

## *Isolated Intracranial Relapse of Acute Myelocytic Leukemia (AML) Following 4 and 1/2 Years of Complete Remission*

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### Abstract

A seven year old Hispanic girl developed headache, backache and vomiting. A computed tomography showed 2 intracranial masses. A complete blood count was normal. Bone marrow aspiration showed hypoplastic but otherwise normal marrow. However, cerebrospinal fluid contained leukemic myeloblasts. Four and a half years earlier the patient had presented with an orbital mass, lethargy, and loss of appetite. MRI demonstrated a mass in left maxillary sinus extending to the left orbital cavity causing left proptosis. Bone marrow aspiration was diagnostic of Acute Myelogenous Leukemia (AML). She was treated with the standard AML chemotherapy regimen. Patient achieved complete remission and remained in remission during the subsequent 4 and a half years until the above event.

AML recurrence after 4 years of remission is rare. In addition this patient initially showed the recurrence only in the extramedullary site which is also unusual. We postulate that the intracranial recurrence was due to late activation of latent leukemic cells that had seeded in the leptomeningeal space at the time of original presentation. Because of these 2 unusual aspects we wish to report this case.

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### Introduction

Prognosis of AML in children is far inferior to that of ALL (Acute Lymphoblastic Leukemia). Current 5 year survival for de novo AML was quoted to be 60-75% [1], but only fewer than 50% of children have been cured [2].

Extramedullary presentation (myeloid sarcoma, chloroma, granulocytic sarcoma) with or without simultaneous bone marrow involvement occurs much more commonly in AML than in ALL, but still rare constituting only 2-4% of all AML cases [3].

We wish to describe a case with AML that showed two unique characteristics. First, the patient relapsed after 4.5 years of continuous uninterrupted remission. Second, the relapse was initially isolated intracranial relapse while bone marrow was uninvolved. Although a second malignancy cannot be totally excluded, considering the similar immunophenotypic markers and the morphology of the relapsed myeloblasts, it is highly unlikely. This case reminds us that a late relapse does occur, though rare, and one needs to be vigilant in excluding relapse during the late follow up of these patients. When suspected, a

LP should be done promptly, since blasts in CSF (CerebroSpinal Fluid) are diagnostic and would circumvent a risky surgical biopsy of tumor mass.

#### Description of a Case

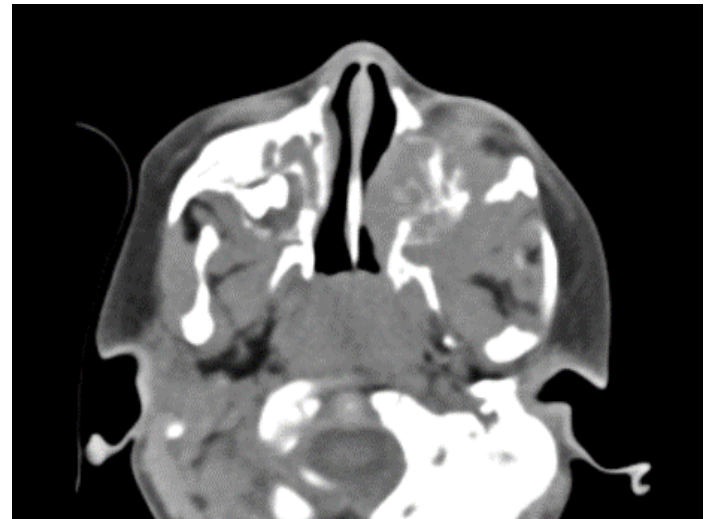
The patient initially presented at age of 2 years with swelling of the left eye for 1 week. She also had loss of appetite, decreased oral intake, low grade fever and lethargy for the preceding 3-4 weeks. Earlier, a CBC ordered by a primary care physician's office had shown neutropenia and anemia. Pt was admitted to our hospital for a further investigation. Past medical history was unremarkable. The details of the biological family was not available, since she was adopted.

Physical examination showed bilateral periorbital edema with left proptosis. Extra ocular movements bilaterally were intact. The liver and spleen were not enlarged.

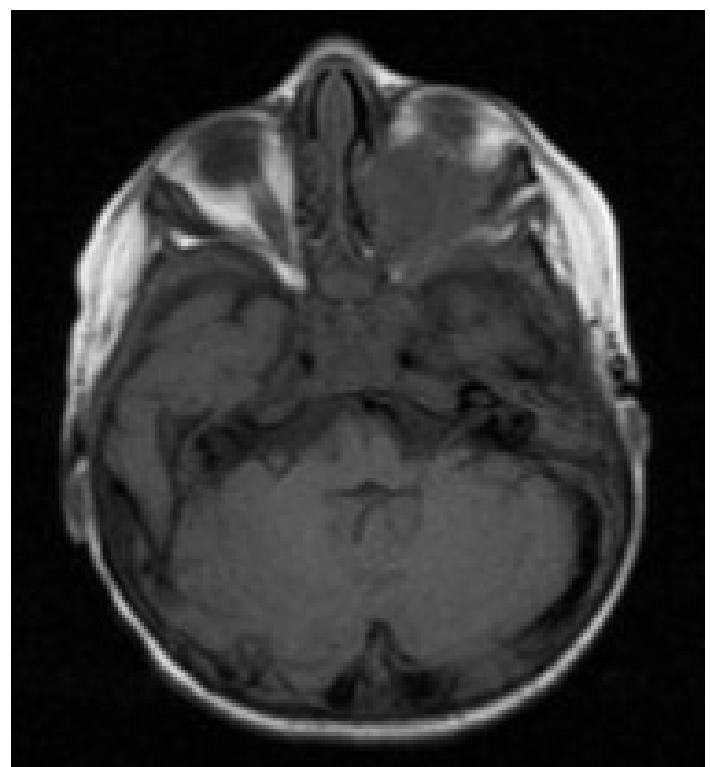
The initial CBC showed Hb of 10.3g/dL, WBC of 7,300/ $\mu$ L, and platelet count of 157,000/ $\mu$ L. The differential of WBC showed 12% blasts, 1% progranulocytes, 86 % lymphocytes, and 1 % monocytes. The bone marrow was very cellular and 90 % of the cells consisted of myeloblasts and progranulocytes. The immunofluorescence by the flow cytometer of the marrow cells (CD45 positive cells) showed CD11b (65%), CD15 (100%), CD33 (100%), CD117 (72%), and HLA-DR (100%) positivity. FAB classification was M1. Cytogenetic study showed no specific abnormalities.

CT scan of orbits was performed. Soft tissue mass was seen involving left maxillary sinus and retro bulbar region of left orbit with bone destruction (Figure 1A).Magnetic Resonance Imaging (MRI) demonstrated a T1/T2 isointense mass originating from the left maxillary sinus extending superiorly to the left orbit causing proptosis of the left globe (Figure 1B and Figure 1C). The mass extended medially into the nasal cavity, and laterally to the left infra temporal fossa. There was, however, no detectable intracranial lesions noted. CerebroSpinal Fluid (CSF) showed no cells, and protein and glucose were normal. She was diagnosed to have AML (FAB M1) and was given induction chemotherapy COG (Children's Oncology Group) AAML 0531 protocol. Patient achieved complete remission. The orbital mass completely resolved. She

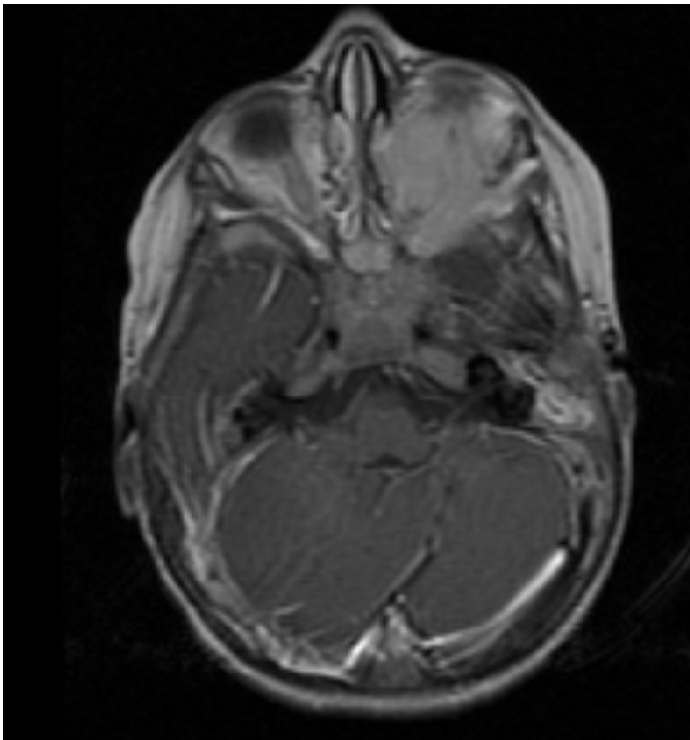
remained in remission throughout the duration of chemotherapy and after completion of chemotherapy for the next 4.5 years.



**Figure 1A.** CT scan of orbits and maxillary sinuses at the initial presentation. Soft tissue mass is seen involving left maxillary sinus and retro bulbar region of left orbit with bone destruction.



**Figure 1B.** An MRI of head, axial, T1 image demonstrates isointense mass in retrobulbar region of left orbit

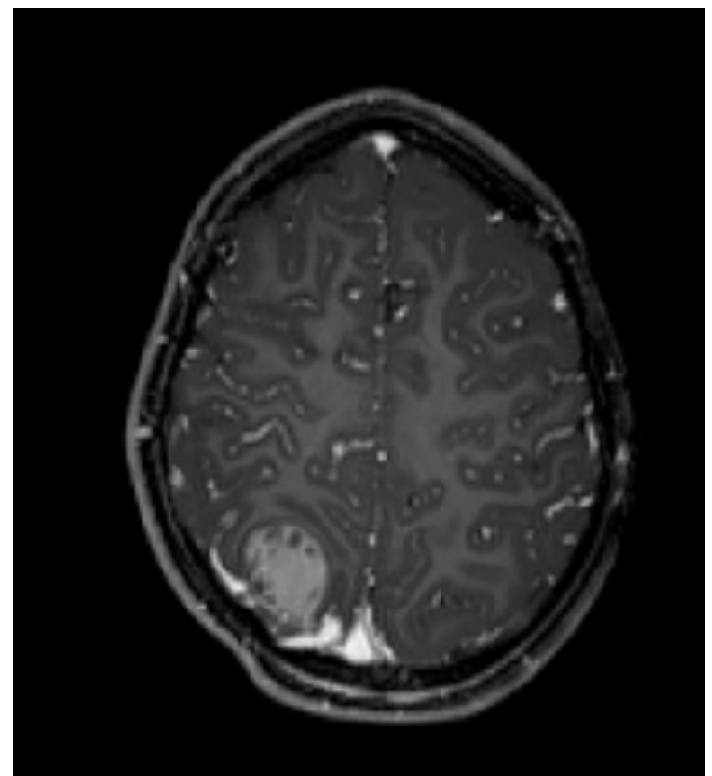


**Figure 1C.** MRI of head demonstrates enhancing mass in left orbit.

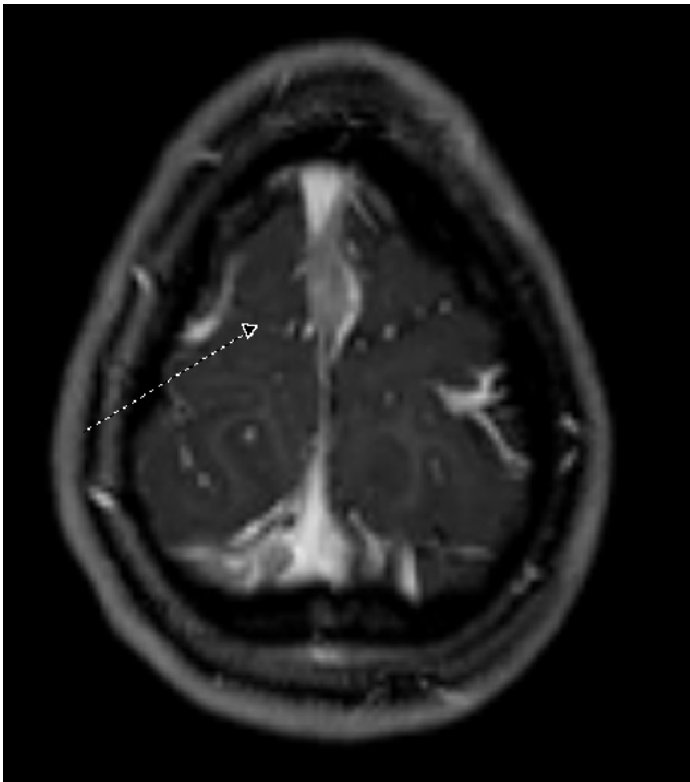
Four and a half years from her initial presentation, patient presented with progressively worsening headache of one month duration, backache, and vomiting of 1 week duration. MRI of brain demonstrated a 2.6 x 2.1 cm well defined enhancing mass in the extra-axial space of right parietal region, and a 1.8 x 0.8 cm mass of similar appearance in the left parasagittal location (Figure 2A and Figure 2B). MRI of spine showed mild thickening and nodularity of the cauda equina suggesting leptomeningeal spread of the tumor. There was no apparent cord compression. A CBC and chemistry profile were normal. A bone marrow aspiration and biopsy were normal. However, CSF obtained by a lumbar puncture showed 86 WBCs and 2 RBCs / $\mu$ L. The immunophenotypic markers were positive for CD33, CD117, and CD56, but negative for CD34. The findings are consistent with extramedullary relapse of the original AML. Because of the paucity of the number of cells, cytogenetic analysis could not be performed on CSF cells.

The patient received remission induction chemotherapy consisting of daily Clofarabin and daily Cytarabin each for 5 days in addition to weekly intrathecal Cytarabin. The second

induction course was given 35 days later. It consisted of high dose Cytarabin q 12 h x 4 doses followed by L-asparaginase. The Cytarabin and L-asparaginase were repeated 1 week later. Following the 2 remission induction courses, the patient developed profound neutropenia, and alpha hemolytic streptococcus sepsis ensued followed by acute respiratory failure. She was placed on ventilator support. Though eventually she was weaned off ventilator, her leukemia progressed rapidly with the highest blood white blood cell count of 115,300/ $\mu$ L with 78 % blasts about 3 months after initial intracranial relapse. A subsequent attempt to induce complete remission was aborted due to her poor condition, and was given small doses of 6-mercaptoputine and Etoposide which kept her white cell count in check, but the intracranial tumors progressively increased in size, and she developed intracranial hemorrhage and expired 5 months after the presentation of the relapse.



**Figure 2A.** An MRI done at the time of relapse showing a 2.7 x 2.1 cm enhancing lesion in right sided parietal region at the time of relapse



**Figure 2B.** An MRI done at the time of relapse showing 1.8 x 0.8 cm mass in the left parasagittal region adjacent to the falx (arrow)

## Discussion

In an earlier review of adult AML studies conducted by CALGB (Cancer and Leukaemia Group B), the authors stated that “Patients with AML who are in complete remission for 3–4 years can be assured that late relapse and death are relatively uncommon events” [4]. A large retrospective study reported by the Toronto group showed a frequency of very late relapse (a relapse occurring 5 or more years after the initial achievement of remission) to be 3% in adult AML [5]. Subsequent literature, however, has occasionally reported later relapses of AML as late as 18 years following the diagnosis of the original leukemia [6]. Nonetheless a relapse occurring 4.5 years later such as in this patient is a very uncommon event. Thus at the initial evaluation of her symptoms of headache, AML relapse was not strongly suspected. Intracranial masses with normal CBC favored a diagnosis of brain tumor, rather than a relapse. Thus the patient was referred to a neurosurgeon at the time of initial

evaluation at an emergency department that did not have a benefit of detailed past medical history.

However, examination of CSF cells conclusively showed that the patient developed a relapse of the original AML, even though bone marrow failed to show evidence of leukemia at that time. This is again an unusual presentation of a relapse, though similar events have been described in the literature; a 40 year old male developed a cerebropontine angle mass eight years after the original diagnosis of M4 AML. Bone marrow was normal. One month later he developed multiple intrathecal masses, and CSF showed myeloblasts, and he was diagnosed to have a relapse [7]. A 31 year old man developed pulmonary parenchymal chloroma that had been preceded 7 years earlier by leukemia cutis. He did not have bone marrow involvement at either time [8]. Sano et al [9] reported that among pediatric AML patients, patients with RAS (K-RAS or N-RAS) mutation exhibited a significantly higher rate of late relapse, relapses occurring 2nd or 3rd year after the diagnosis.

Unlike Acute Lymphoblastic Leukaemia (ALL), AML more often presents as a solid mass of leukemic cells outside the bone marrow (extramedullary site), commonly known as chloroma, Myelocytic Sarcoma (MS), or granulocytic sarcoma [10]. A review article by Byrd et al on extramedullary AML cited the frequency of MS to be 3% in living adults. According to this article, most common involved sites are skin, lymph nodes, spine and small intestines [10]. In children the frequency was 10.9% at the time of initial diagnosis in one study [11] most commonly involved sites in children were skin, orbit, head and neck, and spine and brain [10]. In this study 39% of children who initially presented with extramedullary leukemia relapsed at extramedullary sites alone without bone marrow leukemia. Thus in this regard, our patient’s isolated CNS relapse may not be as uncommon as initially thought. In another pediatric study of 1459 patients, 1% and 2% of patients had CNS and orbital myelocytic sarcoma respectively [12], and thus Orbital and CNS presentations are still very uncommon.

Several adult and pediatric studies showed a high frequency of t (8; 21) in leukemic cells [2, 8, 9] in patients with extramedullary leukemia. Our patient did not have this

translocation. The largest pediatric study of AML with extramedullary disease report a significantly higher event free survival of patients who presented with orbital or CNS mass than those without. In fact their survival curve plateaus before 2 years after the study entry [12].

Studies published thus far cited several factors that were associated with late relapse. They include t (8:21), inversion 16, FAB M2 or M4/M5, a high initial WBC count, and RAS mutation [5, 9, 11-13]. Our patient had none of these characteristics, though we did not look for RAS mutation. What triggers a late relapse in AML patients remains a myth. We postulate that her late relapse was reactivation of the original leukemic cells that had not been eradicated by the initial chemotherapy and remained dormant in the leptomeningeal cavity from the outset. It is also possible that her bone marrow could have harbored dormant leukemic cells which ultimately travelled to leptomeningeal space while the patient totally remained asymptomatic, but this possibility is much less likely. It is quite unclear as to what triggered this reactivation if the dormant cells.

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