Chronic eosinophilic leukemia with monosomy 8 in a five-year-old girl: a rare case

Meriç Kaymak-Cihan, Ajlan Tükün, Barış Kuşkonmaz, Bilgin Arıbaş, İşınsu Kuzu, Serpil Dizbay-Sak, Nazire Terzi, Ayşenur Paç, Nural Kiper, Lale Olcay


A 5-year-old girl was admitted to our hospital due to fatigue and fever lasting for six months. She had systolic murmur in the mesocardiac and apex regions and hepatosplenomegaly. Laboratory evaluation revealed leukocyte and eosinophil counts of 176 and 144.32 x 10^9/L, 3.4% blasts in bone marrow and monosomy 8. She developed pulmonary, cardiac, nervous system, ocular and bone involvement. Upon diagnosis of “chronic eosinophilic leukemia, not otherwise specified” (WHO 2008 classification), she received methylprednisolone, vincristine, cytarabine and 6-thioguanine. After hematopoietic stem cell transplantation from a full-matched sibling was performed, the patient expired due to graft failure and septicemia.

Key words: hypereosinophilia, CEL-NOS, monosomy 8.

Chronic eosinophilic leukemia (CEL) is a very rare disorder. After secondary eosinophilia is excluded in a patient with hypereosinophilia, primary disorders such as myeloid and lymphoid neoplasms (myeloproliferative neoplasms [MPNs], acute myeloblastic leukemia [AML], acute lymphoblastic leukemia [ALL], lymphoma) with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1, lymphocyte-variant hypereosinophilia, and idiopathic hypereosinophilic syndrome (HES), as well as chronic eosinophilic leukemia, not otherwise specified (CEL-NOS), should be evaluated for differential diagnosis. CEL is distinguished from HES by the presence of either a cytogenetic abnormality or excess blasts in peripheral blood or bone marrow (blasts >2% in peripheral blood; or blasts >5% in bone marrow). The only curative treatment of CEL is hematopoietic stem cell transplantation (HSCT). We diagnosed a 5-year-old girl as CEL-NOS with monosomy 8, according to the WHO 2008 classification. As far as we know, monosomy 8 has not been reported in CEL-NOS before.

Case Report

A girl 5 years and 3 months of age was admitted to our hospital for headache, fatigue and occasional fever over the course of the preceding six months. Her past history was negative for drug usage and allergic diseases. She had pallor and a 2/6 systolic murmur in the mesocardiac area and apex. Her liver and spleen extended below the right and left costal margins by 3.5 and 7 cm respectively and were nontender. The remainder of the physical examination, including ophthalmologic examination, was normal. Her hemoglobin (Hb) was 92 g/L, hematocrit (Htc) 27%, white blood cell count (WBC) 176 x 10^9/L with eosinophils 144.32 x10^9/L, platelets 123 x 10^9/L. A peripheral blood smear revealed 58% eosinophils, 15% eosinophilic myelocytes, 10% neutrophils, 9% eosinophilic bands, 6% lymphocytes and 2% neutrophilic bands. Biochemical tests were normal except that...
LDH was 639 U/L. Her immunoglobulin (Ig) E was 31.6 kU/L (N: 0-100), IgA 171 mg/dl (N:82-453), IgM 327 mg/dl (N:46-304) and IgG 1830 mg/dl (N: 751-1560). Vitamin B12 was 754 pg/ml (N:126.5-505) and folic acid 3.1 ng/ml (N:3-20). Screening for serum antibodies against CMV, EBV, Toxoplasma and Toxocara canis; western blotting for toxocariasis, stool examinations for parasites (five times); and tests for connective tissue diseases (like antinuclear antibody and anti-double-stranded DNA antibody) were negative. Both T- and B-lymphocytes were within normal limits, and no clonal population was detected by flow cytometry.

The patient’s bone marrow aspiration smear showed 3% blasts, 1% eosinophil myelocytes, 10% eosinophilic myelocytes, 1% neutrophilic myelocytes, 1% eosinophil myelocytes, 1% eosinophilic myelocytes, 3% neutrophils, 36% eosinophils, 5% eosinophil bands, 33% lymphocytes, 3% monocytes and 4% basophilic erythroblasts out of 500 nucleated cells, the myeloid/erythroid ratio being 14.8/1. Extreme dysmorphisms in eosinophilic cells and mild to moderate dysmorphism in megakaryocytes were striking. Bone marrow biopsy showed 90% cellularity, increased eosinophil leukocytes and precursors in paratrabeucular regions in large areas, increased interstitial erythroid cells without dysmorphism and scattered micromegakaryocytes, some being dysplastic. Mature eosinophils had hyperpigmented nuclei. There were no blastic cells. Storage iron was decreased and reticulin fibers were not increased. Mast cells stained by mast cell tryptase were mildly increased and scattered. There were scattered reticulin fibers (Fig. 1-A, B, C).

Cerebrospinal fluid revealed normal glucose and protein levels, and cytology was negative.

The chest X-ray was normal (Fig. 2-A). A lytic lesion on the proximal left humerus and reduced vertebral height were striking in the chest X-ray (Fig. 2-B). The other long bone and skull X-rays were normal. Her echocardiography (ECHO) revealed minimal mitral valve insufficiency. Cranial, abdominal and pelvic computed tomography (CT) was normal.

Standard cytogenetic evaluation of the bone marrow was normal, and twenty metaphases were assessed. On the first genetic examination, BCR/ABL and FIP1L1-PDGFRA fusions were negative. FISH evaluation of the bone marrow, which could be tested two months later, showed 2/100 positivity for trisomy 8 and 4/100 positivity for monosomy 8. (The cutoff value is 3% and the value of false positivity is 2.26%—Düzen Laboratories Group Genetic Diagnosis Center; ISO15189.) Monosomy 7 and deletion 5q were negative. Defining the cells on FISH analysis is not particularly easy. However, the existence of correlation between percentages of blasts and monosomic cells could be regarded as a clue for clonal monosomy 8. We could not test eosinophilic activators such as MBP and ECP and chemokines such as TARC and exotaxin, as well as IL-5 level.

Hydration, alkalinization and partial exchanges were administered three times after admission. After one week, the patient’s chest X-ray revealed bilateral diffuse, small nodular infiltrations, without reticular density or vascular or bronchial distortion, and no traction, honeycomb lung or fibrotic components (Fig. 2-B). There were bullous amphimeterate areas, micronodular infiltrations, thin reticular honeycomb images and thickening of the paraseptal regions in two lobes of the lung (Figs. 2-E, F, G).

Fine-needle aspiration biopsy of the lungs, taken during CT, showed intense eosinophilic infiltration, with frequent histiocytes, rare
neutrophils, lymphocytes and plasmocytes, but no parasitic larvae nor malignant cell infiltration was observed (Fig. 1-D). After the bone marrow and lung biopsies were conducted, methylprednisolone (MP-5 mg/kg/day) was started, and vincristine (1 mg/m²/dose) was administered upon the diagnosis of “myeloproliferative hypereosinophilic syndrome-etiology unknown subgroup”⁴ (Fig. 3). Eosinophilia can cause a hypercoagulable state, the etiology of which is unclear. Eosinophil major basic proteins inactivate thrombomodulin, thus resulting in the unavailability of activated protein C. In hypereosinophilia, intracardiac thrombus, deep vein thrombosis, dural sinovenous thrombosis and/or arterial thrombosis can occur.⁵ Therefore, prophylactic low-molecular-weight heparin was also started to prevent possible thrombosis.

On first week of therapy, the patient’s WBC decreased to 73 x 10⁹/L, and she developed paralysis of the left sixth cranial nerve. The ophthalmologic examination, which was completely normal at admission, revealed left esotropia in primary position and alternation in cover test, restriction in abduction of the left eye, bilateral sluggish indirect light reflex, bilateral swollen optic disc with ambigious boundaries and bilateral pericapillary splinter hemorrhage. Bilateral anterior segments and right eye movement to all directions were normal.

In cranial magnetic resonance imaging (MRI), there were spots with enhanced contrast material in the left and right centrum semiovale and left forceps major, suggestive of a vasculitic process due to hypereosinophilia (Figs. 2-H, I). The sixth cranial nerve paralysis, bilateral swollen optic discs with ambigious boundaries
and bilateral sluggish indirect light reflex were attributed to leukostasis and/or eosinophilic infiltration of the nerve sheaths. The bilateral pericapillary splinter hemorrhage was attributed to eosinophilic retinal vasculitis.

On the ninth day of therapy, the WBC count was 96.5 x 10⁹/L, and the MP dose was increased to 10 mg/kg/day and a second dose of vincristine was administered (1 mg/kg/dose) (Fig. 3). In the second week of therapy, we tapered the dose of methylprednisolone down from 10 mg/kg/day to 7.3 mg/kg/day when the WBC was 37.4 x 10⁹/L; but on the same day her condition deteriorated and she developed dyspnea, tachypnea, tachycardia and a mild increase in hepatomegaly. The chest X-ray revealed increased infiltration in both lung fields (Fig. 2-C). The ECHO showed thickening of the interventricular septum and left ventricular wall, in addition to ongoing mitral valve insufficiency. Creatinin kinase-MB (CKMB) was 80 IU/L (N:0-25), and troponine T was 0.06 μg/L (N:<0.1 μg/L). Believing that the patient had developed myocardial involvement, we increased the MP dose to 20 mg/kg/day and started cytosine arabinoside (100 mg/m²/day two days a week) and 6-thioguanine (40 mg/m²/day). CKMB declined rapidly, and her respiratory distress resolved. The MP dose was tapered down gradually, taking the eosinophil counts into account (Fig. 3).

The bone marrow aspiration taken in the third week of therapy, when her WBC and eosinophil counts were 19.3x10⁹/L and 9.64x10⁹/L respectively, revealed that the eosinophilic cells comprised 52% of all nucleated cells and the M/E was 27. The ECHO revealed that the thickening in the left ventricular wall had disappeared but that the thickening in the interventricular septum persisted minimally. Strabismus resolved gradually. During follow-up, her WBC and eosinophil counts fluctuated (Fig. 3).

The high-resolution CT (HRCT) taken in the first month revealed bilateral diffuse, fine reticular structures and honeycomb scenery, septal thickening in the right middle lobe lateral region, pleural thickening and little pleural fluid (Fig. 2-F, G). The lytic lesion on the humerus had disappeared, but respiration sounds were found to have progressively diminished in the bilateral lower lung fields. Respiratory function tests were compatible with restrictive pulmonary disease. So, cyclosporine (5 mg/kg/day) was added to the treatment (Fig. 3).

The bone marrow taken in the second month revealed that the eosinophil series in the bone marrow had declined to 11% and blasts were still below 5%. The molecular genetic studies, which became available in the second month of admission, revealed clonal monosomy 8. The diagnosis of the patient, who had been followed under the diagnosis of myeloproliferative hypereosinophilic syndrome (HES) until the above-mentioned genetic evaluation, was changed to chronic eosinophilic leukemia. Since our patient was resistant to medical therapy and had multiorgan involvement, she was evaluated for hematopoietic stem cell transplantation (HSCT) from her HLA full-matched sibling.

Since the WBC and eosinophil counts continued to decline, and the spirometric tests, which were compatible with restrictive pulmonary disease, started to indicate alleviation, we continued the same medical therapy until the HSCT.

When the patient was discharged to come back for HSCT, her Hb was 97 g/L, WBC and eosinophil counts 4.7x10⁹/L and 1.8x10⁹/L respectively and platelet count 362x10⁹/L. She had no hepatosplenomegaly but Traube’s space was found dull on percussion. The spirometric tests revealed normalization.

Although the patient had undergone HSCT from her HLA-matched sibling, the post-transplant outcome was unsatisfactory due to failure of engraftment. We had to attempt a second transplantation, after which a severe neutropenic fever and a second engraftment failure developed.

A third transplantation from the same donor was performed 4.5 months after the second one, with engraftment failure again occurring. The patient succumbed to sepsis after a prolonged period of neutropenia.

**Discussion**

The upper limit of the normal range for percentage of eosinophils in the peripheral blood is 3-5% with a corresponding absolute eosinophil count (AEC) of 0.3-0.5x10⁹/L. Eosinophilia is considered as “mild” if this count is 0.5-1.5x10⁹/L, moderate if 1.5-5.0x10⁹/L and severe if >5.0x10⁹/L. Blood
eosinophilia signifies either a cytokine-mediated reactive phenomenon (secondary) or an integral phenotype of an underlying hematological neoplasm (primary). Secondary eosinophilia is usually associated with parasitosis in developing countries. In the West the main causes of secondary eosinophilia are allergic or vasculitic conditions, drugs and nonmyeloid malignancies, although parasite infections should also be considered. In our case we excluded parasitic infections and other secondary causes by evaluation of connective tissue disease markers, serum antibody screening, western blotting for toxocariasis, and stool examination for parasites, all of which were negative. The patient’s history was negative for allergic diseases and drug usage. Other secondary causes like T-cell lymphomas, Hodgkin’s disease and acute lymphoblastic leukemias were also excluded, on the basis of the bone marrow and radiological findings.

The original defining criteria for HES proposed in 1975 by Chusid et al. is as follows: 1) AEC over 1.5 x 10^9/L for more than six months, 2) lack of secondary causes of eosinophilia, and 3) presumptive signs and symptoms of eosinophilia-associated organ involvement. The requirement that eosinophilia persist for more than 6 months is less consistently embraced today because there are new rapid methods to evaluate hypereosinophilia, and some patients need receive expedited treatment to minimize organ damage.

A new clinical classification of HES proposed in 2006 addressed some of the controversial issues that were not addressed by the definition proposed by Chusid et al.; it covers myeloproliferative, lymphocytic, overlap, undefined, familial and associated variants.

Our case, whose t(9,22) was negative, met the criteria of “myeloproliferative-HES (M-HES)"-“myeloproliferative-etiolog unknown subgroup,” in displaying negativity of the FIP1L1-PDGFRA fusion gene, dysplastic eosinophils in the peripheral blood and bone marrow, anemia, thrombocytopenia, hepatosplenomegaly, increased bone marrow cellularity (90% cellularity) and mast cell increase in the bone marrow (Fig. 1-C). Due to normal IgE levels, no clonal lymphocyte population or T-cell phenotypes such as CD3-CD4+; CD3+ CD4- CD8- in the blood as indicated by flow cytometry, no cutaneous manifestations, no history of atopy and the lack of a good response to steroids, we did not consider lymphocytic-HES (L-HES). When the patient was admitted, the World Health Organization (WHO) 2008 classification of myeloid malignancies had not yet been published. In this classification, cases previously considered as HES now fall into two different categories: 1) chronic eosinophilic leukemia, not otherwise specified (NOS); or 2) myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1. The WHO 2008 classification defines idiopathic HES as comprising an absolute eosinophil count over 1.5x10^9/L that persists for more than 6 months, along with tissue damage, in addition to exclusion of the following: 1) reactive eosinophilia; 2) lymphocyte-variant hypereosinophilia (cytokine-producing, immunophenotypically-aberrant T-cell population; 3) chronic eosinophilic leukemia, NOS; 4) WHO-defined myeloid malignancy-associated eosinophilia (such as MDS, MPNs, MDS/MPNs or AML); and 5) eosinophilia-associated MPNs or AML/ALL with rearrangement of PDGFRA, PDGFRB, or FGR1. We could not evaluate PDGFRB, or FGR1. Therefore, upon diagnosis of myeloproliferative-HES (M-HES)-myeloproliferative-etiolog unknown subgroup, we started corticosteroids, which constitute the first-line therapy for HES (other than PDGFRA-associated HES), with the recommendation that the dose be tapered down very slowly, closely following the eosinophil count. Since vincristine is also recommended for patients with AEC> 100 x 10^9/L, in order to rapidly decrease eosinophilia, we added vincristine as well.

Imatinib mesylate is recommended in patients with a FIP1L1-PDGFRA mutation. Its use in cases lacking the mutation remains controversial, although some patients have responded. Hydroxyurea can be used as palliative chemotherapy to control leukocytosis and eosinophilia. Interferon-α (IFN-α) can produce hematologic and cytogenetic remission in HES refractory to other therapies including prednisone and/or hydroxyurea, 6-mercaptopurine, cyclophosphamide, etoposide, 2-chlorodeoxyadenosine alone or in combination with cytarabine, cyclosporine-A.
Mepolizumab (anti-IL-5 antibody) and alemtuzumab (anti-CD52 monoclonal antibody) are investigational therapies for HES. However, since new organ involvement (cardiac, brain) emerged and preexisting organ involvement (pulmonary) progressed under steroid and vincristine treatment in our patient, and vincristine is not recommended in chronic therapy, cytosine arabinoside (2 times weekly) and 6-thioguanine (6-TG) therapy was started instead of vincristine.

The eosinophil count had decreased, although with fluctuations; the ocular findings had regressed; and the lytic lesion on the humerus had disappeared by near the end of the second month of admission. But the pulmonary pathology progressed, taking on the character of a restrictive pulmonary disease. Moreover, the level of blood eosinophilia is known to correlate inconsistently with eosinophil-mediated tissue damage and is not always an effective way to monitor the response to treatment. So, cyclosporine was added to the treatment.

When the molecular genetic screening of the bone marrow in the second month of admission revealed clonal monosomy 8, the diagnosis was changed to CEL. Specifically, chronic eosinophilic leukemia (CEL) is distinguished from HES by the presence of either a cytogenetic abnormality or excess blasts in the peripheral blood or bone marrow (blasts >2% in peripheral blood; or blasts >5% in bone marrow). This case therefore fit the description of “chronic eosinophilic leukemia-NOS” according to the WHO 2008 classification.

Chronic eosinophilic leukemia-NOS tends to be aggressive and unresponsive to therapy and harbors a high risk of acute transformation, so early HSCT should be considered, although there are also other options for therapy, such as IFN-alpha, imatinib, hydroxyurea and busulphan.

Since our patient was resistant to steroid and vincristine therapy, we had to start 6-thioguanine and cytosine arabinoside treatment. The eosinophil count decreased, but her pulmonary function tests revealed restrictive pulmonary disease under these therapy modalities. Steroid resistance and organ involvement are negative factors for prognosis, and HSCT is indicated when resistant disease is present. So, allogeneic BMT from HLA-matched siblings was planned, and the same medical therapy was continued until BMT.

Although not many cases concerning BMT and eosinophilic disorders are available in the literature, BMT has been attempted in patients with aggressive disease. Disease-free survival ranging from eight months to five years has been reported.

Chronic eosinophilic leukemia-NOS is extremely rare. However, advances in genetics have led to the recognition that many patients who would previously have been regarded as having idiopathic hypereosinophilia actually have chronic eosinophilic leukemia. For example, pediatric HES cases that were associated with chromosomal abnormalities, including trisomy, very probably were actually chronic eosinophilic leukemia cases. One such case was reported to respond to corticotherapy; but the long-term follow-up was not reported.

Trisomy 8 is the most common chromosomal abnormality in chronic eosinophilic leukemia-NOS, and may be an important factor in subsequent disease progression and transformation. Other chromosomal abnormalities are: monosomy 7, 20q-, I (17q); trisomy 10, 17q+, 15q-, t(7;12), t(4;16), complex [+Y, t(3;5), +8, +mar] (20), -16; and trisomy 15. Our patient displayed monosomy 8. As far as we know, monosomy 8 has not so far been reported in chronic eosinophilic leukemia-NOS. Monosomy 8 could be either a random association or a disease-related abnormality. The role of monosomy 8 in CEL requires further evaluation. We did not evaluate the patient’s bone marrow for monosomy 8 immediately before HSCT, since monosomy 8 had been established quite recently (less than two months before the procedure). Sustained hypereosinophilia, whether reactive or clonal, could potentially lead to eosinophilic end-organ damage. Although clonal disorders of eosinophils seem more likely to produce eosinophilic end-organ damage, there are controversies. Tissue injury in hypereosinophilia is mediated by material released from eosinophilic granules, including major basic proteins, eosinophil-derived endotoxins, neurotoxins and...
eosinophilic cationic proteins. For every one blood eosinophil, there are 100 tissue eosinophils. Theoretically, any organ can be infiltrated by eosinophils. Clinical manifestations are markedly heterogeneous, and the disease can either be completely asymptomatic or involve multiple organs, including the skin (pruritus, urticaria, angioedema, erythematous papules or nodules, mucosal ulcers), the heart (fibroelastic endocarditis, valvular disease, mural thrombi, cardiomyopathy, elevated troponin levels), the nervous system (sensory motor polyneuropathies, mononeuritis multiplex, isolated CNS vasculitis, optic neuritis, acute transverse myelitis), the lungs (pulmonary infiltrates, lung nodules, pleural effusion), the gastrointestinal system (hepatosplenomegaly, gastroenteritis, sclerosing cholangitis, ascites, pancreatitis, Budd-Chiari Syndrome), the eyes (microthrombi, vasculitis, retinal arteritis), the joints (arthralgia, effusions, polyarthritis, Raynaud’s phenomenon, digital necrosis), the hematopoietic system (cytopenias, bone marrow fibrosis) and the kidneys (thrombotic microangiopathy). In our case, there was cardiac (cardiomyopathy, elevated troponin levels, cardiac failure), lung (pulmonary infiltrates, lung nodules), nervous system (isolated central CNS vasculitis involving the bilateral centrum semiovale, left forceps major, abducens and optic nerves), ocular (retinal vasculitis giving rise to splinter haemorrhage) and bone involvement. Of the known factors predictive of worse outcome, our patient had severe eosinophilia, cardiac disease and refractoriness to corticosteroid treatment.

The presence of concurrent myeloproliferative syndrome, corticosteroid-refractory hypereosinophilia, cardiac disease, male sex and severity of eosinophilia are factors predictive of worse outcome.

This case was presented to draw attention to the fact that cases of chronic eosinophilic leukaemia-NOS without excess blast in the bone marrow may easily be misdiagnosed as myeloproliferative HES unless a detailed genetic and molecular examination is made. Detailed pathological interventions are also required for correct diagnosis. In addition, we want to note that BMT may be unsuccessful for these patients, probably due to coexistent microenvironment defects. However, it is obvious that more cases are needed in order to be able to evaluate the therapeutic efficiency of BMT in chronic eosinophilic leukaemia–NOS.

Acknowledgments

We thank the Ege University Faculty of Medicine Department of Parasitology, İzmir, for their kindness in conducting a western blot evaluation for toxocariasis.

REFERENCES


