Oral Vitamin A as an Adjuvant Treatment for Refractory Pityriasis Rubra Pilaris (PRP)

Hanif Sri Utami[1*], Benny Nelson[1], Eyleny Meisyah Fitri[1], Windy Keumala Budianti[1], Endi Novianto[1]
[1]*Department of Dermatology and Venereology Faculty of Medicine Universitas Indonesia/ Dr. CiptoMangunkusumoNational CentralGeneral Hospital, Indonesia*

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Abstract: Pityriasis rubra pilaris (PRP) is a rare and chronic papulosquamous disorder of unknown etiology that often progresses to erythroderma and causes a disabling palmoplantar keratoderma. Genetic factors with an autosomal dominant pattern of inheritance have been supposed to play a critical role for the induction of PRP. Vitamin A deficiency was also believed to be related to the disorder. Treatment of PRP is mainly anecdotal, based on case reports and case series, a feature shared by many disorders in dermatology due to their rarity. Currently, oral retinoids and methotrexate are the first line of therapy in patients with PRP. Response to therapy varies in each patient. We report a 46-year-old male patient with erythroderma and hyperkeratotic palms and soles since two years ago. Histopathological findings were consistent with PRP. The patients had been treated with several systemic therapies, yet showed poor clinical response. Clinical improvement was seen after 16 weeks addition of oral vitamin A at a dosage of 200.000 IU daily in concurrent with 10 mg weekly methotrexate. Evaluation of potential adverse effects was closely monitored.Oral vitamin A, an old regimen, seems to be a favorable adjuvant treatment for refractory PRP.

1 INTRODUCTION

Pityriasisrubrapilaris (PRP) is a rare and chronic skin disorder that often progresses to erythroderma and causes a disabling keratoderma of the palms and soles. The exact cause of this skin disorder remains elusive. The impact of this skin disorder is often devastating on patients' quality of life. There are six different types of PRP based on clinical presentation, age of onset, and prognosis. The most common clinical features are follicular hyperkeratosis, progressing to salmon-colored erythroderma with islands of normal skin (nappesclaires). Palms and soles are frequently involved as waxy and thick hyperkeratotic plaque. These typical features occur in more than 50% of the patients of PRP and the disease resolution usually occurs after an average period of 3 years.(Moretta G et al, 2017;Sehgal VN et al., 2008).

The management of PRP has always been challenging. The management is predominantly based on case reports with limited number of patients. To date, no randomized controlled trial had been conducted due to the scarcity of the disease. The classical therapies include systemic therapies such as retinoids, methotrexate, cyclosporine, and fumaric acid. Psoralen plus ultraviolet A (PUVA) photochemotherapy is also in use. However, response to therapy varies from person to person, and it is not uncommon that patients show poor response to multiple therapies (Ross NA et al., 2016).

Oral vitamin A (retinol) at a dosage of 150,000 to 300,000 IU per day was reported beneficial in some patients. Retinoids, its synthetic derivatives, are considered to be the first line therapy. Isotretinoin, acitretine, and etrenitate have been reported helpful in some patients of PRP. They help regulate the proliferation and differentiation of the epithelial cells. Compared to retinol, the administration of these synthetic agents requires lower dose.[4] However, the prescription of these synthetic agents remains restricted in Indonesia, so that we try oral vitamin A as an adjunctive treatment while monitoring the side effects.

2 CASE

A 46-year-old male patient visited the Dermatovenerology clinic, Cipto Mangunkusumo National Central General Hospital with erythroderma

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since two years ago. The skin eruption appeared first on the neck, and then spread in cephalocaudal direction to the whole body within one month. He has sought treatment to several physicians. However, there was no improvement on his skin lesion.

Physical examination showed generalized salmon-colored patches with islands of normal skin. The scaling was fine and powdery. The palms and soles showed hyperkeratotic plaque with flexion contracture of some fingers. Yellow discoloration of the nails was also present. There was also ectropion of his bilateral lower eyelids.

From histopathological findings, the epidermis showed alternating orthokeratosis and parakeratosis, regular acanthosis, and prominent granular layer. The dermis showed dilated vasculatures. The patient was diagnosed with PRP based on clinical manifestation and histopathology examination.

The hemoglobin level was 14 g/dL, leukocytes 8,520 /µL, thrombocytes 404,000 /µL, SGOT (AST) 33 U/L, SGPT (ALT) 27 U/L, ureum 12 mg/dL and creatinine 0.8 mg/dL. He received methotrexate with weekly dosage up to 17.5 mg. Because there was no significant improvement after five months, the treatment was switched to another therapeutic agent. He was given cyclosporine 4 mg/kg/day. However, after four months the treatment was discontinued because of no improvement.

We decided to give methotrexate with additional oral vitamin A (retinol) to the patient. Oral methotrexate was maintained at weekly dosage of 10 mg with 200,000 IU oral vitamin A per day. After 16 weeks, there was marked improvement clinically. The erythematous patches became fainter and the scaling seemed finer. The hyperkeratotic lesion on his palms and soles also improved.

Duringmethotrexate and retinol therapy, the evaluation of adverse effects was routinely performed. Liver function testwas carried out monthly. The patient was also referred to theophthalmologist to investigate any ocular adverse effect and to treat his ectropion.

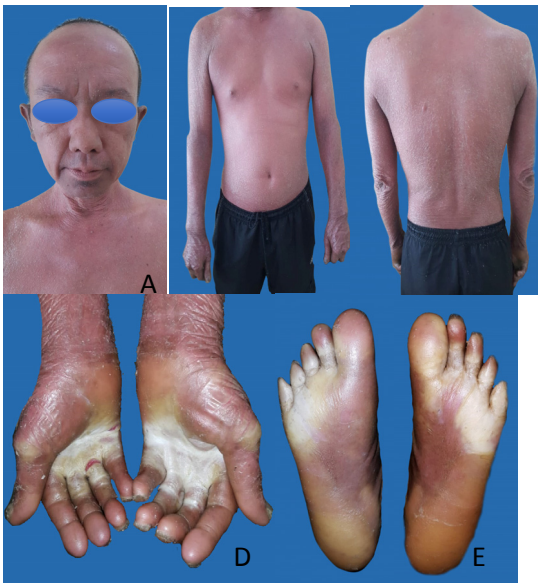

Figure 1.Before retinol administration.Confluence of PRP lesions leads to erythroderma with a reddish orange colors and extensive scales (A-C). Keratoderma in PRP, palmar (D) and plantar (E).

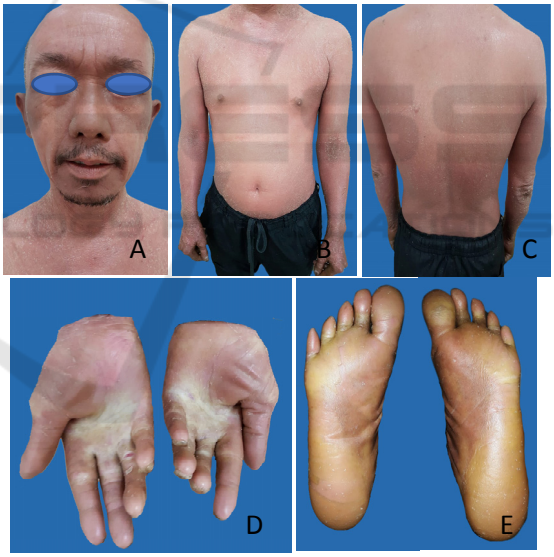

Figure 2.Evaluation after 16 weeks of retinol administration revealed significant improvement. Erythroderma(A-C) and palmo-plantar keratoderma (D-E) partially subsided.

3 DISCUSSION

Successful treatment for patients with PRP have always been a great challenge for dermatologists. Oral vitamin A, usually at a daily dosage of 150,000 to 300,000 IU was reported helpful. The administration of vitamin A is able to accelerate the shedding of keratoderma, and was reported to

reducethe duration of disease. However response to therapy varied. Clinical improvement was experienced in one of three patients.[4]The administration of oral vitamin A was initially based on the hypothesis that PRP occurred as a result of vitamin A deficiency. However, it was revealed later that patients oftenhad normal level of vitamin A. Other investigator proposed another hypothesis that the lack of clinical response to vitamin A was resulted from lack of retinol-binding protein, a specific transport protein of vitamin A. In spite of the unclear linkage between PRP and vitamin A metabolism, it is well-noted that vitamin A plays a significant role in the treatment of PRP. Clinical response to vitamin Aseemed to be related to the pharmacological action.(Cohen et al., 1989). The first line treatment of PRP is the oral retinoids.(Klein A et al., 2010) Isotretinoin was reported effective both in adult and juvenile type PRP.The clinical improvement was experienced by 60% to 95% after 16 to 24 weeks of isotretinoin therapy. The daily dosage varied, ranging from 0.5 to 3.19 mg/kg. Another study reported the lower daily dosage of 1 to 1.5 mg/kg was adequate.Etretinate, an aromatic retinoid, was reported helpful at a daily dosage of 1 mg/kg. Clinical improvement was seen after 20 weeks of etretinate therapy. Compared to isotretinoin, etretinate has longer half-life.(Dicken CH et al., 1987)

Alitretinoin at a dosage of 30 mg per day was reported helpful as an alternative treatment. The therapeutic effect of alitretinoin was considered through itsanti-inflammatory mechanism. In vitro, alitretinoin inhibited of proinflammatory cytokines such as TNFα and IL-12/IL-23.(Amann PM et al., 2015).

Vitamin A and retinoids has the same potential adverse effectsof hypervitaminosis A such as teratogenicity, abdominal pain, visual disturbances, dryness, dizziness, and hypertriglyceridimia.[8] Routine laboratory tests should be performed to monitor any adverse effects.Hypervitaminosis vitamin A was reported in patients obtaining systemic vitamin A more than 50,000 IU daily. However, retinoids do not seem to disturb liver function as it is not stored in the liver like vitamin A.[5]Administration of oral vitamin A for treatment of PRP has been described in previous literature and textbooks, but the effective amount and period of vitamin A has not been specifically described. The administration of vitamin A is suggested only for adults. Children are considered to be more susceptible to its toxicity. Pregnant and childbearing-age women are also restricted due to its teratogenic effect.(Randle HW et al., 1980).

Antimetabolites like methotrexate is often used in patients of PRP. Clinical improvement usually appears after 6 weeks therapy, and complete response is often achieved by week 12 to 16. However, patients refractory to convential therapy often require combination therapy with retinoids and methotrexate. In a study, 22 patients were treated with etretinate 25-75 mg/day or isotretinoin 40 mg twice daily. Half of the patients also received methotrexate at a weekly dosage of 5-30 mg. After 16 weeks, 8 of 11 patients in combination therapy showed clinical improvement of 50-95%.[4]However, due to teratogenicity, oral retinoids including isotretinoin, etretinate and alitretinoin are not available in Indonesia.

In our patient, clinical improvement did not occur after 20 weeks of methotrexate administration as monotherapy, yet marked improvement did appear after 16 weeks of oral vitamin A administration in concurrent with methotrexate at a weekly dosage of 10 mg. Liver function tests were routinely performed as the concurrent use of methotrexate and vitamin A increased the risk of hepatotoxicity.In this patient, we routinely monitored the potential side effects by clinical symptoms and laboratory markers. There was no elevation of liver enzymes. However, there are few similar case reports to date. Hereafter, as more cases become accumulated, we would expect to clarify the effective minimum dosage and optimal dosing period of vitamin A therapy for PRP patients.

4 CONCLUSION

PRP is a rare and chronic skin disorder that often progresses to erythroderma and causes a disabling skin disorder. Finding a suitable management has always been difficult. Although the linkage between PRP and vitamin A metabolism remains intriguing and individual clinical response to therapy exists, it is worth to offer vitamin A therapy for patients with refractory PRP as a favorable alternative. Careful monitoring should be routinely performed to avoid its potential adverse effects. Due to restricted prescription of retinoids in some countries, oral vitamin A is a favorable alternative for patients without any contradictions.

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