CASE REPORT
Small intestine perforation in a 58-year-old man with Darier disease after 25 months of oral acitretin therapy
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A B S T R A C T
Darier disease is a rare autosomal dominant disease characterized by abnormal keratinization of the epidermis, mucosa, and nails. Acitretin, an aromatic form of tretinoin, is widely prescribed in the treatment of Darier disease. However, significant adverse effects can occur and there have been reports associating intestinal inflammation with retinoid therapy. We report the case of a 58-year-old man who developed a small intestine perforation after 2 years of acitretin treatment. Having excluded other common causes, we suspected that the small intestine perforation could be the result of severe inflammation of small intestine due to the long-term use of acitretin. Given the significance of this potential morbidity, it would seem prudent to monitor acitretin treatment for treating Darier disease by paying more attention to clinical symptoms such as abdominal pain or bloody stool.

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Introduction
Darier disease is a rare, autosomal dominant disease caused by a mutation on chromosome 12q23-24, which encodes for the sarcoplasmic/endoplasmic reticulum Ca(2+)-adenosine triphosphatase type 2 isof orm (SERCA2) enzyme. This condition is characterized by abnormal keratinization of the epidermis, nails, and mucous membrane. Typical clinical symptoms include keratotic papules in seborrheic regions as well as flexures and distinct nail changes, with histology of acantholysis and dyskeratosis.

Oral acitretin is the treatment of choice for generalized or severe Darier disease, and the recommended dosage is 0.25–0.5 mg/kg/day. Acitretin could normalize epidermal cell proliferation, differentiation, and cornification. However, it has many metabolic, skeletal, and teratogenic adverse effects, including mucocutaneous effects, hyperlipidemia, hepatotoxicity, and skeletal anomalies. Mucocutaneous adverse effects include dryness of the lips, cheilitis, thinning, redness and scaling of the skin, and hair loss. Here, we describe a case of jejunal perforation in a 58-year-old man suffering from Darier disease receiving oral acitretin therapy for more than 2 years.

Case report
Darier disease was diagnosed by skin biopsy at our clinic in a 58-year-old man 2 years previously. Initial symptoms included brownish, verrucous papules over the back, chest, scalp, and inguinal and axillary areas (Figure 1) along with itchiness and foul smell, because the condition had been left untreated for many years. The patient weighed 75 kg and had a history of severe itching that was not responsive to topical steroids and emollients.

Acitretin 25 mg daily and an oral antihistamine, desloratadine 5 mg every night, were prescribed for 13 months. Initially, the itchiness decreased and skin lesions improved, but the improvement gradually faded after 1 year. Therefore, the dose of acitretin was increased to 50 mg daily for 1 month. Due to dryness of the mouth and intolerable skin xerosis, we adjusted the dose of acitretin back to 25 mg daily and maintained this dosage for another 11 months. The patient continued to experience occasional episodes of severe skin pruritus, but his symptoms showed improvement most of the time.

Complete blood count, monitoring of electrolytes and lipid profile, and liver function and renal function tests were conducted regularly (approximately every 1–2 months). Persistent elevated triglyceride levels (TG: approximately 163–288 mg/dL) were noted. The patient was referred to the endocrinology outpatient department for lipid control.

The patient had intermittent abdominal pain for 1 week after a 2-year-period of acitretin treatment. In the emergency department,
left upper abdominal tenderness with rebound pain was noted. Laboratory data revealed mild leukocytosis (white blood cells = 10,500/µL), but there was no fever. Abdominal computed tomography was performed which showed jejunal mesenteric lesions with regional adhesion and ileus. Based on a diagnosis of intra-abdominal abscess, the patient received emergent exploratory laparotomy.

During the operation, jejunal perforation with mesenteric abscess and small bowel tight adhesion at the upper abdomen were found (Figure 2). Segmental resection of small bowel with primary anastomosis was then performed. The patient was then transferred to a surgical intensive care unit and received systemic antibiotics. He was discharged after 37 days without any serious sequelae.

The patient returned to our clinic after discharge. We carefully examined his complete medical and drug history and found no relevant contributing factors for his jejunal perforation. Although acitretin appeared to be the most likely cause, there was no direct evidence to prove this theory. After discussing with the patient, we stopped acitretin and prescribed oral antihistamines (desloratadine 5 mg daily and levocetirizine 5 mg daily) together with topical steroids and adapalene gel 0.1% to relieve his symptoms.

**Discussion**

Perforation of the small bowel is a rare but serious condition. Perforation from duodenal ulcers was the most common cause in the past. *Helicobacter pylori* infection or prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs) may all contribute to perforation in the small intestine. Currently, perforation that occurs during endoscopy is not an uncommon cause. Other causes of perforation include infections (e.g., tuberculosis and cytomegalovirus), Crohn's disease, ischemia, injury from radiation therapy, cancer (such as lymphoma or adenocarcinoma), and swallowed foreign bodies.

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**Figure 1** Multiple brownish, verrucous papules on the patient's (A) chest, (B) back, (C) inguinal area, and (D) nails with longitudinal ridging and subungual hyperkeratotic debris are shown.

**Figure 2** Surgical specimen revealing a small bowel tight adhesion with mesenteric abscess and jejunal perforation.
Our patient developed jejunal perforation after using acitretin for 2 years. After reviewing his medical history, we found that he had been taking atorvastatin and valsartan regularly for more than 1 year. Atorvastatin and valsartan have no known adverse effects of inflammatory bowel disease or bowel perforation, and are used for lowering blood triglyceride levels and controlling hypertension, respectively. The patient also took amoxicillin, dextromethorphan, and theophylline intermittently for more than 1 year due to smoking-induced chronic cough and dyspnea. No other obvious life stress or use of NSAIDs was recorded. The test for H. pylori infection was not conducted because H. pylori is often associated with gastrointestinal ulcers above the duodenum, unlike the findings in our case.

In the past 2 years, the patient neither received any endoscopic procedure nor experienced any blunt abdominal injury. During the operation, we only found perforations on a part of the small intestine along with mesenteric abscess and adhesion. The pathology of resected jejunum showed inflammatory ulcers with micro-perforation (Figure 3). Yamada et al. reported a case of all-trans retinoic acid-induced vasculitis and hemonecrosis of the ileum in a patient with acute promyelocytic leukemia. However, the skin lesions and pathology of our case did not show the characteristics of leukocytoclastic vasculitis as described by Yamada et al. Comparing it with clinical manifestations and pathologic findings, we could rule out retinoic acid-induced vasculitis, uncommon inflammatory bowel disease, underlying malignancy, or atypical infection.

Retinoids are derivatives of vitamin A that have been shown to normalize keratinocyte differentiation and proliferation. Acitretin is an aromatic form of tretinoin, and is useful for controlling extensive or severe Darier disease. A wide range of adverse effects may occur with its use, including cheilitis, xerosis, retinoid dermatitis, dyslipidemia, desquamation, photosensitivity, paronychia, pyogenic granuloma, and onycholysis, which usually disappears when acitretin is used at lower doses or when the medicine is withdrawn. Rare serious adverse effects, including pancreatitis, seizures, and cerebral pseudotumor, have also been noted. Mood changes, depression, suicide risk, and inflammatory bowel disease are also controversial outcomes.

13-cis-Retinoic acid, also known as isotretinoin is a second-generation retinoid acid that is particularly useful in severe cases of acne such as severe cystic acne. It shows beneficial activity in pityriasis rubra pilaris, Darier disease, and keratosis palmosus. Although data are currently limited, it is probable that isotretinoin can cause intestinal inflammation. A small number of case reports have reported the development of ischemic bowel disease (IBD) while receiving isotretinoin therapy. Reddy et al. reviewed 85 cases of IBD associated with isotretinoin reported to the US Food and Drug Administration (FDA) between 1997 and 2002, and found that the causal association with isotretinoin was considered probable or highly probable in 75% of the cases. According to the summary of previous case reports, the period between isotretinoin initiation and IBD onset is most commonly in months, although it can range between days to a year.

The main forms of IBD are Crohn’s disease and ulcerative colitis. Crohn’s disease can affect any part of the gastrointestinal tract, from mouth to anus (i.e., skip lesions), although most of the cases start in the terminal ileum. By contrast, ulcerative colitis is restricted to the colon and rectum. Compared with Crohn’s disease, our case showed small intestine inflammation restricted only to the jejunum. Based on the sudden onset of clinical symptoms and surgical findings, the clinician did not favor the diagnosis of IBD, nor arranged for an endoscopic examination thereafter.

Retinoic acid can interfere with epithelial integrity and this may predispose a patient to intestinal inflammation. Proposed mechanisms include the following: (1) isotretinoin affects intestinal epithelial growth and is involved in cell repair and apoptosis; (2) isotretinoin increases T lymphocyte proliferation and gut homing as well as altering T lymphocyte subsets predisposed to inflammation; (3) isotretinoin causes neutrophil dysfunction, inhibition of glycoprotein synthesis, dendritic cell activation and its effects on plasma cell may also predispose a patient to inflammation. It is reasonable that acitretin and isotretinoin share certain common adverse effects. However, there have been no reports on small bowel perforation associated with acitretin.

Hyperlipidemia occurs in certain patients on acitretin therapy. It is regarded as a modifiable risk factor for cardiovascular disease due to its influence on atherosclerosis. In addition, some cases may predispose patients to acute pancreatitis. In our case, persistent elevation in triglyceride levels was noted.

Questions still remain about whether any relationship exists between atherosclerosis due to hyperlipidemia and IBD. Nonetheless, there is no direct evidence that retinoid toxicity is an additional risk factor for development of IBD, not even a case report. Despite this ambiguity, we can consider this event from a different viewpoint.

Small bowel perforation is a rare disease, especially in those patients without specific etiology. Patients who have had a perforated bowel will need regular follow-up and treatment for the underlying conditions that may have caused the perforation. In our case, the duration of follow-up after discharge was approximately 9 months, and the patient continued with regular monthly follow-up at our clinics. No more abdominal symptoms or signs were recorded, after withdrawal of acitretin.

The common causes of small bowel perforation in our study were pursued and excluded. A possibility of coincidence could not be excluded, but was deemed unlikely. In addition, retinoids may contribute to intestinal inflammation and the pathology of this case also revealed severe intestinal inflammation. Therefore, it supports the view that severe inflammation and perforation of small intestine could be associated with acitretin.
Conclusion

We present a case of small bowel perforation after 25 months of oral acitretin therapy, in which the common causes were excluded. In light of the significance of this potentially life-threatening adverse event, further studies are required to clarify the association between small bowel perforation and oral acitretin therapy and to identify the precise underlying mechanisms.

References