

removed from the peripheral blood of the patients. One round of cytopheresis removed approximately  $3.9 \times 10^9$  WBC from approximately 2000 mL blood. Short-term rapid removal of leukocytes from peripheral blood may cause some kind of alteration of phenotype, particularly the expression of the homing receptors of leukocytes to the skin, such as leukocyte adhesion molecule (LCAM)-1.<sup>8</sup> Furthermore, IL-8, a potent leukocyte chemotactic agent, which is mainly produced by monocytes, is overexpressed in PG ulcers;<sup>1</sup> however, the serum level of IL-8 did not increase in our case. LCAP using both leukocyte-absorbing filter and CCS may be more effective than GCAP alone, because the former can remove not only granulocytes but also IL-8-producing monocytes.<sup>5</sup> The clinical efficacy of LCAP using CCS was equivalent to that of LCAP using leukocyte-absorbing filter in the treatment of IBD, but its efficacy in the treatment of PG remains to be investigated.<sup>8</sup>

In conclusion, LCAP using CCS can serve as an important and new treatment option for patients with steroid and immunosuppressant-resistant PG, and the efficacy of this treatment is similar to that of GCAP or LCAP using a leukocyte-absorbing filter.

Takaaki HANAFUSA,<sup>1</sup> Hiroaki AZUKIZAWA,<sup>1</sup>  
Noriko UMEGAKI,<sup>1</sup> Mamori TANI,<sup>1</sup>  
Yuji YAMAGUCHI,<sup>2</sup> Ichiro KATAYAMA<sup>1</sup>

<sup>1</sup>Department of Dermatology, Osaka University Graduate School of Medicine, Osaka, and <sup>2</sup>Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

## REFERENCES

- 1 Ruocco E, Sangiuliano S, Gravina AG, Miranda A, Nicoletti G. Pyoderma gangrenosum: an updated review. *J Eur Acad Dermatol Venereol* 2009; **23**: 1008–1017.
- 2 Callen JP. Pyoderma gangrenosum. *Lancet* 1998; **351**: 581–585.
- 3 Kanekura T, Maruyama I, Kanzaki T. Granulocyte and monocyte adsorption apheresis for pyoderma gangrenosum. *J Am Acad Dermatol* 2002; **47**: 320–321.
- 4 Fujimoto E, Fujimoto N, Kuroda K, Tajima S. Leukocytapheresis treatment for pyoderma gangrenosum. *Br J Dermatol* 2004; **151**: 1090–1092.
- 5 Kohgo Y, Hibi H, Chiba T *et al*. Leukocyte apheresis using a centrifugal cell separator in refractory ulcerative colitis: a multicenter open label trial. *Ther Apher* 2002; **6**: 255–260.
- 6 Hidaka T, Suzuki K, Matsuki Y *et al*. Filtration leukocytapheresis therapy in rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 1999; **42**: 431–437.
- 7 Miller FW, Leitman SF, Cronin ME *et al*. Controlled trial of plasma exchange and leukapheresis in polymyositis and dermatomyositis. *N Engl J Med* 1992; **326**: 1380–1384.
- 8 Kohgo Y, Ashida T, Maemoto A, Ayabe T. Leukocytapheresis for treatment of IBD. *J Gastroenterol* 2003; **38**(Suppl 15): 51–54.
- 9 Rembacken BJ, Newbould HE, Richards SJ *et al*. Granulocyte apheresis in inflammatory bowel disease: possible mechanisms of effect. *Ther Apher* 1998; **2**: 93–96.
- 10 Sawada K, Ohnishi K, Kosaka T *et al*. Leukocytapheresis with leukocyte removal filter as new therapy for ulcerative colitis. *Ther Apher* 1997; **1**: 207–211.

## Rosacea (erythematotelangiectatic type) effectively improved by topical xylometazoline

Dear Editor,

Rosacea is a common chronic cutaneous disorder that primarily occurs on the convex surfaces of the central face and is often characterized by exacerbations and remissions.<sup>1</sup> Erythematotelangiectatic type rosacea, characterized by centofacial erythema

occasionally with telangiectasias, is one of the most common types of rosacea in patients of Korean descent. A number of medications, including metronidazole, sodium sulfacetamide with sulfur, azelaic acid gel, oral tetracycline and isotretinoin, have been used in various combinations to treat rosacea. However,

Correspondence: Sung Ku Ahn, M.D., Ph.D., Department of Dermatology, Yonsei University Wonju College of Medicine, 162 Ilsan-Dong, Wonju 220-701, Korea. Email: skin@yonsei.ac.kr

these treatments are less effective in the erythematotelangiectatic type than in the papulopustular type of rosacea. Reported here is a case of erythematotelangiectatic type rosacea which was controlled by topical application of xylometazoline 0.05%, with a brief review of the relevant published work.

A 61-year-old postmenopausal woman presented with a history of several months of moderate centrofacial erythema. She complained of multiple episodes of flushing with occasional pruritus in the erythematous area. She was diagnosed with rosacea in a pri-

vate clinic prior to presentation and had been treated with a topical application of metronidazole and p.o. administration of minocycline for several months. In addition, two rounds of laser treatment with intense pulsed light were not effective. Physical examination revealed diffuse erythema with telangiectasias in the centrofacial area, including both cheeks. There were no definite papules or pustules noted. These findings were more prominent on cross-polarizing photographs (Fig. 1a). Laboratory studies, including complete blood cell count, blood chemistry, anti-nuclear



**Figure 1.** Baseline cross-polarizing photographs of the patient immediately prior to application of xylometazoline 0.05% solution (a) and 3 h after topical application (b), demonstrating improvement in macular erythema and fine telangiectasias.

antibody and thyroid function tests, were within normal limits, except a total cholesterol level of 275 mg/dL (normal <200), a triglyceride level of 240 mg/dL (normal <200) and an alanine aminotransferase level of 46 U/L (normal <35). On the basis of medical history and clinical findings, the patient was diagnosed with erythematotelangiectatic type rosacea. We prescribed Otrivin (xylometazoline) (Novartis, Sweden) 0.05% (0.5 mg/mL), which possesses vasoconstrictive effects. She was instructed to apply this solution 0.5 mL/day to both cheeks after washing without any other cosmetics. Three hours after application of xylometazoline 0.05% (0.5 mg/mL), the skin lesions had significantly improved (Fig. 1b) and subjective symptoms such as flushing and itching were also reduced. These improvements persisted for hours following application. Eight months after initiating daily application of xylometazoline, her facial erythema and telangiectasias were significantly reduced, and the patient suffered no side-effects related to the medication.

While the pathogenesis of rosacea remains unknown, several factors have been implicated, including inherent abnormalities in cutaneous vascular homeostasis and thermal dysregulation. There are various cutaneous signs of rosacea such as flushing, erythema, telangiectasias, edema, papules and pustules. Among them, persistent erythema and abnormal flushing have been known to arise from abnormalities in cutaneous vascular homeostasis triggered by many factors such as neurogenic, hormonal, thermal and topical stimuli.<sup>2,3</sup> The complex regulation of cutaneous vascular circulation is mediated by systemically and locally excreted catecholamines. There are two types of adrenergic receptors that modulate cutaneous vascular responses to catecholamines.<sup>4</sup> One is the  $\alpha$ -adrenergic receptor, activation of which causes vasoconstriction. The other is the  $\beta$ -adrenergic receptor, which antagonizes the actions of the  $\alpha$ -receptor, causing vasodilation. In *in vivo* and *in vitro* studies, contraction of peripheral vascular smooth muscle was primarily mediated by  $\alpha_{1A}$ - and  $\alpha_{1D}$ -receptors, which are two subtypes of  $\alpha$ -adrenergic receptors.<sup>5-7</sup> In studies of the actions of the  $\alpha_2$ -receptor subtypes,  $\alpha_{2A/D}$ - and  $\alpha_{2B}$ -receptors are responsible for the contraction of the arterial component, while  $\alpha_{2A/D}$ - and  $\alpha_{2C}$ -receptors regulate contraction of the venous component.<sup>5-7</sup>

Xylometazoline is one of the imidazoline-type sympathomimetic agonists. It acts as a highly selective agonist for the  $\alpha_{1A}$ -adrenergic receptor and is also partially selective for the  $\alpha_{2A}$ -adrenergic receptor that produces vasoconstrictive effects. Worldwide, there are multiple preparations containing xylometazoline. Two xylometazoline preparations, 0.1% (1 mg/mL) and 0.05% (0.5 mg/mL), are commercially available in Korea. These have been shown to reduce erythema, edema and congestion through the vasoconstrictive properties of the medication when applied to the skin and mucosa. Xylometazoline has been prescribed for the treatment of allergic rhinitis to reduce congestion of nasal mucosa due to the same properties. In addition, there have been reports of treatment of ocular hypertension and glaucoma using selective  $\alpha_{2A}$ -adrenergic receptor agonists. However, there have been few reports of using adrenergic receptor agonists in the dermatological field, especially in the treatment of rosacea.<sup>8</sup>

As mentioned above, one possible mechanism of the therapeutic effects of xylometazoline in the erythematotelangiectatic type of rosacea is due to the vasoconstrictive properties of this medication. In addition, recent studies have demonstrated that several  $\alpha$ -adrenergic receptor agonists also have anti-inflammatory properties. In upper respiratory tract infections, oxymetazoline and xylometazoline have been shown to reduce the levels of pro-inflammatory cytokines by inhibiting the migration of neutrophils and the oxidative burst of phagocytes.<sup>9</sup> Moreover, oxymetazoline affects arachidonic acid metabolism and reduces leukotriene B<sub>4</sub>.<sup>9</sup> These results suggest that reducing inflammation may be another therapeutic mechanism of xylometazoline in erythematotelangiectatic type rosacea.

There are some side-effects related to the long-term use of  $\alpha$ -adrenergic receptor agonists on the nasal mucosa. Tachyphylaxis caused by desensitization is a well-known side-effect of these medications. Another complication of treatment is a rebound phenomenon that produces vasodilation with recurrent flushing.<sup>8</sup> In the general population, the incidences of tachyphylaxis and rebound phenomenon were increased with increased duration of treatment and a larger cumulative dose of the medication.<sup>10</sup> Fortunately, in this case, neither of these adverse effects were observed during the 8-month

treatment period. In addition, there were no other side-effects related to the medication. Further investigations with larger numbers of subjects and a longer follow-up period are needed to evaluate the efficacy of xylometazoline in erythematotelangiectatic type rosacea.

In summary, we report a case of a 61-year-old woman who presented with moderate, centropacial erythema with telangiectasias, which was controlled by topical application of xylometazoline solution once a day. This case study demonstrates that topical application of  $\alpha$ -adrenergic receptor agonists could be a new treatment option for the erythematotelangiectatic type of rosacea.

Jae-Hong KIM,<sup>1</sup> Yoon Seok OH,<sup>1</sup> Jae Hong JI,<sup>1</sup>  
Hana BAK,<sup>2</sup> Sung Ku AHN<sup>1,3</sup>

<sup>1</sup>Department of Dermatology and

<sup>3</sup>Institute of Basic Medical Science, Yonsei University  
Wonju College of Medicine, Wonju, and <sup>2</sup>Asan Medical Center,  
University of Ulsan College of Medicine, Seoul, Korea

## REFERENCES

- 1 Wilkin J, Dahl M, Detmar M *et al*. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *J Am Acad Dermatol* 2002; **46**: 584–587.
- 2 Crawford GH, Pelle MT, James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. *J Am Acad Dermatol* 2004; **51**: 327–341. (quiz 342–4)
- 3 Pelle MT, Crawford GH, James WD. Rosacea: II. Therapy. *J Am Acad Dermatol* 2004; **51**: 499–512. (quiz 513–4)
- 4 Ahlquist RP. The adrenotropic receptor-detector. *Arch Int Pharmacodyn Ther* 1962; **139**: 38–41.
- 5 Guimaraes S, Moura D. Vascular adrenoceptors: an update. *Pharmacol Rev* 2001; **53**: 319–356.
- 6 Civantos Calzada B, Aleixandre de Artinano A. Alpha-adrenoceptor subtypes. *Pharmacol Res* 2001; **44**: 195–208.
- 7 Leech CJ, Faber JE. Different alpha-adrenoceptor subtypes mediate constriction of arterioles and venules. *Am J Physiol* 1996; **270**: H710–H722.
- 8 Shanler SD, Ondo AL. Successful treatment of the erythema and flushing of rosacea using a topically applied selective alpha1-adrenergic receptor agonist, oxymetazoline. *Arch Dermatol* 2007; **143**: 1369–1371.
- 9 Beck-Speier I, Dayal N, Karg E *et al*. Oxymetazoline inhibits proinflammatory reactions: effect on arachidonic acid-derived metabolites. *J Pharmacol Exp Ther* 2006; **316**: 843–851.
- 10 Graf P. Long-term use of oxy- and xylometazoline nasal sprays induces rebound swelling, tolerance, and nasal hyperreactivity. *Rhinology* 1996; **34**: 9–13.

## Erysipelas-like erythema with familial Mediterranean fever

Dear Editor,

Familial Mediterranean fever (FMF) is an autosomal recessive disease, characterized by recurrent and self-limited attacks of fever and peritonitis, pleuritis, arthritis or erysipelas-like skin disease. These attacks are usually short-lived and subside within 24–72 h.<sup>1</sup>

Cutaneous manifestations in FMF were noted in 25–47% of cases in different reports.<sup>1,2</sup> Diffuse erythema of the face and/or trunk, angioneurotic edema, diffuse erythema of the palms and soles followed by mild desquamation of the skin, pyoderma, Raynaud's

phenomenon and subcutaneous nodules are non-specific skin problems seen in FMF.<sup>1–3</sup> Vasculitic skin lesions related to Henoch–Schönlein purpura and polyarteritis nodosa can also occur.<sup>1,4</sup> Erysipelas-like erythema (ELE) is an unusual but well-known and pathognomonic skin manifestation of FMF.<sup>3</sup> Lesions are characterized by tender, erythematous plaques, usually located on the joints, lower legs and dorsal aspect of the feet. They may be triggered by physical effort and subside spontaneously within 48–72 h of bedrest. Fever, arthritis and leukocytosis may accompany this condition.

Correspondence: Fatma Aydin, M.D., Ondokuz Mayıs University School of Medicine, Department of Dermatology, TR-55139 Kurupelit, Samsun, Turkey. Email: bennet@mynet.com