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Spectrum of features in Darier's disease: A case report with emphasis on differential diagnosis

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ABSTRACT

Oral genodermatoses includes a spectrum of inherited dermatological disorders with varying oral mucosal manifestations. Darier's disease is an autosomal dominant disorder with defect in desmosomal attachment. This case report presents oro cutaneous manifestations of Darier's disease in a 40 year old female patient with a detailed review on etiology, pathogenesis, differential diagnosis and management of the condition.

1. Introduction

Genodermatoses refers to a group of inherited disorders with dermatological manifestations. Genodermatoses with associated oral manifestations are referred to as oral genodermatoses. It includes a spectrum of disorders that include Dystrophic Epidermolysis Bullosa, Peutz-Jegher's Syndrome, Neurofibromatosis, Multiple Endocrine Neoplasia Syndrome, Cowden Syndrome, Gardner's Syndrome, Basal Cell Nevus Syndrome, Dyskeratosis Congenita, Ehlers-Danlos Syndrome, Marfan's Syndrome, Haemorrhagic Telangiectasia etc.,. Falling in this category is Darier's disease, which is an autosomally inherited dermatological disorder named after the French dermatologist Ferdinand-Jean Darier.[1]

Darier's disease, also known as keratosis follicularis, dyskeratosis follicularis or Darier-white disease is characterized by hyperkeratotic papules or plaques in the seborrheic areas, palmoplantar pit, nail abnormalities and mucosal changes. It is included along with Hailey-Hailey disease under hereditary acantholytic dermatoses (International Classification of Diseases ICD-11 EC 20.2) (Online Mendelian Inheritance in Man OMIM: 124,200) as the condition is characterized by epidermal acantholysis and loss of epidermal integrity.[2] The condition was first described by Prince Marrow in 1886, later independently by Darier and White in 1889. Darier named the disease *psorospermose folliculaire vegetante.*[3]

This condition is caused by heterozygous mutation in the ATP2A2 gene, which encodes the sarcoplasmic reticulum Ca^{2+}-ATPase-2, on chromosome 12q24. At least 120 ATP2A2 mutations have been reported, and the majority of them are missense mutations. It has variable expressivity with complete penetrance.[4]

The onset of the condition is usually seen during childhood and adolescence before the third decade of life. About 1:100,000 of the population are affected by this condition. Although males and females have equal predilection to develop this disorder, a male predominance has also been described.[5]

Here we present a case report of a 40 year old female patient presenting with oro cutaneous manifestation of Darier's disease.

2. Case report

A 40 year old female patient presented to the outpatient Department of Oral Medicine and Radiology with the chief complaint of burning sensation in mouth for the past 15 years. The burning sensation as the patient described aggravated on eating spicy food. On eliciting medical history, the patient had been diagnosed with Darier's disease 25 years ago and was on regular medication for the same. The patient's family history and personal habit history were noncontributory. No other maternal or paternal family member were diagnosed with this condition.

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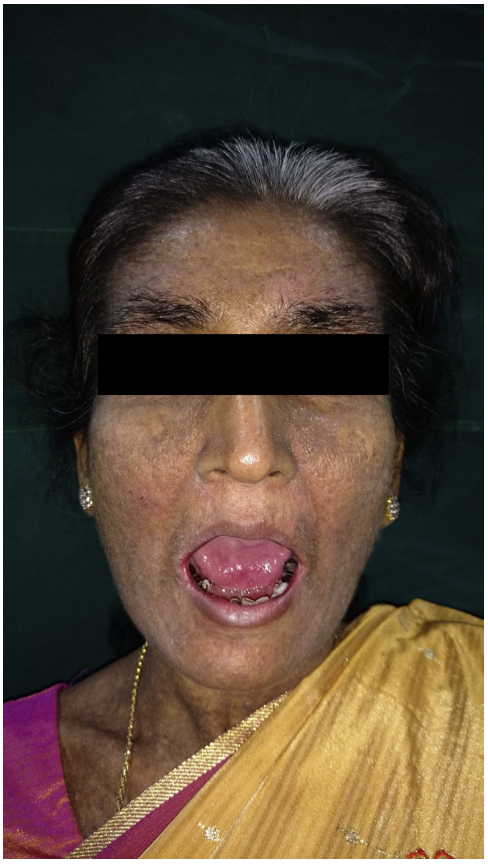

Fig. 1. Extra oral photograph showing waxy plaques with varying degree of crustation involving skin of face and scalp, and microstomia.

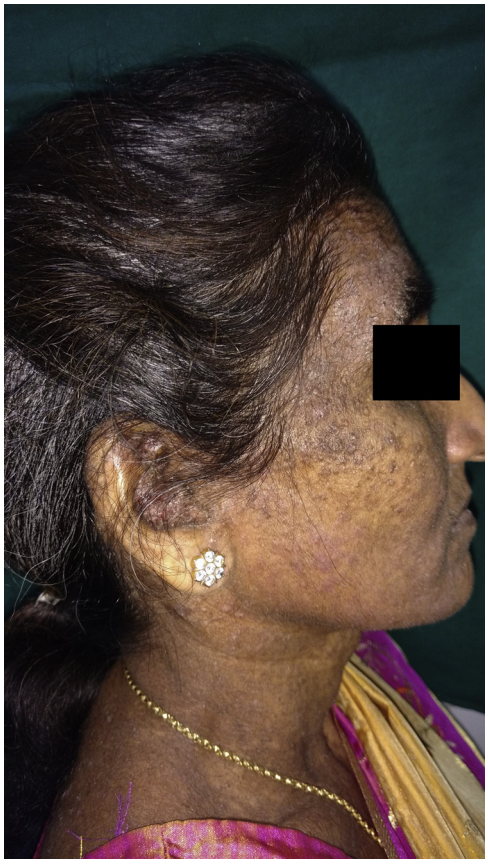

Fig. 2. Waxy plaques involving postauricular and preauricular region, pinna and external auditory meatus.

On extraoral examination widespread waxy plaques with varying degree of crustation and ulceration was noticed symmetrically involving the skin of face, scalp (Fig. 1), postauricular and preauricular region, pinna and external auditory meatus (Fig. 2), nape of the neck, dorsal and ventral aspect of right and left arm and legs (Figs. 3 and 4). These lesions as the patient described were pruritic and aggravated on exposure to sunlight and heat. The lesions were interspersed with brownish black hyperpigmented macules. There were no secondarily infected lesions or any form of discharge (purulent or blood) from these lesions. Lips were dry and exhibited desiccation. Right and left commissure of the lip showed crusting and bleeding. The palpebral conjunctiva was pale and nail beds were devoid of flushing.

On intra oral soft tissue examination blanching of the oral mucosa involving the labial, buccal, palatal and retro molar areas was noticed (Figs. 5 and 6). The surface of the tongue was smooth with significant depapillation. Manipulation of the salivary glands revealed normal salivation. No oral mucosal lesions like macule, papule, patch, plaque or ulcers were noticed. Intra oral hard tissue examination revealed multiple deep dental caries with infected root stumps and a solitary sinus opening in the buccal aspect of attached gingiva corresponding to maxillary first molar.

The burning sensation in the oral cavity was considered as a part of oral manifestation of Darier disease. A complete blood count, hemoglobin percentage and peripheral smear were obtained to exclude anemia. To exclude the possibility of underlying oral candidial infection, an exfoliative cytological smear was obtained. A panoramic radiograph was made to assess the periapical condition of the carious teeth and to strategize the treatment plan.

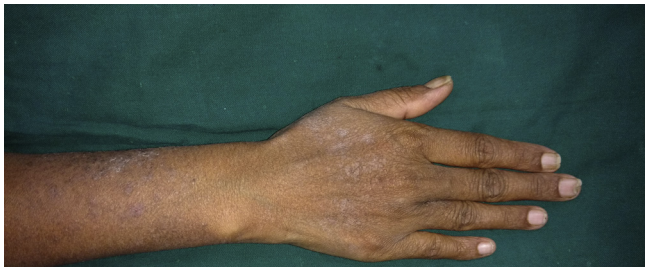

Fig. 3. Lesions involving dorsal aspect of right arm.

The hemogram was suggestive of normocytic and normochromic anemia and the exfoliative cytology was negative for candidial infection. Subsequently in consultation with the dermatologist, the patient was prescribed oral iron and folic acid supplements to correct the anemic status. Following consent from the physician, the patient underwent extraction of the infected root stumps and root canal treatment for teeth with deep dental caries.

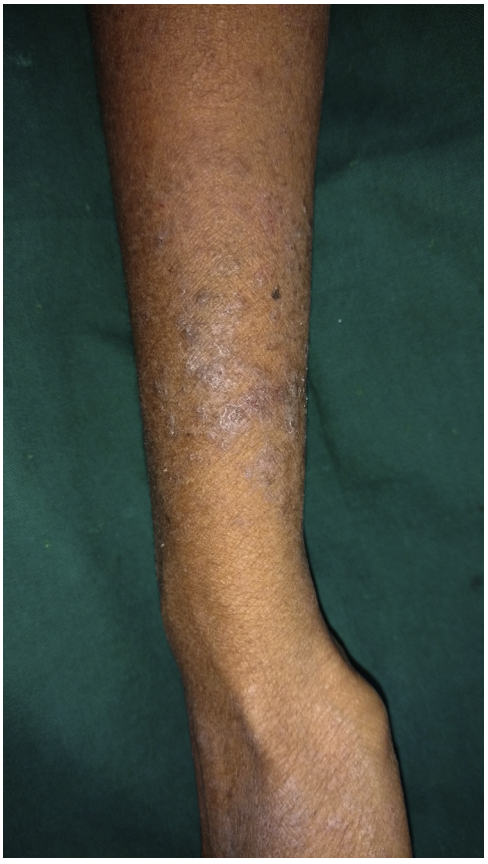

Fig. 4. Lesions involving ventral aspect of right arm.

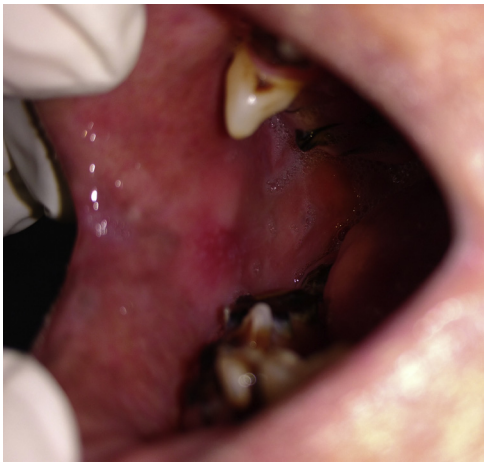

Fig. 5. Intra oral photograph of right buccal mucosa with considerable paleness.

3. Discussion

Darier's Disease is a rare genodermatoses inherited as an autosomal dominant condition. In our case, the patient reported a complete absence of a positive family history suggesting a new mutation or an

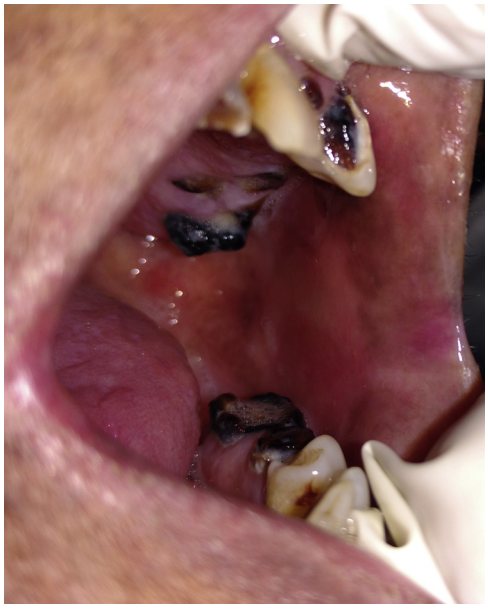

Fig. 6. Intra oral photograph of left buccal mucosa with considerable paleness.

Table 1
Classification of Darier's Disease.

Based on molecular etiology
●Acral hemorrhagic
● Segmental
Based on clinical presentation
●Cornifying
● Comedonal
● Hypertrophic
● Linear

evidence of incomplete penetrance. The mutated gene ATP2A2 involved in the pathogenesis of this condition, encodes for the sarcoplasmic/endoplasmic calcium adenosine triphosphatase (SERCA2), which is involved in regulating cytosolic Ca^{2+} concentration which in turn regulates the assembly of desmosomes. This mutation can be inherited in an autosomal dominant manner or can be a sporadic form. Two thirds of the cases reported constitute sporadic form.[6] The isoform SERCA2b is widely expressed in epidermis. Mutation in ATP2A2, thus results in deregulation of the intercellular keratinocyte attachment through impaired localization of desmoplakins to the desmosomes, resulting in acantholysis. Acantholysis, dyskeratoses, presence of "corps ronds" in malpighian layer and "grains" in stratum corneum are characteristic histopathologic features of this condition. Corps rods and grains are apoptotic keratinocytes that harbor a mutant SERCA2 that fail to upregulate the p21 ^{WAF1} gene and hence exit the cell cycle under stress. Persistent lesions seen in this case is attributed to this failure to exit cell cycle.[3,7]

Based on the clinical manifestation and location of ATP2A2 gene mutation, two types of Darier's disease have been described, acral hemorrhagic and segmental type. In acral hemorrhagic type, hemorrhagic

Table 2
Clinical Presentation of Darier's Disease.

Dermatological And Mucosal
●Greasy, hyperkeratotic brown-yellow papules
● Palmoplantar pits
● Hemorrhagic macules
● Acral keratosis
● Nail fragility
● Nicking of free edge of nail
● Susceptibility to herpes simplex, pyogenic (Staphylococcus aureus) and dermatophyte infections
● skin fragility with painful erosions
● White papules in oesophagus, vulva and rectum
● Leukodermic macules
Oral Manifestation
●Cobblestone appearance of mucosa
● White papules with central depression in hard palate
● Large nodular and verrucous plaques in gingiva, buccal mucosa and tongue
● Salivary duct calculi
● Periductal fibrosis
● Sialdenitis
● Malodor
● Burning sensation
● Papillary palatal hyperplasia
Ocular Manifestation
●Peripheral corneal opacities
● Punctate corneal epithelial defect
● Corneal subepithelial infiltration
● Corneal ulcerations
● Photophobia
● Pannus formation
● Conjunctival keratosis
● Ecchymosis and subconjunctival hemorrhage
● 0Retinal detachment
● Retinitis pigmentosa
● Basal cell carcinoma
● Cataract
● Episcleritis
Others
●Neuropsychatric abnormalities like epilepsy and mood disorders
● Urogenital abnormalities such as polycystic kidneys, gonadal hypoplasia and renal and testicular agenesis
● Gynecomastia
● Fanconi anemia
● Visceral malignancy

vesicles are seen on the palms and dorsal aspect of fingers that give rise to black macules eventually. Disruptive mutations involving ATP2A2 gene have been described in vascular endothelium apart from keratinocytes and hence has a secondary effect on blood vessels. In segmental type, acantholytic dyskeratotic nevi along the lines of Blaschko have been described indicating somatic mosaicism in ATP2A2 gene. Accordingly this subtype is also termed as segmental Darier disease with post zygotic mutation.[4]

Nails exhibit longitudinal red and white lines with increased fragility and V-shaped nicking of the free nail edge. During the life time of the individual, the severity of the condition varies with exacerbations following exposure to sunlight or ultra violet rays, but remissions do not occur. Morphological variants of Darier's disease include cornifying, hypertrophic, comedonal, and linear form. Cornifying Darier's disease typically presents as hypertrophic plaques on the lower legs and is characterized by the presence of cutaneous horns. Hypertrophic Darier's disease is predominantly seen in intertriginous areas. Comedonal Darier's disease presents as an acneiform eruption on the head and neck and with clinical and histopathological resemblance to warty dyskeratomas. Unilateral presentation associated with genetic mosaicm following post zygotic mutation is seen in linear, or localized form.[7] The cutaneous lesions are usually pruritic (Table 1).

In our case the patient had hyperkeratotic papules in dorsal aspect of arms, legs, preauricular region, auricles and in face. This presentation is similar to the presentation reported by Suryawanshi et al.[5] The age of onset and characteristic exacerbations with heat, trauma, stress and humidity in this case are typical of Darier's disease.

Oral mucosal involvement has been described in fifty-percent of the affected individuals. The oral lesions are predominantly localized to palatal and alveolar mucosa with appearance of multiple firm papules with normal, whitish, or reddish color. The papules may coalesce exhibiting crusting followed by ulceration. Whitish papules with central depression may form irregular plaques mimicking the appearance of nicotinic stomatitis. Gingiva, buccal mucosa and tongue can also be affected. Involvement of parotid salivary glands, periductal fibrosis and ductal obstruction can cause intermittent swelling.[1]

Kaposi-Juliusberg syndrome is a severe generalized cutaneous herpetic infection which is a rare complication of Darier disease. Neuropsychiatric disorders such as epilepsy, major depression, bipolar disorder, schizophrenia, and learning difficulties may accompany Darier disease. The various cutaneous, ocular, mucosal and urogenital manifestations of the disorder is summarized in Table 2.[3,5,6,8,9]

The differential diagnosis includes acne vulgaris, seborrheic dermatitis, acanthosis nigricans, confluent reticulate papillomatosis, prurigo pigmentosa and reticulate erythematomucinous syndrome. Acrokeratosis verruciformis of Hopf, a localized disorder of keratinization of distal extremities, is closely related to Darier's disease and appears to be caused by mutations in the same gene. Histologically, the disease needs differentiation from benign familial pemphigus, Grover's disease, Hailey-Hailey disease and pemphigus vulgaris (Table 3).

Topical application of corticosteroid creams, retinoids, simple emollients, and sunscreen is considered as the first line of management. Topical retinoids include topical isotretinoin (0.05%), tretinoin cream (0.05%), adapalene gel (0.1%), and tazarotene gel (0.1% short contact for 15 min). Severe and extensive lesions are treated with oral retinoids. Acitretin (10–25 mg daily and can be gradually increased), isotretinoin (0.5–1.0 mg/kg daily), and alitretinoin (30 mg daily) are effective. In our case the patient is on oral retinoid, acitretin 10 mg once daily.[10]

Protection from trauma and sunlight is crucial. Urea or lactic acid–containing emollients may reduce crusting. Secondary infections can be treated with topical disinfectants, topical or systemic antibiotics, antivirals, or antifungals. Other treatment modalities mentioned in the literature include, dermabrasion, electrosurgery, laser ablations of recalcitrant plaques, photodynamic therapy with five aminolevulinic acid and surgical excision of hypertrophic intertriginous keratosis follicularis.[5]

4. Conclusion

Secondary infection, particularly with herpes simplex virus and Kaposi's varicelliform eruption are a major concern. Regardless of the clinical severity and treatment option, the patient should receive genetic counseling with information on the inherited condition and risk of transmission to the offspring. A biopsy is fundamental in oral lesions to allow final diagnosis; based on this result; the patient should be referred to dermatological examination.

Table 3
Differentiating Features from Closely Related Genodermatosis.

Features	Darier's disease	Hailey- hailey disease	Acrokeratosis verruciformis of Hopf	Grove's disease (Transient acantholytic dermatosis)	Pemphigus vulgaris	Warty Dyskeratoma
Onset	Adolescence	Second and third decade of life	Lesions are usually present at birth may appear later in infancy as papules or at puberty as ichthyosis, or may be delayed until the fifth decade of life	Middle aged	Fifth and sixth decade of life	Middle aged
Sex predilection	Common in both	No sex prediliction	No sex prediliction	Male predilection (3:1)	No sex predilection	No sex prediliction
Etiology	Mutation in ATP2AT	Mutations IN ATP2C1	Mutation in ATP2A2	Sunlight, excessive heat, ionizing radiation, adverse reaction to drugs, radiotherapy, chemotherapy	Autoantibodies to desmoglein 1 & desmoglein 3	Actinic radiation or viral infection of dilated hair follicle
Inheritance	Autosomal dominant, sporadic	Autosomal dominant	Autosomal dominant	Acquired	Autoimmune condition	Acquired
Cutaneous lesions	Greasy hyperkeratotic papules in seborrheic areas; palmoplantar pits, and distinctive nail abnormalities	Vesicles and blisters erosive skin lesions on areas of skin subjected to friction like flexor surfaces of axilla and groin	Multiple, flat-topped papules symmetrically distributed on dorsal aspect of hands, feet, wrists and/or ankles, palmo plantar keratosis. The forehead, scalp and flexures are mot involved.	polymorphic, consisting of 1–3-mm erythematous, red-brown papules, vesicles, and eczematous plaques, photo distributed palms and soles are unaffected, Nails may be whitish and thickened, and have longitudinal ridges breaking at the distal edge	Vesicles and bullae that rupture to leave raw eroded surface, periungual blisters, hemorrhagic paronychia, chronic paronychia, trachyonychia, onycholysis or onychomadesis	hyperkeratotic, umbilicated, persistent nodule that usually presents on the sun-exposed skin of the head and neck
Oral mucosal lesions	Hard palate and alveolar mucosa commonly involved with cobblestoning	Rare mucosal lesions, crops of vesicles rapidly rupturing leaving raw eroded areas	Seldom involved	Mucosa usually spared	First clinical manifestation, ill-defined, irregularly shaped gingival, buccal or palatine erosions	keratinized mucosa of the palate, alveolar ridge, and gingiva, subungual warty dyskeratoma
Histopathology	Hyperkeratosis, acantholysis, suprabasilar cleft, crops ronds and grains, keratinization is accentuated, altered and faulty	Acantholysis, dilapidated brick wall effect, benign dyskeratotic cells similar to corps ronds	Hyperkeratosis, increase in thickness of the granular layer, acanthosis, papillomatosis, circumscribed epidermal elevations resembling church spires. The rete ridges are slightly elongated and extend to a uniform level. No parakeratosis or vacuolization. keratinization is exaggerated but normal	Association of both spongiosis & acantholysis, hyperkeratosis, parakeratosis, accompanied by corps ronds formation & grains of Darier, brick wall appearance	Intraepithelial vesicle or bullae, suprabasilar split, acantholysis, Tzanck cells, tombstone pattern of basal cells	widely dilated cup-shaped or cystic lesion containing keratinous debris and often associated with a hair follicle & containing conspicuous corps ronds and grains of Darier, marked acantholysis of adjacent deeper epithelium, suprabasal villi, lymphocytic & histiocytic infiltration of dermis

Conflict of interest

None.

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References

1. Kumar K, Shilpasree AS, Chaudhary M. Oral manifestations and molecular basis of oral genodermatoses: a review. *J Clin Diagn Res.* 2016;10(May (5)):ZE08–ZE12. [Internet] Available from:. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4948553/.
2. World Health Organisation. *ICD-11 Beta Draft – Mortality and Morbidity Statistics.* . [Internet] [cited 2017 Dec 21]. Available from:. 2017; 2017https://icd.who.int/dev11/l-m/en.
3. Engin Burhan, Kutlubay Zekayi, Erkan Emine, Tüzün Yalçın. Darier disease: a fold (intertriginous) dermatosis. *Clin Dermatol.* 2015;33(4):448–451. [Internet]. [cited 2017 Dec 21] Available from:. https://www.clinicalkey.com/#!/content/journal/1-s2.0-S0738081X15000735.
4. Sakuntabhai A, Ruiz-Perez V, Carter S, et al. Mutations in ATP2A2, encoding a Ca2+ pump, cause Darier disease. *Nat Genet.* 1999;21(March):271. http://dx.doi.org/10.1038/6784. [Internet] Available from:.
5. Suryawanshi H, Dhobley A, Sharma A, Kumar P. Darier disease: a rare genodermatosis. *J Oral Maxillofac Pathol.* 2017;21(August (2)):321. [Internet]. Available from:. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5596695/.
6. Wilder Elizabeth G, Frieder J, Sulhan Suraj, et al. Spectrum of orocutaneous disease associations. *J Am Acad Dermatol.* 2017;77(5):809–830. [Internet]. [cited 2017 Dec 21] Available from:. https://www.clinicalkey.com/#!/content/journal/1-s2.0-S0190962217302372.
7. Gehris RP, Ferris LK. *Genodermatoses. General Dermatology*. Elsevier Ltd.; 2009:277–296.
8. Kanakpur SH, Caculo DU. Rare ocular manifestations in keratosis follicularis (Darier–White disease). *Indian J Ophthalmol.* 2017;65(September (9)):874–876. [Internet]. Available from:. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5621275/.
9. Calonje Eduardo, Brenn Thomas, Lazar Alexander. *Acantholytic disorders. Mckee's Pathology of the Skin*. fourth ed. Elsevier Ltd.; 2012:151–179. [Internet]. [cited 2017 Dec 21]. Available from:. https://www.clinicalkey.com/#!/content/book/3-s2.0-B9781416056492000056?scrollTo=%23top.
10. Casey GA, Cooper SM. *Darier disease. Treatment of Skin Disease: Comprehensive Therapeutic Strategies*. fifth ed. Elsevier Ltd.; 2018:179–180. [Internet] [cited 2017 Dec 28] Available from:. https://www.clinicalkey.com/#!/content/book/3-s2.0-B9780702069123000537?scrollTo=%23hl0000106.