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 chemotherapy- 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 radiochemotherapy, 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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Introduction

Filgrastim (G-CSF) is a recombinant human granulocyte colony-stimulating factor derived from E. coli bacteria. It significantly stimulates the production of neutrophiles 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/µl. 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 µg, 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/µl. 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.
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