Comedonal Darier’s Disease: A Rare Variant and a Common Misdiagnosis

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Abstract

Comedonal Darier’s disease is an extremely rare variant demonstrating unique clinical and histopathological findings; however, it is commonly misdiagnosed. Herein, we report a case of comedonal Darier’s disease and discuss its different diagnostic and therapeutic challenges.

Keywords: Darier’s disease; Comedones; Acne vulgaris; Dyskeratosis; Isotretinoin

Abbreviations:

DD: Darier’s disease; F: Female; M: Male; NM: Not mentioned; NMSC: Non melanoma skin cancers; UK: United Kingdom; -ve: Negative; +ve: Positive

Case Report

A 19-year-old male presented with three years duration of multiple disfiguring acneform lesions on the face. Skin examination revealed multiple white and black-heads, soft nodules, oily skin and ice-pick scars (Figure 1).

Moreover, there were brown keratotic papules affecting the neck, trunk, axillae, ears and scrotum. Careful inspection of these papules revealed surmounted black-heads. Palmar pits and V-shaped distal notching of the nails were also found. The patient was otherwise healthy with no family history of similar condition. Microscopic examination of one papule demonstrated a cup-shaped invagination with keratotic plug, dyskeratosis, suprabasal acantholysis with prominent villi (Figure 2) and mild dermal lymphocytic infiltrate.

Furthermore, microscopic findings of one nodular lesion revealed a markedly dilated hair follicle cyst with acantholysis and dyskeratosis (Figure 3). Finally a diagnosis of comedonal Darier’s disease was established and surgical excision of the largest facial cystic lesions was done for cosmetic purpose. Isotretinoin (40 mg/day for 8 weeks) was given with unsatisfactory response, so it was terminated upon patient request.

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Furthermore, microscopic findings of one nodular lesion revealed a markedly dilated hair follicle cyst with acantholysis and dyskeratosis (Figure 3). Finally a diagnosis of comedonal Darier’s disease was established and surgical excision of the largest facial cystic lesions was done for cosmetic purpose. Isotretinoin (40 mg/day for 8 weeks) was given with unsatisfactory response, so it was terminated upon patient request.
**Discussion**

Darier’s disease (DD) is a rare genodermatosis including classic and atypical variants. Comedonal DD is an extremely rare variant with unique presentation. It was first described by Derrick et al. in 1995 and since then only 14 cases have been reported including the presented one with different demographic features. Surprisingly, it is a diagnostic pitfall for two decades evidenced by the time lag between onset of symptoms and final diagnosis (Table 1).

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. Of Cases</th>
<th>Country</th>
<th>Age</th>
<th>Sex</th>
<th>Family History</th>
<th>Sites</th>
<th>Associations</th>
<th>Treatment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derrick et al. 1995</td>
<td>2</td>
<td>UK</td>
<td>61</td>
<td>M</td>
<td>Negitive</td>
<td>Face, Scalp, Nails, Palms</td>
<td>Pruritus</td>
<td>Topical steroid, Emollients</td>
<td>Initial improvement then recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10s</td>
<td>M</td>
<td>Positive</td>
<td>Face, Trunk</td>
<td>Scalp nodules</td>
<td>Etretinate 50 mg/day</td>
<td>Improved, except for persistent scalp nodules</td>
</tr>
<tr>
<td>Song et al. 1997</td>
<td>1</td>
<td>Korea</td>
<td>16</td>
<td>M</td>
<td>Negitive</td>
<td>Face, Scalp, Trunk, Nails</td>
<td>None</td>
<td>Etretinate 30 mg/day</td>
<td>Improved</td>
</tr>
<tr>
<td>Lee et al. 2002</td>
<td>2</td>
<td>Korea</td>
<td>25</td>
<td>M</td>
<td>Negitive</td>
<td>Face, Trunk</td>
<td>Greasy skin, Pruritus, Facial ice-pick scars &amp; nodules with a leonine appearance</td>
<td>Oral Isotretinoin 30 mg/day</td>
<td>Stopped after 4 weeks due to side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24</td>
<td>M</td>
<td>Negitive</td>
<td>None</td>
<td>Facial nodules</td>
<td>Minocyclin</td>
<td>No response after several months</td>
</tr>
<tr>
<td>Aliagaoglu et al. 2006</td>
<td>1</td>
<td>Turkey</td>
<td>18</td>
<td>M</td>
<td>Negitive</td>
<td>Face, Neck, Trunk, Legs</td>
<td>Cornifying &amp; hypotrophic variants</td>
<td>Acitretin 1 mg/kg/day</td>
<td>No response after 4 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24</td>
<td>M</td>
<td>Negitive</td>
<td>Face, Scalp Trunk</td>
<td>None</td>
<td>Long-term antibiotics</td>
<td>No response</td>
</tr>
<tr>
<td>Yegin et al. 2007</td>
<td>1</td>
<td>Turkey</td>
<td>7</td>
<td>M</td>
<td>Negitive</td>
<td>Face, Scalp Trunk</td>
<td>Scalp syringocystadenoma papilliferum &amp; scarring alopecia, Pitted scars on face, scalp, trunk, Malodor</td>
<td>Isotretinoin 1 mg/kg/day for 3 months</td>
<td>Poor response</td>
</tr>
<tr>
<td>Tsuruta et al. 2010</td>
<td>1</td>
<td>Japan</td>
<td>10s</td>
<td>M</td>
<td>Negitive</td>
<td>Face, Trunk</td>
<td>Ice-pick scars on face</td>
<td>Oral: biotin, Korean ginseng, anti-histamins</td>
<td>No response</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>22</td>
<td>M</td>
<td>Negitive</td>
<td>None</td>
<td>None</td>
<td>Topical: bufexamac, calcipotriol, steroid</td>
<td>No response</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Etretinate 10 mg/day &amp; topical adapalene</td>
<td>Mostly improved</td>
</tr>
<tr>
<td>Chung et al. 2011</td>
<td>1</td>
<td>Korea</td>
<td>Late</td>
<td>F</td>
<td>Positive</td>
<td>Face</td>
<td>Greasy skin</td>
<td>Oral minocycline &amp; Topical tacrolimus</td>
<td>Little improvement</td>
</tr>
<tr>
<td>Goel et al. 2012</td>
<td>1</td>
<td>India</td>
<td>66</td>
<td>M</td>
<td>Negitive</td>
<td>Face</td>
<td>None</td>
<td>NM</td>
<td>NM</td>
</tr>
<tr>
<td>Buchanan &amp; Strutton</td>
<td>1</td>
<td>Australia</td>
<td>22</td>
<td>M</td>
<td>Negitive</td>
<td>Not defined</td>
<td>NMSC</td>
<td>NM</td>
<td>NM</td>
</tr>
</tbody>
</table>

Lora et al. 2013 [11] 2 Italy NM 46 M Negitive Scalp, Trunk, Palms NM NM NM
25 68 F Negitive Face, Trunk Palms NM NM NM

Our case 1 Egypt 16 19 M Negitive Face, Trunk, Scrotum, Palms, Nails Greasy skin, Ice-pick scars, Facial nodules Surgical removal of large nodulo-cystic facial lesions & then oral isotretinoin 40 mg/day Improved cosmetic results after removal of the nodules. No response after 2 months

<table>
<thead>
<tr>
<th>Table 1: Summary of the reported cases of comedonal Darier’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Note:</strong> NM: not mentioned; NMSC: non-melanoma skin cancer; UK: United Kingdom; M: male; F: female; *Face involvement is almost a constant finding. N.B: None of the 14 cases showed neurological or infectious complications and only two cases reported a positive family history.</td>
</tr>
</tbody>
</table>

The hallmark of comedonal DD is prominent comedones invariably involving the face however, other sites can be also affected (Table 1) [1-4]. Greasy skin, nodulo-cystic lesions and even ice-pick scars have been reported [4]. Furthermore, these acne-like lesions may or not be associated with characteristic warty papules of classic DD representing a real diagnostic challenge [4,5]. Also, nails, palms and mucous membranes lesions of classic DD may or not be found (Table 1) [3,6-8]. Other associated cutaneous manifestations include pruritus, leonine face, syringocystadenoma papilliferum and even other Darier variants [9].

In contrast to classic DD, all reported comedonal DD patients did not show any neurological disorders or increased susceptibility to bacterial/or viral infections [10]. This may be explained by the paucity of the reported cases or by different underlying pathogenic mechanisms.

Acantholytic dyskeratosis is the main histopathologic picture in DD [5]. However, comedonal DD is characterized by prominent follicular involvement and marked elongation of dermal villi with papillary projections which may be surrounded by dermal lymphocytes and plasma cells resembling warty dyskeratoma [4,9].

Classic DD is an autosomal dominant trait with a high penetrance, however, in comedonal DD there are only two genetic studies in the literature [10]. First, Tsuruta et al. [4] by direct sequencing of ATP2A2 in patient’s genomic DNA, revealed a heterozygous three-base deletion in exon 2 leading to deletion of leucine at the 41st amino acid residue from the amino terminus. However recently, Lora et al. [11] found no evidence of pathogenic mutations in the ATP2A2 gene in their patient suggesting that other genes may be implicated. In agreement with that we noticed that almost all reported patients (12 out of 14 as shown in Table 1) were males which raise the possibility for an X-linked pattern of transmission, an observation that deserves further genetic studies. Furthermore, familial comedonal DD was reported only in two patients [1]. Additionally, Kurokawa et al. [12] demonstrated that keratin and filaggrin expression pattern in comedonal DD has similar characteristics to classic DD rather than acne vulgaris.

In addition to differentiating comedonal DD from classic DD (Table 2), acne vulgaris and familial dyskeratotic comedone are the main clinical differential diagnoses while warty dyskeratoma is the main histopathological mimicker [13]. So, careful history taking and clinical examination of the whole skin, mucous membranes and nails in any suspected case is critical for the diagnosis of comedonal DD and proceeding to histopathological examination in doubtful cases is a must.

<table>
<thead>
<tr>
<th>Items</th>
<th>Comedonal Darier’s disease</th>
<th>Classic Darier’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Extremely rare</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of onset</td>
<td>Ranges from 10s to 66</td>
<td>2nd decade usually</td>
</tr>
<tr>
<td>Sex</td>
<td>Predominantly in males</td>
<td>Equal in both sexes</td>
</tr>
<tr>
<td>Geographic distribution</td>
<td>Asia, East &amp; Middle East</td>
<td>Worldwide</td>
</tr>
<tr>
<td><strong>Aetiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defective Gene</td>
<td>ATP2A2</td>
<td>ATP2A2</td>
</tr>
<tr>
<td>Reported mutation types</td>
<td>Deletion [only one report]</td>
<td>Missense &amp; splicing [many reports] &amp; others e.g. deletions</td>
</tr>
<tr>
<td>Mode of inheritance</td>
<td>Autosomal dominant with a possible X-linked inheritance</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td><strong>Clinical Manifestations</strong></td>
<td></td>
<td></td>
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</table>

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Comedonal lesions (Open & / or Closed) | Must be present | Absent
---|---|---
Facial ice-pick scars | May be present | Absent
Dirty warty papules / plaques | May be absent | Must be present
Palmar pits / keratoses | May be present | May be present
Nail changes | May be present | May be present
Mucosal lesions | May be present | May be present

**Associations**
- Neurological disorders: None reported
- Susceptibility to infections: None reported

**Histopathological Findings**
- Acantholytic dyskeratosis: Invariably present
- Follicular involvement: Present & prominent
- Villi & papillary projections: Markedly elongated

**Course**
- Chronicity: Chronic
- Remissions: Not reported
- Exacerbations by sun, heat & lithium: Absent

**Table 2: Key differentiating features between comedonal and classic Darier’s disease**

Like classic DD, treatment options for comedonal variant are largely unsatisfactory. Topical treatments (emollients, steroids, retinoids, calcipotriol, tacrolimus and bufexamac) and systemic therapies (etretinate, isotretinoin, acitretin, antibiotics, biotin, Korean ginseng and anti-histamines) have all showed guarded success (Table 1) [1,3-5,7,9].

In the present report, no response was associated with the use of isotretinoin for 2 months. Lee et al. [5] were the first to introduce oral isotretinoin (30 mg/day) for their patient but it was stopped after just 4 weeks due to uncomfortable chelitis and xerosis. Similarly, Yegin et al. [7] used systemic isotretinoin for their case (1 mg/kg/day) for 3 months with a poor response.

On the other hand, surgical excision of large nodulo-cystic lesions can enhance cosmetic results and patients’ satisfaction as in the presented case. However, this should be considered before initiating systemic retinoids to avoid the possibility of a complicating hypertrophic scarring.

The clinical course of comedonal DD is unpredictable1, which can be explained by the extreme rarity of the condition. In comparison to classic DD, lacking of associated neurological or infectious complications may provide patients with comedonal DD with a better quality of life. However, recently Buchanan and Strutton [13] reported non-melanoma skin cancers in one patient.

In conclusion, we reported a new patient with comedonal DD. Because of the extreme rarity of the reported cases, and the closely similar clinical features with acne vulgaris, comedonal Darier’s disease represents a real diagnostic challenge. Treatment options for comedonal variant are largely unsatisfactory, as for classic DD. We hope that the presentation of this report and future similar cases would help dermatologists to minimize missing of patients that may be responsible for paucity of reports. Finally this should provide comedonal DD patients with the proper therapeutic and prognostic information.

**References**


