Successful Medical Treatment of Rhinocerebral Mucormycosis Complicating Acute Leukemia

Hisashi FUNADA, Yasuhiro MOCHIZUKI, Toshihiko MACHI, Shigeki OHTAKE and Tamotsu MATSUDA
The Protected Environment Unit and Third Department of Medicine, Kanazawa University School of Medicine, Kanazawa 920, Japan
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Introduction

Rhinocerebral mucormycosis in patients with acute leukemia, although a rare complication, has been reported to be a devastating condition, with a rapidly fatal outcome in all cases1-3). Recently, however, we have experienced a successfully treated case of rhinocerebral mucormycosis during the treatment of a patient with acute leukemia.

Case Report

A 21-year-old male with acute lymphoblastic leukemia of 14 months' duration was admitted to Kanazawa University Hospital on January 25, 1990 because of fever and worsening bone marrow histology. Physical findings included a temperature of 38.9°C, pallor, mild hepatomegaly, and peripheral lymphadenopathy. Laboratory studies revealed a hematocrit of 18.3%, platelet count 118000/mm³, and leukocyte count of 5200/mm³ with 81% lymphoblasts, 1% myelocytes, 4% neutrophils and 14% lymphocytes. The bone marrow smear showed 95% blast cells.

Intravenous piperacillin and gentamicin therapy was started on an empirical basis. After 10 days without response to the antibiotic regimen, he received a 7-day course of intensive chemotherapy with doxorubicin, enocitabine, etoposide, and prednisolone (referred to as HBEP), followed by treatment with recombinant human granulocyte colony-stimulating factor (rhG-CSF, Kirin Brewery Co., Ltd., Tokyo; 75 µg/day per body subcutaneously4)). Informed patient consent was obtained for the use of rhG-CSF. On the third day of antileukemic therapy, he complained of lacrimation in the right eye with slight lid edema, followed a few days later by pain and swelling in the right cheek and right upper medial area of the nose, and a seromucous nasal discharge from the right naris. Radiographic examination of the paranasal sinuses revealed opacification of the right maxillary, frontal, and ethmoid sinuses, without air-fluid levels. Computed tomography (CT) demonstrated soft-tissue densities in the right nasal cavity and right paranasal sinuses except for the sphenoid sinus (Fig. 1A). No bone destruction or intracranial involvement was seen. Examination of the nose revealed crusting over the right inferior turbinate with black discoloration. Biopsy of the lesion showed necrotic tissue with intensive invasion by non-septate hyphae of the Mucorales (Fig. 2). Cultures of the nose, however, were negative for fungi. Intravenous amphotericin B
Fig. 1 Computed tomographic (CT) scans showing soft-tissue densities in the right nasal cavity and right maxillary sinus, with increased density of the right nasozygomatic space (A: pretreatment), steadily improving sinus aeration (B: about two and a half months later), and complete clearing of the right maxillary sinus and right nasal cavity, with disappearance of inflammatory changes in the nasozygomatic space (C: five months later).

Fig. 2 Biopsy of the right inferior turbinate showing mucormycotic hyphae invading a blood vessel wall (methenamine silver, original magnification, ×400).

was instituted, with a progressive dose escalation to a daily dose of 0.8—1.0 mg/kg. His symptoms and signs improved gradually paralleling a rise in the neutrophil count from the nadir, despite persistent blast forms. Another course of HBEP with rhG-CSF treatment was given, and a complete remission was reached. The ocular and nasal symptoms, however, relapsed temporally during consolidation therapy with the same HBEP and rhG-CSF. Concomitantly, his clinical course was complicated by bacteremia due to Staphylococcus aureus, which was successfully treated with fosfomycin and imipenem/cilastatin in combination. After about one month of remission, his leukemia relapsed, and he was again placed on other antileukemic regimens with rhG-CSF treatment. Following this there was no further remission. The neutrophil count remained above 1000/mm³, and daily amphotericin B therapy was changed to an alternate-day regimen. Follow-up CT scans, however, revealed steadily improving sinus aeration (Fig. 1B), resulting in complete clearing of all the involved sinuses (Fig. 1C), as indicated by sinus X-ray films, by July 15, when amphotericin B was discontinued with a total dosage of 3555 mg. His renal function, judged by blood urea nitrogen and serum creatinine levels, remained within normal limits. Examination of the nose...
one month later revealed a healed ulceration of the right inferior turbinate.

Discussion

This is the first case report, to our knowledge, of rhinocerebral mucormycosis complicating acute leukemia with a successful outcome.

No patients with acute leukemia developing rhinocerebral mucormycosis have survived, although amphotericin B and aggressive debridement on the basis of early diagnosis have been emphasized as the indicated combination treatment\(^1\)\(^-\)\(^3\). Surgical intervention is liable to run a risk in the presence of thrombocytopenia or early leukemic relapse. On the other hand, neutropenic patients with cancer are at increased risk of developing invasive mucormycosis\(^2\)\(^,\)\(^5\)\(^,\)\(^6\). It is improbable, therefore, that rhinocerebral mucormycosis can be successfully treated in a patient with acute leukemia without achievement of hematologic remission. This is strongly suggested by the fact that invasive pulmonary mucormycosis could be cured with amphotericin B alone in a patient with acute leukemia who achieved a complete remission\(^7\). There is, however, no agreement about the total dose of amphotericin B or the duration of treatment in patients with mucormycosis\(^9\).

Invasive mucormycosis, whether rhinocerebral or pulmonary, produces thrombosis and infarction through a special tropism for blood vessels\(^3\)\(^,\)\(^5\), as seen in our case (Fig. 2). Localization of the infectious process in neutropenic patients usually occurs in association with a rise in the neutrophil count\(^7\). Leukocyte enzymatic activity is assumed to play an important role in the disappearance of necrotic tissue\(^8\). In our patient, therefore, a beneficial effect of rhG-CSF on recovery from the chemotherapy-induced neutropenia was suggested in parallel with hematologic remission. The rhG-CSF was administered at a daily dose of 75 \(\mu\)g/body, which is recommended to significantly shorten the period of chemotherapy-induced neutropenia\(^4\). Thus, it seems that recent progress in cancer chemotherapy has produced a favorable change in the clinical picture of rhinocerebral mucormycosis.

In conclusion, we described a case of rhinocerebral mucormycosis during the treatment of a patient with acute leukemia. The mucormycosis was successfully treated with amphotericin B and rhG-CSF in close association with control of the underlying disease.

References

内科的治療が奏効した急性白血病患者の鼻脳型ムーコル症

金沢大学医学部附属病院高密度無菌治療部・第3内科
舟田 久 望月 康弘 眞智 俊彦
大竹 茂樹 松田 保

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要 旨
21歳、男性の急性リンパ性白血病患者の治療中に、右副鼻腔炎（前頭洞、篠骨洞、上顎洞の罹患）がみられ、下鼻甲介の生検によって鼻脳型ムーコル症と診断された。アムホテリンB治療が行われたが、抗白血病療法の奏効と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による好中球数の速やかな増加に一致して、臨床症状、鼻腔所見、副鼻腔のX線写真やCTスキャンの所見が著明に改善した。原疾患の覚解が抗真菌剤治療の効果発現に重要なように思われた。本例は、急性白血病に合併した鼻脳型ムーコル症の内科的治療に成功した第1例目と考えられる。

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