Journal of Pakistan Association of Dermatologists.2023;**33(1)**:317-321.

Case Report

Severe ichthyosis vulgaris with vitamin D insufficiency and multiple flexion contractures

Bobby Febrianto, Suci Widhiati, Endra Yustin Ellistasari, Indah Julianto, Annang Giri Moelyo*, Adhitya Indra Pradhana**

Department of Dermatology and Venerology, Dr. Moewardi Hospital/ Medical Faculty of Sebelas Maret University. Surakarta, Indonesia.
* Department of Pediatric, Dr. Moewardi Hospital/ Medical Faculty of Sebelas Maret University. Surakarta, Indonesia.
** Department of Orthopaedic and Traumatology, Surgery Dr. Moewardi Hospital/ Medical Faculty of Sebelas Maret University. Surakarta, Indonesia.

Abstract Ichthyosis vulgaris (IV) is a non-syndromic form of congenital ichthyoses and mainly affects the skin, moreover in severe case followed by joints involvement and vitamin D imbalance as chronic complication due to skin barrier impairment. A 16-years-old female presented with scaly skin all over her body. Changes on her hands appeared when she was 8-years-old and several years later gradually she could not use her hands. Dermatological examination obtained thick scales, xerotic skin, and palmo-plantar hyperkeratosis. The dermoscopic finding was a fine white scale with a criss-cross pattern. Her skin biopsy showed hyperkeratosis and thinning of granular layer, meanwhile laboratory results indicated vitamin D insufficiency. Hand x-ray revealed flexion contractures. She received oral vitamin D3 400 IU once daily, calcitriol 0.5 mcg twice daily, and topical emolients. Surgical contracture release was conducted to repair the joints deformity. Manifestation of IV is limited to the skin and rarely accompanied by other systemic disorders. Joint anomaly might be seen in some syndromes accompined with ichthyoses, however IV does not lead to joint contractures. Skin thickness and impaired barrier could lead to reduced ultraviolet B penetration, so that it disturbed and diminished vitamin D synthesis. Those conditions are more likely to cause muscle weakness and atrophy which finally lead to joints contractures.

Key words
Flexion contracture, ichthyosis vulgaris, insufficiency, vitamin D.

Introduction

Ichthyosis vulgaris (IV) is the most common form of non-syndromic congenital ichthyosis with the worldwide incidence of 1:250 to 1:1000. This disease caused by decreaded function of mutating filaggrin encoding gene (FLG) which semidominant inheritance. Clinical manifestations of IV commonly limitted on the skin which characterized by general scales, xerotic skin, and hyperkeratosis, meanwhile in severe cases it can involve eyes and joints.[1]

Physiological effects of vitamin D play a role in maintaining skin barrier and regulating immune system. Keratinization disorders on congenital ichthyoses causes several complications including vitamin D metabolism due to skin barrier abnormalities and reduced of ultraviolet B (UVB) exposure. Chronic vitamin D insufficiency in IV increases the risk of rickets and osteomalacia caused by calcium disruption in the bone.[2,3] Several case reports of syndromic congenital ichthyoses along with joint disorders have been reported, but to date only one case

Address for correspondence
Dr. Bobby Febrianto
Department of Dermatology and Venerology,
Dr. Moewardi Hospital/ Medical Faculty of Sebelas Maret University, Surakarta, Indonesia.
Ph: +6281233795070
Email: bobbyf100289@gmail.com

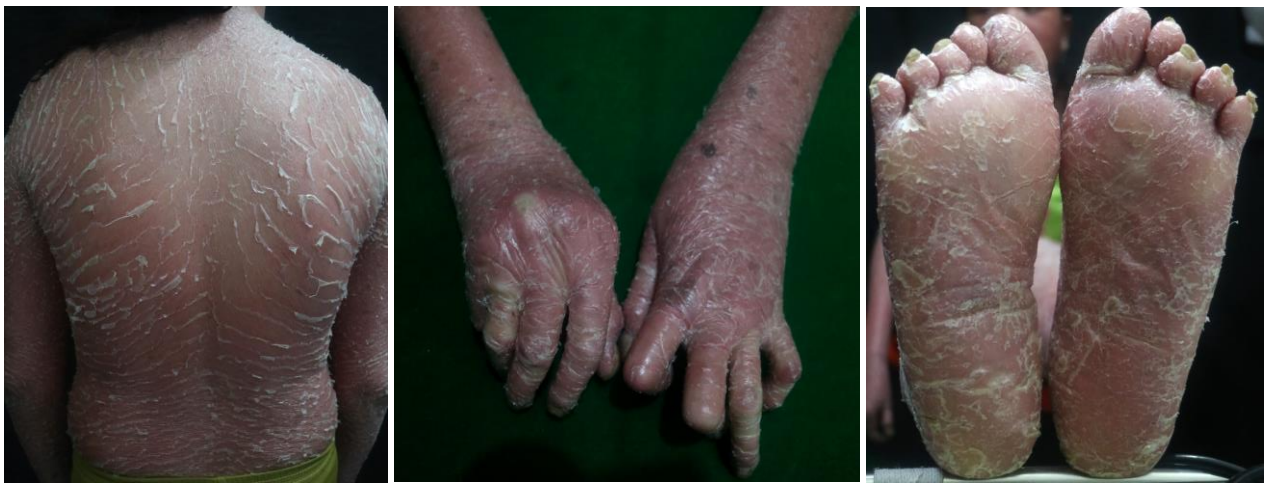

Figure 1 Cllinical manifestation : thick greyish white scales all over the body, palmo-plantar hyperkeratosis, onychodistrophy and multiple contractures on both hands.

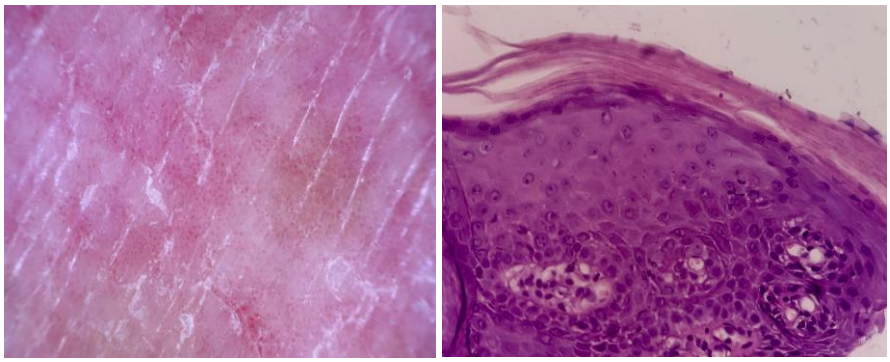

Figure 2 (A) Dermosocpic findings: fine white scales with criss-cross pattern. (B) Histopathological examination: hyperkeratosis, thining of granular layer, and acanthosis.

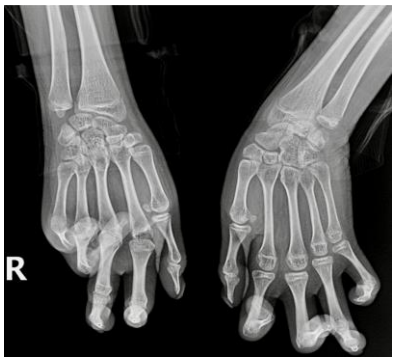

Figure 3 X-ray of the hands: multiple flexion contractures, osteopenia, and cartilagge erosion.

report of severe IV followed by ectropion and multiple flexion contratures has been reported by Akdeniz *et al*. in 2011.[4] The relation between severe IV and joints deformity remains unclear due to lack of documented cases, hence we reported a case of severe IV with vitamin D insufficiency followed by multiple flexion contratures to improve the knowledge and related management.

Case Report

A 16-years-old female presented to Dermatology and Venereology Outpatient clinic of Dr. Moewardi General Hospital, Surakarta, Central Java, Indonesia due to scaly skin all over her body. First it appeared as dry reddish skin lesion when she was 5-years-old. She was born without a history of keratinization disorders. Her joints started to change when she was 8-years old and gradually could not use her hands due to pain and limited movement.

Dermatological examination obtained thick greyish white scales on her neck, trunk, upper and lower extremities including flexural areas as well as palmo-plantar hyperkeratosis, onychodistrophy and deformities of both hands **(Figure 1)**. Dermoscopic findings were fine white scales on the erythematous skin with a criss-cross pattern **(Figure 2A)**. The histopathological examination showed hypereratosis, thining of granular layer, and acanthosis with elongation of rete ridges **(Figure 2B)**. Laboratory examination obtained thyroid stimulating hormone (TSH) 2.28 uIU/mL, free

T4 (FT4) 9.51 pmol/l, total vitamin D 25-OH 13.3 ng/mL, serum alkaline phosphatase 143 U/L, calcium 10.3 mg/dL and anorganic phosphor 5.1 mg/dL. Hand x-ray revealed multiple flexion contractures, osteopenia, and cartilage erosion **(Figure 3)**. Based on history taking and examination findings this patient was diagnosed with severe IV accompanied by vitamin D insufficiency and multiple flexion contractures. Topical emolients was given to moist the skin then she was reffered to the Pediatric Clinic and received oral vitamin D3 400 IU once daily and calcitriol 0.5 mcg twice daily. Regarding joint deformity we consulted her to Othopaedic Clinic then surgical contracture relase was performed. The treatment continued and her condition improved.

Discussion

Ichthyosis vulgaris is the most common form of non-syndromic ichthyoses. It estimated prevalences are 4% and 3% in Europe and Asia, respectively. It affects men and women equally. The onset occurs from 3 months to first year of life without a history of collodion baby or Harlequin ichthyosis.[5] This disease results from autosomal semidominant mutation in FLG gene located in chromosome 1q21.3. One thirds of individuals with heterozygous mutations show a mild phenotype in contrast to two thirds of patients with homozygous mutations who have more severe forms of ichthyosis.[6]

Clinical features of IV are characterized by xerosis, greyish white scales, pruritus, and eczema in which the extensor surfaces of the lower legs and the back are predominantly affected. Keratosis pilaris and palmoplantar hyperlinearity are commonly found.[1] Several studies reported dermoscopic findings of IV such as fine white scales whith criss-cross pattern and epidermal cleft with ill-defined edge.[7,8] Histopathologically IV is typically characterized by hyperkeratosis of corneal layer and thining to loss of granular layer, while the epidermal layer is slightly thinned to normal.[9]

In this case the skin lesion appeared when she was 5-years-old without a history of keratinization disorder at birth. On dermatological examination we found thick scales all over the body accompanied by palmo-plantar hyperkatosis and joint deformities. Dermosopy examination showed fine white scales on the erythematous skin with criss-cross pattern, whereas the histopathological features indicated hyperkeratosis and thinning of granular layer. Hence we diagnosed the patient with severe IV.

Several factors influencing vitamin D metabolism in IV patients include lack of UV penetration due to hyperproliferation of keratinocytes, poor sunbathing, Fitzpatrick skin type IV and V, excessive calcium loss through the skin, long-term use of systemic retinoids, and prolonged breastfeeding or inadequate vitamin D supplementation.[10] The laboratory findings indicated vitamin D insufficiency so that we administered oral D3 400 IU once daily and calcitriol 0.5 mcg twice daily. Vitamin D plays role in the proliferation and differentiation of keratinocytes either directly or through interaction with calcium. In vitro study reported that 1.25(OH)2D3 triggers the proliferation of keratinocytes by inducing the synthesis of cornified envelope proteins consists of involucrine, transglutaminase, loricine, and filaggrin.[11] The recommended daily intake of cholecalciferol for children with congenital inchthyoses is 400-600 IU to prevent vitamin D deficiency and risk of rickets.[12]

Previous studies documented syndromic congenital ichthyoses accompanied by joint involvement or vitamin D imbalance, based on our knowledge none of severe IV cases followed

by vitamin D insufficiency and joints contractures has been previously reported. The certain mechanism of joint deformity in IV remains unclear, but Daio *et al*. suggested that mutations of FLG gene was associated wih growth retardation, intellectual disability, joint contractures, and hepatopathy. However its mechanism is unclear.[13] Another study by Groseanu *et al*. revealed that vitamin D insufficiency are more likely to cause muscle weakness, atrophy, and contracture.[14] Iudici *et al*. suggested that decreased expression of vitamin D receptors (VDR) which depends on transforming growth factor beta (TGF-β) will lead to increased TGF-β1 thus it stimulates fibroblast. In addition, high TGF-β1 level will also enhance reactive oxygen species (ROS) production which plays role in fibrosis and myofibroblast differentiation allowing the occurrence of joint contracture.[15]

Conclusion

In severe cases, ichthyosis vulgaris may be accompanied by systemic disorders. Severe ichthyosis vulgaris can disrupt vitamin D metabolism resulted from chronic keratinocyte hyperproliferation. Examining vitamin D level and thyroid hormone function are required to prevent vitamin D insufficiency which may cause joint contracture. In severe ichthyosis vulgaris, vitamin D supplementation is not only for stabilizing vitamin D metabolism but also for improving skin condition as well as joint pain. Multidisciplinary approach is necessary to prevent worsening of ichthyosis vulgaris.

References

1. Choate KA, Milstone LM. Cornification disorders. In: Kang S, Amagi M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, *et al.* (editor). Fitzpatrick's dermatology in general medicine. 9th Ed. United States: Mc Graw Hill. 2019. p: 775-815.
2. Leung DYM, Boguniewicz M, Howel MD, Nomura I, Hamid QA. New insights into atopic dermatitis. *J Clin Invest*. 2004; **113(5)**:651-7.
3. Manchón SR, Giner CP, Villarroya EC, Codoceo RAM, Martin AH. Malnutrition in children with ichthyosis: Recommendations for monitoring from a multidisciplinary clinic experience. *J Am Acad Dermatol*. 2020;**85(1)**:1-22.
4. Akdeniz N, Karadağ AS, Çalka Ö, Ediz L, Karadağ R, Çeçen I. A case report of ichthyosis vulgaris with arthropathy and ophthalmic findings. *J Turk Acad Dermatol*. 2011;**5(3)**:1-4.
5. Hernández A, Gruber R, Oji V. Mendelian disorders of cornification: The ichthyoses. In: Hoeger P, Kinsler V, Yan A (editor). Harper's textbook of pediatric dermatology. 4th Ed. United States: Willey-Blackwell. 2020. p: 1549-98.
6. Fischer J, Bourrat E. Genetics of inherited ichthyoses and related diseases. *Acta Derm Venereol*. 2020;**100(7)**:186-96.
7. Gajjar PC, Mehta HH, Gosai M. Dermoscopy of congenital dermatoses in pediatric age group: An observational study. *Indian J Paediatr Dermatol*. 2019;**20(3)**:219-26.
8. Silverberg NB. Ichthyoses and palmoplantar keratoderma. In: Silverberg NB (editor). Atlas of pediatric cutaneous biodiversity: Comparative dermatologic atlas of pediatric skin of all colors. New York: Springer. 2012. p: 61-8.
9. Pinkova B, Buckova H, Borska R, Fajkusova L. Types of congenital nonsyndromic ichthyoses. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2020;**164(4)**:357-65.
10. Litaiem N, Chabchoub I, Bacha T, Slouma M, Zeglaoui F, Khachemoune A. Rickets in associationwith skin diseases and conditions: A review with emphasis on screening and prevention. *Photodermatol Photoimmunol Photomed*. 2020;**36(5)**:339-50.
11. Bikle DD. Vitamin D metabolism and function in the skin. *Mol Cell Endocrinol*. 2011;**347(1-2)**:80-9.
12. Sethuraman G, Marwaha RK, Challa A, Yenamandra VK, Ramakrishnan L, Thulkar S, *et al*. Vitamin D: A new promosing therapy for congenital ichthyosis. *Pediatrics*. 2016;**137(1)**:1-5.

13. Diao H, Zhu P, Dai Y, Chen W. Identification of 11 potentially relevant gene mutations involved in growth retardation, intellectual disability, joint contracture, and hepatopathy. *Medicine*. 2018;**97(46)**:1-5.
14. Groseanu L, Bojinca V, Gudu T, Saulescu I, Predeteanu D, Balanescu A, *et al*. Low vitamin D status in systemic sclerosis and the impact om disease phenotype. *Eur J Rheumatol*. 2016;**3(2)**:50-5.
15. Iudici M, Moroncini G, Cipriani P, Giacomelli R, Gabrielli A, Valentini G. Where are we going in the management of interstitial lung disease in patients with systemic sclerosis ? *Autoimmun Rev*. 2015; **14(7)**:575-8.