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Case Report Open Access

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).

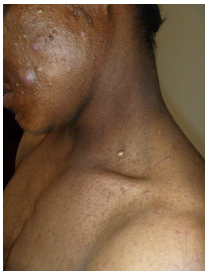

Figure 1: Comedonal Darier's disease: Classic and comedonal lesions. Diffuse dirty brown keratotic papules affecting the trunk associated with typical nodulo-cystic acne-like facial appearance.

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.

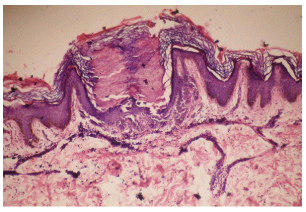

Figure 2: Comedonal Darier's disease: Histopathological findings from a papular lesion. A cup shaped epidermal invagination filled with keratotic plug and some dyskeratotic cells, suprabasal acantholysis with lacunae, prominent villi and surrounding dermal lymphocytic infiltrate (H&E, original magnification × 10).

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. Isotretinion (40 mg/day for 8 weeks) was given with unsatisfactory response, so it was terminated upon patient request.

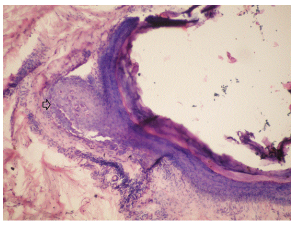

Figure 3: Comedonal Darier's disease: Histopathological findings from a nodular lesion. A markedly dilated hair follicle cyst with acantholysis and prominent dyskeratosis involving the wall of the cyst (Arrow) (H&E, original magnification × 40).

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 19953 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).

Reference	No. Of Cases	Country	Age		Sex	Family History	Sites		Associations	Treatment	Response
			Of Onset	Of Diagnosis			Comedones Open &/or Closed	Classic Darier's Disease			
Derrick et al. 1995 [3]	2	UK	61	65	M	Negitive	*Face,Scalp	Nails, Palms	Pruritus	Topical steroid, Emolients	Initial improvement then recurrence
			10s	55	M	Positve	Face,Trunk	Nails,Palms, Trunk	Scalp nodules	Etretinate 50 mg/day	Improved, except for persistent scalp nodules
Song et al. 1997 [6]	1	Korea	16	43	M	Negitive	Face, Scalp,Trunk	Trunk,Nails	None	Etretinate 30 mg/day	Improved
Lee et al. 2002 [5]	2	Korea	25	47	M	Negitive	Face,Trunk	Trunk, Face	Greasy skin, Pruritus, Facial ice-pick scars & nodules with a leonine appearance	Oral Isotretinion 30 mg/day	Stopped after 4 weeks due to side effects
			24	34	M	Negitive	Face	None	Facial nodules	Minocyclin	No response after several months
Aliagaoglu et al. 2006 [9]	1	Turkey	18	42	M	Negitive	Face,Neck, Trunk,Legs	None	Cornifying & hypertrophic variants	Acitretin 1 mg/kg/day	No response after 4 months
										Long-term antibiotics	No response
										Topical adapalene for comedonal & cornifying lesions	No response after 4 months
Yegin et al. 2007 [7]	1	Turkey	7	42	M	Negitive	Face,Scalp Trunk	Face,Scalp Trunk, Palms, Soles, Nails, Oral	Scalp syringocyst-adenoma papilliferum & scarring alopecia, Pitted scars on face, scalp, trunk, Malodor	Isotretinion 1 mg/kg/day for 3 months	Poor response
Tsuruta et al. 2010 [4]	1	Japan	10s	22	M	Negitive	Face,Trunk	None	Ice-pick scars on face	Oral: biotin, Korean ginseng, anti-histamins	No response
										Topical: bufexamac, calcipotriol, steroid	No response
										Etretinate 10 mg/day & topical adapalene	Mostly improved
Chung et al. 2011 [1]	1	Korea	Late 20s	31	F	Positve	Face	None	Greasy skin	Oral minocycline & Topical tacrolimus	Little improvement
Goel et al. 2012 [8]	1	India	66	70	M	Negitive	Face	Scalp, Palms	None	NM	NM
Buchanan & Strutton 2013 [13]	1	Australia	22	52	M	Negitive	Not defined		NMSC	NM	NM
							Face,Neck,Chest,Abdomen, Back				

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	Trunk, Scrotum, Palms, Nails	Greasy skin, Ice-pick scars, Facial nodules	Surgical removal of large nodulo-cystic facial lesions & then oral Isotretinion 40 mg/day	Improved cosmetic results after removal of the nodules. No response after 2 months

Table 1: Summary of the reported cases of comedonal Darier's disease

Note: 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.

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 histiopathologic 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.

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

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	Higher liability
Susceptibility to infections	None reported	Increased susceptibility
Histopathological Findings		
Acantholytic dyskeratosis	Invariably present	Invariably present
Follicular involvement	Present & prominent	Present
Villi & papillary projections	Markedly elongated	Elongated
Course		
Chronicity	Chronic	Chronic
Remissions	Not reported	Spontaneous remission rarely reported
Exacerbations by sun, heat & lithium	Absent	Present

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 (emolients, steroids, retinoids, calcipotriol, tacrolimus and bufexamac) and systemic therapies (etretinate, isotretinion, 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 isotretinion for 2 months. Lee et al. [5] were the first to introduce oral isotretinion (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 isotretinion 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.

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