

A Case of Monosomy-7 Eosinophilic Leukemia and Neurofibromatosis, Terminated with Disseminated Cryptococcosis

Hong Suck Song, M.D. and Soong Kook Park, M.D.

Department of Internal Medicine, School of Medicine,
Keimyung University, Taegu, Korea

A 17-year-old boy was admitted with fever, generalized lymphadenopathy, hepatosplenomegaly, multiple café-au-lait spots, and a family history of neurofibromatosis. The peripheral blood showed anemia, leukocytosis with 9% blasts, 54% eosinophils of abnormal morphology, and thrombocytopenia. No cause for hypereosinophilia was found. Bone marrow aspiration revealed hypercellularity with 20% myeloblasts and 35% eosinophilic leukocytes. The cytogenetic analysis of bone marrow cells with G-banding techniques showed a karyotype of 45, XY, -7. Based upon these findings, the authors believed that the patient had eosinophilic leukemia and neurofibromatosis. The patient rapidly declined and died from disseminated cryptococcosis.

This case provided additional evidence of a link between aneuploidy of the group C chromosome and hematologic malignancy.

Key Words: Eosinophilic leukemia, Monosomy-7, Neurofibromatosis, Disseminated cryptococcosis

INTRODUCTION

Since the initial description of eosinophilic leukemia, there has been much controversy over the existence of such entity. Hardy and Anderson¹⁾ proposed the term "hypereosinophilic syndrome", which is a heterogeneous syndrome in its presentation. Chusid et al.²⁾ concluded that there was a continuum of hypereosinophilic diseases with eosinophilic leukemia existing at one pole. A chromosome analysis has served to differentiate "eosinophilic leukemia" from many others constituting the hypereosinophilic syndrome.

The occurrence of malignancy of non-neural origin in patients with neurofibromatosis has received much attention in recent years³⁾.

In this paper, the authors describe a case of eosinophilic leukemia, which was associated with neurofibromatosis.

REPORT OF A CASE

A 17-year-old boy was admitted to the hospital in March, 1986, due to high fever. He was well until seven months prior to admission, when intermittent pustules developed in the left thumb, accompanied by fever, night sweats, and dry cough. Three weeks before hospitalization, an ache in his left upper quadrant, high fever, chill, dry cough, and general weakness developed. On admission, the temperature was 38.2°C, the pulse 94, the respiration 32, and the blood pressure 120/70 mmHg. He was pale and slightly dyspneic. He had multiple petechiae, especially over the abdominal wall and many large and small café-au-lait spots over the trunk and extremities of his body. There also was a family history of neurofibromatosis (father, 2 brothers, and a sister).

Nontender firm enlarged lymph nodes, up to 3 cm in diameter, were palpated in bilateral periauricular, submandibular, cervical, axillary, and inguinal regions. The neck was supple. The lungs were clear except for a few inspiratory crackles at the right base, and the heart was normal. The edge

Address reprint requests: Hong Suck Song, M.D., Department of Internal Medicine, School of Medicine, Keimyung University, #194, Dongsan-Dong, Taegu 630-00, Korea

of the liver descended 8 cm below the right costal margin with vertical span of 18 cm, the spleen was felt 10 cm below the left costal margin with tenderness. Examination of the nervous system was not remarkable. Laboratory studies included a hemoglobin 7.4 gm/dl, white cell count of 25,500/mm³ with 9% blasts, 5% neutrophils, 8% lymphocytes, 19% monocytes, 54% eosinophils, and 23 normoblasts/100 WBC. Most of the eosinophils showed abnormal features: hypersegmentation of nuclei and hypogranulation and vacuoles in the cytoplasm (Fig. 1). The reticulocyte was 1.2%, the leukocyte alkaline phosphatase (LAP) score 52, the platelet count 35,000/mm³ and the erythrocyte

sedimentation rate 73 mm/hour. The bone marrow was hypercellular and had marked diminished megakaryocytes with a myeloid/erythroid ratio of 3:1; and the differential counts disclosed 20% myeloblasts and 35% eosinophils (bone marrow aspiration and differential counts from the peripheral blood are listed in detail in Table 1).

Serum iron was 96 µg/ml, transferrin 161 µg/dl, ferritin 708 ng/ml and serum vit. B₁₂ 1,475 pg/ml (normal range: 200-950 pg/ml). Alkaline phosphatase was 531 IU/L, SGOT 58 IU/L, SGPT 42 IU/L, total bilirubin 1.7 mg/dl, HBsAg⁻, Anti-HBs⁺, and the serum LDH 1,311 U/L. IgG was 2,430 mg/dl (normal range: 700-1,500 mg/dl), IgA 365 mg/

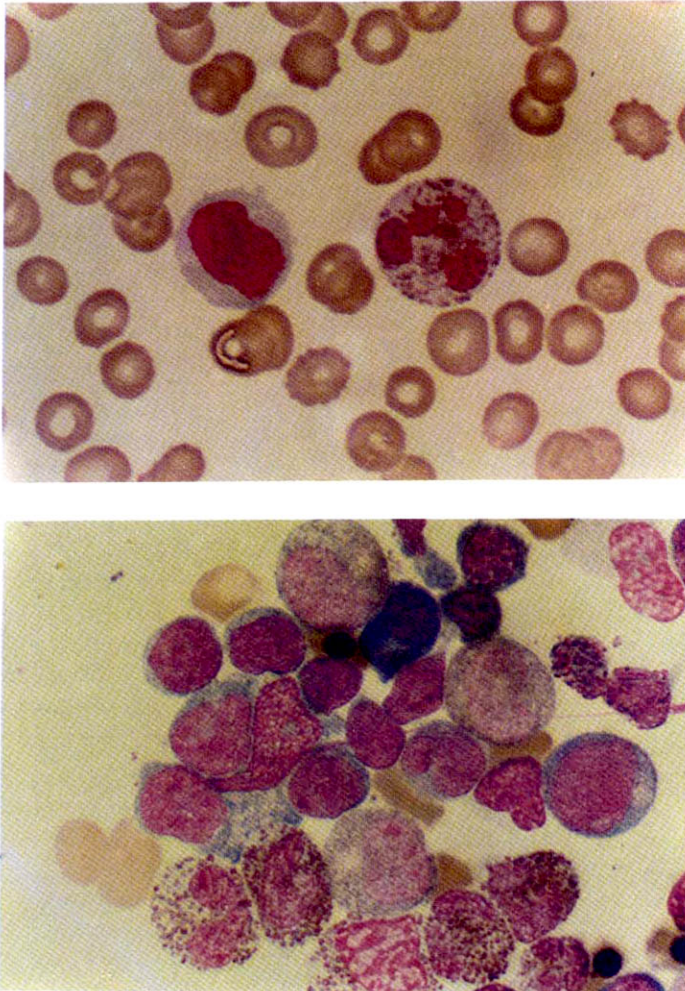


Fig. 1. *Photomicrograph of peripheral blood (upper) and bone marrow (lower) with Wright stain : note sparse granule and hypersegmentation of eosinophils.*

dl (normal: 0~450 mg/dl), IgM 288 mg/dl (normal: 40~200 mg/dl), IgE 4.635 IU/ml (normal: 0~450 IU/ml), and serum protein electrophoresis disclosed polyclonal gammopathy (gamma-globulin fraction was 34.8%). Skin test, sputum, and stool examination for parasites were negative. X-ray films and a computerized tomographic scan

of the chest showed a diffuse enlargement of hilar and mediastinal lymph nodes, and extensive infiltrations of both lung bases.

The cytogenetic analysis of bone marrow cells with G-banding showed a karyotype of 45, XY, -7, however, the peripheral blood leukocytes showed a consistent number of 46 with a normal male karyotype (Fig. 2).

After admission, the patient's condition rapidly deteriorated and he died 10 days later. The right cervical lymph node biopsied during the fourth hospitalization day, and liver, spleen, and lung tissues taken postmortemly revealed multiple single-budding encapsulated organisms, cryptococci, with evidence of splenic infarction. However, there were no recognizable eosinophilic infiltrations.

Table 1. Differential Cell Count of Peripheral Blood and Aspirated Bone Marrow

	Peripheral blood (%)	Bone marrow (%)
Myeloblasts	9.0	20.0
Promyelocytes		5.0
Myelocytes, neutroph.		1.5
eosinoph.		4.0
Metamyelocytes, neutroph.		1.0
eosinoph.		5.0
Banded form, neutroph.	2.0	
eosinoph.		10.0
Segmented form, neutroph.	5.0	2.5
eosinoph.	54.0	16.5
basoph.	1.0	
Lymphocytes	8.0	7.0
Monocytes	19.0	0.5
Plasmocytes		0.5
Phagocytic histiocytes		1.5
Pronormoblasts		3.5
Basophilic normoblasts		2.5
Polychromatic normoblasts		11.5
Orthochromatic normoblasts	23/100 WBC	7.5

DISCUSSION

Eosinophilia is found in a variety of benign and malignant diseases. The differentiation of reactive eosinophilia from the rare neoplastic eosinophilic leukemia is considerably difficult, as both conditions may present with increased peripheral blood and bone marrow eosinophilic leukocytes, and there are no available morphologic criteria.

In 1961, Bently et al.⁴⁾ defined eosinophilic leukemia, as a marked eosinophilia in the peripheral blood with blasts above normal in the bone marrow and/or peripheral blood during the course of the illness. Benvenisti and Ulmann⁵⁾ defined more rigid criteria: hepatosplenomegaly, lymphadenopathy, and marked persistent eosinophilia, usually

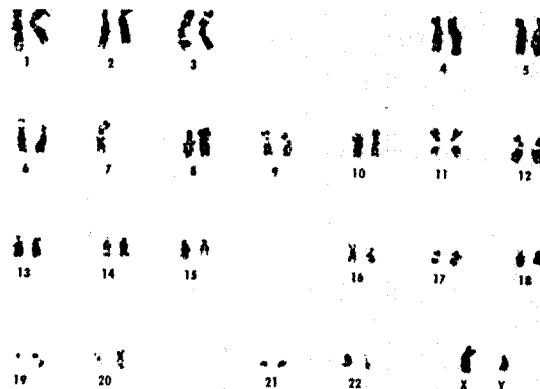


Fig. 2. Chromosome pairs from G-banded metaphases, demonstrate the deletion of chromosome number 7.

accompanied by anemia and thrombocytopenia, and accepted 43 previously reported cases as eosinophilic leukemia. On the other hand, Hardy and Anderson¹⁾ applied the term "hypereosinophilic syndrome" rather than eosinophilic leukemia, and considered that the disease may represent a hypersensitivity reaction. In 1975, Chusid et al.⁵⁾ reviewed the English literature extensively in search of eosinophilic leukemia cases, and also the hypereosinophilic syndrome: he accepted the point of view that there is a continuum in hyper-eosinophilic disease with eosinophilic leukemia existing at one pole as a myeloproliferative disorder.

Chromosome analysis is a useful strategy in differentiating benign and malignant diseases. However, it has been performed only in a limited number of patients with eosinophilic leukemia. Recent cytogenetic studies report that eosinophilic leukemia is not a mere variant of chronic myelocytic leukemia with eosinophilic proliferation⁶⁾.

This patient's chromosomal analysis of bone marrow cell with G-Banding techniques, showed a karyotype of 45, XY, -7. C-monosomy myeloproliferative disorders have distinctive features: hepatosplenomegaly, lymphadenopathy, leukocytosis, thrombocytopenia, leukoerythroblastic anemia, hypercellularity of bone marrow, decreased chemotaxis of neutrophils, and frequent transition to AML^{7,8)}; and also several recent studies report on an increased susceptibility to infection in monosomy-7⁹⁾. Although the authors favor the opinion that the patient exhibited eosinophilic leukemia with monosomy-7, it must be stated that it was not possible to exclude the possibility that the present case was a preleukemic phase of monosomy-7 myeloproliferative disorder from the onset with a prominent eosinophilic reaction.

Neurofibromatosis is a frequent autosomal dominant disorder of neuroectodermal abnormality. In recent years, it was established that the link between non-neural tumors and neurofibromatosis, especially childhood leukemia, is highly possible and could be interpreted as illustrating

the general effect of this mutation upon cancer risk. Hapex et al.¹⁰⁾ documented the evidence of chromosomal instability in neurofibromatosis and held the opinion that this lead to the susceptibility of malignancy and the tendency to malignancies can also be provoked or enhanced by any of the carcinogens.

In summary, the authors presented a boy with blastic eosinophilic leukemia associated with neurofibromatosis. Chromosomal analysis of the bone marrow cells showed monosomy-7. Several biopsies of multiple organs showed cryptococci. The authors believe the disseminated cryptococcosis to be a secondary infection in this compromised host, and not a primary process.

REFERENCES

1. Hardy WR, Anderson RE: *The hypereosinophilic syndromes. Ann Int Med* 68:1220, 1968
2. Chusid MJ, Dale DC, West BC, Wolff SM: *The hypereosinophilic syndrome: analysis of fourteen cases with review of literature. Medicine* 54: 1, 1975
3. Hope DG, Mulvihill JJ: *Malignancy in neurofibromatosis. In: Riccardi VM, Mulvihill JJ, eds, Advances in neurology, p 33, Raven, New York 1981*
4. Bentley HP, Reardon AE, Knoedler JP: *Eosinophilic leukemia. Am J Med* 30:310, 1961
5. Benvenisti DS, Ultmann JE: *Eosinophilic leukemia. Report of five cases and review of literature. Ann Int Med* 71:731, 1969
6. Marcovitch H, Cain F, Harvard CWH: *Eosinophilic leukaemia. Br J Clin Pract* 27:185, 1973
7. Sieff CA, Chessells JM, Harvey BAM, Pickthall VJ, Lawler SD: *Monosomy-7 in childhood: a myeloproliferative disorder. Br J Haematol* 49:235, 1981
8. Oshima Y, Kuribayashi T, Kuroume T: *A case of monosomy-7 myeloproliferative disorder with marked eosinophilia. Rinsho Ketsueki* 25:1433, 1984
9. Ruutu P, Ruutu T, Repo H, Vuopio P, Timonen T, Kosunen TU, Chapelle A: *Defective neutrophil migration in monosomy-7. Blood* 59:739, 1981
10. Hapex M, Sharaf L, El-Nabi SMA, El-Wehedy G: *Evidence of chromosomal instability in neurofibromatosis. Cancer* 55:2434, 1985