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CASE REPORT

Management of isolated recurrence of extramedullary myeloid tumor at a single site

Muddu Vamshi Krishna, Ashok K. Yadav, Brijesh Arora, Shripad D. Banavali[1]

Departments of Medical Oncology and [1]Medical and Pediatric Oncology, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India

Address for correspondence:
Prof. Shripad D. Banavali, Department of Medical and Pediatric Oncology, Tata Memorial Hospital, Dr. Ernest Borges Road, Parel, Mumbai, Maharashtra, India.
E-mail: banavali_2000@yahoo.com

ABSTRACT

Extramedullary myeloid tumors (EMMT) can precede, occur with or follow AML. Rarely, they can present as isolated relapses. We present a 9-year-old child with t (8, 21) positive AML who was treated with induction regimen and achieved remission. While on high-dose cytarabine consolidation, he had isolated relapse in a single cervical lymph node with uninvolved marrow. He was treated with salvage chemotherapy alone. There are no clear guidelines for treatment of isolated extramedullary relapse. Chemotherapy, radiotherapy followed by stem cell transplant is the usual option. Our patient is unique for the unusual site of relapse and prolonged remission with cladribine-based chemotherapy, mitoxantrone-based consolidation, and oral maintenance therapy.

Key words: *2-CDA, AML, chemotherapy, extramedullary relapse*

INTRODUCTION

Extramedullary myeloid tumor (EMMT), also known as granulocytic sarcoma, myeloid sarcoma or chloroma, is composed of myeloid blasts in sites outside the bone marrow. First described in 1811, they were named as chloromas due to the green color imparted by myeloperoxidase.[1] EMMT can precede or occur concurrently with bone marrow involvement or present as relapses.[2] While the great majority of EMMT relapses occur along with or immediately preceding bone marrow relapse, they may rarely present without bone marrow involvement.[3] We present a patient with cytogenetically good-risk AML, who had an isolated extramedullary relapse at a single site. There are no clear guidelines regarding the optimal management in such patients.

CASE REPORT

A 9-year-old male child presented with fever, weakness, and easy fatiguability for 1 month. There was no history of cough, chest pain, and bleeding manifestations. Family history was insignificant and there was no other significant past medical history. Physical examination was significant for pallor, bilateral subcentrimetric cervical, axillary and inguinal lymphadenopathy, and hepatomegaly. Investigations revealed hemoglobin of 8.6 gm%, leukocyte count 22.40 × 10^9/L and platelet count of 78 × 10^9/L. Peripheral blood examination showed 84% myeloblasts which were myeloperoxidase (MPO) positive. Bone marrow was hypercellular with 58% blasts that showed auer rods and were MPO positive. On flow cytometry, the blasts were positive for CD 13, CD 33, CD117, CD34, CD38, CD15, and CD19 and negative for CD11b and CD64. Fluorescent *in situ* hybridization (FISH) analysis of the bone marrow revealed the presence of t (8,21) translocation. The patient was classified as having good-risk AML and was treated with standard 3+7 induction with daunorubicin 60 mg/m^2 iv push for 3 days and cytarabine 100 mg/m^2 continuous 24-h infusion for 7 days. Day 10 marrow was dilute with no excess of blasts, suggestive of good response to therapy. Marrow examination done on day 30, after the recovery of counts, was in morphologic and cytogenetic remission. He was planned for consolidation with three cycles of cyatrabine at 18 g/m^2. Following the 1st consolidation, he was detected to have a single hard 1 cm × 2 cm right cervical lymph node. Excisional biopsy of the lymph node revealed the presence of extramedullary myeloid tumor / granulocytic sarcoma. Cytogenetic evaluation showed the presence of translocation t (8, 21) in the aspirate from the lymph node. Imaging failed to reveal any other sites of lymphadenopathy. Bone marrow continued to be in morphological and cytogenetic remission by FISH. He was treated with salvage chemotherapy with two cycles

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continuous infusion cytarabine (500 mg/m^2), Day 1-5, along with cladribine (9 mg/m^2) Day 2-6.[4] Following two cycles, patient continued to be in both clinical and hematological remission. Though allogenic stem cell transplant was considered as an option, the patient did not have a HLA-matched sibling and matched unrelated transplant was not financially feasible. Further consolidation was given with one cycle of mitoxantrone 8 mg/m^2 for 1 day, cytarabine 75 mg/m^2 for 5 days and etoposide 75 mg/m^2 for 5 days. Maintenance was with six cycles of oral 6-TG 40 mg/m^2 for 21 days of 28 days, oral etoposide 50 mg/m^2 for 21 days of 28 days, and oral sodium valproate 500 mg twice daily. Following the oral maintenance, the patient was treated with external beam radiotherapy to the right hemi-neck at a dose of 25.2 Gy in 14 fractions. Presently, the child is disease-free and is doing well 18 months post-diagnosis of relapse and 6 months of completing chemotherapy.

DISCUSSION

EMMTs are a collection of leukemic cells that can occur in any soft tissue area, including GIT, bone, skin, lymph nodes, breast, ovary, meninges, orbit, optic nerve and unusual sites like pleura, uterus, paranasal sinus, nasopharynx, peritoneal cavity, and bladder.[3] They usually precede marrow involvement by months to years and are associated with a poorer outcome. The risk factors include high WBC count, FAB M 4 and M 5 morphology, immune dysfunction, cytogenetic abnormalities [t (8, 21), inv (16)], delay in treatment, lack of auer rods, co-expression of T-cell markers, and CD 56.[5] A potential explanation of the distribution of myeloid sarcomas could be due to the expression of NCAM in neural tissue, muscle tissue and GIT, and its co-expression in myeloid sarcomas.[6]

Extramedullary relapses (EMR) occurring as granulocytic sarcomas after chemotherapy or stem cell transplant have been reported commonly and occur at sites similar to isolated granulocytic sarcomas. Isolated EMR are generally defined as isolated focus of EMR that occur during the period of marrow remission and are not associated with marrow relapse for at least 30 days.[3] In one survey by the European transplantation centers, 0.65% of the patients developed EMR, 95% of whom had a bone marrow relapse within 1-12 months.[7] Management in such patients is a complex issue with treatment being complicated by prior high-dose chemotherapy, radiotherapy, and immunosuppressive therapy.

Byrd *et al.* reported a patient of acute myeloid leukemia, who had a series of 11 extra medullary relapses over 29 months.[6] They reviewed a total of 24 patients with isolated EMR. These patients had a marrow relapse with a mean interval of 7 months (range of 1 to 19 months). Twelve patients were treated with a combination of systemic chemotherapy with local RT and had a mean survival time of 10 months (range 2-24+ months). High dose chemotherapy with allogenic transplant prevented relapses in two patients treated with this approach; however, both the patients later died due to treatment toxicity after 2 and 5 months. Nine patients received local therapy and radiotherapy alone and had a mean survival of 6 months with only two patients surviving for more than 10 months. Five patients underwent standard induction alone. The mean time to death among these patients was 4 months. Thus, standard induction alone appears to be ineffective. The authors concluded that the ideal treatment for isolated extra medullary recurrence was induction therapy followed by radiation to the tumor where needed.

Isolated testicular relapses have been treated with systemic therapy as well as radiotherapy to testes. Gahdiatny reviewed isolated testicular relapse and reported survival of more than 3 years following RT and systemic induction followed by consolidation.[8] None of the other cases in literature have had survival for more than a few months and are usually followed by systemic relapse.

Isolated EMR following SCT has been reported in several reports and usually heralds incurable marrow relapse. Koc *et al.* analyzed 134 consecutive patients undergoing allogenic SCT for AML.[9] There were five cases of isolated EMR who were subsequently treated with chemotherapy, radiation, or second allogenic SCT. One patient treated with allogenic SCT following local radiation remained in CR for more than 33 months while those treated with chemotherapy and radiation alone had survival of less than 4 months.

The median survival across various studies has been reported to range between 4 and 7 months. Even where localized blastic tissue is responsive to local therapy, there is systemic and bone marrow recurrence within a short while which is usually chemoresistant. Patients with primary refractory disease and with early relapse have poor prognosis and require innovative therapeutic approaches.

Our patient had isolated extramedullary relapse while on consolidation phase with high dose cytarabine. Though extensive lymph nodal involvement and skin involvement have been reported earlier, we could not find any similar reports of isolated single lymph node as a site of relapse in the literature. Our patient raises several intriguing questions regarding further therapy. Normally, patients with marrow relapse while on treatment have a poor prognosis and allogenic transplant is the usual treatment. However, the appropriate approach in isolated extra medullary relapse is

not clearly defined. Moreover, in our patient, the disease was completely excised surgically and there has been no marrow relapse for the past 15 months. Further local therapy in the form of radiotherapy alone is logically untenable given that the nodal disease is completely excised; however, we did not find any justification for this approach in literature. The need for systemic therapy is again logically required given that patients with isolated EMR have a propensity to relapse in the marrow; moreover, our patient had not completed the primary therapy. The exact chemotherapy regimen to be used is not known. We used reinduction with two cycles of cladribine-based therapy followed by consolidation with one cycle of mitoxantrone-based chemotherapy. This was followed by 9 months of oral etoposide/6-thioguanine maintenance therapy. Cladribine increases cytotoxic effects of ara-C in leukemic blasts and impairs DNA repair mechanisms; therefore, its association with ara-C results in synergistic activity. This regimen was found to be highly effective in both newly diagnosed as well as relapsed/refractory poor-risk patients of AML.[4,10-12] Mitoxantrone has been associated with improved outcomes in AML patients, especially in patients with t (8,21).[13] While some studies have compared cladribine-based regimen with mitoxantrone-based regimen, others have combined both. We have used a sequential approach in our patient. At our institute (TMH, Mumbai), we are routinely using oral maintenance therapy in all children of AML in remission after induction and consolidation therapy. This approach has helped decrease the overall relapse rate.[14]

To conclude, our case report illustrates that relapse of acute myeloid leukemia can occur at unusual sites and can often pose a therapeutic dilemma. There is need for a consensus doctrine for the management of isolated EMR and a clarification of the role of transplant in this setting. In this context, the use of cladribine-based reinduction followed by mitoxantrone-based consolidation and oral maintenance was found to be effective in the management of our patient.

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