Successful Treatment of Breakthrough Bacteremia due to *Pseudomonas aeruginosa* with Recombinant Human Granulocyte Colony-Stimulating Factor in a Patient with Acute Leukemia

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Introduction

Bacteremia remains a veritable scourge for patients with hematologic malignancy undergoing intensive chemotherapy¹⁾. Patients with profound granulocytopenia are most likely to develop persistent or recurrent bacteremia despite appropriate antibiotic therapy²⁻⁴⁾, that is, breakthrough bacteremia²⁾. Most patients whose granulocyte counts increase during the course of the infection, however, have a substantially better prognosis^{3,5,6)}. Recent studies^{7,8)} have confirmed that treatment with recombinant human granulocyte colony-stimulating factor (rhG-CSF) accelerates recovery from chemotherapy-induced granulocytopenia. We describe here a case of breakthrough bacteremia with *Pseudomonas aeruginosa*, which was successfully treated with the short-term addition of rhG-CSF to antipseudomonal antibiotics, during the treatment of a patient with acute leukemia.

Case Report

A 60-year-old housewife was referred to Kanazawa University Hospital on October 27, 1989, because of general weakness, loss of appetite, fever, and pancytopenia (Fig. 1). On admission the temperature was 39.3°C. She had multiple missing teeth and moderate, generalized periodontitis, with the remaining teeth showing some degree of mobility. Laboratory values included a hematocrit of 23.1%; leukocyte count of 700/mm³, with 6% myeloblasts, 32% neutrophils, 59% lymphocytes, and 3% monocytes; and a platelet count of 99000/mm³. Evaluation of a bone marrow biopsy specimen revealed a marked hypercellularity with predominance of myeloblasts, although bone marrow aspiration resulted in a dry tap. Further hematologic work-up confirmed a diagnosis of acute myelogenous leukemia.

Directly after admission, antibiotic therapy was begun, with periodontitis considered to be the probable cause of the fever. Defervescence occurred during the second hospital day, but antibiotic treatment was continued for three weeks. After intensive cytoreduction, the neutrophil count dropped to 0/mm². On November 20, her temperature spiked to 39.4°C. She complained of toothache. Intraoral examination revealed acute inflammatory gingival alterations consistent with advanced periodontitis

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Fig. 1 Clinical course of a patient with acute leukemia who developed breakthrough bacteremia with *Pseudomonas aeruginosa*.

Abbreviations: AML, acute myelogenous leukemia; BW, body weight; CMZ, cefmetazole; GM, gentamicin; PIPC, piperacillin; CAZ, ceftazidime; DNR, daunorubicin; BHAC, encitabine; NCS, neocarzinostatin; PDN, prednisolone; BM, bone marrow; and rhG-CSF, recombinant human granulocyte colony-stimulating factor.

involving the periodontium of the remaining mandibular teeth. Therapy was initiated with intravenous gentamicin (3 mg/kg per day) and piperacillin (150 mg/kg per day). Blood cultures performed at initiation of empiric therapy grew *P. aeruginosa* (serogroup A), which was sensitive by standardized in vitro disk susceptibility testing⁹⁾ to gentamicin, piperacillin and ceftazidime. She had already had the identical *P. aeruginosa* recovered from surveillance cultures of the throat and gingival inflammatory sites. Despite high-dose antipseudomonal therapy, blood cultures continued to be positive. She remained severely neutropenic and febrile with temperatures up to 39.7°C. On November 25, therefore, ceftazidime (100 mg/kg per day) was substituted for piperacillin. After informed consent was obtained, she was also begun on a regimen of rhG-CSF (Kirin Brewery Co., Ltd., Tokyo; 75 µg/body per day), which was administered as a daily subcutaneous injection for five days. She tolerated the rhG-CSF treatment well. The increase in the leukocyte count was substantial with a rise of more than 10000/mm³ (leukocyte count of 10100/mm³ with 96% neutrophils on November 30). No increase in reticulocytes or platelets was observed. The leukocyte count gradually declined after discontinuation of the rhG-CSF treatment. She became afebrile and her toothache improved. Repeat blood cultures were negative. Antibiotic therapy was stopped on December 2.

Subsequent hematologic recovery was favorable. She went into complete remission, with the bone marrow aspirate on December 8 showing 5% myeloblasts. On April 10, 1990, she was discharged in complete remission after receiving three courses of consolidation chemotherapy.

Discussion

Patients with acute leukemia are at especially increased risk of developing *P. aeruginosa* bacteremia during intensive induction chemotherapy^{1,3,4}). Persistent bacteremia with this organism occasionally occurs during treatment with seemingly adequate doses of appropriate antibiotics in combination, which are highly effective in vitro against the infecting organism²⁻⁴). Such breakthrough bacteremia is in most cases related to the presence of profound granulocytopenia, often resulting in a grave prognosis^{2-4,6}). This supports the opinion of Weinstein and Reller²) that the occurrence of breakthrough bacteremia illustrates the potential limitations of antibiotic therapy alone for sepsis. In short, endogenous granulocyte recovery,

together with appropriate antibiotic therapy, is essential to the clearing of breakthrough bacteremia^{3,5,6}. In our case, therefore, prompt defervescence with negative blood cultures on follow-up was inferred to have occurred largely in parallel with a rapid increase in the granulocyte count during treatment with rhG-CSF, although therapy was changed from piperacillin plus gentamicin to ceftazidime plus gentamicin.

Recent studies^{7,8,10,11} have revealed that therapy with rhG-CSF for patients with a variety of neutropenic disorders, especially those with chemotherapy-induced granulocytopenia, often produces normalization of the absolute neutrophil counts, with the presence of functional cells. In our patient, rhG-CSF was administered at a minimum effective daily dose of 75 μg /body, which is recommended to significantly shorten the period of chemotherapy-induced granulocytopenia⁹. No side effects associated with this growth factor were observed. There is, however, some concern that treatment with rhG-CSF may result in an increase in the number of leukemic blast cells in the bone marrow of patients with myelodysplastic syndrome or acute myelogenous leukemia, although no obvious evidence for this has yet been reported¹¹. It is, therefore, suggested that use of this growth factor as an adjunct to antibiotic therapy for persistent bacteremia be limited to periods of time sufficient to produce defervescence particularly in granulocytopenic patients whose diagnosis is acute myelogenous leukemia.

The observations in this single patient suggest a beneficial effect of rhG-CSF in the treatment of breakthrough bacteremia associated with chemotherapy-induced granulocytopenia, which merits study in additional patients.

In conclusion, we described a case of breakthrough bacteremia with *P. aeruginosa* during the treatment of a patient with acute myelogenous leukemia, which was successfully treated with the short-term addition of rhG-CSF to antipseudomonal antibiotics. No adverse effects associated with this growth factor were observed.

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遺伝子組換えヒト型顆粒球コロニー形成刺激因子の投与が奏効した 急性白血病患者の緑膿菌による Breakthrough bacteremia

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要 旨

60歳，主婦の急性白血病患者が多剤併用による寛解導入療法を受けた直後に緑膿菌血症を発症した。適切と考えられる抗生薬療法にもかかわらず，高度の顆粒球減少のために菌血症が持続した

(breakthrough bacteremia)。しかし，遺伝子組換えヒト型顆粒球コロニー形成刺激因子の併用により，急速な顆粒球数の回復とともに速やかな解熱がみられた。このコロニー形成刺激因子の投与による副作用は認められなかった。