CASE REPORT

Chronic Eosinophilic Leukemia With a Unique Translocation

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We report a case of chronic eosinophilic leukemia in a 9 year old girl who presented with anemia, thrombocytopenia, leucocytosis (mostly dysplastic eosinophils), lymphadenopathy and hepatosplenomegaly. There was no increase in blasts but myelofibrosis was seen in the bone marrow. A previously unreported translocation 46,XX,t(1;4)(q24;q35), was found on cytogenetic analysis and involvement of the myocardium was also present. Shortly after commencing steroids, the family abandoned therapy.

Keywords: *Cardiomyopathy, Chronic eosinophilic leukemia, Hypereosinophilia, t(1;4)(q24;q35)*

Eosinophilia in children is usually due to allergic rhinitis, asthma, and atopic dermatitis. Infrequent causes include Churg–Strauss vasculitis, hyper-IgE syndrome, tropical pulmonary eosinophilia, eosinophilic gastroenteritis and connective tissue disorders. There are also a diverse group of myeloproliferative and neoplastic diseases such as acute and chronic eosinophilic leukemia, chronic granulocytic leukemia, and acute myeloid and lymphoblastic leukemia. When no etiology is established, it is termed as idiopathic hypereosinophilic syndrome (IHES) as described by Chusid, *et al.* in 1975(1). Sustained hypereosinophilia, whether reactive, clonal or idiopathic could potentially lead to eosinophilic end organ damage. The frequency of organ involvement in a review of 105 patients was hematologic 100%, cardiovascular 58%, cutaneous 56%, neurologic 54%, pulmonary 49%, splenic 43%, hepatic 30% and ocular 23%(2).

CASE REPORT

A nine year old girl presented to Moolchand Khairatiram Hospital in New Delhi with a one month history of fever and bone pains. There was no history of bleeding from any site, allergy to drugs, history of asthma or worm infestation. There was no contact with tuberculosis. On examination the child was pale and there were no petechiae. There was significant bilateral axillary lymphadenopathy, hepatosplenomegaly and sternal tenderness. Systemic examination was otherwise unremarkable.

Her initial blood count revealed hemoglobin of 8.0 g/dL, marked eosinophilia (total leukocyte count of 162×10^3/µL with absolute eosinophil count of 140×10^3/µL) and platelet count of 102×10^3/µL. The blood film confirmed the marked eosinophilia with abnormally lobulated and hypogranular forms (***Fig.*1**). Eosinophil metamyelocytes and myelocytes were present but no blasts were seen. Erythrocyte sedimentation rate (ESR) was 32mm/hour, liver enzymes were slightly above the normal range and renal function tests were normal. The immunoglobulin E (IgE) level was 173 IU/mL (normal <180 IU/mL). Urine and stool analysis was normal. Bone marrow showed increased cellularity with near complete population of eosinophils and eosinophil precursors but no increase in blasts. Megakaryocytes were seen and erythroid series was normal.

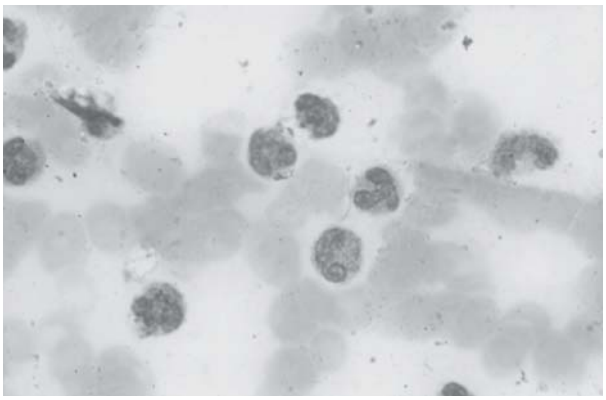

FIG.1 *Blood smear showing abnormal, mature eosinophils, abnormally lobulated with unilobed and trilobed cells. There is marked hypogranularity.*

Myelofibrosis was also seen. Karyotyping revealed presence of translocation 46,XX,t(1;4)(q24;q35). On echocardiogram the apex of both left and right ventricles appeared obliterated by echogenic tissue. The ejection fraction was 60%.

The final diagnosis was chronic eosinophilic leukemia with eosinophilic cardiomyopathy. The child was started on steroids to minimize organ damage from the eosinophilic granules. Unfortunately, before further treatment could be commenced, the family self-discharged themselves and failed to follow-up. Attempts were made to contact the family by phone and post with no success.

DISCUSSION

Eosinophilia can be classified into mild (eosinophils $<1.5\times10^3/\mu L$), moderate (eosinophils $1.5\text{-}5\times10^3/\mu L$) or severe ($>5\times10^3/\mu L$)(3). The increase in eosinophil count in most cases is because of generation of cytokines, particularly GM-CSF, IL-3 and IL-5 which stimulate its production and differentiation. It is important to distinguish between reactive, clonal and idiopathic eosinophilia as their treatment and prognoses are different. The most easily available methods being bone marrow cytogenetic analysis and fluorescent in-situ hybridization (FISH). The detection of any abnormalities confirms a clonal disorder(4). Indirectly, the presence of dysplastic eosinophils, increased serum B12, increased serum tryptase, anemia/thrombocytopenia, increased bone marrow cellularity with left shift, myelofibrosis, and dysplastic mast cells or megakaryocytes in bone marrow also favors diagnosis of clonal eosinophilia(3,5). The absence of increased blasts, increased mast cells and negative Philadelphia and BCR-ABL probes on cytogenetic analysis suggests chronic eosinophilic leukemia.

Our child had a karyotype of 46,XX,t (1;4)(q24;q35). This translocation has not been reported previously. However, a balanced translocation in all cells with unusual breakpoints could also have been possible. As the patient abandoned further management we were unable to either confirm this or do the mapping of the genes at the breakpoints to confirm specific gene involvement and possible fusion gene formation. Several cytogenetic abnormalities have been reported(6,7), including trisomies of chromosome 1,8,10 and 15, monosomy of 7 and translocations of the long arm of chromosome 5 q31-33 zone (where the genes encoding for IL-5, GM-CSF, and IL-3 are localized). The new advancement has been the discovery of the FIP1L1-PDGFRA (F-P) fusion gene created by the del(4)(q12q12), an 800-kb deletion on chromosome 4q12 and the excellent response to imatinib of this subgroup of F-P + chronic eosinophilic leukemia (CEL) patients. Based on the limited number of patients evaluated, this group currently accounts for 50% to 60% of all HES and CEL cases(8). Similar success to imatinib has also been seen in patients with chronic myeloproliferative disease and eosinophilia where activation of the gene for platelet-derived growth factor receptor beta (PDGFRB) was caused by a t(5;12)(q33;p13) translocation(9).

This distinction is important because there is a potentially curative treatment available for clonal marrow disorders (particularly F-P+ hypereosinophilia). For idiopathic HES the aim is to limit eosinophilic end organ damage with use of steroids as first-line therapy. In the past hydroxyurea has been used in those resistant to steroids but now interferon-alpha is considered the treatment of choice in corticosteroid-refractory patients(10). If the CEL is F-P+ then imatinib is the drug of choice(11). Also, since clonal cytogenetic abnormalities may develop during the course of IHES, it is important to make

regular cytogenetic and more sensitive assessment of clonality on bone marrow samples. In presence of signs of malignant transformation chemotherapy and bone marrow or stem cell transplantation would be needed.

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