

Adult Type Chronic Myeloid Leukemia in Children: A Case ReportHendi Rajae^{1*}, Tlamçani Imane¹, Mahha Mariam¹, Tadmori Ilham², Benmiloud Sara², Hida Moustapha², Amrani Hassani Moncef¹¹Department of Hematology, Universitary Hospital Hassan II, 30000 Fes, Morocco²Department of Pediatrics, Universitary Hospital Hassan II, 30000 Fes, Morocco***Corresponding author**

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Abstract: Chronic myeloid leukemia is a malignant clonal expansion of hematopoietic progenitor cells causally linked to a specific chromosomal abnormality, the Philadelphia chromosome. It occurs uncommonly in childhood, accounting for only 2 to 5% of all pediatric leukaemias with an annual incidence of about 1 per million in this age range. We describe one such case of chronic myeloid leukemia in an 11 year old boy, who presented with massive splenomegaly and hyperleukocytosis. The diagnosis was made from peripheral blood smear examination, supported by karyotypic study. Because of the infrequency of its occurrence, it was thought of interest to report this case of CML and to review certain interesting features of this entity in the pediatric population.

Keywords: Chronic myeloid leukemia-child-Philadelphia chromosome.

INTRODUCTION**Background**

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder characterized by an uncontrolled proliferation of myeloid cells in all stages of maturation. It is the first pathology directly correlated to a clonal acquired cytogenetic abnormality. This anomaly was discovered in 1960 as an abnormal chromosome called the Philadelphia (Ph) chromosome, which results from reciprocal translocation between the BCR gene on chromosome 22 and the ABL gene on chromosome 9 [1]. CML typically progresses through three sequential phases: chronic, accelerated, and blastic phases.

It is mainly a disease of adults and its incidence is rare in children since it accounts for only 3% of leukemias in this age group, 9% in adolescents, whereas it can reach 15% in adults [2].

Two variants of CML are seen in childhood: the juvenile form, also known as juvenile myelomonocytic leukemia (JMML), which affects mostly young children below 3 years and lacks the Ph chromosome, and the adult form which is indistinguishable from classic Ph chromosome positive CML seen in adults and usually appeared at higher age.

We present a case of an 11 year old child, diagnosed with adult type CML and we recall through a review of the literature the peculiarities of this malignancy in children.

CASE REPORT

The patient is an 11-year-old boy born out of a non-consanguineous marriage, with no significant finding in his past medical history. He presented with chief complaints of dragging sensation in the abdomen, general weakness and a 4 kg weight loss over 4 months.

Physical examination showed pallor, a huge splenomegaly extended below the umbilicus, with cervical and inguinal lymphadenopathy. The liver was palpable.

At initial evaluation, his complete blood count revealed marked elevation of white blood cells (WBC, 295.74 G/L), aregenerative normochromic normocytic anemia (hemoglobin, 8.2 g /dl), and a normal platelet count (202 G / L).

Peripheral blood smear stained by May-Grunwald-Giemsa (MGG) showed granulocytosis exhibiting 14% of neutrophils, 5% of basophils, 2% of eosinophils, 4% of lymphocytes, with presence of immature granulocytes at various stages (27% of metamyelocytes, 46% of myelocytes and 1% of promyelocytes) and 1% of circulating blasts (Figure-2).

The diagnosis of chronic myeloproliferative disorder suggestive of CML was given. Serum chemistry revealed elevated levels of lactate dehydrogenase (1018 IU / L). Renal, hepatic and coagulation profiles were all within normal limits.

Viral serology for cytomegalovirus (CMV), Epstein Bar virus (EBV), human immunodeficiency virus (HIV), hepatitis B and C viruses was negative.

The chest radiograph detected a rounded opacity well limited on the right lung parenchyma. Abdominal ultrasound examination described an enlarged homogeneous spleen. Bone marrow aspirate showed increased cellularity with pronounced granulocytic hyperplasia (86%), eosinophilia (7%), basophilia (10%) and a small increase in blast cells (7%). The erythroid lineage was hypoplastic (3%)

(Figure-2). Cytogenetic analysis confirmed the diagnosis by revealing the presence of the Ph chromosome (9; 22) (q34; q11).

On the basis of clinical features and laboratory findings, the patient was diagnosed to be suffering from adult type CML in chronic phase. Treatment was started with imatinib (tyrosine kinase inhibitor) at the standard dose of 400 mg per day. The patient was recalled after the treatment for follow up and evaluation. He has been in chronic phase for 3 years from his initial presentation.

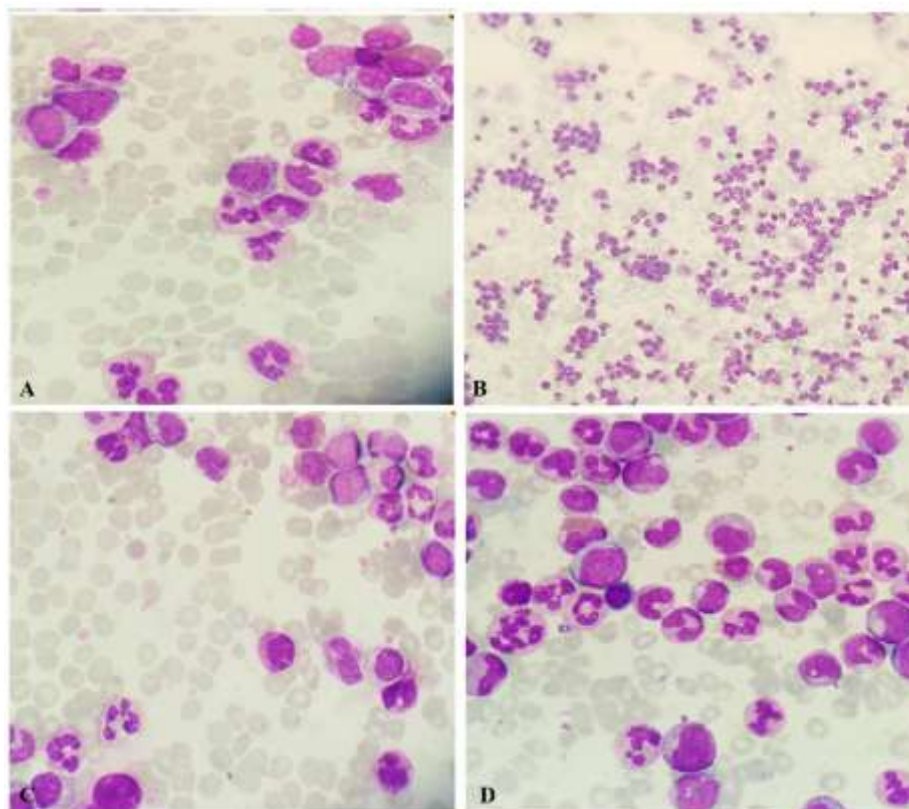


Fig-2: (A): Peripheral blood smear showing hyperleucocytosis with circulating immature cells (MGG-Giemsa stain, x100). (B): Bone marrow aspirate smear showing marked hypercellularity with marked granulocytic hyperplasia, (MGG-Giemsa stain, x10). (C, D): Bone marrow aspirate smear showing myeloid hyperplasia including basophils and eosinophils. All stages of myeloid elements including blasts, promyelocytes, myelocytes, metamyelocytes, band neutrophils, and segmented neutrophils are observed, (MGG-Giemsa stain, x100)

DISCUSSION

Amongst childhood leukemias, chronic myeloid leukemia is a rare entity. Few reports in the developing countries have been published. The largest series are available in the International Register of CML in Children and Adolescents [3]. Adult-type chronic myeloid leukemia in a child, as presented in this case, is even rarer.

The vast majority of pediatric cases are diagnosed over the age of 5 [4]. In a German study, the average age at presentation was 11 years [5]. Similar trends were seen in a French study carried out among 40 patients in which the median age of diagnosis was

12.5 years and 67% of them were older than 10 years [6].

As in adults, a male predominance of childhood CML has been reported but has never been demonstrated because of the small number of cases involved in studies.

Most pediatric patients are diagnosed in the chronic phase with a median duration of 4-5 years which is consistent with previous studies in adults [6]. However, in some cases, the disease will be discovered in accelerated or even blastic phase. Then,

the clinical and biological manifestations will be more aggressive requiring immediate hospital management.

Many of the clinical features at the time of presentation are similar to adult patients. The most common symptoms are asthenia, weight loss, bleeding episodes, bone pain and abdominal swelling. On physical examination, splenomegaly represents the predominant sign. A recent study on 150 patients younger than 18 years old reported that the spleen was palpable in 78% of children, with a median value of 8 cm below costal margin [7]. This number is not very different from that of adults; however, it is proportionally larger in children because the age-based normal size of the spleen in children is smaller than in adults.

Otherwise, other studies have shown that splenomegaly is a consistent a finding. Less common manifestation of childhood CML include hepatomegaly and enlarged lymph nodes. They are observed in only 10% of pediatric cohorts [6].

A definitive diagnosis of CML is impossible without appropriate laboratory tests, of which a blood count smear is by far the most important. Children tend to present with a markedly raised leukocyte count than adults. The median WBC count in a French pediatric cohort in which 102 patients have been registered was

258.45 G / L. This finding was very similar to that observed in 39 childhood patients from the Castro-Malaspina study carried out in 1983. This excessive leukocytosis is composed of a broad range of myeloid differentiated cells, including increased basophils and eosinophils [12]. Besides these hematological feature, anemia and thrombocytosis are present more frequently (60 %) in children [8].

According to various studies, the median WBC count in adults rarely exceeds 120 G / L at diagnosis, (median: 12 - 174 G / L) [9].

The myelogram makes the diagnosis of CML virtually certain. It is essential to quantify the percentage of blasts and to specify the phase of the disease [10]. Granulocytes show orderly maturation to the neutrophil stage without significant dysplasia, sometimes an hyperplasia of the megakaryocytic line is associated.

CML in our patient was confirmed by the presence of the almost specific chromosomal abnormality: the Philadelphia chromosome (Figure1) which results from the reciprocal translocation (9; 22) (q34; q11). This finding puts the diagnosis beyond doubt. It is present in about 95% of pediatric cases. However, in rare cases with clinical and hematologic signs suggesting CML, the Ph chromosome is absent.

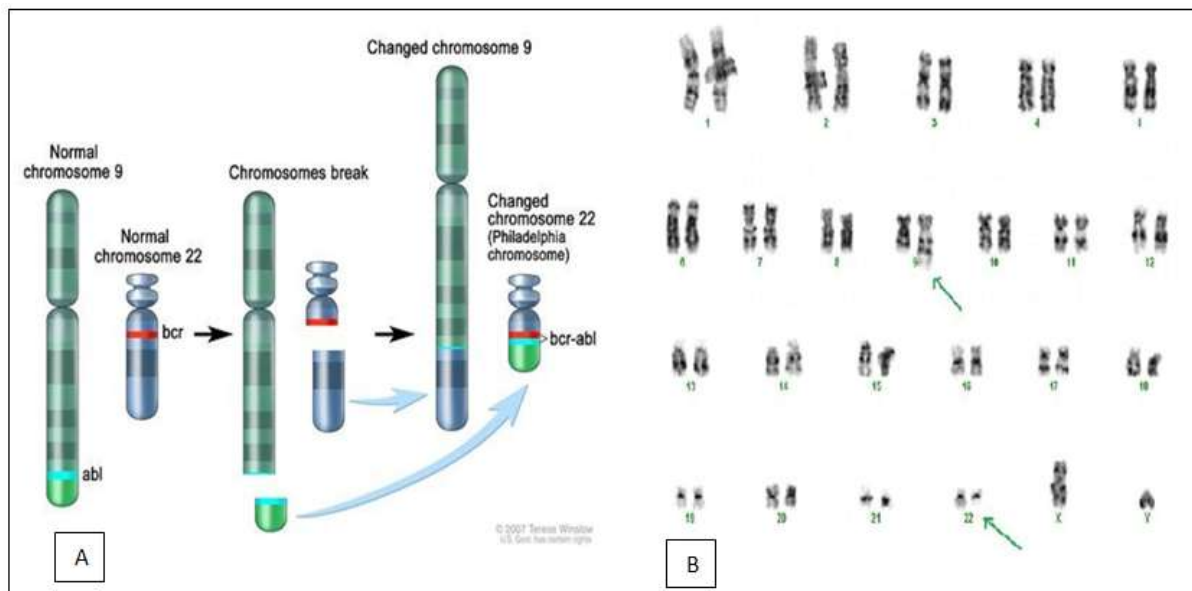


Fig-1: A: Philadelphia chromosome, the (9;22) translocation transposes the ABL (Abelson) protooncogene from chromosome 9 into a relatively small, 5.8-kb genomic region on chromosome 22 named the breakpoint cluster region (bcr). Picture source: <https://visualonline.cancer.gov/details.cfm%20?imageid=7153>. B: Karyotype analysis depicting t(9;22) indicative of CML. Picture Source: <https://labtestsonline.org/tests/chromosome-analysis-karyotyping>

Additional chromosomal abnormalities can be found in the karyotype of patients depending on the stage of disease progression. The most common are trisomy 8 (33%), additional Philadelphia chromosome

(30%), isochromosome 17 (20%), trisomy 19 (12%), loss of Y chromosome (8% of male patients), trisomy 21 (7%) and monosomy 7 (5%) [11].

Our case fulfills the morphological and cytogenetic criteria required for the diagnosis of adult type CML. However, it is necessary to know how to distinguish this adult form of CML from the juvenile form (LMMJ).

The term JMML is used to include all childhood leukemias, formerly classified as juvenile CML, chronic myelomonocytic leukemia, and infantile monosomy 7 syndrome. According to WHO 2008 classification, the JMML was classified among the MDS/MPN Overlap Syndromes. In children, it accounts for 3% of hematological malignancies and 18% of MDS. It occurs mainly in infants and young children below 2 years of age. Patients often show a large hepatosplenomegaly, multiple adenopathies, recurrent infections and various cutaneous signs [12]. The diagnosis of JMML is based on the association of leukocytosis with myeloid and monocytosis, hypochromic anemia, early and severe thrombocytopenia and the constant absence of the Philadelphia chromosome [13]. These characteristics were absent in our patient.

The management of childhood CML is another challenge for the pediatrician. Algorithms regarding therapeutic interventions are derived from practice standards used in adult patients. In our case, a treatment with Imatinib has been introduced. It is regarded as the first line drug for children newly diagnosed CML in chronic phase.

CONCLUSION

Adult type CML is exceedingly rare in the pediatric population. It usually presents with aggressive features such as hyperleucocytosis and massive splenomegaly. This entity remains one of the major problems, because of the lack of specific pediatric treatment guidelines and the goal of treatment which is cure rather than disease suppression like in many adult patients. A prospective analysis of a larger cohort of children is highly recommended, so as to help make better treatment recommendations for pediatric CML.

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