OBSERVATION

Cutaneous Features of Crouzon Syndrome With Acanthosis Nigricans

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Importance: Crouzon syndrome with acanthosis nigricans is a distinct disorder caused by a mutation in the *FGFR3* gene, featuring craniosynostosis, characteristic facial features, and atypical and extensive acanthosis nigricans. Other cutaneous findings have not been thoroughly described.

Observations: We report 6 cases and summarize the existing literature with regard to the cutaneous manifestations of this disorder. All patients have widespread, early-onset acanthosis nigricans. Patients often have prominent hypopigmented scars at surgical sites and nevi arising early in childhood.

Conclusions and Relevance: In addition to craniofacial malformations, Crouzon syndrome with acanthosis nigricans results in characteristic cutaneous findings.

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Acanthosis nigricans (AN) associated with Crouzon syndrome was initially described in the 1960s as an unusual subtype of AN.[1] Since then, more than 35 case reports of this genetically distinct disorder known as Crouzon syndrome with acanthosis nigricans (CSAN) have been described.[2-17] Typical craniofacial and skeletal features of CSAN overlap with classic Crouzon syndrome; all described cases present with craniosynostosis, proptosis, hypertelorism, posteriorly rotated ears, and midface hypoplasia. In addition, patients with CSAN often present with choanal atresia and hydrocephalus, which are absent in classic Crouzon syndrome.[18]

Unlike classic Crouzon syndrome, which lacks any specific cutaneous features, the presence of AN is essential for the clinical diagnosis of CSAN. Affected individuals develop early-onset, severe, and widespread rugose thickening and hyperpigmentation of the skin; 2 reports describe the presence of AN at birth.[9,14] In addition to the most common locations on the neck and axillae, patients with CSAN are affected perioorally and periorbitally, on the chest, around the umbilicus, and on the breasts. Notably, the endocrine abnormality typical of patients with AN is lacking.[19]

Compared with Crouzon syndrome, which results from mutations in the fibroblast growth factor receptor 2 gene (*FGFR2* [OMIM 176943]) on chromosome 10q26.13, CSAN is caused by a specific missense mutation in the fibroblast growth factor receptor 3 gene (*FGFR3* [OMIM 134934]) on chromosome 4p16.3, which leads to an Ala391Glu substitution and results in constitutive activation of the receptor.[18] The rare disorder is inherited in an autosomal dominant fashion, although most cases are sporadic mutations. The diagnosis is generally made clinically and based on the highly distinctive constellation of findings; genetic testing is not routinely performed. As with other disorders caused by *FGFR* mutations, increased paternal age appears to be a risk factor.[16] Female patients appear to predominate, and no racial predilection has been noted. Different *FGFR3* mutations have been linked to the development of severe AN associated with multiple forms of achondroplasia and to AN without notable craniofacial or skeletal defects.[20-22] Localized somatic mutations

Table. Summary of Clinical Presentations in the Present Series and in a Literature Review of Patients With CSAN

Source	Sex/Age at Onset	Mutation Confirmed	Distribution of AN	Nevi	Other Cutaneous Findings
Present study	F/4 y	Not tested	Neck, axillae, perioral, chest, and abdomen	Trunk and arms in globular pattern	Plantar verruca and keratosis pilaris
Present study	F/4 y	Yes	Neck, axillae, groin, and abdomen	Neck and trunk in globular pattern	Prominent hypopigmented scars within AN, sacral pit within pink plaque, and dermal melanosis of lower back/sacrum
Present study	F/3 y	Not tested	Neck, axillae, trunk, and extremities	NA	Prominent hypopigmented scars within AN, sacral pit within pink plaque, molluscum contagiosum, and seborrheic dermatitis
Present study	M/5 y	Not tested	Neck, axillae, groin, nasolabial folds, chin fold, periorbital, chest, abdomen, and antecubital and popliteal fossae	Abdomen and shoulder	Prominent hypopigmented scars within AN, plantar verruca, seborrheic dermatitis, and xerosis
Present study and Meyers et al,[18] 1995	F/10 y	Yes	Neck, axillae, perioral, chest, and abdomen	Face and trunk	Prominent hypopigmented scars within AN, seborrheic dermatitis, and acne vulgaris
Present study	F/6 y	Not tested	Periorbital, perinasal, perioral, neck/trunk, and axillae	Trunk	Prominent hypopigmented scars within AN
Di Rocco et al,[4] 2011	F/6 y	Not tested	Neck, axillae, and elbows	NA	
Di Rocco et al,[4] 2011	M/14	Not tested	Unknown	NA	Xerosis
Sharda et al,[14] 2010	M/Birth	Yes	Unknown	NA	
Arnaud-López et al,[2] 2007	F/1 y	Yes	Neck, flexors, perioral, perialar, nipples, and abdomen	NA	
Arnaud-López et al,[2] 2007	F/4 y	Yes	Neck, flexors, periorbital, perinasal, perioral, thorax, and abdomen	Face and thorax	Hypopigmented surgical scars
Lapunzina et al,[10] 2002	F/2 mo	Yes	Neck, chest, abdomen, and arms	NA	Deep palmoplantar linearity with hyperpigmentation
Meyers et al,[18] 1995	F/Unknown	Yes	Neck, axillae, perioral, periorbital, chest, and abdomen	Face, trunk, and extremities	
Meyers et al,[18] 1995	F/Unknown	Yes	Neck, axillae, perioral, periorbital, chest, and abdomen	Face, trunk, and extremities	
Meyers et al,[18] 1995	M/Unknown	Yes	Neck, axillae, perioral, periorbital, chest, and abdomen	Face, trunk, and extremities	
Suslak et al,[15] 1985	M/2 y	Not tested	Neck folds	NA	
Suslak et al,[15] 1985	F/Unknown	Not tested	Neck, axillae, and lower back	NA	
Witkowski and Parish,[27] 1976	F/Unknown	Not tested	Neck, elbows, and knees	NA	Xerosis and skin hyperelasticity
Koizumi et al,[9] 1992	F/Birth	Not tested	Neck, axillae, nose, eyelids, perialar, and perioral	NA	
Breitbart et al,[3] 1989	F/2 y	Not tested	Neck, axillae, perioral, perialar, and lower eyelids	NA	
Breitbart et al,[3] 1989	F/1 y	Not tested	Neck, perioral, perialar, and lower eyelids	NA	Prominent surgical scarring within AN
Breitbart et al,[3] 1989	F/4 y	Not tested	Neck, perioral, and lower eyelids	NA	Prominent surgical scarring within AN
Breitbart et al,[3] 1989	M/2 y	Not tested	Neck, perioral, and eyelids	NA	
Breitbart et al,[3] 1989	F/Unknown	Not tested	Neck, axillae, perioral, eyelids, and lower back	NA	
Reddy et al,[12] 1985	M/7 y	Not tested	Neck, axillae, face, and groin	NA	
Gines et al,[6] 1996	F/6 y	Not tested	Neck, axillae, groin, and periumbilical	Face and axillae	Xerosis, hypopigmented scars, and papillomatous scalp growth
Wilkes et al,[17] 1996	M/9 y	Yes	Neck, axillae, periorbital, perioral, and groin	Face and upper trunk	Warty acanthomas
Wilkes et al,[17] 1996	F/6 y	Yes	Neck, axillae, perioral, periumbilical, and antecubital fossae	NA	
Wilkes et al,[17] 1996	M/Unknown	Yes	Neck, axillae, perioral, periorbital, and groin	NA	Warty acanthomas
Nagase et al,[11] 2000	M/12 y	Yes	Neck, axillae, lower eyelids, and antecubital fossae	NA	
Schweitzer et al,[13] 2001	M/1 y	Yes	Neck, axillae, groin, chest, and abdomen	NA	Xerosis and hypopigmented scars
Schweitzer et al,[13] 2001	M/Unknown	Yes	Neck, chest, groin, and axillae	NA	
Schweitzer et al,[13] 2001	F/7 y	Yes	Neck, axillae, perioral, chin, periorbital, groin, and periumbilical	Present No description	Café au lait macules

Abbreviations: AN, acanthosis nigricans; CSAN, Crouzon syndrome with AN; NA, not applicable.

in the *FGFR3* gene also underlie benign neoplastic epidermal proliferations, such as seborrheic keratoses, lentigines, and dermatosis papulosa nigra.[23-25]

The finding of AN in patients with CSAN is severe and widespread. Unlike commonly found AN, CSAN is independent of endocrine abnormalities, driven instead by

the activation of *FGFR3*.[19,26] In addition to AN, development of melanocytic nevi and hypopigmented postsurgical scars is common.[2,3,6,13] Verrucous lesions and café au lait macules also develop in a few patients.[13,17] In this report, we describe the cutaneous features of 6 cases of CSAN and review previously reported cases.

REPORT OF CASES

We identified 6 cases of CSAN evaluated in a university-based pediatric dermatology practice from January 1, 1992, through December 31, 2008, by searching the electronic medical record for the *International Classification of Diseases, Ninth Revision* code for AN. In addition, we identified 38 previously published cases of CSAN by performing a PubMed search using the terms *Crouzon* and *acanthosis nigricans*. Of those cases, 27 had sufficient cutaneous findings to be included in this study. One of the patients included herein has been described in a previous publication, but we included the patient with further description of the cutaneous findings. The clinical features of these patients are presented in the **Table**. We found no discernible racial predilection for CSAN. The ratio of female to male patients was 2:1. Mutational analysis was performed in 16 patients, all of whom were found to carry the Ala391Glu substitution in *FGFR3*.

ACANTHOSIS NIGRICANS

For the 27 cases in which it has been reported, the mean age at onset of AN was about 4.5 years, with 2 patients affected at birth. Acanthosis nigricans was invariably present on the neck, and in 25 of 31 patients (81%), in the axillae (all 6 [100%] in the present study, and including involvement of the "flexors" described in 2 cases). Acanthosis nigricans was also found on the face (21 of 31 [68%]), chest (13 of 31 [42%]), abdomen (14 of 31 [45%]), groin (9 of 31 [29%]), upper extremities (7 of 31 [23%]), lower extremities (3 of 31 [10%]), and lower back (2 of 31 [6%]); the total number excludes cases in which location was not described. Acanthosis nigricans on the face was found around the eyelids, eyes, mouth, nose, and ears (**Figure 1**). On the abdomen, we found a predilection for the periumbilical area; on the extremities, in the antecubital and popliteal fossae. The neck and axillae were usually more severely affected (**Figure 2**). In most patients over time, the AN was severe, giving the skin an appearance resembling the bark of an oak tree.

MELANOCYTIC NEVI

Dark nevi have been reported previously in 7 patients with CSAN, with a predilection for the face. Of our 6 patients, 5 had melanocytic nevi, all of them dark. Most nevi were present on the trunk, with a few on the extremities. They were uniformly dark brown, symmetric, and well demarcated, without variegation or other atypical features. On dermoscopy in 2 patients, all nevi were of the globular pattern (**Figure 3**A). Nevi seemed more prominent in areas affected by AN.

Figure 1. Acanthosis nigricans on the face of a patient with Crouzon syndrome with acanthosis nigricans at 16 years of age.

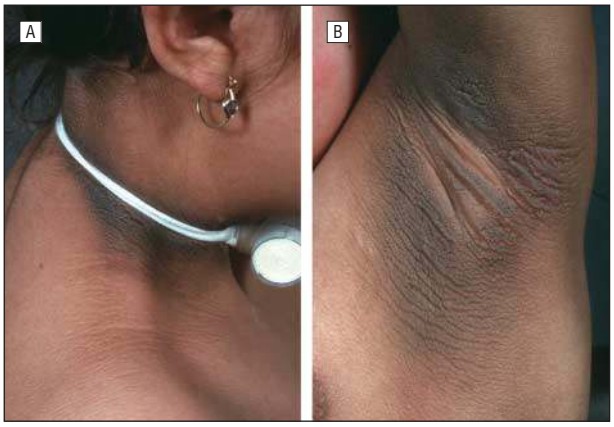

Figure 2. Severe acanthosis nigricans in a patient with Crouzon syndrome with acanthosis nigricans. A, Neck. B, Axilla.

HYPOPIGMENTED SCARS

Prominent, hypopigmented postsurgical scarring was reported in 5 patients with CSAN and observed in 5 of the 6 patients in the present study (Figure 3B and C). In all patients, the scarring was within areas of AN. The most typical location was the tracheostomy site on the neck, which tends to be the darkest area of AN. The patient in the present study who was not affected had the mildest AN.

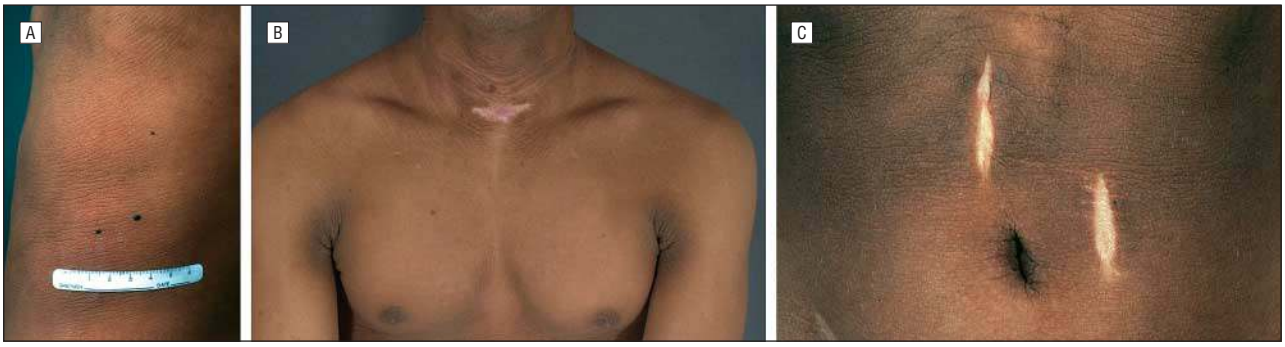

Figure 3. Two patients with Crouzon syndrome with acanthosis nigricans (AN). A, Dark melanocytic nevi, which are globular in dermoscopic pattern. B and C, Hypopigmented scars on a background of AN.

OTHER CUTANEOUS FINDINGS

Several other cutaneous findings were noted in the present study. Sacral pits associated with pink plaques were present in 2 patients, verrucae vulgaris were present in 2 patients, and another presented with molluscum contagiosum. Three patients had seborrheic dermatitis of the scalp, which developed at 8 years of age in two and at 22 years of age in the third. One patient was diffusely xerotic, a finding reported previously in 4 patients. The hair and nails of all patients were normal.

COMMENT

Crouzon syndrome with AN is a distinct genetic disease caused in all cases by a specific mutation in *FGFR3*. Previous studies have focused largely on craniofacial and skeletal abnormalities in affected patients. Although many reports describe the associated AN, other cutaneous manifestations have been poorly characterized.

Acanthosis nigricans in affected patients is most severe on the neck and axillae. The face and trunk are also affected in most of these patients. In classic AN related to an endocrine abnormality, these areas are typically unaffected. The limbs were relatively spared in CSAN. Another interesting and further disfiguring result of this pattern is the presence of striking hypopigmented scars at sites of prior operations. Indeed, most patients with CSAN have had many surgical procedures. These surgical sites heal without AN, leaving prominent, flat, white scars on a background of hyperpigmentation and thick skin. The scars are distinctive in that, unlike surgical scars in unaffected individuals, they are never red and remain profoundly hypopigmented, even after many years.

Dark melanocytic nevi have been reported in children with CSAN, although nevus counts compared with matched healthy controls have not been reported. These nevi tend to be dark brown, uniform lesions without suspicious features. In 2 of our patients whose nevi we examined dermoscopically, the globular pattern was found. This finding is not surprising because it is the most common pattern seen in the first 2 decades of life.[28] The significance of the presence of nevi in patients with CSAN is unclear. Although aberrant activation of *FGFR3* clearly affects keratinocyte proliferation, as indicated by its role in the pathogenesis of AN, epidermal nevi, and seborrheic keratosis, aberrant activation has been ascribed no direct role in melanocyte proliferation.

Less common cutaneous manifestations of CSAN have been noted. Two of our patients, one of whom was Japanese and the other white, had sacral pits associated with pink plaques. The significance of these findings is unknown. Seborrheic dermatitis of the scalp, a common condition, nonetheless appeared relatively overrepresented in the available data. In addition, isolated findings such as molluscum contagiosum, acne, skin hyperelasticity, and café au lait macules are likely unrelated. More investigation is needed to determine whether further relevant cutaneous manifestations are associated with CSAN.

Although we have not formally studied the psychosocial effects of the disfiguring AN variant in CSAN, all parents and patients old enough to express an opinion were desirous of treatment if available. To date, little success has been achieved in the amelioration of the AN when associated with Crouzon syndrome. Unlike common AN of endocrine origin, little can address the underlying cause in CSAN. Some of our patients had modest improvement from the use of topical alpha hydroxy acids or retinoids. However, any improvement seen was lost after discontinuation of the treatment. Because of the similarity of AN to confluent and reticulate papillomatosis (Gougerot-Carteaud syndrome), minocycline hydrochloride was prescribed to 2 patients; this treatment has been shown to be effective in confluent and reticulated papillomatosis.[29,30] This treatment resulted in temporary modest improvement but no lasting benefit. Our best results have been achieved by rotating agents as they start to lose effectiveness.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Mir and Orlow. *Acquisition of data:* Mir and Wu. *Analysis and interpretation of data:* Mir, Wu, and Orlow. *Drafting of the manuscript:* Mir and Wu.

Critical revision of the manuscript for important intellectual content: Mir and Orlow. *Administrative, technical, and material support:* Orlow. *Study supervision:* Orlow.

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