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UNUSUAL CLINICAL PRESENTATION OF RELAPSE IN PATIENT WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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SUMMARY:

Acute lymphoblastic leukemia is a disease, which is more common in children. We report a clinical case of a patient aged 25. Thirty-two months before his last admission in Hematology clinic, acute pre- B lymphoblastic leukemia had been diagnosed and treated till March 2012.

In September 2013 after bone marrow aspiration, flow cytometric analysis, trepan biopsy and biopsy of the kidney had been carried out, the patient was diagnosed with first late relapse, involving bone marrow and kidney. A second remission was achieved using Berlin- Frankfurt– Munster chemotherapy [BFM] and allogenic stem cell transplantation was performed.

Key words: leukemia, relapse, polycythemia, kidney,

INTRODICTION:

Acute lymphoblastic leukemia [ALL] is a malignant hematological disease characterized by abnormal proliferation, accumulation and tissue infiltration of immature lymphocytes [1, 2, 3]. It is more common with children aged 2 to 5, but it has bimodal distribution with second peak in patients about 50 years of age [1]. The prognosis of disease depends on a number of factors, some of which are the length of first remission and site of relapse [4]. The greater part of the cases of relapse are manifested by isolated bone marrow involvement or in combination with the involvement of the central nervous system and/ or testicles and much rarely involving other extramedullary sites [5, 6].

Case Report:

We present a case of a 25- year- old man treated in University Hospital, Pleven from May 2009 till March 2012 for pre – B- ALL with testicle involvement, proved through a complex of laboratory tests including: bone marrow biopsy, flow cytometric and cytogenetic analysis of the bone marrow. Induction, consolidation and re- induction courses according BFM- protocol have been carried out. The complete remission was reported after prophylactic radiotherapy of the central nervous system in dosage 24 Gray.

In August 2013 the patient was admitted to emergency department on account of headache, joint and muscle pains. On admission he denied fever and weight loss. He reported having had several episodes of arterial blood pressure of 180/100 mmHg, treated with Chlophadon and Enalapril on an outpatient basis. Physical examination did not reveal enlargement of lymph nodes or pathological changes in respiratory, digestive tract and central nervous system. No bleeding involving mucous membranes or skin was found. His blood pressure was 160/110 mmHg, the heart rate was 72 bpm and the results from complete and differential blood counts were normal. He was admitted to the Department of Nephrology because of increased levels of urea (20 mmol/l) and creatinine (460 umol/l), with a diagnosis of nonoliguric acute renal failure. Abdominal ultrasound revealed enlarged kidneys 190/90mm, parenchyma 32mm, preserved drainage. No enlarged paraaortic and parailiac lymph nodes were visualized. Kidney biopsy with cytological and immunofluorescence tests were performed, which showed massive lymphoid infiltrates in the kidney.

In September 2013 the patient was admitted to the Clinic of Hematology in the University Hospital in Pleven. The results from the laboratory tests ordered were as follows: WBC- 5.5 G/l, RBC- 6.94T/l, Hb- 203g/l, Hct- 0.551, MCV-79fl, MCH- 92.2pg, MCHC-368, Plt- 168G/l, differential counting- St – 0.275G/l, Sg-4.67G/l, Mo- 0.11G/l, Ly- 0.44G/l; Urea– 12.01mmol/l, creatinine- 294.78 umol/l. Because of the high levels of hemoglobin and haematocrit, trephine biopsy with immunohistochemistry of bone marrow were performed that showed a marked erythroid hyperplasia. The presence of a small number of large lymphoid cells, positive for CD 20, CD 34 and a considerable number of Tdt positive cells, makes flow cytometric analysis obligatory in order to make the presence of relapse of pre- B- ALL more precise. Molecular analysis of bone marrow was made and the result was: RT –PCR t (9:22) / M-BCR -ABL (π210):/-/ negative. t (9:22) / m-BCR -ABL (π190):/-/ negative. JAK 2 V617F RFLP: /-/ negative. JAK 2 V617F allele specific/-/ negative.

Flow cytometric analysis of the bone marrow revealed the following results: blast cells - 20%: low FCS/ SSC phenotype: CD45+ low, CD 19+ , CyCD79a + , nuTdT + , CD10+, CD22+, CD38+, CD81+, CD34-,

CD20-, sIgM-Granulocytes -60% with phenotype: CD15+, CD13+, CD33+. Monocytes: CD14+. Erythroblast cells CD45-. These finding made us conclude that the patient had a relapse of pre- B- ALL. A significantly high level of erythropoietin (EPO) was found 108.54 mUI/ml (2.59-18.50mUI/ml).

Based on the results of the laboratory tests it was accepted that this was a case of first late relapse of ALL involving bone marrow and kidneys. The patient was referred to the National Specialized Hospital for Active Treatment of Hematological Diseases in Sofia, where chemotherapy by BFM- protocol was started. After remission was proved in March 2014, allogeneic stem cell transplantation was successfully made.

DISCUSSION:

The described case is of diagnostic and therapeutic interest due to the unusual manifestation of the disease relapse. At the time of the relapse the laboratory results can be interpreted as symptomatic polycytemia / Hb - 203.0 g/l; Ht - 0.551, Leu - 5.5 G/l; Er - 6.94 T/l; 168.0 G/l/. The lack of lymphoblasts in blood smear makes the relapse of leukemia uncertain. In contrast to the above described case, Leslie Skeith et al report late extramedular relapse of ALL, involving the kidneys but accompanied by anemic syndrome which is due to the presence of blasts cells in the bone marrow, kidneys infiltration and microscopic haematuria [7]. In most cases in which the kidneys are involved, anemia is caused by the decreased production of EPO. In the cases of renal-cell carcinoma, increased levels of EPO are due to autonomous production of the tumor itself and is related to a specific paraneoplastic phenomenon [8].

The biology of the extramedular relapse in patients with ALL is not yet known but its presence is always proved by biopsy and immunohistochemistry. It is supposed that the tropism and the invasion of blast cells depend on: proangiogenic /VEGF, bFGF/ [9] cytokines and chemokines in the serum, abnormal expression of surface adhesion molecules and cytokine receptors. Roman Crazzolara et al were the first to report increased expression of chemokine receptor type 4 /CXCR4/ on leukemic cells in patients with extramedular organ infiltration [10, 11]. CXCR4 is expressed by haemopoietic cells, tissue-committed stem cells, renal tubular epithelium [11, 12, 13] and is found in 23 different type of carcinoma [14, 15]. The interactions between stromal derived factor-1 /CXCL12/ - CXCR4 are very important for the cell chemotaxis, survival, proliferation as well as for the retention of the leukemia cells in the bone marrow [11, 12]. On the other hand CXCR4 expression can be stimulated by hypoxia-inducible factor 1 /HIF-1/, the latter being activated in low oxygen concentration [14, 16, 17].

The case reported in our article is most probably one of minimal residual disease accomplished at the end of the induction treatment. Due to different tissue penetration of the cytotoxic drugs the presence of lymphoblasts below the threshold of detection could be assumed. In time these cells migrate through the vascular endothelium of the kidneys and proliferate. This leads to increased size of the kidneys because of infiltration with leukemic cells, renal ischemia followed by expression of HIF-1α in the renal tubule, increased production of EPO and secondary polycythemia [18].

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