

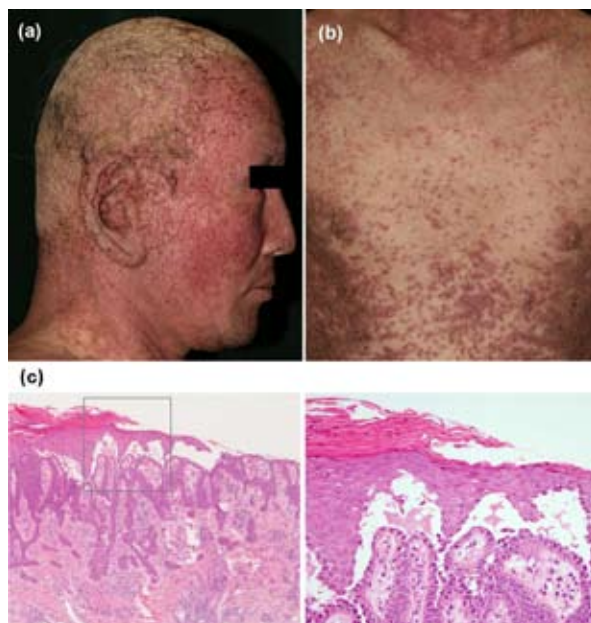
## Darier's Disease with Esophageal Involvement

Dear Editor,

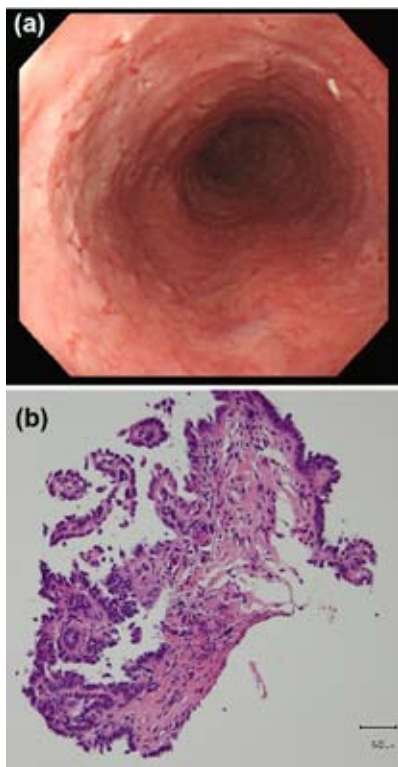
We report the case of a Japanese man with Darier's disease (DD) that affected the esophagus as well as the skin. A 49-year-old man, who was diagnosed with DD 19 years earlier, visited us again in October 2008 because his skin lesions had exacerbated. Physical examination revealed reddish-brown crusted follicular papules mostly coalesced to produce irregularly-shaped warty plaques on his trunk, hip, upper and lower limbs, and scalp (Figure 1, a, b). Skin biopsy taken from the hip showed hyperkeratosis, papillomatosis, and suprabasal acantholysis with lacunae formation (Figure 1, c). The diagnosis of DD was confirmed and treatment with etretinate at 20 mg daily was started. The dose was increased to 50 mg 22 days later because his skin lesions failed to respond to the initial dose. When the dose was tapered to 20 mg after 2 months, painful erosions appeared on the hip. Tzanck smear testing showed balloon cells, and the serum level of Immunoglobulin M (IgM) antibody against herpes simplex virus (HSV) was elevated. The erosion was successfully treated with intravenous acyclovir (750 mg/day for 5 consecutive days). The oral administration of valaciclovir (500 mg/day) was continued as prophylaxis against the recurrence of HSV infection. While the disease was well managed with 20 mg etretinate/day, the patient experienced aggravation in April 2010 and painful swallowing in September 2010. Gastrointestinal endoscopy revealed multiple hyperkeratotic lesions in the middle of the esophagus (Figure 2, a). A biopsy showed histology similar to lesions on the skin including acantholysis and lacunae formation (Figure 2, b). Immunostaining did not detect either HSV-1, HSV-2, or human papilloma virus (HPV) in the esophageal mucosa. The skin lesions improved but the esophageal lesions persisted unchanged 8 months after increasing the daily dose of etretinate to 40 mg.

DD is a rare autosomal dominant genodermatosis characterized by abnormal keratinization that primarily affects the skin. A total of 8 cases of DD affecting the esophagus have been reported previously (1-6). Several important issues emerged from our experience and literature review.

Firstly, DD predisposes to infections with HSV, varicella-zoster virus (VZV), HPV, and pox virus (7,8). HSV infection was diagnosed in 1 of 8 previously-reported cases of esophageal DD. In one case, a 20-year-old man had severe thoracic pain; his esophageal lesion was immunohistochemically positive for HSV type I, and acyclovir treatment produced an early clinical response (6). In our case, HSV was detected in the cutaneous lesions but not the esophagus; esophageal lesions developed and persisted during the administration of acyclovir or valaciclovir. Although a partial immune-deficiency has been proposed as causative in some reports, no specific immune function anomaly has been demonstrated (6,7). It is possible that suprabasal acantholysis, a characteristic histological feature of DD, may provide a favorable environment for viral infections and result in innate host defense system deficiencies (8).



**Figure 1.** Reddish brown crusted follicular papules mostly coalesced to produce irregularly-shaped warty plaques. (a) Scalp. (b) Trunk. (c) A biopsy specimen taken from the hip shows hyperkeratosis, papillomatosis, and suprabasal acantholysis with lacunae formation (original magnification: left  $\times 40$ , right  $\times 200$ ).



**Figure 2.** (a) Upper gastrointestinal endoscopy showing multiple hyperkeratotic lesions in the middle of the esophagus. (b) A biopsy specimen taken from the esophagus with a histology similar to the skin including acantholysis and lacunae formation (original magnification:  $\times 400$ ).

Secondly, there is a hypothetical association between DD and malignant neoplasms. Among patients with DD, one patient with the esophageal form developed squamous cell carcinoma (SCC) (4). DD is attributed to a null-mutation in the ATP2A2 gene encoding the sarcoplasmic/endoplasmic reticulum Ca<sup>2+</sup>-ATPase isoform 2 (SERCA2) (9). The functional association of the ATP2A2 gene mutation with the development of SCC has been demonstrated. Mice with a single functional Atp2a2 allele, a mouse homolog of ATP2A2, manifested reduced levels of SERCA2; subsequent perturbations in calcium homeostasis or signaling served as a primary initiating event in the development of SCC. Heterozygous mutant Atp2a2 (+/-) mice developed SCC in the skin, oral mucosa, and esophagus where SERCA2 protein levels were decreased (10).

We reported a rare case of DD with esophageal involvement and encourage dermatologists to be alert to viral infections and the possible development of cancer in patients with DD.

## References

1. Pesce G, Perroni L. A case of Darier's dyskeratosis follicularis with esophageal localization. *Minerva Otorinolaringol* 1958;8:275-9.
2. Stein G. Roentgenologically discovered changes in the esophagus in Darier's disease. *Radiol Diagn (Berl)* 1962;3:483-5.
3. Larregue M, Katz M, Gasquet C, Lansmann M. Esophageal localization of Darier's disease. Radiological description apropos of 4 cases. *Med Cutan Ibero Lat Am* 1977;5:33-8.
4. Shimizu H, Kinoshita MT, Suzuki H. Darier's disease with esophageal carcinoma. *Eur J Dermatol* 2000;10:470-2.
5. Ahmed Al Robaee, Issam R, Hamadah R, Khuroo S, Alfadley A. Extensive Darier's disease with esophageal involvement. *Int J Dermatol* 2004;43:835-9.
6. Vieites B, Seijo-Ríos S, Suárez-Peñaranda JM, Lariño-Noia J, Macías-García F, Domínguez-Muñoz JE, et al. Darier's disease with esophageal involvement. *Scand J Gastroenterol* 2008;43:1020-1.
7. Burge S. Darier's disease – the clinical features and pathogenesis. *Clin Exp Dermatol* 1994;19:193-205.
8. Nikkels AF, Beauthier F, Quatresooz P, Piérard GE. Fatal herpes simplex virus infection in Darier's disease under corticotherapy. *Eur J Dermatol* 2005;15:293-7.
9. Sakuntabhai A, Ruiz-Perez V, Carter S, Jacobsen N, Burge S, Monk S, et al. Mutations in ATP2A2, encoding a Ca<sup>2+</sup> pump, cause Darier disease. *Nat Genet* 1999;21:271-7.
10. Prasad V, Boivin GP, Miller ML, Liu LH, Erwin CR, Warner BW, et al. Haploinsufficiency of Atp2a2, encoding the sarco (endo) plasmic reticulum Ca<sup>2+</sup> - ATPase isoform 2 Ca<sup>2+</sup> pump, predisposes mice to squamous cell tumors via a novel mode of cancer susceptibility. *Cancer Res* 2005;65:8655-61.

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