Case Reports in Dermatology

Case Rep Dermatol 2023;15:182–189
DOI: 10.1159/000533987
Received: May 31, 2023
Accepted: August 30, 2023
Published online: October 16, 2023

Single Case

Intravenous Immunoglobulin Therapy-Induced Erythema Multiforme in a Patient with Chronic Lymphocytic Leukemia

Angelina Konovalova[a, b] Natālija Gerula[a, c] Ilona Hartmane[a, b]
Ilze Upeniece[a, b] Mihails Ščerbuks[d] Kristīne Bernāte[a]
Lelde Reinberga[a, b] Ingmārs Mikažāns[a, b]

[a]Riga Stradins University, Riga, Latvia; [b]Department of Dermatology and Venereology, Pauls Stradiņš Clinical University Hospital, Riga, Latvia; [c]Dermatology and STI Clinic, Riga 1st Hospital, Riga, Latvia; [d]Central Laboratory, Riga, Latvia

Keywords
Erythema multiforme · Intravenous immunoglobulin

Abstract
This case report discusses immunoglobulin-induced erythema multiforme (EM), a rare and understudied condition that requires further investigation. The report presents the case of a 69-year-old woman with a history of chronic lymphocytic leukemia who developed an acute hypersensitivity reaction to intravenous gamma globulin medication. The patient received intravenous immunoglobulin (IVIG) to normalize and stabilize her immunoglobulin levels and reduce the risk of recurrent infections due to her immunodeficiency with predominantly antibody defects. However, after the second administration of the medication, the patient experienced an acute skin rash and was admitted to the hospital for treatment. The treatment plan included systemic desensitizing therapy, systemic antihistamine therapy, corticosteroid therapy, and local therapy. After a course of therapy, the patient's skin condition improved, and her overall well-being improved. However, due to the acute hypersensitivity reaction, the IVIG therapy was discontinued. The multidisciplinary team of specialists concluded that the patient had developed EM. The discussion provides an overview of EM, including its causes, clinical presentation, diagnostic tools, and therapy principles. The discussion also describes the use of human IVIG preparations in treating various immunodeficient and inflammatory diseases, highlighting the importance of monitoring patients for adverse effects. The case of this patient

Correspondence to:
Angelina Konovalova, a.konovalova1515@inbox.lv

Case Rep Dermatol 2023;15:182–189
DOI: 10.1159/000533987

underscores the potential risks associated with immunoglobulin therapy and emphasizes the need for healthcare providers to remain vigilant for adverse reactions. By promptly diagnosing and treating EM, healthcare providers can minimize its impact on patients' overall well-being.

Introduction

Intravenous immunoglobulin (IVIG) therapy is commonly used to treat a variety of autoimmune and inflammatory conditions. While it is generally considered safe, some patients may experience skin reactions as a side effect. It is important for patients to be aware of these possible side effects and to immediately report any symptoms to their healthcare provider.

Erythema multiforme (EM) is a skin disorder that is characterized by the development of distinctive lesions on the skin and mucous membranes. While it can have many causes, one is drug-induced EM. Drug-induced EM is typically a benign condition that resolves on its own once the offending medication is discontinued, but in rare cases, it can progress to a more severe form of the disease known as Stevens-Johnson syndrome or toxic epidermal necrolysis, which can be life-threatening.

Case Report

A 69-year-old woman visited an immunologist for consultation after being referred by a hematologist due to progressive changes in her immunoglobulin (IG) levels, particularly with regards to IgG. She has a history of stage 1A chronic lymphocytic leukemia (CLL) since 2016. To treat this illness, the patient takes intravenous rituximab solution 100 mg according to the protocol. In her medical history, she also has other comorbidities, including chronic rhinosinusitis, recurrent stomatitis, autoimmune thyroiditis, which do not respond well to drug therapy and spontaneous abortions. The patient also reports seasonal allergic reactions, allergies to insect bites, and an episode of angioedema.

The patient underwent immunological testing which revealed the following results: an IgG level of 442 mg/dL (normal range 650–1,600 mg/dL), IgA level of 48 mg/dL (normal range 40–350 mg/dL), IgM level of 39 mg/dL (normal range 50–300 mg/dL), IgE level of 597 IU/mL (normal range 0–100 IU/mL), while her IgE-specific antibody panel remained unchanged. Given her immunodeficiency with predominantly antibody defects, unspecified (ICD-10 code: D80.9), therapy with intravenous gamma globulin was recommended. After obtaining approval from the National Health Service (NHS), the patient was prescribed human IG medication for intravenous use, 50 mg/mL (200 mL) once a month (total monthly dose of 400 mL or 20 g of IG) for a course duration of 1 year to normalize and stabilize her IgG levels and reduce the risk of recurrent infections.

The first administration of the drug was documented as successful in the NHS records. However, the day after the second IVIG administration (August 5, 2022), the patient experienced an acute reaction with a skin rash on her feet accompanied by itching, redness, and bullae. Her overall health has deteriorated, and she has reported a fever. On the same day, she visited an allergist for an outpatient consultation, who conducted skin tests for classical respiratory and food antigens. The results showed no indication of allergy, leading the allergist to conclude that the high level of IgE was likely related to the patient's CLL rather than

an allergic reaction to the drug. After consulting with her attending physician, the patient was admitted to the Riga 1st Hospital, Dermatology and Sexually Transmitted Infections Clinic's day hospital for medical care, and was prescribed temporary therapy with antihistamines.

On August 16, 2022, when the patient was admitted to the hospital, she presented with annular target-like pink infiltrated macular elements on her hands, feet, and right knee, all of which had a lighter center. In some places, there were blisters of varying diameters with serous content that were tense and did not burst spontaneously (Fig. 1). The mucosa was not involved; no rash appeared. The main differential diagnoses were bullous pemphigoid, erythema multiforme, fixed erythema, and a hypersensitivity reaction to the administered medication. To confirm the diagnosis, 3-mm punch biopsies were taken from two distinct skin lesions.

For treatment in the day hospital, the patient received systemic desensitizing therapy and systemic antihistamine therapy. The initial therapy did not produce improvement, and systemic corticosteroid therapy with 8 mg of dexamethasone solution intravenously, with a gradual dose reduction until withdrawal, was indicated. For local therapy, the patient was prescribed prednisolone cream with boric paste.

After undergoing a course of oral glucocorticoid therapy, an improvement in the patient's skin condition was observed and the skin elements continued to regress (Fig. 2). The patient's overall well-being also noticeably improved. With a significant clinical improvement on August 26, 2022, the patient was discharged from the hospital for further treatment under the supervision of an immunologist and a hematologist.

The patient was monitored for a while, and no further symptoms were reported. Further immunological testing was performed, and the results showed that the patient's IgG level had returned to normal. The patient was advised to continue with regular checkups and monitoring of her immune system. The multidisciplinary team of specialists, after considering the risks and benefits, decided to stop the IVIG therapy due to the patient's acute immune-mediated skin reaction to the protein-containing preparation.

In the epidermis, there is a small blister containing lymphocytes. Edema is present in the dermal papillary layer, where subepidermal blisters have formed. In the dermis, there is a pericapillary lymphohistiocytic infiltrate with eosinophil leukocytes and lymphocytes in the interstitium (Fig. 3). Based on the examination of the morphological preparations, the first pathologist established two diagnoses: bullous pemphigoid (L.12.0) and erythema multiforme (L51). Based on the negative direct immunofluorescence, the diagnosis of bullous pemphigoid (L.12.0) was excluded. A multidisciplinary team of specialists concluded that the patient had developed EM (L51). This diagnosis was consistent with the clinical presentation.

Discussion

EM is an immune-mediated reaction that affects the skin and, sometimes, the mucous membranes. It is often characterized by target-like appearance lesions. The lesions can be isolated, recurrent, or persistent and most commonly appear symmetrically on the extremities. While the exact cause of EM is not fully understood, it is believed to be triggered by infections, medications, and other factors that can cause an immune response in the body. Immunizations and autoimmune diseases have also been linked to this condition [1].

One of the rare causes of EM is drug-induced EM, where certain medications can trigger the immune system to produce an abnormal response, leading to the development of EM. This is a relatively uncommon occurrence and is estimated to occur in less than 1% of patients who take medications [2].

Case Rep Dermatol 2023;15:182–189
DOI: 10.1159/000533987

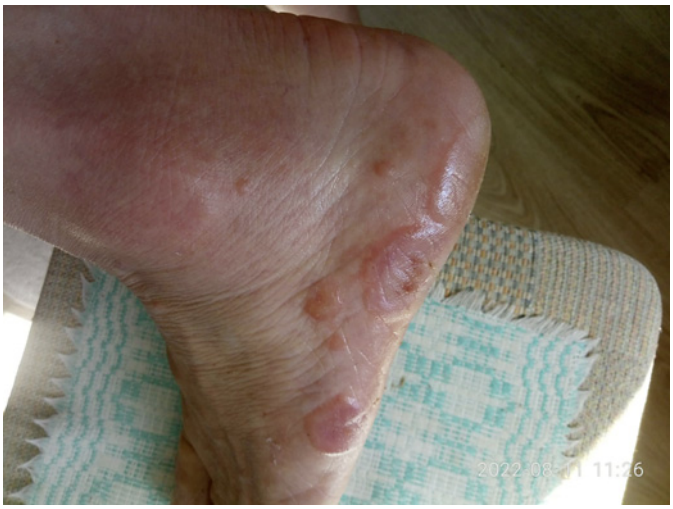

Fig. 1. Target-like skin rash the day after the second IVIG administration.

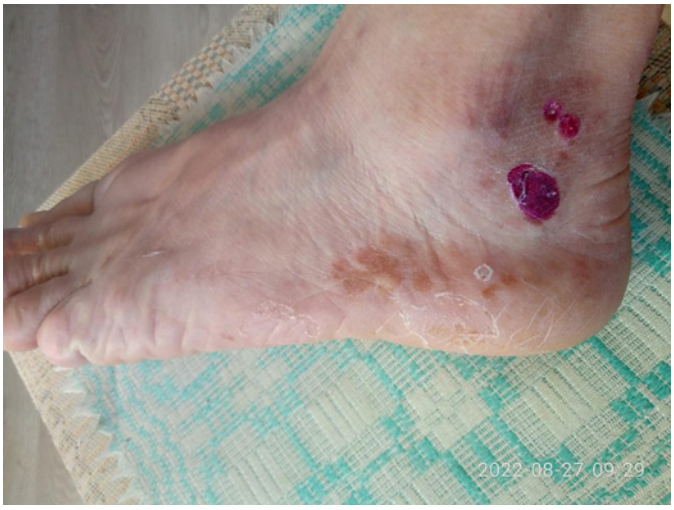

Fig. 2. Skin rash after therapy course in the hospital.

On the other hand, IG-induced EM is a less common type of EM that occurs as a side effect of IVIG therapy. Immunoglobulins are proteins that are used to treat a variety of conditions by boosting the immune system. However, in some cases, IVIG therapy can trigger an immune response that leads to the development of EM [3].

While drug-induced EM is rare, it is still a well-known condition that has been studied extensively. In contrast, IG-induced EM is a relatively new phenomenon that has only recently been recognized as a possible side effect of IVIG therapy. As such, there is a need for more research and information about this condition to help healthcare providers identify and manage it in their patients [3].

Therefore, an article that describes IG-induced EM is very relevant and timely, as it can help raise awareness of this rare condition among healthcare providers and provide guidance on how to diagnose and manage it. It can also help researchers better understand the mechanisms behind this condition and develop new treatments to address it [4].

Case Rep Dermatol 2023;15:182–189
DOI: 10.1159/000533987

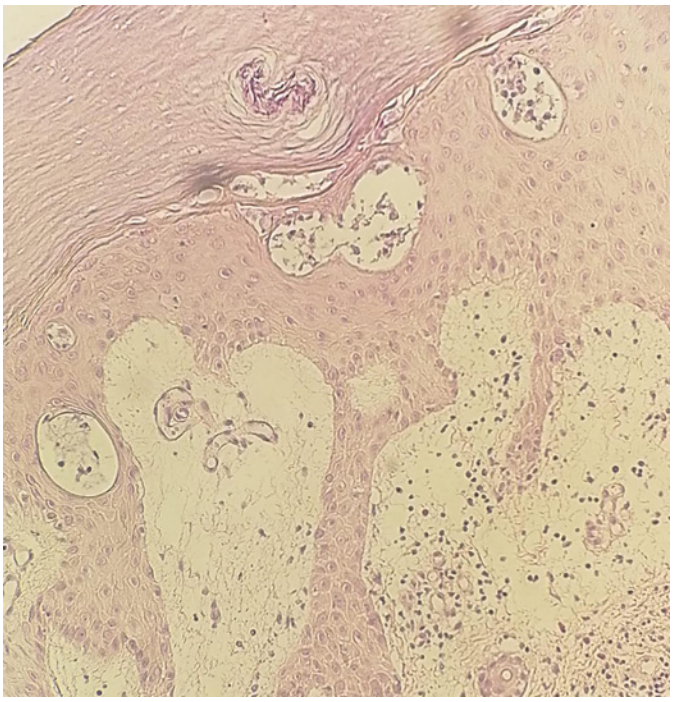

Fig. 3. Erythema exsudativum multiforme, histological image (dermoepidermal type).

The lesions of EM typically start as pink or red papules that may cause itching or burning. Over time, the lesions can transform into a variety of appearances, including the classic target or iris lesion, which has three concentric segments. Lesions are initially found symmetrically on the extremities, especially on extensor surfaces. They usually spread centripetally but tend to be fewer on patients' trunks. Palms and soles may also be involved. EM has a predilection for areas of sunburn or physical trauma. Cutaneous lesions usually heal without complication, but skin hyperpigmentation may occur [1, 5].

The diagnosis of EM is based on clinical evaluation, with a focus on the patient's history of recent infections and medication use. Skin biopsies and laboratory tests may be helpful in unclear cases [5]. The results of skin biopsies vary based on the timeline of the lesion and the location of the biopsy within the lesion. Direct immunofluorescence can help differentiate between EM and autoimmune blistering diseases, such as bullous pemphigoid [5].

The treatment of EM depends on the underlying cause and the severity of the condition. Symptomatic treatment using topical steroids or antihistamines is often recommended for acute, uncomplicated cases. When the cause is an infection or medication, treating the underlying issue is necessary [5].

Human IVIG preparations have been used for the treatment of a wide range of immunodeficient and inflammatory diseases. Indications for use also include replacement therapy for patients with secondary immunodeficiency. It is considered that the administration of IG has first-class evidence for the treatment of patients with myeloma and CLL [6, 7].

The main component of IVIGs is IgG, which makes up at least 90–98% of the preparation. It is the most prevalent IG in blood plasma and plays a leading role in humoral immunity. However, all preparations also contain IgA, IgM in various concentrations [8]. Secondary hypogammaglobulinemia (SHG) is characterized by reduced IG levels due to acquired causes of decreased antibody production or increased antibody loss [9].

IgG level cut-offs used to define hypogammaglobulinemia (HG) vary in the literature. This report aims to standardize future studies by proposing the definition of HG in adult patients as a serum IgG level below 700 mg/dL, further stratified into the following brackets: 400–699 mg/dL, 200–399 mg/dL, and 0–199 mg/dL. It is important to consider age-appropriate reference ranges for pediatric patients and variability in reference ranges between laboratories for IGs [9].

CLL is associated with a high risk of developing SHG and infections due to both the underlying nature of the condition and the availability of immunosuppressive treatments [9]. The clinical spectrum of SHG in CLL ranges from an asymptomatic laboratory abnormality to an increased infectious burden, with frequent or chronic severe sinopulmonary and/or opportunistic infections [9].

Currently, the FDA has approved IVIG only for the replacement therapy of SHG associated with B-cell CLL. The recommended therapy is for individuals with a serum IgG level of less than 500 mg/dL and recurrent or severe infections. When IgG-RT is clinically indicated, a dosing range of IVIG 0.4–0.8 mg/kg of absolute body weight every 28 days is recommended [9].

According to the literature, IG drugs for IV administration are generally well tolerated. The most common adverse events may include chills, headache, facial flushing, myalgia, back pain, and nausea. They may have a mild degree of expression and are usually reversible. In general, the frequency of mild and moderate adverse events per infusion is 5–15% [6, 10, 11]. Studies of the tolerability of IVIG used in this case in 6,357 patients with primary and secondary immunodeficiencies or autoimmune diseases showed adverse events in only 0.35%. Most reactions were of mild or moderate intensity [12].

However, there are also serious adverse events associated with such treatment, such as acute renal failure, stroke, myocardial infarction, venous thromboembolism, anaphylaxis, septic meningitis, and hemolysis. These are extremely rare. Such events are potentially life-threatening and raise concerns among researchers [13, 14]. Studies have noted that the risk of severe complications is higher in females, patients with severe inflammatory diseases, and patients with blood groups different from those of the first group, indicating a possible role of passive transfer due to hemagglutinins in the development of hemolysis [15].

The case report offers insights into the rare condition, IG-induced EM, aiding healthcare providers in its diagnosis and management. It details the patient's history, tests, and treatments, emphasizing the need to monitor adverse reactions to IVIG therapy. However, its scope is limited to 1 case, and it lacks data on prior treatments and long-term outcomes. Further research is crucial to understand the prevalence and nuances of IG-induced EM. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533987).

Conclusions

IVIG is a commonly used therapy for immunodeficient and inflammatory diseases and is generally well tolerated, although rare serious adverse events can occur. Further research is needed to understand the underlying mechanisms, develop new treatments, and identify patients at a higher risk of adverse events.

Statement of Ethics

This study protocol was reviewed and approved by the Riga Stradins University ethics committee, approval number 2-PĒK-4/453/2023. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was funded by Riga Stradins University. However, the funding source had no role in the preparation of this manuscript.

Author Contributions

Dr. Konovalova contributed to data collection, case report description, and clinical treatment. Prof. Hartmane provided supervision, study design, and data interpretation. Dr. Gerula played a key role in recommending gamma globulin therapy based on the initial consultation and test results, as well as contributing to the writing of the discussion. Dr. Upeniece played a key role in diagnosing and treating erythema multiforme. Dr. Ščerbuks, as a pathologist, established diagnoses of bullous pemphigoid and erythema multiforme. Prof. Mikažāns provided dermatological expertise, clinical management insights, and manuscript revisions. Dr. Bernāte, a hematologist, contributed valuable input on the patient's chronic lymphocytic leukemia. Dr. Reinberga observed and documented dermatological manifestations and contributed to the writing of the discussion.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Huff JC, Weston WL, Tonnesen MG. Erythema multiforme: a critical review of characteristics, diagnostic criteria, and causes. J Am Acad Dermatol. 1983;8(6):763–75.
2 Handfield-Jones SP, Heymann AD. Drug-induced erythema multiforme. Am Fam Physician. 2003;68(11):2243–8.
3 Elkins MJ, Lauer SJ. Immunoglobulin-induced erythema multiforme: a case report and review of the literature. J Clin Aesthet Dermatol. 2014;7(8):47–51.
4 Hart K. Immunoglobulin-induced erythema multiforme: a rare but potentially serious side effect of immunoglobulin therapy. J Infusion Nurs. 2017;40(5):288–94.
5 Sokumbi O, Wetter DA. Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. Int J Dermatol. 2012;51(8):889–902.
6 Ballow M. Safety of IGIV therapy and infusion-related adverse events. Immunol Res. 2007;38(1–3):122–32.

7 Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the primary immunodeficiency committee of the American academy of allergy, asthma and immunology. J Allergy Clin Immunol. 2006;117(4 Suppl l):S525–53.
8 Shah S. Pharmacy considerations for the use of IGIV therapy. Am J Health Syst Pharm. 2005;62(16_Supplment_3):S5–11.
9 Practical guidance for the diagnosis and management of secondary hypogammaglobulinemia: a work group report of the AAAAI primary immunodeficiency and altered immune response committees. [online]. Available from: https://www-sciencedirect-com.db.rsu.lv/science/article/pii/S009167492200152X.
10 Looney RJ, Huggins J. Use of intravenous immunoglobulin G (IVIG). Best Pract Res Clin Haematol. 2006;19(1):3–25.
11 Debes A, Bauer M, Kremer S. Tolerability and safety of the intravenous immunoglobulin Octagam: a 10-year prospective observational study. Pharmacoepidemiol Drug Saf. 2007 Sep;16(9):1038–47.
12 Brennan VM, Salome-Bentley NJ, Chapel HM; Immunology Nurses Study. Prospective audit of adverse reactions occurring in 459 primary antibody deficient patients receiving intravenous immunoglobulin. Clin Exp Immunol. 2003 Aug;133(2):247–51.
13 Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. Transfus Med Rev. 2003 Oct;17(4):241–51.
14 Bonilla FA. Intravenous immunoglobulin adverse reactions and management. J Allergy Clin Immunol. 2008 Dec;122(6):1238–9.
15 Daw Z, Padmore R, Neurath D, Cober N, Tokessy M, Desjardins D, et al. Hemolytic transfusion reactions after administration of intravenous immune (gamma) globulin: a case series analysis. Transfusion. 2008 Aug;48(8):1598–601.