Facial Angioedema Associated with Granulocyte Colony-Stimulating Factor (G-CSF) Treatment

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Key Words

G-CSF

Facial angioedema
Head and neck cancer
Radiation therapy

Summary

Background: Granulocyte colony-stimulating factor (G-CSF) is widely used to treat chemo- or radiotherapy-induced neutropenia and is also effective in the treatment of severe oral mucositis induced by chemotherapy. With the common use of G-CSF the description of rare or new side effects becomes more important. Case Report: The 44-year-old male patient suffered from an inoperable carcinoma of the nasopharynx and underwent a combined radio-chemotherapy, consisting of paclitaxel weekly and irradiation with 70 Gy over 7 weeks. During the course of treatment, he developed a severe oral mucositis. Since conventional therapy of mucositis did not alleviate the symptoms, he was treated with G-CSF. Within 18 h after the subcutaneous administration of G-CSF he developed a severe facial angioedema. Within 3 days the patient recovered spontaneously from the angioedema. Because the relationship of the symptoms and the G-CSF treatment was not clearly evident, a second dose of G-CSF was given. 14 h after the subcutaneous injection of the same dose of G-CSF, the patient developed the identical symptoms of angioedema. Conclusion: Facial angioedema is a rare but important side effect after G-CSF treatment. A possible role of paclitaxel or radiation therapy in the pathogenesis of this side effect cannot be ruled out.

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Schlüsselwörter

G-CSF · Angioödem · Kopf-Hals-Tumoren · Strahlentherapie

Zusammenfassung

Hintergrund: Die Anwendung von Granulocyten-Kolonie-stimulierenden Faktoren (G-CSF) in der Behandlung von Neutropenien, die im Rahmen von Chemotherapien oder Bestrahlung auftreten, ist weit verbreitet. G-CSF ist auch wirksam in der Behandlung schwerer, durch Zytostatikatherapie induzierter oraler Mukositiden. Die häufige Anwendung von G-CSF während onkologischer Therapien macht die Beschreibung seltener oder bisher unbekannter Nebenwirkungen wichtig. Kasuistik: Der 44-jährige, männliche Patient litt an einem inoperablen Karzinom im Bereich des Nasopharynx und wurde mit einer kombinierten Radio-Chemotherapie behandelt, die aus einer wöchentlichen Gabe von Paclitaxel und einer Radiotherapie von 70 Gy, eingestrahlt über 7 Wochen, bestand. Da sich eine schwere, durch konventionelle Therapie nicht beeinflussbare Mukositis entwickelte, wurde der Patient mit G-CSF behandelt. Innerhalb von 18 h entwickelte der Patient ein schweres faziales Angioödem. Da der Zusammenhang zwischen dem Angioödem und der G-CSF-Gabe zunächst nicht eindeutig war, wurde der Patient ein zweites Mal mit G-CSF behandelt, nachdem es ohne spezifische Therapie zu einer vollständigen

Rückbildung der Symptome gekommen war. Erneut stellten sich die Symptome eines schweren Angio-ödems ein. Schlußfolgerung: Das Auftreten eines fazialen Angioödems ist eine seltene, aber wichtige Nebenwirkung nach G-CSF-Applikation. Ein Einfluß der vorher durchgeführten Chemotherapie mit Paclitaxel bzw. Bestrahlung auf die Pathogenese dieser Nebenwirkung kann nicht ausgeschlossen werden.

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Introduction

Filgrastim (G-CSF) is a recombinant human granulocyte colony-stimulating factor derived from *E. coli* bacteria. It significantly stimulates the production of neutrophils and is used to treat chemotherapy-induced neutropenia and to prevent neutropenia after cancer chemotherapy [1-4]. More recently, G-CSF has been used to treat radiation-induced neutropenia [5]. Several clinical trials demonstrated, that the drug is also active in the treatment of severe oral mucositis induced by chemotherapy in different malignancies [6, 7]. Generally, treatment with G-CSF is well tolerated. The main side effects are bone pain, hypotension, splenomegaly and an elevation of liver enzymes. Cutaneous vasculitis and anaphylactic reactions are rare events. To our knowledge, facial angioedema has been reported only in one publication which dealt generally with the safety profile of G-CSF [8].

Case Report

The 44-year-old patient suffered from an inoperable carcinoma of the nasopharynx and underwent a combined radio-chemotherapy. The area of the nasopharynx and the supraclavicular lymph nodes were irradiated to a dose of 50.4 Gy in 5 daily fractions of 1.8 Gy per week. An additional boost of 20 Gy was applied to the primary tumor. Chemotherapy consisted of a weekly intravenous dose of 40 mg/m² paclitaxel. After 4 cycles of paclitaxel and a radiation dose of 48.6 Gy, the patient developed a severe oral mucositis WHO grade III. Due to this adverse event the radio-chemotherapy was stopped and the patient was admitted to the hospital. Conventional therapy of mucositis, consisting of panthenol, amphotericin B, polyvidon-iodine, and a suspension of an antacid did not alleviate the symptoms over one week. At this time the white blood count (WBC) was 5,300/ μ l. Because in this situation all conventional therapeutic attempts did not influence the severe symptoms, we decided to treat with G-CSF in order to accelerate the recovery from the severe mucositis, despite a normal WBC. Simultaneously we continued with the conventional treatment of the above mentioned drugs. Approximately 4-6 h after the subcutaneous administration of G-CSF in a total dose of 150 μ g, the patient complained about pain in the lips and the tongue combined with a tension in this area. 12 to 18 h later he developed a severe angioedema of the lips, tongue and the cheeks. These changes occurred outside the radiation fields. The WBC increased to 6,500/ μ l. After 3 days the patient recovered completely from the angioedema. Because the relationship of the above mentioned symptoms and the administration of the G-CSF was not clearly evident, a second dose of G-CSF was given. 14 h after the subcutaneous injection of the same dose of G-CSF, the patient developed identical symptoms: pain in the lips and mouth combined with an angioedema of the lips, tongue and cheeks.

Discussion

An association of facial/oral angioedema with the application of G-CSF has only been reported in one publication dealing generally with the safety profile of filgrastim. To our knowledge this potentially life-threatening side effect has not been published in a case report. We believe that in

our case an association between G-CSF and angioedema was evident, since the patient developed the identical symptoms twice after the application of G-CSF with an identical latency period. In our case we decided to treat the patient with G-CSF since he had a severe iatrogenic mucositis which did not respond to conventional supportive therapy. Recent evidence suggests that colony-stimulating factors can influence oral mucositis independent of neutrophil levels [9]. Therefore, we found it justified to offer G-CSF despite a normal WBC. The pathogenesis of angioedema has been explained by different mechanisms: In many cases angioedema is due to a type I hypersensitivity reaction mediated by IgE antibodies and a release of mast cell factors. Another described mechanism is the development of immune complexes which induce a vasculitis with the clinical symptoms of angioedema and/or urticaria. In this context it seems to be of interest, that immune complexes are also involved in the pathogenesis of cutaneous vasculitis, a side effect which has also been observed in patients who were treated with G-CSF [10].

Hypersensitivity syndromes after application of G-CSF are rare but well known side effects. In approximately 50% of these cases those reactions occurred after the first administration of the drug [8]. We conclude that angioedema can occur after G-CSF treatment and, in our observed case, resolved spontaneously after cessation of the G-CSF application. Since, previously, this complication has only been described in one publication [8], it is supposed to be rare. A possible role of paclitaxel or radiation therapy for the development of this side effect cannot be ruled out.

References

- 1 Groopman JE, Molina JM, Scadden DT: Hemato-poietic growth factors. Biology and clinical applications. *N Engl J Med* 1989;321:1449-1459.
- 2 Morstyn G, Campbell L, Souza LM, Alton NK, Keech J, Green M, Sheridan W, Metcalf D, Fox R: Effect of granulocyte colony stimulating factor on neutropenia induced by cytotoxic chemotherapy. *Lancet* 1988;i:667-672.
- Lieschke GJ, Burgess AW: Granulocyte colony-stimulating factor and granulocyte-macrophage stimulating factor. A review, part 1. *N Engl J Med* 1992;327:28-35.
- Lieschke GJ, Burgess AW: Granulocyte colony-stimulating factor and granulocyte-macrophage stimulating factor. A review, part 2. *N Engl J Med* 1992;327:99-106.
- Schmidberger H, Hess CF, Hoffmann W, Reuss-Borst MA, Bamberg M: Granulocyte Colony-Stimulating factor treatment of leucopenia during fractionated radiotherapy. *Eur J Cancer* 1993;29A:1927-1931.
- Gabrilove JL, Jakubowski A, Scher H, Sternberg C, Wong G, Grous J, Yagoda A, Fain K, Moore MA, Clarkson B: Effect of granulocyte colony stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. *N Engl J Med* 1988;318:1414-1422.
- Lieschke GJ, Ramenghi U, O'Connor MP, Sheridan W, Szer J, Morstyn G: Studies of oral neutrophil levels in patients receiving G-CSF after autologous marrow transplantation. *Br J Haematol* 1992; 82:589-595.
- Decoster G, Rich W, Brown SL: Safety profile of filgrastim; in Morstyn G, Dexter TM (eds): *Filgrastim (r-metHug-CSF) in Clinical Practice*. New York, Marcel Dekker, 1994, pp 267-288.
- Chi KH, Chen CH, Chan WK, Chow KC, Chen SY, Yen SH, Chao JY, Chang CY, Chen KY: Effect of granulocyte-macrophage colony-stimulating factor on oral mucositis in head and neck cancer patients after cisplatin, fluorouracil and leucovorin chemotherapy. *J Clin Oncol* 1995;13:2620-2628.

10 Wodzinski MA, Hampton KK, Reilly JT: Differential effect of G-CSF and GM-CSF in acquired chronic neutropenia. *Br J Haematol* 1991;77:249-250.

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