hyperhidrosis, with an acromegaly-like aspect (8). This is a hereditary condition also affecting the face, hands and feet (9).

Skin rash has been reported in relationship to specific therapy against GH excess such as pegvisomant or somatostatin analogues (10). Lipodystrophy, either lipoatrophy or lipohypertrophy, may be associated with these drugs as well as insulin in severe secondary cases of GH-induced diabetes mellitus (DM) (11).

2. Aim of the review

We aimed to introduce the clinical aspects of the dermatological findings in acromegaly on a multidisciplinary perspective.

This is a literature review of skin anomalies found in acromegaly, either related to the disease itself, or related to its complications such as secondary DM, or involving associated conditions such as genetic syndromes. The research is based on PubMed. The key words used were based on different combinations: 'acromegaly', 'diabetes mellitus', 'MEN1 syndrome', on the one hand, respective 'skin', 'acanthosis nigricans', 'angioma', 'melanoma', on the other hand. The selection of 60 cited papers is based on clinical relevance. We included papers published between 2011 and 2021.

3. GH/IGF-1 and melanoma

GH/GH-R (receptor) and IGF are considered growth factors involved in different tumors; however, their role in melanoma is less clear (12). Experiments on human cell lines have shown that GH/IGF-1 excess results in EMT in melanoma (13). Somatostatin analogues may be future therapeutic targets in melanoma if somatostatin receptor expression is highlighted, as currently seen in GH-producing pituitary tumors and gastro-entero-pancreatic neuroendocrine neoplasia (14). In

non-acromegalic subjects, the skin tumorigenic role of IGF-1 and GH/GH-R is yet to be determined (15). For instance, a large prospective study on 412,645 individuals (UK Biobank) who were followed up for 7.2 years showed a positive correlation between IGF-1 overexpression and melanoma with a modest hazard ratio (HR) of 1.08 (95% CI, 1.01-1.15) (15). Yet, statistical correction of the data extracted from the same bio-base (394,388 individuals followed for 6.9 years) showed no association between IGF-1 and malignant melanoma (16).

IGF axes may also modulate chemotherapy resistance in melanoma through communication with long noncoding RNAs (lncRNAs) (17). Modulation of the estrogen receptor (ER)/IGF-1 signal transduction communication may explain the gender differences in melanoma presentation (18). Furthermore, IGF-1 receptor distribution on uveal melanoma explains its aggressive profile, especially the risk of hepatic spreading (19). Pristimerin may contra-regulate the IGF-1 receptor downstream in uveal melanoma, and its use in clinical practice is under evaluation (19).

In addition, downregulation of the IGF-1 receptor in melanoma may enhance the tumoral cell response to mitogen-activated protein kinase (MAPK) inhibitors (20). When it comes to acromegalic patients, a higher risk of various cancers has been reported such as colonic carcinoma (21). However, this is mostly related to uncontrolled disease, and recent data showed a massive improvement of the oncologic risk in these patients during the last decade due to multi-modal therapy (22). Overall, no specific risk has been reported in relationship with malignant melanoma in acromegalic subjects; neither case finding strategies in individuals diagnosed with melanoma in order to seek a source of GH/IGF-1 excess (23,24).

4. Syndromic context

Carney complex includes thyroid, adrenal, and gonadal anomalies as well as acromegaly in association with myxomas which are located at different regions including the skin (25). Additional lesions in this *PRKARIA* (protein kinase CAMP-dependent type I regulatory subunit α) gene-related autosomal dominant condition include blue nevi, pigmented spots, lentiginosis features, and psammomatous melanotic schwannomas (26).

McCune-Albright syndrome, exceptionally associated gigantism-acromegaly, requires a differentiation of facial dysplasia to GH excess-associated features. Also, other skin anomalies that are found in these patients include café-au-lait spots (27).

Pituitary somatotropinomas have been reported in some subjects confirmed with neurofibromatosis type 1 (28-30). This is not a traditional endocrinopathy of the syndrome, in contrast to pheochromocytomas or somatostatinomas; they may also be associated with other anomalies of the glucose profile that, on a long term, might express on the skin among other complications (31,32). Individuals presenting this autosomal dominant RASopathy may have multiple dermatological anomalies such as café-au-lait macules, neurofibromas of different types with early onset at childhood and adolescence (even oral neurofibromas have been recently reported), nevus anemicus, juvenile xanthogranuloma (a rare condition of non-Langerhans cell histiocytes), and intertriginous

freckling (33-35). Pigmented skin tags are found in individuals diagnosed with GH-producing hypophyseal tumors with lentiginous-like aspects which need to be differentiated from similar skin anomalies in neurofibromatosis type 1 (36). Melanocytic proliferation in neurofibromatosis type 1 may be suboptimally screened nowadays (37).

Non-endocrine manifestations of multiple endocrine neoplasia type 1 syndrome may include skin findings such as basocellular carcinoma, collagenomas, fibromas/angiofibromas, low-grade fibromyxoid sarcoma, and lipomas (38,39). Since there is no genotype-phenotype correlation in this *MEN-1* gene-related hereditary syndrome, the clinical aspects of acromegaly or of different dermatological lesions cannot be exclusively predicted based on genetic assessments (40,41).

5. Acanthosis nigricans

Endocrine-related conditions associated with acanthosis nigricans include DM, acromegaly, polycystic ovary syndrome, Cushing syndrome, and obesity with insulin resistance (the skin lesion is the hallmark of insulin resistance) (42). Dermoscopic and skin biopsy might bring supplementary information (43). Androgen excess may also cause it, also inducing hirsutism (hirsutism has been reported in acromegaly and prolactinoma, too, as well as acne) (44). Paraneoplastic presentation of acanthosis nigricans has been described (45).

Acanthosis nigricans represents a hyperplastic muco-cutaneous lesion that is also reported in teenagers and the pediatric population; it is due to local growth factors including GH/IGF-1 (46). It may represent an early sign of an endocrine-metabolic anomaly which is mainly focused on insulin resistance (47). Hyperkeratotic plaques are either local or diffuse, associated with hyperpigmentation; they are part of a fold dermatosis and exceptionally they are reported at the oral mucosa level (48).

6. Other dermatological findings

Cherry angiomas have been reported in acromegaly according to some studies with a higher prevalence than the global population (49). Generally, cherry angiomas are related to aging or to different pro-angiogenesis elements, despite the fact that the exact cause remains unknown (50). Most angiogenetic factors involve small vessel obstruction due to anomalies of lipid profile as seen in acromegaly (51). Oily aspect of the skin may be associated with keratosis, epidermoid cysts and crochordons and pseudo-acanthosis nigricans (52).

The GH/IGF-1 system acts as a prone of vessel proliferation such as retinal vessels, but also dermal; varicose veins in the legs also have been found with increased prevalence according to some authors (53). A potential increased risk of developing psoriasis has been suggested (54). Rare cases of co-incident basal cell carcinoma are reported (55). Case reports with hidradenitis suppurativa, a follicular condition, have been linked to acromegalic status, but the association is not typical (56). A few studies have shown a higher prevalence of autoimmune conditions such as Hashimoto thyroiditis among individuals with acromegaly; the most common non-endocrine autoimmune

correlate of chronic autoimmune thyroiditis is vitiligo (57). In cases with severe, complicated, uncontrolled, secondary (acromegaly-related) DM, we need to take into consideration the large area of multiple dermatological complications such as necrobiosis lipoidica diabetorum, diabetic dermopathy, skin bacterial infections, scleroderma, skin complications of diabetic neuropathy, and nephropathy (58-60).

7. Conclusions

Skin in acromegaly speaks for itself, either as a first step of disease identification or as a complication or part of a syndromic context. A multidisciplinary team is needed for the management of acromegalic patients, including a dermatological assessment.

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FS drafted the manuscript and critically revised the final form. AP drafted the manuscript, and DNP researched the literature. AF is the corresponding author and researched the literature. MC drafted the manuscript and researched the references, and AG revised the bibliography and approved the final form. All authors read and approved the final manuscript for publication.

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Competing interests

The authors declare that they have no competing interests.

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