Letter to the Editor

Darier's disease with epilepsy in an elderly patient after surgery for aortic dissection

Yuya Murase, MD[1], Takuya Takeichi, MD, PhD[1], Tomoyuki Shibata, MD[2], Yoshinao Muro, MD, PhD[1], Masashi Akiyama, MD, PhD[1]

[1]Department of Dermatology, Nagoya University Graduate School of Medicine
65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
[2]Department of Dermatology, Toyota Memorial Hospital, Toyota, Japan

Corresponding author: Masashi Akiyama
Department of Dermatology, Nagoya University Graduate School of Medicine
65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan
Tel: +81-52-744-2314, Fax: +81-52-744-2318
E-mail: makiyama@med.nagoya-u.ac.jp

Running head: Darier's disease in an elderly patient after surgery
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Dear Editor,

Darier's disease (DD) is a rare autosomal dominant genetic disease. Clinical features, including an association with neuropsychiatric abnormalities such as mental retardation and epilepsy, have been reported in several families with DD.[1]

A 75-year-old man presented to our department with numerous red to brown hyperkeratotic papillary papules and plaques with strong pruritus on the back, groins, and abdmen (Fig. 1a-c). The skin lesions had occurred and developed from two years earlier, when he underwent a surgical operation for Stanford type-A aortic dissection. After the surgical operation, he was prescribed strict bedrest in a supine position for 6 weeks, including the first 2 weeks of ICU care. In addition, his level of consciousness was depressed occasionally about one year after DD onset. Electroencephalography led to the diagnosis of temporal lobe epilepsy.

Histopathological examinations of punch biopsy samples showed acantholytic keratinocytes and dyskeratotic cells in the suprabasal layers and clefts in the epidermis (Fig. 1d).

Following ethical approval, informed written consent was obtained in compliance with the Declaration of Helsinki guidelines. Sanger sequencing of the PCR products obtained using genomic DNA extracted from peripheral blood mononuclear cells revealed a previously unreported heterozygous *ATP2A2*mutation, c.1070C>T (p.Thr357Ile) (Fig. 1e). Two DD cases, one classical DD and one comedonal DD, with a mutation at the same codon in *ATP2A2* have been reported.[2, 3] In addition, *in silico* analysis with PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) predicted the mutation to be 'probably damaging', and the SIFT program (http://sift.jcvi.org/) predicted it to be 'damaging'. According to the American College of Medical Genetics (ACMG) guidelines, we consider the present mutation as 'likely pathogenic'. From these genetic and histopathological findings, we diagnosed DD. Since this diagnosis, he has received oral retinoid therapy, and his skin lesions have significantly improved.

In the present patient, the skin lesions first occurred at 73 years of age. DD rarely has an onset in elderly patients.[1, 4]

Skin lesions are exacerbated by certain external factors such as heat, stuffy environment, and sweating.[4] In the present case, the skin lesions first appeared after surgery for aortic dissection. Excessive sweating and stuffy condition from him being on his back due to long-term bedrest and/or proinflammatory cytokine secretion induced by major surgery might had led to the development and exacerbation of

the DD skin lesions.[5] As far as we know, no other patient is reported to have developed DD soon after a surgical operation.

The present case was accompanied by temporal lobe epilepsy one year after DD onset. Thus, his epilepsy might have been triggered by the DD onset, although we cannot exclude the possibility that the epilepsy could have been induced simply by the surgery and ICU treatment. In the literature, no specific subtype of epilepsy was found to commonly occur as a complication of DD.

This case suggests that, even in elderly patients, we have to keep DD in mind as a diagnosis for widespread warty hyperkeratotic papules and plaques triggered by certain external/environmental factors and episodes including major surgery and long-term bedrest.

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Conflicts of interest: The authors have no conflicts of interest to declare.

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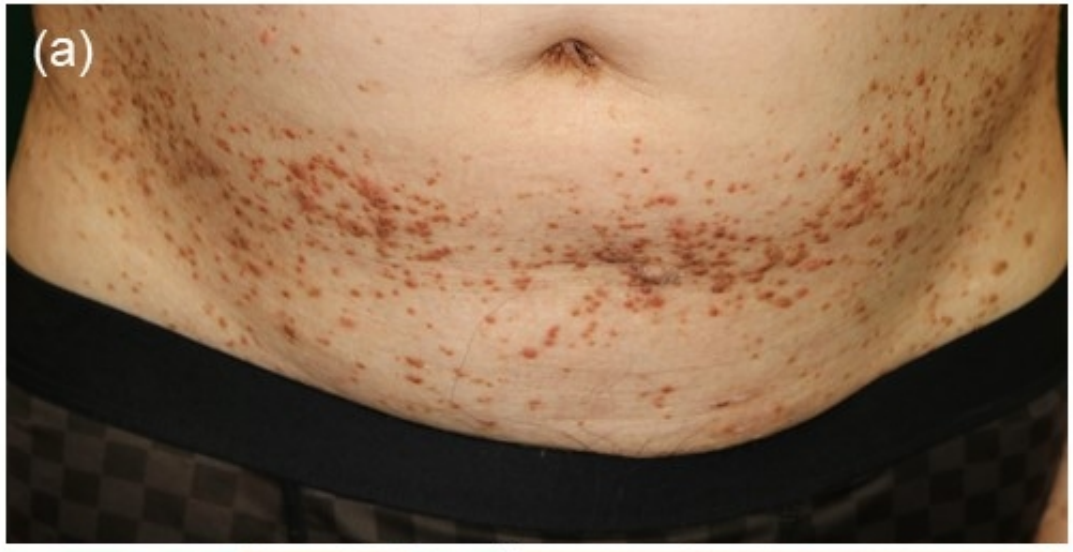
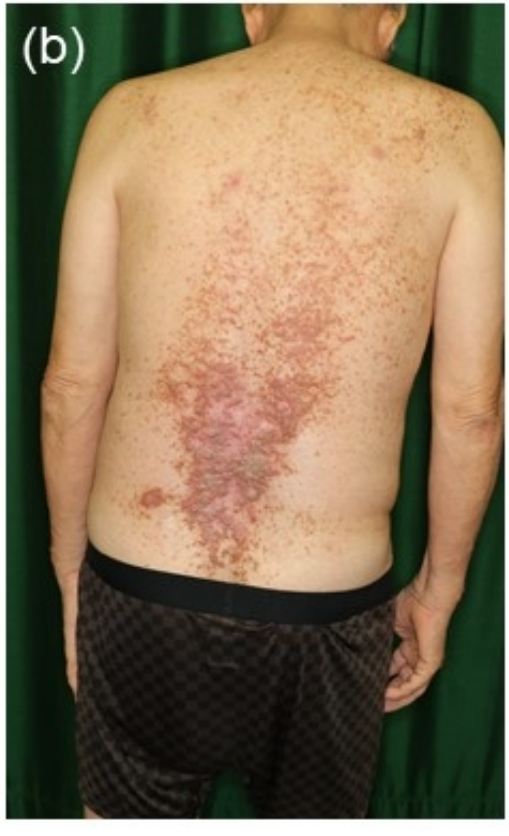
Figure legends

Figure 1. Clinical, histopathological, and genetic findings of the patient's skin lesions and the causative *ATP2A2* mutation.

(a) Many red to brown warty hyperkeratotic papules on the lower abdomen are observed. (b, c) Numerous warty, reddish, hyperkeratotic papules and plaques are seen on the back, especially the lower back. (d) A skin biopsy sample from a hyperkeratotic lesion on the back shows marked hyperkeratosis and acantholysis, dyskeratosis and clefts in the suprabasal layers of the epidermis (Original magnification × 400).
(e) Sanger sequencing of genomic DNA from the patient reveals the novel missense mutation c.1070C>T (p.Tyr357Ile) in *ATP2A2*.


(a)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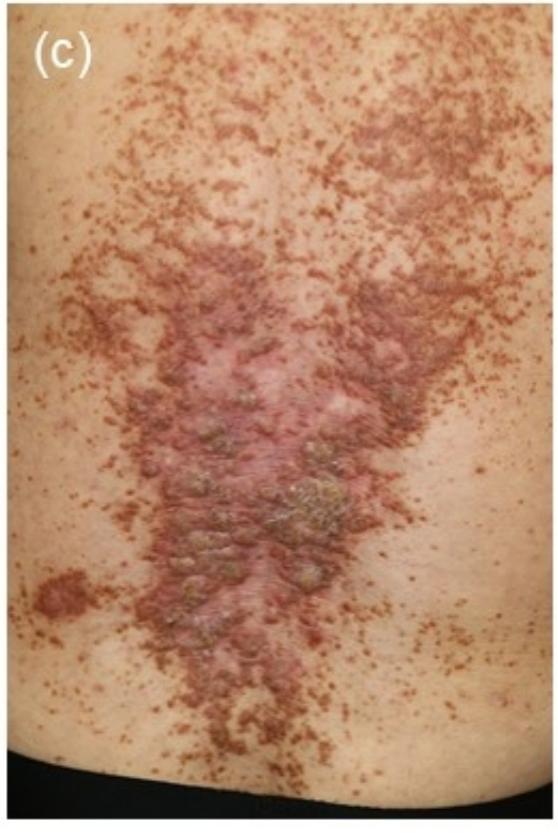
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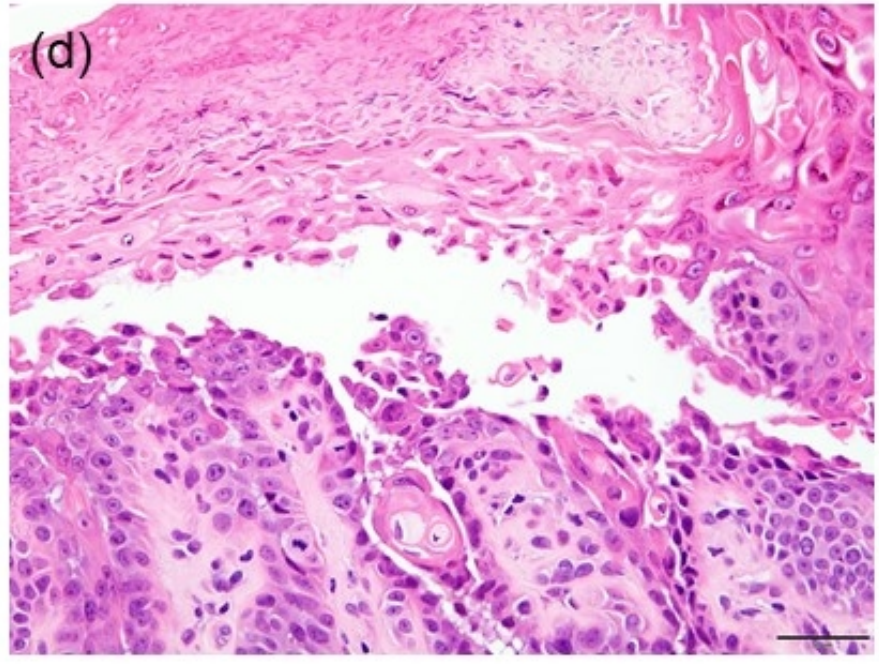
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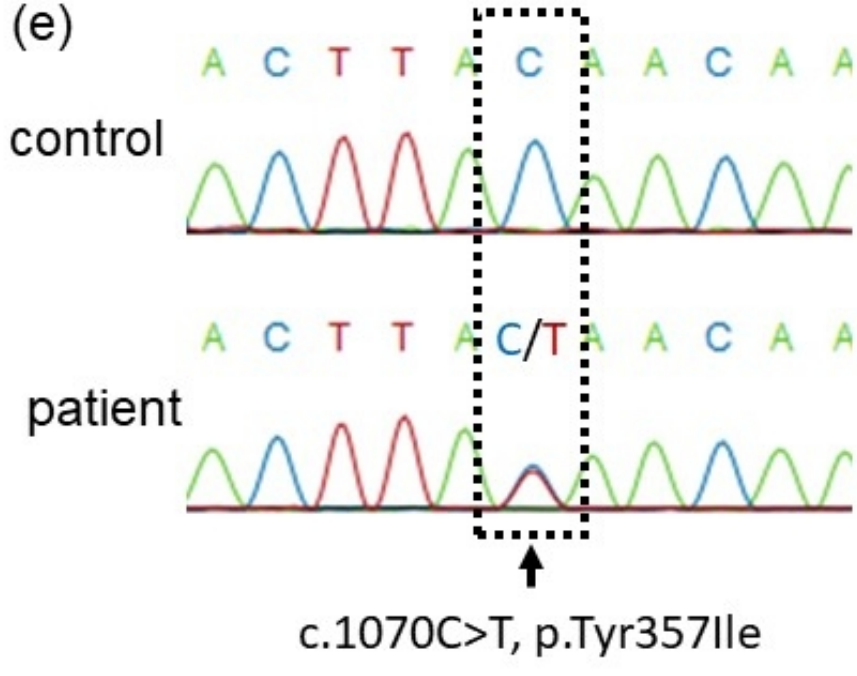
(e)
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patient
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