A Case of Agnogenic Myeloid Metaplasia

Agnojenik Myeloid Metaplazili Bir Olgu Sunumu

İbrahim Bayram, MD.
Departments of Pediatrics,
Çukurova University, Medical Faculty
mrbairam@cu.edu.tr

Kenan Özcan, MD.
Departments of Pediatrics,
Çukurova University, Medical Faculty
kozcan@cu.edu.tr

Fatih Erbey, MD.
Departments of Pathology,
Çukurova University, Medical Faculty
erbeyf@cu.edu.tr

Figen Doran, MD.
Departments of Pediatrics,
Çukurova University, Medical Faculty
fdoran@cu.edu.tr

Atila Tanyeli, MD.
Departments of Pediatrics,
Çukurova University, Medical Faculty
atanyeli@gmail.com

This study was presented on XXXIXth Turkish Pediatrics Congress, June, 17-22, 2003, Kapadokya, Nevşehir, Turkey.

Abstract
A 1.5 year-old male child was hospitalized with the complaints of fever, cough, nausea and diarrhea. He had a prolonged jaundice with no specific findings in family history. General appearance was good, skin and conjunctivas were pale. He had hepatosplenomegaly and anemia, as well. The case was diagnosed as Agnogenic Myeloid Metaplasia with clinic and laboratory findings. On following days, organomegaly was progressed (5 cm liver and 8 cm spleen). 30 mg/kg/day methylprednisolone was administered as a treatment. Although liver and hematologic parameters were not changed during the therapy, spleen became 5 cm. Patient was discharged by his family while treatment was going on.

Key Words: **Myeloid Metaplasia; Methylprednisolone, Child.**

Özet
1.5 yaşında erkek çocuğu ateş, öksürük, mide bulantısı ve ishal şikayetleri ile hastaneye yatırıldı. Öyküde, ailesel olmayan uzamış sarılık hikayesi vardı. Genel görünüşü iyi, deri ve skleralarında solukluğu vardı. Hepatosplenomegali ve anemisi vardı. Klinik ve laboratuar bulguları sonucunda Agnogenic Myeloid Metaplasia tanısı kondu. Takip eden günlerde karaciğer 5 cm, dalak ise 8 cm'e kadar büyüdü. 30 mg/kg/gün dozunda metil prednizolon tedavisi başlandı. Tedavi sırasında karaciğer ve kan değerleri ve bulgularında değişiklik olmazken, dalak 5 cm'e geriledi. Tedavide iken olgu, aile tarafından taburcu edildi.

Anahtar Kelimeler: **Çocuk; Myeloid Metaplazi; Prednizolon.**

Submitted : November 19, 2007
Revised : January 20, 2008
Accepted : June 09, 2008

Corresponding Author:
Assist. Prof. Dr. İbrahim Bayram
Departments of Pediatrics,
Çukurova University, Medical Faculty
Adana, Turkey

Telephone : +90 - 322 3387444
E-mail : mrbairam@cu.edu.tr

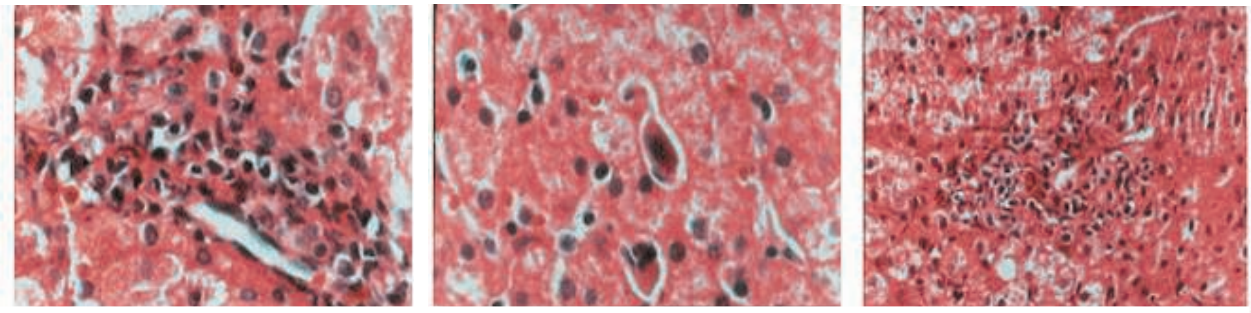
Introduction

Agnogenic Myeloid Metaplasia (AMM), (Idiopathic Myelofibrosis); is a disease of the group of myeloproliferative and myelodysplastic disorders. It is characterized by pancytopenia resulting in excess collagen deposition in bone marrow, on going fibrosis and splenomegaly (1). Mean survival time is generally 5 years. Although the etiology is uncertain, toluene, benzene, petroleum products and ionized radiations are suspected (1-3). In Hiroshima following atomic bomb and after receiving torium as a contrast material, the incidences were found to be higher (1).

Moreover, hepatosplenomegaly, anemia, myeloid metaplasia and myelofibrosis reported in the some cases with rickets (3, 4). 25% of the patients have no clinical symptoms. Hepatosplenomegaly, normochromic-normocytic anemia, leukocytosis, thrombocytosis or thrombocytopenia are the most common findings. Morphologic evaluation of bone marrow aspirates is hardly done. Neutrophilic and megakaryocytic hyperplasia can be seen in bone marrow examinatons. The structure of megakaryocytes is also abnormal. Fibrosis may be seen as a result of bone marrow biopsies (1). Here, a case with AMM which is rarely seen in childhood is presented.

Case Report

A 1.5 year-old male child was hospitalized with complaints of fever, cough, nausea, and diarrhea. He was discharged after transfusion because of anemia during the treatment. Because of the on going complaints, he was referred to our hospital. He had a prolonged jaundice with no specific findings in family history. Physical examination has revealed that his weight was 10 kg, height was 80 cm. General appearance was good, and skin and conjunctivas were pale. Microlymphadenopathies were palpated at cervical and inguinal regions. He had hepatosplenomegaly with a 2 cm liver and a 3 cm spleen below the respective costal margins. Other system examinations were normal. Laboratory examinations yields a hematocrit: 27.1%, hemoglobin: 9.4 g/dl, reticulocyte count of 2%, leukocyte count of $7.1x10^9$/L, platelet count of $110x10^9$/L, and mean corpuscular volume: 94 fentoliter. In peripheral blood smear 60% lymphocytes, 8% monocytes, 2% bands, 2% metamyelocytes, 28% neutrophils were detected. Erythrocytes were normochromic and normocytic. When examined for hemolytic anemia, results of direct and indirect Coombs' test were found to be negative. Erythrocyte sedimentation rate was 136 mm/hour and blood biochemistry was normal except for a higher lactate dehydrogenase (1164 IU/dl). Serological examinations were found to be normal except for positive Cytomegalovirus IgG and IgM but negative inclusion bodies in urine. Intrauterine infections were not considered. Abdominal ultrasonography and computerized tomography have revealed hepatosplenomegaly. Superior parts of upper and lower lobes of both lungs, posteriorly located paravertebral subpleural atelectasis and in bilateral lungs mild emphysematous appearance were detected at computerized tomography of the chest. On following days, organomegaly were progressed and 5 cm, liver and 8 cm spleen have been palpated. Bone marrow biopsy was done because of failed bone marrow aspirations. No marrow elements were found in the marrow biopsy material and myeloid metaplasia was detected in liver biopsy (Picture 1). Bone marrow scintigraphy has revealed showed amply decreased functioning marrow. 30 mg/kg/day methylprednisolone was started as a treatment (30 mg/kg/daily x 5; 20 mg/kg/daily x 3; 10 mg/kg/daily x 3; 5 mg/kg/daily x 3, 2 mg/kg/daily x 10; total 24 days). During the therapy spleen became 5 cm, liver size and hematologic parameters were not changed. Bone marrow transplantation was decided to be performed, however the family disagreed and in turn discharged their patient and left the treatment.



Picture1. Myeloid metaplasia in hepatic specimen (Hematoxylin-Eosin, X250)

Discussion

The case was diagnosed as AMM based on both clinic and laboratory findings. AMM is usually seen in adulthood but rarely seen in childhood. It was classified firstly by Dameshak (6) with chronic myeloid leukemia, polycytemia vera and essential thrombocytopenia. In these chronic myeloproliferative disorders, the bone marrow shows hyperplasia, hematopoiesis independent of physiological stimulus, fibrosis by time and leukemia at the end. Half of the patients have cytogenetical abnormalities. Marrow examination yields type I and III collagen fibers produced by fibroblasts in extracellular fields. At first type III collagen is found in the bone marrow then it is replaced by more stable type I collagen as it progresses. Myelofibrosis in AMM is seen after clonal hemopathy (7, 8). Fibroblasts and hematologic cells were understood to have different origins in the studies. The collagen accumulation in bone marrow is because of same cytokines secreted by neoplastic megakaryocytes and other clonally proliferating hematologic cells (9, 10). The increased production and decreased break down of the collagen is seen at the same time. Platelet factor 4 has some roles in preventing the collagen break down, while platelet derived growth factor (PDGF), epidermal growth factor, transforming growth factor-â (TGF-â) in increased production of collagen. Increased procollagen degredation products are showed. The treatment is supportive. None of the treatment modalities were shown to be increase the survival up-till now. Transfusions, steroids and androgens, splenectomy and chemotherapy in resistant disease are considered in the treatment (1).

Calcium, inorganic phosphate and alkaline phosphatase were normal and hence findings of vitamin D deficiency were not present in our case. Furthermore, serological examination of our case was found to be positive for Cytomegalovirus IgG and IgM but negative inclusion bodies in urine. CMV is in the Herpesviridae family. It can cause a variety of clinical illnesses. Clinical symptomatic CMV infection or cytomegalic inclusion disease is approximately 5% of congenital CMV infection. Other infants with congenital CMV infection have 5% with mild grade clinical symptom, and 90% with subclinical symptoms, but stil chronic diseases. There are intrauterine growth retardation, prematurity, hepatosplenomegaly and jaundice, rash, thrombocytopenia and purpura, microcephaly and intracranial calcifications, neurologic problems in the infants (chorioretinitis, sensorineural hearing loss and increases in cerebrospinal fluid protein). It may also cause pneumonitis, gastrointestinal disease, and fever with leukopenia or findings of generalized disease. Furthermore, bone marrow may be affected. On the other hand, perinatal CMV infection transmit via mother's cervikal-vaginal secretions and breast milk, but it is remain asymptomatic and do not occur sequelae. However in the this our case had hepatosplenomegaly, jaundice and anemia, other clinical finding of CMV infection was not found. Moreover, CMV is not caused myeloid metaplasia in the liver and spleen at literature (11).

Hessling et al (12) performed bone marrow transplantation in three patients with AMM of myelofibrosis and hematologically remission achieved in all of the three patients. Terrefi et al (13) had treated 23 AMM patients with imatinib mesylate with a dose of 400 mg/dl in 2 phased study. Because of some adverse effects of the drug (in 6 patient neutropenia, muscle and skeletal ache in 5 patients, thrombocytosis in 4 patients, edema in 3 patients and diarrhea in 1 patient) 16 patient were excluded from study. Treatment was continued for 3 months with decreased doses in one patient. None of the remaining patients who were continued the treatment got benefit from treatment in respect to anemia, platelet were increased 50% in 11 patients and in two patients splenomegaly were regressed partially. So that it was concluded that imatinib mesylate treatment suppresses the myeloid and erythroid growing but here no clinical benefit is seen.

In other studies, it is reported that radiotherapy (14), androgens, clodronate (15), cytosine arabinoside (16) are all effective in the treatment of AMM especially in splenomegaly. In childhood, corticosteroids (17, 18), danasole (19), interferon-alpha (20), bone marrow transplantation (21), partial splenectomy were used in the treatment of AMM (22). On the other hand there are some patients recovering spontaneously (23). In our case, after high dose methylprednisolone only splenomegali was regressed but no other benefit was detected. Rossbach et al (21) have reported that busulphan and cyclophosphamide pretreatment before bone marrow transplantation is more effective.

In conclusion AMM should be kept in mind with pancytopenia and organomegaly, even though the patient is a child. In spite of the high dose steroid treatment blood elements and other clinical findings have not seemed to get benefit, splenomegaly has been improved partially in this patient. Interferon-alpha could be used or bone marrow transplantation could be performed in this patient if he were discharged by his family.

References

1.Clark DA, Williams WL. Myelofibrosis. In: Pizzo PA, Poplack DG, editors. Principles and Practice of Pediatric Oncology. Philadelphia: Lippincott-Wilkins. 2002; 2390-2404.

2.Hu H. Benzene-associated myelofibrosis. Ann Intern Med 1987; 106:171-172.

3.Visfeldt J, Andersson M. Pathoanatomical aspects of malignant haematological disorders among Danish patients exposed to thorium dioxide. APMIS 1995;103:29-36.

4.Yetgin S, Yalcın SS. The effect of vitamin D3 on CD34 progenitor cells in vitamin D deficiency rickets. Turk J Pediatr 2004; 46: 164-166.

5.Gruner BA, DeNapoli TS, Elshihabi S et al. Anemia and Hepatosplenomegaly as Presenting Features in a Child With Rickets and Secondary Myelofibrosis. J Pediatr Hematol Oncol 2003;25:813–815.

6.Dameshek W. Some speculations on the myeloproliferative syndromes. Blood 1951; 6:372-375.

7.McCarthy DM. Fibrosis of the bone marrow: content and causes. Br J Haematol 1985; 59:1-7.

8.Reilly JT. Pathogenesis of idiopathic myelofibrosis: present status and future directions. Br J Haematol 1994; 88:1-8.

9.Golde DW, Hocking WG, Quan SG, Sparkes RS, Gale RP. Origin of human bone marrow fibroblasts. Br J Haematol 1980; 44:183-187.

10.Wang JC, Lang HD, Lichter S, Weinstein M, Benn P. Cytogenetic studies of bone marrow fibroblasts cultured from patients with myelofibrosis and myeloid metaplasia. Br J Haematol 1992; 80:184-188.

11.Stagno S. cytomegalovirus. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, editors. Nelson Textbook of Pediatrics, 18th edition. Philadelphia, by Saunders 2007; 1377-1379.

12.Hessling J, Kroger N, Werner M, et al. Dose-reduced conditioning regimen followed by allogeneic stem cell transplantation in patients with myelofibrosis with myeloid metaplasia. Br J Haematol 2002; 119:769-772.

13.Tefferi A, Mesa RA, Gray LA, et al. Phase 2 trial of imatinib mesylate in myelofibrosis with myeloid metaplasia. Blood 2002; 99:3854-3856.

14.Weinschenker P, Kutner JM, Salvajoli JV, et al. Whole-pulmonary low-dose radiation therapy in agnogenic myeloid metaplasia with diffuse lung involvement. Am J Hematol 2002; 69:277-280.

15.Froom P, Elmalah I, Braester A, Aghai E, Quitt M. Clodronate in myelofibrosis: a case report. Am J Med Sci 2002; 323:115-116.

16.Camba L, Aldrighetti L, Ciceri F, et al. Locoregional intrasplenic chemotherapy for hypersplenism in myelofibrosis. Br J Haematol 2001; 114:638-640.

17.Ozsoylu S, Ruacan S. High-dose intravenous corticosteroid treatment in childhood idiopathic myelofibrosis. Acta Haematol 1986; 75:49-51.

18.Cetingul N, Yener E, Oztop S, Nisli G, Soydan S. Agnogenic myeloid metaplasia in childhood: a report of two cases and efficiency of intravenous high dose methylprednisolone treatment. Acta Paediatr Jpn 1994; 36:697-700.

19.Levy V, Bourgarit A, Delmer A, et al. Treatment of agnogenic myeloid metaplasia with danazol: a report of four cases. Am J Hematol 1996; 53:239-241.

20.Kikawa Y, Fukumoto Y, Obata K, et al. Mayumi. Successful treatment of essential thrombocythemia evolving into agnogenic myeloid metaplasia with interferon-alpha. J Pediatr Hematol Oncol 1998;20(5):463-466.

21.Rossbach HC, Grana NH, Chamizo W, Barrios NJ, Barbosa JL. Successful allogeneic bone marrow transplantation for agnogenic myeloid metaplasia in a 3-year-old boy.ÊJ Pediatr Hematol Oncol 1996; 18:213-215.

22.Petroianu A. Subtotal splenectomy for treatment of patients with myelofibrosis and myeloid metaplasia. Int Surg 1996; 81:177-179.

23.Shreiner DP. Spontaneous hematologic remission in agnogenic myeloid metaplasia. Am J Med 1976; 60:1014-1018.