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CASE REPORT

Venous insufficiency in patients with necrobiosis lipoidica

Takeshi NAKAJIMA[1], Atsushi TANEMURA[2], Shigeki INUI[1], Ichiro KATAYAMA[2]

Departments of [1]Regenerative Dermatology and [2]Department of Dermatology, Graduate School of Medicine, Osaka University, Osaka, Japan

ABSTRACT

The pretibial area is the most frequently affected site in necrobiosis lipoidica (NL), but proposed mechanisms of NL cannot fully explain this high frequency. Although a few case reports indicate NL patients are complicated with venous insufficiency, no accurate assessment of the relationship between these two conditions has been performed. By using color Doppler ultrasonographic screening of four NL patients for venous insufficiency, we detected venous insufficiency in at least one leg of each patient. NL lesions were observed on all legs with venous insufficiency, and laboratory examination findings revealed that all the patients had hypercholesterolemia. The skin lesions did not respond satisfactorily to 6-month use of anticholesterolemic medication and elastic stockings. However, these results indicate that both hyperlipidemia and venous reflux, in addition to other pathogenic factors, can trigger tissue damage in the lower legs and lead to the onset of NL.

Key words: hyperlipidemia, necrobiosis lipoidica, venous insufficiency.

INTRODUCTION

Necrobiosis lipoidica (NL) was first described as sharply demarcated yellow-brown plaques on the anterior pretibial region in diabetic patients.[1] Previous reports indicated diabetes or glucose intolerance was detected at the time of diagnosis in two-thirds of NL cases, while a recent study revealed only 11% had diabetes mellitus.[2] At present, therefore, it seems unlikely that one metabolic condition is sufficient for the onset of NL. Many reported cases had backgrounds of aberrant conditions, including diabetic microangiopathy, lipid disorders, collagen abnormalities, abnormal leukocyte function and abnormal immune mechanisms.[3] However, these pathogenic mechanisms cannot explain the pretibial preference of the disease. One case study reported the effectiveness of hyperbaric oxygen therapy for refractory NL,[4] indicating that hypoxic status of the lesion is causative for the prolonged course of the disease. As venous insufficiency of the lower legs causes stasis, leading to local hypoxia, we assumed it may also contribute to the refractory clinical course of the disease in the pretibial region. For this report, we examined metabolic conditions and venous insufficiency in four NL patients at our clinic.

CASE REPORT

All four patients were woman aged 52–62 years. Patients' backgrounds are shown in Table 1. Physical and laboratory examinations revealed that all the patients had hypercholesterolemia and that none of them had diabetes mellitus or stasis-related skin conditions, including stasis dermatitis, sclerosing panniculitis and leg ulcer. All NL lesions were observed only on the lower legs, bilaterally in three patients. Clinical findings of all the lesions showed the indurated and atrophic plaques with a brownish periphery and yellow-brownish center (Fig. 1). Histological analysis of biopsy specimens obtained from three of the patients showed widespread necrobiosis

Correspondence: Takeshi Nakajima, M.D., Ph.D., Department of Regenerative Dermatology, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka, Japan. Email: nakajima@r.derma.med.osaka-u.ac.jp

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Table 1. Clinical backgrounds and contrast of skin lesion and venous insufficiency

	Case 1	Case 2	Case 3	Case 4
Age	61	62	52	52
Sex	Female	Female	Female	Female
Duration of the NL lesion(s)	1 year	3 years	3 years	10 years
Past history	n.p.	Thyroid adenoma and rectal cancer	n.p.	n.p.
Local trauma on the pretibial area before the onset of NL	n.p.	Abraded wound by motorcycle accident	Occasional minor trauma	n.p.
Previous treatment(s) to the NL lesions	Topical emollients application	Topical corticosteroid injection	PUVA	Topical steroid ointment application
Location and comparison of the size of NL lesions at first visit	Bilateral shins (rt > lt)	Bilateral shins (rt < lt)	Bilateral shins (rt = lt)	Right shin
Detected venous insufficiencies	Right GSV	Right GSV	Bilateral GSV	Right SSV and Cockett perforator
Serum glucose (mg/dl)	100	111		85
Serum HbA1c (%)	5.3	5.2	5.1	4.9
Serum total cholesterol (mg/dl)	265	237	271	279
Serum triglyceride (mg/dl)	69	118	162	235

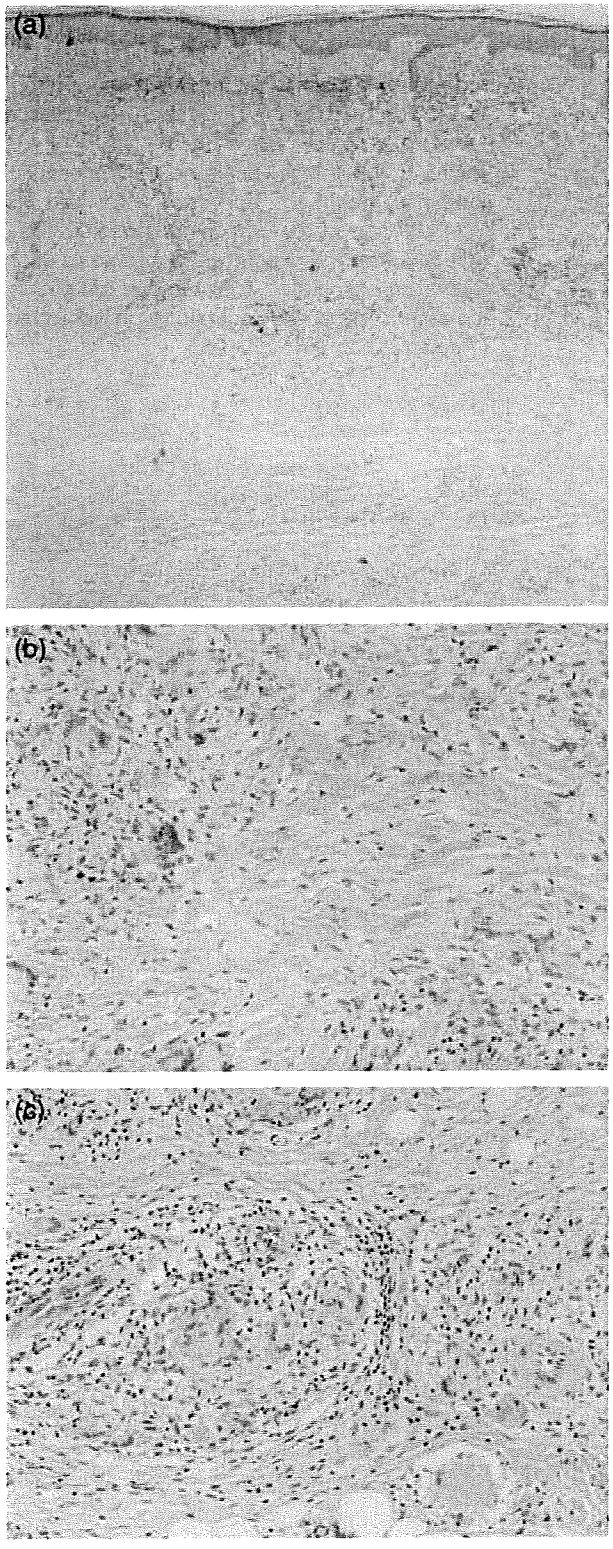
Underline indicates the laboratory data are above the normal limits. GSV, great saphenous vein; HbA1c, hemoglobin A1c; lt, left; NL, necrobiosis lipoidica; n.p., nothing particular; rt, right; SSV: small saphenous vein.

Figure 1. Well demarcated brownish peripheral and yellow-brownish to whitish centered shiny plaques on the shins of case 2. The larger lesion is observed on the left lower leg, while great saphenous vein reflux was detected only in the right leg.

with less inflammatory cells in cases 1 and 3, while conspicuous granuloma and giant cell infiltrate were evident in the reticular dermis of case 2 (Fig. 2).

Venous insufficiency was evaluated with color Doppler ultrasonography (US). As shown in Table 1, US demonstrated that cases 1 and 2 had venous insufficiency only in their right legs, while NL lesions appeared on the bilateral shins. There was larger NL plaques on the right shin in which great saphenous vein (GSV) reflux was detected in case 1. In contrast, case 2 had a larger lesion on the side opposite to the one with detectable venous insufficiency. In cases 3 and 4, venous insufficiency was detected in the same legs as the ones with the NL lesions. Although venous insufficiency was detected in the right small saphenous vein (SSV) and Cockett perforator, but not in the GSV in case 4, no clinically significant difference with the other cases was observed including the pretibial location of the NL lesions.

Three patients were advised to use elastic stockings and they were started on antihyperlipidemic medication. After 6 months, serum cholesterol level



was normalized and stiffness of the lower legs was alleviated, but no satisfactory effect on the sclerotic skin lesion was observed. Further treatments were started only for case 2. Psoralen plus ultra violet A (PUVA) treatment (cumulative UV-A dose, 15.8 J/cm^2) was not effective either clinically or histologically, but monthly topical injection of 13.3 mg triamcinolone acetonide had some effects on the sclerosis and elevation of the lesion.

DISCUSSION

This report presented four cases of NL. While none of the patients had diabetes mellitus, all of them had hypercholesterolemia and venous insufficiency in either or both of the legs. An association between NL and hyperlipidemia has been reported in the published work.[5,6] Although one of these reports suggested lipid deposition in tissue leads to the onset of NL, this cannot explain why NL is frequently seen on the pretibial region. Skin conditions related to venous insufficiency, including sclerosing panniculitis and stasis ulcer, are commonly seen in lower extremities. Some reports have also suggested that there is a relationship between venous insufficiency and NL.[7,8] As all our four cases had venous insufficiency and hypercholesterolemia, we presumed that both hyperlipidemia and venous reflux, in addition to other pathogenic factors, triggered tissue damage in the lower legs to lead the onset and the refractory clinical course of NL. However, no clinical or locational difference was observed among the NL lesions with reflux in GSV or SSV and the lesions without venous insufficiency. To elucidate the relationship between NL and venous insufficiency or hyperlipidemia and to assess the therapeutic response to the use of elastic stockings or phlebo-

Figure 2. Histological examination of the skin biopsy specimen from case 1 (a) and case 2 (b,c). (a) The epidermis is unaffected. Eosinophilic swollen or degenerate collagen is surrounded by inflammatory infiltrate in the reticular dermis. Degeneration of collagen and sclerosis are extensive in the lower dermis (HE stain, original magnification ×10). (b) The degenerate collagen is surrounded by histiocytes intermingled with multinucleate giant cells (HE stain, original magnification ×100). (c) Well-defined non-caseating granulomata are conspicuous particularly in the lower dermis (HE stain, original magnification ×100).

surgery and antihyperlipidemic medication in combination with other treatments, more NL patients should be screened for the presence of stasis of the lower legs and abnormal lipid metabolism.

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Intractable Wounds Caused by Pyoderma Gangrenosum in a Patient with Critical Limb Ischemia Treated with Cyclosporine and Adjuvant Sympathectomy

Yuji Takahashi, MD,* Yuji Yamaguchi, MD, PhD,*† Koichi Itoh, MD, PhD,* Shigetoshi Sano, MD, PhD,* Akimichi Morita, MD, PhD,† and Ichiro Katayama, MD, PhD*

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Intractable wounds are caused by extrinsic factors[1] (e.g., burns, trauma, pressure sores, radiation ulcers, contact dermatitis); arterial insufficiency secondary to arteriosclerosis obliterans,[2] Buerger's disease (thromboangiitis obliterans), collagen diseases,[3] vasculitis, diabetes mellitus,[4] and calciphylaxis or calcific uremic arteriolopathy;[5] venous insufficiency secondary to stasis dermatitis, varicose veins, and deep venous thrombosis; neural factors (spina bifida, diabetes mellitus); severe infections (aerobic and anaerobic bacteria, fungi, acid-fast bacilli, virus[6]); malignancies (amelanotic melanoma, squamous cell carcinoma, basal cell carcinoma, angiosarcoma, B cell lymphoma, epithelioid sarcoma); and other conditions related to diseases peculiar to dermatology, including pyoderma gangrenosum and bullous diseases. Although most intractable wounds are relatively easy to diagnose macroscopically, the combination of those risk factors may mask important factors underlying the true nature of the disease. We recently experienced a case of intractable ulcers that showed different clinical courses between the medial (Figure 1) and lateral (Figure 2) sites on the left lower leg of a patient with diabetes mellitus. The medial ulcers were caused by pyoderma gangrenosum and a methicillin-resistant *Staphylococcus aureus* (MRSA) infection, whereas in addition to those two factors, arterial insufficiency secondary to an arteriovenous fistula and steroid-induced diabetes mellitus caused the lateral ulcers. The ischemic characteristics were totally masked because of the irregular, boggy, blue-red ulcers with undermined borders surrounding a purulent necrotic base, characteristic of pyoderma gangrenosum.

Case Report

A 62-year-old man with a past history of bad teeth, hemorrhoids, and cigarette smoking for 43 years had pyoderma gangrenosum treated with 5 mg/day (d) of prednisolone and 75 mg/d of diaminodiphenylsulphone for 12 years on his left lower leg and steroid-induced diabetes mellitus treated with insulin for 10 years. The patient was admitted to our hospital on February 8, 2006, because the chronic, painful wounds with irregular borders on his left lower leg were refractory to local wound care, and prednisolone had been increased to 20 mg/d since October 18, 2005. The clinical appearances of the medial (Figure 1A) and lateral (Figure 2A) wound sites of his leg were similar, with no edematous swelling on admission.

The results of laboratory examination revealed a white blood cell count of $9.6 \times 10^3/\mu L$; C-reactive protein of 12 mg/L; erythrocyte sedimentation rate of 22 mm/hour; fasting plasma glucose of 280 mg/dL; hemoglobin A1c 7.6%; platelet factor

Department of Dermatology, Osaka University Graduate School of Medicine, Osaka, Japan; †Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
The first two authors contributed equally to this study.

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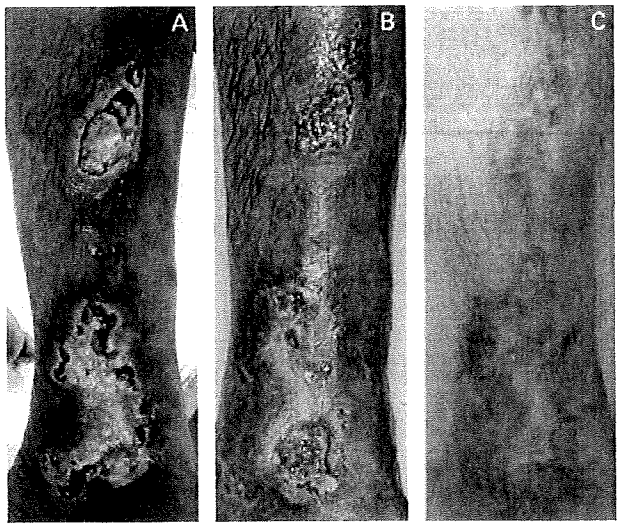

Figure 1. Clinical course of left medial lower leg ulcers. A 62-year-old male patient showed irregular and boggy ulcers on admission (A). Cyclosporine for 3 weeks was effective (B) in healing the wounds (C).

4 of 27 ng/mL; ß-thromboglobulin of 76 ng/mL; soluble interleukin-2 receptor of 511 U/mL; high neutrophil migration in response to classic chemoattractants, indicating the inflammation, uncontrolled diabetes mellitus, and activation of platelets and neutrophil activities. The patient had the HLA-B51 major histocompatibility type with inflammatory bowel disease (and with pyoderma gangrenosum-like lesions) but did not satisfy the criteria for Behcet's disease because he did not show recurrent oral and genital ulcerations or have a positive pathergy test. Other laboratory tests, including antinuclear antibody and anticardiolipin antibody, were within normal limits. Culture results indicated MRSA and *Escherichia coli* infections. No venous insufficiency was detected using sonography. The results of a skin biopsy obtained from an ulcer

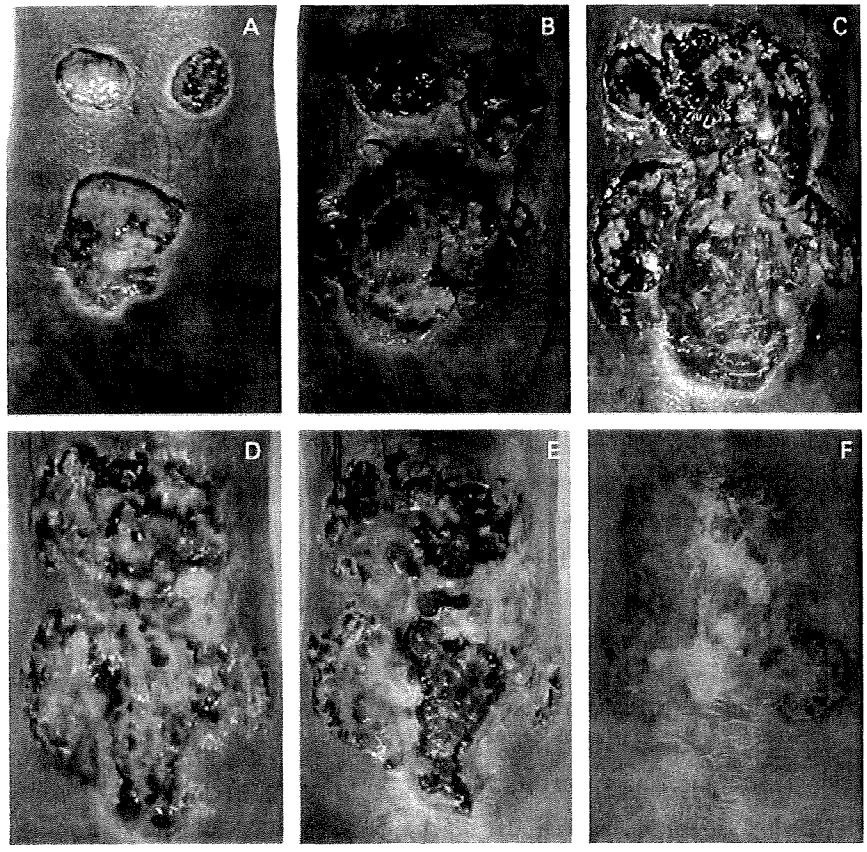

Figure 2. Clinical course of left lateral lower leg ulcers. A 62-year-old male patient showed ulcers with undermined borders surrounding purulent necrotic bases on admission that were similar to his medial wounds (A). Cyclosporine for 3 weeks exacerbated his ulcers (B), but the cessation of cyclosporine for 3 weeks did not improve his ulcers (C). Six days (D), 28 days (E), and 62 days (F) after a lumbar sympathetic nerve block in addition to cyclosporine treatment.

showed multifocal neutrophilic perivascular inflammation in the dermis without leukocytoclastic vasculitis or atypical cells.

We diagnosed his lower leg ulcers as pyoderma gangrenosum. From the clinical and pathological data, we could exclude intractable ulcers caused by rheumatic disease, including antiphospholipid syndrome, and by malignant tumors, including squamous cell carcinoma. We did not initially consider arterial insufficiency because his left posterior tibial artery was palpable at the medial malleolus; his toes and ulcers did not show any sign of ischemic changes; and previous angiography did not show any arterial obstruction caused by diabetes mellitus, arteriosclerosis obliterans, or Buerger's disease (thromboangiitis obliterans). In addition to the previous medication, we started local wound care, including topical application of tacrolimus ointment and intralesional triamcinolone. We used intravenous antibiotics for 1 week, after which we had to stop them because of renal failure (creatinine clearance 29 mL/min.). The ulcers increased in size and depth and were accompanied by severe resting pain, because his diabetic condition did not improve in spite of the increased use of sulfonylureas and insulin. We considered treatment with cyclosporine instead of increasing the dose of prednisolone or steroid pulse therapy and carefully monitored his creatinine clearance and trough level not to exceed 100 ng/mL. Oral medication with 100 mg/d (2 mg/kg/d) cyclosporine for 3 weeks resulted in an improvement of the medial site of the ulcers (Figure 1B), whereas his lateral wounds followed their natural course, with no further improvement (Figure 2B). The cessation of cyclosporine further deteriorated his lateral wounds (Figure 2C), suggesting its effectiveness for both sites of wounds, so cyclosporine was readministered up to 150 mg/d (3 mg/kg/mL). The medial wounds healed remarkably (Figure 1C).

Abrupt bleeding from his lateral wounds prompted us to reexamine the angiography (Figure 3) to exclude the possible involvement of a pathosis other than pyoderma gangrenosum and chronic infection.

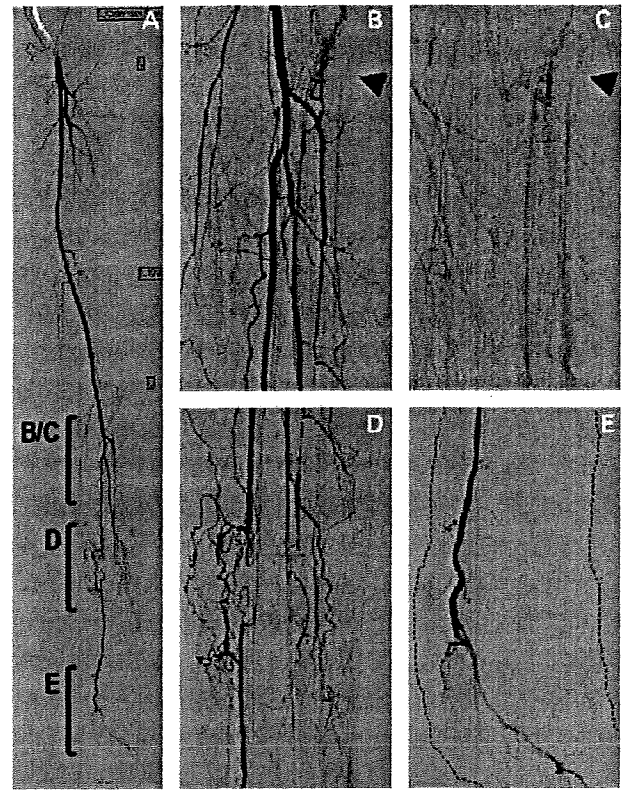

Figure 3. Angiographic images of the left femoral to arcuate artery. Normal femoral to popliteal artery (A). Arteriovenous shunt in anterior tibial artery by the arterial phase (B) and the venous phase (C). Corkscrew appearance in posterior tibial artery and peroneal artery (D). Total obstruction of the lateral site of the left lower leg, with dots indicating the outline (E).

The angiography showed a normal left femoral to popliteal artery (Figure 3A); an arteriovenous fistula in the left anterior tibial artery determined by the arterial phase (Figure 3B) and the venous phase (Figure 3C); a corkscrew appearance, which is commonly observed in Buerger's disease, in the left posterior tibial artery and the peroneal artery (Figure 3D); and total obstruction of the lateral site of his left lower leg (Figure 3E). Although the patient was a heavy cigarette smoker with typical angiographic images, he did not satisfy the criteria for Buerger's disease by Olin because he had steroid-induced diabetes mellitus.[7] This patient satisfied the criteria of critical limb ischemia according to TASC II (TransAtlantic Inter-Society Consensus) issued in 2007.[8] We concluded that the patient had developed critical limb ischemia associated with diabetes mellitus, heavy tobacco use, and arteriovenous fis-

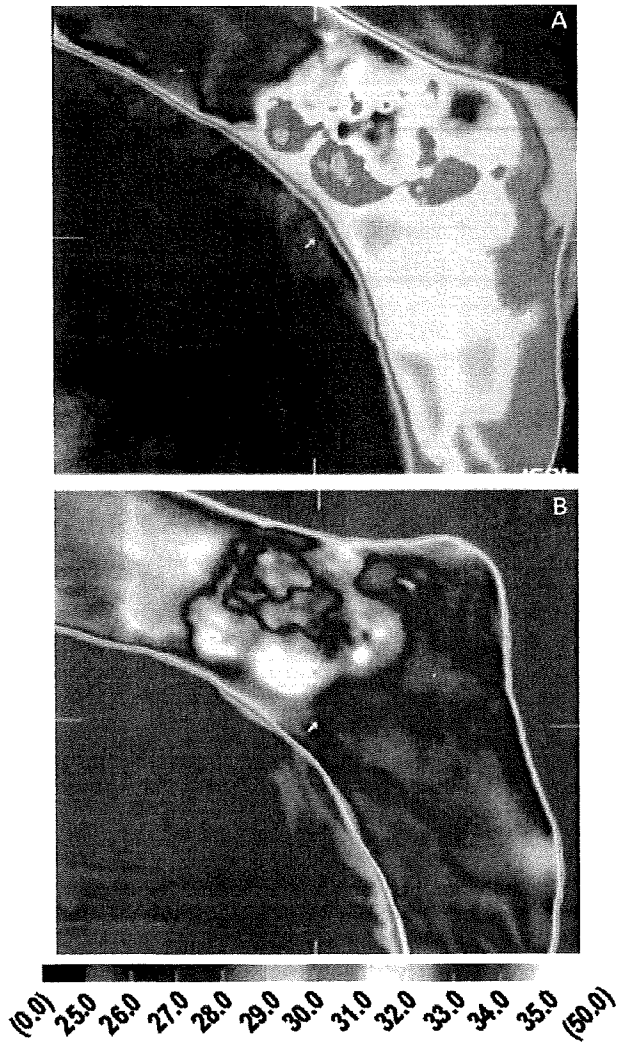

Figure 4. Thermographic images of left lateral lower leg ulcers before (A) and after (B) the lumbar sympathetic nerve block. More than 2°C up-regulation of local temperature was observed.

tula, and that is why the ulcers on the lateral aspect were extremely intractable to healing. We consulted a vascular surgeon and a radiologist, but this case had no indication for angioplasty, including bypass and stenting, respectively, because of the anatomical location of the arteries. We decided to treat his arterial insufficiency using a lumbar sympathetic ganglion block followed by a chemical sympathectomy,[9] which improved his resting pain and his blood supply according to thermography (Figure 4) and the reepithelialization (Figure 2D–F).

Discussion

Pyoderma gangrenosum is an inflammatory and ulcerative condition with an unknown etiology. It is characterized by irregular and boggy wounds with undermined necrotic borders and is related to inflammatory bowel disease, particularly ulcerative colitis,[10] as was detected in this case. The patient had been medicated with 5 mg/kg of prednisolone for 12 years, which resulted in diabetes mellitus with poor control of serum glucose levels because of the lack of consciousness of disease.

Diabetic foot ulcers are one of the most common limb-threatening wounds, with every effort being focused on the prevention of amputation. We previously reported on the usefulness of aggressive debridement until bone marrow cells are exposed in the wounds[3,4] to promote granulation tissue formation.[11] However, we did not apply that protocol to this patient because aggressive debridement is a contraindication for pyoderma gangrenosum and calcific uremic arteriolopathy.[5] As for his lateral ulcers, the blood supply was totally disrupted because of the ischemic steal syndrome caused by an arteriovenous fistula[12] in the anterior tibial artery (which was incurable with embolization) and of the obstruction of the peroneal artery and anterior tibial artery probably caused by diabetes mellitus and heavy cigarette smoking, which aggravates ischemic intractable wounds.[13] The angiographic findings were consistent with those observed in Buerger's disease, with corkscrew images in the posterior tibial artery and the peroneal artery.[14] This patient satisfied Shionoya's criteria for Buerger's disease,[15] because diabetes mellitus is not an exclusion criterion,[16] as it is for Olin's criteria.[7] Diabetic atherosclerosis is commonly observed below the popliteal artery,[17] with long occlusions.[18]

The causes of intractable wounds were multiple in the same site of the lower leg. Cyclosporine was effective in healing the lateral and medial sites of ulcers caused by the pyoderma gangrenosum and in stabilizing the steroid-induced diabetes mellitus. Tapering off the

steroid therapy and sympathetic nerve block (with xylocaine followed by ethanol) was effective in healing the lateral ulcers caused by arteriolopathy secondary to the heavy tobacco use, arteriovenous fistula, and diabetes mellitus, although the ulcers were clinically similar between the lateral and medial sites of the lower leg. The sympathetic nerve block was particularly effective in reducing the severe pain, enabling a mild debridement to remove the MRSA infection. The use of sympathectomy is recognized to treat ischemic ulcers caused by severe arterial diseases, considering its effectiveness and its relative noninvasiveness compared with vascular reconstruction.[19] We conclude that multidisciplinary approaches are sometimes required to avoid major amputations when seeing patients with intractable wounds.

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Address correspondence and reprint requests to: Yuji Yamaguchi, MD, PhD, Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, 1-Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan, or e-mail: yujin@ med.nagoya-cu.ac.jp

A randomized double-blind trial of intravenous immunoglobulin for pemphigus

Masayuki Amagai, MD,[a] Shigaku Ikeda, MD,[b] Hiroshi Shimizu, MD,[c] Hajime Iizuka, MD,[d] Katsumi Hanada, MD,[e] Setsuya Aiba, MD,[f] Fumio Kaneko, MD,[g] Seiichi Izaki, MD,[h] Kunihiko Tamaki, MD,[i] Zenro Ikezawa, MD,[j] Masahiro Takigawa, MD,[k] Mariko Seishima, MD,[l] Toshihiro Tanaka, MD,[m] Yoshiki Miyachi, MD,[n] Ichiro Katayama, MD,[o] Yuji Horiguchi, MD,[p] Sachiko Miyagawa, MD,[q] Fukumi Furukawa, MD,[r] Keiji Iwatsuki, MD,[s] Michihiro Hide, MD,[t] Yoshiki Tokura, MD,[u] Masutaka Furue, MD,[v] Takashi Hashimoto, MD,[w] Hironobu Ihn, MD,[x] Sakuhei Fujiwara, MD,[y] Takeji Nishikawa, MD,[a] Hideoki Ogawa, MD,[b] Yasuo Kitajima, MD,[z] and Koji Hashimoto, MD,[aa] for the Pemphigus Study Group

Tokyo, Sapporo, Asahikawa, Hirosaki, Sendai, Fukushima, Kawagoe, Yokohama, Hamamatsu, Ogaki, Ohtsu, Kyoto, Suita, Osaka, Kashihara, Wakayama, Okayama, Hiroshima, Kitakyusyu, Fukuoka, Kurume, Kumamoto, Yufu, Gifu, and Toon, Japan

Background: Pemphigus is a rare life-threatening intractable autoimmune blistering disease caused by IgG autoantibodies to desmogleins. It has been difficult to conduct a double-blind clinical study for pemphigus partly because, in a placebo group, appropriate treatment often must be provided when the disease flares.

Objective: A multicenter, randomized, placebo-controlled, double-blind trial was conducted to investigate the therapeutic effect of a single cycle of high-dose intravenous immunoglobulin (400, 200, or 0 mg/kg/d) administered over 5 consecutive days in patients relatively resistant to systemic steroids.

Methods: We evaluated efficacy with time to escape from the protocol as a novel primary end point, and pemphigus activity score, antidesmoglein enzyme-linked immunosorbent assay scores, and safety as secondary end points.

Results: We enrolled 61 patients with pemphigus vulgaris or pemphigus foliaceus who did not respond to prednisolone (≥20 mg/d). Time to escape from the protocol was significantly prolonged in the 400-mg group compared with the placebo group ($P < .001$), and a dose-response relationship among the 3 treatment groups was observed ($P < .001$). Disease activity and enzyme-linked immunosorbent assay scores were significantly lower in the 400-mg group than in the other groups ($P < .05$ on day 43, $P < .01$ on day 85). There was no significant difference in the safety end point among the 3 treatment groups.

From the Departments of Dermatology, Keio University School of Medicine, Tokyo[a]; Juntendo University School of Medicine, Tokyo[b]; Hokkaido University Graduate School of Medicine, Sapporo[c]; Asahikawa Medical College[d]; Hirosaki University School of Medicine[e]; Tohoku University Graduate School of Medicine, Sendai[f]; Fukushima Medical University[g]; Saitama Medical Center, Kawagoe[h]; University of Tokyo School of Medicine[i]; Yokohama City University Graduate School of Medicine[j]; Hamamatsu University School of Medicine[k]; Ogaki Municipal Hospital[l]; Shiga University of Medical Science, Ohtsu[m]; Kyoto University Graduate School of Medicine[n]; Osaka University Graduate School of Medicine, Suita[o]; Osaka Red Cross Hospital, Osaka[p]; Nara Medical University, Kashihara[q]; Wakayama Medical University[r]; Okayama University Graduate School of Medicine[s]; Hiroshima University Graduate School of Medicine[t]; University of Occupational and Environment Health, Kitakyusyu[u]; Kyushu University Graduate School of Medicine, Fukuoka[v]; Kurume University School of Medicine[w]; Faculty of Medical and Pharmaceutical Sciences, Kumamoto University[x]; Oita University Faculty of Medicine, Yufu[y]; Gifu University Graduate School of Medicine[z]; and Ehime University Graduate School of Medicine, Toon.[aa]

Other investigators in the Pemphigus Study Group are listed in the Appendix.

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Reprint requests: Koji Hashimoto, MD, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime 791-0295, Japan. E-mail: hashik@m.ehime-u.ac.jp.

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Limitation: Prednisolone at 20 mg/d or more may not be high enough to define steroid resistance.

Conclusion: Intravenous immunoglobulin (400 mg/kg/d for 5 d) in a single cycle is an effective and safe treatment for patients with pemphigus who are relatively resistant to systemic steroids. Time to escape from the protocol is a useful indicator for evaluation in randomized, placebo-controlled, double-blind studies of rare and serious diseases. (J Am Acad Dermatol 2009;60:595-603.)

Pemphigus is a life-threatening, rare intractable autoimmune blistering disease caused by IgG autoantibodies to desmoglein (Dsg) (epidermal adhesion factor). It is characterized by the development of blisters and erosions of the skin and mucosa.[1] Currently, oral steroids are the drugs of first choice for pemphigus, and may be used in combination with immunosuppressants or plasma exchange. However, many patients with pemphigus experience cycles of remission and recurrence, and accordingly become unresponsive to conventional therapy. On the other hand, patients with complications such as diabetes mellitus, gastrointestinal disease, osteoporosis, infection, or immunodeficiency are relatively contraindicated for use of high-dose (HD) steroids. For such patients, an alternative effective treatment strategy is required.

Although several reports suggesting the effectiveness of HD intravenous immunoglobulin (IVIG) in the treatment of pemphigus have been published since its introduction as monotherapy in 1989, most are case reports with a low evidence level or involved clinical research with a limited number of patients using multiple treatment cycles.[2] No well-controlled, double-blind clinical study to demonstrate the efficacy of HD-IVIG has been conducted.[3-13] This is because: (1) pemphigus is a rare intractable disease; (2) appropriate treatment must be provided in a timely manner if symptoms are aggravated or unchanged for a certain period of time; (3) inclusion of a placebo group compromises compliance with the study protocol; and (4) it is not ethical to treat patients with pemphigus using placebo because mortality is high.

We developed a novel evaluation end point to solve these problems and verified the usefulness of HD-IVIG in a single treatment cycle for this rare intractable disease.

Abbreviations used:

ADRs:	adverse drug reactions
Dsg:	desmoglein
HD:	high dose
IVIG:	intravenous immunoglobulin
PAS:	pemphigus activity score
PF:	pemphigus foliaceus
PV:	pemphigus vulgaris
TEP:	time to escape from the protocol

METHODS

Patients

This study was conducted in 27 medical institutions in Japan with affiliated dermatologists specialized in autoimmune blistering disease. Patients were given the diagnosis of pemphigus vulgaris (PV) or pemphigus foliaceus (PF) as confirmed based on our national diagnostic criteria as follows: pemphigus was diagnosed when at least one item from every 3 findings, or two items from clinical findings and one item from immunologic findings were satisfied.

1. Clinical findings
   - Multiple, easily rupturing, flaccid blisters of the skin
   - Subsequent progressive, refractory erosions or crust after blisters
   - Noninfectious blisters or erosions of visible mucosa including oral mucosa
   - Nikolsky sign
2. Histologic findings
   - Intraepidermal blisters caused by loss of adhesion between epidermal cells (acantholysis)
3. Immunologic findings
   - IgG (or complement) deposition in the intercellular spaces of the lesional or normal-appearing skin and mucosa as detected by direct fluorescent antibody assay
   - Antiepidermal intercellular IgG autoantibody (anti-Dsg IgG autoantibody) identified by indirect fluorescent antibody assay or enzyme-linked immunosorbent assay

The study patients had to meet all the following inclusion criteria and none of the exclusion criteria.

1. Inclusion criteria: patients aged 20 years or older who provided written informed consent to participate in the study and met all of the following criteria.

Table I. Criteria for pemphigus activity score

Variable score	Skin lesion area*	No. of new blisters/d	Oral mucosal lesions†
3	≥15%	≥5	≥30%
2	≥5% and <15%	1 to 4	≥5% and <30%
1	<5%	Occasionally‡	<5%
0	None	None	None

*Percentage of entire surface area.
†Score is doubled for patients who have only oral mucosal lesions at time of study enrollment.
‡Blisters sometimes newly develop within 1 week but not every day.

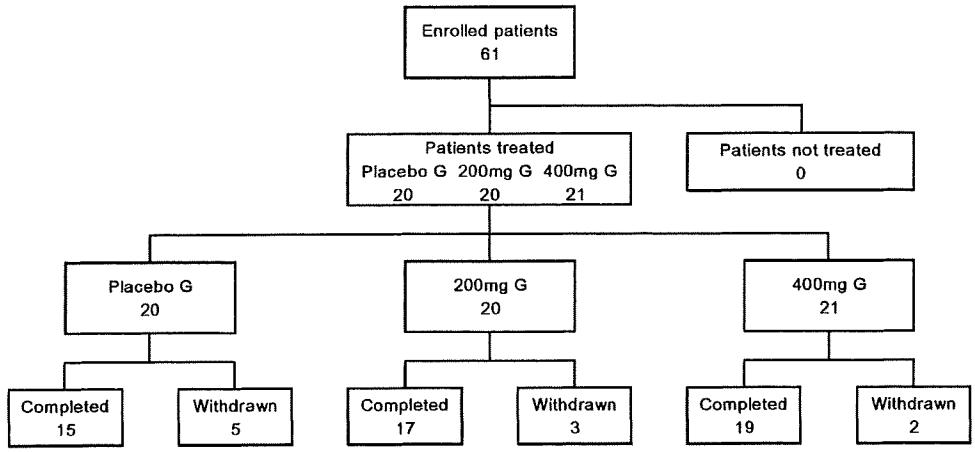

Fig 1. Disposition of patients. *G*, Group.

- Treatment with any steroid at greater than or equal to 20 mg/d (prednisolone equivalent)
- Symptoms (total pemphigus activity score [PAS] [Table I]) did not respond to steroid therapy

2. Exclusion criteria: patients who met any of the following criteria were excluded from the study because efficacy evaluation of the test drug might be affected and to assure the safety of patients.
   - Patients treated with plasma exchange therapy, steroid pulse therapy, or HD-IVIG within 30, 14, or 42 days, respectively, before informed consent and the start of study treatment
   - Patients with a history of shock or hypersensitivity to the test drug
   - Patients with IgA deficiency, hepatic disorder, renal disorder, or hemolytic or blood loss anemia
   - Patients with any previous or existing cerebrovascular or cardiovascular disorder

Study design

This was a multicenter, randomized, placebo-controlled, double-blind, parallel-group study. The study protocol and written informed consent form approved by the institutional review board at each study institution were used in the study. Observation of the first patient was started on November 4, 2004, and that of the last patient was completed on September 25, 2006.

Treatment groups

The IVIG group received IV drip infusion at 200 or 400 mg/kg/d administered in divided dose over 5 consecutive days. The placebo group received IV drip infusion of physiologic saline for 5 consecutive days.

Investigational drugs manufactured by Nihon Pharmaceutical Co Ltd (Higashikanda, Tokyo, Japan) were used in the study.

Methods of allocation

Patients were randomized by a central enrollment system to the treatment groups according to a dynamic allocation scheme to ensure that there were no between-group differences in the dose of prior steroid, total PAS, or disease type.

Blinding

Because the investigational drugs were distinguishable in terms of appearance and viscosity after

Table II. Demographic and other baseline characteristics

Characteristic	Category	Dose: Placebo n = 20	Dose: 200 mg n = 20	Dose: 400 mg n = 21	Between-group comparison
Sex	Male	9	10	8	NS* (P = .766)
	Female	11	10	13	
Age, y	Mean ± SD	53.1 ± 10.9	57.0 ± 14.6	50.1 ± 11.7	NS† (P = .225)
Body weight, kg	Mean ± SD	57.8 ± 11.6	58.0 ± 10.4	57.7 ± 9.1	NS* (P = .686)
Disease type	PV	13	14	13	NS* (P = .942)
	PF	7	6	8	
Disease duration, mo	Mean ± SD	16.1 ± 13.6	28.6 ± 32.3	28.5 ± 46.9	NS† (P = .414)
Baseline PAS	Mean ± SD	3.3 ± 1.4	3.6 ± 1.8	3.7 ± 1.1	NS† (P = .660)
Steroid dose, mg	Mean ± SD	27.6 ± 9.7	23.9 ± 11.1	27.4 ± 11.1	NS† (P = .461)
Immunosuppressants	No. of patients (%)	2 (10.0)	7 (35.0)	5 (23.8)	NS* (P = .179)

NS, Not significant difference; *PAS*, pemphigus activity score; *PF*, pemphigus foliaceus; *PV*, pemphigus vulgaris.
Two-sided test for both analyses.
*Fisher exact test.
†One-way analysis of variance.

reconstitution, independent staff at each study institution separately prepared and administered the dosing solution, and evaluated efficacy and safety in each patient to maintain blinding. The bottles of the investigational drugs were covered with a masking cover and provided to the independent staff member in charge of administration. Each independent staff member involved signed a blinding confirmation form at the end of the study to assure that blinding was maintained.

End points

Time to escape from the protocol (TEP) was used as the primary efficacy end point. TEP was defined as the length of the period until a patient stayed on the protocol without any additional treatment. When symptoms were unchanged for 2 weeks or aggravated, the treatment given was considered to be ineffective and additional treatment was required such as increase in steroid dose, change in steroid type, use of additional immunosuppressive agents, or plasma exchange; these patients were considered escaped from the protocol. This methods allow doctors in charge to have flexibility to rescue patients with other treatment when needed.

The secondary end points used in the study included: (1) PAS over time (scores [0-3 point] for skin lesion area, number of new blisters/d, and oral mucosal lesions, and their total scores [Table I]); and (2) the titers of pemphigus autoantibodies over time (anti-Dsg1 autoantibody titer and anti-Dsg3 autoantibody titer). Titers of pemphigus autoantibodies were determined by enzyme-linked immunosorbent assay.[14,15] As a safety end point, the occurrence of adverse events by 85 days after the start of the study treatment (day 85) was investigated. Adverse events were recorded up to day 43 if patients escaped from the protocol by day 43 or up to TEP if patients escaped from the protocol after day 44.

Statistical analysis

The cumulative rate of TEP, which was estimated by evaluation of the dose-response relationship of TEP and by analysis using the Kaplan-Meier method, was compared among the treatment groups by log rank test. Scores for skin lesion area, number of new blisters/d, and oral mucosal lesions, and total score, the secondary end point, up to day 85 were compared with baseline data by the paired t test for each treatment group. The data after TEP were imputed from the data at the TEP (last observation carried forward). Adverse events occurring up to day 85 for which the causal relationship with HD-IVIG or placebo was judged to be other than "not related" were handled as adverse drug reactions (ADRs). A two-sided significance level of .05 was used for analyses.

RESULTS

Disposition of patients

The disposition of patients enrolled in the study is shown in Fig 1. A total of 61 patients were treated with the investigational drug (placebo, 20; 200 mg, 20; and 400 mg, 21). All the enrolled patients including 10 patients (placebo, 5; 200 mg, 3; and 400 mg, 2) who were withdrawn from the study according to the requirements in the protocol were included in the analyses. The main reasons for study withdrawal were the evaluator's decision to withdraw the patient and the occurrence of adverse events. The demographic and other baseline

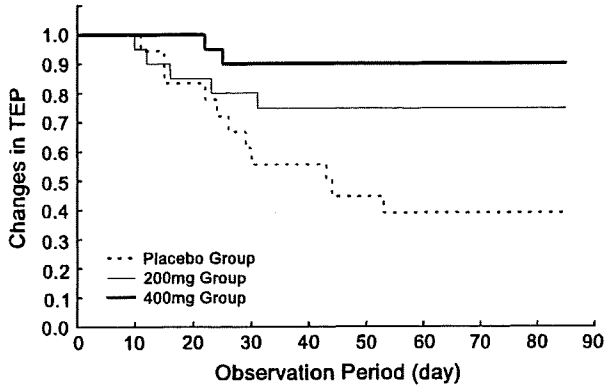

Fig 2. Changes in time to escape from protocol (*TEP*). TEP was significantly prolonged in 400-mg group compared with placebo group with dose-dependent fashion. Cumulative TEP on day 85 was 10.0% in 400-mg group, 25.0% in 200-mg group, and 61.0% in placebo group (log rank test). Between-group comparison demonstrated significant prolongation of TEP in 400-mg group compared with placebo group ($P < .001$, log rank test). In contrast, difference between 200-mg and placebo groups was not significant ($P = .052$). In addition, dose-response relationship was observed in TEP ($P < .001$). Data are stated using TEP ratio.

characteristics are presented in Table II. There were no significant between-group differences in the distribution of baseline characteristics. The average disease durations of 200- and 400-mg groups are longer than in the placebo group, but this is because the former group happened to contain patients with extremely long duration (116 months in 200 mg; 142 and 169 months in 400 mg) and the difference was not statistically significant.

Efficacy (primary end point): TEP

TEP was evaluated as the primary end point (Fig 2). In the 400-mg group, 19 of 21 patients stayed on the protocol during the observation period. Two patients escaped from the protocol with TEPs of 22 and 25 days. In the 200-mg group, 15 of 20 patients stayed on the protocol and the shortest TEP was as early as 10 days among the 5 escaped patients. In the placebo group, only 9 patients stayed on the protocol, and the shortest TEP was as early as 11 days. TEP was within 30 days for 8 patients.

TEP in the active treatment groups was compared with that in the placebo group (log rank test). The TEP in the 400-mg group was significantly longer than that in the placebo group ($P < .001$), whereas the difference between the 200-mg and placebo groups was not significant ($P = .052$). Log rank test of TEP for the 61 patients indicated a dose-response relationship for this parameter ($P < .001$).

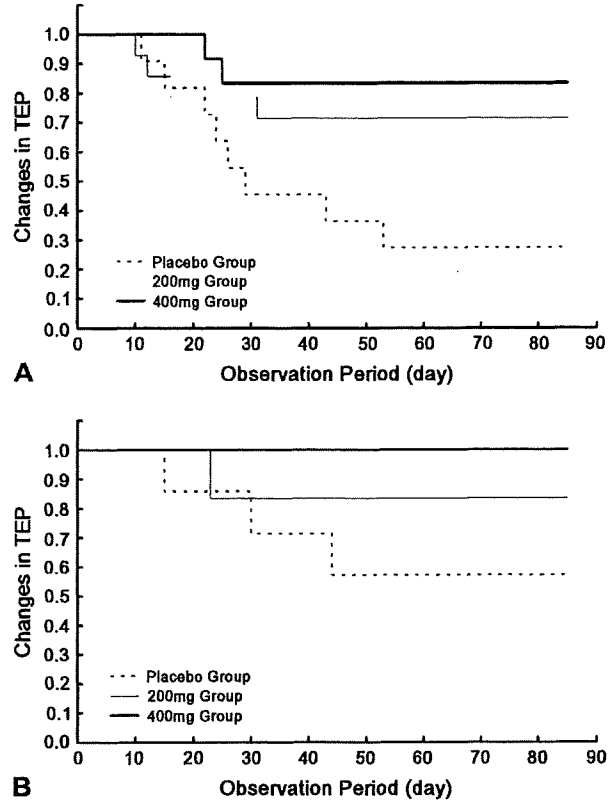

Fig 3. Cumulative time to escape from protocol (*TEP*) shown by pemphigus subtype. Cumulative TEP estimated by Kaplan-Meier method was divided in disease subtype of pemphigus vulgaris (PV) (**A**, n = 13 in 400-mg group, n = 14 in 200-mg group, n = 13 in placebo group) and pemphigus foliaceus (PF) (**B**, n = 8 in 400-mg group, n = 6 in 200-mg group, n = 7 in placebo group). Cumulative TEP in patients with PV on day 85 was 15.0% in 400-mg group, 29.0% in 200-mg group, and 73.0% in placebo group, whereas that of patients with PF was 0.0% in 400-mg group, 17.0% in 200-mg group, and 43.0% in placebo group. Between-group comparison demonstrated significant prolongation of TEP in 400-mg group compared with placebo group (PV, $P = .007$; PF, $P = .044$; log rank test). In contrast, difference between 200-mg and placebo groups was not significant (PV, $P = .055$; PF, $P = .416$). In addition, dose-response relationship was observed in TEP (PV, $P = .007$; PF, $P = .043$).

Analyses stratified by baseline characteristics (disease type and PAS) also demonstrated dose-response relationships and significant differences between the 400-mg and placebo groups, as in the overall analyses (Figs 3 and 4).

Efficacy (secondary end point)

Pemphigus activity score. Efficacy was also evaluated based on the changes in clinical symptoms, ie, changes in PAS determined based on skin lesion area, number of new blisters/d, and oral mucosal lesions. In the 400-mg group, total PAS

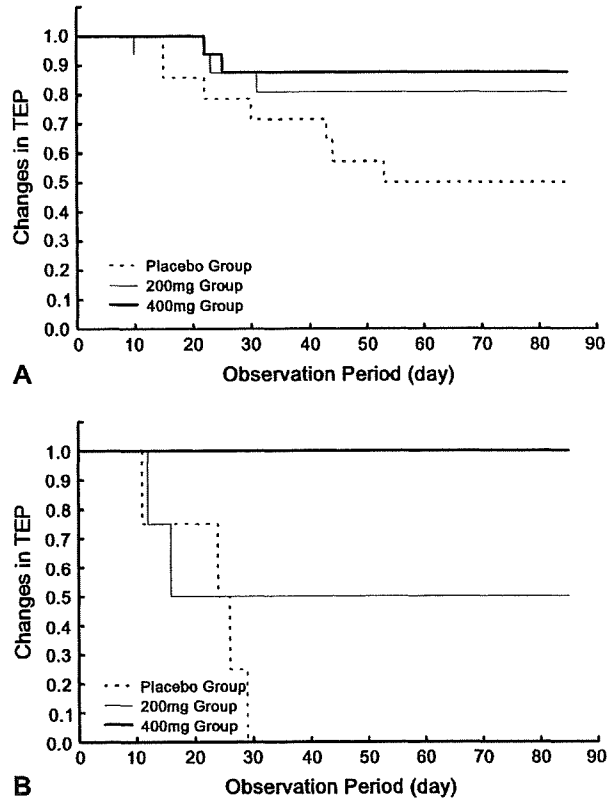

Fig 4. Cumulative time to escape from protocol (*TEP*) shown in different pemphigus activity score (PAS). Data were divided by PAS into two groups: total PAS of 0 to 4 (**A**, n = 17 in 400-mg group, n = 16 in 200-mg group, n = 16 in placebo group) and total PAS of 5 to 9 (**B**, n = 4 in 400-mg group, n = 4 in 200-mg group, n = 4 in placebo group). Cumulative TEP in patients with total PAS of 0 to 4 on day 85 was 12.0% in 400-mg group, 19.0% in 200-mg group, and 50.0% in placebo group, whereas those of patients with total PAS of 5 to 9 was 0.0% in 400-mg group, 50.0% in 200-mg group, and 100.0% in placebo group. Between-group comparison demonstrated significant prolongation of TEP in 400-mg group compared with placebo group (total score 0-4, P = .028; total score 5-9, P = .006). In contrast, difference between 200-mg and placebo groups was not significant (total score 0-4, P = .109; total score 5-9, P = .345). In addition, dose-response relationship was observed in TEP (total score 0-4, P = .024; total score 5-9, P = .012).

was significantly decreased from the baseline score at all points of observation (day 8, P = .05; after day 15, $P < .01$). It was decreased from 3.7 on day 1 to 2.0 on day 85 (by 46.8%) (Fig 5). In the 200-mg group, total PAS was significantly decreased from the baseline score at all points of observation after day 15 (day 15-43, $P < .05$; day 57-85, $P < .01$). It was decreased from 3.7 on day 1 to 2.3 on day 85 (by 36.6%). On the other hand, in the placebo group, no significant decrease from baseline score was observed at any of the points of observation. Each PAS

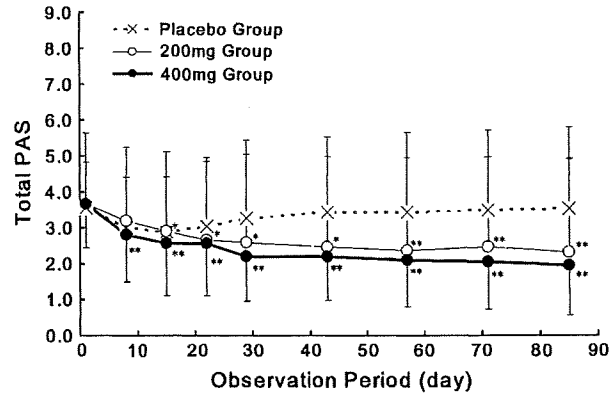

Fig 5. Changes of pemphigus activity score (*PAS*) over time. Total PAS was significantly lower in 400- and 200-mg groups than in placebo group. Significant difference from day 1 at hazard ratio of *0.05 and **0.01.

(skin lesion area, number of new blisters/d, and oral mucosal lesions) also exhibited a significant change from baseline in the 400-mg group ($P < .01$) but not in the placebo group (data not shown).

Titers of anti-Dsg IgG autoantibodies

It has been reported that levels of IgG autoantibodies to Dsg1 and Dsg3 in patients with pemphigus correlate with disease activity.[14,15] Accordingly, efficacy was also evaluated based on the changes in anti-Dsg1 IgG autoantibody titer for patients with PF and PV or in anti-Dsg3 IgG autoantibody titer for patients with PV (Fig 6). In the 400-mg group, anti-Dsg1 and −Dsg3 IgG antibody titers were significantly decreased from baseline on days 43 and 85 (day 43 and 85, $P < .01$). In the 200-mg group, anti-Dsg1 and −Dsg3 IgG antibody titers also exhibited significant decreases on day 85 but not day 43 (day 43, $P < .05$; day 85, $P < .01$). On the other hand, in the placebo group, no significant decrease from baseline was observed in either anti-Dsg1 or −Dsg3 IgG antibody titer.

Safety

The incidence of ADRs was 28.6% (n = 6/21) in the 400-mg group, 35.0% (n = 7/20) in the 200-mg group, and 25.0% (n = 5/20) in the placebo group. No significant difference was observed between the placebo and 200- or 400-mg groups. ADRs reported in the study included: headache in two patients, aggravated chronic hepatitis C, decreased lymphocytes, palpitations, abdominal discomfort, constipation, nausea, pain at the injection site, increased creatinine, increased blood pressure, and decreased platelet count in one patient each in the 400-mg group; and increased alanine aminotransferase in 3 patients; increased γ-glutamyltranspeptitase, hepatic dysfunction, and increased bilirubin in two patients each; and common cold, muscle pain, increased

aspartate aminotransferase, increased blood pressure, decreased lymphocytes, increased neutrophils, decreased white blood cell count, bleeding tendency, anorexia, hypoalbuminemia, hepatic encephalopathy, gastrointestinal bleeding, malaise, fever, increased ammonium, increased C-reactive protein, decreased hematocrit, decreased hemoglobin, decreased platelet count, decreased red blood cell count, and decreased urine volume in one patient each in the 200-mg group. All these ADRs were consistent with the information displayed on the Food and Drug Administration Web site (http://www.fda.gov/cber/gdlns/igivimmuno.htm).

One patient in the 200-mg group died of hepatic failure as a result of aggravation of hepatitis C, which was an underlying complication reported before the start of the study.

This event was judged as probably related to the investigational drug in the evaluator's opinion.

DISCUSSION

Most clinical research involving a rare disease is based on case reports or data from limited samples obtained in open-label studies. In particular, in life-threatening, serious, and intractable diseases, such as pemphigus, appropriate treatment must be provided in a timely fashion if symptoms are aggravated or unchanged for days. This makes performance of a placebo-controlled, double-blind comparison study infeasible. On the other hand, the efficacy of new drugs for malignant tumors or for patients requiring pain relief is evaluated based on the time to recurrence of tumor or the number of patients requiring rescue analgesia.[16-21] Based on these considerations, we developed a novel efficacy indicator (ie, TEP) with reference to the end points used for efficacy evaluation of drugs for malignant tumors or for patients requiring pain relief, to conduct a placebo-controlled, double-blind comparison study in patients with pemphigus who were relatively resistant to systemic steroids. This new efficacy end point provides flexibility for physicians to rescue patients when required and proved to be useful to evaluate the efficacy of a single cycle of HD-IVIG in a double-blind comparison design. However, some concerns remain regarding the rigidity: a period of 3 to 7 days before the start of study treatment was required to confirm the unresponsiveness of patients to steroids, and switching to other treatments was prohibited during the first 5-day treatment period.

The mode of action of HD-IVIG is complex. It is found to exert its effect through modulation of expression and function of Fc receptors, interference with complement activation and the cytokine

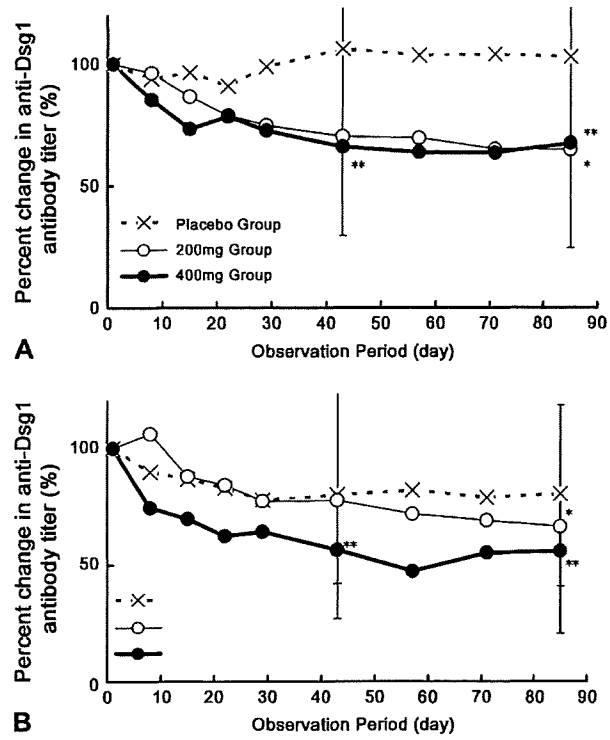

Fig 6. Changes of anti-desmoglein (*Dsg*) IgG titers. Anti-Dsg IgG titers were significantly lower in 400-mg intravenous immunoglobulin group than in placebo group over time. Changes of titers in anti-Dsg1 IgG autoantibodies (**A**) in patients with pemphigus vulgaris (PV) and pemphigus foliaceus and in anti-Dsg3 IgG autoantibodies (**B**) in patients with PV were shown (mean ± SD). Significant difference from day 1 at hazard ratio of *0.05 and **0.01.

network, provision of anti-idiotypic antibodies, modulation of dendritic cell, T- and B-cell activation, differentiation, and their effector functions.[22,23] Thus, HD-IVIG has multiple modes of action and is thought to act synergistically. HD-IVIG exerts immunomodulatory effects in autoimmune and inflammatory disorders without suppressing the immune system, which provides a distinctive advantage over conventional treatment.

Most of the previous studies suggesting efficacy of HD-IVIG for treatment of pemphigus involved multiple treatment cycles. However, our study demonstrated that a single cycle with HD-IVIG for 5 days has a therapeutic benefit to suppress the disease activity of pemphigus. Like rituximab, for which efficacy was recently reported in a single cycle,[24] IVIG is expensive and should be considered for patients who show difficulty with or resistance to conventional treatments.

In conclusion, our study suggests that TEP is a useful indicator for evaluation for rare intractable diseases such as pemphigus, and that a single cycle of HD-IVIG appears to be an effective treatment for

patients with pemphigus who are relatively resistant to systemic steroids.

We thank members of the Pemphigus Study Group described below for cooperation with registration and precise observation of patients with pemphigus. We also acknowledge data management and analysis support from Bellsystem24 Inc and EPS Co Ltd, Tokyo, Japan.

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APPENDIX

Independent Data and Safety Monitoring Committee: K. Nishioka, Minato Red Cross Hospital, Yokohama; H. Tagami, Tohoku University Graduate School of Medicine, Sendai; and T. Kiuchi, University of Tokyo Graduate School of Medicine.

Principal investigators: Hokkaido University Graduate School of Medicine — T. Shimizu, R. Abe, M. Abe; Tohoku University Graduate School of Medicine — S. Nakagawa, K. Kikuchi; Fukusima Medical University — M. Otsuka; Saitama Medical Center — K. Hitomi; University of Tokyo School of Medicine — N. Yazawa, M. Jinnin; Yokohama City University Graduate School of Medicine — K. Takahashi; Juntendo University School of Medicine — N. Mayuzumi, K. Sumiyoshi, T. Hasegawa; Keio University School of Medicine — R. Kou; Hamamatsu University School of Medicine — H. Hashizume, T. Ito; Ogaki Municipal Hospital — T. Fujisawa; Gifu University Graduate School of Medicine — Y. Ichiki, Y. Aoyama, H. Ichikawa; Shiga University of Medical Science — N. Fujimoto, B. Yamamoto; Kyoto

University Graduate School of Medicine — N. Matsuyoshi; Osaka University Graduate School of Medicine — T. Nakamura; Nara Medical University — H. Niizeki; Wakayama Medical University — T. Kishi; Okayama University Graduate School of Medicine — T. Ohno, G. Nakanishi; Ehime University Graduate School of Medicine — K. Sayama, Y. Shirakata, S. Murakami; Kyushu University Graduate School of Medicine — Y. Moroi, M. Takahara, H. Kuniba, T. Uenotsuchi; Kurume University School of Medicine — N. Momosaki, K. Hashikawa; Oita University Faculty of Medicine — O. Okamoto; University of Occupational and Environment Health — R. Yoshiki, C. Koga, D. Nishio; and Faculty of Medical and Pharmaceutical Sciences, Kumamoto University — S. Wakasugi.

SPECIAL NOTICE REGARDING CASE REPORTS

The *Journal of the American Academy of Dermatology*, like other medical journals, receives many more case reports than we are able to publish. To accommodate our authors and to give our readers access to a more diverse collection of interesting cases, effective January 1, 2009 all case reports must be submitted in the more abbreviated case letter format. A full description of the case letter format can be found in the most recent written and online Instructions for Authors.

Additionally, because of our current high inventory, lengthy delays may occur before already accepted case reports and case letters appear in the print journal. To circumvent this, authors may elect "online-only" publication of their cases. Online-only articles are accessible at http://www.eblue.org. "Online-only" is a bonafide form of publication. Online articles may be listed on the author's curriculum vitae and are cited on PubMed. For further information regarding online publication, please contact Melissa Derby, Managing Editor, at mderby@aad.org.

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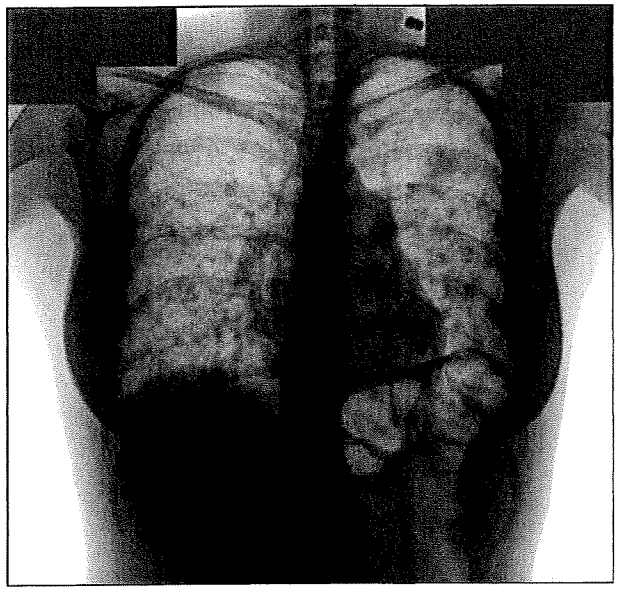

Figure 3. Chest radiograph reveals interstitial and nodular diffuse changes and a cavitary lesion in the left upper lobe.

pulmonary artery pressure to normal. After 1 year, she had no recurrence of Sweet syndrome; her complete blood cell counts were normal; and she showed no sign of hematologic dyscrasia.

Comment. Pulmonary Sweet syndrome is rare, having been reported in about 23 cases in the literature, to our knowledge, 12 of which were associated with a hematologic malignant neoplasm.[1-4] The characteristic eruption of Sweet syndrome can occur before, concomitantly, or after the pulmonary symptoms.[2] Imaging can reveal unilateral or bilateral interstitial infiltrates, nodules, cavitary lesions, pleural effusions, or bronchiolitis obliterans organizing pneumonia (BOOP).[2] Lung biopsy specimens usually reveal intra-alveolar sterile infiltrates of neutrophils. Cardiovascular disease is also a rare complication of Sweet syndrome, with cardiomegaly, cardiac arrest, and diffuse vascular disease reported.[5]

The mainstay of treatment for Sweet syndrome is systemic corticosteroids, which act as inhibitors of superoxide anion production by neutrophils. Other treatment options include dapsone, colchicine, indomethacin, or potassium iodide.

The present case reminds us of the potential extracutaneous manifestations of Sweet syndrome. Our case is also unique given the young age of the patient, no known malignancy, and the associated pulmonary and cardiovascular findings. Finally, this case highlights the importance of making an accurate and timely diagnosis of Sweet syndrome so that treatment with corticosteroids can be promptly instituted.

Courtney M. Robbins, MD
Stephen E. Mason, MD
Lauren C. Hughey, MD

Correspondence: Dr Hughey, Department of Dermatology, University of Alabama at Birmingham, 1530 3rd Ave S, EFH 414, Birmingham, AL 35294 (lchughey@uab.edu).

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Stage III Melanoma Treated With Chemotherapy After Surgery During the Second Trimester of Pregnancy

Alexander et al[1] found that approximately 31% of 87 reported cases of melanoma in pregnancy had transplacental metastases. We describe herein a patient with stage III melanoma treated with chemotherapy.

Report of a Case. A 29-year-old pregnant Japanese woman noticed the enlargement, elevation, and erosion of a pigmented spot on the anterior aspect of her left thigh. She was referred to our hospital at 17 weeks' gestation. An ulcerated blackish nodule, 20 mm in diameter, had arisen from an asymmetrical, multicolored nevoid lesion, 25 × 30 mm, with irregular borders (**Figure 1**).

Based on the findings of an excisional biopsy (**Figure 2**), we diagnosed T4b nodular-type melanoma. Because the ulcerated melanoma was 6.0 mm thick, and to avoid multiple surgical procedures and prevent the patient's exposure to radioactive materials, we performed a 5-cm-wide total excision and radical left inguinal lymph node dissection at 21 weeks' gestation instead of sentinel node biopsy. One lymph node had an N1a micrometastasis. No metastatic lesions were revealed under magnetic resonance imaging of the brain, computed tomographic scan of the chest, and ultrasonographic examination of the abdomen. All laboratory results were within normal limits. We diagnosed her condition as stage IIIb melanoma.

On our recommendation, the patient chose to continue her pregnancy and was treated with chemotherapy called DAV-feron (dacarbazine, 750 mg; nimustine, 75 mg; vincristine, 1.2 mg; and interferon beta, 2500 IU) during the second trimester (beginning at 26 weeks' gestation) to decrease the possibility of melanoma metastases to both the mother and the fetus. She gave birth to a healthy 2208-g baby at 35 weeks' gestation without signs of placental involvement. At last follow-up, she had completed 5 treatment cycles, and her disease-free interval was 35 months. Her 32-month-old son also had no signs of melanoma.

Comment. The decision to recommend continuation of the pregnancy was based on available meta-analyisis data indicating that transplacental metastasis is rare.[1] Neonates born

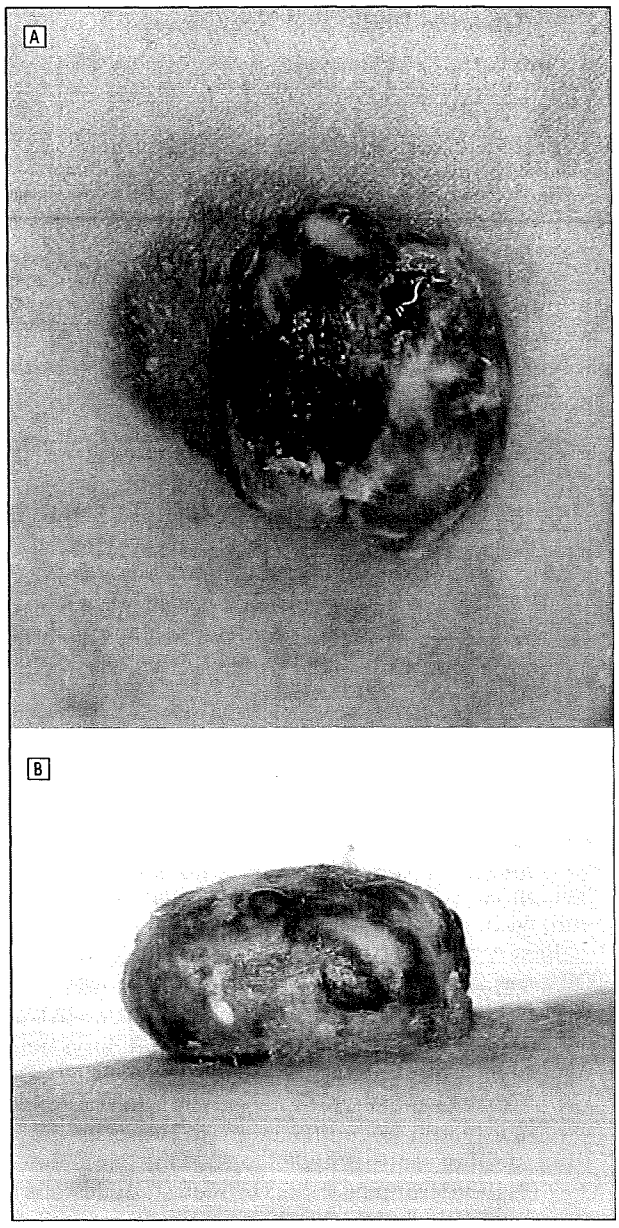

Figure 1. Clinical view of the melanoma on the thigh of a pregnant 29-year-old Japanese woman. A, Frontal view. B, Lateral view.

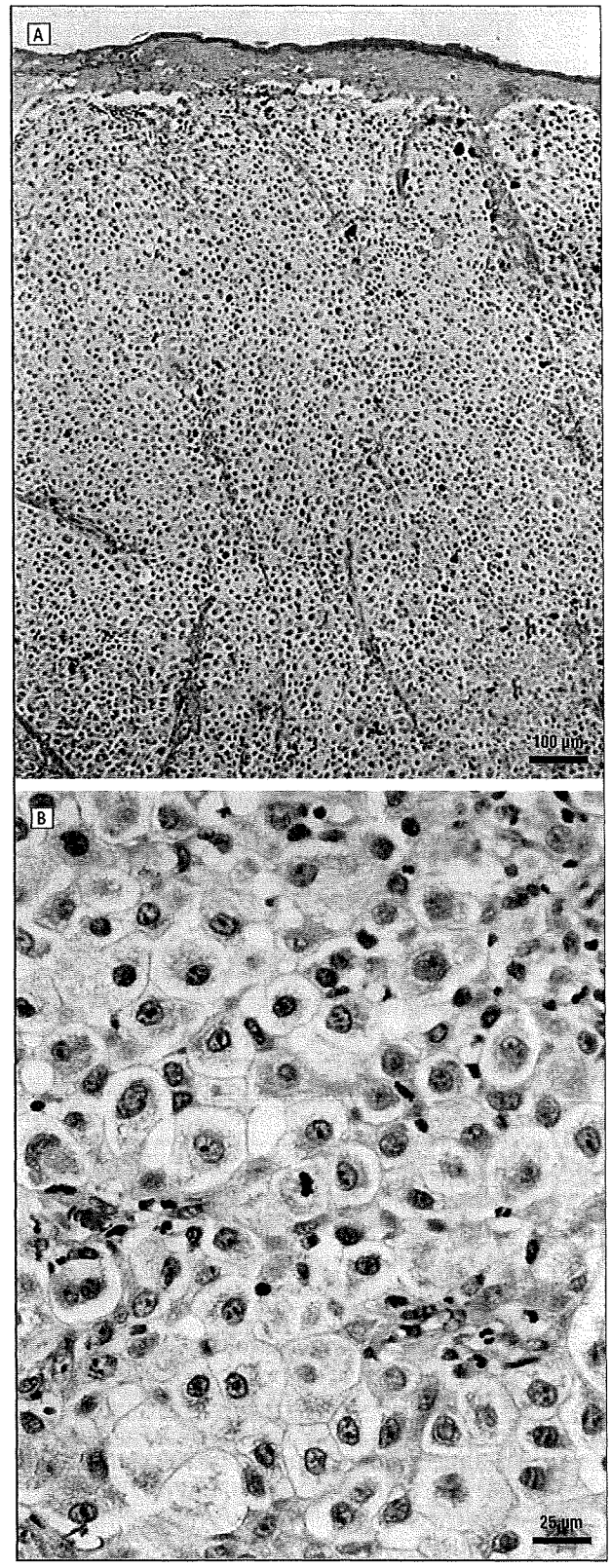

Figure 2. Low-magnification (A) (original magnification ×100) and high-magnification (B) (original magnification ×400) hematoxylin-eosin–stained specimens taken from the melanoma on the thigh of a pregnant 29-year-old Japanese woman showed atypical cells with hyperchromasia and various sizes of nuclei in addition to mitotic figures.

to women with melanoma do not differ in birth weight, prematurity, or neonatal death from those born to women without malignant neoplasms.[2] The use of chemotherapy during pregnancy remains controversial because of the limited efficacy and potential adverse effects on the fetus. Although the ideal treatment for stage I or II melanoma during pregnancy is surgical resection without adjuvant chemotherapy, other treatment options must be considered when treating stage III or IV melanoma.

Few case studies report the results of chemotherapy treatment for advanced melanomas during pregnancy. In 1 case, when chemotherapy was given to a patient with metastatic melanoma in the first trimester, the infant developed microphthalmos and hypermetropia.[3] This suggests that chemotherapy should be discouraged during the first trimester, a critical period of organogenesis. In 2 other cases of metastatic melanomas treated with chemotherapy during pregnancy, the children survived, but the mothers died shortly after delivery.[4,5]