# Urticaria and angiodema following subcutaneous injection of recombinant human granulocyte-macrophage colony-stimulating factor (rhuGM-CSF) in a patient with metastatic melanoma*

# *Urticária e angiodema associados a fator estimulador das colônias de granulócitos e macrófagos recombinante humano (rhuGM- CSF) em portador de melanoma metastático**

Mario Geller[1] Priscila Geler Wolff[2]

**Abstract:** A case of metastatic melanoma controlled for the last six months using periodic subcutaneous injection of recombinant human granulocyte-macrophage colony-stimulating factor (rhuGM-CSF) is presented. To our knowledge, it is the first time in Brazil that urticaria and angioedema associated with this treatment are reported. The classical combination of dexchlorpheniramine and prednisone was able to prevent these adverse reactions. Epinephrin auto-injector was made available during the rhuGM-CSF administration.
Keywords: Angioneurotic edema; Hypersensitivity; Immunomodulator; Melanoma; Urticaria

***Resumo**: É apresentado um caso de melanoma metastático controlado há seis meses com o fator estimulador das colônias de granulócitos e macrófagos recombinante humano (rhuGM-CSF), administrado periodicamente por via subcutânea. Os autores descrevem, pela primeira vez no Brasil, a presença de urticária gigante e angioedema associados a essa bioquimioterapia imunoestimulatória, tendo controlado essas reações adversas com o emprego de um esquema clássico antialérgico preventivo composto de dexclorfeniramina e prednisona. Epinefrina auto-injetora tornou-se disponível durante a administração do rhuGM-CSF.*
*Palavras-chave: Edema angioneurótico; Hipersensibilidade; Imunomodulador; Melanoma; Urticária*

The recombinant human granulocyte-macrophage colony-stimulating factor (rhuGM-CSF) belongs to the family of glycoproteins that influence in proliferation, maturation and function of hematopoietic stem cells.[1]

The recombinant human granulocyte-macrophage colony-stimulating factor (rhuGM-CSF) is available through cloning.[2] Some adverse reactions, such as facial hyperemia, tachycardia, arterial hypotension, musculoskeletal pain, dyspnea, nausea and vomiting, muscle rigidity, involuntary spasms in lower limbs and syncope, have been described after the first dose of this immunostimulanting factor, but they usually do not persist after subsequent doses.[3]

The authors believe they are pioneers in Brazil in describing the presence of urticaria and angioedema after subcutaneous administration of rhuGM-CSF in a patient suffering from metastatic melanoma. Since the patient had a good therapeutic response to stimulatory biochemotherapy, the treatment was maintained and the patient was premedicated with antihistamine (anti-H1) and prednisone. The allergy symptoms in skin were properly inhibited in further cycles.

A 75-year-old Caucasian male patient, with metastatic melanoma (axillary lymph node, liver, colon and adrenal gland), on biochemotherapy with recombinant human granulocyte-macrophage colony-stimulating factor (rhuGM-CSF), a single daily dose, subcu-

Received on December 17, 2005.
Approved by the Editorial Council and accepted for publication on September 10, 2005.
* Work done at the Clínica Geller de Alergia e Imunologia, Rio de Janeiro, RJ - Brazil.

[1] President of the Brazilian Chapter of the American College of Allergy, Asthma and Immunology PR-Network.
[2] Physician. Graduate course (lato sensu) in the field of allergy and immunology at the Universidade de São Paulo - USP - São Paulo (SP), Brazil.

taneously. This immunostimulation was initiated after diagnosis of melanoma six months ago, and comprised cycles of four-series lasting 14 days each, at regular monthly intervals. In the beginning, the patient had diffuse and progressive pruritus, coinciding with administration of the immunostimulating agent. This symptom was controlled by dexchlorpheniramine, 6mg, per os, twice a day. Later, the patient presented episodes of diffuse giant urticaria, together with labial and perioral angioedema controlled by adding prednisone (40mg/day). He presented one event of arterial hypotension, short-lasting dizziness and no sequela after the first therapeutic cycle dose. No laryngeal edema or any other associated clinical symptoms were observed. Since the patient was responding well to rhuGM-CSF, with a significant reduction of metastatic lesions, it was decided to not discontinue treatment and to keep the previous anti-allergy regimen with dexchlorpheniramine and prednisone, during the immunostimulatory cycles. It was also recommended to have epinephrin auto-injector available during biochemotherapy cycles.

The rhuGM-CSF has been widely used to treat and control complications related to several hematological conditions, different types of cancer and infections.[4,5] Its therapeutic profile is considered safe. However, significant allergic reactions and anaphylaxis associated to its use were described. A syndrome characterized by difficulty breathing (dyspnea), hypoxia, facial peripheral vasodilatation, arterial hypotension, syncope and tachycardia may occur after the first administration in a single therapeutic cycle. This syndrome usually does not occur in subsequent doses of the same therapeutic cycle. The most prevalent dermatological side effects were erythematous rash, alopecia and pruritus. In immunologic/allergic processes, the mast cells mediators may stimulate eosinophilic protein degranulation.[6]

The case of a patient with metastatic melanoma controlled with rhuGM-CSF, who presented urticaria and angioedema a few hours after use is described. The patient never suffered from laryngeal edema. The skin symptoms were appropriately controlled and prevented with the combination therapy of dexchlorpheniramine and prednisone. The patient rejected having skin prick tests with rhuGM-CSF. The skin manifestations presented could be mediated by IgE (type I allergic reactions) or be anaphylactoid reactions (non-specific stimulation of mast cell and/or basophil cytoplasmic degranulation). In both cases, the main mediator released is histamine. Emotional factors associated with treatment for metastatic cancer may have contributed to aggravating these adverse reactions. Considering the good clinical and therapeutic results obtained, the immunostimulating biochemotherapeutical regimen with rhuGM-CSF was safely maintained.

GM-CSF is a glycoprotein secreted by several types of cells in order to stimulate macrophage and granulocyte proliferation. In humans, neutrophilia is observed with its use and results from greater availability of neutrophils in bone marrow towards blood stream and reduced migration of neutrophils from peripheral blood to tissues.[7] Today, rhuGM-CSF is effectively and safely used. It is accepted worldwide as an adequate immunostimulating modality. There are increasingly more adverse reactions to drugs as they are more often prescribed.[8] The chemotherapeutics could induce release of cytoplasmic anaphylactic mediators by mast cells.[9] The authors believe that this fact may have occurred in the reported case. ❑

**REFERENCES**


1. Morstyn G, Burgess AW. Hemopoietic growth factors: a review. Cancer Res. 1988;48:5624-37. Review.
2. Groopman JE, Mitsuyasu RT, DeLeo MJ, Oette DH, Golde DW. Effect of recombinant human granulocyte-macrophage colony-stimulating factor on myelopoiesis in the acquired immunodeficiency syndrome. N Engl J Med. 1987;317:593-8.
3. Lieschke GJ, Cebon J, Morstyn G. Characterization of the clinical effects after the first dose of bacterially synthesized recombinant human granulocyte-macrophage colony-stimulating factor. Blood. 1989; 74: 2634- 43.
4. Lieschke GJ, Burgess AW. Granulocyte colony-stimulating factor and granulocyte –macrophage colony – stimulating factor (First of two parts). N Engl J Med. 1992;327: 28- 35.
5. Lieschke GJ, Burgess AW. Granulocyte colony-stimulating factor and granulocyte –macrophage colony – stimulating factor (Second of two parts). N Engl J Med. 1992;327:99-106.
6. Takafugi S, Tadikoro K, Ito K. Release of granule proteins from human eosinophils stimulated with mast-cell mediators. Allergy. 1998;53:951-6.
7. Dale DC, Liles WC, Llewellyn C. Effects of granulocyte-macrophage colony-stimulating factor (GM-CSF) on neutrophil kinetics and function in normal human volunteers. Am J Hematol 1998; 57:7-15.
8. Gruchalla RS. Drug allergy. J Allergy Clin Immunol. 2003; 111: S548-59.
9. Zanotti K, Markman M. Prevention and management of antineoplastic- induced hypersensitivity reactions. Drug Saf. 2001;24:767-79.



*MAILING ADDRESS:*
*Mario Geller*
*Rua Visconde de Pirajá, 303 - conj. 603 - Ipanema*
*22410-001 Rio de Janeiro RJ*
*Fax: (21) 2287-4360*
*E-mail: gellerm@attglobal.net*