

Hypersensitivity to Aldesleukin (Interleukin-2 and Proleukin) Presenting as Facial Angioedema and Erythema

Daryn Abraham, M.D., and Kris G. McGrath, M.D.

ABSTRACT

Aldesleukin is a human recombinant interleukin-2 product. It also is known as interleukin-2 and Proleukin in the United States. It is indicated for the treatment of adults with metastatic renal cell carcinoma as well as for adults with metastatic melanoma. However, its use has been limited because of severe systemic toxicity. There have been no reports of aldesleukin producing a hypersensitivity reaction. This is the first reported case of an immediate systemic hypersensitivity reaction occurring after aldesleukin administration confirmed by enzyme-linked immunosorbent assay for specific immunoglobulin E against aldesleukin. (Allergy and Asthma Proc 24:291-294, 2003)

Aldesleukin is a human recombinant interleukin (IL)-2 product. It is a highly purified protein and has a molecular weight of ~15,300 Da. Aldesleukin, a lymphokine, is produced by recombinant DNA technology using a genetically engineered strain of *Escherichia coli* containing an analog of the human IL-2 gene.¹ Aldesleukin has been shown to possess the biological activity of human IL-2.^{2,3}

The major limitations on the use of aldesleukin (IL-2) relate to its toxicity.⁴ High-dose IL-2 (600,000-IU/kg dose

administered every 8 hours for an average of 14 doses) has been associated with the capillary leak syndrome (CLS), characterized by episodic capillary hyperpermeability with a shift of fluid and protein from intravascular to interstitial space.⁵ This results in a drop of the mean arterial blood pressure within 2–12 hours after the start of the treatment. A massive loss in vascular tone follows, resulting in hypotension and reduced organ perfusion, which can result in death. Five percent of patients have experienced fatal outcomes, usually caused by myocardial infarction or arrhythmia.⁶ Aldesleukin also is associated with impaired neutrophil function and consequently carries an increased risk of infection and possible sepsis. In addition, it has been associated with exacerbation of preexisting autoimmune conditions such as Crohn's disease, inflammatory arthritis, diabetes mellitus, and glomerulonephritis. Other toxicities include prerenal azotemia and elevation of liver enzymes. The rate of drug-related deaths in the 255 metastatic renal cell carcinoma patients who received single-agent aldesleukin was 4% (11/255); the rate of drug-related deaths in 270 metastatic melanoma patients who received single-agent aldesleukin was 2% (6/270).¹ Most adverse reactions are reported to be self-limiting and resolve within 2 or 3 days after discontinuation of the drug. There have been no reports of immunoglobulin E (IgE)-mediated hypersensitivity to recombinant IL-2.

CASE REPORTS

A 61-year-old woman developed facial swelling and erythema after receiving high-dose IL-2 therapy. Fourteen hours after receiving her first dose of aldesleukin, the patient initially noticed erythema of her cheeks that

From the Division of Allergy-Immunology and the Ernest S. Bazley Asthma and Allergic Diseases Center, Department of Medicine, Northwestern Memorial Hospital and Northwestern University Medical School, Chicago, Illinois

Supported by the Ernest S. Bazley Grant to Northwestern Memorial Hospital and Northwestern University Medical School

Address correspondence and reprint requests to Kris G. McGrath, M.D., 303 East Chicago Avenue S207, Chicago, IL 60611-3008



Figure 1. A 61-year-old woman with facial and neck angioedema and erythema 14 hours after receiving high-dose aldesleukin (IL-2) therapy.

proceeded to encompass her entire face. The erythema progressed to her upper chest and back. There were no bullae, blisters, or pain associated with the rash. Within 30 minutes of noticing the erythema, she began to experience facial swelling involving primarily her cheeks, eyelids, and neck (Fig. 1). The patient denied any wheezing, shortness of breath, lightheadedness, chest tightness, or difficulty swallowing.

The patient had a past medical history significant for hypertension and metastatic melanoma. She had no history of drug allergies. She had a history of developing hives after radiocontrast media, which occurred 1 month earlier. She has no history of asthma, urticaria, or food allergies. Family history was significant for a father who died at the age of 78 years from bladder cancer. Her mother also died at the age of 78 years from complications of multiple sclerosis. She was not taking any prescription medications. The patient denied the use of any herbal, dietary supplements, and over the counter medications including nonsteroidal anti-inflammatory drugs, aspirin, or sleep aids. There was no recent food ingestion.

On physical examination the patient appeared well and in no distress at rest. Her temperature was 98.1°F. Pulse was regular at a rate of 100 bpm. Respirations were 20/minute. Pulse oximetry was 96% on room air. Head and neck examination revealed diffuse facial edema including peri-orbital swelling and neck swelling. Comparison to driver's



Figure 2. A 61-year-old woman with complete resolution of angioedema and erythema 2 days after completion of high-dose aldesleukin (IL-2) therapy.

license photograph did reveal a significant increase in facial tissue. Diffuse erythema also was present on her face, upper chest, and back. Nasal mucosa was pink without edema or discolored secretions. Oropharynx was patent without edema. Neck was supple without lymphadenopathy. Lungs were clear to auscultation bilaterally. Cardiac examination revealed normal S1 and S2. Abdomen was soft, nontender, and nondistended with no hepatosplenomegaly. Extremities did not reveal any clubbing, cyanosis, or edema.

The white blood cell count was 10,100 with no evidence of eosinophilia. The hemoglobin was 14.6 and the platelet count was 170,000. Her renal function and electrolytes were normal. Liver function tests, albumin, and tryptase level were also normal. Chest x-ray was unremarkable. Complement CH50, C3, and C4 were within normal range as well. The patient received a total of 75 mg of Diphenhydramine with minimal improvement. Steroids were recommended but not started because glucocorticoids have been shown to reduce the antitumor effectiveness of aldesleukin.⁷ The patient was started on 25 mg of hydroxyzine three times per day. However, the facial angioedema and erythema persisted. Nevertheless, no progression of symptoms occurred. Within 2 days of completing her course of IL-2 therapy, her symptoms completely resolved (Fig. 2). The patient suffered recurrence of similar symptoms during her second and

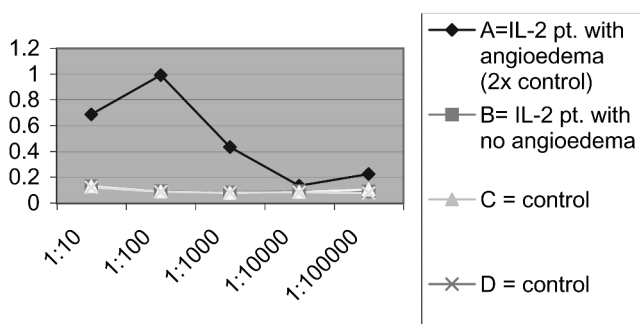


Figure 3. Graph displaying IgE levels to aldesleukin (at a dilution of 1:100) at various serum dilutions. (A) Patient who developed angioedema; (B) patient who was administered aldesleukin without reaction; (C and D) control patients.

third courses of high-dose aldesleukin therapy. Her symptoms would always abate within 2–3 days of discontinuing aldesleukin.

INVESTIGATION

Approximately 1 month after the patient's first course of aldesleukin, the patient underwent aldesleukin skin testing with the commercial preparation that was implicated, as well as positive control with histamine and negative control with phenol saline solution. Aldesleukin was diluted with phenol saline solution, and she failed to have any reaction to prick testing at a dilution of 1:100. She had a 2-mm wheal without flare during intradermal testing at dilutions of 1:10,000 and 1:1000. She did have a positive response within 20 minutes to a 1:100 dilution of aldesleukin intradermally (8-mm wheal with 11-mm flare). However, four control subjects also reacted positively to intradermal testing at the 1:100 dilution. It was concluded that the reaction produced by all subjects at the 1:100 intradermal dilution was likely an irritant effect.

Each milliliter of aldesleukin is equivalent to 8 million IU of aldesleukin, which contains 1.1 mg of protein. The stock solution was diluted 100-fold with calcium carbonate coating buffer. An enzyme-linked immunosorbent assay was subsequently performed for specific IgE against aldesleukin. The results are displayed in Fig. 3. Various dilutions of the patient's serum (A) ranging from 1:10 and 1:100,000 were checked for specific IgE against aldesleukin. Her serum was compared with two control subjects who had no exposure to aldesleukin (C and D) as well as to another patient (B) who had received 10 doses of aldesleukin in the past. The serum of the patient (B) was obtained ~6 weeks after her last dose. As is displayed in Fig. 2 evidence of IgE was detected even at serum dilutions of 1:100,000 for our patient (A). The optical density was twice that of the control patients. Neither the controls nor the other patient with aldesleukin exposure in the past developed any evidence of IgE.

Unfortunately, a greater sample size of patients receiving aldesleukin was not able to be tested because of the scarcity

of patients on aldesleukin therapy in our institution. Moreover, the high cost of aldesleukin also limited the amount available for research testing.

DISCUSSION

Aldesleukin, has been shown to possess the biological activity of IL-2. *In vitro* studies have shown profound immunoregulatory effects including (1) enhancement of lymphocyte mitogenesis and stimulation of long-term growth of human IL-2-dependent cell lines, (2) enhancement of lymphocyte cytotoxicity, (3) induction of killer cell activity, and (4) induction of interferon γ production.¹ *In vivo* studies also have shown that aldesleukin produces multiple immunologic effects. It has been shown to cause profound lymphocytosis, eosinophilia, and thrombocytopenia, and the production of cytokines including tumor necrosis factor, IL-1, and interferon γ .³ The powerful immunoregulatory effects of aldesleukin allow it to function as an effective agent for advanced-stage metastatic cancer.

Aldesleukins' immunologic effects also contribute to its potential for toxicity. Activation of natural killer cells by aldesleukin has been proposed to mediate its toxicity.⁸ One of the toxicities known to occur with aldesleukin is CLS, characterized by hypotension, edema, pleural effusions, and weight gain caused by fluid retention. Vascular leak syndrome has been defined by the presence of two or more of the following three symptoms: hypotension, edema, and hypoalbuminemia.⁹ With regard to aldesleukin therapy, CLS begins immediately after aldesleukin treatment starts and results in increased capillary permeability and decreased vascular tone. With continued therapy, significant hypotension can occur leading to reduced organ perfusion and possibly death. It has been associated with cardiac arrhythmias, angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding, renal insufficiency, and mental status changes. Because our patient did present with edema, the diagnosis of CLS initially was entertained. However, she did not suffer from hypotension or any other symptoms commonly associated with CLS and she did not have any evidence of hypoalbuminemia. It may be possible that the patient's reaction was a *forme fruste* of CLS in that it failed to progress beyond angioedema.

To our knowledge, this is the first reported case of hypersensitivity reaction occurring after administration of aldesleukin. Hypersensitivity reactions have been reported only in patients receiving combination therapy. Such therapies have included regimens containing sequential high-dose aldesleukin and antineoplastic agents, specifically dacarbazine, *cis*-platinum, tamoxifen, and interferon α . These hypersensitivity reactions consisted of erythema, pruritus, and hypotension and occurred within hours of administration of chemotherapy.¹

As the use of aldesleukin increases, the medical community needs to be aware of the potential for serious reactions.

Moreover, the reluctance to use steroid therapy for hypersensitivity reactions to aldesleukin makes for a challenging treatment. As more chemotherapeutic agents such as aldesleukin become more available as lifesaving interventions, physicians also must maintain a heightened awareness for potential life-threatening adverse reactions.

ACKNOWLEDGMENTS

The authors thank Donna Watkins (Division of Allergy/Immunology, Northwestern University Medical School) for her technical assistance with the enzyme-linked immunosorbent assay preparation and analysis.

REFERENCES

1. Aldesleukin. In Mosby's Drug Consult. Nissen D (Ed). St. Louis, MO: Mosby, Inc., 53–57, 2001.
2. Ralph P, Nakoinz I, Doyle M, et al. Human B and T lymphocyte stimulating properties of interleukin-2 (IL-2) muteins. In *Immune Regulation by Characterized Polypeptides*. Goldstein G, Bach J, and Wigzell H (Eds). New York: Alan R. Liss, Inc., 453–462, 1987.
3. Winkelhake JL, and Gauny SS. Human recombinant interleukin-2 as an experimental therapeutic. *Pharmacol Rev* 42:1–28, 1990.
4. Siegel JP, and Puri RK. Interleukin-2 toxicity. *J Clin Oncol* 9:694–704, 1991.
5. Rosenstein M, Ettinghausen SE, and Rosenberg SA. Extravasation of intravascular fluid mediated by the systemic administration of recombinant interleukin-2. *J Immunol* 137:1735–1742, 1986.
6. Rosenberg SA, Lotze MT, Muul LM, et al. Experience with the use of high-dose interleukin-2 in the treatment of 652 cancer patients. *Ann Surg* 210:474–484, 1989.
7. Mier JW, Vachino G, Klempner MS, et al. Inhibition of interleukin-2-induced tumor necrosis factor release by dexamethasone: Prevention of an acquired neutrophil chemotaxis defect and differential suppression of interleukin-2-associated side effects. *Blood* 76:1933–1940, 1990.
8. Shanfelt AB. A T-cell-selective interleukin 2 mutein exhibits potent antitumor activity and is well tolerated in vivo. *Nat Biotechnol* 18: 1197–1202, 2000.
9. Railan D. Capillary leak syndrome in a patient treated with interleukin 2 fusion toxin for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 43:323–324, 2000. □

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.