An extremely rare lineage switch from T-cell lymphoblastic lymphoma into B-cell acute lymphoblastic leukemia at relapse

Niezwykle rzadki przypadek konwersji T-komórkowego chłoniaka limfoblastycznego w ostrą białaczkę limfoblastyczną w nawrocie

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ABSTRACT

Lymphoblastic leukemia/lymphoblastic lymphoma (ALL/LBL) is a neoplasm of precursor B or T-cells. These neoplastic cells may infiltrate bone marrow and peripheral blood (acute lymphoblastic leukemia) or their presence is confined to nodal or extranodal sites with only minimal evidence of blood and bone marrow involvement (lymphoblastic lymphoma). Herein, we report a male patient with infrequent neurological manifestation of T-LBL who failed autologous hematopoietic stem cell transplantation (AHSCT). A lineage switch from T-cell lymphoblastic lymphoma into B-cell acute lymphoblastic leukemia was observed at relapse and this phenomenon has not been described so far. Our case demonstrates difficulties which may occur in diagnosis and treatment of LBL/ALL. It should be underlined that neurological deficits resulting from spinal cord compression may be the first symptom of lymphoma. A switch within the lymphoblastic line may occur but it is an extremely rare finding. Its pathogenesis remains unclear, therefore further studies are highly required.

Key words: T-cell lymphoblastic lymphoma; B-cell lymphoblastic leukemia; lineage switch

Słowa kluczowe: T-komórkowy chłoniak limfoblastyczny, B-komórkowa białaczka limfoblastyczna, konwersja

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Introduction

Acute lymphoblastic leukemia/lymphoblastic lymphoma (ALL/LBL) is a neoplasm of lymphoblasts committed to the T-cell (T-ALL/T-LBL) or B-cell lineage (B-ALL/B-LBL). In LBL, lymphoblasts are found in nodal and extranodal sites whereas they involve bone marrow and blood in patients with ALL [1]. Rarely, the phenomenon called lineage switch may occur, in which the leukemic cell lineage at diagnosis converts to another lineage at relapse and most patients have the conversion from acute myeloid leukemia (AML) to ALL [2]. The long-term results after conventional chemotherapy are unsatisfactory and therefore both autologous (AHSCT) and allogeneic hematopoietic stem cell transplantations (alloHSCT) should be considered for high risk ALL/LBL [3]. Moreover, alloHSCT should be introduced in second and subsequent remission regardless of risk group [4, 5]. Herein, we report a 35-year-old male who was initially diagnosed with T-LBL with atypical clinical presentation as a tumor mass in his cervical spine. He went into remission after chemotherapy and AHSCT. One year later he relapsed as B-ALL and eventually underwent alloHSCT from his HLA-matched sibling.

Case report

A 35-year-old male was admitted to our department on May 2009 with diagnosis of T-LBL. One year before a previously healthy male started to complain of acute left shoulder pain, numbness of the lower limbs, progressive muscle weakness and dysuria. He was referred to the Neurological Department. On admission physical examination revealed incoordination and four limb weakness. No cranial nerve deficits were observed. He became paraplegic in next few days. Magnetic Resonance Imaging (MRI) of the central nervous system (CNS) showed tumor mass which infiltrated the cervical spine. Due to progressive paraparesis, an emergency treatment consisting of corticosteroids (CS) was introduced despite the lack of histological examination. CS have been continued for three mon-

ths and this therapy resulted in complete resolution of neurological deficits. A repeated MRI of the CNS showed no abnormalities. CS have been slowly tapered. Five months later he noted nodular skin lesions in his back. Similar lesions have been also found in upper and lower limbs. On physical examination an increased left inguinal lymph node was detected. Positron emission tomography (PET) scan showed increased glucose uptake in the left groin and in the posterior superior iliac crest. Histological examination of the excised lymph node was consistent with the diagnosis of T-LBL. Immunophenotyping of tumour cells was following: CD1a-, CD2-, cCD3+, CD4+, CD5-, CD7+, CD8-, CD10-/+, Tdt+, CD99+, CD34+, CD79a+, cyclinD1-, CD23-, CD20-, Ki67-100%. Biopsy of the skin lesion showed an infiltration consisting of lymphoblasts of T-cell origin.

On admission to our Hematological Unit the patient was in good condition overall. Hemoglobin (Hgb) concentration and platelet count (PLT) were normal. White blood cell (WBC) count was 6.6×10^9/L with 73% of neutrophils, 20% of lymphocytes and 7% of monocytes. No blast cells were found in peripheral blood. Serum lactate dehydrogenase (LDH) activity, C-reactive protein (CRP) and B_2-microglobulin (B_2M) concentrations were within normal range. Bone marrow aspirate and trephine biopsy showed no abnormalities. Cytogenetic examination revealed diploid male karyotype and molecular studies were not performed.

CT scan of the thorax and abdomen revealed no lymphadenopathy. Cerebrospinal fluid was also normal. Patient received several cycles of intensive chemotherapy which consisted of CS, anthracycline, vinca alkaloid, cyclophosphamide, cytarabine and methotrexate with complete resolution of skin lesions and lymphadenopathy.

Due to aggressive nature of lymphoma he was offered AHSCT. As a conditioning patient received CAV regimen (cyclophosphamide, etoposide and cytarabine). He was transplanted with 6.63×10^8/kg of nucleated cells including 1.03×10^6 of CD34+ cells. Bone marrow regeneration was following: absolute neutrophil count (ANC) $>0.5\times10^9$/L on day +17 and PLT count $>50\times10^9$/L on day +20. Post-transplant period was free of severe complications. One year later patient was hospitalized in our Unit due to durable lumbosacral pain and night sweats. Blood tests were normal whereas marrow aspiration revealed 95% of blast cells resembling lymphoblasts. Immunophenotyping of blast cells was as follows: CD10+, CD19+, CD79a+, Tdt+, HLA-DR+. The diagnosis of B-ALL (common) was established. Cytogenetic study reveled diploid karyotype and molecular assays did not detect BCR-ABL and MLL-AF4 fusion proteins. Patient was started chemotherapy and achieved complete hematological remission after first induction course. He had matched sibling donor and therefore he was proceeded to transplant procedure. Conditioning consisted of cyclophosphamide and TBI (12Gy). Graft versus host disease (GVHD) prophylaxis included methotrexate and ciclosporin. The source of stem cells was granulocyte-colony stimulating factor (G-CSF)-mobilized peripheral blood. The patient was transplanted with 6.1×10^8/kg of mononuclear cells including 3.78×10^6 of CD34+ cells. Post-transplant period was complicated by skin changes consistent with graft versus host disease (GVHD) but promptly resolved after CS introduction. Currently, one year after transplant, patient remains in complete remission with no signs of GVHD.

Discussion

T-lymphoblastic lymphoma frequently presents as a mediastinal mass, however it may involve any lymph node and extranodal site. CNS may be involved although presentation at this site without nodal involvement is rare [1]. It is estimated that less than 10% of patients with T/B-ALL have CNS involvement at presentation [6,7]. It may have different clinical manifestations, e.g. headache, exophtalmus or unilateral 7th nerve paresis (Bell's palsy) [7]. However, spinal cord lesion as a first disease manifestation of LBL/ALL is rarely seen [8]. It was reported that spinal cord compression may mask the onset of B-cell diffuse large B-cell lymphoma, T-cell lymphoma and lymphoblastic lymphoma [9]. It should be mentioned that our patient developed neurological deficits without any other symptoms of lymphoma. Mediastinum and other nodal sites were free of disease. CS were given as a emergency treatment and this resulted in prompt resolution of neurological deficits. Lumbar puncture was not performed at that time and cerebrospinal fluid (CNS) was not evaluated towards the presence of lymphoblasts. The rapid introduction of CS did not allow to carry out proper diagnostic procedure. We may only suspect based on the further course of the disease that the presence of tumor mass in the cervical spine in our patient was consistent with the diagnosis of lymphoma, however tissue biopsy for histological study was not obtained.

It is estimated that about 7% of acute leukemias may demonstrate the phenomenon of lineage switch. Most cases have shown the conversions from ALL to AML and they have been reported mostly in children [2,10]. There was only single published data on lineage switch from AML to ALL [10, 11]. It was found that in most reported cases the time from diagnosis to conversion from AML to ALL was about 1 year and all these patients achieved remission after lineage switch [11]. In contrary conversions from ALL to AML were

resistant to chemotherapy [10]. Herein, we present a patient who developed an extremely rare lineage switch from T-cell lymphoblastic lymphoma into B-cell lymphoblastic leukemia at relapse and this phenomenon hasn't been described so far. It should be underlined that the diagnosis of T-LBL was confirmed by two independent and experienced pathologists based on lymph node and skin specimens. The pathogenesis of lineage switch remains unexplained, however some hypotheses were proposed. One of them assumes that the uncommitted progenitor cells originally have both myeloid and T- or B-lymphoid markers and later they maturate and differentiate toward the other lineage losing one lineage marker [12]. Another mechanism relates to prior chemotherapy which may eradicate the predominant leukemic clone and thereby causing the proliferation of subclones with different phenotype [11, 13]. In every case of lineage switch we should also consider the possibility of secondary neoplasia due to prior therapy. However in our patient there are some arguments against this theory. The interval between treatment and conversion was relatively short (1 year) and patient received agents which are not considered to be highly leukemogenic except cyclophosphamide at consolidation and conditioning. Moreover, we did not find any chromosomal abnormalities at relapse, particularly those involving chromosomes 5 and 7 which preferentially occur at transformation [10].

In conclusion, our case demonstrates difficulties which may occur in diagnosis and treatment of LBL/ALL. It should be underlined that neurological deficits resulting from spinal cord compression may be the first symptom of lymphoma. A switch within the lymphoblastic line may occur but it is an extremely rare finding. Its pathogenesis remains unclear, therefore further studies are highly required.

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