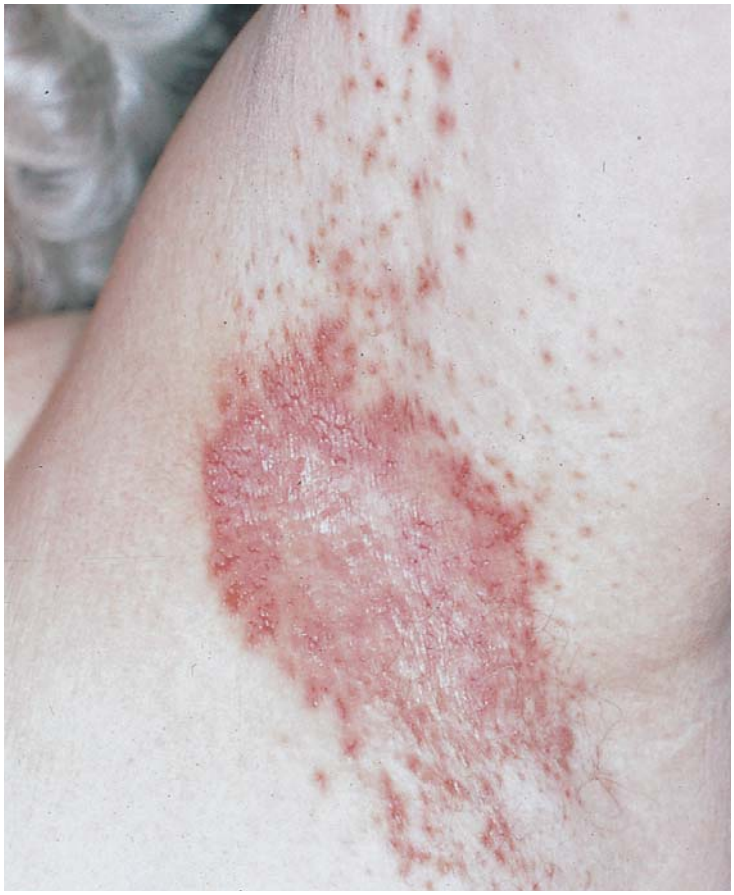
What Is Your Diagnosis?



A 67-year-old woman presented with a severely pruritic rash over the left axilla.

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The Diagnosis: Benign Familial Chronic Pemphigus

The rash on the left axilla of a 67-year-old woman is consistent with benign familial chronic pemphigus, also known as Hailey-Hailey disease (Figure 1). The patient presented with pruritic erythematous plaques with multiple vesicles and crusted erosions over the posterior neck, left flank, right arm, and axillae bilaterally. The lesions were minimally responsive to topical corticosteroid treatment and recurred intermittently. The patient had atopic dermatitis and contact dermatitis in childhood that was responsive to topical corticosteroid treatment. The patient's mother and aunt had similar rashes that recurred intermittently since early adulthood also.

The results of a biopsy showed suprabasilar epidermal acantholysis, confirming the diagnosis of benign familial chronic pemphigus (Figure 2). As the disease progressed, the patient was treated with trials of various topical and oral corticosteroids, antifungals, antibiotics, and antihistamines without significant relief. Isotretinoin was the only successful treatment for minimizing lesions and preventing flares in this patient.

Benign familial chronic pemphigus is a rare autosomal-dominant disorder first described in 1939 by Hailey and Hailey.[1] The presentation varies, but the disorder is typically characterized by intraepidermal vesicles or bullae on an erythematous base.[2] These lesions rupture easily and progress to form crusted erosions and scaling plaques (Figure 3). The flexion creases, intertriginous areas, and posterior neck primarily are affected, while mucosal surfaces typically are uninvolved. In addition, 70% of patients present with asymptomatic longitudinal white bands of the fingernails. The vesicles and plaques are pruritic and painful, particularly if they develop in the groin and perineal regions. Lesions often develop following minimal trauma to skin caused by wearing clothing such as bras or high-collared shirts. Other exacerbating factors include excessive heat or cold, sweating, UV radiation, toxic compounds, allergens, and infection.[2]

The lesions of benign familial chronic pemphigus can occur in childhood but typically manifest in the third or fourth decades of life.[3] However, a delay in diagnosis frequently occurs because of prior response to topical corticosteroids. Men and women are equally affected, and there is a family history of a similar condition in 70% of patients. The disease is rarely life threatening and follows a waxing and waning course with exacerbations occurring seasonally, particularly in the summer. Adverse reactions from medications include griseofulvin-induced drug eruptions and superimposed infections such as cellulitis; herpes simplex virus; and candidiasis, which can cause severe generalized disease.[3] Depression is a risk in these patients, especially in cases with frequent recurrence and severe presentation.

A skin biopsy is required to diagnose benign familial chronic pemphigus.[4,5] Biopsy results characteristically reveal suprabasilar epidermal acantholysis with a dilapidated brick-wall appearance. The specific mechanism of acantholysis is unknown, but

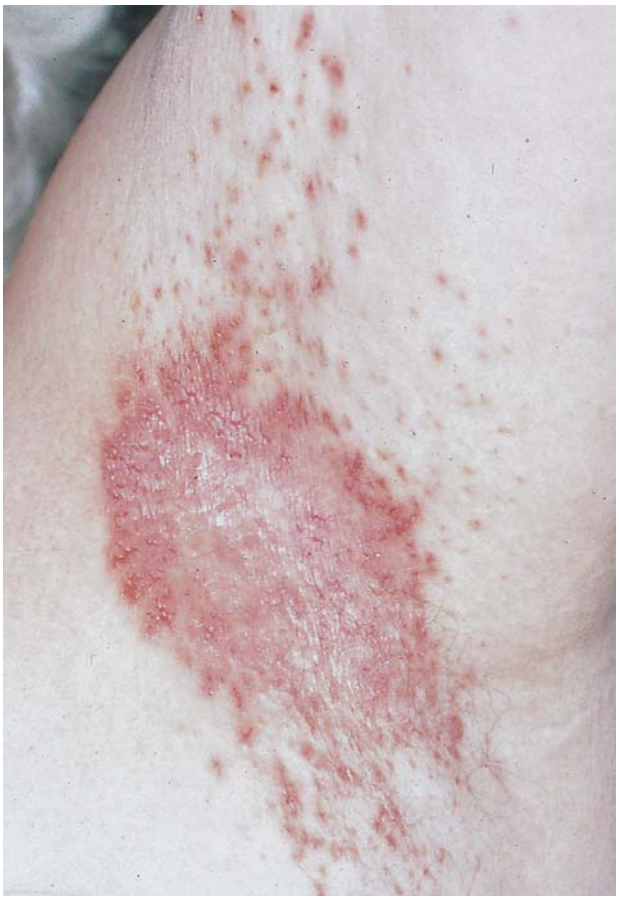

Figure 1. Left axilla with erythematous plaques with multiple vesicles and crusted erosions.

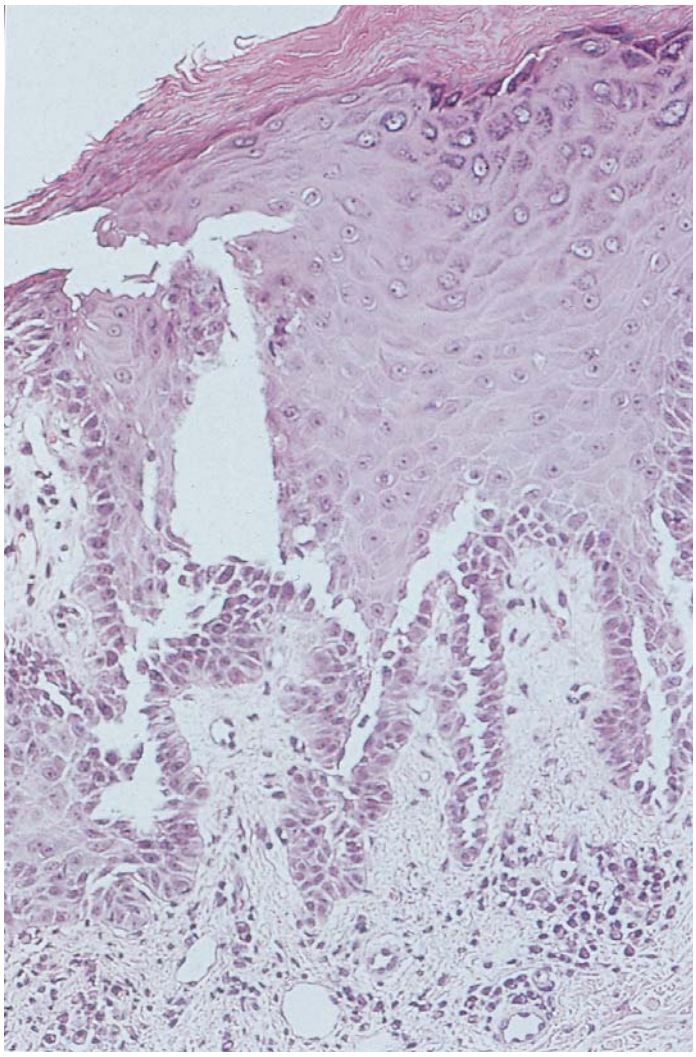

Figure 2. Biopsy of suprabasal blister with acantholysis (H&E, original magnification ×100).

the literature suggests it is due to dysfunction in an adenosine triphosphate–powered calcium (Ca^{2+}) pump found in keratinocytes. Abnormal intracellular Ca^{2+} concentrations develop leading to abnormal functioning of the cadherins, transmembranous polypeptides that link cells together through calcium-ion dependant homophilic binding. The gene responsible for this abnormal Ca^{2+} pump is *ATP2C1*, located on the long arm of chromosome 3, bands 21-24.[4,5]

The diagnosis of benign familial chronic pemphigus frequently is delayed because it resembles other disorders.[6] In particular, Darier disease has a similar histologic and clinical presentation, to the extent that benign familial chronic pemphigus was once thought of as a vesicular variant of Darier disease. However, genotyping and linkage analysis revealed that these disorders are separate entities.[7] The underlying cause of Darier disease is the abnormal gene *ATP2A2*, which encodes the sarco-endoplasmic reticulum Ca^{2+} pump (SERCA2). The gene has been localized to 12q23–12q24.1. Histologically, Darier disease has less acantholysis and more prominent dyskeratosis than benign familial chronic pemphigus. Clinically, it presents in the first decade of life with wart-crusted papules or plaques in seborrheic areas and symptomatic fingernail lesions such as notching of the free end, fragility, painful splitting, and red lines.[8] Chronic candidiasis

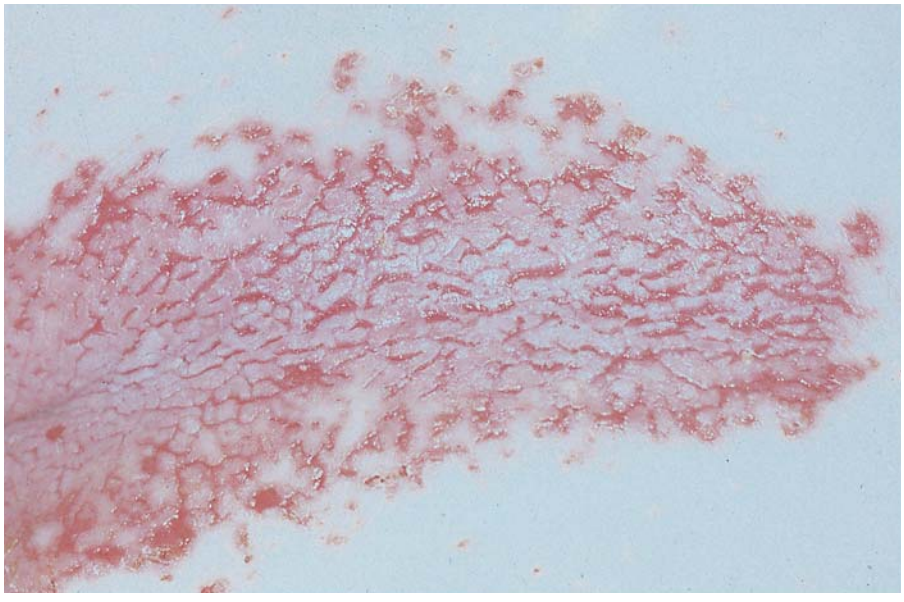

Figure 3. Confluent vesicles on erythematous base with crusted erosions.

and herpes simplex virus can be misdiagnosed and should be differentiated through culture and/or biopsy. Allergic contact dermatitis must be considered and can be evaluated through patch testing. Immunofluorescence can be used to differentiate benign familial chronic pemphigus from pemphigus vulgaris and vegetans, which are both immunofluorescence positive. Grover disease is also on the differential diagnosis. Benign familial chronic pemphigus is distributed more on the trunk and extremities and differs histologically from Grover disease by having less prominent acantholysis and greater dyskeratosis. In cases involving the posterior scalp, severe seborrheic dermatitis also has been found to mimic benign familial chronic pemphigus.

First-line treatment of Hailey-Hailey disease consists of moderate to high potency topical corticosteroids and antibiotics, with the addition of oral corticosteroids and/or oral antibiotics for exacerbations.[9] Corticosteroids and antibiotics decrease inflammation and suppress protease activation. In cases resistant to first-line therapy, medications such as methotrexate, isotretinoin, acitretin, etretinate, cyclosporine, and thalidomide can be considered. In addition, psoralen and UVA, tacrolimus ointment, and active vitamin D ointment (tacalcitol) have been found to be useful in resistant cases.[9] Surgical measures can be considered alone or in conjunction with medical therapy, particularly in recalcitrant cases. Specific procedures shown to be effective include cryosurgery, skin excision, skin grafting, dermabrasion, short-pulsed and short–dwell time carbon dioxide lasers, and YAG laser ablation.[10-12] Antifungals, antivirals, and additional or higher dosed antibiotics should be used to treat superinfection. Patients are instructed to control their weight through diet therapy in an effort to decrease intertriginous folds. Aluminum chloride solution can be effective in controlling excessive perspiration, and hydroxyzine can be an effective medication for controlling pruritis.

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