Title

Cushing disease in a patient with nonbullous congenital ichthyosiform erythroderma: lessons in avoiding glucocorticoids in ichthyosis.

Journal

Journal of Pediatric Endocrinology and Metabolism, 32(8)

Authors

Hartley, Iris
Costa Beber Nunes, Julia
Lodish, Maya
et al.

Publication Date

2019-08-27

DOI

10.1515/jpem-2019-0055

Peer reviewed

HHS Public Access

Author manuscript

J Pediatr Endocrinol Metab. Author manuscript; available in PMC 2020 August 14.

Published in final edited form as:

J Pediatr Endocrinol Metab. 2019 August 27; 32(8): 911–914. doi:10.1515/jpem-2019-0055.

Cushing disease in a patient with nonbullous congenital ichthyosiform erythroderma: lessons in avoiding glucocorticoids in ichthyosis

Iris R. Hartley,

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Inter-Institute Endocrinology Fellowship Program, Bethesda, MD, USA

Julia Costa Beber Nunes,

Federal University of Parana, Curitiba, Brazil

Maya Lodish,

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), NIH and Section on Endocrinology and Genetics (SEGEN), NICHD, NIH, Bethesda, MD, USA

Constantine A. Stratakis*

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), NIH and Section on Endocrinology and Genetics (SEGEN), NICHD, NIH, Bethesda, MD 20892, USA

Abstract

Nonbullous congenital ichthyosis erythroderma (CIE) is an autosomal recessive disorder of ineffective keratinization. We present a unique case of a 16-year-old female with CIE who developed Cushing disease (CD) at age 13 with concomitant worsening of her skin disease. After transsphenoidal resection of her pituitary adenoma, she had both resolution of her Cushing symptoms and significantly milder skin manifestations of her CIE. To the best of our knowledge, this is the first reported case of a patient with both CD and CIE, one that is important in demonstrating the role of glucocorticoids in this disorder.

Keywords

Cushing disease; Cushing syndrome; nonbullous congenital ichthyosis erythroderma

*Corresponding author: **Constantine A. Stratakis**, MD, DMSci, stratakc@mail.nih.gov.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

Conflict of interest: No conflict of interest.

Employment or leadership: None declared.

Honorarium: None declared.

Ethical statement: Informed consent was obtained from the individual included in this study. The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Introduction

Cushing syndrome (CS) is a rare condition of hypercortisolemia with an incidence of two to five new cases per million people per year [1]. Only 10% of these cases occur in children. The most common first manifestation of CS in children is a decline in growth velocity accompanied by significant weight gain. Subsequent typical symptoms include headaches, hypertension, insulin resistance, amenorrhea, hirsutism and delayed sexual development. CS frequently presents with prominent skin findings including facial plethora, violaceous striae, easy bruising, acne and acanthosis nigricans. The most common cause of CS in children is exogenous glucocorticoid administration, but the most common cause of endogenous CS is Cushing disease (CD), in which hypercortisolemia results from autonomous production of adrenocorticotrophic hormone (ACTH) by a pituitary adenoma [1]. Treatment of CD is surgical and is often curative.

Congenital ichthyosis erythroderma (CIE) is an autosomal recessive disorder characterized by abnormal skin function due to defective cornification, the final step in keratinization [2]. The prevalence of CIE is estimated to be 1 per 200,000 in the US. CIE features include erythroderma, fine white scaling and palmoplantar keratoderma [3]. Patients with CIE may also present with impaired temperature regulation due to hypohidrosis [4]. There is no cure for ichthyosis, and treatment focuses on improving skin condition and appearance [3]. Treatments vary from mechanical elimination of scales, emollients, topical keratolytic agents and oral retinoids. Topical corticosteroids are not usually indicated as they do not improve the disease process and confer a risk of systemic absorption [2].

In this report, we present a female patient with non-bullous CIE who developed elevated endogenous cortisol levels due to CD with subsequent worsening of her skin disease. Her skin symptoms improved after resolution of her CD.

Case presentation

A female patient with CIE presented at age 13 with worsening skin disease and symptoms consistent with CD.

Her first manifestation of CIE was noticed at birth with peeling of the palms and soles. She subsequently experienced desquamation, erythroderma and heat intolerance throughout childhood. She has no family history of skin disorders. A biopsy performed at 2 years of age was consistent with nonbullous CIE. A genetic test was positive for a mutation in the *NIPAL4* gene, with two heterozygous variants identified: R153Q, a novel variant, and A176D, a pathogenic variant already associated with autosomal recessive ichthyosis [5].

At 13 years of age she developed significant weight gain, decreased height velocity, moon facies, dorsocervical fat deposition, abdominal striae and primary amenorrhea. Her CIE skin manifestations worsened with facial erythroderma of her face and extremities (Figures 1A and 2A).

Adrenocorticotropic hormone (ACTH)-dependent hypercortisolemia was confirmed with elevated midnight cortisol of 12.3 μg/dL (<1.8 μg/dL); free urinary cortisol of 298.3 mg/24 h

(4.0–56.0 mg/24 h); morning cortisol after 1 mg dexamethasone suppression test of 21.8 μg/dL (<1.8 μg/dL); morning ACTH level of 42 pg/mL (5–46 pg/mL). Pituitary magnetic resonance imaging (MRI) failed to identify a pituitary adenoma; however, an 8 mg dexamethasone suppression test and inferior petrosal sinus sampling were consistent with a pituitary source. She underwent transsphenoidal resection with pathology showing a 5 × 6 × 4 mm pituitary adenoma. A post-operative corticotropin-releasing hormone (CRH) stimulation test showed an undetectable cortisol and an ACTH lower than 20 pg/mL on post-operative day 8.

One year post-operatively, she exhibits resolution of her CD. She grew 3 cm and lost 12 kg over the last year. The dorsocervical fat pad and striae have resolved and she experienced menarche 3 months after surgery.

Her CIE-related skin manifestations also improved remarkably (Figures 1B,C and 2B,C). She had no further desquamation, no facial rash and she reports good tolerance to heat and exercise. Her only remaining manifestation is xerosis. She is using moisturizing cream daily and no other treatment for CIE.

Discussion

We present a patient with significant worsening of CIE skin manifestations in association with findings consistent with CD. Her skin findings worsened during times of hypercortisolemia and improved after her cortisol levels normalized. This is the first reported case of a patient with both CD and CIE; several cases of CS have been reported in this journal but none with this particular combination [6–8]. However, two previous cases of exogenous CS associated with CIE have been reported in the literature. Both were pediatric patients who were treated with excessive topical glucocorticoids and subsequently developed CS [9]. Similar to our patient, hypercortisolemia led to exacerbation of skin symptoms which improved with discontinuation of steroids.

Glucocorticoids directly impair normal epidermal cell function resulting in many of the skin manifestations associated with CS [10, 11]. This effect is mediated, in part, through the high expression of glucocorticoid receptors found on basal keratinocytes and through suppression of keratinocyte growth factor which is important for wound healing [11, 12]. In CIE, which is characterized by impaired cornification, exposure to supraphysiologic glucocorticoids likely results in further inhibition of already impaired keratinocyte function. Thus, it follows that glucocorticoids would exacerbate CIE skin manifestations, as demonstrated in this patient.

This case allows us to observe the unique interplay of two rare conditions in a single patient and highlights the direct effect of glucocorticoids on epidermal function. To the best of our knowledge, this is the first reported case of a patient with both CD and CIE and shows that glucocorticoids that are so extensively used in treating various skin disorders may in fact be contra-indicated in others.

Acknowledgments

Research funding: Research was funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Funder Id: http://dx.doi.org/10.13039/100009633, Grant Number: Grant Z01-HD008920-1 "Molecular Genetics of Endocrine Tumors and Related Disorders", National Institutes of Health intramural research program.

References

1. Stratakis CA. Cushing syndrome in pediatrics. Endocrin Metab Clin 2012;41:793–803.
2. Vahlquist A, Ganemo A, Virtanen M. Congenital ichthyosis: an overview of current and emerging therapies. Acta Derm Venereol 2008;88:4–14. [PubMed: 18176742]
3. Rodriguez-Pazos L, Ginarte M, Vega A, Toribio J. Autosomal recessive congenital ichthyosis. Actas Dermosifiliogr 2013;104:270–84. [PubMed: 23562412]
4. Oji V, Traupe H. Ichthyosis: clinical manifestations and practical treatment options. Am J Clin Dermatol 2009;10:351–64. [PubMed: 19824737]
5. Palamar M, Onay H, Ertam I, Ates EA, Dereli T, et al. Genotype and anterior segment phenotype in a cohort of Turkish patients with lamellar ichthyosis. Ophthalmic Genet 2015;36:229–33. [PubMed: 24397709]
6. Goldberg AS, Stein R, Merritt NH, Inculet R, Van Uum S. A pediatric patient with Cushing syndrome caused by ectopic ACTH syndrome and concomitant pituitary incidentalomas. J Pediatr Endocrinol Metab 2014;27:123–8. [PubMed: 23945121]
7. Bulus AD, Andiran N, Kocak M. Cushing's syndrome: hidden risk in usage of topical corticosteroids. J Pediatr Endocrinol Metab 2014;27:977–81. [PubMed: 24854522]
8. Choudhary A, Haafiz A, Ramakrishnaiah R, Thrailkill K. Cushing's disease presenting as cholestatic hepatitis. J Pediatr Endocrinol Metab 2014;27:1037–41. [PubMed: 25210756]
9. Borzyskowski M, Grant DB, Wells RS. Cushing's syndrome induced by topical steroids used for the treatment of non-bullous ichthyosiform erythroderma. Clin Exp Dermatol 1976;1:337–42. [PubMed: 793745]
10. Stratakis CA. Skin manifestations of Cushing's syndrome. Rev Endocr Metab Disord 2016;17:283–6. [PubMed: 27943005]
11. Chedid M, Hoyle JR, Csaky KG, Rubin JS. Glucocorticoids inhibit keratinocyte growth factor production in primary dermal fibroblasts. Endocrinology 1996;137:2232–7. [PubMed: 8641170]
12. Serres M, Viac J, Schmitt D. Glucocorticoid receptor localization in human epidermal cells. Arch Dermatol Res 1996;288:140–6. [PubMed: 8967782]

Key learning points

- CIE is a rare skin condition which presents with erythroderma, fine white scaling, palmoplantar keratoderma and hyperhidrosis.
- Skin manifestations of CIE may be worsened by exogenous or endogenous glucocorticoids.

What is new?

- This is the first reported case of a patient with both CD and CIE.
- This case demonstrates the effect CD can have on skin and underlying skin disorders.

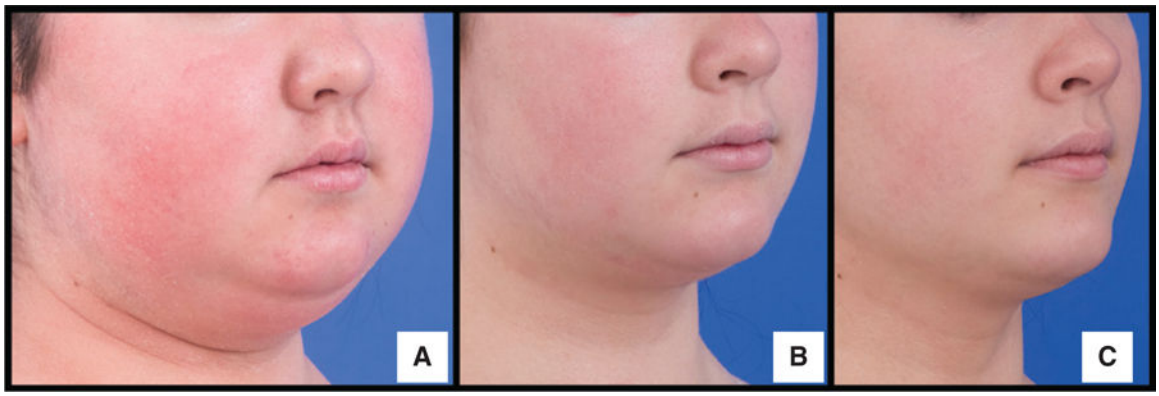

Figure 1:
Erythema on the patient's face improved after pituitary surgery with biochemical cure of her CD. (A) Preoperative; (B) 6 months after surgery; (C) 1 year after surgery.

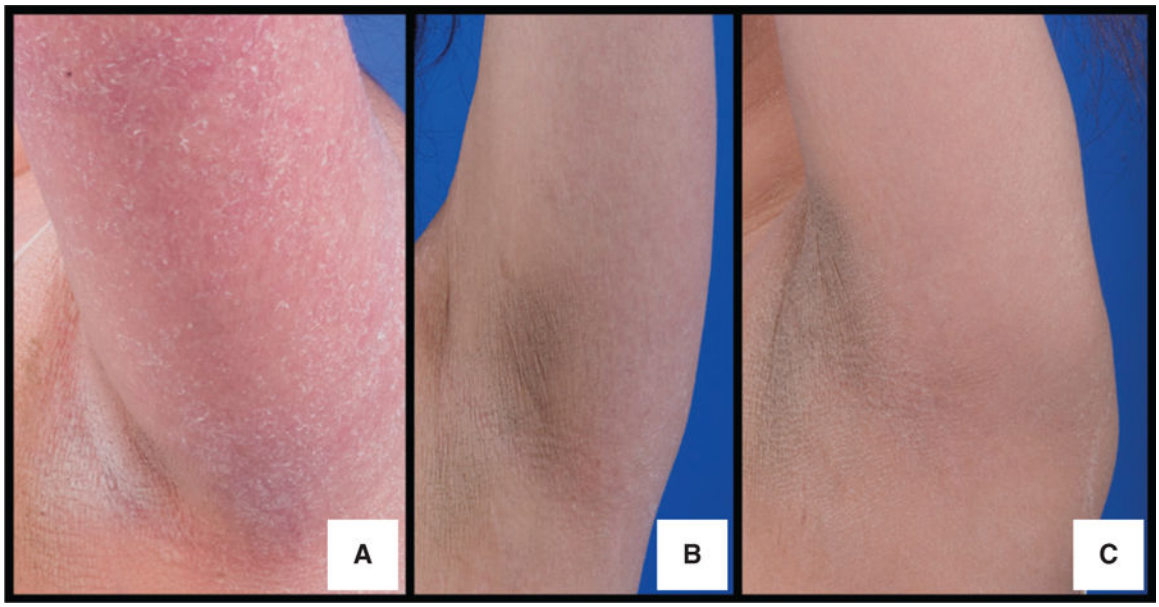

Figure 2:
Erythema on the patient's arm improved after pituitary surgery with biochemical cure of her CD. (A) Preoperative; (B) 6 months after surgery; (C) 1 year after surgery.