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CASE REPORT

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A t (9;11) translocation in childhood acute mixed leukemia

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We present the case of a child with acute lymphoid leukemia (ALL) who was morphologically classified as FAB L1 (PAS and peroxidase were negative). Remission was achieved with an ALL-type protocol (GBTLI). Five months after the discontinuation of therapy, the patient presented mixed leukemia (CD10, CD19, CD13 and CD33 were positive) with t (9;11) (p21;q23) translocation. Unfortunately, as cytogenetic and immunophenotype studies were not performed at diagnosis, two possibilities could be considered for the relapse; secondary mixed leukemia with clonal chromosome changes, or mixed leukemia from the beginning.

UNITERMOS: Leukemia, karyotipe. Epipodophillotoxin derivative.

CASE REPORT

An 8 year-old boy was first seen in August 1989 with the following readings: Hg= 9.5g percent, WBC= 185,000/mm^3 with 90 percent blasts and platelet count= 30,000/mm^3. A bone marrow aspiration revealed lymphoblast replacements that were negative for myeloperoxidase and PAS stains. No immunophenotyping or cytogenetics was performed. The morphological diagnosis of ALL, L1 by FAB criteria[1] was made, and the child was treated according to the ALL-85 protocol of the Brazilian Cooperative Group for the Treatment of Acute Leukemia, which consists of: 1) induction with Vincristine, Dexamethasone, Daunomycin, L-asparaginase and Cytosine Arabinoside; 2) intensification with Etoposide (epipodophyllotoxin derivative) and Cytosine Arabinoside and: 3) maintenance with a rotation of the following drug pairs for 123 weeks: Dexamethasone and Etoposide; Teniposide and Cytosine Arabinoside; and 6-Mercaptopurine and Methotrexate. Central nervous system prophylaxis consisted of cranial irradiation (24 Gy) and triple intrathecal therapy.[2]

Five months after treatment was completed, a bone marrow relapse occurred. At that time, bone marrow aspirate showed 80 percent myeloblasts. Myeloperoxidase and Sudan Black B were negative, PAS was 39 percent positive and diffusely granular, alpha naphtyl acetate esterase was 55 percent positive without being inhibited by NaF, and ASD esterase was negative. The immunophenotype was determined on bone marrow cells by performing the standard method

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of indirect immunofluorescence[4] using the following panel of monoclonal antibodies with the respective results: CD33 (My9) = 24 percent, CD13 (My7) = 22 percent, CD14 (My 4) <5 percent, CD19 (B 4) = 35 percent, CD10 (calla) = 37 percent, CD7 (leu 9) = 12 percent, CD41 (plt1) <2 percent, and sIg = 11 percent. Results greater than 20 percent were considered positive. In addition, stained immunophenotyping on bone marrow smears was performed by the alkaline phosphatase/anti-alkaline phosphatase technique (APAAP), confirming previous results of monoclonal antibodies.[6] Chromosome studies were performed on bone marrow cells examined after 24 hours of unstimulated culture at 37°C using standard techniques.[18] The chromosomes were classified according to ISCN.[5] Results were: 46,XY, t(9;11) (p21;q23) (14 cells)/45,XY, t(9;11) (p21;q23),-13 (6 cells)/ 46,XY (2 cells).

The patient was placed on a new therapeutic regimen, once again achieving a complete remission that lasted for 5 months, when a marrow relapse occurred.

DISCUSSION

Translocations involving (11q23) are common in acute myeloid leukemia (AML) of the M5 FAB subtype.[15] The t (9;11) (p21;q23) translocation has been associated with characteristic clinical features, and is a superior treatment outcome for previously untreated pediatric AML.[17,13,7] Although rare, this translocation has also been seen in newly diagnosed ALL.[8] It has been speculated that acute cases of leukemia associated with abnormalities of (11q23) originate from a multipotential stem cell that is capable of differentiating along myeloid or lymphoid pathways.[15]

A (11q23) translocation was found to have relapsed in several cases of common pre-B ALL that had either converted to calla negative pre-B ALL or ANLL.[12] Authors have suggested the possibility of the emergence of the pluripotent stem cell following chemotheraputic eradication of the original B-cell precursor line.[16]

More recently, a t (9;11) translocation has been described in AML secondary to acute lymphoid leukemia previously treated with epipodophyllotoxins, etoposide and teniposide.[11,10,14] This syndrome is clinically, pathologically and cytogenetically distinct from classical therapy related to myelodysplastic syndromes and AML.[14] Other authors confirm that this rearrangement is a non-random cytogenetic abnormality of therapy-related AML.[17,10,9,20,19]

Around 8 percent of the children treated for ALL develop secondary leukemia 5 to 36 months after treatment,[11] and 9 out of 91 secondary AML cases studied by PERDERSEN-BJERGAARD et al.[10] showed rearrangement of (11q23). The latency for development of secondary leukemia was shorter when compared to patients without abnormalities of chromosome 11.

The cumulative risk of secondary AML is apparently increased among certain groups, especially those with a T-cell phenotype (19.1 percent at 6 years)[11] and those who received epipodophyllotoxins once or twice a week (12 percent at 6 years).[9] It seems that it is the treatment frequency, and not the leukemia cell phenotype, that is critical in influencing the risk of secondary AML arising during remission of ALL.[9] Immunophenotypic studies in the present case revealed that blast cells expressed early pre-B and myeloid markers.

Unfortunately, as cytogenetics and immunophenotype studies were not performed at diagnosis, we cannot affirm what happened in relapse. We could consider the possibility of a secondary mixed leukemia with clonal chromosome changes of t(9;11) (p21;q23), if we interpret the initial

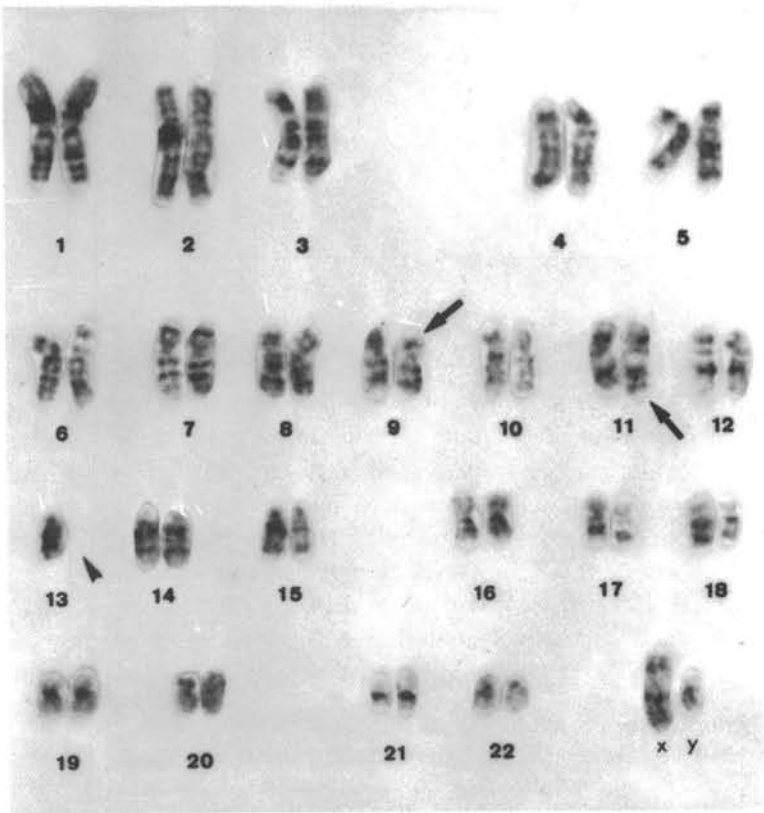

Figure 1 - Bone marrow karyotype showing 45,XY, t(9;11)(p21; q23), -13.

morphology and prolonged first remission with an ALL-type protocol as a commonly-seen childhood ALL. Previous exposure to drugs, particularly epypodophyllotoxins,[10] could suggest that the acute leukemia was drug induced, although a second primary leukemia in a previously mixed case cannot be excluded.[3] Perhaps chemotherapy changed the original clone by altering its phenotypic expression. We could also consider the case as being a mixed leukemia from the beginning which remitted and, after discontinuation of therapy, had a later relapse.

Notwithstanding the lack of immunophenotype and cytogenetic studies at diagnosis, we would like to alert hematologists that intensive chemotherapy may be also capable of inducing secondary or treatment-related leukemia in children. This ought to be a concern here in Brazil, as it is in the rest of the world.

RESUMO

Apresentamos o caso de uma criança com leucemia aguda classificada morfologicamente como LLA (leucemia linfóide aguda) FAB L1 (PAS e peroxidase negativos) que alcançou remissão com protocolo para LLA (GBTLI). Após cinco meses fora de terapia desenvolveu uma leucemia mista (CD10, CD19, CD13 e CD33 positivos) com translocação t(9;11)(p21;q23). Como, infelizmente, os estudos de citogenética e imunofenotipagem não foram realizados ao diagnóstico, pode-se considerar duas possibilidades para a recaída: uma leucemia mista secundária com alteração cromossômica clonal ou uma leucemia mista desde o início.

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