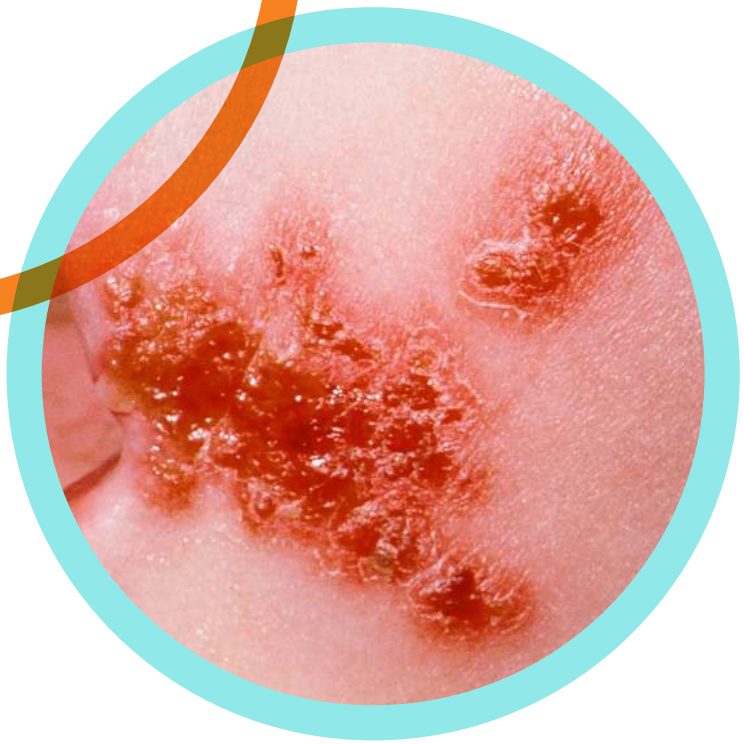

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Case Report
A Combined Approach to the Treatment of Nevus Comedonicus using Topical Adapalene and Oral Doxycycline

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Abstract

Background and Objective: Nevus Comedonicus (NC) is a rare benign hamartoma presenting with grouped, dark, firm, comedo-like papules sometimes forming pustules and cysts, commonly seen on face and neck areas. The authors report a case of a 16-year-old female with lesions consistent with NC on biopsy. There was no extra cutaneous involvement since infancy when the lesions first appeared. **Materials and methods:** The patient was treated with adapalene 0.3% gel, twice a day and oral doxycycline 100 mg/cap, twice a day for one month. **Results:** There was a decrease in the size of cysts and improvement in the depth of the pits; however, the formation of comedo-like papules remained unchanged. **Conclusion:** To date, there have been no published studies of the use of topical adapalene in NC. In addition, the combined treatment of topical adapalene and oral doxycycline has not been previously reported in the literature.

Key words: Nevus comedonicus, topical adapalene, doxycycline, treatment, dermatology

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Nevus Comedonicus (NC) is a rare type of epidermal nevus characterized by aggregation of dilated follicular orifices filled with pigmented keratinous material in a honeycomb pattern[1,2]. The etiology of NC is unclear[3]. Various types of treatments have been used in NC from topical keratolytics, tretinoin and corticosteroids, oral antibiotics and isotretinoin and lasers[4]. To date, there have been no published studies of other retinoids, such as topical adapalene[1]. The patient in this report was treated with the combination of topical 0.3% adapalene gel and oral doxycycline. This combination treatment has not been reported previously in the literature.

CASE REPORT

The authors report a case of a 16-year-old female patient presenting with multiple, grouped, darkly pigmented papules and macules with crateriform pits on the patient's right posterior auricular area, right mastoid area, right occipital area and right lateral side of the neck following the lines of Blaschko. Cysts were also appreciated on the right posterior auricular area (Fig. 1a, b). Similarly, multiple, grouped, darkly pigmented papules and macules, with some forming cysts connected by sinuses were seen on the right upper back (Fig. 2a, b).

When the patient was one month old, her mother noted hyperpigmented macules on the right posterior auricular area evolving into papules. There were no accompanying symptoms. At the age of 7, the patient developed hyperpigmented macules and papules on the right mastoid area, slowly involving the right occipital area and the right upper back. As the patient grew, the lesions grew in size as well. Her past medical, drug, family and social histories were noncontributory.

Cutaneous examination showed that these papules were adherent to the skin and not amenable for extraction. The rest of the general physical examination was unremarkable.

On dermoscopy, there were multiple, dark brown to black clods. Nests with milia-like cysts with dark brown and black dots were also appreciated (Fig. 3). Fine, white scales were noted in the background of one of the black clods.

The histopathological examination of a 4 mm skin punch biopsy of a papule on the right posterior auricular area showed a dilated follicular plug filled with orthokeratotic keratin. This was surrounded by moderately dense infiltrates of lymphocytes and monocytes. The epidermis was normal (Fig. 4a-c).

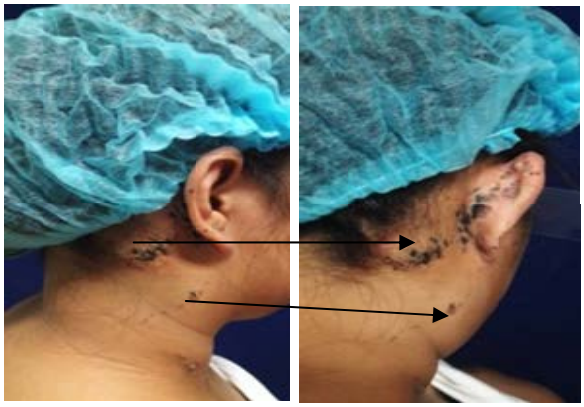

Fig. 1: There were grouped, dark, firm papules and macules with pits on the patient's right posterior auricular area and right lateral side of the neck

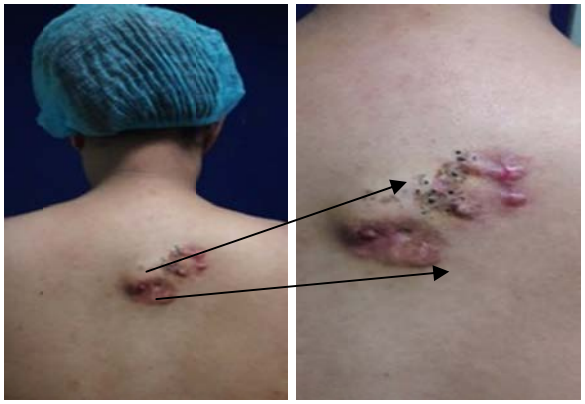

Fig. 2: There were grouped, dark, firm papules, brown macules and cysts on the patient's right upper back. Some of the cysts were connected by sinuses

Fig. 3: Dermoscopic appearance of the lesions on the right posterior auricular area

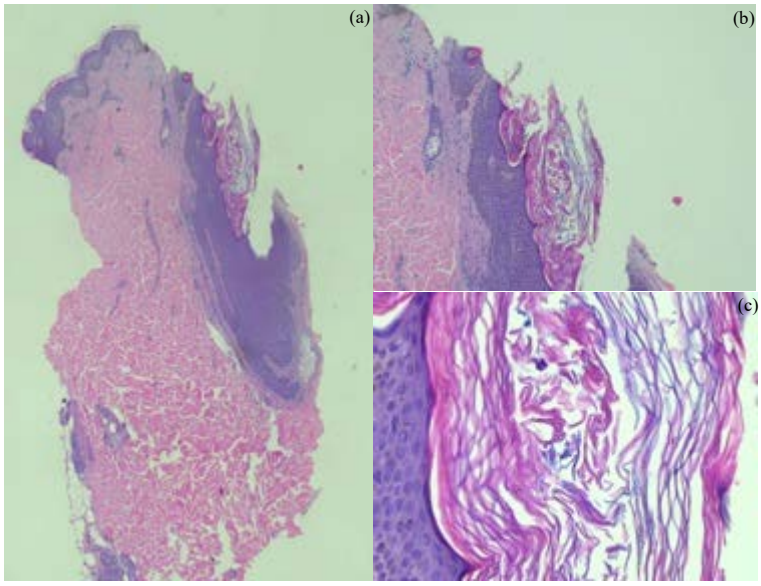

Fig. 4(a-c): (a) Normal epidermis with a dilated follicular plug (H and E; original magnification 4x), (b) Surrounded by moderately dense infiltrates of lymphocytes and monocytes (H and E; original magnification 20x) and (c) With orthokeratotic keratin (H and E; original magnification 40x)

Fig. 5(a-b): (a) There was no appreciated difference from baseline and (b) A 4 weeks of treatment on the papules. The patient claimed decrease in the depth of the pits and there was a decrease in the size of the cysts on the right posterior auricular area

A diagnosis of NC was made. The patient was treated with adapalene 0.3% gel, twice daily and oral doxycycline 100 mg/cap, twice a day for 4 weeks. After 4 weeks, no significant difference from the baseline photos was noted but the patient reported a decrease in the depth of the pits and the size of the cysts on the right posterior auricular area (Fig. 5a, b). There was a decrease in the size of the cysts on the upper back (Fig. 6a, b).

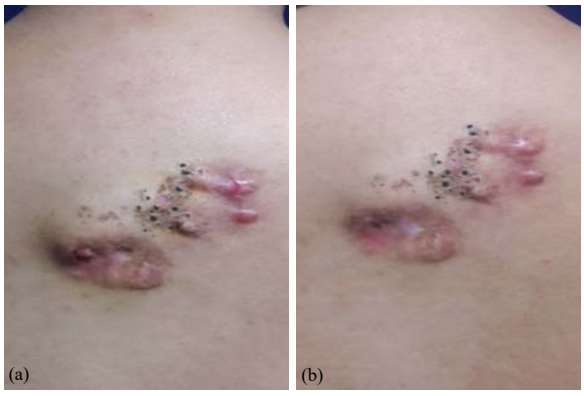

Fig. 6(a-b): (a) There was a decrease in the size of the cysts from baseline and (b) A 4 weeks of treatment on the right upper back

DISCUSSION

The NC is hypothesized to result from a hamartomatous proliferation of pilosebaceous tissue. The prevalence of NC has been estimated from 1 in 45,000 to 1 in 100,000 with no gender or racial preference[1]. Since the first description by Kofmann, about 200 cases of NC have been reported[2]. According to the data in the Philippine Dermatological Society-Health Information System, which collects data on skin diseases from the 11 dermatology training accredited institutions, only 26 cases were reported[5] from 2011-2017.

This rare developmental abnormality results in the clinical appearance of grouped, often linearly arrayed and elevated follicular openings. With time, the follicular openings fill with dark keratin plugs, imparting the appearance of open comedones[6]. Two types of NC have been identified, the first is predominantly non-inflammatory comedone-like in character and the second consists of inflammatory cysts and sinuses[2]. The NC can appear on any part of the body but has a predilection for the face and the neck areas. In 50% of cases, the condition develops immediately after birth[7]. When NC is associated with cataracts, skeletal defects or central nervous system abnormalities, it is called NC syndrome[4].

The patient presented with multiple, grouped, darkly pigmented papules and macules with crateriform pits on the right posterior auricular area, right mastoid area, right occipital area and right lateral side of the neck following the lines of Blaschko. Cysts were also appreciated on the right posterior auricular area. Similarly, multiple, grouped, darkly pigmented papules and macules, with some forming cysts connected by sinuses were seen on the right upper back. Both types of NC were present in the patient and this might suggest a spectrum of the disease beginning in the formation of the follicular plug resembling acne vulgaris, complicating to the formation of sinuses when untreated. Fortunately in this case, no neurologic, ophthalmologic and orthopedic findings were noted.

Kaminska-Winciorek and Spiewak[8] reported dermoscopic findings of NC. The study described the distinctive pattern consisting of dark, sharply demarcated keratin plugs of 1-3 mm diameter, numerous structureless, circular and barrel-shaped, homogenous areas with hyperkeratotic plugs of various shades of brown. In the patient, there were multiple, dark brown to black clods. The clods represent comedo-like openings commonly found in seborrheic keratosis. Also, nests with milia-like cysts with dark brown and black dots were appreciated. Fine, white scales were noted in the background of one of the black clods. The finding of clods with scales implies severity of the patient's lesions in contrast to the patient in the study by Kaminska-Winciorek and Spiewak[8].

The pathogenesis of NC remains unknown. Although an autosomal mutation that survives by mosaicism has been implicated, the genetic basis has yet not been identified. A mutation of a fibroblast growth receptor (FGFR-2), which is exclusively found in epithelial cells including epidermal keratinocytes and sebocytes, might play an important role in the development of NC[9]. Levinsohn *et al.*[10] recently identified gain-of-function mutations in somatic NEK9. The affected cells showed loss of markers of follicular differentiation with ectopic expression of keratin 10 (K10), a marker of interfollicular differentiation. The expansion of these cells produced comedo formation in NC.

The characteristic histopathologic findings of NC include aggregation of dilated follicular infundibula with prominent orthokeratotic plugging, absent or rudimentary sebaceous elements and an absence of true follicles[2]. In the patient, there was a dilated follicular plug filled with orthokeratotic keratin. This was surrounded by moderately dense infiltrates of lymphocytes and monocytes. The epidermis was normal.

Schecter *et al.*[11] reported a case of NC with epidermolytic hyperkeratosis (EHK). The characteristic perinuclear vacuolization in the stratum spinosum and stratum granulosum and large, irregular keratohyalin granules in the granular cell layer were indicative of EHK. Somatic mosaicism for a mutation in the K10 gene has been implicated in the development of epidermal nevus with EHK. Paller *et al.*[12] found that there were point mutations in 50% of K10 alleles in keratinocytes from epidermal nevi with EHK but did not find mutations in adjacent non-lesional skin. However, the exact significance of this finding remains uncertain until a clear understanding is reached as to whether this defect represents a purely somatic mutation or also affects germline cells[2].

The NC may be treated conservatively by topical medications, with or without oral medications. Ito *et al.*[13] published a case of bilateral NC syndrome treated with a topical retinoic acid for three months and then followed by vitamin D3 analog for three months. No improvement was appreciated. Capusan *et al.*[14] described a case of localized NC on the forehead of an elderly patient treated with a combination of tretinoin 0.025% clindamycin 1% gel once daily. The lesions resolved three months after treatment and were maintained on weekly applications thereafter. Kaminska-Winciorek and Spiewak[8] used topical tazarotene 0.05% gel twice a day on a linear NC localized on a female patient's right breast. Keratin plugs were decreased after ten weeks of treatment. Polat *et al.*[15] utilized topical tretinoin, thrice a week for 2 months in a patient with bilateral NC of the eyelids associated with bladder cancer. The patient's lesions improved after two months. Wakahara *et al.*[16] tried topical tacalcitol ointment twice a day for 6 months to a 15 year old patient. The lesions resolved without recurrence after 40 months.

Kirtak *et al.*[17] used oral isotretinoin 30 mg/day in a patient with extensive unilateral NC on the right side of the trunk and right lower extremity for 6 months. Improvement of the cysts initially was seen but eventually recurred after

discontinuation of treatment. No effect on comedo-like papule formation was appreciated. Chhabra *et al.*[18] published a case of an 18 year old patient with inflammatory unilateral NC with epidermoid cysts. The patient was treated with isotretinoin 0.8 mg kg^{-1}/day and ammonium lactate 12% lotion twice a day for 3 months. Epidermoid cysts present were surgically excised. After 3 months, pus-discharging lesions subsided; however, minimal improvement of comedones was appreciated. Qian *et al.*[9] administered acitretin at 0.5 mg kg^{-1} from spring to autumn intermittently for 2 years in a patient with NC syndrome. This alleviated the recurrences of hidradenitis suppurative-like lesions from 6-7 times to once to twice a year. However, retinoid-dermatitis and elevated serum alkaline phosphatase levels were noted. If NC lesions are unresponsive to conservative treatment, they may be surgically excised. Milburn *et al.*[19] performed surgical excision with skin grafting on two cases of unilateral NC successfully. However, this resulted to delayed healing time and hypertrophic scarring. No reports regarding recurrences were mentioned.

Lasers, such as carbon dioxide, erbium: YAG and recently, diode lasers, have produced good results but recurrences and adverse effects do occur[4,6,20,21]. Caers *et al.*[20] performed erbium-YAG laser on an 18 year old with unilateral NC on his right lower extremity. About 4-6 passes were done for only one session. This resulted to erythema after the procedure and minimal scarring. Six months after, recurrence of the lesions was noted. Zhu and Sun[21] utilized an ultra pulse CO_2 laser on a bilateral facial NC patient. However, recurrence was noted one month after the procedure. Givan *et al.*[6] administered 1450 nm diode laser on a unilateral NC patient for 4 sessions at 1 month interval for 4 months. This achieved 80% improvement after the 3rd session from the baseline and clinical resolution after the 4th session. Mild erythema and edema were noted immediately after each treatment session. Mild recurrence of texture irregularity was noted after 1 year from the last procedure.

The use of oral retinoids has been limited due to its systemic toxicity. Surgical excision and the use of lasers have produced improvement on the lesions of NC; however, recurrences of lesions have been noted. This may require repeatedly doing the procedures; hence, the greater risk of scarring. The conventional use of topical retinoids has been proven to be effective in improving the lesions of NC. There were no reported adverse effects in patients with NC treated with topical retinoids; hence, the use of conventional therapy should not be set aside.

To date, there have been no published studies of the topical retinoid, adapalene, for treating NC[1]. Adapalene acts to normalize desquamation by reducing keratinocyte proliferation and promoting differentiation in acne vulgaris. It also blocks several important inflammatory pathways that are activated in acne: toll-like receptors, leukocyte migration and the AP-1 pathway[22]. Doxycycline is a commonly prescribed antibiotic in acne vulgaris. Aside from its antimicrobial properties, its anti-inflammatory properties have been used successfully to treat non-infectious dermatological conditions by inhibiting neutrophil chemotaxis and activation, down regulating inflammatory cytokines and inhibiting matrix metalloproteinases[23]. Because acne vulgaris and NC are both pilosebaceous disorders characterized by the formation of keratinous plugs, the authors opted to try a combination of topical adapalene and oral doxycycline for the conservative treatment of NC in the patient.

The patient did not desire surgical removal of her lesions on consultation. It was treated with adapalene 0.3% gel, twice a day and oral doxycycline 100 mg/cap, twice a day for one month without any complications. There was a decrease in the size of cysts and improvement in the depth of the pits; however, the formation of comedo-like papules remained unchanged. The treatment could not be extended because the patient failed to follow up. The authors were not able to assess the lesions thereafter.

CONCLUSION

The NC is a rare clinical entity that can manifest with comedo-like papules, cysts and sinuses. Its pathogenesis is still unclear. The NC may be treated conservatively by topical medications, with or without oral medications. Surgical excision and lasers have been successfully used to treat the disease but with the risk of having complications and recurrence. The use of adapalene, a topical retinoid, in combination with an oral antibiotic such as doxycycline, may provide an alternative without any complications.

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