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Juvenile myelomonocytic leukaemia

Emaduddin Siddiqui
Aga Khan University, emaduddin.siddiqui@aku.edu

Shaheena Hanif
Aga Khan University

Case Report

JUVENILE MYELOMONOCYTIC LEUKAEMIA

Emad uddin Siddiqui[1], Shaheena Hanif[2]

Summary

Juvenile Myelomonocytic Leukemia (JMML) is a rare hematopoietic malignancy of early childhood. Infection remains the principal cause of death in patients with myelodysplastic syndrome (MDS). Sixty percent of patients are anemic and 26 percent have petechiae and/or purpura (thrombocytopenia). Bone Marrow Transplant (BMT) is the best available treatment option. We describe the management of an eight months old male child who presented with complaints of fever, cough and pallor since six months. Despite medication his fever did not subside. He developed meningitis and intracranial bleed and expired on 11th day of hospitalization.

KEY WORDS: Juvenile Myelomonocytic Leukaemia.

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INTRODUCTION

Juvenile myelomonocytic leukemia (JMML) is a rare hematopoietic malignancy of early childhood, representing 2 to 3% of all pediatric leukemia. Juvenile myelomonocytic leukemia (JMML) usually runs an aggressive clinical course, with median duration of survival for children left untreated being less than 12 months from diagnosis.[1]

JMML share both myelodysplastic and myeloproliferative features.[2] Two groups of MDS are found in children. JMML has a unique clinical presentation in children and infants. Adult type is MDS. Patients less than one year of age at diagnosis have a significantly better survival than older children. Low platelets, elevated HbF and complex cytogenic abnormalities i.e. monosomy 7 are unfavorable prognostic indicators.[3]

1. Dr. Emad uddin Siddiqui
2. Dr. Shaheena Hanif

Correspondence

Dr. Emad uddin siddiqui
R- 215-19 Alnoor Society,
Federal-B-Area
Karachi - Pakistan.
E-mail: emaduz@yahoo.com

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The pathogenesis of JMML arises from dysregulation of signal transduction through the RAS pathway. Potential causative mutations or other genetic abnormalities in three genes (e.g. RAS, neurofibromatosis type 1 and PTPN11), all of which are positioned in the Granulocyte-monocytes, colony stimulation factor (GM CSF) RAS signal transduction pathway, accounts for up to 75% of cases of JMML.[4]

CASE REPORT

An eight month old male child was admitted with complaints of fever, cough and pallor since last 6 months. He was well up to the age of two months when he developed fever and cough. He was treated by different medications but symptoms used to subside temporarily and than recur, with gradually increasing pallor.

The natal and postnatal history was uneventful. There was no history of maternal fever, rash, lymphadenopathy or past history of premature birth/abortion considering torch infection. There was no history of convulsions and regression of milestone. He had two admissions in hospital due to pneumonia.

On examination general condition was stable with temperature of 99 F, pulse 99/minutes, R/R 29/minute, moderately anemic, one café-au-lait spot about 5mm in size on the

anterior chest wall. There was no cyanosis, jaundice, lymphadenopathy, no petechael rash and no other skin rash was detected. His weight was 6.8 Kg, length was 67cm and FOC was 43cm.

Spleen was palpable 8cm along its long axis below left sub costal margin; it was firm in consistency with well defined border. Liver was 3.5cm palpable below the right costal margin, firm in consistency with sharp borders and smooth surface, total span of liver was 7cm in the mid clavicular line. Rest of the systemic examination was unremarkable.

The investigations showed Hb 6gm/dl, TLC 29,400/cumm, (Neutrophil 58%, Lymphocytes 22%, Eosinophils 2%, Monocytes 10%, Myelocytes 2% and Metamyelocytes 6%). Peripheral smear showed anisocytosis, poikilocytosis, rouloux formation, leucocytes shift to left. Reticulocytes 6%. Electrophoresis revealed HbF 6%. Blood culture showed no growth. Chest X-ray was normal, Ultrasound abdomen showed hepatospleenomegally. Bone marrow D/R showed myelopoiesis with hyperplasic and moderately active dysplasia. Most myeloid precursors show a granular cytoplasm. Blast 5%, M:E ratio was 10:1, lymphocytes and plasma cells were normal. Increase in monocytes and its precursors were noted.

DISCUSSION

In 1976, the French-American-British (FAB) Cooperative Group initially defined refractory anemia with excess blasts (RAEB) and CMML as preleukemic states. Six years later, the FAB group added three more categories to this classification scheme and adopted the present term "myelodysplastic syndromes (MDS).[5]

The characteristic features, include spleenomegaly, leukocytosis with monocytosis, frequent skin involvement, thrombocytopenia and anemia. Many patients are asymptomatic, with the diagnosis established upon routine laboratory screening.[6]

Infection remains the principal cause of death in patients with MDS. Although fungal, viral and mycobacterial infections can occur, they are rare in the absence of concurrent administration of immunosuppressive agents.[7]

We treat our patient with antibiotics for infections, packed cell (filtered) and platelet transfusions for symptomatic anemia and thrombocytopenia. The use of pre storage leuko reduced transfusion products is recommended. Along with the management of the symptoms and complications we planed to start the recommended treatment protocol but his fever did not subside rather he developed meningitis and intracranial bleed and expired on 11th day of admission.

Cytogenetic analysis, in vitro bone marrow progenitor cultures, trephine biopsies, flow cytometry and immunohistochemical studies may be helpful, only those cases where the morphology of the white cells were difficult to appreciate or differentiate as opposed to this case in which history, clinical finding and smear of blood film was clear enough to make the diagnosis.

International Prognostic Scoring System (IPSS) is of mutation and/or loss of heterozygosity of the tumor suppresses gene p53. Such alterations in the p53 configuration have been commonly noted in MDS.[8]

Growth factors such as recombinant human granulocyte colony-stimulating factor (G-CSF), recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF), and recombinant human erythropoietin (EPO) may be used in MDS.[9] The response of patients with MDS to treatment with GM-CSF has been disappointing.

On May 2, 2006, the United States FDA approved decitabine (Dacogen®, MGI Pharma, Inc.) for the treatment of patients with previously treated, untreated, de novo, and secondary MDS of all FAB subtypes and intermediate-1, intermediate-2, and high-risk IPSS groups.

There is increasing use of matched unrelated donor (MUD) transplants, which may be as effective as HLA-matched sibling transplants. For these patients, use of umbilical cord blood as the donor source is being investigated.[10]

Recommendations: All available treatments in MDS are experimental, other than hematopoietic cell transplantation (HCT). Prompt treatment of infection, bleeding and anemia is necessary for all patients, and may include use of antibiotics and transfusions.

Future Directions: For interested patients, relatives, and physicians, the Aplastic Anemia and MDS International Foundation maintains a website containing list of clinical trials. http://www.aamds.org/

REFERECNES

1. Franco L, Peter N, Marco Z, Elisabeth K, Edoardo L, Christine P, et al. Hematopoietic stem cell transplantation in children with Juvenile Myelomonocytic Leukaemia. Blood 2005;(1):410-19.
2. Stary J, Locatelli F, Niemever CM. European Working Group on Myelodysplastic Syndrome (EWOG-MDS) and Pediatric Diseases Working Party of the EBMT. Bone Marrow Transplant 2005;35 Suppl(1):13-6.
3. Mc Kenna RW. Myelodysplasia & myeloproliferative disorders in children. Bone Marrow Transplant 2005;36(5):453-4.
4. PD Emanuel. Juvenile Myelomonocytic Leukemia. Curr Haematol Rep 2004;3(3):203-9.
5. Bennett JM, Catovsky D, Daniel MT. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982;51:189-90.
6. Donald DC, Stephen LA. Clinical feature and diagnosis of MDS. From http://www.uptodate.com/ 2006 license to AKU. Accessed on 10th April 2006.
7. Pomeroy C, Oken MM, Rydell RE, Filice GA. Infection in the myelodysplastic syndromes. Am J Med 1991;90:338-40.
8. Christiansen DH, Andersen MK, Pedersen, Bjergaard J. Mutations with loss of heterozygosity of p53 are common in therapy-related myelodysplasia and acute myeloid leukemia after exposure to alkylating agents and significantly associated with deletion or loss of 5q, a complex karyotype, and a poor prognosis. J Clin Oncol 2001;19:1405-6.
9. Ozer H, Armitage JO, Bennett C, Jeffrey D, George A, Philips, et al. Update of recommendations for the use of hematopoietic colony-stimulating factors: Evidence-based, clinical practice guidelines. J Clin Oncol 2000;18:3558-85.
10. Ruter B, Wijermans PW, Lubbert M. Superiority of prolonged low-dose azanucleoside administration? Results of 5-aza-2'-deoxycytidine retreatment in high-risk myelodysplasia patients. Cancer 2006;106:1744-6.

Correspondence

Audit of pediatric prescriptions for common paediatric problems

This is with reference to the above-cited article published in the Oct-Dec 2007 Part-II of Pakistan Journal of Medical Sciences.[1] The study concluded that medicines are misused by the pediatricians with both lower and higher qualifications. The authors have pleaded for active measures to rationalize the prescribing habits of the pediatricians. In this regards, I would like to say that there have been numerous publications highlighting the enormous problem of 'irrational use of medicines' in all the disciplines of medical science.[2]

Basically there is a huge "therapeutic deficit" in the medical education and training of both undergraduates and postgraduates. There is also no programme of continued medical education for the practicing doctors. This is due to the fact that medical institutions in Pakistan do not have departments of clinical therapeutics while in foreign countries every teaching hospital has a professional unit of clinical therapeutics and clinical pharmacology where education and training is imparted to the undergraduate and post-graduate students, drug formularies for hospitals and treatment guide-lines are made, medical audit of treatments, research and continued education of doctors is carried out. There, even the general hospitals have specialists of this discipline.

It is important to understand that clinical therapeutics and clinical pharmacology is also a major specialty, just like cardiology, pulmonology, gastroenterology, pediatrics etc. with an indispensable role in the discipline of the art and science of medicines. Thus, establishment of such departments is the only way to tackle the problem of misuse of drugs. Drugs are increasing in numbers explosively and nothing short of what is stated above will work. The WHO Expert Committee has also advocated the dire necessity of such departments.

REFERENCES

1. Javed M. Audit of paediatric prescriptions for the common paediatric problems. Pak J Med Sci 2007;23(6):932-5.
2. Akhter MA. Misuse of drugs. Pak A F Med J 1974;25(4):

Lt. Gen. Mahmmud Akhter,
Rawalpindi, Pakistan.