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A Case of Acute Lymphoblastic Leukaemia Complicated with Sinonasal Mucormycosis Infection

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ABSTRACT

Acute lymphoblastic leukaemia (ALL) is an aggressive hematologic malignancy of lymphoid progenitor cells. During treatment of ALL, the patients may be complicated by fatal infections such as sinonasal mucormycosis. In patients with immunocompromised conditions like haematologic malignancies, mucormycosis can be deadly. Once mucormycosis has been detected, it is critical to act quickly to begin treatment. Amphotericin B, posaconazole, or isavuconazole are the medications of choice. Effective treatment requires a long-term course of therapy. Switching to other effective medications should be considered when the preferred treatment is not working. The factors contributing to mucormycosis must also be treated, such as the underlying conditions (haematologic malignancies). Herein, we aimed to discuss a clinically stable ALL patient complicated with extensive sinonasal mucormycosis. She improved with amphotericin B (5 mg/kg/day) and oral posaconazol (300 mg/day) treatment.

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Case Report

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INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is an aggressive neoplasm of lymphoid progenitor cells. The annual incidence of ALL is 1.7 cases per 100,000 people in the United States.1 Pediatric ALL is a highly curable disease with survival rates above 90%. In contrast, the long-term overall survival (OS) of ALL in adults is about 35-45%.[1] Mucormycosis is an infection with high mortality caused by filamentous mold fungi.[2] In Europe and America, mucormycosis cases are most commonly seen in hematologic malignancies (38-62%).[3] Invasive fungal infections in the paranasal sinuses have a progressive course and high mortality rates in immunocompromised patients.[4] The global guidelines for treating mucormycosis recommends controlling the underlying conditions (uncontrolled diabetes and immunosuppression), an early diagnosis and an effective treatment. This treatment includes systemic antifungal therapies with extensive surgical debridement.[5] We aimed to present a patient diagnosed with Pre-B-ALL who was complicated with sinonasal mucormycosis infection.

CASE REPORT

A 28-year-old woman, who received chemotherapy and radiotherapy for Ewing sarcoma nine years ago, was followed up in remission. She was diagnosed with pulmonary embolism after receiving the COVID-19 vaccine one year ago. Anti-cardiolipin IgM and IgG, anti-beta 2 glycoprotein IgM and IgG, and antiphospholipid IgM and IgG were negative. In the thyrombophilia panel, while MTHFR mutation was heterozygously positive, factor V Leiden and prothrombin mutations were negative. In whole blood count, platelet $100x10^9$/L, leukocyte $9.10x10^9$/L, lymphocyte $1.92x10^9$/L, haemoglobin 12.9 g/dL. Low molecular weight heparin (LMWH) was started to treat the pulmonary embolism. Thrombocytopenia ($18x10^9$/L) developed under LMWH treatment. Peripheral blood smear showed leukocyte $10.7x10^9$/L, neutrophil $5.24x10^9$/L, lymphocyte $4.78x10^9$/L, haemoglobin 10.1 g/dL, platelet $15.0x10^9$/L, and %40 lymphoblast. A bone marrow biopsy was performed, and 74% lymphoblastic infiltration was observed in the bone marrow aspirate (flow cytometry: CD19+, CD20+, CD22+). The Philadelphia (Ph) chromosome was negative in cytogenetic analysis. The patient was diagnosed with Ph(–) B-ALL. She was hospitalised for HYPER-CVAD (cyclophosphamide 900 mg/day, vincristine 2 mg/day, doxorubicin 75 mg/day, dexamethasone 40 mg/day, mesna 900 mg/day, methotrexate 1.5 g/day, cytarabine 9 g/day, rituximab 560 mg) treatment. After the first cycle of HYPER-CVAD, the patient went into remission and received four HYPER-CVAD chemotherapy cycles and five doses of intrathecal methotrexate therapies for CNS prophylaxis during 8-month period.

In April 2022, she was hospitalised for the fourth course of HYPER-CVAD chemotherapy. During HYPER-CVAD, she received prophylactic ciprofloxacin, fluconazole, acyclovir. She had complaints of headache and fullness in the ear. Skull base magnetic resonance imaging (MRI) was reported as oedema findings extending from Rosenmüller fossa, Meckel's cave, masticator cavity, and carotid cavity and contrast enhancement findings in the dynamic examination. There were signal intensity changes consistent with inflammation in the ethmoid cells, bilateral maxillary sinus, sphenoid sinus, and unstained area in the mucosa on the posterior wall of the sphenoid sinus on the right. The findings were consistent with mucormycosis-like invasive infection *(Figure 1)*. During otorhinolaryngology (ENT) examination, a mass lesion was observed in the nasopharynx. The serum galactomannan was negative. Liposomal amphotericin B was started at a high dose of 5 mg/kg/day because the patient had central nervous system involvement (Sphenoid sinuses were involved.). A biopsy was performed on the lesions in the nasopharynx. In the nasopharynx debridement material, there were hyphae, spores, and fungi formations that belong to the group of mucorales. The nasopharynx debridement biopsy results also revealed mucormycosis. After eight weeks of liposomal amphotericin B treatment, no mucor was detected in the nasal re-biopsy specimens. However, the appearance favoring mucormycosis infection was persisted in the control skull base MRI. The patient was discharged with 300 mg/day oral posaconazole treatment, and ALL maintenance treatment was postponed.

After two months of posaconazole treatment, cranial MRI revealed; "Intense inflammatory appearance and abscess formation (mucormycosis) over 4 cm extending into the pterygomaxillary fissure, orbital fissure, cavernosal sinus and infratemporal fossa on the right" *(Figure 1)*. Posaconazole medication was continued despite the demonstrated improvement over the last MRI. The patient was clinically stable

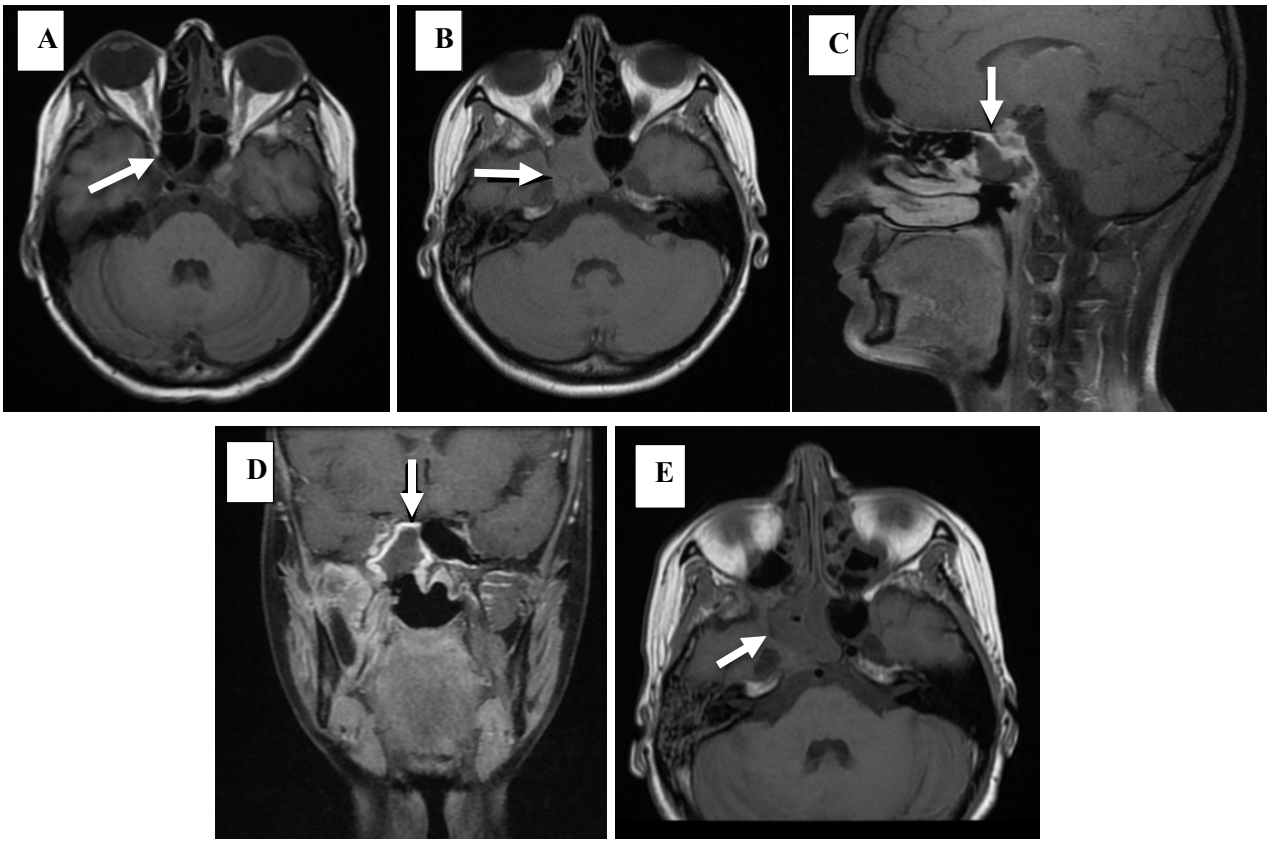

Figure 1. Cranial MRI findings at the onset of the first symptoms on 01.06.2022 (A), on the 69th day of liposomal amphotericin B treatment on 09.08.2022 (B, C and D) and on the 5th month of antifungal treatment on 02.11.2022 (E)

with no evidence of recurrence. It was decided to start ALL maintenance treatment (vincristine 2 mg/day, mercaptopurine 100 mg/day, methotrexate 15 mg/day) under 4th month of posaconazole treatment. The patient continued to be followed up with the infectious disease and ENT department under outpatient posaconazole maintenance treatment, and no signs or symptoms of mucormycosis infection were observed.

DISCUSSION

The diagnosis of ALL generally requires demonstration of ≥20% bone marrow lymphoblasts on hematopathology review of bone marrow aspirate and biopsy materials.[6] The most common treatment regimens include multiagent chemotherapy regimens. Hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methotrexate and cytarabine (Hyper-CVAD) is one of them. In general, the treatment phases of ALL can be grouped as induction, consolidation, and maintenance therapies. All treatment regimens for ALL include central nervous system (CNS) prophylaxis and/or treatment.[6] Our case had given HYPERCVAD regimen. Since she was CD20 positive in her flow cytometry, she received rituximab therapy.

Mucormycosis is an infection with high mortality caused by filamentous mold fungi. It requires long-term treatment.[4,7] It also requires extensive surgical debridement. According to the ESCMID/ECMM 2019 guidelines, both conventional amphotericin B or liposomal amphotericin B (at a dose of 5 mg/kg/day) are recommended for the first-line antifungal monotherapy for mucormycosis. When amphotericin B formulations are unavailable or in instances of fungal infections that are refractory or intolerant to amphotericin B, posaconazole or isavuconazole are strongly suggested as salvage therapy.[5] Treatment dose for oral isavuconazole is 200 mg three times a day (first two days), followed by 200 mg once a day maintenance dose, and for oral posaconazole is 300 mg twice a day g (first day), followed by 300 mg once a day maintenance dose.[9] In our case, after eight weeks of liposomal amphotericin B treatment, no mucormycosis was found in biopsy specimens, but findings in favour of

mucormycosis persisted in imaging studies. Therefore, posaconazole (300 mg/day oral) treatment and close clinical follow-up were planned at discharge. Posaconazole treatment was scheduled to be continued in the patient who was clinically responsive and had cranial MRI that could be in favor of mucormycosis.

Remission maintenance therapy is a standard component of the treatment of ALL after induction therapy. According to NCCN Guidelines, most maintenance regimens are based on a backbone of daily mercaptopurine (6-MP) and weekly methotrexate (typically with the addition of periodic vincristine and corticosteroids) for 2 to 3 years.[9] In our case, after four months of oral posaconazole treatment, the clinically stable patient was given maintenance ALL treatment (vincristine 2 mg/day, mercaptopurine 100 mg/day, methotrexate 15 mg/day) under posaconazole therapy. She was still under posaconazole treatment and had ALL maintenance treatments.

As in our case, cases of rhino-cerebral mucormycosis have been reported in the literature, but these cases are usually in the pediatric age group ALL.[8] Bonifaz *et al*.[7] conducted a retrospective study including 55 mucormycosis patients with oral involvement. This study has showed that the main comorbidity in patients infected with mucormycosis was diabetes (%71) and second most associated comorbidity was neutropenia (%27) mainly related to acute lymphocytic leukaemia.[7] In our case, the patient was having HYPER-CVAD therapy and was in neutropenia a week before being diagnosed with mucormycosis.

Liang *et al*.[5] reported a case of 11-year-old pulmonary mucormycosis treated with oral posaconazole. They continued the anticancer regimen during voriconazole treatment. Popa *et al*.[8] reported a 5-year-old girl diagnosed with severe rhino-cerebral mucormycosis (facial and cerebral structures were involved) after completing induction treatment of ALL, which discontinued leukaemia therapy during the episode of febrile mucormycosis. They then started chemotherapy as soon as the patient got better.[8] As in our case, we continued with posaconazole treatment for mucormycosis, and the patient was given ALL maintenance treatment under posaconazole treatment.

CONCLUSIONS

Our case is one of a few surviving cases of rhino-cerebral mucormycosis arising in patients with ALL reported in the literature. As Popa *et al*.[8] mentioned, the complete remission of leukaemia in our patient was a particular advantage. The mucormycosis infection was improved with posaconazole treatment. The importance of this case is being a self-limiting case of mucormycosis controlled with amphotericin B and posaconazole treatment. Our case highlights the importance of continuing oral regimens (posaconazole) if there is an unresponsiveness after parenteral amphotericin B. It is essential to cure underlying aetiology in mucormycosis treatment. That's why the clinicians should start maintenance therapies for underlying etiologies (like ALL) as soon as possible, the patient's infection is cured or stabilised.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: AŞH, BO; Study Design: AŞH, BO; Literature Review: AŞH, BO; Critical Review: BO, TE, VÖ, FÖ; Data Collection and/or Processing: AŞH, BO,; Analysis and/or Data Interpretation: AŞH, BO, TE, VÖ, FÖ; Manuscript preparing: AŞH, BO.

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