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CASE REPORT

A Novel Nonsense Mutation of the ATP2C1 Gene in an 18-Year-Old-Female with Papular Acantholytic Dyskeratosis of the Anogenital Area

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Abstract: Papular acantholytic dyskeratosis (PAD), often found to occur in the vulvar or anogenital area, is an exceedingly rare skin condition that usually presents in adulthood and features multiple smooth skin-colored or grayish-white papules with or without pruritus. Although the pathogenesis of PAD is unknown, PAD may be associated with mutations in ATP2C1 and ATP2A2 genes. Here, we report on an 18-year-old female patient with multiple gray-white flat papules in the anogenital area. Skin biopsy revealed hyperkeratosis of the epidermis, acantholysis, formation of fissures or lacunae, and disappearance of desmosomes. Whole exon sequencing (WES) of the patient indicated mutations in the ATP2C1 gene.

Keywords: Papular acantholytic dyskeratosis, Whole exon sequencing, ATP2C1

Case Report

An 18-year-old Chinese woman presented to the dermatology department with papules in the anogenital area accompanied by pruritus. The patient had developed gray-white papules in the anogenital area more than 4 years ago, which gradually increased with pronounced itching. During physical examination, multiple gray-white flat papules were found in the anogenital area and were symmetrically distributed (Figure 1a). No skin lesions were found in the other parts of the body, and the nails were intact. The patient denied a family history of similar dermatosis. Dermatoscopy revealed focal white patches and white scales, which resembled stars in a cloudy sky, and radial white stripes were observed around some leukoplakia (Figure 1c). Skin biopsy revealed hyperkeratosis of the epidermis, acantholysis, formation of fissures or lacunae, and disappearance of desmosomes, like a "dilapidated brick wall". The epithelial cells were rich in the cytoplasm, basophilic and like perinuclear halo (Figure 1d and e). The patient was diagnosed with PAD in the anogenital area. Based on the above findings, we made a diagnosis of papular acantholytic dermatosis. Then she was treated with 10mg acitretin capsule and creborol ointment twice a day, and the skin lesions were gradually improved (Figure 1b). The patient is still being followed up.

To determine whether this patient had ATP2C1 or ATP2A1 gene mutations, genetic testing was performed on the patient and her parents. With the patient's informed consent, peripheral blood was collected from the patient, and whole exome sequencing (WES) was performed. We detected a heterozygous nonsense mutation in the ATP2C1 gene in the patient. Subsequently, the ATP2C1 gene was tested after obtaining consent from the healthy parents. We found that the patient's mother had a heterozygous mutation at the same gene locus as the patient, whereas no mutation was found in her father. The mutation of the ATP2C1 gene occurs at nucleotide 2239, from cytosine to thymine, resulting in the mutation of amino acid 747 from glutamine to termination (c.2239C > T, p. Gln747Ter) (Figure 2a). This nonsense mutation was reported for the first time. No mutations were found in the ATP2A2 gene.

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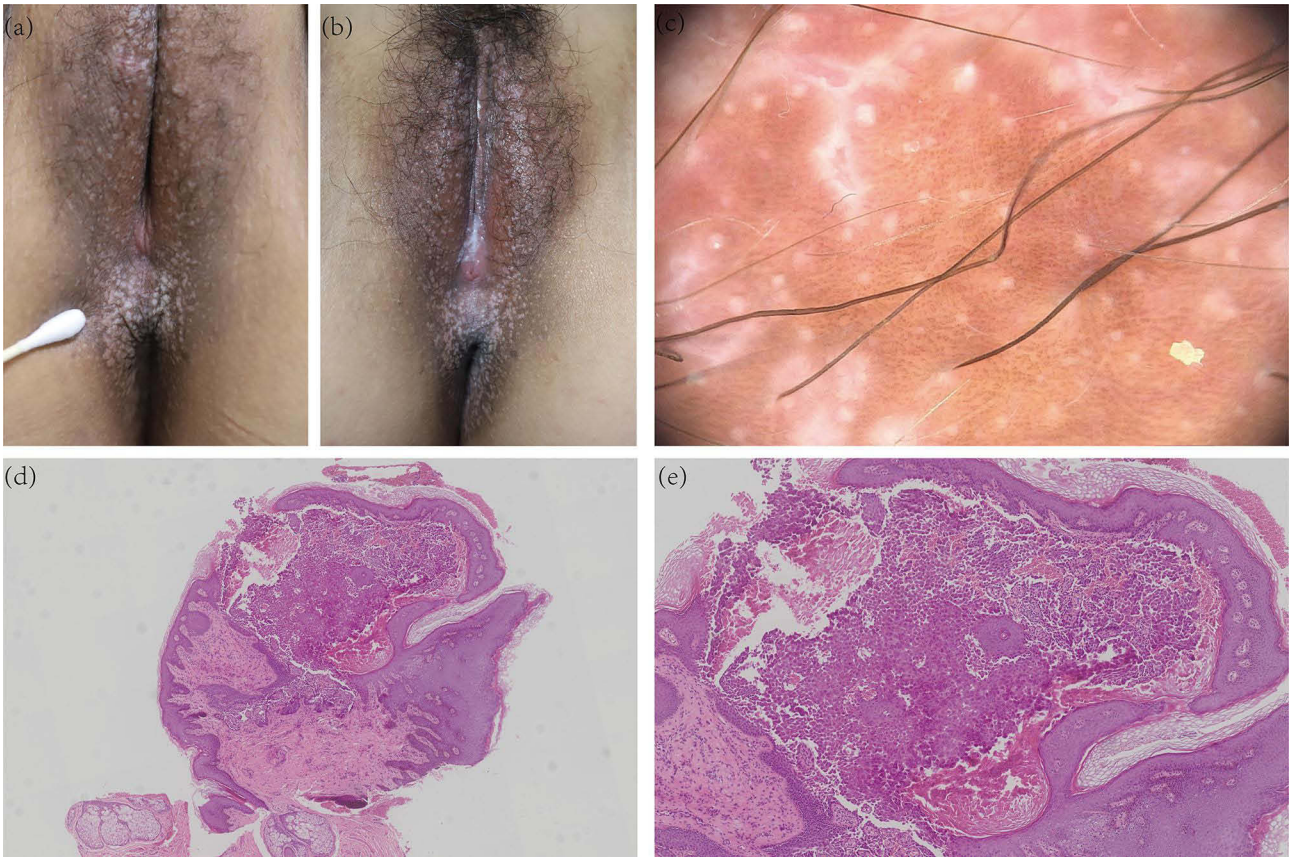

Figure 1 (**a**) Multiple gray-white flat and slightly firm papules in the vulvar and anal areas, which are roughly symmetrically distributed. (**b**)The rashes were treated with Avitra capsules and creborol ointment after 25 days. (**c**) Dermoscopic image displaying white patches and radiating white streaks. (**d** and **e**) Histopathological examination of the vulvar papules from the patient revealed hyperkeratosis of the epidermis, acantholysis, formation of fissures or lacunae, and disappearance of desmosomes, like a "dilapidated brick wall". The epithelial cells are rich in the cytoplasm, basophilic and like perinuclear halo (hematoxylin and eosin; d, original magnification ×40; e, original magnification ×100).

Discussion

The skin lesions of this patient were multiple small gray papules confined to the anogenital area. Histopathology indicated hyperkeratosis and acantholysis, and gene sequencing indicated ATP2C1 gene mutation, all of which were consistent with PAD characteristics and could be diagnosed as PAD. PAD was recently suggested to be a mosaic form of Darier disease (DD) or Hailey-Hailey disease (HHD).[1] The histopathology of DD and HHD is also characterized by hyperkeratosis and acantholysis, which are associated with mutations in genes encoding intracellular calcium pumps.[2] DD is caused by mutations in the ATP2A2 gene, while the ATP2C1 gene is associated with HHD. Patients will be followed for a long period of time to identify these two diseases.

There are other treatment methods for PAD, such as CO2 laser and cryotherapy. During the follow - up process, if it turns out that acitretin capsules and creborol ointment fail to yield a satisfactory curative effect, we will make adjustments to the treatment plan accordingly.

ATP2C1 gene codes for the secretory pathway $Ca(^{2+})/Mn(^{2+})$-ATPase pump type 1 (SPCA1) localized at the Golgi apparatus.[3] This ATPase responsible for pumping calcium from the cytoplasm to the Golgi apparatus. Several different mutations in the ATP2C1 gene have been suggested as the cause of PAD in previous studies.[4,5] Is the nonsense mutation of the ATP2C1 gene in this patient pathogenic? The mutation in this patient and her mother was not found in the 1000 genomes database, the Genome Aggregation Database, or the Exome Aggregation Consortium database. The application of ACMG rules should yield a pathogenic classification of PVS1+PM2 (absent from the population). This nonsense mutation has been suggested to be a possible pathogenic mutation. In addition, it was predicted to be a disease-causing mutation by Mutation Taster. We found that the mutant protein ATPase_P-typ_cation-transptr_C domain was deleted

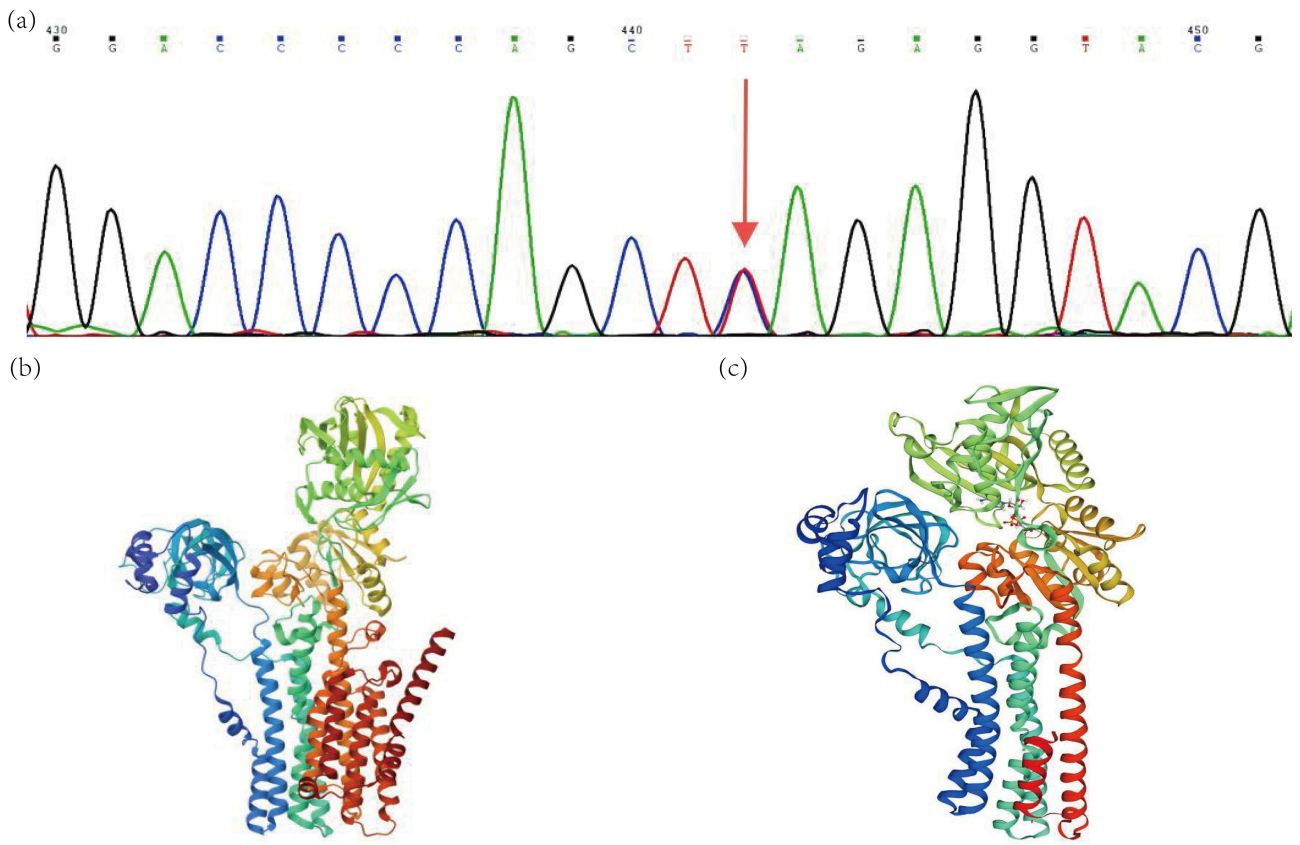

Figure 2 (**a**) Heterozygous c. 2239C>T (p. Gln747Ter) mutation in the ATP2C1 gene. (**b**)Three-dimensional structural model of normal ATP2C1 protein. (**c**)Swiss-model prediction of the three-dimensional structure of mutant ATP2C1 protein.

based on the protein sequence alignment method using InterPro domain database. This domain is the conserved C-terminal region of cation-transporting P-type ATPase. P-ATPase can use the energy of ATP hydrolase to transport ions through the membrane.[6] The lack of this domain may lead to a deficiency in protein transport Ca++ function, affect cell adhesion and lead to disease. The mutated amino acid sequence was input into the protein structure website Swiss-model, and a three-dimensional model was obtained after a build-model step. The results demonstrated that compared with the three-dimensional structure of the normal ATP2C1 protein on PDB (https://www.rcsb.org/), most of the structure of the mutant protein was similar, and some of the protein structure at the tail end was missing, suggesting that the mutant protein may lead to functional defects (Figure 2b and c). The above evidence suggests that this nonsense mutation is pathogenic and may be the cause of the disease in this patient.

To our knowledge, the mode of inheritance of ATP2C1 gene was autosomal dominant. Notably, the patient's mother had the same nonsense mutation but did not get sick. We speculate that the mother of the patient had incomplete clinical penetrance of this nonsense mutation. This is common in primary immunodeficiency with autosomal dominant inheritance (eg, the penetrance rates of CTLA-4[7] and TNFRSF6/Fas[8] mutations are 67% and 30%, respectively).

In summary, we report a young female patient with PAD and found a new nonsense mutation in the ATP2C1 gene, and confirmed its pathogenicity. For this patient, we recommend long-term follow-up to exclude other similar diseases.

Consent Statement

Informed consent for publication of the case details and associated images was obtained from the patient, and all procedures were performed in accordance with the Helsinki Declaration. Institutional approval was not required to publish the case details. The genetic data has been filed as required (No. PFKWC20240530).

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Disclosure

The authors report no conflicts of interest in this work.

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