Chronic myeloid leukemia in children and adolescents (A bout 2 cases)

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Abstract

Pediatric chronic myeloid leukemia is a rare entity (2-5% of childhood leukemias) classified as a myeloproliferative neoplasia characterized by the presence of the BCR-ABL fusion gene, the oncogenic translocation product (9; 22) responsible for the disease through its deregulated tyrosine kinase activity.

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Selection: case report

Key words: Leukemia, Hyperleukocytosis, Imatinib, BCR-ABL1, Blast.

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Abstract :

Pediatric chronic myeloid leukemia is a rare entity (2-5% of childhood leukemias) classified as a myeloproliferative neoplasia characterized by the presence of the BCR-ABL fusion gene, the oncogenic translocation product (9; 22) responsible for the disease through its deregulated tyrosine kinase activity.

Observations :

First Observation:

This 11-year-old girl had physical asthenia with diffuse bone pain and vomiting. On clinical examination, there was an enormous splenomegaly (14cm below the costal grill) with hepatomegaly at 11 cm and no palpable adenopathy. Biologically, the Blood Count revealed hyperleukocytosis (White Blood Cells: 400190/mm^3), anemia (hemoglobin level: 7.7g/dl) and moderate thrombocytopenia (platelet level 100,000/mm^3). The myelogram showed hyperplasia of the granular lineage and reactive hypoplasia of the erythroblastic lineage containing 6% of blasts (figure 1). The tumor lysis test is negative. The genetic study shows the presence of the transcript BCR-ABL1**.** The child is actually stable with regression of hepatomegaly and splenomegaly after receiving imatinib 100mg (1 capsule×4 / Days).

Observation 2:

A 6-year-old patient was admitted for a hemorrhagic syndrome with ecchymotic spots, especially on the lower limbs, and an infectious syndrome with a fever of 38.5°C associated with hypoacusis. On clinical examination, hepatomegaly, infra-centimetric cervical and thoracic adenopathies and bilateral exophthalmos were found. The blood count on admission revealed severe bicytopenia (hemoglobin level: 5.7 and platelet count: 23,000/mm^3) and hyperleukocytosis (white blood cells: 196170/mm^3). The tumor lysis test was negative. The myelogram showed an infiltration of blasts estimated at 31% and hypoplasia of the erythroblastic lineage (figure 2), cytochemical staining for peroxidase was positive. Lymphocyte immunophenotyping on marrow blood showed a low CD45 blast population estimated at 36% of myeloid phenotype (figure 3, 4). The karyotype showed the presence of the Ph chromosome, completed by the molecular study, which confirmed the presence of the BCR-ABL1 transcript. The child was treated according to the AML-MA 2011 protocol, DTT, and she presented a febrile neutropenia put on triaxon + gentamicin during 48h with persistence of fever and increase of CRP from where the decision to switch the antibiotic therapy to ciproxine + amiklin + vancomycin. The follow-up cerebral CT scan of the orbit shows a significant regression of tissue infiltration of the bilateral external orbital walls with complete regression of the exophthalmos.

Discussion:

Pediatric chronic myeloid leukemia (PCML) is a rare hematologic malignancy in children (2-3% of pediatric leukemias) [1], resulting from clonal expansion of granular lineage progenitors leading to an accumulation of immature, non-functioning myeloid cells. CML tumor cells are characterized by a t (9; 22) translocation, which leads to the formation of the Philadelphia (ph) chromosome. This translocation, which leads to the formation of the BCR-ABL fusion gene, is responsible for the disease through its dysregulated tyrosine kinase activity [2,3]. The diagnosis of pediatric CML is based on clinico-biological data: the disease can be revealed by isolated splenomegaly or associated with hepatomegaly with other lymph node and visceral determinations in the advanced phases. It comprises three evolutionary phases: a first chronic phase of progressive installation which can be asymptomatic in many patients at the time of diagnosis suspected in front of a haemogram which shows a hyperleukocytosis, usually higher than 250,000/mm^3, thrombocytosis in 30 to 50% of the cases with basophilia on the myelogram, a hyper-cellularity with an increase in the ratio of erythroblasts to granules and in the number of megakaryocytes, and less than 10% of blasts and promyelocytes. The first case of our observation was diagnosed at the chronic stage by a clinical and biological picture in favor of the disease. Accelerated phase characterized by the presence of blood or marrow blasts lower than 20% with blood basophilia higher than 20% and thrombocytopenia lower than 100,000/mm^3 not related to the treatment, this phase corresponds to the transition between the chronic phase and the blastic phase being then explosive defined by the presence of more than 20% of marrow blasts [4,5]. The immunophenotypic study by flow cytometry makes it possible to confirm the acutisation and the myeloid or lymphoid nature of the blasts, as in the case of the second observation diagnosed for pediatric CML in the

acutisation phase with 36% of blasts of a myeloid nature with strong expression of the CD13CD33CD117 markers and a postive myeloperoxidase (Egil score greater than 2 in favour of the myeloid lineage).

The biological diagnosis is based on the realization of the haemogram, the key examination allowing to evoke the diagnosis by the hyperleucocytosis, observed in the two cases of our observation with a normochromic normocytic anaemia and a thrombopenia. The myelogram shows a hypercellular marrow with marked granular hyperplasia and the presence or absence of blasts to confirm the phase of the disease.

The cytological study is completed by the genetic study, a fundamental tool of the diagnosis by the realization of a RT-PCR (reverse transcriptase polymerase chain reaction) which highlights the BCR-ABL1 fusion transcript in the medullary or peripheral blood, indispensable test for diagnosing pediatric CML and which allows the differential diagnosis with juvenile myelomonocytic leukemia: borderline entity between myelodysplastic syndrome and myeloproliferative syndrome with the presence of cytological signs of myelodysplasia and hyperleukytosis, with reactive myelmia and with acute lymphocytic leukemia with Philadelphia chromosome in the acute phase.

The treatment of pediatric CML is based primarily on the use of tyrosine kinase inhibitors such as imatinib, which is currently considered the best treatment for CML, even though it poses significant side-effect problems, including growth restriction and the possibility of developing resistance to the treatment, which has an impact on the treatment decision. However, in case of treatment failure, the research of other mutations of the tyrosine kinase domain is recommended in view of the new therapeutic possibilities [6, 7].

Conclusion :

Pediatric CML is a serious hematologic malignancy whose differential diagnosis can be difficult because of the clinical and biological similarities, particularly with atypical CML. Early diagnosis and treatment of juvenile chronic myeloid leukemia allows for better stabilization of the disease, especially with the advent of tyrosine kinase inhibitors, whose discovery was the key to treating pediatric CML.

Declaration of interest :

The authors declare that they have no conflicts of interest.

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