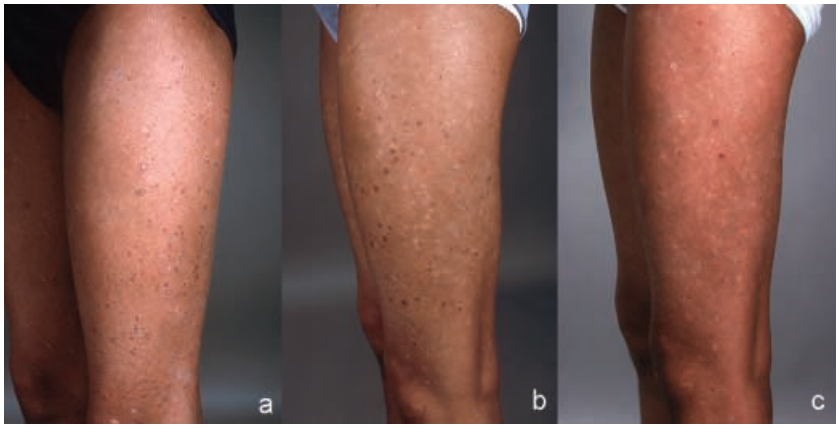

Figure 2. Clinical appearance of pityriasis lichenoides in patient 2. (a) Before treatment with tacrolimus 0·03% ointment, (b) after 6 weeks, and (c) after 4 months, showing dramatic improvement of the skin eruption.

cells, especially Th2 cells, we chose tacrolimus for the treatment of patients with PL.

This is the first report using tacrolimus ointment for the treatment of PL. Further studies involving representative numbers of patients are required to evaluate the therapeutic efficacy of tacrolimus in this inflammatory skin disease.

Departments of Dermatology and D. SIMON
**Pharmacology, Inselspital,* C. BOUDNY
University of Bern, 3010 Bern, H. NIEVERGELT
Switzerland H-U. SIMON*
E-mail: dagmar.simon@insel.ch L.R. BRAATHEN

References

1 Weedon D. *Skin Pathology*, 1st edn. London: Churchill Livingstone, 1997; 209–10.
2 Nghiem P, Pearson G, Langley RG. Tacrolimus and pimecrolimus: from clever prokaryotes to inhibiting calcineurin and treating atopic dermatitis. *J Am Acad Dermatol* 2002; **46**: 228–41.
3 Reitamo S, Rissanen J, Remitz A *et al.* Tacrolimus ointment does not affect collagen synthesis: results of a single-center randomised trial. *J Invest Dermatol* 1998; **111**: 396–8.
4 Romani J, Puig L, Fernandez-Figueras MT *et al.* Pityriasis lichenoides in children: clinicopathologic review of 22 patients. *Pediatr Dermatol* 1998; **15**: 1–6.
5 Gelmetti C, Rigoni C, Ermacora E *et al.* Pityriasis lichenoides in children: a long-term follow-up of eighty-nine cases. *J Am Acad Dermatol* 1990; **23**: 473–8.
6 Groisser DS, Griffiths CE, Ellis CN, Voorhees JJ. A review and update of the clinical uses of cyclosporine in dermatology. *Dermatol Clin* 1991; **9**: 805–17.
7 Lynch PJ, Saied NK. Methotrexate treatment of pityriasis lichenoides and lymphomatoid papulosis. *Cutis* 1979; **23**: 634–6.
8 LeVine MJ. Phototherapy of pityriasis lichenoides. *Arch Dermatol* 1983; **119**: 378–80.
9 Boelen RE, Faber WR, Lambers JC, Cormane RH. Long-term follow-up of photochemotherapy in pityriasis lichenoides. *Acta Derm Venereol (Stockh)* 1982; **62**: 442–4.
10 Magro C, Crowson AN, Kovatich AL, Burns F. Pityriasis lichenoides: a clonal T cell lymphoproliferative disorder. *Hum Pathol* 2002; **33**: 788–95.

A case of interstitial granulomatous drug reaction due to sennoside

DOI: 10.1111/j.0007-0963.2004.05916.x

SIR, Sennoside is one of the most frequently used laxatives in the world. Abdominal pain is the most frequent side-effect reported in the gastrointestinal literature. To our knowledge, few cases of drug eruption have been reported in international journals. We report a patient with a drug eruption induced by sennoside, which demonstrated pathological changes of interstitial granulomatous drug reaction (IGDR).

A 55-year-old woman presented with a 2-year history of pruritic scaly erythematous plaques on the palmoplantar regions, which had gradually enlarged during the last 6 months (Fig. 1A,B). Examination revealed asymptomatic, slightly infiltrated plaques on the popliteal fossae (Fig. 1C). She had no lymphadenopathy, arthritis, photosensitivity or any signs of collagen disease. Her medical history included severe constipation, and she had been prescribed sennoside for 20 years. Laboratory examination demonstrated a low positive titre of antinuclear antibody (1 : 40). Rheumatoid factor was 61·6 IU mL^{-1} (normal < 10) and other autoantibodies were negative. Skin biopsy from the right popliteal fossa revealed vacuolar degeneration, and histiocytes with sparse giant cells and mucin deposition in the perivascular and interstitial dermis. There were no palisaded histiocytes or necrobiosis (Fig. 2). First, we discontinued sennoside to rule out the possibility of a drug reaction. The skin lesions subsided remarkably after approximately 6 weeks (Fig. 1D–F). The patient started to take sennoside as a provocation test, and similar plaques reappeared on the palmoplantar areas over 8 weeks. We finally diagnosed our patient as having IGDR induced by sennoside. Patch testing and drug lymphocyte stimulation tests for sennoside were negative.

Sennoside is a major laxative agent derived from the leaves/pods of *Cassia acutifolia* and *C. angustifolia* (India or Tinnevelly senna). It is an anthranoid or anthraquinone derivative, whose basic structure is a tricyclic anthracene ring. In the lower gastrointestinal tract, it is digested by bacteria to a rhein anthrone moiety, which stimulates

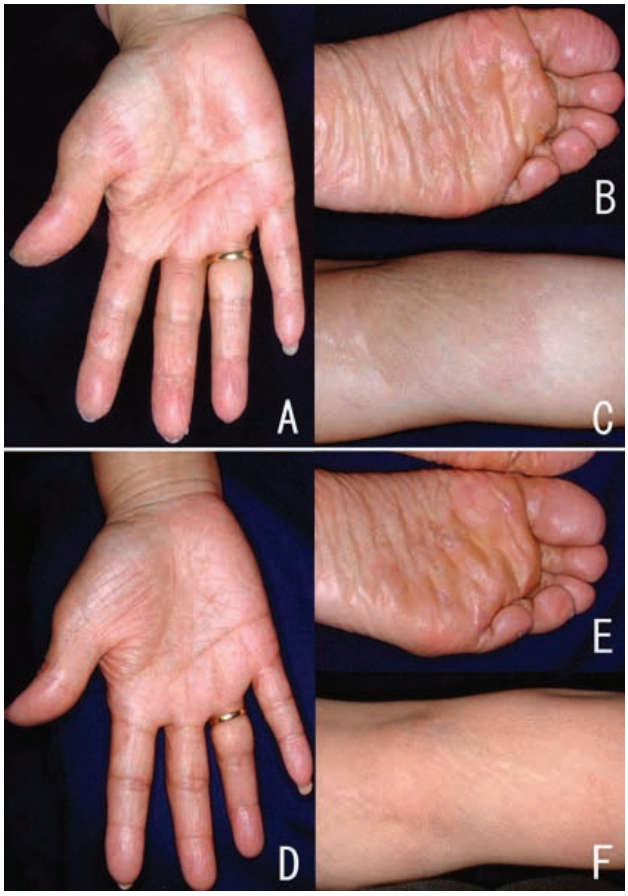

Figure 1. Scaly, erythematous plaques on (A) the palm and (B) the sole. (C) Asymptomatic, slightly infiltrated plaques on the popliteal fossa. (D–F) After cessation of sennoside intake, all lesions subsided in 6 weeks.

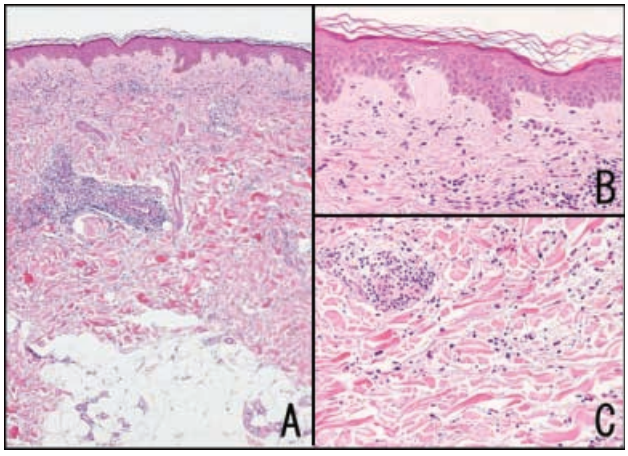

Figure 2. (A) Inflammatory cell infiltrate in the perivascular/interstitial areas of the dermis. (B) Vacuolar degeneration around the dermoepidermal junction. (C) Histiocytes (sparse and multinuclear) infiltrating in the interstitial area. Note sparse mucin deposition. Haematoxylin and eosin; original magnification: A, ×20; B,C, ×200.

intestinal motility and induces net fluid secretion. The known side-effects of sennoside are abdominal pain and electrolyte imbalance. Pseudomelanosis coli proliferation[1] and potential neoplastic change[2] have also recently been reported. Skin side-effects include three infantile cases of contact dermatitis on the buttock, which was induced by rhein anthrone contained in stools.[3] There have been several reports of other sennoside drug eruptions in Japanese dermatology journals, including a fixed drug eruption, photosensitivity and urticaria-like eruption.[4] The mechanisms of sennoside-induced drug eruptions are uncertain. Toshitani *et al.* reported a case of an urticaria-like eruption, and found an elevation in interferon-γ concentration in the patient's T-cell culture mixed with sennoside.[4] They hypothesized that the urticarial lesion was caused by a delayed T-cell hypersensitivity, which might explain why the skin eruptions persist long after the sennoside intake. Some of the skin lesions were suggested to be associated with T-cell reactions, but further studies are needed for full understanding of these mechanisms.

IGDR is a recently proposed drug-induced entity described by Magro *et al.* in 1998.[5] Most patients presented erythematous to violaceous plaques on the axillary folds and groin. Lesions were usually caused by intake of the drug over a long duration (average 8 weeks), and improved soon after cessation of the drug. The clinical differential diagnosis includes cutaneous T-cell lymphoma, erythema chronicum migrans and granuloma annulare (GA). Similar plaques can appear in association with arthritis and collagen diseases, described as interstitial granulomatous dermatitis (IGD) with arthritis/plaques.[6] IGDR is pathologically characterized by an interstitial granulomatous reaction: interstitial/perivascular histiocytic infiltration in the superficial dermis with mucin deposition and piecemeal fibre fragmentation. Half of the cases show atypical lymphocytes, which is characteristic of IGDR. An interstitial granulomatous reaction is also seen in IGD with arthritis/plaques,[6] interstitial GA, and cutaneous borreliosis.[7] In IGD, histiocytic infiltration throughout the reticular dermis, and severe collagen degeneration resembling 'flame figures' can be observed.[6] In interstitial GA, vacuolar degeneration is absent, and complete collagen necrobiosis is demonstrated.[6] Atypical or overlapping cases between these disorders have also been reported recently.[8,9] Taking these into consideration, the concept has been proposed that IGDR may manifest as variable pathological findings.[8,10]

In our case, the clinical course and the provocation test strongly suggest IGDR. Pathologically, mucin deposition and histiocytic infiltration were deeper than in typical IGDR. Taking these factors and previous reports into consideration, we suppose that IGDR may cover a wider pathological range, from GA-like to IGD-like, with the clinical features of drug-induced eruptions, that remits rapidly after discontinuation of the causative drug.

In conclusion, sennoside is generally believed to be a safe agent because of its natural origin. Thus, patients tend to use it frequently and persistently as self-medication for constipation. We should recognize that sennoside can cause dermatological side-effects including IGDR.

Department of Dermatology, Y. FUJITA
Hokkaido University Graduate School T. SHIMIZU
of Medicine, North 15 West 7, H. SHIMIZU
Kita-ku, Sapporo 060-8638, Japan
E-mail: michiki@med.hokudai.ac.jp

References

1 Steer HW, Colin-Jones DG. Melanosis coli: studies of the toxic effects of irritant purgatives. *J Pathol* 1975; **115**: 199–205.
2 van Gorkom BAP, Karrenbeld A, van der Sluis T *et al.* Influence of a highly purified senna extract on colonic epithelium. *Digestion* 2000; **61**: 113–20.
3 Sitzmann FC, Büttner M, Dockter G. Lokale Nebenwirkungen an der Haut durch Anthraglykoside. *Pediatr Prax* 1979; **21**: 355–8.
4 Toshitani S, Koga T, Nonaka Y. A case of urticaria-like drug eruption induced by sennoside (laxative). *Allergol Immunol* 1998; **5**: 206–9 (in Japanese).
5 Magro CM, Crowson AN, Schapiro BL. The interstitial granulomatous drug reaction: a distinctive clinical and pathological entity. *J Cutan Pathol* 1998; **25**: 72–8.
6 Aloi F, Tomasini C, Pippione M. Interstitial granulomatous dermatitis with plaques. *Am J Dermatopathol* 1999; **21**: 320–3.
7 Morneo C, Kutzner H, Palmedo G *et al.* Interstitial granulomatous dermatitis with histiocytic pseudorosettes: a new histopathologic pattern in cutaneous borreliosis. Detection of *Borrelia burgdorferi* DNA sequences by a highly sensitive PCR-ELISA. *J Am Acad Dermatol* 2003; **48**: 376–84.
8 Perrin C, Lacour JP, Castanet J, Michiels JF. Interstitial granulomatous drug reaction with a histological pattern of interstitial granulomatous dermatitis. *Am J Dermatopathol* 2001; **23**: 295–8.
9 Lim AC, Hart K, Murrell D. A granuloma annulare-like eruption associated with the use of amlodipine. *Australas J Dermatol* 2002; **43**: 24–7.
10 Lee MW, Choi JH, Sung KJ *et al.* Interstitial and granulomatous drug reaction presenting as erythema nodosum-like lesions. *Acta Derm Venereol (Stockh)* 2002; **82**: 473–4.

Near-fatal anaphylaxis to patent blue V

DOI: 10.1111/j.0007-0963.2004.05931.x

SIR, Sentinel lymph node biopsy, a standard procedure in the staging of melanoma and breast cancer, requires preoperative visualization with radioactive colloids and/or the dye patent blue V or its derivative isosulfan blue (Fig. 1). These blue dyes cause hypersensitivity reactions in 1–2% of cases.[1] The symptoms are usually mild and include erythema, hives, urticaria and angio-oedema. Severe reactions such as pulmonary oedema, hypotension and vascular collapse are rare,[1] and no fatalities have been reported.

A woman was referred for revision with a 2-cm margin of a superficial spreading melanoma (Clark level III, Breslow thickness 1·8 mm). A sentinel lymph node biopsy under general anaesthesia was planned for the same surgical session. Ten minutes following the intraoperative, intradermal injection of 0·5 mL 0·5% patent blue V (Guerbet, Roissy, France) around the primary melanoma, a severe anaphylactic reaction occurred. Within minutes, there occurred generalized urticaria followed by a life-threatening drop in blood

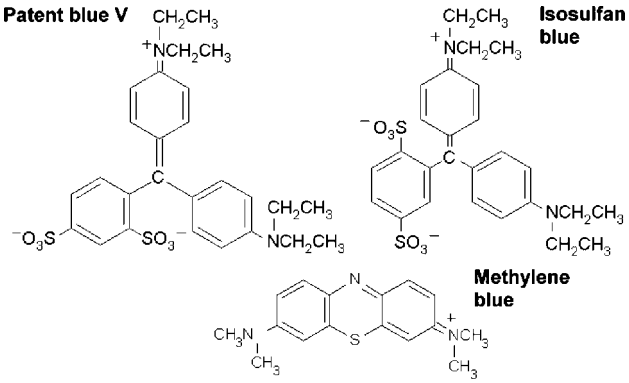

Figure 1. Structural formulae of patent blue V, isosulfan blue and methylene blue. From http://www.sigmaalrich.com (cited 30 July 2003).

pressure and severe bronchial spasms rapidly leading to cardiac arrest. After 10 min of mechanical cardiopulmonary resuscitation and the rapid intravenous administration of fluid, adrenaline and prednisolone, a sinus rhythm was re-established. The operation was terminated. The patient recovered without any neurological sequelae. Three weeks later, the revision was completed under local anaesthesia without further complications. The diagnostic sentinel lymph node biopsy was omitted for safety reasons.

The patient had a negative history for allergic diseases. Total IgE and serum tryptase were normal. Skin prick tests and RAST/CAP™ (Pharmacia Diagnostics, Vienna, Austria) for aeroallergens and latex as well as intradermal tests to the surgical premedication midazolam gave negative results. All other drugs used during the incident were subsequently well tolerated. Experimental radioallergosorbent tests (kindly performed by Pharmacia Diagnostics) to patent blue V and isosulfan blue (Tyco Healthcare, Bedford, MA, U.S.A.) detected no IgE antibody-binding activity. Enzyme-linked immunosorbent assay (ELISA) tests were performed to both dyes. Briefly, plates coated with 100 μg mL^{-1} dye and blocked with 1% gelatine were covered with sera at 1 : 10 dilution. Measurements were made following 3 h exposure to $1 : 10^3$ diluted alkaline phosphatase–antihuman IgE antibody. ELISAs to both dyes were positive, whereas they were negative in eight controls (Fig. 2). We performed *in vivo* skin testing under emergency conditions because of the intensity of the initial incident. Upon intradermal testing, the patient developed a 1·2-cm weal to both dyes diluted at $1 : 10^4$, but had no systemic side-effects.

The mechanism underlying anaphylaxis to sulfa dyes is unclear. Positive skin tests could either be caused by direct mast cell activation or by cross-linking of specific IgE antibodies. Evidence for the involvement of specific IgE was missing.[2] A single old report suggested an immunological mechanism in a passive transfer test.[3] The ELISA (Fig. 2) demonstrating IgE binding may suggest an IgE-mediated mechanism, i.e. allergy to patent blue V *sensu strictu*.