Case Report

Squamous Cell Carcinoma Transformation of Acrokeratosis Verruciformis of Hopf

Khan MSI

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Abstract

Acrokeratosis verruciformis of Hopf is a rare genodermatosis with an autosomal dominant mode of inheritance. It is a disorder of keratinization, characterized by multiple, skin-colored keratotic lesions resembling warts typically observed on the dorsum of the hands and feet. Histopathologically, the lesion shows considerable hyperkeratosis, acanthosis, and papillomatosis, mimicking a "church spire", and a thickened granular layer. It arises in early life, often at birth or infancy and rarely transform to squamous cell carcinoma. A rare case of acrokeratosis verruciformis of Hopf with squamous cell carcinoma transformation is reported in the department of Dermatology and Venereology, Combined Military Hospital, Dhaka. A 36 year old lady presented with multiple verrucous, hyperkeratotic, dyspigmented papules and plaques on her both legs since her early childhood and ulcer developed on the hypertrophic plaque about 20 years after the initiation of cutaneous lesions. Lesions were asymptomatic in the initial stage and subsequently developed mild pruritus and occasional bleeding from the ulcer. Histopathological finding from verrucous plaque is compatible with Acrokeratosis verruciformis of Hopf and skin biopsy from ulcerated plaque is compatible with Squamous cell carcinoma.

Key-words: Acrokeratosis verruciformis of Hopf, Squamous cell carcinoma

Introduction

Acrokeratosis verruciformis of Hopf (AVH) is a rare genodermatosis characterized by keratotic lesions on the dorsum of the hands and feet[1,2]. Lesions are usually present from birth or early childhood, but some cases in adult life are reported[3-5]. Acrokeratosis verruciformis of Hopf (AVH) was first described by Hopf[1,4,6] in 1931. The disease follows a chronic course without spontaneous remission. It has an autosomal dominant pattern of inheritance with incomplete penetrance, which may explain the difficulty of finding of similar cases in the family. Sporadic cases with later onset have also been reported[1,7]. The disease has no gender preference[1,4,5]. Its probable etiology would be a mutation in ATP2A2 gene located on chromosome 12q24. This heterozygous pro602Leu mutation (P602L) in ATP2A2 leads to amino acid substitutions within the ATP binding domain[1,6,8].

Some authors describe AVH as a variant of Darier-White's disease due to clinical similarities and inheritance pattern. However, Darier's disease features dyskeratotic cells, has a predilection for sebaceous areas, can affect the oral mucosa, and presents no signs of carcinomatous transformation[1,3-6]. Some authors studied a family affected with AVH in six generations and analyzed a P602L mutation in ATP2A2. The study showed that P602L lost its ability to transport calcium due to the loss of function of the sarcoendoplasmic reticulum Ca_2+ ATPase2, similar to Darier's disease. The similarities provide evidence that acrokeratosis verruciformis and Darier's disease are allelic disorders[6].

Acrokeratosis clinically manifests itself as flat-topped, polygonal, papules and verrucous plaques. The brownish to skin-colored lesions have hard consistency, and its friction can produce vesicles[1,4,9]. The lesions are usually located on the back of the proximal and distal interphalangeal joints of the hands and feet[1,3]. Less frequently, lesions occur on the legs, knees, arms, and elbows and rarely on other parts of body[1,3,4]. The disease does not affect sebaceous areas – frontal scalp, flexures, or oral mucosa[4]. Nail changes are frequently reported, such as thickening of the nail plate, leukonychia and longitudinal ridges and nicks in the free edges[1,3-5]. Diagnosis is defined by histopathological features that include papillomatosis (circumscribed epidermal elevations known as "church spires), acanthosis, hyperkeratosis, and hypergranulosis without parakeratosis[1,3-6]. Although the hypertrophic variant of seborrheic keratosis may present similar histological changes, clinical findings are completely different[1]. Squamous cell carcinoma transformation may occur although it is rare phenomenon[2,4].

The only effective treatment available is superficial ablation. Although not the recommended treatment due to frequent recurrences, cryotherapy, laser therapy and surgical excision are other options[3]. Conservatively, keratolytic solutions can be applied. Some reports describe the positive effects of acitretin on the lesions and on the reduction of malignant transformations[2,7].

Case Report

Nazmun Nahar, 36 year old, hailing from Mirzapur, Tangail, presented in the department of Dermatology and Venereology, Combined Military Hospital, Dhaka with multiple verrucous,

Col Md Shirajul Islam Khan, MBBS, DDV, MCPS, FCPS, Classified Specialist in Dermatology and Venereology, CMH, Dhaka.

hyperkeratotic, dyspigmented papules and plaques on her both legs since her early childhood. Patient noticed that some of these asymptomatic papules coalesce to form plaque and ulcer developed on the hypertrophic plaque about 20 years after the initiation of cutaneous lesions. Lesions were asymptomatic in the initial stage and subsequently developed mild pruritus and occasional bleeding from the ulcer. No history of any complaints in the form of burning and pain. Family history revealed that her grandmother had similar lesions. Skin biopsy was performed from verrucous plaque on 2 october 2017 and histopathological findings revealed hyperkeratosis, mild acanthosis and papillomatosis resembling church spires. The rete ridges are slightly elongated and extend to a uniform level but no malignancy was seen. The histopathological finding was compatible with Acrokeratosis verruciformis of Hopf. Skin biopsy was performed from ulcerated plaque on 9 November 2017 and histopathological findings revealed a well differentiated squamous cell carcinoma infiltrating into the stroma. Surface is ulcerated. The depth of tumour invasion is less than 5 mm,

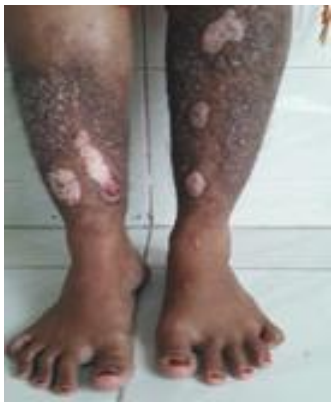

Fig-1: Diffuse dyspigmented, hyperkeratotic papules, plaques and ulcerative lesions on both extensor legs.

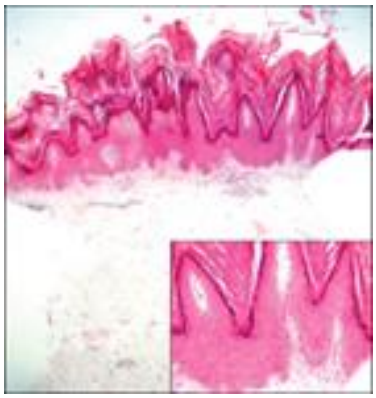

Fig-2: Histopathological finding-Hyperkeratosis and hypergranulosis with a "church spire" (H&E, ×40). Magnified view of pure hyperkeratosis, acanthosis and papillomatosis without parakeratosis, dyskeratosis, and vacuolization (H&E, ×100).

Discussion

Cordeiro de Andrade reported a 58-year-old white male patient presented with multiple warts on the hands and feet. Lesions started at the age of eight years with progressive growth. Personal history revealed unspecified arrhythmia, but patient did not use any medication. Family history revealed that the father of the patient had similar lesions. Dermatological examination showed multiple brownish flat-topped warty plaques on the hands and feet with dystrophic nails. Biopsy of the lesions revealed irregular epithelial hyperplasia, hyperkeratosis and papillomatosis, histologically compatible with acrokeratosis verruciformis of Hopf. Their therapeutic attempt with topical 3% salicylic acid showed no clinical improvement. Then they prescribed acitretin 25mg every other day with satisfactory results[10]. Rallis et al reported a 19-year-old man with the presence of skin-colored, warty hyperkeratotic lesions that were located mainly on the dorsum of the hands and feet. Clinical examination also revealed similar, discrete lesions on the elbows, knees, and forearms. Dermatophytosis of the feet was also present. According to patient, the lesions were present at birth and increased in number since then. Nine more members of his family, including his father and his uncle (father's brother), had similar skin lesions and some of them also reported varying degrees of nail involvement. His father, among other findings, had Darier-like, thickened nails with V-shaped nicks at their free margins. Leuconychia and longitudinal grooves were also seen in some nails. All his family is currently under investigation. Skin biopsy was performed and histological examination showed mild acanthosis with slight papillomatosis. There was also hyperkeratosis, most marked at the edges of the lesion, with moderate hypergranulosis and a thin layer of orthokeratosis. The dermis was infiltrated with a few inflammatory cells surrounding the vessels. Both clinical and laboratory findings were compatible of acrokeratosis verruciformis of Hopf[11].

Bang et al presented a 44-year-old Caucasian man with multiple asymptomatic papules on both shins and dorsa of feet, which had been present for more than one year. Physical examination revealed numerous whitish papules measuring 0.2~0.3 cm, which appeared to be stuck on the skin, not easily removed by scratching with finger nails. The wart-like lesions were first detected on the dorsa of the feet and showed a gradual increase in number and size. Similar lesions spread to the anterior aspect of the legs, while the dorsa of hands were spared. Their reported patient denied any personal or familial history of skin diseases, like multiple warts, Darier's disease, or AKV. Biopsy specimens showed marked hyperkeratosis, acanthosis, and papillomatosis, with an increased granular layer. The epidermis looked like a "church spire", which is a typical finding of AKV. There were

no signs of parakeratosis, acantholysis, dyskeratosis, or vacuolization of epidermis. Based on the clinical and histological findings, they diagnosed their case as a non- familial AKV. In terms of the clinical features and histopathological findings, they noticed no difference between familial AKV and non-familial cases. Clinically, both show asymptomatic flesh-colored to reddish brown flat papules resembling flat warts on the dorsa of the feet[12]. Niedelman and McKusick described 24 cases of AKV in 4 generations of a family, and suggested that AKV is inherited in an autosomal fashion[13]. Herndon and Wilson suggested that AKV results from a single dominant genetic defect with variable expressivity[14]. According to Dhitavat et al. AKV is an allelic disorder arising from a missense mutation in ATP2A26. However, a few sporadic cases have also been reported[15].

The onset age of classical AKV is different from that of sporadic AKV. Classical AKV often occurs during childhood[6,15] where Panja[16] reported the average onset age of AKV as 11-years-old. However, the onset age of sporadic AKV is much later than that of classical AKV. Four of the seven cases, developed disease in patients over 40-years of age, and the average onset age of the seven cases was 32-years-old[14,16] in sporadic AKV. However, there is insufficient data for determination of differences of prognosis and recurrence rate between classical AKV and sporadic AKV. Some authors have reported on ATP2A2 gene mutations in AKV[6,17]. Dhitavat et al reported a novel P602L mutation within the ATP-binding domain of ATP2A2 in classical AKV[6]. On the other hand, Berk et al reported a A698V codon change in ATP2A2 in sporadic AKV. In addition, A698V codon change has never been described in patients with either classical AKV or Darier's disease[17]. These results suggest that the mechanism and gene mutation in sporadic AKV may differ from that of classical AKV. In the future, more cases should be studied and genetic studies of sporadic AKV should be conducted.

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