Successful Isavuconazole Salvage Therapy for Cerebral Mucormycosis in A child With Relapsed Leukemia, A light in The Dark Tunnel

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Abstract

Mucormycosis is an angioinvasive lethal fungal infection in pediatric cancer patients. We present 10-year-old female with relapsed B-cell acute lymphoblastic leukemia undergoing chemotherapy was diagnosed with isolated cerebral mucormycosis (ICM). Despite surgical debridement and liposomal amphotericin B, repeat imaging showed concern for disease progression. Chemotherapy was discontinued and the patient was discharged on salvage therapy oral isavuconazole (ISAV). Over two months later, the patient was unexpectedly clinically stable, and imaging showed near resolution. After confirming continuous disease remission, the patient was restarted on modified chemotherapy. Serial MRI's during continued chemotherapy showed stable MRI findings. This case illustrates a rare presentation of successful salvage monotherapy ISAV for this deadly infection with complete remission for relapsed leukemia.

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abbreviations

ICM	Isolated cerebral mucormycosis
ISAV	Isavuconazole
B-ALL	B-cell acute lymphoblastic leukemia
COG	Children's Oncology Group

Abstract

Mucormycosis is an angioinvasive lethal fungal infection in pediatric cancer patients. We present 10-year-old female with relapsed B-cell acute lymphoblastic leukemia undergoing chemotherapy was diagnosed with isolated cerebral mucormycosis (ICM). Despite surgical debridement and liposomal amphotericin B, repeat imaging showed concern for disease progression. Chemotherapy was discontinued and the patient was discharged on salvage therapy oral isavuconazole (ISAV). Over two months later, the patient was unexpectedly clinically stable, and imaging showed near resolution. After confirming continuous disease remission, the patient was restarted on modified chemotherapy. Serial MRI's during continued chemotherapy showed stable MRI findings. This case illustrates a rare presentation of successful salvage monotherapy ISAV for this deadly infection with complete remission for relapsed leukemia.

Case presentation

A 10-year-old female was diagnosed with late combined (bone marrow and central nervous system (CNS)) relapse of B-cell acute lymphoblastic leukemia (B-ALL) approximately 3.5 years after completing chemotherapy for standard risk B-ALL. She had a high burden of CNS disease at time of relapse diagnosis. She was started on therapy per the low-risk control arm of the Children's Oncology Group (COG) study AALL1331 with regimen as previously published(1). She was started on prophylactic trimethoprim-sulfamethoxazole and fluconazole at time of relapse diagnosis. Her bone marrow and CNS were negative for leukemia at the end of Block 1 of therapy. She completed Block 2 chemotherapy and started Block 3 chemotherapy per protocol.

One week after receiving Day 8 high-dose cytarabine, she was admitted with febrile neutropenia. She was found to have Enterobacter cloacae bacteremia which was treated with a course of cefepime; fevers resolved, and blood cultures cleared quickly. Five days later, while still on cefepime, fevers recurred along with left-sided headache, photophobia, and emotional lability. On exam, she had a subtle superficial scalp lesion initially concerning for leukemia cutis. CT head showed a large left parieto-occipital lesion concerning for fungal infection. MRI brain/spine showed a 4.3 x 3.7 cm area of abnormality in the left parieto-occipital area, and no abnormal spine findings (Fig2/panel A). Fungal biomarkers (serum aspergillus galactomannan and (1,3)-β-D-glucan) were negative. Dual broad anti-fungal therapy was initiated including liposomal amphotericin B and voriconazole, and fluconazole was stopped.

Based on imaging demonstrating enhancing tissue in the scalp adjacent to the lesion, and given risk of brain biopsy, a CT-guided biopsy of the scalp lesion by interventional radiology was obtained but was non-conclusive. Ultimately, an open brain biopsy was performed with tissue samples sent for oncology and infectious disease diagnostics including bacterial, fungal, and AFB cultures and molecular PCR-based testing. PCR testing returned positive for Rhizomucor pucillus. Pathology showed a hypocellular sample with some neutrophils and lymphocytes, and flow cytometry was negative for relapsed leukemia. While the initial fungal cultures were reported as negative, further fungal immunostaining (H&E, GMS) of specimens

showed findings consistent with mucormycosis (Figure1). Expanded work up including pan-CT imaging looking for disseminated disease showed no sinus or orbital disease. CT chest did not show specific signs of pulmonary mucormycosis such as the "reverse halo" sign; however, there was one small focal ground-glass nodule in the lung(2). The patient had no respiratory symptoms during hospitalization. Based on otherwise negative imaging, she was diagnosed with isolated cerebral mucormycosis (ICM). Liposomal amphotericin B was increased to high-dose therapy at 10 mg/kg/day, micafungin was added as synergistic therapy based on literature (2)(3) and voriconazole was stopped. Based on histopathological findings, she underwent emergent aggressive surgical debridement by neurosurgery comprising the enhancing and necrotic tissue in the superior parietal lobule and the adjacent gyri but sparing the occipital cortex and the peri-ventricular white matter to decrease the morbidity of the surgery and the risk of peri-ventricular spread. The immediate postoperative MRI reflected resection of the enhancing tissue but persistent FLAIR hyperintensity in the margins of the resection cavity (Figure 2/panel B). Repeat brain MRI brain 13 days later showed abnormalities consistent likely with progression of ICM including increase in enhancement around the resection cavity, leptomeningeal enhancement within the left posterior frontal and parietal sulci, and worsening mass effect with new 3 mm left-to-right midline shift (Figure 2/panel C). Given the progression and extension of the disease there was concern that further surgical debridement would have unacceptable morbidity and be possibly life-threatening. After multidisciplinary discussions with the patient's family, her parents elected to discontinue chemotherapy and engage hospice services rather than pursue additional aggressive treatment. She was discharged on oral ISAV as compassionate salvage treatment.

Unexpectedly, over two months after hospital discharge on hospice care, the patient continued doing well without further deterioration on ISAV monotherapy. Brain MRI was repeated and showed near resolution of previously seen concerning areas of enhancement. Bone marrow and spinal fluid evaluations were negative for leukemia. After discussion with family, the patient was re-initiated on a modified chemotherapy regimen with the goal of maintaining leukemia remission while avoiding excessive myelosuppression which was felt to increase risk for recurrence of ICM if any microscopic fungal disease were still present. She was treated with 28 days of continuous blinatumomab per AALL1331 and MRI after this cycle showed only expected post-operative changes in the left parieto-occipital resection cavity with slight enhancement of this cavity (Fig2/panel D). She completed one additional cycle of blinatumomab per AALL1331 followed by 16 weeks of continuation therapy per a modified version of the St. Jude Total XVI protocol weeks(4) Intermittent imaging during therapy showed stable CNS findings and she remained clinically stable aside from episodes of dizziness and occasional headaches, managed by neurology. She remained in continuous remission and was started on Maintenance chemotherapy per AALL1331.

Discussion

Invasive CNS mucormycosis (CNS-M) is a rare but often deadly invasive fungal infection in the pediatric population (4)(5). The acute and rapidly progressive evolution generally causes unfavorable outcomes with very high mortality rates of up to 65% despite appropriate treatment (5).

CNS-M can manifest in three distinct clinical forms: as rhinocerebral mucormycosis (RCM), disseminated mucormycosis with CNS involvement, or as ICM(6). The latter is the least frequent form, accounting for only 8% of CNS-M cases (7, 8)

Isolated cerebral mucormycosis has been described in the literature as having an exceedingly poor prognosis(7, 9-11){Kerezoudis, 2019 #143;Kerezoudis, 2019 #143}. The pooled mortality rate in a meta-analysis by the Mayo clinic was noted at 65%in adults(12), Rhizopus has been shown to be the most common isolated organism (59%)(13). Cases of isolated cerebral mucormycosis usually involve the basal ganglia or thalamus(7). Lesions are usually deep-seated with common basal ganglia involvement which is thought to be due to seeding from the middle cerebral artery, especially in intravenous drug users(6). However, interestingly, it has been shown that in immunocompromised patients, cortical lesions are more common like our case(6, 14)

Our case outlines the major obstacles in diagnosis of ICM as the clinical symptoms were initially fairly

subtle, conventional stains and cultures were negative, and obtaining a CNS biopsy specimen is not always feasible in vulnerable populations such as pediatric cancer patients (9). There are currently no clinically available circulating biomarkers of mucormycosis (9). Serum tests such as the 1,3-β-D-glucan assay and the aspergillus galactomannan assay are typically negative in invasive mucormycosis (10). Therefore, definitive diagnosis requires microbiological analysis of tissue obtained by biopsy or surgical debridement (11), high degree of clinical suspicion and prompt intervention (9, 12). The inclusion of PCR based testing for infectious organisms was critical in this cryptogenic presentation as the first finding to indicate the correct diagnosis(11, 15).

There are limited prospective clinical data on optimal therapies for CNS-M in children(10, 12, 16). A combined medical and surgical approach has repeatedly been shown to lead to the best outcomes(17), though aggressive surgical debridement is not always feasible depending on location of the infection, such as the CNS, where severe sequelae may result from attempting to surgically remove all fungal disease(12, 18). It has been widely accepted that early and aggressive surgical debridement in rhinosinus mucormycosis is essential to survival but this has not been established for isolated cerebral mucormycosis(13). Some studies have shown decreased mortality with stereotactic aspiration/debridement, but others have shown no differences in outcome(14). In our case, an aggressive debridement of all radiologically involved tissue would have conferred a neurological deficit that was not acceptable to the patient or family. The positive outcome in this case from a more limited debridement in combination with a salvage medical regimen supports a measured approach(15, 18).

Until recently, amphotericin B and the triazole antifungals (Posaconazole and ISAV) were the only systemic antifungals available with good activity against Mucorales species (18, 19). Posaconazole has been used in invasive mucormycosis in adults and adolescents as salvage therapy; however, CNS penetration has been reported to be poor (20), and Posaconazole monotherapy in CNS-M has not been adequately studied(20). Furthermore, there are concerns about the oral bioavailability of Posaconazole oral suspension in younger children who can't swallow the extended-release tablet(21).

ISAV, a second-generation triazole, was approved for the treatment of invasive aspergillosis (IA) or invasive mucormycosis(22). There is limited information on the CNS penetration of ISAV, however, a few studies demonstrated efficacy with ISAV treatment for CNS infections caused by a wide range of different fungi(9, 23). More recently, ISAV was assessed prospectively in a single-arm study of patients with mucormycosis and other rare fungal infections (the VITAL trial) (16, 24). In this study, ISAV showed promising results against mucormycosis with efficacy and outcomes similar to amphotericin B, these results turn light in horizon for ISAV not only as salvage but also as first-line agent of mucormycosis treatment(22). VITAL trial didn't look specifically effectiveness of ISAV in CNS-M, but 29% of cases had CNS involvement. Meanwhile, the pediatric dosing regimen of this drug has not been established. Desai et al. extrapolated an adult population pharmacokinetic model to determine the appropriate dose of ISAV for children(16). Accordingly, our patient received 10mg/kg of the prodrug isavuconazonium sulfate (equivalent to 5.4mg/kg of isavuconazole) every 8 hours for the first 2 days and once daily thereafter. Duration of therapy is always a question. Although our patient achieved radiographic resolution(10), we would continue ISAV suppressive treatment until the patient completes chemotherapy, is no longer in an immunosuppressive state and has reconstitution of the immune system.

In summary, our case is noteworthy in highlighting several challenges encountered in the diagnostics and management of ICM with eventually successful salvage treatment with monotherapy ISAV with complete clinical and radiologic responses. We hope that our case adds to the growing evidence supporting of ISAV as well-tolerated, safe, and efficacious therapy in ICM and promising therapy for salvage treatment and could be hope in horizon in children with ICM. The availability of an IV and oral of ISAV makes an attractive oral step-down therapy for with invasive or disseminated mucormycosis. Prospective clinical trials are needed to evaluate the established pediatric dose, safety, and efficacy of ISAV in children and its role as first-line treatment for ICM.

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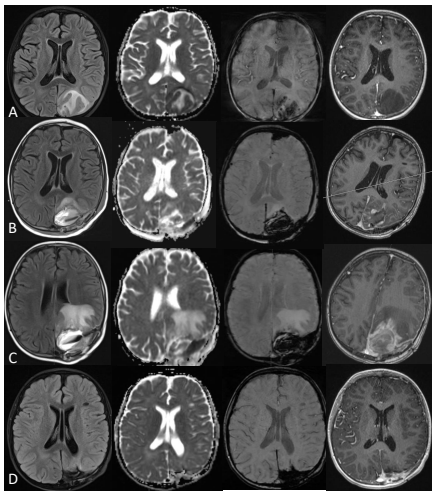

MR images of the brain without and with intravenous contrast with representative images including axial FLAIR, axial ADC, axial susceptibility weighted imaging, and axial post-contrast T1 weighted images obtained at different stages of presentation.
(A) Pre surgical debridement (B), twelve days following surgical debridement, and subsequent four-month follow-up imaging.
(A) At time of diagnosis : demonstrate an expansile mass-like focus of FLAIR hyperintensity in the left parietal and occipital lobes with gyriform diffusion restriction, gyriform susceptibility artifact indicating hemorrhage, and no significant contrast enhancement
(B) Immediate post-operative images demonstrate debridement of the area of fungal infection with heterogeneous fluid and blood products in the surgical cavity with mild adjacent parenchymal edema and presumed reactive contrast enhancement
(C) 10 days following surgical debridement : Short interval imaging reveals new confluent FLAIR hyperintense signal extending deep to the surgical cavity into the white matter consistent with marked increased vasogenic edema with mass effect on the posterior left lateral ventricle and new ill-defined parenchymal enhancement.
(D) Four-month follow-up imaging demonstrates complete resolution of vasogenic edema in the left posterior cerebral white matter with contraction of the surgical cavity and evolving enhancement in the cavity, likely post-surgical.