Systematized Verrucous Epidermal Nevus Partially Responsive to Acitretin: A Case Report

Felix Paolo J. Lizarondo[1] and Eileen Liesl A. Cubillan[2]

[1]*Section of Dermatology, Department of Medicine, Philippine General Hospital, University of the Philippines Manila*
[2]*Section of Dermatology, Department of Medicine, College of Medicine and Philippine General Hospital, University of the Philippines Manila*

ABSTRACT

A 5-year-old female presented a 4-year history of generalized well-demarcated asymptomatic brown to dark brown thin verrucous plaques with a Blaschkoid distribution. Histopathology was consistent with an epidermal nevus. Patient was diagnosed to have systematized verrucous epidermal nevus. Due to the extent of the lesions, surgical management was not feasible. Hence acitretin was given which showed partial decrease in the thickness of the lesions.

Key Words: systematized verrucous epidermal nevus, systemized verrucous epidermal nevus, systemic verrucous epidermal nevus, acitretin

INTRODUCTION

Verrucous epidermal nevus is a hamartomatous proliferation of the epithelium of which the predominant histologic component are keratinocytes.[1] Since keratinocytes are the implicated cell, verrucous epidermal nevus is also known as non-organoid or keratinocytic nevus, in contrast to organoid nevus that consists of sebaceous glands or hair follicles.[2] It occurs in 1 in 1000 infants with no gender predilection and with the majority appearing within the 1st year of life.[1] It usually presents as asymptomatic solitary linear papillomatous papules or plaques following Blaschko's lines but can also uncommonly present with extensive distribution as systemized or systematized verrucous epidermal nevus.[1,3] Variants of systematized verrucous epidermal nevus include nevus unius lateralis and ichthyosis hystrix when extensive unilateral and bilateral lesions are present, respectively.[1]

Epidermal nevus is a form of cutaneous mosaicism which occurs due to single post-zygotic mutations in the precursor cell in the embryonic epidermis.[4] The dorsoventral migration of the said mutated precursor cells from the neuroectoderm is thought to reflect the Blaschko's lines which appears as S-shaped or arcuate, V-shaped, whorled and streaked patterns.[5]

CASE

A 5-year-old female without developmental delays and co-morbidities was brought in due to generalized hyperpigmented verrucous plaques distributed along the Blaschko's lines (Figure 1A, B). Lesions started when the patient was around one-year-old when the mother noted generalized brown patches gradually thickening into

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Corresponding author: Felix Paolo J. Lizarondo, MD
Section of Dermatology
Department of Medicine
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Manila 1000, Philippines
Telephone: +632 554 8400 local 5105/5106
Email: fjlizarondo@up.edu.ph

darker, verrucous plaques more pronounced on the neck and bilateral axillae. On physical examination, there were multiple well-demarcated verrucous papules and plaques, which were in an S-shaped or arcuate, V-shaped, whorled, and streaked patterns distributed all over the body with sparing of the oral and genital mucosa (Figure 1C, D, E, F, and 2A, B, C). Systemic, neurological and ophthalmological examinations were all normal. Histopathology of a verrucous plaque on the arm was consistent with a verrucous epidermal nevus showing acanthosis, papillomatosis with basketweave orthokeratosis and superficial perivascular infiltrates consisting of lymphocytes and histiocytes; there were no changes of epidermolytic hyperkeratosis (Figure 3). Based on the clinical picture, absence of extracutaneous symptoms and histopathology, the patient was diagnosed with systematized verrucous epidermal nevus. Baseline electrolytes including calcium and phosphate levels were all within normal limits, which were measured due to hypophosphatemia being commonly associated with multiple verrucous epidermal nevi.[4]

Due to the mother's concern for cosmesis and the implication of the lesions for socialization, topical treatment was started with tretinoin 0.05% but with no significant response. Surgical excision was not feasible due to the extent of the lesions and the patient's age. Patient was started on acitretrin initially at 0.5 mg/kg/day (10 mg a day) for 1 month with noted slight decrease of the lesions and only mild dryness of the lips. With follow-up, liver enzymes profile of aspartate aminotransferase (AST) and alanine aminotransferases (ALT) and lipid profile (cholesterol and triglycerides) were noted to be normal, dose was increased to 1 mg/kg/day (20 mg a day) for 2 months with lesions becoming thinner and less verrucous more notably on the neck and bilateral axillae (Figure 2D, E, F). Photoprotection with sunscreen SPF 30 Broad Spectrum was also initiated for the patient as a countermeasure for possible photosensitivity. Acitretin was well tolerated, noting only dryness of the lips, and regular monitoring of liver enzymes (AST, ALT) and lipid profile were found to be consistently within normal limits. Long term monitoring for the patient also includes watching out for rare development of neoplasms such as basal cell carcinoma, squamous cell carcinoma, and keratoacanthoma in an epidermal nevus.[3]

DISCUSSION

Systematized verrucous epidermal nevus, an extensive form of a hamartomatous proliferation of keratinocytes, is a form of cutaneous mosaicism resulting from a single postzygotic mutation originating from a precursor within

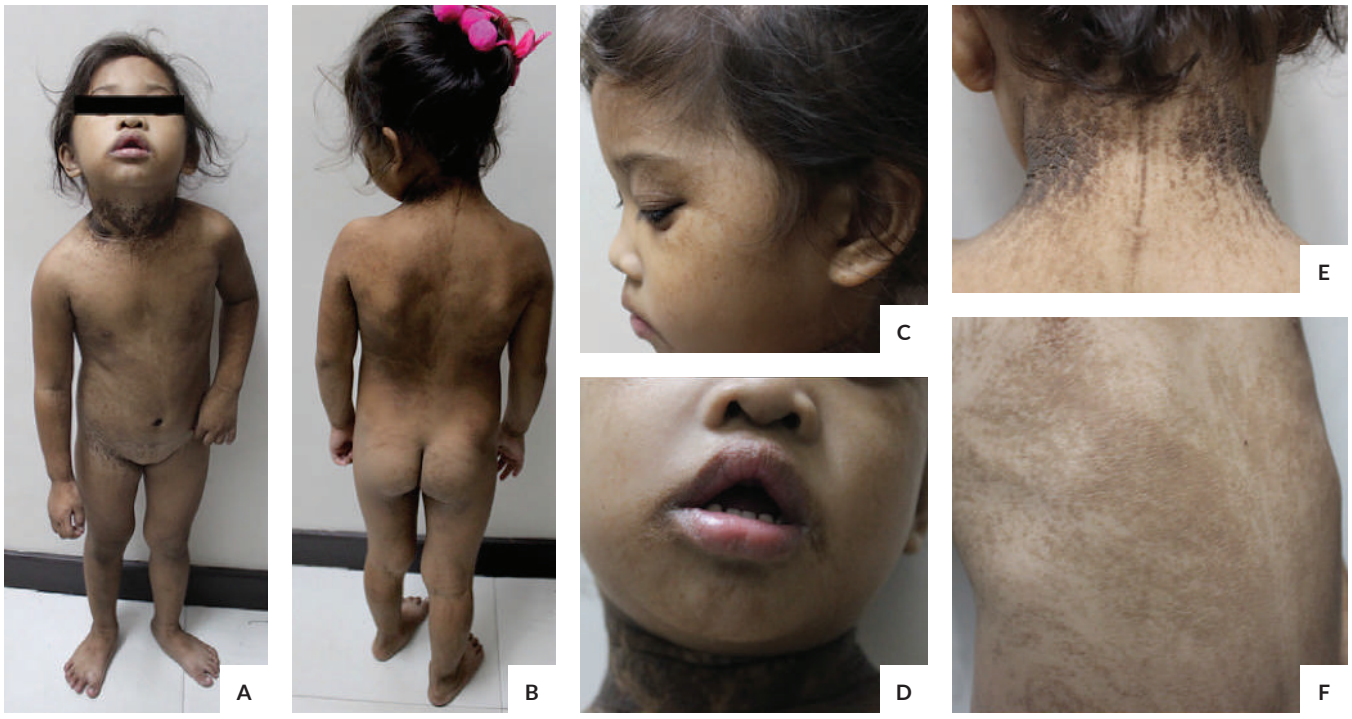

Figure 1. A. Anterior view showing the generalized distribution of the hyperpigmented verrucous plaques distributed along the Blaschko's lines. **B.** Posterior view showing the generalized distribution of the hyperpigmented verrucous plaques distributed along the Blaschko's lines; note the V-shaped configuration of lesions along the midline. **C, D, E.** Closer view of the lesions on the periorbital **(1C)**, perioral area **(1D)** and posterior neck. **F.** Closer view of the anterior trunk; note that there are both narrow and broad Blaschko's lines (Type 1a and 1b), which is a non-classical presentation of cutaneous mosaicism and is associated with decreased chance of extracutaneous abnormalities, consistent with the patient not presenting with systemic involvement.

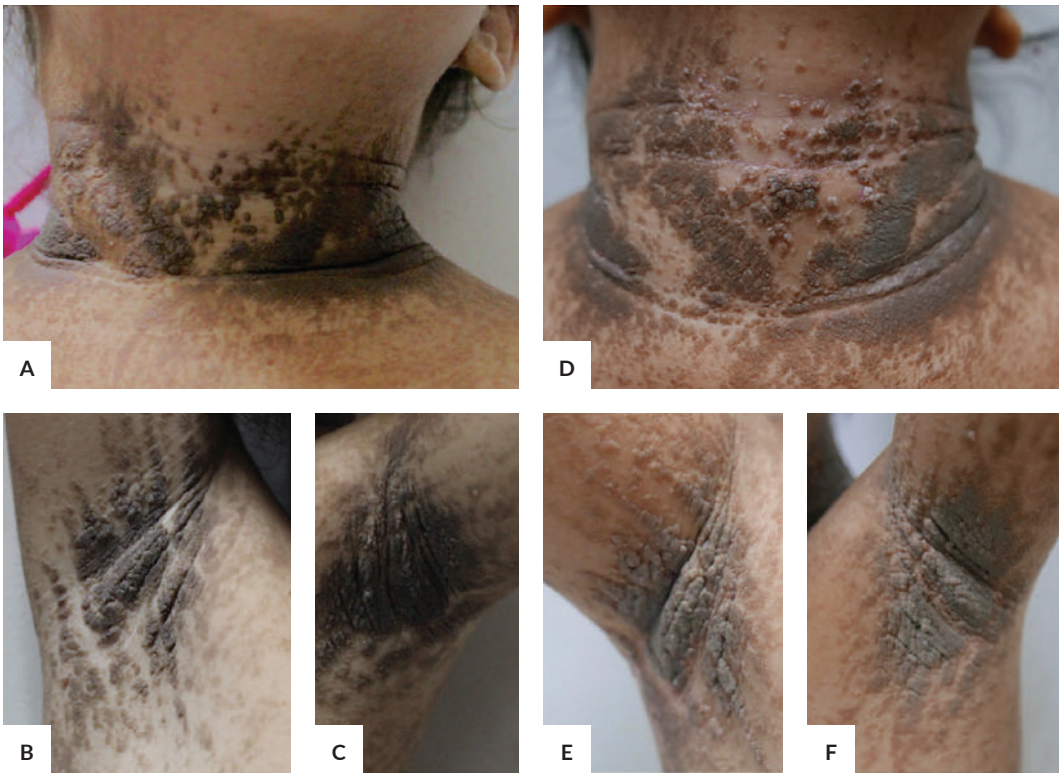

Figure 2. **A.** Well-demarcated irregularly shaped dark brown plaques with verrucous surface along the Blaschko's lines on the anterior neck. **B.** Linear verrucous plaques along the Blaschko's lines on the right axilla. **C.** Similar lesions noted on the left axilla but slightly darker and more confluent than lesions on the right axilla. **D, E, F.** After 3 months of acitretin (0.5 mg/kg/day for the 1st month and 1 mg/kg/day for next 2 months), lesions were markedly less verrucous and some with decreased pigmentation on the anterior neck **(2D)**, right axilla **(2E)** and left axilla **(2F)**.

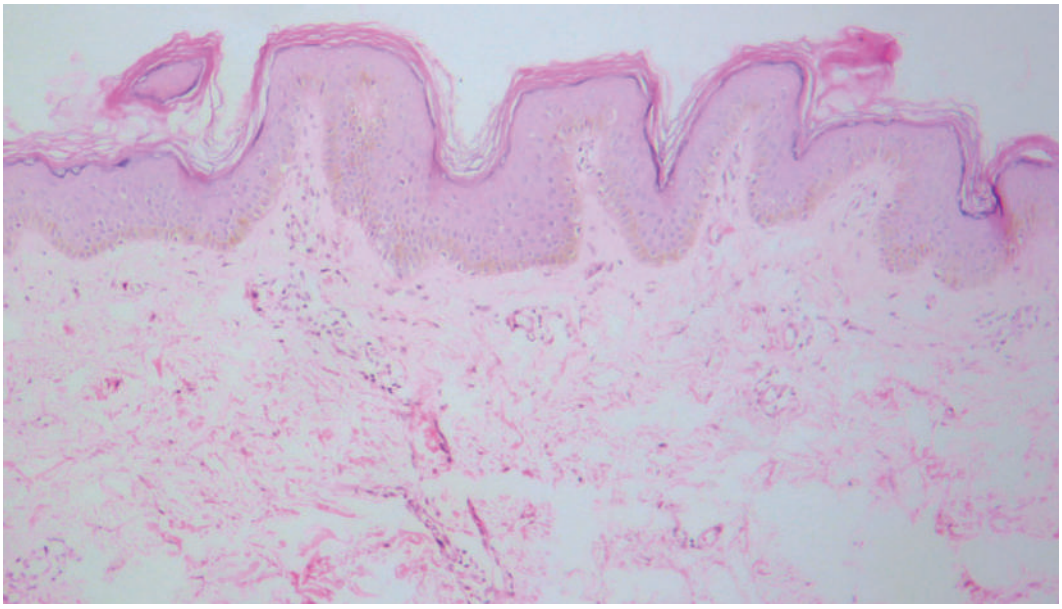

Figure 3. Histopathology of verrucous plaque on the forearm consistent with a verrucous epidermal nevus, showing acanthosis, papillomatosis with basketweave orthokeratosis, multiple melanocytes on spinous epidermal layers and superficial perivascular infiltrates consisting of lymphocytes and histiocytes; there was no presence of epidermolytic hyperkeratosis.

the embryonic epidermis. Activating mutations of Fibroblast Growth Factor Receptor 3 (*FGFR3*), specifically R248C of a single keratinocyte stem cell has been implicated in the formation of this non-organoid nevus.[6,7,8] A neurocutaneous syndrome called FGFR3 epidermal nevus syndrome or Garcia-Hafner-Happle Syndrome has recently been described on a patient with systematized non-organoid epidermal nevus with an FGFR mutation.[9] The patient had associated cerebral defects such as corpus callosum agenesis causing seizures.[9] Facial dysmorphism has also been noted to occur with a verrucous epidermal nevus.[10] Other genes implicated in nonorganoid nevus include *PIK3CA*, *KRAS,* and epidermal differentiation genes at 1q23.[11]

Patterns of cutaneous mosaicism reflect the cell affected by the mutation. The pattern of distribution seen in the patient is Type 1 or Blaschko lines which is the most common pattern of cutaneous mosaicism consistent with the keratinocyte being affected in verrucous epidermal nevus.[12,13] The Blaschko lines can further be divided into subtypes based on the width of the bands; narrow (Type 1a) and broad (Type 1b). For this patient, combination of narrow and broad bands of verrucous epidermal nevus was seen. This non-classical presentation has a decreased predisposition to extracutaneous abnormalities compared to so-called classic presentation. This is consistent with the patient presenting with cutaneous lesions only and no other associated systemic abnormality.[12]

Verrucous epidermal nevus can be classified based on the presence of epidermolytic hyperkeratosis on biopsy. Epidermolytic verrucous epidermal nevus are caused by keratin 1 or keratin 10 mutations, which are not expressed in the brain hence neurologic complications are not seen in this condition.[11] The presence of epidermolytic hyperkeratosis on histopathology suggests possible gonadal mosaicism and warrants genetic counseling.[4] For this patient, there was no evidence of epidermolytic hyperkeratosis, implying that the systematized verrucous epidermal nevus is unlikely to be passed on to her future offspring.

The extensiveness of the lesions warranted systemic work up for extracutaneous abnormalities. Currently, there are no standard screening for extracutaneous abnormalities. The suggested approach is that screening should be done depending on the possible syndromic associations based on the type of nevus.[4] For non-epidermolytic verrucous epidermal nevus as seen in this patient, possible syndromic associations include central nervous system and skeletal abnormalities.[11] Systemic physical examination and neurologic exam did not point to the presence of extracutaneous abnormalities. For multiple verrucous epidermal nevus, hypophosphatemia is commonly associated hence, baseline electrolytes measurement were determined.[4] For this patient, baseline electrolytes including calcium and phosphate levels were all within normal limits.

For localized verrucous epidermal nevus, full thickness surgical excision is curative although keloid or hypertrophic scarring is a possible complication.[3] If only the epidermis is removed however, lesions may recur.[3] Due to the extent of the lesions of the patient, surgical management is not a viable option for all the lesions. Another contraindication against surgery is the age of the patient. The lesions are expected to evolve as the patient grows and are expected to stabilize around puberty.[1] Thickness of the verrucous lesions may be decreased using ablative lasers such as carbon dioxide laser (continuous wave and pulsed) and erbium:yttrium aluminum garnet (Er:YAG).[14] Topical therapies such as corticosteroids, retinoic acid, anthralin, tar, podophyllin, and 5-fluorouracil often have limited benefit. [3,4]

Even though the lesions are asymptomatic, the patient's appearance has hampered her socialization and relationship with other children. Tretinoin 0.05% cream was prescribed for about 2 months with no significant response. Surgical excision was not an option in this case because of the extent of the lesions, therefore oral retinoids were offered. Earlier case reports used the aromatic retinoid Ro 10- 9359 (etretinate) with good results.[15,16] Another type of retinoid, which was used for a systematized epidermal nevus is isotretinoin.[17] For verrucous epidermal nevus, case reports have mostly cited use of acitretin. Acitretin was used in an extensive verrucous epidermal nevus on a 20-year old male which resulted in flattening of the lesions with 1.1 mg/kg/day (75 mg) for about 3 weeks then tapered to 50 mg for 3 months then eventually discontinued.[18] This was well tolerated and the only side effect which was reversed on discontinuation was palmoplantar desquamation.[18] For a systematized inflammatory linear verrucous epidermal nevus (ILVEN) in a 34-year old female, acitretin was started at 0.4 mg/kg/day (25mg) slowly titrated to 30 mg for about 2 weeks with noted significant improvement of hyperkeratosis as well as the erythema.[19] A 24-year old fem[19]ale with an epidermal nevus syndrome was also given 25 mg of acitretin for 5 weeks with significant decrease of hyperkeratosis and erythema.[20] A more recent case report with 2 cases of inflammatory linear verrucous epidermal nevus showed response with doses of 25 mg (0.5 mg/kg/day) in an 18-year old female for 6 weeks then 25 mg every other day for 12 weeks; similar regimen was started on a 12-year old male with marked improvement.[21] For this patient, partial improvement of the lesions was noted on the patient especially on the neck with some of the lesions showing decreased pigmentation; the rest of the lesions demonstrating decreased verrucous surface.

Most common side effect of acitretin is mucocutaneous including lip dryness, cheilitis, hair loss, nail fragility and photosensitivity.[22] Other side effects include hepatotoxicity, hyperlipidemia, skeletal abnormalities, and teratogenicity.[22] Of special concern to the pediatric population are the bone changes such as hyperostosis, extraosseous calcification and premature epiphyseal closure that are not dose and duration dependent.[22] Of concern to a female patient, but not yet applicable to this 5-year old patient, is teratogenicity

which should be discussed when the female pediatric patient reaches puberty.[22] Chronic therapy of acitretin in the pediatric population has been shown to be safe with doses ranging from 0.7-1.07 mg/kg/day with duration of treatment ranging from 2-36 months with the growth and development not being affected.[23] The patient while on acitretin only noted mild dryness of the lips and slight pruritus of the skin (resolving with emollients), without other side effects with consistent normal monthly monitoring of laboratory parameters (AST, ALT, lipid profile).

CONCLUSION

This case demonstrates an unusual presentation of a common benign hamartoma, a systematized verrucous epidermal nevus. Although the lesions were extensive, they were not associated with any other abnormalities, ruling out an epidermal nevus syndrome. There are no standard screening examinations to date but it is important to note that verrucous/keratinocytic/non-organoid epidermal nevi are usually associated with abnormalities of the central nervous system and the skeletal system, which were not affected in this patient. Histopathology did not demonstrate an epidermolysis, which is important to rule out since its presence implies gonadal mosaicism hence making the condition potentially inheritable. Due to the extent of the lesions, surgical management of the lesions was not feasible hence the patient was started on acitretin at 0.5 mg/kg/day then increased to 1 mg/kg/day which resulted in partial decrease in the thickness of the lesions. During the course of treatment, only dryness of the lips was noted. Liver enzymes and lipid profile were within normal limits. This case demonstrates that acitretin is a viable alternative for systematized verrucous epidermal nevus.

Statement of Authorship

All authors approved the final version submitted.

Author Disclosure

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