Pompholyx and eczematous reactions associated with intravenous immunoglobulin therapy

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Introduction: Intravenous immunoglobulin (IVIG) is used to treat many inflammatory and autoimmune disorders and although generally well tolerated, cutaneous side effects occur.

Objective: We reviewed reports of pompholyx and eczematous reactions associated with IVIG.

Methods: A literature search was performed using the PubMed and MEDLINE databases with the search terms “intravenous immunoglobulin pompholyx,” “intravenous immunoglobulin eczema,” “intravenous immunoglobulin cutaneous adverse effects,” “intravenous immunoglobulin cutaneous effects,” “intravenous immunoglobulin skin effects,” and “intravenous immunoglobulin adverse effects.” Relevant English-language articles or articles in other languages cited in English-language articles were included.

Results: We identified 64 cases of eczematous reactions associated with IVIG therapy, including a patient treated on our inpatient consult service. In reported cases, the majority of patients (62.5%) had pompholyx alone or a combination of pompholyx on the hands or feet and two or fewer additional body surfaces involved. The majority of reported cases (75%) experienced the eczematous reaction after their first IVIG treatment. Neurologic conditions were the most common (85.9%) diseases for which IVIG was used. Most patients responded well to topical steroids or did not require treatment.

Limitations: Some reported cases had insufficient descriptions to be included in this review. A literature review may underestimate the frequency of eczematous reactions to IVIG because these reactions are often limited and may not be reported.

Conclusions: With the use of IVIG increasing, it is important for dermatologists to recognize this cutaneous side effect of IVIG. (J Am Acad Dermatol 2012;66:312-6.)

Key words: adverse skin reactions; dyshidrotic eczema; eczema; intravenous immunoglobulin; pompholyx.

Intravenous immunoglobulin (IVIG) was developed more than 30 years ago and is currently used on- and off-label for several dermatologic, neurologic, hematologic, and immunologic disorders. As a blood product consisting of only IgG antibodies pooled from at least 1000 different human donors, IVIG must be manufactured using viral inactivation measures and screened for infections to ensure its safety. Minor adverse effects occur in about 30% to 40% of patients and include headache, chills, fatigue, nausea, arthralgias, myalgias, and back pain. Rarely, more serious reactions may occur, including aseptic meningitis, renal failure, anaphylactic shock, hemolytic anemia, and thromboembolic complications. Although minor adverse effects may be related to the rate of infusion, some of the serious reactions may be related to the particular osmotic and sodium loads of the IVIG preparation, the rate of infusion, and host factors. For example, the risk of renal failure with IVIG is related not only to the sucrose content of the IVIG preparation and rate of infusion, but also host factors such as pre-existing renal disease, diabetes,
and hypertension. Cutaneous adverse effects may occur and vary in presentation from localized to generalized reactions and are estimated to occur in 0.4% to 6% of treated patients. There are several reports of urticaria and isolated reports of alopecia, erythema multiforme, lichenoid dermatitis, purpuric erythema, vasculitis, and morbilliform eruptions associated with IVIG, however, an underappreciated cutaneous reaction is eczema, often localized to the palms and soles as the vesicular variant, pompholyx.

METHODS

We conducted a literature review using the PubMed and MEDLINE databases and the search terms “intravenous immunoglobulin pompholyx,” “intravenous immunoglobulin eczema,” “intravenous immunoglobulin cutaneous adverse effects,” “intravenous immunoglobulin cutaneous effects,” “intravenous immunoglobulin skin effects,” and “intravenous immunoglobulin adverse effects,” for English-language articles. Relevant English-language articles or articles in other languages cited in English-language articles were included. We reviewed the titles and abstracts identified in the literature searches. We also reviewed references from bibliographies of pertinent articles.

RESULTS

We identified 64 cases to date of eczematous reactions associated with IVIG therapy, including a patient treated on our inpatient consult service. Two articles were non-English-language articles; one could be translated and one included a table in English with enough detail to be included in our analysis. Few additional cases were reported without the demographic and clinical data needed to be included.

Table 1 summarizes the clinical characteristics of the identified patients, including age; sex; history of atopy, including hand eczema, childhood asthma, and seasonal allergies; the underlying disease being treated with IVIG; the type of IVIG preparation and its dose and treatment course if reported; the type of eczematous reaction; the time for the reaction to appear and resolve; the treatments for the reaction if any; and the response to subsequent IVIG courses. Noneczematous skin reactions or reactions not specifically described as pompholyx or eczematous were excluded from our analysis. Biopsy specimens were obtained in only 13 patients; therefore, eczematous reactions were classified largely on a morphologic basis. Typical findings of pompholyx are shown in Fig 1, A and B, with multiple, grouped pinpoint clear and erythematous vesicles occurring on the palms and soles bilaterally. Representative histopathology reveals a loculated, spongiform vesicle, typical of dyshidrosis; a perivascular infiltrate consisting of lymphocytes and eosinophils; and exocytosis of lymphocytes into the epidermis (Fig 1, C).

Forty of the reported cases (62.5%) presented with pompholyx alone or a combination of pompholyx (hands or feet) and fewer than two body surfaces involved; 8 (12.5%) had pompholyx in association with a generalized, widespread eczematous eruption; 3 (4.7%) had widespread eczematous eruptions; and 13 (29.7%) had other unspecified eczematous reactions. The majority of eczematous reactions occurred during the first IVIG treatment course (75.0%). Most patients (85.9%) were being treated with IVIG for neurologic conditions. Interestingly, only 3 cases are reported of pompholyx occurring in patients treated with IVIG for dermatologic conditions, including one patient with Stevens-Johnson syndrome and two patients with chronic urticaria. Another patient with Stevens-Johnson syndrome developed vesicles on the palms after IVIG treatment, with histopathology showing an intracorneal vesicle without inflammatory cells in the epidermis or dermis, findings not entirely consistent with pompholyx.

There are no known risk factors for developing cutaneous adverse effects with IVIG therapy. When assessed, the majority of affected individuals did not have a personal history of atopy, eczema, allergic reactions, or another dermatologic condition. In our review, eczematous reactions and pompholyx were reported with multiple IVIG preparations but occurred most frequently with Sandoglobulin (Novartis, East Hanover, NJ), which may reflect its widespread use. Interestingly, switching the type of IVIG in 5 patients resulted in variable responses. One patient with pompholyx developed an identical reaction, one patient with pompholyx developed noneczematous skin eruptions of increased severity (Baboon syndrome and a morbilliform rash), one patient with no prior cutaneous
reaction developed a new vesicular facial eruption, and two patients with pompholyx or eczema improved with no subsequent reaction after a change in IVIG formulation. Most of the patients responded well to topical steroids or did not require therapy, although oral steroids were occasionally necessary. In 74.1% of reported cases, the reaction subsided in 3 or more weeks. For all reported cases, the eczematous reactions improved, although in one case, pruritus occurred for several months after IVIG treatment. There were no mortalities reported in these patients with eczematous reactions to IVIG; however, for many patients, IVIG was not continued because of these eczematous reactions.

DISCUSSION

IVIG use is becoming more widespread as the numbers of both indications and patients with autoimmune and inflammatory disorders increase. IVIG has several proposed mechanisms of action;
however, there is no clear mechanism that can explain the association with eczema. Interestingly, we were unable to identify any cases of pompholyx or eczematous reactions occurring in patients being treated with IVIG for an underlying immunodeficiency. There are two potential hypotheses to explain the near absence of eczematous reactions in the immunodeficient population treated with IVIG. First, this type of reaction may not occur in association with IVIG in individuals with true immune deficiency. Alternatively, the dose used to treat immunodeficiency is typically lower than that used in neurologic, hematologic, and dermatologic conditions described here (0.4 and 2 g/kg, respectively), which could suggest that pompholyx and eczematous reactions occur only when high-dose IVIG is used. This may reflect a possible dose response for eczematous reactions.

Although eczematous reactions to IVIG are reported to wane over time, in our review we found that the reaction was likely to recur with subsequent treatments, and, in the majority of patients, the reaction worsened. Because pompholyx is treatable, the general recommendation is for IVIG treatment to be continued for patients experiencing clinical benefit. In the case of severe cutaneous reactions, IVIG should be discontinued.

Dermatologists should be aware that pompholyx and eczema are common cutaneous adverse effects of IVIG that can occur alone or in combination, and that these effects may worsen upon subsequent IVIG treatments. However, these effects can be successfully treated, allowing continuation of IVIG therapy if warranted.

REFERENCES