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T Lymphoblastic Leukaemia with an Unusual Burkitt Lymphoma Morphology – A Case Report

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ABSTRACT

Precursor T-cell acute lymphoblastic leukaemia (T-ALL)/lymphoma (T-LBL) is a neoplasm with cytological features that include blast cells of medium size, high nuclear cytoplasmic ratio and inconspicuous nucleoli, which are usually TdT (Terminal Deoxynucleotidyl Transferase) positive and variably express T-cell markers. We report a case of T-ALL with atypical cytological presentation which showed lymphoblasts with homogenous nuclear pattern, larger amounts of cytoplasm with vacuoles and prominent nucleoli. A 56-year-old male was hospitalized due to high fever and kidney infection. Further examination confirmed anemia, thrombocytopenia, normal level of white blood cells and high level of lactat-dehydrogenase (LDH). Bone marrow aspiration revealed 87% and peripheral blood 41% of lymphoblasts with cytoplasmic vacuoles which suggested Burkitt lymphoma (BL) morphology. Patient's karyotype showed no chromosomal aberrations. Identification of immunophenotype discovered cells which were CD2 and CD3 positive and CD20 negative with focal acid phosphatase activity in 67% of blasts. This excluded Burkitt lymphoma and led to diagnosis of T-ALL. The patient was submitted to two cycles of chemotherapy, autologous stem cell transplantation, and intrathecal chemotherapy, but he died after 10 months because of disease complications (lung aspergillosis and pleural effusion). Our case report showed how morphology alone can be misleading and sometimes is not enough in diagnosing ALL. Beside morphologic criteria, setting correct diagnosis depends on identification of immunophenotype by flow cytometry and cytogenetic-molecular abnormalities. Further improvements in the molecular definition of ALL subtypes, development of new and targeted drugs will improve patient's outcome and prognosis.

Key words: acute lymphoblastic leukaemia, immunophenotype, flow-cytometry, cytological features

Introduction

The differential diagnosis between T-ALL and other B-cell malignancies is possible only by immunophenotype. T-ALL shows a quite variable cytological pattern ranging from monomorphous, medium size cells with high nuclear cytoplasmic ratio to large cells with prominent nucleoli. Cytoplasmic vacuoles and »starry-sky« effect are occasionally seen. The number of mitotic figures is reported to be higher in T-ALL than B-ALL¹.

T-ALL is clinically usually presented with high leukocyte number and T-LBL with large mediastinal mass and pleural effusions^{1,2}. T-ALL has poor prognosis especially in older adults with higher blood cell counts³. Complications, such as bacterial sepsis and opportunistic infections with Cytomegalovirus (CMV), Candida, Pneumo-

cystis carinii can occur at any time during course of treatment⁴. Meningeal involvement is also common. We present a case of T-ALL with leukaemic manifestation of disease and cytological features which might suggest Burkitt lymphoma. The final diagnosis of T-ALL was made by identification of cell immunophenotype.

Case Report

A 56-year-old male was first hospitalized at the beginning of July 2008 because of high fever and kidney infection. Laboratory results showed normal white blood count – WBC ($4.07 \times 10^9/L$), anemia (red blood count – RBC

$3.40 \times 10^{12}/L$, hemoglobin 96 g/L), thrombocytopenia (platelet count $8 \times 10^9/L$) and high level of LDH (1512 U/L). The patient was submitted to bone marrow aspiration. The smears revealed hypercellular bone marrow with 87% and peripheral blood with 41% of lymphoblasts whose morphology showed round shaped nuclei, homogeneous nuclear pattern, mitoses and cytoplasmic vacuoles which suggested Burkitt lymphoma morphology (Figure 1). Immunocytochemistry yielded positive reaction to CD2 in 93% of blasts (Figure 2) and CD3 (Figure 3), however negative reaction to CD 20 and TdT. These results excluded the B-cell origin of the disease. Blasts showed negative cytochemical reaction to myeloperoxidase (MPO), nonspecific esterase (ANAE), and Periodic Acid Schiff (PAS), while acid phosphatase revealed positivity in 67% of blasts (Figure 4). On flow cytometry, the phenotype of blasts was cytCD3+, CD2+, CD5+, CD7+, CD1a+, CD4+/-, CD8+/-, CD10-, CD3-, TdT-. Based on the morphology, cytochemical characteristics and immunophenotype, it was considered a case of T-ALL. On the basis of banded chromosomes and fluorescent in situ hybridization (FISH), cytogenetic analysis showed no abnormalities. Bone marrow biopsy was also performed and confirmed the diagnosis of T-ALL. He received induction chemotherapy Hyper – CVAD protocol (cyclophosphamide, vincristine, adriamycin, dexamethasone). In October 2008 the patient was admitted for another chemotherapy treatment, but the recovery was compli-

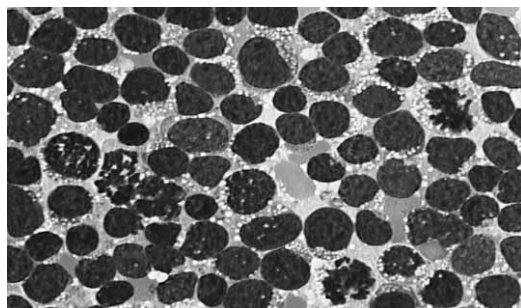


Fig. 1. Lymphoblasts in bone marrow showing round shaped nuclei, homogenous nuclear pattern, mitoses and cytoplasmic vacuoles (May-Grünwald-Giemsa, $\times 1000$).

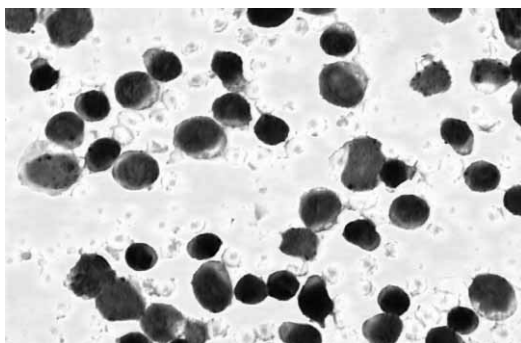


Fig. 2. Bone marrow lymphoblasts showing CD2 positivity on immunocytochemical stains (LSAB, $\times 1000$).

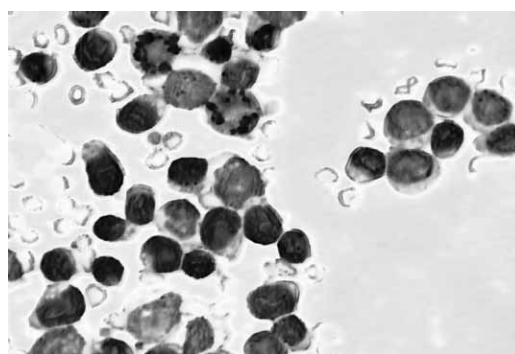


Fig. 3. Bone marrow smear showing lymphoblasts which are CD3 positive on immunocytochemical stains (LSAB, $\times 1000$).

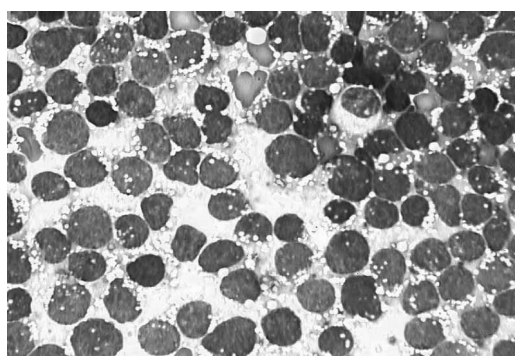


Fig. 4. Lymphoblasts in bone marrow showing focal acid phosphatase activity (cytochemistry, $\times 1000$).

cated by high fever and pancytopenia. In November 2008 the patient was submitted to autologous stem cell transplantation. Despite these efforts, he went into relapse and two months later the bone marrow smear revealed the presence of 27% of lymphoblasts. Evidence of meningeal involvement was documented by lumbar puncture and his condition gotten worse in spite of intrathecal chemotherapy. Laboratory results in March 2009 showed anaemia, thrombocytopenia and leukocytopenia. In May 2009 cytology confirmed another relapse of disease and revealed 62% of blasts in peripheral blood and 63% of blasts in bone marrow. The patient deceased due to disease complications, lung aspergillosis and pleural effusion.

Discussion and Conclusion

T-ALL/LBL is a neoplasm committed to the T-cell lineage. It comprises about 20–25% of adult cases of ALL and about 85–90% of LBL. The aetiology is unknown¹. Although some studies indicate that many patients can be cured with chemotherapy alone², T-ALL/LBL is still a disease with unfavorable prognosis with median survival of about 12 months⁴. The use of terms leukaemia/lymphoma is arbitrary depending on blood and bone marrow involvement. If patient presents with a mass lesion and 25% or fewer lymphoblasts in the marrow, the term lymphoma is preferred¹. The aetiology of these tumors is un-

known, but it is shown to be associated with HTLV1 (human T-cell leukaemia virus type 1) infection in parts of the world where the virus is endemic like Japan, South America, parts of Africa⁴⁻⁷. Infection usually remains latent for decades, and only 3–10% of infected individuals develop leukaemia⁴. The treatments of T-ALL and Burkitt lymphoma are generally different and BL shows better prognosis than T-ALL¹.

The present case was unusual because cytologically he was presented with lymphoblasts whose morphology might suggest Burkitt lymphoma/leukaemia. Lymphoblasts in T-ALL/LBL (L1, L2) are usually cells of medium size with high nuclear cytoplasmic ratio^{2,5}. The cell size and morphology vary from small blasts with scant cytoplasm, condensed nuclear chromatin and no evident nucleoli to larger blasts with moderate amounts of light-blue, grey cytoplasm, finely dispersed chromatin and prominent nucleoli^{1,8}. The nucleus shape can be round, irregular or indented. Lymphoblasts in Burkitt lymphoma are medium-size cells whose nuclei are round with homogeneous nuclear pattern and centrally placed nucleoli. The cytoplasm is deeply basophilic and contains numerous lipid vacuoles^{1,2}. Immunophenotypic features of T-ALL/LBL include TdT positivity and expression of

CD1a, CD2, CD3, CD4, CD5, CD7 and CD8 antigens¹. CD10 may also be positive and those patients are more likely to achieve remission³.

When our patient was submitted to the first bone marrow aspiration, smear revealed blast morphology typical for Burkitt lymphoma. Therefore we expected markers positive for B-cell lineage. In spite of our expectation, CD20 turned out to be negative and so were cytochemical reactions such as PAS, MPO and ANAE which excluded myeloid and B-cell origin of disease. Blasts revealed CD2 and CD3 positivity (Figure 3) on immunocytochemical staining along with acid phosphatase activity. Differential diagnosis of T-ALL includes B-ALL, acute myeloid leukaemia¹ which was excluded by immunophenotype and cytochemical analysis. This confirmed our suspicion that patient's diagnosis was T-ALL in spite of cell morphology which suggested Burkitt lymphoma. Our case report showed how morphology alone can be misleading. It points out that today the French-American-British (FAB) distinction of L1, L2 and L3 morphologies is no longer relevant. Identification of the immunophenotype has become a major part of diagnosing ALL⁵.

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T LIMFOBLASTIČNA LEUKEMIJA SA NEUOBIČAJENOM MORFOLOGIJOM BURKITOVOG LIMFOMA – PRIKAZ SLUČAJA

SAŽETAK

Prekursorska T-akutna limfoblastična leukemija/limfom (T-ALL/LBL) je bolest morfološki karakterizirana srednje velikim limfoblastima s visokim omjerom jezgre i citoplazme i diskretnim nukleolima. Limfoblasti su pretežno TdT (Terminalna Deoksinukleotidil Transferaza) pozitivni uz različito izražavanje T-staničnih biljega (CD1a, CD2, CD3, CD4, CD5, CD7 i CD8). Prikazujemo slučaj T-ALL-a atipične citološke slike s limfoblastima, homogene strukture kromatina, izraženih nukleola te izrazito vakuolizirane citoplazme. 56-godišnji muškarac je hospitaliziran zbog vrućice i infekcije urotakta. Dodatne pretrage pokazale su anemiju i trombocitopeniju te visoku razinu laktat-dehidrogenaze (LDH) uz uredan broj leukocita. U punkatatu koštane srži nađeno je 87% a u perifernoj krvi 41% limfoblasta izrazito vakuolizirane citoplazme, što je sugeriralo morfološkiju Burkittovog limfoma (BL). Kariotip nije pokazao kromosomske aberacije. Imunofenotipski blasti su bili CD2 i CD3 pozitivni a CD20 negativni, s fokalnom citokemijskom pozitivnošću kisele fosfataze u 67% stanica. Na osnovu toga je isključen Burkittov limfom te je postavljena dijagnoza T-ALL-a. Na-

kon dva ciklusa kemoterapije pacijent je podvrgnut autolognoj transplantaciji koštane srži i intratekalnoj kemoterapiji. Unatoč provedenoj terapiji, bolesnik umire nakon 10 mjeseci zbog komplikacija bolesti (plućna aspergiloza i pleuralni izljev). Naš slučaj pokazuje kako ponekad sama morfološka slika nije dovoljna za postavljenje dijagnoze ALL-a. Osim morfoloških kriterija, za ispravnu dijagnozu neophodno je odrediti imunofenotip limfoblasta te prisutnost citogenetsko-molekularnih abnormalnosti. Budući napretci u molekularnim definiranjima ALL subtipova i razvoj novih ciljanih lijekova poboljšat će ishod i prognozu pacijenata.