CASE REPORTS

AN ELDERLY LADY WITH MULTIPLE BLISTERS ALL OVER THE BODY: HAILEY HAILEY DISEASE

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Abstract:

Hailey-Hailey disease (HHD) is an autosomal-dominant genoderma-tosis, associated with abnormal epithelial cell adhesion due to altered calcium metabolism. Clinical features involve painful red blisters, erosions, fissured and hypertrophic plaques predominantly in the intertriginous areas. Heat, friction, minor trauma, superimposed bacterial or viral infection can aggravate the condition. Here, we report a case of a 50-year old lady with no previous family history presented with severe attack of HHD since last 5 months. Histology showed acantholysis of keratinocytes resembling characteristic dilapidated brick wall appearance in the epidermis layer of skin which helped for the confirmed diagnosis.

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Introduction:

Hailey–Hailey disease (HHD) is a rare autosomal dominant skin disorder which is also known as familial benign chronic pemphigus. Clinically it is characterized by painful rash and blistering in skin folds, such as the armpits, groin, neck, under the breasts, and between the buttocks. Specially, abnormal epithelial cell adhesion occurs which involves the epidermis and occasionally the mucous membranes.[1,2,3,4]Secondary infection by bacteria and fungi often is associated with the lesion and produce pain and unpleasant odor. In majority cases clinical symptoms first appears after puberty, with highest rate of onset in the second to fourth decades of life.[1]Several precipitating factors such as friction, heat, sweat, inflammation, or infection commonly play vital role for initiating or aggravating the clinical symptoms of HHD.In addition to discomfort, pain, and limitation of physical activities,the disorder generally follows a chronic recurrent course. Histology of HHD showed loss of cohesion between suprabasal keratinocytes (acantholysis) leading to intraepidermal lacunae, splits, and blisters and dyskeratosis (abnormal keratinization of keratinocytes) of the epidermis.[5]Diagnosis of HHD is challenging asetiology, clinical features and histological findings show similarity to another dominantly inherited dermatosis, Darier's disease (DD), otherwise named as keratosis follicularis.[6]To diagnose HHD, thorough examination of clinical morphology, distribution of lesions, positive family history, and histological demonstration of a characteristic dilapidated brick wall appearance of the epidermis are recommended. Here,we report an elderly patient who presented with a 5-month history of multiple blisters spreading all over the body at 50 years of age. To the best of our knowledge, there are very few such cases reported earlier. The unusual presentation of HHD which caused significant diagnostic dilemma and challenge to the clinician is the prime focus of discussion in this case report.

Case Report:

A 50 years old lady with no previous co morbid condition admitted into Dhaka Medical College Hospital with the complaints of multiple blisters all over the

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body with some excoriations for last 5 months. According to the statement of the patient's attendant, patient initially noticed some blisters over the dorso-lateral aspects of tongue, lip and some portion of the oral-cavity 5 months back. The lesions were fragile, flaccid and easily ruptured leaving a denuded area (as shown in Fig: 1).They were painful but non-itchy, malodorous. Some excoriations were also present for which she consulted with a physician and received some oral drugs and ointments, though the name of those drugs were not documented. However, patient's symptoms were not improved rather her condition was deteriorating as the lesion involved the oral cavity and started to involve the trunk(as shown in Fig: 1). There was no positive family history of similar disease in any of the family members. Furthermore, she did not mention previous history of similar attack. Patient did not have any respiratory or urinary symptoms. In addition, her bowel and bladder habit were normal and she did not have any complaints of headache, vomiting, and abdominal pain.

Upon arrival, she was well-alert, co-operative, non anemic, non tachypnoeic, and was febrile with a temperature of 99°F. She had no koilonychia, leukonychia, clubbing, dehydration and edema. Her thyroid gland was not enlarged, lymph-nodes were not palpable, JVP was not raised. Besides, her pulse and blood pressure were within normal limit. The findings of local examination of skin reveal multiple blisters all over the body which weretender on touch, fragile, flaccid, easily ruptured, leaving a denuded area. Moreover, there were areas of excoriations and Nikolsky sign was positive. Onycholysis was present on the nail of ring finger of right hand with longitudinal white lines on the other nails of similar hand.Mucous membrane of oral cavity was also affected. Although no blister was seen in the nasal cavity, ear, urethral and anal orifice, some blisterswerefoundon the faces and over the scalp. Her other systemic examinations were unremarkable. Our initial differential diagnoses were Bullous Pemphigoid or Toxic Epidermal Necrolysis (TEN).

Her initial laboratory investigations were taken and revealed hemoglobin of 11.2gm/dl, white blood cell and platelet count were 26X 10^3/cumm and 565000/ cumm respectively. Differential count showed Neutrophil 55%,Lymphocyte 30%, and Eosinophil 10%. She had normal hepatic and renal function as her alanine aminotransferase, aspertate amino transferase, and creatinine were 18U/L, 22 U/L, and 0.5 mg/dL respectively. Her anti nuclear antibody was negative and serum albumin level was 32g/dl. Her serum electrolyte showed mild hyponatraemia with

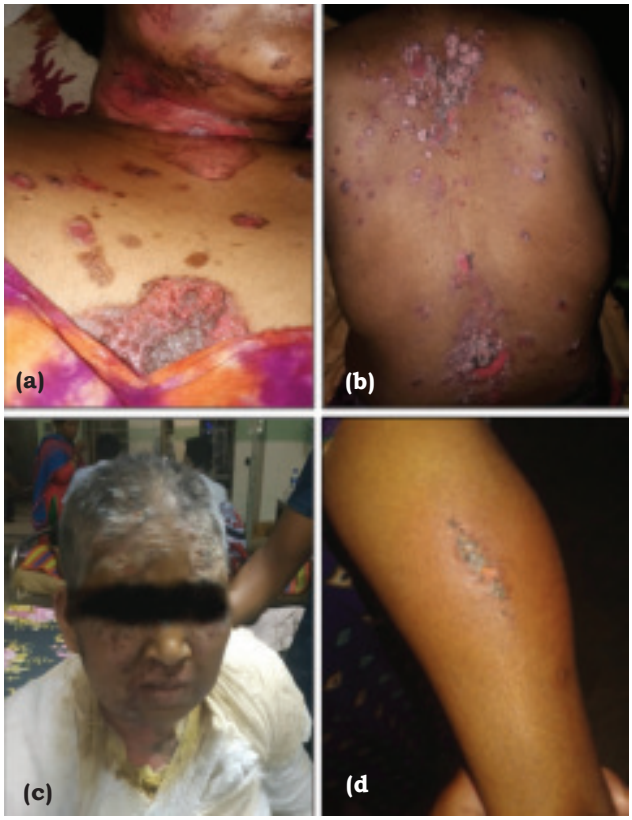

Fig.-1: *Multiple blisters spreading all over the body.*

Multiple painful red lesions on a) neck and upper part of the chest b) back, c) face and salp, and d) leg

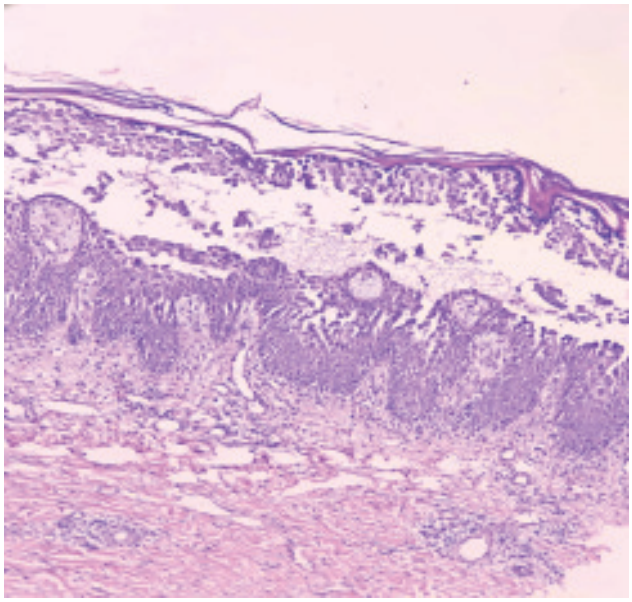

Fig.-2: *Histopathological features of skin lesin.* Suprabasilar and intraepidermal clefing and acantholysis of keratinocytes resembling dilapidated brick wall in the epidermis and mild chronic inflammatory infiltrate n dermis.

sodium 134 mmol/L, however, potassium was normal with a level of 3.5 mmol/L. Routine microscopic examination of urine showedRBC: 2-4/HPF,Pus Cell: 4-6/HPF,Albumin: (+), Sugar: Nil, and Calcium Oxalate: (+++).

To confirm the diagnosis, histopathological examination of the skin lesion was done and the microscopic features included suprabasilar & intraepidermal clefting & acantholysis of keratinocytes resembling dilapidated brick wall in the epidermis layer of skin (as shown in Fig:2) which is the characteristics feature of HHD. There was no pronounced dyskeratosis seen. However, the dermis showed mild chronic inflammatory infiltrate. As the patient had a severe outbreak of the disease involving a wide area of the body, in addition to broad spectrum antibiotic, she was treated with combination of oral and topical steroid, and regular dressing with antiseptic cleansing product. Unfortunately, her condition deteriorated and she passed away.

Discussion:

HHD occurs in 1 to 4 per 100,000 individuals. There is no preference for any sex or ethnic group was reported.[6] HHD was initially identified and described by theHailey brothers in 1939.[2]Similar to another autosomal dominant genodermatosis Darier disease (DD), HHD is caused by abnormal epidermal calcium homeostasis. Though these diseases follow hereditary inheritance, the genetic mutations are also responsible for the symptoms, as some cases were identified without any medical history. However, they are mapped to different sites in the chromosome.Using a random marker search Ikeda et allocalized the HHD gene to a 14cM interval on chromosome 3 q21-q24.[7]The linkage of HHD to chromosome 3q21-q24 was confirmed by another group who searched in six multi generational families.[8]They found location for HHD gene is consistent in all families reported to date, which supports genetic homogeneity.Genetic analysis revealed that Darier's disease is caused by mutations in the ATPase sarcoplasmic/endoplasmic reticulum Ca2+ transporting 2(ATP2A2)gene, located on chromosome12 q23-24.On the other hand, HHD is caused by heterozygousmutations in the ATPase secretory pathway Ca^{2+} transporting 1 gene (ATP2C1) gene, located on chromosome 3q21–24.[9,10]This gene encodes the secretory pathway Ca2þ/Mn2þ ATP-ase protein (hSPCA1) of the Golgi-apparatus.[11] The function of the hSPCA1 protein is to maintain calcium storage inside the cells. Calcium has significant roles for instance, regulating cell growth, division, and cellular adhesion. This protein is specifically crucial for the normal function of cells located in the outer layer of the skin known as epidermis. This particular cell type is called keratinocytes. If mutations occur in the *ATP2C1* gene, the amount of functional hSPCA1 protein decreases which hampers normal calcium storage ability.[12,13]Abnormal calcium storage affects keratinocytes more than any other cells causing impaired cellular adhesion.[14]Alterations in Ca2þ-dependent intracellular signaling happen.Therefore, keratinocytes do not stick tightly to one another resulting fragile epidermis which is less resistant to minor trauma. As a result, skin becomes damaged easily and blistered areas affect the skin, particularly in the areas where moisture and friction present like skin folds.

HHD is a distinct entity of skin disorder which is often confused with pemphigus.Pemphigus is an autoimmune disorder, in which the body produces auto-antibodies and attacks its own cells. Whereas, HHD is not an autoimmune disorder as it is devoid of any auto-antibodies. To differentiate HHD from pemphigus, direct immunofluorescence studies are performed, which would be negative in HHD.[15]

As there is no cure for Hailey-Hailey disease, prime objectives of physicians treating HHD are reducing symptoms and preventing flares. Topical medication such as vitamin D3 analogs, antibiotics, and corticosteroids are advised for mild cases.A number of systemic treatments such as doxycycline, methotrexate, cyclosporine, acitretin, thalidomide, alefacept, alitretinoin, afamelanotide, terbinafine, and naltrexone are reported effective in many patients producing long remissions.[16,17,18] In case of severe diseases or those which are recalcitrant to conventional therapy, invasive treatments have also been attempted, such as laser ablation, photodynamic therapy, electron beam radiotherapy, botulinum toxin injection, surgical excision, and grafting of the lesions have been reported beneficial for patients.[19,20,21,22]Some patients are advised to keep away fromtriggers like certain foods, stress, excessive heat, prolonged sweating and constant friction to avoid an outbreak.

Conclusion:

Hailey-Hailey disease is a rare but challenging disease for both patients and physicians as it causes significant disabilities for the patients and often become resistant or refractory. Combination of multiple treatment modalities may be required to achieve optimal benefit.Unfortunately, previous reports on literatures show that no one regimen works for all patients. Individualized treatment approaches are essential which makes it difficult for clinicians.Further researches are required for clear understanding of the molecular pathogenesis and to provide recommendations of efficient therapies for successful treatment of HHD.

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