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LETTER TO THE EDITOR

Acute lymphocytic leukemia with eosinophilia and unusual karyotype

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Acute lymphoblastic leukemia (ALL) with eosinophilia is an uncommon disorder with several distinctive clinical and pathologic features. Eosinophilia associated with ALL usually precedes the diagnosis of ALL; however, it can occur concomitantly or after the diagnosis of the leukemia. The eosinophilia often resolves with the remission of ALL, but frequently reappears at relapse. Whether this reappearance is due to relapsed leukemia or an associated infection remains unclear. Mortality has been reported from complications of both leukemia and eosinophilia. Few cytogenetic abnormalities have been reported for this disorder, some of them involving chromosome 5. Here, we report the case of a 9-year-old male who was diagnosed with ALL with eosinophilia and an unusual karyotype.

The patient was a 9-year-old boy with no significant past medical history who presented to the UMass Memorial Medical Center following 2 – 3 weeks of intermittent low-grade fevers, a mildly productive cough and decreased activity. His physical examination was notable only for rare wheezes on the left side of the chest. Significant laboratory findings included a white blood cell count of 63 000 th/mm^3 with 85% eosinophils, 4% segmented neutrophils, 8% lymphocytes and 2% pathologic cells. Hemoglobin and hematocrit levels were mildly decreased at 10.8 g/dl and 31.5%, respectively, with a normal mean corpuscular volume of 78.7 fl. His platelet count was 444 000 th/mm^3. A chest X-ray and computed tomography scan showed a left upper lobe cavitary lesion, which was aspirated and found to contain purulent material that grew *Streptococcus intermedius*. Treatment with clindamycin resulted in resolution of the pulmonary lesion.

Multiple complete blood counts were performed over the next 3 weeks that demonstrated persistent eosinophilia. The corresponding peripheral smears showed some immature and hypergranulated eosinophils, which raised the suspicion of a leukemic process. A bone marrow biopsy was performed approximately 3 weeks after the initial presentation that revealed a hypercellular bone marrow with more than 90% replacement by medium-sized blasts that had prominent nucleoli with scant to moderate agranular cytoplasm. Some normal myeloid and erythroid activity was present, with a relative increase in the number of morphologically normal eosinophils among the non-blast population (Figure 1).

Flow cytometric studies demonstrated that the blasts were CD34+, CD19+, CD10+ and CD20 negative, which is consistent with a precursor-B cell ALL immunophenotype. Molecular diagnostic studies using the polymerase chain reaction (PCR) detected a clonal rearrangement of the immunoglobulin heavy-chain (IgH) region. However, the following translocations were not detected using reverse transcriptase-PCR: BCR/ABL, E2 A/PBX, TEL/AML1 or MLL/AF4.

Cytogenetic analysis (Figure 2) revealed two related abnormal clones described by the following karyotype: 46,XY,+add(1)(p12),del(7)(q22),add(15)

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(q25),−21[9]/46,XY,dup(1)(q21q31),+add(1)(p12),del(2)(q11.2q21),del(5)(q13 ~ q15q31 ~ q35),del(7)(q22),add(15)(q25),−21[5]/46,XY[6].

The deletion of the long arm of chromosome 7 present in both abnormal clones and the deletion of chromosome 5 present in the sideline clone are typically associated with a myeloid abnormality and raised the possibility of a stem-cell disorder. The following three rare possibilities were consistent with the pathologic and cytogenetic data: (i) *de novo* ALL with eosinophilia and a highly unusual karyotype; (ii) myelodysplastic syndrome (MDS) with eosinophilia and transformation to ALL; and (iii) myeloproliferative disease (MPD) with transformation to ALL.

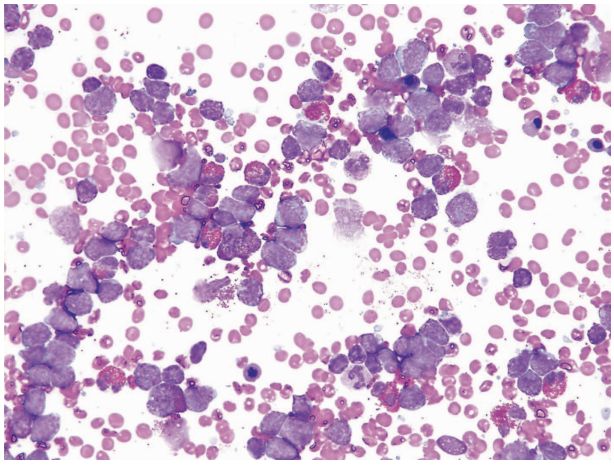

Figure 1. Bone marrow aspirate smear showing predominance of lymphoblasts with scattered eosinophils present.

To distinguish between these possibilities, interphase fluorescence *in situ* hybridization (FISH) analysis was performed with dual-colour FISH with Vysis, Inc. (Downer's Grove, IL, USA) probes for D7S486 (7q31) and D7Z1 (7 centromere). The results of this analysis showed the deletion of chromosome 7q31 to be present in 70% of mononuclear cells (35 of 50 mononuclear cells) and in 0% of eosinophils and mature granulocyte cells (0 of 50 biloped and trilobed cells, half of which were eosinophils and half of which were mature granulocytes) (Figure 3). This result was most consistent with the diagnosis of *de novo* ALL and did not support the alternate possibility of a stem cell disorder. Dual-colour FISH with Vysis, Inc. probes for EGR1 (5q31) and D5S721/D5S23 (5p15) was normal, with 99/103 mononuclear cells showing no 5q31 deletion. This finding suggests that the observed cytogenetic 5q deletion does not involve the EGR1 locus.

The patient was started on induction chemotherapy with dexamethasone, vincristine, asparaginase, and central nervous system prophylaxis with intrathecal methotrexate (ITMTX). The cerebrospinal fluid, prior to starting chemotherapy, showed no malignant cells or white blood cells. A bone marrow biopsy and aspirate performed at the end of the induction phase of the

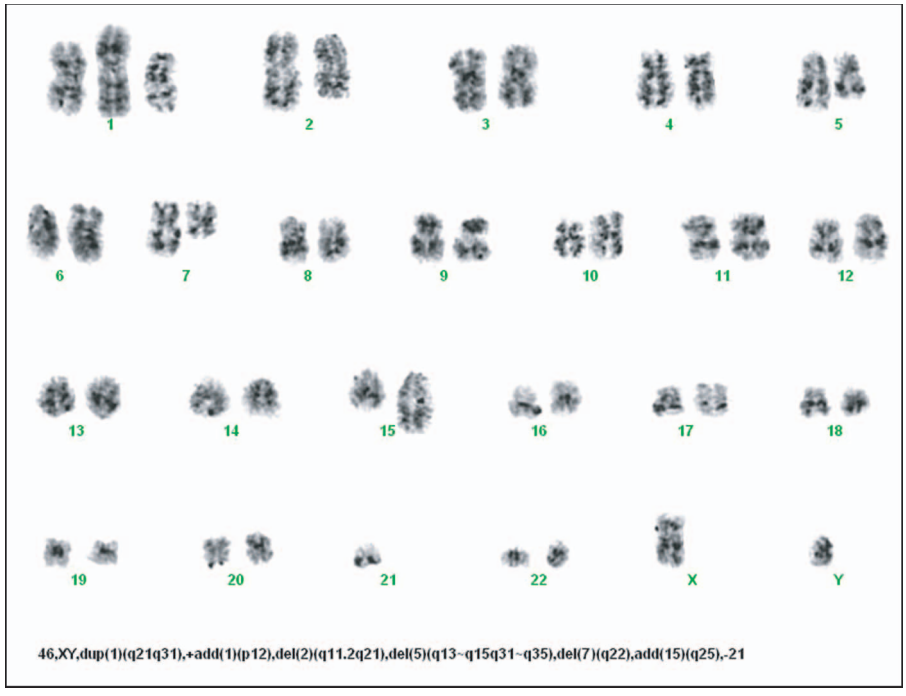

Figure 2. Karyotype of the patient showing the following chromosomal abnormalities: 46,XY,+add(1)(p12),dup(1)(q21q31),del(2)(q11.2q21),del(5)(q13q33),del(7)(q22), add(15)(q25),−21.

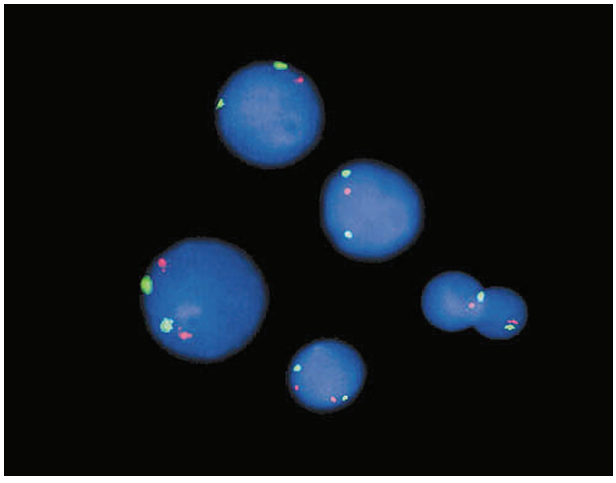

Figure 3. Dual colour FISH for D7S486 at 7q31 (red) and D7Z1 at centromere of chromosome 7 (green) was applied to interphase cells. Two of the four mononuclear cells had a 7q deletion and the bilobed cell (which could be either an eosinophil or granulocyte) lacked the deletion.

chemotherapy revealed 50% cellularity with relative erythroid hyperplasia and no evidence of leukemia. However, the patient suffered a relapse of his ALL with central nervous system involvement approximately 1 year after the end of the consolidation therapy. Eosinophilia (13%) was noted in his bone marrow and the patient carried the same cytogenetic aberrations that were present pre-treatment. The patient received ARA-C and L-asparaginase and his most recent bone marrow biopsy showed complete remission with no eosinophilia. No cytogenetic abnor-malities were detected and the patient is currently awaiting a bone marrow transplant.

Acute lymphoblastic leukemia with eosinophilia is a rare but distinctive clinical entity first described in 1973 by Spitzer and Garson [1]. The disease can affect both children and adults with a median age of 14 years [2]. Most case reports in the literature suggest a male preponderance [3,4]. The majority of ALL cases with eosinophilia are of B-cell type; however, few cases of T-cell ALL with eosinophilia have been reported [4,5]. Eosinophilia usually precedes the diagnosis of ALL; however, it can also occur concomitantly or after the diagnosis of the leukemia [2,6]. The eosinophilia often resolves with the remission of ALL, but frequently reappears at or shortly prior to relapse [7]. Whether this reappearance is due to relapsed leukemia or an associated infection remains unclear. Morbidity and mortality in this disease result from complications of both ALL and eosinophilia [8]. In some instances, death can occur from complications of eosinophilia despite a low leukemic burden [8].

The associated eosinophilia with ALL has no fully known etiology; however, several theories have been proposed. One hypothesis is that a tumor-associated antigen causes T-cell activation and secondary eosinophilia due to activation of lymphokines such as interleukin (IL)-3 or IL-5, which induce eosinophil production [2]. A second theory promotes the idea that lymphoblasts themselves stimulate a growth factor that causes both neoplastic proliferation and eosinophil production [9]. A few authors have theorized that ALL with eosinophilia is due to an underlying stem cell defect [10,11]. Another possibility is that the increased eosinophils are not related to the de novo ALL, but rather associated with one of the most common causes of eosinophilia: infection, drug effect, or allergic disease. In our case, these possibilities were excluded by the corresponding appropriate laboratory work-up; however, our patient had a travel history, history of animal exposure, and a sibling with asthma. Because most investigators have reported that eosinophils in ALL are mature with no cytogenetic abnormalities, it is generally believed that the eosinophilia is a non-neoplastic reaction to the circulating lymphoblasts [2,8,12].

Due to the rarity of the diagnosis, few cytogenetic abnormalities have been reported for B-cell ALL with hypereosinophilia [13–15]. In a recent review of 25 reported cases of ALL and eosinophilia [12], 13 cases were reported with accompanying cytogenetic results. Of these 13 cases, six (46%) had cytogenetic abnormalities. Three of these carried a balanced translocation involving chromosomes 5 and 14, t(5;14)(q31;q32), and one carried an interstitial deletion of chromosome 5, del(5)(q15q33). The t(5;14) fuses the IL-3 gene of chromosome 5 and the IgH gene on chromosome 14, which results in over-expression of IL-3 that leads to increased eosinophil production [9,16,17].

The chromosome 5 deletion in our case is unlikely to encompass the IL-3 gene, because the EGR1 gene that maps within a few Mb of the IL-3 gene [18] was not deleted by FISH. However, it remains possible that IL-3 gene expression is altered, as the chromosome 5 deletion may have moved the IL-3 gene in proximity to an enhancer sequence on chromosome 5. Studying IL-3 expression was beyond the scope of this case report.

Although one of the cytogenetic abnormalities identified in our case involved chromosome 5, it did not have the specific t(5;14) previously reported. Instead, a deletion in chromosome 5 was detected in our case. Aberrations in chromosome 5 may affect the hematopoietic process and have been associated with MDS and acute myeloid leukemia. However, Faderl et al. [13] were able to demonstrate that abnormalities in chromosome 5 are not restricted

only to myeloid disorders, but can also occur in ALL. The deletion of chromosome 5 in association with ALL with eosinophilia has been rarely reported [2,12].

The deletion of chromosome 5 reported previously is similar to the deletion 5 present in the sideline clone of the present case. However, the deletions of the long arm of chromosome 7 and the monosomy 21 present in the mainline clone of our case have not been reported previously in ALL with eosinophilia. The combination of these three cytogenetic abnormalities, particularly the deletions of the long arms of chromosomes 5 and 7, were strongly suggestive of a myeloid disorder [19,20], and introduced the possibility of a stem cell disorder that had transformed to ALL. The structural abnormality in the long arm of chromosome 1 was the only chromosome aberration typical of ALL.

Although the cytogenetic abnormalities are more in keeping with MDS, the pronounced eosinophilia, pediatric age and lymphoblastic transformation are all criteria against the same diagnosis. The possibility of eosinophilic myelodysplasia with transformation to ALL is unlikely but possible, because at least one such case has been reported previously [21]. Eosinophilia is more typical in MPD than in other disorders in our differential diagnosis; however, the cytogenetic data and the pediatric age do not favor that diagnosis. Cell-specific interphase FISH analysis was critical for the resolution of these possibilities. Because the deletion of chromosome 7 was present in mononuclear cells, but not in eosinophils or mature granulocytes, the cytogenetic aberration appeared to be limited to the lymphoblasts. The FISH result supported the diagnosis of *de novo* ALL with an unusual karyotype rather than a stem-cell disorder with transformation to ALL.

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