REVISTA BRASILEIRA DE REUMATOLOGIA

www.reumatologia.com.br

SOCIEDADE BRASILEIRA DE REUMATOLOGIA

Case report

Generalized morphea in a child with harlequin ichthyosis: a rare association

Maria F.A. Giacomin[a], *Camila M.P. França*[a], *Zilda N.P. Oliveira*[b], *Maria C.R. Machado*[b], *Adriana M.E. Sallum*[c], *Clovis A. Silva*[a,c,*]

[a] *Pediatric Rheumatology Unit, Children's Hospital, Faculdade de Medicina, Universidade São Paulo, São Paulo, SP, Brazil*
[b] *Pediatric Dermatology Unit, Faculdade de Medicina, Universidade São Paulo, São Paulo, SP, Brazil*
[c] *Division of Rheumatology, Faculdade de Medicina, Universidade São Paulo, São Paulo, SP, Brazil*

ARTICLE INFO

Article history:
Received 24 October 2013
Accepted 21 May 2014
Available online 26 November 2014

Keywords:
Harlequin ichthyosis
Children
Morphea
Scleroderma

ABSTRACT

Introduction: Harlequin ichthyosis (HI) is a severe and rare hereditary congenital skin disorder characterized by excessive dryness, ectropion and eclabion. The association of ichthyosis with systemic sclerosis has been described in only three children. No patient with generalized morphea (GM) associated with harlequin ichthyosis was described.
Case report: A 4-years and 6-months girl, diagnosed with harlequin ichthyosis based on diffuse cutaneous thickening, scaling, erythema, ectropion and eclabium since the first hours of birth was described. She was treated with acitretin (1.0 mg/kg/day) and emollient cream. At 3 years and 9 months, she developed muscle contractures with pain on motion and limitation in elbows and knees, and diffuse sclerodermic plaques on the abdomen, back, suprapubic area and lower limbs. Skin biopsy showed rectified epidermis and mild hyperorthokeratosis, reticular dermis with perivascular and periadnexal infiltrates of lymphocytes and mononuclear cells, and reticular dermis and sweat gland sclerosis surrounded by a dense collagen tissue, compatible with scleroderma. The patient fulfilled the GM subtype criteria. Methotrexate and prednisone were introduced. At 4 years and 3 months, new scleroderma lesions occurred and azathioprine was associated with previous therapy, with no apparent changes after two months.
Discussion: A case of harlequin ichthyosis associated with a GM was reported. The treatment of these two conditions is a challenge and requires a multidisciplinary team.

Morfeia generalizada em uma criança com ictiose arlequim, uma associação rara

Palavras-chave:
Ictiose arlequim

RESUMO

Introdução: Ictiose arlequim é uma doença cutânea congênita grave, autossômica e rara, caracterizada por ressecamento excessivo da pele e hiperqueratose. A associação de ictiose

* *Corresponding author.*
E-mail addresses: clovis.silva@icr.usp.br, clovisaasilva@gmail.com (C.A. Silva).
http://dx.doi.org/10.1016/j.rbre.2014.05.004

Crianças
Morfeia
Esclerodermia

com esclerose sistêmica foi descrita em apenas três crianças. Ainda não foi descrito nenhum paciente com morfeia generalizada (MG) associada à ictiose arlequim.

Relato de caso: Menina de quatro anos e seis meses de idade com diagnóstico de ictiose arlequim baseado em espessamento cutâneo difuso, com fissuras, descamação, eritema e sangramento da lesão desde as primeiras horas de vida. A paciente foi tratada com acitretina (1,0 mg/kg/dia) e creme emoliente. Aos três anos e nove meses, desenvolveu contraturas musculares com dor à movimentação e limitação nos cotovelos e joelhos e placas esclerodérmicas difusas no abdômen, nas costas, na região suprapúbica e nas extremidades inferiores. A biópsia de pele mostrou epiderme retificada e hiperqueratose leve, derme reticular com linfócitos, infiltrado mononuclear perivascular e perianexial e esclerose da derme reticular e glândula sudorípara rodeada por um tecido colágeno denso, compatível com esclerodermia. A paciente preencheu os critérios para o subtipo MG. Metotrexato e prednisona foram introduzidos. Aos quatro anos e três meses, apresentou novas lesões esclerodérmicas, associando-se azatioprina à terapêutica anterior, sem resposta após dois meses.

Discussão: Um caso de ictiose arlequim associada à MG foi descrito. O tratamento dessas duas condições é um desafio e requer uma equipe multidisciplinar.

Introduction

Juvenile cutaneous scleroderma is a rare condition in pediatric patients characterized by the involvement of the skin and/or subcutaneous tissue.[1,2] Generalized morphea (GM) is an uncommon subtype of localized scleroderma and occurs in 7% of the patients.[2] The association of GM with other cutaneous diseases was rarely reported in the literature, especially with ichthyosiform diseases.

Of note, ichthyosis comprehends a heterogeneous group of skin diseases characterized by cutaneous hyperkeratinization and may be congenital or acquired.[3] Harlequin ichthyosis is a congenital form, transmitted in an autosomal recessive mode. It is the most severe and often fatal form of ichthyosis.[4]

The association of ichthyosis with scleroderma has been described in only four patients. Three of them had juvenile systemic sclerosis, and one of them had localized scleroderma. Two of the juvenile systemic sclerosis patients were associated with ichthyotic-appearing lesions,[5] and one of them with acquired ichthyosis.[6] The localized scleroderma patient was associated with ichthyotic-appearing lesions.[5] However, to our knowledge, no patient with GM scleroderma associated with the harlequim subtype of ichthyosis was reported. This case is described herein.

Case report

A 4-years and 6-months girl was diagnosed with harlequin ichthyosis at neonatal period, based on diffuse cutaneous thickening, diffuse plate-like scales, erythema, fissures, bleeding lesions, bilateral ectropion and eclabium since the first hours of life. No history of parental consanguinity and harlequin ichthyosis were observed. She was a term newborn after cesarean delivery. Her birth weight and height were 2.650 gm and 43 cm, respectively. Microcephaly, auricular pinna and nasal abnormalities, alopecia and flexion contracture were not evidenced. She was treated with acitretin (1.0 mg/kg/day) and emollient cream. During the first 3 months of life, she had been hospitalized three times due to skin infections, with improvement after antibiotic treatment. At 3 years, she presented growth retardation with height of 84 cm, with delayed motor development. Skin biopsy of abdominal epidermis showing hyperkeratosis paraketatotic, agranulose, regular epidermal acanthosis and thickening of the dermis with proliferation of vessels with mild lymphocytic inflammatory infiltrate and psoriasiform dermatitis (Fig. 1) confirmed diagnosis of ichthyosis.[7] After 9 months, she developed painful flexion muscle contractures, with pain on motion and limitation affecting elbows and knees, associated with generalized ichthyosis lesions, with diffuse pain upon palpation, bilateral ectropion and diffuse scleroderm plaques without distribution pattern on: abdomen (11 lesions ranged from 0.5 × 0.5 cm to 3.3 × 3.0 cm), back (13 lesions ranged from 1.0 × 1.0 cm to 2.8 × 3.0 cm), supra-pubic area (3 lesions varied from 0.8 × 1.4 cm to 3.5 × 2.0 cm) and proximal aspects of thighs (2 lesions ranged from 1.0 × 1.0 cm to 3.0 × 2.5 cm). Skin biopsy showed rectified epidermis and mild hyperorthokeratosis, reticular dermis with lymphocyte and mononuclear cells that infiltrate perivascular and periadnexal, and sclerosis of reticular dermis and sweat gland surrounded by a dense collagen tissue, compatible with scleroderma. Hemoglobin, leukocyte and platelet counts, renal function and urinalysis were normal. The C-reactive protein was 14.4 mg/dL (reference value <5). The rheumatoid factor, antinuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA), anti-Sm, anti-RNP, anti-Ro and anti-La antibodies were negative. Thoracic computer tomography, echocardiography, barium meal examination and slit-lamp examination were normal. The nailfold capillaroscopy was performed without being able to visualize capillaries due to crusts periungual. Therefore, the patient fulfilled the juvenile localized scleroderma criteria (GM subtype)[8] and methotrexate (0.5 mg/kg/week) and prednisone (1.0 mg/kg/day) were introduced at the age of 3 years 11 months. At 4 years and 1 month, methotrexate dosage was increased to 1.0 mg/kg/week. At 4 years and 3 months, she presented generalized ichthyosis lesions with new scleroderma

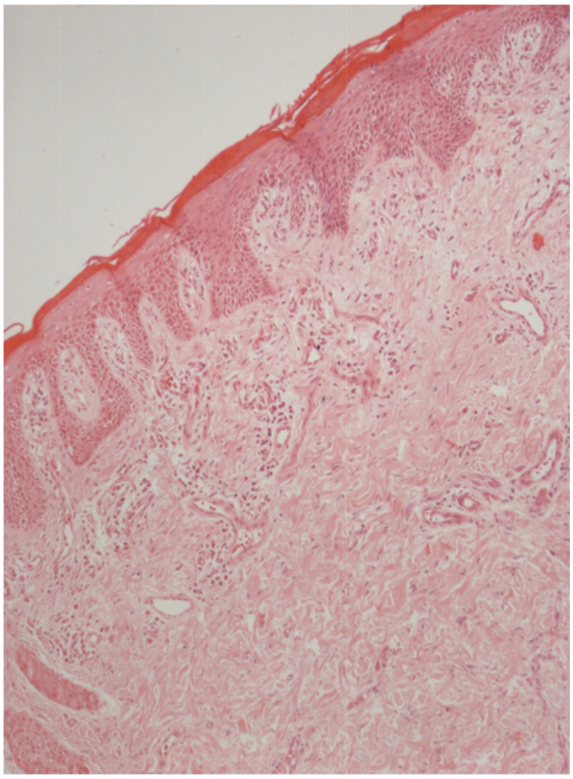

Fig. 1 – Hyperkeratosis paraketatotic, agranulose, regular epidermal acanthosis and thickening of the dermis with proliferation of vessels with mild lymphocytic inflammatory infiltrate and psoriasiform dermatitis.

lesions in abdomen (Fig. 2), lower limbs, back and supra-pubic areas and azathioprine (3.0 mg/kg/day) was introduced along with prednisone and methotrexate with no improvement after two months of therapy. Topical corticosteroid was not used. At present, her follow-up is composed of a multidisciplinary team with a rheumatologist, dermatologist, ophthalmologist, geneticist, physiotherapist and occupational therapist.

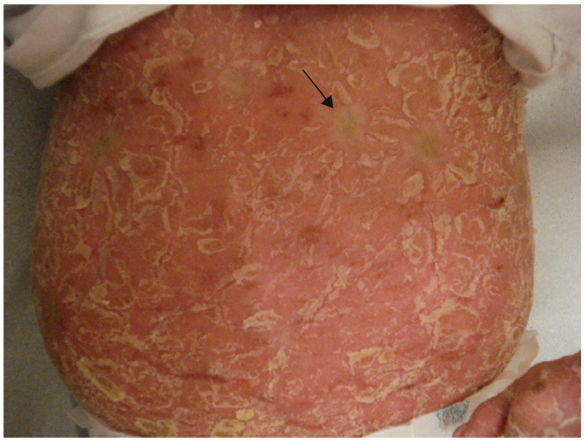

Fig. 2 – Diffuse cutaneous thickening, cracking, scaling, erythema, bleeding and ichthyosiform lesions, and diffuse scleroderm plaques (arrow) on the abdomen.

Discussion

To our knowledge, we describe herein the first case of harlequin ichthyosis associated to GM diagnosis. This congenital disease occurred previously to the scleroderma diagnosis, not in agreement with the rare cases of acquired ichthyosis and scleroderma reported in the literature.[5,6]

According to the new classification criteria, localized scleroderma has four different subtypes: plaque morphea, GM, linear scleroderma and deep morphea.[8–10] The GM is defined by the presence of four or more plaques, with individual plaques greater than 3 cm and involving at least two out of seven anatomic sites,[2] as evidenced in our patient that presented lesions occurring in upper and lower limbs, and trunk.

Furthermore, ichthyosis is composed of cutaneous keratinization diseases that can be inherited or acquired.[3] Congenital ichthyosis is often associated with a variety of typical neonatal phenotypes with scaling and erythema. The main subtypes are congenital ichthyosiform erythroderma, lamellar and harlequin ichthyosis, including overlapping phenotypes. The mild subtype is congenital ichthyosiform erythroderma with fine and white scaling, and different degrees of erythema. Coarse and brown/dark scaling are observed in lamellar ichthyosis, generally with collodion membrane and ectropion. The harlequin ichthyosis is a more severe subtype associated with very scaling erythroderma, collodion membrane and pronounced ectropion.[5,11] Of note, a collodion baby is defined by erythroderma, shiny and tight skin, like parchment, covering the entire body at birth. It is an initial presentation of several genetic conditions, including congenital ichthyosis,[12] as observed in our case.

The disease course is generally severe with multiple joint contractures.[13,14] Our patient presented contractures mainly in elbows and knees, possibly due to association with GM.

One limitation of the present case was the absence of electronic microscopy in the skin biopsy and genetic evaluations, since this is an autosomal recessive congenital disease.[5] ABCA12 mutation analysis showed that 52% of survivors had heterozygous mutations, and all deaths were associated with homozygous mutations, while missense mutations are usually related with milder phenotypes.[5,15,16] The association between harlequin ichthyosis and scleroderma, an autoimmune disease, is probably coincidental.

Of note, acquired ichthyosis with systemic sclerosis has been described in four patients after this autoimmune diagnosis,[6,7] however the rare subtype of harlequin had not been previously reported. Other associations between harlequin ichthyosis and autoimmune chronic disorders have been rarely described without a clear relationship with pathogenesis of autoimmunity, such as hypothyroidism,[13] celiac disease[17] and juvenile idiopathic arthritis.[13,14]

The ichthyosis treatment is based on the severity of the disease and included topical formulations and oral retinoids,[18] as indicated in our patient with unsatisfactory response. Moreover, the cutaneous juvenile scleroderma includes pharmacological (glucocorticosteroids and methotrexate) and non-pharmacological (physical exercises and early physiotherapy) therapies.[19] Azathioprine may also be administered in refractory cases,[20] as used in the present case. The difficulty

of the treatment concomitantly of these two severe and rare conditions should have contributed to the poor response therapy in our case.

The outcome of harlequin ichthyosis is generally related to stillbirth or first weeks of life death due to prematurity, renal failure, respiratory insufficiency and infection.[21] To our knowledge, only eight cases with isolated harlequin ichthyosis or associated with juvenile rheumatoid arthritis survived the neonatal period, with a median of current age of 4 years (ranged from 6 months to 14 years).[13]

In conclusion, we reported the first case of harlequin ichthyosis associated with a rare type of juvenile scleroderma. The treatment of these two simultaneous illnesses is very challenging indeed and requires a multidisciplinary team.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

This study was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP (grant #08/58238-4 to C.A.S.), Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPq (302724/2011-7 to C.A.S.), Federico Foundation to C.A.S. and Núcleo de Apoio à Pesquisa "Saúde da Criança e do Adolescente" da USP (NAP-CriAd).

REFERENCES

1. Hedrich CM, Fiebig B, Hahn Suttorp M, Gahr M. Presentations and treatment of childhood scleroderma: localized scleroderma, eosinophilic fasciitis, systemic sclerosis, and graft-versus-host disease. Clin Pediatr (Phila). 2011, 04-614.
2. Zulian F. Systemic sclerosis and localized scleroderma in childhood. Rheum Dis Clin N Am. 2008;34:239–55.
3. Tlacuilo-Parra JA, Guevara-Gutiérrez E, Salazar-Páramo M. Acquired ichthyosis associated with systemic lupus erythematosus. Lupus. 2004;13:270–3.
4. Vahlquist A. Pleomorphic ichthyosis: proposed name for a heterogeneous group of congenital ichthyosis with phenotypic shifting and mild residual scaling. Acta Derm Venereol. 2010;90:454–60.
5. Oji V, Tadini G, Akiyama M, Blanchet Bardon C, Bodemer C, Bourrat E, et al. Revised nomenclature and classification of inherited ichthyoses: results of the First Ichthyosis Consensus Conference in Sorèze 2009. J Am Acad Dermatol. 2010;63:289–97.
6. Williams CM, Storm CA, Burns C, Rigby W, Dinulos JG. Ichthyotic-appearing skin changes associated with childhood morphea, systemic sclerosis, and systemic lupus erythematosus/scleroderma overlap. Pediatr Dermatol. 2010;27:170–3.
7. Lee H, Anh S, Choi J, Chang SE, Choi JH, Moon KC, et al. Acquired ichthyosis associated with an overlap syndrome of systemic sclerosis and systemic lupus erythematosus. J Dermatol. 2006;1:52–4.
8. Chakraborti C, Tripathi P, Bandopadhyay G, Mazumder DB. Congenital bilateral ectropion in lamellar ichthyosis. Oman J Ophthalmol. 2011;4:35–6.
9. Zulian F, Woo P, Athreya BH, Laxer RM, Medsger TA Jr, Lehman TJ, et al. The Pediatric Rheumatology European Society/American College of Rheumatology/European League Against Rheumatism Provisional Classification Criteria for Juvenile Systemic Sclerosis. Arthritis Rheum. 2007;57:203–12.
10. Zulian F, Martini G. Preliminary classification criteria for juvenile systemic sclerosis. In: Zulian F, Ruperto N, editors. Proceedings of the II Workshop on nomenclature and diagnostic criteria for juvenile Scleroderma Syndromes. 2005. p. 5–16.
11. Zannin ME, Martini G, Athreya BH, Russo R, Higgins G, Vittadello F, et al. Ocular involvement in children with localized scleroderma: a multi-centre study. Br J Ophtalmol. 2007;91:1311–4.
12. Prado R, Ellis LR, Gamble R, Funk T, Arbuckle HA, Bruckner AL. Collodion baby: an update with a focus on practical management. J Am Acad Dermatol. 2012;67:1362–74.
13. Chan YC, Tay YK, Tan LK, Happle R, Giam YC. Harlequin ichthyosis in association with hypothyroidism and juvenile rheumatoid arthritis. Pediatr Dermatol. 2003;20:421–6.
14. Beazley JC, Ho K, Ilchyshyn A, Foguet P. Total hip replacement in an adolescent patient with harlequin ichthyosis; a case report. Hip Int. 2011;21:487–9.
15. Rajpopat S, Moss C, Mellerio J, Vahlquist A, Gånemo A, Hellstrom-Pigg M, et al. Harlequin ichthyosis: a review of clinical and molecular findings in 45 cases. Arch Dermatol. 2011;147:681–6.
16. Walsh DM, Shah SH, Simpson MA, Morgan NV, Khaliq S, Trembath RC, et al. A novel *ABCA12* mutation in two families with congenital ichthyosis. Scientifica (Cairo). 2012;2012:649090, http://dx.doi.org/10.6064/2012/649090 [Epub 2012 Dec 31].
17. Nenna R, D'Eufemia P, Celli M, Mennini M, Petrarca L, Zambrano A, et al. Celiac disease and lamellar ichthyosis. Case study analysis and review of the literature. Acta Dermatovenerol Croat. 2011;19:268–70.
18. Bassoti A, Moreno S, Criado E. Successful treatment with topical N-acetylcysteine in urea in five children with congenital lamellar ichthyosis. Pediatr Dermatol. 2011;28:451–5.
19. Macedo PA, Shinjo SK, Goldenstein-Schainberg C. Esclerodermia juvenile. Acta Reumatol Port. 2008;33:289–97.
20. Zulian F, Athreya BH, Laxer R, Nelson AM, Feitosa de Oliveira SK, Punaro MG, et al. Juvenile localized scleroderma: clinical and epidemiological features in 750 children. An international study. Rheumatology (Oxford). 2006;45:614–20.
21. Akiyama M. Severe congenital ichthyosis of the neonate. Int J Dermatol. 1993;37:722–8.