Severe Eczematous Skin Reaction After High-Dose Intravenous Immunoglobulin Infusion

Report of 4 Cases and Review of the Literature

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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 steroids, 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.

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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.

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 see also page 247

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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 spongiosis 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-

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.
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), and simvastatine (Zocor) was not followed by the appearance of cutaneous lesions. Findings of a complete blood cell count and blood chemical analyses were normal. Serologic findings for human immuno deficiency virus, hepatitis B virus, B burgdorferi, M pneumoniae, herpes simplex virus type 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.

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.
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 spongiotic dermatitis. In 27 of 33 cases in the literature, extensive skin involvement was reported with biopsy specimens, histologic analysis revealed spongiotic dermatitis. In 27 of 33 cases in the literature, extensive skin involvement was reported with biopsy specimens, histologic analysis revealed spongiotic dermatitis. In 27 of 33 cases in the literature, extensive skin involvement was reported with biopsy specimens, histologic analysis revealed spongiotic dermatitis.

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

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

Abbreviations: ALS, amyotrophic lateral sclerosis; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; EBV, Epstein-Barr virus; GBS, Guillain-Barré syndrome; HTLV-1, human T-cell lymphotrophic 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; Sandoglobulin, Novartis, Basel, Switzerland; Tegeline, LFB Laboratories, Paris, France; Venoglobulin, Alpha Therapeutics Corp, Los Angeles, Calif.

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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 re-

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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 alpha, and IL-6 in a manner that is anti-inflammatory. 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.

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 databases 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.

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