

Severe Eczematous Skin Reaction After High-Dose Intravenous Immunoglobulin Infusion

Report of 4 Cases and Review of the Literature

Gianluca Vecchietti, MD; Katrin Kerl, MD; Christa Prins, MD; Gürkan Kaya, MD, PhD;
Jean-Hilaire Saurat, MD; Lars E. French, MD

Background: High-dose intravenous immunoglobulins (IVIGs) are increasingly used to treat inflammatory and/or autoimmune disorders. In dermatology, they provide therapeutic benefit in Kawasaki disease and certain cases of dermatomyositis. While most adverse effects following IVIG treatment are not severe, occasionally more severe adverse effects occur, including anaphylactic reactions and acute, usually transient, renal failure.

Observations: We report 4 cases of a characteristic severe extensive eczematous reaction that occurred approximately 10 days after IVIG infusion for polyradiculoneuritis. In all cases, onset was characterized by dyshidrotic lesions on the palms, rapidly followed by pruriginous maculopapular lesions involving the whole body. All patients were treated with topical and/or systemic ste-

roids, and complete resolution of skin lesions was observed within 1 month. To date, 33 cases of cutaneous rash following IVIG infusion have been reported in the literature, mostly in neurology journals, and the features are identical to those reported herein.

Conclusions: Severe eczematous skin reaction with a characteristic initial localization to the palms and/or soles that then extends to the rest of the body is a rare but characteristic adverse effect of high-dose IVIG therapy. Although the precise mechanism of this cutaneous eruption remains to be elucidated, its occurrence within days of IVIG infusion, its characteristic distribution at onset, and its clinical course should be recognized by dermatologists.

Arch Dermatol. 2006;142:213-217

SINCE ITS INITIAL USE IN THE early 1950s, intravenous immunoglobulin (IVIG) therapy has been increasingly used to treat hematologic, neurologic, nephrologic, autoimmune, immunodeficiency,¹⁻³ and dermatologic disorders.⁴ In 1982, the US Food and Drug Administration approved the use of IVIG therapy, and now it is recognized to treat 6 conditions: (1) primary immunodeficiencies; (2) immune-mediated thrombocytopenia; (3) Kawasaki syndrome⁵; (4) recent bone marrow transplantation in patients older than 20 years; (5) chronic B-cell lymphocytic leukemia; and (6) pediatric human immunodeficiency virus type 1 infection. In clinical practice, IVIG therapy is used off-label to treat more than 50 medical conditions, principally immune-mediated disorders including acquired hemophilia, idiopathic thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, Guillain-Barré syndrome, systemic lupus erythematosus, immunodeficiency, Kawasaki disease, Stevens-Johnson syndrome, and toxic epidermal necrolysis.^{1,6}

Intravenous immunoglobulin is a blood product prepared from the pooled plasma of 10 000 to 20 000 donors per batch with

purification procedures that vary somewhat among manufacturers. In all cases, according to the World Health Organization, preparations have to contain at least 90% intact IgG with a normal IgG subclass distribution, as little IgA as possible, and no Ig fragments and aggregates. Several measures are used by manufacturers to ensure the safety of the product: (1) careful selection of donors, with importance placed particularly on voluntary, unpaid donations; (2) screening of every donation for infectious agents; and (3) the use of modern viral inactivation procedures.

See also page 247

Adverse effects of IVIGs are usually minor. They include vasomotor symptoms, headache, chills and fever, or transient biological disorders such as leukopenia, neutropenia, or proteinuria. Rarely, more severe complications such as aseptic meningitis,⁷ hemolytic anemia,⁸ thrombosis,⁹ anaphylactic shock,¹⁰ and acute renal failure¹¹ have been reported. Dermatologic adverse effects from IVIG are rare and include pruritus, rash, and anecdotal case reports of alopecia and erythema multiforme.^{12,13} We report 4 cases of severe eczematous skin reaction after high-dose IVIG infusion; we

Author Affiliations:
Department of Dermatology,
University of Geneva, Geneva,
Switzerland.



Figure 1. Clinical photographs of patient 1 (A and B) and patient 3 (C-E). Dyshidrotic eczematous skin lesions on the palmar and dorsal surfaces of the hands. C-E, Widespread pruriginous eczematous rash associated with desquamation of the palms and soles.

precisely delineate the cutaneous signs of this adverse effect and review the existing literature.¹⁴⁻²³

REPORT OF CASES

CASE 1

A 61-year-old man was diagnosed with amyotrophic lateral sclerosis. Despite treatment with riluzole (Rilutek; Aventis Pharma Specialites, Compiègne, France), vitamins of the B group (Becozyme Forte; Roche Pharma, Basel, Switzerland) and thiamin (Benerva; Roche Pharma), the neurologic symptoms progressed in a period of 2 months. Then the patient received IVIG therapy (Redimmune; ZLB Bioplasma AG, Bern, Switzerland) at a dose of 0.4 mg/kg for 5 consecutive days. Two days after the first IVIG perfusion, pruriginous, dyshidrotic skin lesions appeared on the patient's palms (**Figure 1A**), the dorsal surface of the hands (**Figure 1B**), and the soles. Histologic analysis of a biopsy specimen from the palm revealed marked spongi-

sis with intraepidermal vesicle formation and a dermal inflammatory infiltrate composed mainly of lymphocytes and histiocytes (**Figure 2**). The lesions regressed progressively with topical application of corticosteroids (betamethasone dipropionate ointment). No new lesions developed after stopping IVIG infusions.

CASE 2

A 56-year-old man with a history of inflammatory bowel disease was hospitalized for polyradiculoneuritis (Guillain-Barré syndrome) and treated with IVIG therapy (Redimmune) at a dose of 0.4 g/kg for 5 days. Ten days after an initial improvement, the neurologic symptoms deteriorated again, and the patient received another course of IVIG. Two days after this IVIG infusion he developed pruriginous, eczematous skin lesions of dyshidrotic type, localized on the palms and soles. Treatment with low-dose systemic corticosteroids (5 mg/d of prednisone) and potent topical corticosteroids (betamethasone ointment) was ini-

tiated, but the skin lesions extended to erythroderma during the following month. A skin biopsy specimen revealed diffuse epidermal spongiosis and a perivascular lymphocytic infiltrate with some eosinophils, suggesting an allergic drug reaction. Findings of a complete blood cell count, blood chemical analysis, and viral serologic analysis (including for parvovirus and the VDRL test) were normal. Systemic corticosteroids were then increased to 0.5 mg/kg, and the skin lesions completely regressed. The patient's usual daily treatments included mesalazine (Asacol; Sanofi-Synthelabo, Paris, France), clomipramine (Anafranil; Novartis, Basel, Switzerland), clorazepam (Tranxilium; Sanofi-Synthelabo), and gabapentine (Neurontin; Pfizer, New York, NY), and these treatments were continued without alteration.

CASE 3

A 64-year-old man with a history of myocardial infarction in 1996 and hyperlipidemia treated by simvastatine (Zocor; Merck & Co, Whitehouse Station, NJ) was hospitalized for polyradiculoneuritis (Guillain-Barré syndrome) and treated with IVIG (Sandoglobulin; Novartis) at a dose of 0.4 g/kg for 5 consecutive days. This treatment resulted in an improvement of his neurologic status, but 15 days after the beginning of IVIG infusion, it was associated with the development of pruriginous erythematous maculopapulovesicular skin lesions localized to the palms and the face. Over a period of 3 weeks, the skin lesions extended to the entire body becoming a confluent eczematous rash with some lichenification on the legs and desquamation on the palms and soles (Figure 1C-E). Results of laboratory investigations, including complete blood cell counts, blood chemical analyses, and serologic analyses for syphilis, hepatitis B and C, *Borrelia burgdorferi*, *Mycoplasma pneumoniae*, and varicella zoster virus, were normal. Serologic findings for herpes simplex virus, cytomegalovirus, Epstein-Barr virus, and parvovirus B19 were positive for IgG but negative for IgM. Histologic findings from a skin biopsy specimen taken from an erythematous lesion on the leg revealed an acanthosis with focal parakeratosis, spongiosis, exocytosis of lymphocytes, rare necrotic keratinocytes, and a dermal inflammatory infiltration composed of lymphocytes, histiocytes, and eosinophils.

CASE 4

A 55-year-old man with a history of coronary bypass surgery in 1997 and hyperlipidemia and embolic occlusion of the right ophthalmic artery in 1998, treated with acetylsalicylic acid (Aspirin Cardio; Bayer, Pittsburgh, Pa), felodipine (Plendil; Astra-Zeneca, London, England), metoprolol (Logimax; Astra-Zeneca), losartan (Cosaar; Merck & Co), and simvastatine (Zocor), was hospitalized for a polyradiculoneuritis secondary to a recent Epstein-Barr virus infection (IgM- and IgG-positive serologic findings 10 days after the beginning of the symptoms) and treated 10 days later with IVIG (Sandoglobulin) at a dose of 0.4 g/kg for 5 consecutive days with rapid resolution of the neurologic symptoms. Fifteen days after the onset of IVIG infusion he developed a pruriginous erythematous maculopapulovesicular rash localized initially on the palms and soles. Progressively, within 2 weeks, the palms and soles became edematous, and the maculopapular lesions extended to the entire body in con-

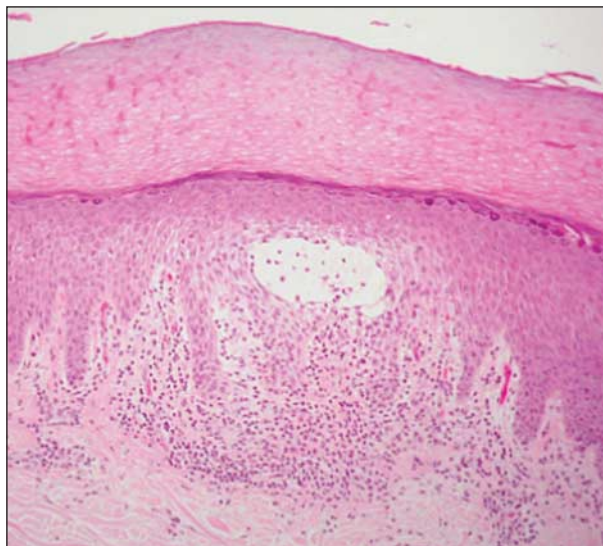


Figure 2. Histologic specimen obtained from a lesion on the palms of patient 1 showing acanthosis, marked spongiosis with intraepidermal vesicle formation, lymphocyte exocytosis, and a dermal inflammatory infiltrate mainly composed of lymphocytes and histiocytes (hematoxylin-eosin, original magnification $\times 20$).

fluent form. Results of laboratory investigations including complete blood cell counts and blood chemical analyses were normal. Serologic findings for human immunodeficiency virus, hepatitis B virus, *B burgdorferi*, *M pneumoniae*, herpes simplex virus types 1 and 2 DNA, and herpes simplex virus type 6 were negative. Serologic findings for varicella zoster virus, cytomegalovirus, and parvovirus B19 were positive for IgG but negative for IgM. A skin biopsy specimen produced an eczematous histologic image. Treatment with all medications was stopped and oral steroid (prednisone) therapy was initiated at 1 mg/kg per day. Cutaneous lesions regressed over a period of 1 month. Subsequent resumption of treatment with 100 mg/d of acetylsalicylic acid (Aspirin Cardio), metoprolol (Logimax), losartan (Cosaar), and simvastatine (Zocor) was not followed by the appearance of cutaneous lesions.

COMMENT

The use of IVIG therapy is increasing because of its therapeutic benefit in a number of conditions and its good safety profile.^{24,25} While the adverse effects of IVIG are rare and in most cases very limited, this report describes 4 cases of a severe, extensive, pruriginous, eczematous eruption that occurred approximately 10 days after IVIG infusion for polyradiculoneuritis. In all cases, the clinical presentation was characteristic, with a pruriginous rash that usually started in the form of dyshidrotic lesions of the palms, followed in 3 of our 4 patients by the development of an extensive eczematous eruption that was erythrodermic. Among the most plausible differential diagnoses considered, a viral rash was eliminated based on the normal laboratory investigations, including viral serologic analyses. A drug reaction to anything other than IVIG was ruled out based on the chronology of exposure to concomitant treatments, their intrinsic imputability, and in the case of patient 4, the absence of recurrence on their reintroduction.

Table. Clinical Characteristics of 37 Cases of Severe Eczematous Skin Reaction After IVIG Perfusion

Patient No./ Sex/Age, y	Indication for IVIG	Treatment*	Skin Reaction	Site of Onset	Recurrence on Rechallenge	Source
1/M/61	ALS	0.4 of Redimmune (5)	Pompholyx	Palms and soles	No	Present observation
2/M/56	GBS	0.4 of Redimmune (5)	Pompholyx	Palms and soles	No	Present observation
3/M/64	GBS	0.4 of Sandoglobulin (5)	Eczematous eruptions	Palms	No	Present observation
4/M/55	Polyradiculoneuritis after EBV infection	0.4 of Sandoglobulin (5)	Eczematous eruptions	Palms	No	Present observation
5/M/60	Inflammatory myopathy (HTLV-1)	0.5 of Sandoglobulin (5)	Eczematous eruptions	Extremities	No	Leclech et al ¹⁹
6/M/58	Cramps, fasciculations syndrome	0.5 of Sandoglobulin (4)	Eczematous eruptions	Palms	Yes	Leclech et al ¹⁹
7/M/53	IBM	0.5 of Sandoglobulin (4)	Scaly eruption	Palms	Yes	Leclech et al ¹⁹
8/F/75	ITP	1 of Sandoglobulin (2)	Severe eczema	Widespread	Yes	Barucha and McMillan ¹⁴
9/M/66	CIDP	0.4 of Sandoglobulin (5)	Eczematous eruptions	Palms	Yes	Whittam et al ¹⁷
10/M/65	CIDP	2 Sandoglobulin (1)	Eczematous eruptions	Widespread	No	Whittam et al ¹⁷
11/F/61	CIDP	2 of Sandoglobulin (1)	Eczematous eruptions	Widespread	No	Whittam et al ¹⁷
12/M/68	Demyelinating neuropathy with IgM paraproteinemia	2 of Sandoglobulin (1)	Eczematous eruptions	Hands	No	Whittam et al ¹⁷
13/F/28	Acute sensorimotor polyneuritis	0.4 of Tegeline/ Sandoglobulin (5)	Baboon syndrome	Palms	Yes	Barbaud et al ¹⁸
14/F/76	MMN	0.4 of Sandoglobulin (5)	Erythroderma	Widespread	Yes	Hamdalla et al ¹⁵
15/M/66	IBM	0.4 of Scottish preparation (5)	Itchy eruption	Widespread	Yes	Hamdalla et al ¹⁵
16/M/48	MMN	ND	Eczematous eruptions	Widespread	No	Hamdalla et al ¹⁵
17/M/55	MMN	ND	Itchy eruption	Widespread	No	Hamdalla et al ¹⁵
18/F/72	CIPD	0.4 of Glovenin-I (5)	Pompholyx	Palms	No	Ikeda et al ²¹
19/NA	CIPD	0.4 of unspecified drug (5)	Pompholyx	Palms	No	Iannaccone et al ²⁰
20/NA	GBS	0.4 of unspecified drug (5)	Pompholyx	Palms	No	Iannaccone et al ²⁰
21/NA	LMND	0.4 of unspecified drug (5)	Pompholyx	Palms	No	Iannaccone et al ²⁰
22-31/NA/20 to 50	MS	1 of Gammagard (2)	Eczema	Palms	No	Sorensen et al ¹⁶
32/F/71	ITP	Unspecified dose of Sandoglobulin	Eczematous eruptions	Widespread	Yes	Uyttendaele et al ²²
33/M/60	Postlaminectomy neuralgia	6 × 0.03 g in 2 wk of Venoglobulin	Eczematous eruptions	Widespread, including palms	Yes	Uyttendaele et al ²²
34/M/41	GBS	0.04 g/kg per day of Panglobin (5)	Pompholyx	Palms	Not reported	Uyttendaele et al ²²
35-37/NA	2 GBS, 1 Miller-Fisher syndrome	0.4 of unspecified drug (5)	Pompholyx and eczematous eruptions	Widespread, including palms	Not reported	Tada et al ²³

Abbreviations: ALS, amyotrophic lateral sclerosis; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; EBV, Epstein-Barr virus; GBS, Guillain-Barré syndrome; HTLV-1, human T-cell lymphotropic virus type 1; IBM, inclusion body myositis; ITP, idiopathic thrombocytopenic purpura; IVIG, intravenous immunoglobulin; LMND, lower motor neuron disease; MMN, multifocal motor neuropathy; MS, multiple sclerosis; NA, not available; ND, not determined.

*Unless otherwise indicated, doses are reported in grams per kilogram per day (number of days). Gammagard is manufactured by Baxter International, Deerfield, Ill; Glovenin-I, Nihon Pharmaceutical Co Ltd, Tokyo, Japan; Panglobin, American Red Cross, Washington, DC; Redimmune, ZLB Bioplasma AG, Bern, Switzerland; Sandoglobulin, Novartis, Basel, Switzerland; Tegeline, LFB Laboratories, Paris, France; Venoglobulin, Alpha Therapeutics Corp, Los Angeles, Calif.

Extensive pruriginous skin eruptions following IVIG infusion are very rare, or at least rarely reported. A review of the literature has enabled us to identify 33 cases reported mostly in the nondermatologic literature in which the skin lesions were considered to be an adverse effect of IVIG infusion. Interestingly, the characteristics of the cutaneous eruptions reported are very similar to those highlighted in our 4 cases (**Table**).

Analysis of the 33 cases reported to date and our 4 observations revealed that this adverse event occurs at any age and affects both men and women. In all cases, the

skin eruption was acute, pruritic, eczematous, and often located on the palms and/or soles at onset (**Table**). There was no oral involvement. On the palms and soles, the lesions were dyshidrotic in most cases, and in cases with biopsy specimens, histologic analysis revealed severe spongiotic dermatitis. In 27 of 33 cases in the literature, extensive skin involvement was reported with eczematous cutaneous lesions progressively extending to involve the entire body. The cutaneous lesions always resolved within a period of 1 to 4 weeks from onset with the use of topical and/or systemic steroids. Frequently,

resolution is accompanied by desquamation. Systemic symptoms that may be suggestive of an infectious cause, such as fever, arthralgias, and headache, are usually not present at the onset of cutaneous lesions.

In 9 patients, IVIG therapy was readministered, and all 9 developed the same skin eruption upon reexposure. The second eruption was more rapid in onset and more intensive than the first episode, suggesting the existence of immunologic memory, and supporting the diagnosis of an adverse allergic reaction to IVIG. Patients followed different dosing schedules, and the IVIGs originated from different producers. It does not appear likely that the mode of IVIG infusion correlates with the development or severity of this skin eruption. The mechanism of this rare adverse cutaneous reaction to IVIG remains unknown. It has been suggested that it may be a hypersensitivity reaction to one or several substances contained within IVIG preparations, such as stabilizers,¹⁵ animal pepsin,^{12,16} or an unidentified constituent. However, since this reaction occurs with IVIGs from different manufacturers that contain different stabilizers or have been virally inactivated in a different manner, this hypothesis is unlikely. Given the initial distribution of lesions, the hypothesis of a viral or paraviral cause related to the IVIG infusions was also considered, particularly parvovirus infection. However, IVIG preparations are currently tested for parvovirus and thus are considered parvovirus free.

Finally, although the predominant immunomodulatory effects of IVIG are anti-inflammatory, under certain circumstances IVIG may have the opposite effect. The IVIGs are known to affect the levels of certain cytokines or receptors including IL-1, IL-1 receptor antagonist, interferon alfa, tumor necrosis factor α , and IL-6 in a manner that is anti-inflammatory.²³ However, sequencing of IVIG-binding antibodies in a small number of patients with autoimmune disorders has suggested that IVIG can act in a manner analogous to a B-cell superantigen, and that certain B cells could be selectively activated following IVIG therapy.^{26,27}

Of the 37 cases reported to date, 35 were treated for a neurologic or neuromuscular disease, and in addition, 10 unpublished cases registered in the French drug surveillance databases¹⁹ received IVIG treatment for a neurologic disease. Although these data may be biased by more frequent use of IVIGs by neurologists, it is intriguing that most reported or registered cases of cutaneous eczematous rash following IVIG infusion have occurred in patients with neurologic disorders. It may be that neurologic disorders, which are often immunologic and frequently related to a past or concurrent viral infection, could predispose patients to this type of adverse reaction on IVIG infusion.

This rare cutaneous adverse drug reaction that occurs as a consequence of IVIG infusion is clinically characterized by an eczematous reaction that is most frequently initially localized to the palms and then becomes generalized to the whole body. The occurrence within days of IVIG infusion, characteristic distribution at onset, and the clinical course should be recognized by dermatologists.

Accepted for Publication: September 20, 2005.

Correspondence: Lars E. French, MD, Department of Der-

matology, Geneva University Hospital, 24, rue Micheli-du-Crest, CH-1211 Geneva 14, Switzerland (Lars.French@medecine.unige.ch).

Author Contributions: *Study concept and design:* French, Prins, and Saurat. *Acquisition of data:* Vecchiotti, Kerl, Prins, and Kaya. *Analysis and interpretation of data:* Vecchiotti, Kerl, and French. *Drafting of the manuscript:* Vecchiotti and Kerl. *Critical revision of the manuscript for important intellectual content:* French, Prins, and Saurat. *Study supervision:* French. **Financial Disclosure:** None.

Acknowledgment: We thank Michele Pisteur and Jose Fraga for the photographic work.

REFERENCES

- Dwyer JM. Manipulating the immune system with immune globulin. *N Engl J Med*. 1992;326:107-116.
- Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Engl J Med*. 2001;345:747-755.
- Sewell WA, Jolles S. Immunomodulatory action of intravenous immunoglobulin. *Immunology*. 2002;107:387-393.
- Jolles S, Hughes J, Whittaker S. Dermatological uses of high-dose intravenous immunoglobulin. *Arch Dermatol*. 1998;134:80-86.
- Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med*. 1991;324:1633-1639.
- Viard I, Wehrli P, Bullani R, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science*. 1998;282:490-493.
- Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy. *Ann Intern Med*. 1994;121:259-262.
- Brox AG, Cournoyer D, Sternbach M, Spurl G. Hemolytic anemia following intravenous gamma globulin administration. *Am J Med*. 1987;82(3 spec No.):633-635.
- Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. *Neurology*. 1994;44:223-226.
- Misbah SA, Chapel HM. Adverse effects of intravenous immunoglobulin. *Drug Saf*. 1993;9:254-262.
- Tan E, Hajinazarian M, Bay W, Neff J, Mendell JR. Acute renal failure resulting from intravenous immunoglobulin therapy. *Arch Neurol*. 1993;50:137-139.
- Chan-Lam D, Fitzsimons EJ, Douglas WS. Alopecia after immunoglobulin infusion. *Lancet*. 1987;1:1436.
- Rodeghiero F, Castaman G, Vespignani M, Dini E, Bertazzoni M. Erythema multiforme after intravenous immunoglobulin. *Blut*. 1988;56:145.
- Barucha C, McMillan JC. Eczema after intravenous infusion of immunoglobulin. *Br Med J (Clin Res Ed)*. 1987;295:1141.
- Hamdalla HH, Hawkes CH, Spokes EG, Bamford JM, Goulding PJ. Intravenous immunoglobulin in the Guillain-Barre syndrome. *BMJ*. 1996;313:1399-1400.
- Sorensen PS, Wanscher B, Jensen CV, et al. Intravenous immunoglobulin G reduces MRI activity in relapsing multiple sclerosis. *Neurology*. 1998;50:1273-1281.
- Whittam LR, Hay RJ, Hughes RA. Eczematous reactions to human immune globulin. *Br J Dermatol*. 1997;137:481-482.
- Barbaud A, Trechot P, Granel F, et al. A baboon syndrome induced by intravenous human immunoglobulins. *Dermatology*. 1999;199:258-260.
- Leclech C, Maillard H, Penisson-Besnier I, Laine-Cessac P, Verret JL. Unusual skin reaction after intravenous infusion of polyvalent immunoglobulins: 3 case reports [in French]. *Presse Med*. 1999;28:531.
- Iannaccone S, Sferazza B, Quattrini A, Smirne S, Ferini-Strambi L. Pompholyx (vesicular eczema) after IV immunoglobulin therapy for neurologic disease. *Neurology*. 1999;53:1154-1155.
- Ikedo K, Iwasaki Y, Ichikawa Y, Kinoshita M. Pompholyx after IV immunoglobulin therapy for neurologic disease. *Neurology*. 2000;54:1879.
- Uyttendaele H, Obadiah J, Grossman M. Dyshidrotic-like spongiotic dermatitis after intravenous immunoglobulin therapy. *J Drugs Dermatol*. 2003;2:337-341.
- Tada M, Tada M, Ishiguro H, Yagi E, Hirota K. Eczematous reactions after intravenous immunoglobulin therapy in two patients with Guillain-Barre syndrome and a patient with Miller Fisher syndrome [in Japanese]. *No To Shinkei*. 2003;55:401-405.
- Dalakas MC. The use of intravenous immunoglobulin in the treatment of autoimmune neuromuscular diseases. *Pharmacol Ther*. 2004;102:177-193.
- Ruetter A, Luger TA. Efficacy and safety of intravenous immunoglobulin for immune-mediated skin disease: current view. *Am J Clin Dermatol*. 2004;5:153-160.
- Osei A, Uittenreuther-Fischer MM, Lerch H, Gaedicke G, Fischer P. Restricted VH3 gene usage in phage-displayed Fab that are selected by intravenous immunoglobulin. *Arthritis Rheum*. 2000;43:2722-2732.
- Leucht S, Uittenreuther-Fischer MM, Gaedicke G, Fischer P. The B cell superantigen-like interaction of intravenous immunoglobulin (IVIG) with Fab fragments of V(H) 3-23 and 3-30/3-30.5 germline gene origin cloned from a patient with Kawasaki disease is enhanced after IVIG therapy. *Clin Immunol*. 2001;99:18-29.