Generalized Hailey-Hailey disease associated with c.2395C>T mutation in the *ATP2C1* gene, and fatal outcome

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Abstract

Hailey-Hailey disease (HHD) is a rare, autosomal dominant genodermatosis caused by a mutation of the *ATP2C1* gene and presenting as an erosive dermatosis, particularly in the intertriginous areas. Generalized HHD is a rare variant. We present a case of widespread, recalcitrant HHD in a middle-aged woman with a fatal outcome. No other underlying dermatosis was identified, with the possible exception of drug sensitivity to carbamazepine. Diagnosis of HHD was confirmed by histology and genetic studies which showed a c.2395C>T mutation in the *ATP2C1* gene. Concurrent pemphigus was excluded. Cases of generalized HHD are extremely rare and present a challenge in diagnosis and management. Increased awareness of this severe clinical variant is needed to improve quality of care for patients with this form of HHD.

Keywords: acantholysis, genodermatosis, Hailey-Hailey, pemphigus

Introduction

Hailey-Hailey disease (HHD) is a rare, autosomal dominant genodermatosis affecting an estimated 1/50,000 persons worldwide [1]. It is caused by an mutation of the *ATP2C1* gene, which results in impaired keratinocyte adhesion and intraepidermal acantholysis caused by dysfunction of the calcium secretory pathway of the Golgi apparatus [2]. The disease typically presents in the second to fourth decade of life with a chronic and recalcitrant blistering, erosive dermatosis particularly in the intertriginous areas [1,2]. Generalized HHD is a rare variant possibly related to exacerbation of intertriginous disease from secondary bacterial infection or sensitivity to nonsteroidal anti-inflammatory drugs [3,4]. We present a case of generalized HHD in a 55-year-old woman affecting the torso, extremities, and scalp with genetic studies confirming a c.2395C>T mutation in the *ATP2C1* gene and ultimately a fatal outcome.

Case Synopsis

A 55-year-old woman with a history of trigeminal neuralgia on carbamazepine presented with a 3-month history of rash on her back, scalp, face, and neck consisting of discrete, red, scaly, crusted papules and plaques. She had no family history of skin disease and no allergies to medications. With the clinical diagnosis of psoriasis, topical therapy was prescribed; however, when the condition progressed to a body surface area of 9% risankizumab was started.

Her subsequent clinic course was characterized by some remissions and exacerbations, with no clear response to the following systemic treatments: risankizumab, ixekizumab, guselkumab, secukinumab, and adalimumab. Topical treatments including fluticasone, calcipotriene and betamethasone, Burow solution, hypochlorous acid, triamcinolone, and over-the-counter topicals, all of which provided minimal relief. At one point her body surface area reached 17%. Viral cultures were negative, but bacterial cultures showed heavy growth of *Staphylococcus aureus* and group G beta

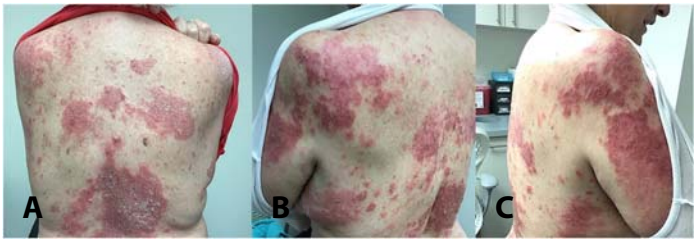

Figure 1. *Red, crusted, and oozing plaques scattered widely on the **A)** back, **B)** posterior shoulders, and **C)** arms.*

hemolytic *Streptococcus*. A course of minocycline 100 mg twice daily was followed by clinical improvement.

A flare was noted 16 months later when she developed new lesions on the bilateral elbows with diffuse redness and scaling throughout the scalp. She had also developed red, crusted, oozing plaques across the back, posterior shoulders, and arms (**Figure 1**). Histopathology from two sites demonstrated prominent acantholysis of the epidermis with a "dilapidated brick wall" appearance and little dyskeratosis (**Figure 2**), consistent with Hailey-Hailey disease. The possibility of superficial pemphigus was considered but was ruled out by negative direct and indirect immunofluorescence studies and by the absence of antibodies to desmoglein-1 and -3.

Owing to the patient's prolonged course of carbamazepine, a drug eruption was also considered and the patient was started on a 40mg taper of prednisone and clobetasol. The patient was instructed to discontinue her medications, which at this time included trimethoprim-sulfamethoxazole, adalimumab, and carbamazepine; however, she refused to discontinue carbamazepine because of the severity of her trigeminal neuralgia. Oral glucocorticoids provided no improvement and were tapered off. Genetic testing showed a c.2395C>T mutation in the *ATP2C1* gene, consistent with HHD.

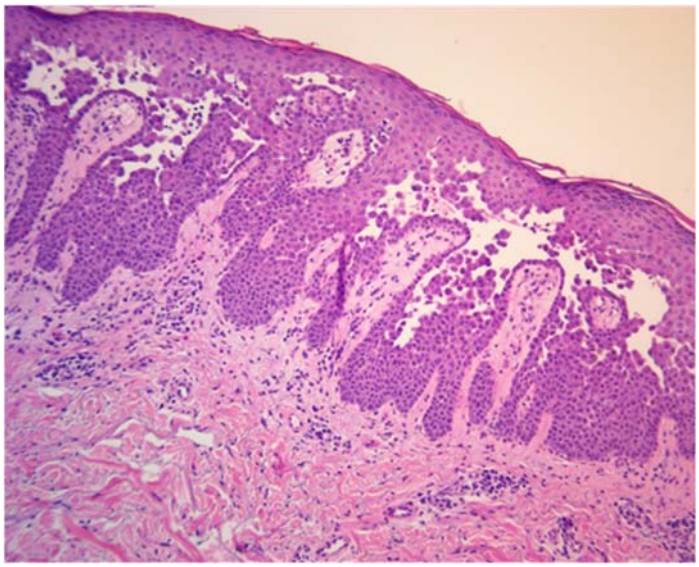

Figure 2. *H&E histopathology from the left mid back displaying prominent acantholysis of the epidermis with a "dilapidated brick wall" appearance, 200×.*

Given a recent report of the possibility that aminoglycosides might induce read-through of nonsense mutations in the treatment of HHD [5], a paired comparison trial of gentamycin ointment, administered by the patient's husband, to one side of her back with petrolatum to the other as a control was performed. After several weeks of this treatment there was no discernable difference between the two sides in terms of disease severity.

The patient was started on glycopyrrolate. After three months, she experienced near complete resolution of disease on 1mg glycopyrrolate four times daily.

Eleven months later, the patient presented to the emergency room due to an HHD flare from chest to knees accompanied by severe skin pain. Dermatology was consulted and the patient was empirically started on doxycycline, cefepime and acyclovir with oral prednisone 60mg daily and topical triamcinolone pending bacterial, viral, and fungal blood and wound cultures. The patient was started on opioid pain management. Wound cultures yielded *Staphylococcus aureus*, *Streptococcus dysgalactiae*, *Morganella morganii*, and HSV1. Blood cultures grew methicillin sensitive Staph aureus. On day 2 of admission, a medical response team was called for altered mental status and slurred speech. Physical exam was inconsistent with stroke or opioid overdose, but concern remained for cefepime neurotoxicity, polypharmacy, or medication adverse effect. All medications were held and piperacillin/tazobactam was started. Acute toxic metabolic encephalopathy was diagnosed with suspected etiology being opioid treatment in setting of patient's treatment with carbamazepine for trigeminal neuralgia. CT head scan showed no abnormality. Infectious disease was consulted, and

doxycycline was discontinued. Owing to lack of improvement in skin findings, oral prednisone was transitioned to IV methylprednisolone at 1mg/kg. Repeat skin biopsy was suggested, but the patient declined. Lumbar puncture was deferred due to concern for inoculation. On day 4 of admission, the patient initiated acitretin 25mg orally and two days later repeat skin biopsy was performed which demonstrated nonspecific skin erosions. Serial blood cultures now resulted negative. On day 8, antibiotics were transitioned to cefazolin, and IV methylprednisolone was tapered down. A transesophageal echo was negative for cardiac vegetations. Throughout the hospital course, the patient experienced re-epithelialization of some skin lesions and improvement in pain. She was discharged on cefazolin via peripherally inserted central catheter, acyclovir, acitretin, and prednisone to a skilled nursing facility (SNF) after 15 days of admission. Carbamazepine was continued at lower dose and glycopyrrolate was maintained.

One month later, the patient was brought to the emergency department from SNF due to repeat HHD flare and extreme skin pain. Vancomycin, piperacillin/tazobactam and acyclovir were started. Workup was significant for metabolic acidosis without leukocytosis or lactic acidosis. The patient was also restarted on IV methylprednisolone 1mg/kg. Blood cultures grew gram positive rods, and wound cultures grew *Acinetobacter calcoaceticus* and *Enterococcus faecalis*. On day 5 of admission, the patient became hypothermic to 94.8 F with waxing and waning confusion and was transferred to the intensive care unit on day 6. A paraneoplastic process was suspected; however, computed tomography of the chest, abdomen, and pelvis was negative for malignancy. Blood cultures yielded *Enterococcus faecium*, therefore piperacillin/tazobactam was switched to ceftriaxone. By day 7, the patient developed palpable purpura and hemorrhagic bullae, raising the possibility of diffuse intravascular coagulation or heparin-induced thrombocytopenia. A skin biopsy of the purpura was performed demonstrating heavy erythrocyte extravasation but no evidence of vasculitis or vasculopathy.

The patient's hemoglobin continued to drop requiring transfusion. A gastrointestinal consultant felt that endoscopy was not indicated. The patient had increasing vasopressor requirements and was intubated for impending airway compromise. On March 14, 2024, the patient was extubated and died.

Case Discussion

This case of HHD is particularly unusual given its presentation and severity, resulting in a fatal outcome. Cases of generalized HHD are rare and are largely reported from outside the United States, with most cases describing a history of intertriginous HHD with evolution to disseminated disease. [6–8]. The patient described in this study did not have a history of intertriginous HHD; the presenting HHD lesion occurred on the lower back, and the initial presentation was clinically psoriasiform.

To the best of our knowledge, only two other published cases of death resulting from complications of HHD were identified by the authors; however, in both cases, no pathogenic mutation was identified to confirm HHD etiology [9,10]. Over 200 mutations in the *ATP2C1* gene have been identified in causing HHD [1]. The c.2395C>T mutation, which results in a premature stop codon, is a common variant; however, no previous case of c.2395C>T causing generalized HHD has been reported to our knowledge. Other frequently reported HHD mutations include c.2374delTTTG and c.457C>T [11].

In cases of extremely severe epidermal erosion such as this, concurrent pemphigus as well as any other cause for exacerbation or complication of HHD must be ruled out. The patient described herein tested negative for pemphigus antibodies and received an extensive inpatient workup, which revealed no identifiable concurrent cause for her severe disease.

Conclusion

In conclusion, we present a case of generalized HHD in a 55-year-old woman starting on the lower back and disseminating to involve the trunk, extremities, and scalp associated with a c.2395C>T mutation in the *ATP2C1* gene and resulting in a fatal outcome.

Potential conflicts of interest

The authors declare no conflicts of interest.

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