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Juvenile Chronic Myeloid Leukaemia (JCML): Report of Two Cases

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Summary:

A baby of four months was admitted into Khulna Shishu Hospital with the complaints of intermittent dyspnoea, fever and cough of one month duration. Systemic examination revealed mild hepatosplenomegaly, superficial cervical lymph node enlargement, facial rash and pallor of conjunctiva. Another two years old male child was admitted into a Private Clinic in Khulna with the history of fever, joint pain, general weakness and gum bleeding of six months duration. Physical examination revealed moderate hepatosplenomegaly, cervical lymph node enlargement and conjunctival pallor. During haematological investigations, both of these patients showed the feature of juvenile chronic myeloid leukaemia.

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Introduction:

Juvenile chronic myeloid leukaemia (JCML) is a clonal expansion of haematopoietic stem cells that typically affects the children younger than two years of age.[1] Patients with this disease do not have philadelphia chromosome, a characteristic finding of juvenile chronic myeloid leukaemia. Leukaemia in infant and children generally is acute. Fewer than 5% of patients with chronic myeloid leukaemia are children.[2] Children and infants may have ph1(+) CML in which case the clinical features of the disease, including the response to therapy are indistinguishable from those in adults.[3] Most patients with JCML present with facial rash, anaemia, breathlessness, mild to moderate hepatosplenomegaly and lymphadenopathy. Analysis of peripheral blood film often shows a considerable elevation of blood leukocyte count and an accumulation of all forms of mature and immature granulocytes.

Chronic myeloid leukaemia is a disorder with considerable historical significance. In 1960, Nowell and Hungerfold working in Philadelphia reported that myeloid cells from patient with chronic myeloid leukaemia showed a deletion of portions of long arm of one member of the G group of chromosome.[4] Subsequently, this chromosome was found to be an almost constant feature of the disease indicating that it was an acquired chromosomal abnormality that could be linked to specific malignant process. The Ph1 chromosome and its relationship to CML provided an exemplary model for studying the effects of genomic changes in the causation of cancer.[5]

In 1973, results of studies showed that the Ph1 chromosome is the result of a reciprocal translocation of genetic material between chromosome 9 and 22. (t9; 22) (q34.1; q11.21).[6] In a small proportion of patients (4-5%), anomalous and complex translocation occur, usually chromosome 9 and 22 are involved and 9 is involved universally.[7]

Details of JCML perhaps has not yet been reported in our country. Here, a rare malignant disorder of children, JCML, diagnosed clinically in two children as bronchopneumonia or pyrexia of unknown origin is reported.

Case report-1: A female baby of four months was admitted into Khulna Shishu Hospital on 22nd January, 2004 with the complaints of intermittent dyspnoea, fever and cough of one month duration. The patient came of an average socio-economic background and her general condition was poor. Systemic examination revealed mild hepatosplenomegaly, superficial cervical lymph node enlargement, facial rash and pallor of conjunctiva.

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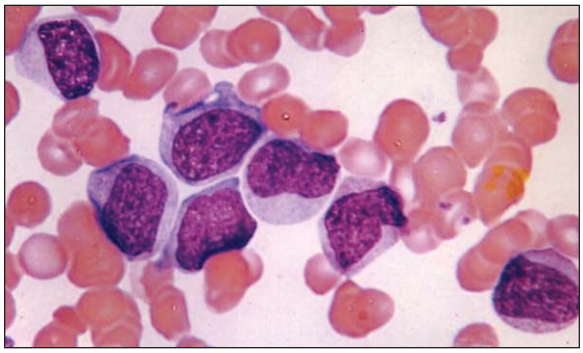

Fig.-1: *Blood film of JCML showing primitive cells of myeloid series promyelocyte, myelocyte and myeloblast and also promonocyte and monocyte (Giemsa stain x 1200)*

Chest X-ray of posterio-anterior and lateral view showed soft opacity involving middle lobe of right lung. Ultrasonography showed that the liver and spleen were mildly enlarged (bipolar length of spleen was about 15 cm) but tissue appearance was uniform with no focal lesion. Fine needle aspiration cytology of enlarged cervical lymph node showed the features of reactive lymphadenitis. Haematological investigations showed the followings: haemoglobin level : 6.6 gm/dl; ESR: 75mm after first hour (Westergren method); total leukocyte count : $120x10^9$/L; differential count: neutrophil 16%, lymphocyte 15%, promonocyte 10%, monocyte 14%, eosinophil 2%, basophil 1%, segmented band form 6%, promyelocyte 17%, myelocyte 9%, metamyelocyte 6%, and myeloblast 4%; and platelet count: $80x10^9$/L. Alkaline denaturation technique showed that foetal haemoglobin (Hb-F) was present in increased proportion. Peripheral blood film analysis showed the followings: red blood cells showed anisochromasia with anisocytosis; a good number of erythroblasts were also seen; white blood cells showed shift to the left with the prominence of promyelocyte, myelocyte and monocyte; and platelets were reduced. Bone marrow study findings were as follows: hypercellular marrow with partial replacement of fat spaces, myeloid and erythroid ratio increased (M: E = 36: 1), granulopoiesis was hyperplastic and showed maturation arrest with the predominance of myelocyte (> 40%), myeloblast (<30%), promyelocyte and metamyelocyte; erythropoiesis was active and dyserythropoietic including asynchrony between maturation of cytoplasm and nucleus, megaloblastoid changes, multinuclearity, nuclear fragmentation and cytoplasmic vacuolation; and megakaryocytes were normal but many of them were morphologically abnormal, micromegakaryocytes and large monolobular megakaryocytes were common findings.

Case report-2: A two years old male child was admitted into a private clinic in Khulna on 14th March, 2004 with history of fever, joint pain, general weakness and gum bleeding of six months duration. Physical examination revealed moderate splenomegaly, cervical lymph node enlargement and conjunctival pallor. Chest x-ray of posterio-anterior and lateral view showed prominent bronchovascular markings with patchy soft opacity in the middle lobe of right lung. Ultrasonography showed that the liver and spleen were moderately enlarged (bipolar length of spleen was about 18 cm) but the tissue appearance was uniform with no focal lesion. The splenic vein at the hilar region was dilated. Fine needle aspiration cytology of the affected lymph node showed the features of reactive lymphadenitis.

Haematological investigations showed the followings: haemoglobin level: 7.5gm/dl; ESR: 32mm after 1st hour (Westergren method); total leukocyte count: $80x\ 10^9$/L; differential count: neutrophil 13%, lymphocyte 18%, promonocyte 8%, monocyte 12%, eosinophil 1%, basophil 2%,

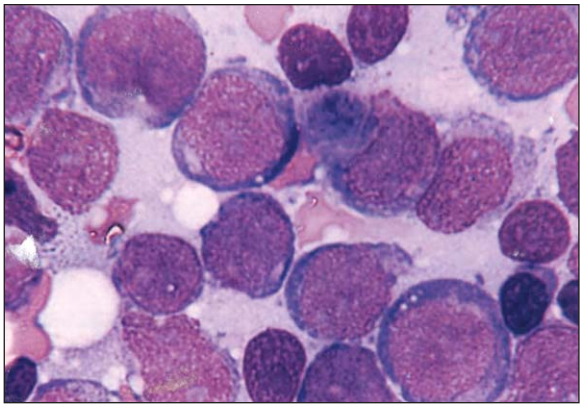

Fig.-2: *Marrow film of JCML showing primitive cells of the myeloid and monocyte series. Myeloblasts bottom right and monoblast top left (Giemsa stain x 1200).*

segmented band form 8%, promyelocyte 19%, myelocyte 10%, metamyelocyte 5%, myeloblast 4%; and platelet count: $100x10^9$/L. Alkaline denaturation technique showed that foetal haemoglobin (Hb-F) was present in increased amount. Peripheral blood film analysis showed the followings: red blood cells showed anisochromia with anisocytosis, some erythroblast were also seen; white blood cells showed marked shift to the left with the predominance of promyelocyte, myelocyte, promonocyte and monocyte; and platelets were mildly reduced. Bone marrow study findings were as follows: hypercellular marrow with increased myeloid and erythroid ratio (M: E = 48: 1); granulopoiesis was hyperplastic with maturation arrest and the predominance of myelocyte (>30%), myeloblast (upto 20%), promyelocyte and metamyelocyte; erythropoiesis was active and dyserythropoietic including megaloblastoid changes, multinuclearity, nuclear fragmentation and cytoplasmic vacuolation; and megakaryocytes were increased and many micromegakaryocytes and large monolobular megakaryocytes were seen.

Discussion:

Juvenile chronic myeloid leukaemia (JCML) is found at an average age ranging from one to two years and there is no sex predominance.[8] Age of the reported patients were four months and two years respectively which agree with the findings of Reisman and Trurjillo.[9]

Both patients presented with mild to moderate hepatosplenomegaly, cervical lymph node enlargement, conjunctival pallor and facial rash. These features agree with the findings of Shapira and Ota.[10] The patients reported here also had intermittent dyspnoea, cough, fever, joint pain and gum bleeding. These seem to be an atypical presentation of patients, with juvenile chronic myeloid leukaemia. Philadelphia chromosomal study was not done in these cases because of lack of availability of the test in Khulna. Moreover, one patient died before doing this investigation and another left the clinic without notification and finally not being followed up. Haematological investigations of both cases showed thrombocytopenia and total leukocyte count lower than in patients, with typical chronic myeloid leukaemia. These haematological investigations agree with the finding of Takanashi.[11]

Cytogenetic and molecular studies showed that approximately 90% of patients with chronic myeloid leukaemia have a chromosomal abnormality known as the Philadelphia chromosome (Ph). This is a shortened chromosome 22 and is the result of reciprocal translocation of material with chromosome 9.

Two major subtypes of CML are recognized on the basis of the presence, Ph1(+), or absence, ph1(-), of Philadelphia chromosome, clinical manifestation, course and survival rate. In a small minority of patients, eosinophilia, basophilia or monocytosis predominantes, but such cases are unusual and are considered variants of "typical" CML.

All patients studied to date had an increase in the proportion of foetal haemoglobin, ranging as high as 85% of the total haemoglobin concentration.[12] The persistence of elevated levels of foetal haemoglobin and the early age of onset of CML infants, as well as it's development in infant siblings, have lead to speculation that the disease may be a variant of congenital leukaemia.[13]

On the basis of the course and the frequent involvement of the monocytic as well as neutrophilic series, certain authors have suggested that the disease is more akin to acute myelomonocytic leukaemia than to CML.[14]

Patients with neurofibromatosis have a predilection for this type of leukaemia.[15] Therapeutic reports are largely anecdotal. Survival rate from the time of diagnosis is usually less than one year, and response to therapy has been poor.[16]

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