Confluent and Reticulated Papillomatosis: Treatment with Topical Combination Isotretinoin-Erythromycin Gel and Topical Urea: Case Report

Konfluant ve Retiküler Papillomatoz: Topikal Izotretinoin-Eritromisin Kombinasyon Jeli ve Topikal Üre Tedavisi

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ABSTRACT Confluent and reticulated papillomatosis is a rare disorder that is manifested by asymptomatic, scaly, hyperkeratotic and hyperpigmented, verrucous papules and plaques which are confluent and reticulated. Patient one, a 16-year-old girl applied with a complaint of an itchy scaling, brown, velvety, confluent and reticulated plaques over the nape of her neck, axillae and intermamarian area. Patient two, a 13-year-old girl applied with persistent hyperkeratotic, gray-brown, verrucous, confluent plaques over the lateral and posterior aspects of the neck and axillae. Both of the patients were diagnosed with confluent and reticulated papillomatosis by clinical and histopathological findings. The patients were prescribed a combination of topical isotretinoin–erythromycin gel and topical 40% urea emulsiogel daily. The patients experienced complete clearance of the lesions within a month. We consider that topical isotretinoin-erythromycin gel and 40% urea emulsiogel treatment should be used as an alternative treatment for patients who do not want to use oral therapies.

Key Words: Skin diseases; skin abnormalities; skin pigmentation; ısotretinoin; erythromycin; keratolytic agents; urea

ÖZET Konfluant ve retiküler papillomatoz; asemptomatik, skuamlı, hiperkeratotik, hiperpigmente, verrüköz, papül ve plaklarla kendisini gösteren nadir bir hastalıktır. İlk hastamız olan 16 yaşında kız olgu ense, aksilla ve intermamarian bölgede yerleşmiş, kaşıntılı, skuamlı, kahverengi, velvetik (kadifemsi), konfluant ve retiküler plaklarla başvurdu. İkinci hastamız olan 13 yaşında kız olgu ise ense, boyun yanları ve aksillada yerleşmiş, persistan, hiperkeratotik, gri-kahverengi, verrüköz, konfluant plaklarla başvurdu. Her iki hastaya konfluant ve retiküler papillomatoz tanısı klinik ve histopatolojik olarak konuldu. Her ikisine de günlük topikal izotretinoin-eritromisin kombinasyonu jel ve topikal %40 üre emülsiyojel olarak önerildi. Hastalarda bir ay içinde tedaviye tam cevap alındı ve lezyonları tamamen geçti. Oral tedavi almak istemeyen hastalarda, topikal izotretinoin-eritromisin jel ve %40 üre tedavisi alternatif bir tedavi seçeneği olarak kullanılabilir.

Anahtar Kelimeler: Deri hastalıkları; deri değişiklikleri; deri pigmentasyonu; izotretinoin; eritromisin; keratolitik ajanlar; üre

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Confluent and reticulated papillomatosis (CRP) (Gougerot–Carteaud Syndrome) is a rare and under-recognized disorder first described in 1927.[1-4] It is a dermatosis manifested usually by asymptomatic, persistent, scaly, hyperkeratotic, hyperpigmented, and verrucous papules and plaques which are confluent centrally and reticulated at the periphery. CRP is located primarily on the upper trunk, neck and axillae.[1-5] The etio-

logy is still unclear.[2] Abnormal reaction to Malassesia furfur is proposed as a cause of CRP in most reports.

In this report we describe two patients with CRP who recovered following treatment with a combination topical 0.05% isotretinoin–2% erythromycin gel (Isotrexin® gel, Embil Pharmaceutical Company) and topical 40% urea (Urederm® %40 emulsiogel, Orva Pharmaceutical Company).

CASE REPORTS

CASE 1

A 16-year-old nonobese female patient applied to the outpatient clinic with a complaint of an itchy persistent stain in the neck, present for 2 years. On the dermatologic examination there was scaling, brown, confluent and reticulated, velvety plaques over the nape of the neck, axillae and intermamarian area (Figure 1). It was regarded as pityriasis versicolor at first glance although potassium hydroxide examination was negative and this was thought to be a false result. She was prescribed 20% ketoconazole shampoo and 2% sertaconazole cream. There was no benefit from the antifungal treatment at the end of one month. A punch biopsy was performed and revealed hyperkeratosis, acanthosis and papillomatosis with focal basal hyperpigmentation and thinning of granular layer associated with superficial perivascular mononuclear inflammatory infiltrate (Figure 2A and 2B) The biopsy result was compatible with a diagnosis of confluent and reticulated papillomatosis. She was prescribed a combination topical isotretinoin–erythromycin gel at night and topical 40% urea at morning after taking bath. At 10th day of treatment a 50% improvement and at 24th day complete clearing of lesions were detected (Figure 3). She was advised to continue the 40% topical urea emulsiogel daily. She developed a milder recurrence on follow up at 6 weeks. She used again topical isotretinoin–erythromycin gel at night and recovered and still is on follow up.

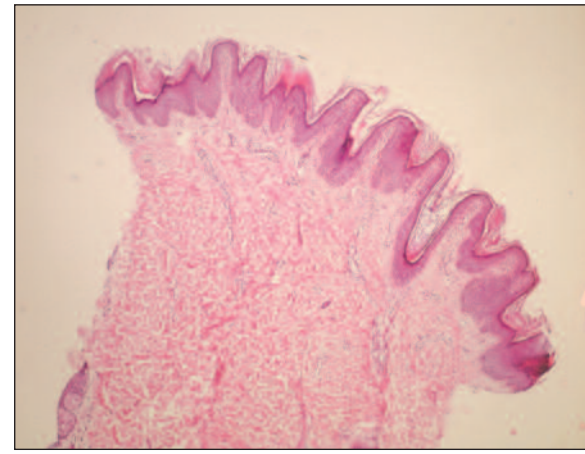

FIGURE 2A: Histopatologic specimen of Case 1. (HE X 40),

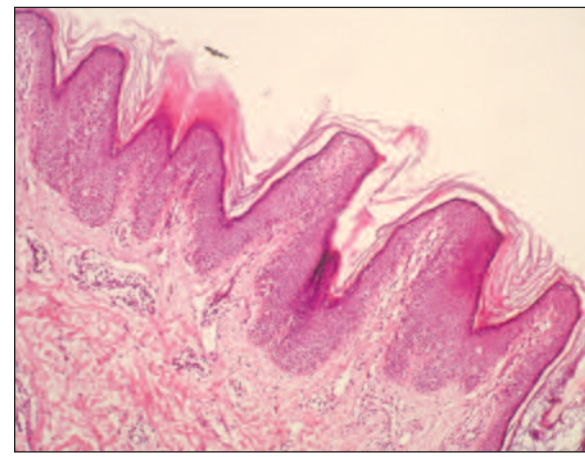

FIGURE 2B: Histopathologic specimen of case 1 showing acanthosis, papillomatosis and hyperkeratosis associated with superficial perivascular inflammatory infiltrate. (HE X 100).

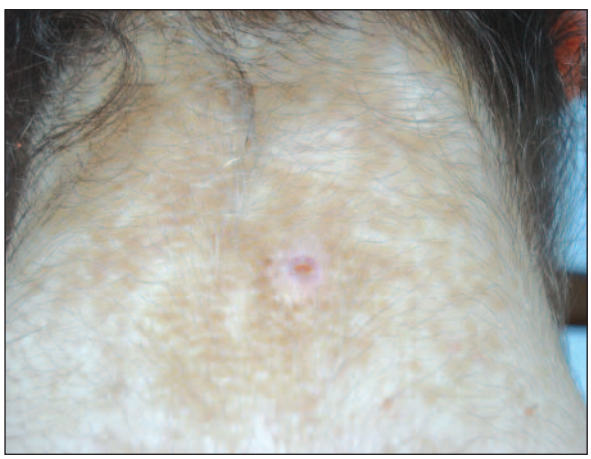

FIGURE 1: Clinical appearance of the reticulated, hiperpigmented, hyperkeratotic, and verrucous plaques over the nape of the neck in case 1.

CASE 2

A 13-year-old girl applied to the outpatient clinic with a 3 year history of persistent dirty appearan-

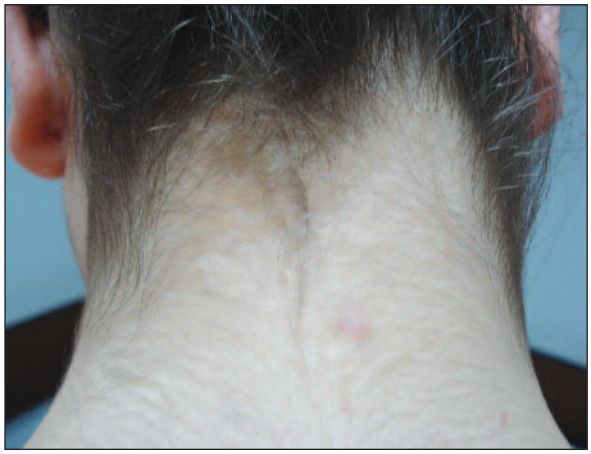

FIGURE 3: Clinical appearance of case 1 after treatment on day 24.

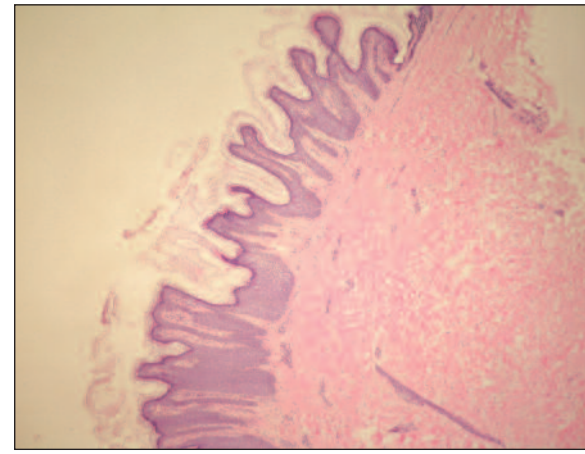

FIGURE 5A: Histopathologic specimen of case 2. (HE x 40).

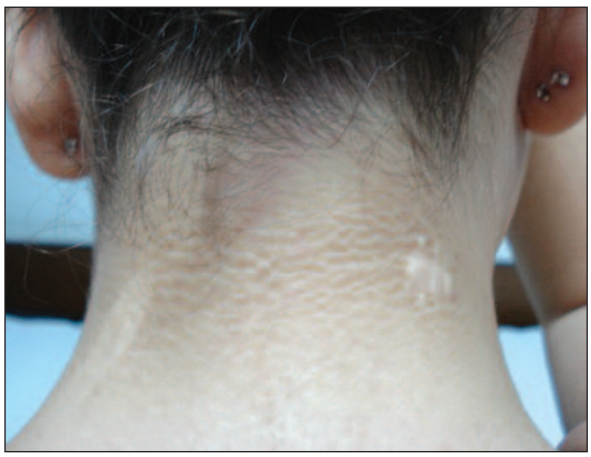

FIGURE 4: Clinical appearance of case 2 with confluent, hyperpigmented, hyperkeratotic and verrucous papules over the nape of the neck.

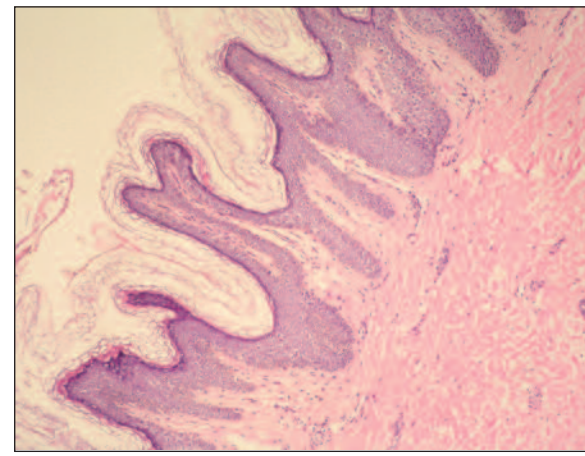

FIGURE 5B: Histopathological specimen of case 2 showing acanthosis, papillomatosis and hyperkeratosis associated with superficial perivascular inflammatory infiltrate. (HE X 100).

ce and color change over the nape of her neck. On dermatologic examination, there were hyperkeratotic, gray-brown, verrucous, and confluent plaques over the lateral and posterior aspects of the neck and axillae (Figure 4). She was healthy and nonobese, using no systemic medications. The patient was prescribed to use topical 1% nimesulide gel and 10% urea without benefit two years ago with the diagnosis of acanthosis nigricans. The family brought a biopsy report performed 2 years ago in another center. Hyperkeratosis, papillomatosis and acanthosis had been observed and any other pathology had not been detected in elastic and colla-

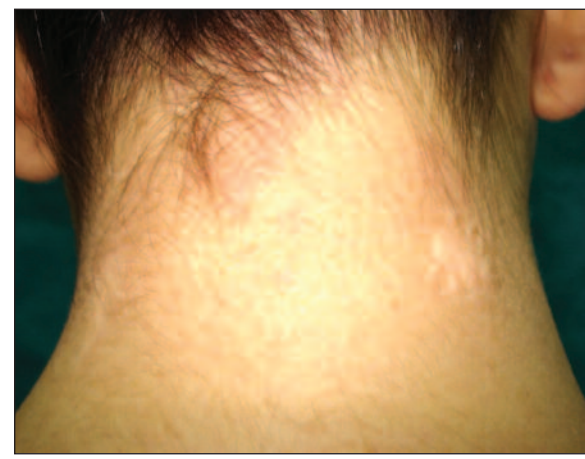

FIGURE 6: Clinical appearance of case 2 after treatment on day 53.

gen tissue with Verhoeff-van Gieson and Masson-Trichrom stains at that time (Figure 5A and 5B). This was interpreted to be compatible with the diagnosis of confluent and reticulated papillomatosis by us. The patient was prescribed combination topical isotretinoin–erythromycin gel at night and topical 40% urea at morning after taking bath. Burning sensation lasting 1 to 2 minutes after application of the isotretinoin–eriythromycin gel and redness were described by the patient and this necessitated one day discontinuance of the treatment. At the 15th day control examination there was an 80% improvement in the clinical condition of the patient and then complete recovery was observed (Figure 6). She was advised to continue the 40% topical urea emulsiogel daily. She developed a milder recurrence on follow up at 3rd month and recovered by using topical isotretinoin–erythromycin gel application.

DISCUSSION

CRP is usually very resistant to therapy.[2] Various treatment modalities may be temporarily successful, but the lesions generally recur within months.[1,2] The recurrence was a problem after minocycline treatment in 6/18 cases.[1] We observed also milder recurrence after 3 to 6 weeks of maintenance topical 40% urea treatment in both cases.

As the etiology of CRP remains unclear, various empirical oral and topical treatments were reported to be effective in CRP in the literature. Therefore there is no standard therapy.[3,5] Various antibiotics such as doxycycline, minocycline, fucidic acid, amoxicillin, azithromycin, clarithromycin, erythromycin and roxithromycin have been found to be effective.[1,5-9] The mechanisms by which antibiotics show efficacy are not well understood.[9] The response to oral antibiotics may be related to the anti-inflammatory and antiproliferative properties of these antibiotics rather than their antimicrobial effects.[7,9] Other therapies like oral retinoids (isotretinoin and etretinate), phototherapy, radiotherapy, cryotherapy and dermabrasion have also been reported with varying effectiveness.[6]

It is proposed that topical agents are initially effective but lesions often recur within a period of months thereby necessitating systemic treatment.[2,6] Topical selenium sulfide was shown to be effective in CRP. The therapeutic effect was proposed to be related to the keratolytic properties of the selenium sulfide.[10] Topical tazarotene[4], topical tretinoin[11], calcipotriol[12] and tacalcitol[3] were reported to be effective in CRP treatment. Topical calcipotriol and tacalcitol appears to be as effective as oral retinoids and minocycline.[3] The effectiveness of topical vitamin D analogues supports the hypothesis of abnormal keratinization for CRP pathogenesis.[3,12]

Topical and oral vitamin A derivatives have been used with success in CRP treatment. Topical tretinoin was found to be effective only in the areas in which it was applied.[11] Kägi et al, reported two cases of CRP associated with atopy and these cases were successfully treated with a cream containing 12% urea and 0.03% tretinoin twice daily with moisturizer used when needed. They have proposed that this treatment should always be tried first.[13] Topical tretinoin has been supposed to be a safer alternative to systemic therapies which should be used with caution in young patients.[11,13] Potential side effects are skin redness, peeling and discomfort[11] (Table 1). Our second patient experienced erythema and burning sensation after application of topical isotretinoin and erythromycin gel that did not necessitate discontinuation of the treatment.

Tretinoin is the first retinoid used in the treatment of follicular and epidermal keratinization disorders[14]. Isotretinoin (13-cis-retinoic acid) was shown to isomerase to tretinoin (all-trans-retinoic acid) intracellularly. Isotretinoin was shown to enhance the proliferation of cultured primary keratinocytes cultured at lower density (representing atrophic sun damaged skin) more than tretinoin. Both of them were shown to exert slight antiproliferative effects at high density primary keratinocyte cultures. Schroeder and Zouboulis, have proposed that retinoids exert a normalizing activity in hyperkeratotic diseases and this effect may be made mostly by modulation of cellular differentiation rather than cellular proliferation.[15] Topical isotretino-

TABLE 1: Properties of topical agents used in our patients

Topical Agent	Application	Proposed Mode of Action	Potential Complications
Isotretinoin	Once daily at night	Antiproliferative Modulation of cellular differentiation Normalization of keratinization	Burning sensation Discomfort Erythema Peeling
Erythromycin		Anti-inflammatory Antiproliferative	
Urea 40%	Once daily at morning after bath	Keratolytic Normalization of keratinization	Peeling Burning sensation

in was found to exert similar effects with tretinoin in hairless mice dorsal skin. The main difference between isotretinoin and tretinoin is that isotretinoin causes adverse effects with a much lower incidence and intensity.[16] For these reasons we have chosen isotretinoin in the treatment of our patients.

Erythromycin, as a macrolide, inhibits neutrophil infiltration, IL-8 secretion and the inflammation caused by bacteria.[17,18] We think that topical erythromycin exerts these similar effects and show efficacy in the treatment of CRP by antiinflammatory and antiproliferative actions as orally used (Table 1).

Topical urea is a keratolytic, proteolytic and moisturizing agent. Hageman and Proksch, have shown that topical urea application decreases epidermal proliferation rate by 51%. Topical urea also influences the expression of involucrin and differentiation related keratin expression in psoriasis. They have suggested that these results indicate that topical urea exerts its effect of improving psoriasis by reducing epidermal proliferation and inducing epidermal differentiation.[19] It is thought that topical 40% urea while exerting enhanced keratolytic effects, it also helps to normalize keratinization as in psoriasis (Table 1).

Topical therapies should be tried first before resorting to systemic therapies because they may be just as effective as systemic therapies but they have fewer side effects.[4] We consider topical isotretinoin-erythromycin gel and 40% urea treatment should be used as an alternative treatment modality for patients who do not want to use oral therapies.

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