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Analysis of cytogenetic aberrations in a bone marrow of patients with malignant head and neck lymphadenopathies - A single center experience

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Abstract

Cytogenetic testing plays a major role in the diagnosis of different types of lymphadenopathies, assessment of survival prognosis, but also in the selection of adequate therapeutic strategies. Reports on aggressive head and neck lymphomas combining (cyto)genetics with pathology are rare, also lacking in Bosnia and Herzegovina. The aim of this retrospective study was to provide all chromosome aberrations data recorded in the group of patients diagnosed with malignant head and neck lymphadenopathy, and to analyze advantages and disadvantages of bone marrow (BM) cytogenetics analysis. Out of 819 patients who underwent cytogenetic analysis of BM in five years' time spread, chromosomal abnormalities were analysed in 54 karyotypes of patients with clinically suspected head and neck lymphadenopathy. We recorded 66,6% Non-Hodgkin lymphoma, 26% Hodgkin lymphoma, 3,7% Acute lymphoblastic leukemia and 3,7% Chronic lymphocytic leukemia. Chromosomal abnormalities in the karyotype were detected in 32 (59.2%) of a total of 54 patients. A normal karyotype was observed in 14 (26%) patients. In 8 (14.8%) subjects, it was not possible to perform cytogenetic analysis. The results of this research are representative in a term of the karyotype characteristics of patients with head and neck lymphoma. This is the first work of its kind in Bosnia and Herzegovina and will continue through a multicenter study in order to characterise the diagnostic and prognostic significance of cytogenetic abnormalities in lymphoma patients.

Introduction

Bone marrow (BM) analysis is an essential part of the routine diagnostics of different hematological diseases including malignant lymphadenopathies. Traditionally, BM samples have been evaluated by morphological examination, which includes immunohistochemical staining, flow cytometry and cytogenetic analysis (Cheson et al., 2014). Cytogenetic testing plays a major role in the diagnostic and prognostic assessment of lymphomas as well as for a selection of therapeutic strategies (Chaganti et al., 2000). According to the lymphoid neoplasms classification of World Health Organization (WHO), unique genetic markers are as important as clinical, morphological and immunophenotypic features (Swerdlow et al., 2016). Although conventional karyotyping is sometimes considered an outdated technique, it is still very powerful because it offers a broad view of the tumoural genomic landscape, including balanced (translocations or inversions) with breakpoints involving specific loci and unbalanced (trisomies, monosomies, duplications, and deletions) chromosomal changes (Poirel and Heimann, 2018). Lymphadenopathy is a term that refers to an abnormality in the size, consistency and number of lymph nodes. It occurs as a result of the reaction of the lymphatic tissue to various external and internal antigens, during which the number of lymphocytes and macrophages in the node increases. It can be localized, where the assessment of etiology is closely related to the region, depending on the lymphatic drainage pathways, or generalized, which is defined by the inclusion of two or more regions and points to a systemic disease. Head and neck lymphadenopathy account for 50% of all localized lymphadenopathies (Freeman, 2019). The differential diagnosis of cervical lymphadenopathy includes infections and neoplasms. Frequent triggers of lymphadenopathies are bacterial pharyngitis, dental abscesses, otitis media, infectious mononucleosis, toxoplasmosis, adenovirus infections. The most common malignant causes are Non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL) and Squamous cell carcinoma (SCC) of the head and neck. Many of them are characterized by chromosomal aberrations that are diagnostically and prognostically very specific (Cuceu et al., 2018).

There is a dilemma, whether the presence of chromosomal aberrations with histological involvement of the bone marrow originates from lymphoma cells or from the malignant transformation of the hematopoietic stem cell. There is also the question of the relevance of BM cytogenetic analysis in relation to analysis of lymph node biopsy sample as primary malignant tissue (Kim et al., 2013).

We aimed to retrospectively investigate the characteristics of chromosomal aberrations in the BM samples of patients with a malignant head and neck lymphadenopathy that underwent routine cytogenetic diagnostics at the University Clinical Center Tuzla (UCC Tuzla) in five years.

Material and methods

Patients

A medical history including sex, age, clinical examination results, histopathology, cytogenetics examination results, and specific location of lymphadenopathy was obtained from 819 patients, hospitalized at the UCC Tuzla, in the period from January 1, 2017 to December 31, 2021. Out of 819 patients, 54 were clinically suspected of head and neck lymphadenopathy and were selected for detailed analysis of karyotype. Of these, 28 were male and 26 female, ages 8-95, with a median age of 52 years.

Karyotyping

Analysis was done according to the standard protocol as a part of the work-up at the time when the initial diagnosis was established. A total volume of 0,5 to 2 mL heparinized BM sample in a test tube with 10 mL RPMI 1640 (Euroclone, Italy) was cultured at 37 °C for 24 to 48 hours. After exposing the culture to cytostatic and 0,56% KCl suspension, the metaphase cells were fixed with a mixture of methanol and acetic acid in relation 3:1. After harvesting, chromosome slides were prepared and G-banded. At least 20 metaphases per patient were completely analyzed. Pathological clone was defined as at least two of 20 analysed cells with the same structural aberration, three or more cells in a case of numerical changes. A case with only one metaphase cell with an abnormal karyotype, was considered as a malignant clone if there were structural changes to be associated with lymphoma. The karyotypes were interpreted according to International System for Human Cytogenetic nomenclature 2016 (Mc Govan-Jordan et al., 2016).

Results and Discussion

A total of 54 patients with clinically suspected lymphadenopathy had BM involvement, as determined through histopathological examinations. Chromosomal aberrations were detected in 32 (59,2%) out of 54 analyzed BM samples. A normal karyotype was observed in 14 (26%) patients. In 8 (14.8%) patients, due to the lack of metaphases in the examined sample, it was not possible to perform cytogenetic analysis. Among the 32 patients with chromosomal aberrations in karyotype, 20 (62,5%) had structural, while 12 (37,5%) of them had numerical chromosomal changes. A total of 87 chromosomal aberrations were recorded in 25 different karyotypes (Table 1). Either alone or in combination with numerical, 34 structural changes were found. Their percentage representation is shown in Figure 1. We have found a large number of malignant lymphadenopathies in the examined patients group, and their percentage is shown in Table 2. Pathological karyotype was recorded in all analyzed cases with HL, CLL and ALL. We had 36 (66.6%) patients with NHL (Burkitt's lymphoma-BL, Small lymphocytic lymphoma-SLL, Follicular lymphoma-FL, Diffuse large B cell lymphoma-DLBCL, mantle cell lymphoma-MCL, B and T cell lymphoma BCL, TCL). Of these, 66.6% (24/36) patients had aberrations, 38.8% (14/36) had a normal karyotype, while in 22.2% (8/36) patients it was impossible to analyze the karyotype (Table 3).

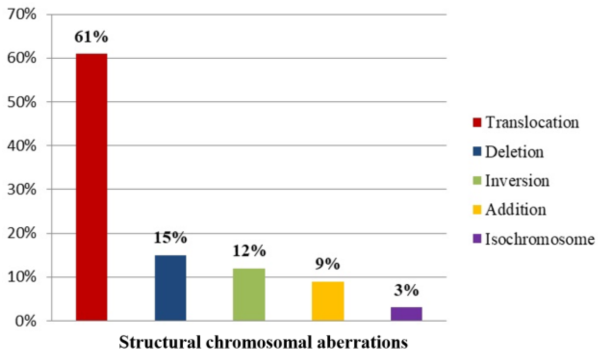

Figure 1. The frequencies of different structural chromosome aberration

The most common hematological malignancies worldwide are malignant lymphadenopathies. The NHL group is the most represented of them. The latest GLOBOCAN data in 2020 estimated 544000 new NHL cases diagnosed globally. Australia, New Zealand, Northern America, Northern and Western Europe have the highest incidence rates (>10/100 000 including both sexes). Incidence of HLs in 2018 ranged from 1.3 cases per 100,000 inhabitants in Romania to 6.6 in Greece, with the average at 2.7. In neighboring countries, Croatia and Slovenia, incidences are 2.2 and 2.3, respectively. On the other side, the last data from 2018 revealed that NHLs incidence ranged from 7.3 cases per 100,000 inhabitants in Romania to 25.8 in Slovenia and 12.8 in Croatia, with an average at 19.1 (EPFIA, 2020; Dyba et al., 2020; Thandra et al., 2021). Unfortunately, there is no available data for Bosnia and Herzegovina. Our study results showed, most lymphoma cases were

NHL, and DLBCL was the most common lymphoma type of NHL, followed by HL, AML, and CLL (Table 2). Pathological karyotype was recorded in all analyzed cases with HL, CLL and ALL. In the NHL patients, 66.6% (24/36) of them had aberrations, 38.8% (14/36) had a normal karyotype, while in 22.2% (8/36) patients it was impossible to analyze the karyotype.

The largest number of patients with detected chromosomal aberrations in the karyotype was in the FL group followed by DLBCL, SLL and HL (Table 3).

Table 1. Specific chromosomal rearrangements found in different lymphoma subtypes

No.	Chromosomal abnormality	No.of patients with chromosome aberrations	Lymphadenopathy
1.	92,XXXX;	1	HL
2.	96,XXYY,inc;	1	HL
3.	46,XY,t(6;9)(p23;q34)	1	HL
4.	46,XX,del(9)(q22),inv(9)(p12q13)	1	HL
5.	184, XXXXXXX;	1	B cell lymphoma
6.	46,XX,t(6;7)(p21,2;q36)	1	T cell lymphoma
7.	62,XY,+Y,+1,+2,+4,+6,+8,+11,+13,+13,+14,+15, +19,+20, +22,+22,+mar.	1	ALL
8.	55,XY,+3,+6,+8,+10,+14,+15, +18,+21x2	1	ALL
9.	46,XX, add(1)(q?)	1	CLL
10.	45,XX,der(3)t(3;17)(p11;q11.1), -5, -6, +8 ,inv(12)(p12q15), -17, +mar	1	CLL
11.	74,XY, inc	1	FL
12.	48,XY,+X,add(1)(q44),t(3;6)(q27;q24),+18	1	FL
13.	47,XX,+8 (1) 47,XY,+8 (2)	3	FL
14.	45,XY,-7	1	FL
15.	45,XY,der(18)t(18;22)(p10;q10),-22	1	FL
16.	47,XY,+mar	1	FL
17.	47,XX,+8/48,XY,+8,+13/46,XY	1	FL
18.	a)46,XX,inv(9)(p11q13)[1] b)46,XY,inv(9)(p11q13)[2]	3	FL DLBCL
19.	46,XX,t(1;6)(p?34;p?23),der(6)t(6;?)(p11;?),+der(?) (?;11),add(10)(p15), ?t(17;9;14)(q11.2;q13;q32), t(11;14)(q13;q32),t(15;?)(p11;?),-17,?del(19)(q23), inc.	1	DLBCL
20.	46,XX, t(2;7)(p23; p14)	1	DLBCL
21.	46,XX,t(2;3)(p23;q21)	1	DLBCL
22.	47,XY,del(14)(q23),+18	1	SLL

No.	Chromosomal abnormality	No.of patients with chromosome aberrations	Lymphadenopathy
23.	43,XX,-3, der(3)t(3;13)(q11.2;p10), t(6;8)(q10;p10),-13, del(17) (p11.2) ,add(19) (p13.3)	1	SLL
24.	46,XY,t(5;12)(p10;q10)	1	SLL
25.	42,X,-Y,-1,der(3)t(3;?)(p?;?),del(5)(q?14),-7,-9,-10,der(12)t(12 ;?)(q22;?),der(4) t(14;?)(q25 ;?),-15,-17,der(17)t(17 ;?) (p11.2 ;?),-18,der(19) t(19;?) (q13,4 ;?), i(21)(q10), +4mar, inc.	1	MCL
26.	46,XX,inv(12)(p13q15)	1	MCL
27.	45,XY,t(8;14)(q24;q32),-10	1	BL
28.	46,XY,t(8;14)(q24;q32)	1	BL

Abbreviations: HL, Hodgkin lymphoma; ALL, Acute lymphoblastic leukemia; CLL, Chronic lymphocytic leukemia; FL, Follicular lymphoma; DLBCL, Diffuse large B cell lymphoma; SLL, Small lymphocytic lymphoma; MCL, MCL, mantle cell lymphoma; BL, Burkitt's lymphoma.

ALL is one of the least prevalent diseases (3.8%), and has the largest number of aberrations on individual chromosomes. All aberrations in the ALL karyotype are numerical.

The clinical significance of cytogenetic analysis is based on the observation and identification of chromosomal aberrations associated with specific hematological diseases (Sandberg, 1991; Vundinti and Ghosh, 2011). Chromosomal aberrations are an important prognostic factor in the diagnosis, prognosis, therapy management and monitoring of hematological malignancies (Grimwade et al., 1998). They provide information on chromosomal changes that introduce the cell into a malignant state and lead to disease progression, the acceleration phase and fatal blast transformation.

It is true that conventional cytogenetic study has low resolution, but this most comprehensive method for chromosome analysis is still in use worldwide in many genetics laboratories, so it is readily applicable in routine practice. The advantages of this genetics test include its ability to detect abnormalities in proliferative clones and to provide information about whole chromosomes.

The disadvantages of cytogenetic analysis using lymph node biopsy samples include very difficult laborious tissue preparation, the presence of poor chromosome morphology, a lack of metaphase cells, and possible contamination. The use of BM samples is easily applicable. There is also an increased sensitivity for detecting BM involvement in lymphoma proving the presence of chromosomal abnormalities found in the BM (Campbell, 2005). That is the reason why we apply BM cytogenetic analysis as a standard process of lymphoma staging. In this research, we analyzed retrospective data from patients suspected to have head and neck lymphadenopathy to record all chromosome abnormalities and to analyze possible advantages and disadvantages of BM cytogenetics analysis.

A total of 54 patients (100%) had bone marrow involvement, as determined through histopathological examinations. Our data revealed,

Table 2. Percentage of lymphadenopathy in the examined group of patients

Lymphadenopathy		(%)
Chronic lymphocytic leukemia, CLL		3,8
Acute lymphoblastic leukemia, ALL		3,8
Hodgkin lymphoma, HL		26
Non Hodgkin lymphoma	Diffuse large B cell lymphoma, DLBCL	20,37
	Follicular lymphoma, FL	24,07
	Burkitt's lymphoma-BL,	3,8
	Small lymphocytic lymphoma, SLL	7,4
	Mantle cell lymphoma, MCL	3,8
	T cell lymphoma, TCL	1,8
	B cell lymphoma, BCL	1,8
	Anaplastic large cell lymphoma, ALCL	1,8
	T cell histiocyte-rich large B cell lymphoma, TCHRLBCL	1,8

59.2% of the total patients exhibited one or multiple chromosomal abnormalities. Considering that all the patients in our research were immunohistochemistry positive the detection rate of cytogenetic abnormalities in bone marrow specimens is not negligible. Karyotype analysis is based on at least 20 cells, so the number of metaphase with chromosomal abnormalities does not represent the real proportion of pathological cells within the bone marrow. A small pathological clone may have a proliferative advantage over normal cells, so conventional cytogenetics may be a sensitive method in its detection (Steensma et al., 2003).

The literature data indicates that the interpretation of data from patients with a single abnormality can be difficult because the abnormality does not necessarily originate from lymph node tissue cells (Lasan-Trčić et al., 2013). Our study results showed, single aneuploidies presented only in 15,36% (5/32), which indicates that a single aneuploidy in karyotype cannot be the definitive evidence for the presence of lymphoma cells. Therefore, the presence of a single chromosomal numerical abnormality cannot be a poor prognostic factor. Single numerical abnormalities also presented a lower concordance rate with histologic bone marrow involvement. We found 3 FL patients with trisomy 8, also with histologic evidence of bone marrow involvement. The previous studies reported that AML, MDS, ALL and also solid tumors including colon, breast, and head and neck cancers are associated with isolated +8 (Mitelman et al., 2022). We noticed also monosomy 7, found in one FL case. The researchers reported that loss of chromosome 7 is a recurrent non-random abnormality in AML, and is associated with prior exposure to carcinogens or leukemogenic agents, and with poor prognosis (Dabaja et al., 1999). In one MCL case, we found loss of chromosome Y, as a part of the complex karyotype (Table 1; No 25). This chromosome abnormality even if is it not the only aberration in the karyotype cannot be an indicator of lymphomagenesis because the loss of chromosome

Y is well known normal age-related phenomenon in older males (UKCCG, 1992).

Some single structural chromosomal aberrations can participate in a primary event in the genesis of lymphoma. In this research, single structural abnormalities such as t(5;12)(p10;q10),t(2;3)(p23;q21),t(2;7)(p23;p14),t(6;7)(p21,2;q36),t(6;9)(p23;q34),t(14;18)(q32;q21) or inv(12)(p13q15) can be reasonably regarded as originated from lymphoma cells considering their well-known chromosomal loci and their concordant pathohistologic BM results. The distribution of the structural chromosomal aberrations we found in this research is shown in Figure 1. It is obvious that we researched a small number of samples, so it is hard to make a reliable conclusion about the significance of these single chromosome aberrations in this work.

Table 3. Percentage of aberrant karyotypes in a diagnosed lymphadenopathy

Lymphadenopathy	No.of patients with an established diagnosis	No.of patients with chromosomal aberrations	No.of patients with a normal karyotype	NO karyotype analysis
ALL	2 3,8%	2 3,8%	-	-
CLL	2 3,8%	2 3,8%	-	-
HL	14 26,0%	4 7,4%	8 14,8	2 3,8%
FL	13 24,0%	10 18,5%	3 5,6%	-
DLBCL	11 20,4%	5 9,3%	2 3,%	4 7,4%
MCL	2 3,7%	2 3,8%	-	-
B cell lymphoma	1 1,8%	1 1,8%	-	-
T cell lymphoma	1 1,8%	1 1,8%	-	-
BL	2 3,7%	2 3,8%	-	-
SLL	4 7,4%	3 5,6%	1 1,8%	-
THRLBCL	1 1,8%	-	-	1 1,8%
ALK ALCL	1 1,8%	-	-	1 1,8%
Total	100.0%	32 59,3%	14 26%	8 14,8%

Abbreviations**:** HL, Hodgkin lymphoma; ALL, Acute lymphoblastic leukemia; CLL, Chronic lymphocytic leukemia; FL, Follicular lymphoma; DLBCL, Diffuse large B cell lymphoma; SLL, Small lymphocytic lymphoma; MCL, MCL, mantle cell lymphoma; BL, Burkitt‘s lymphoma; THRLBCL, T-cell/histiocyte-rich large B-cell lymphoma; ALK ALCL, Anaplastic large cell lymphoma ALK positive.

When these abnormalities in the BM are detected, it is recommended to correlate cytogenetics findings with other diagnostic tests, especially with histopathology and flow cytometry analyses. One is well known, these patients with single chromosome aneuploidies, in comparison with normal karyotype cases, had less aggressive disease (Kim et al., 2013).

Some of these chromosomal aberrations observed in this study were single and random, while some of them were non-random and recurrent, which indicates that they may belong to the lymphomagenesis pathway (Bea et al., 2005). High frequencies of many aberrations found in the malignant lymphadenopathy have been previously reported including rearrangements at 1q21-23, 2p12, 3q27, 8q24, 11q23-q25, 14q32, 18q21-q23 and many others (Kim et al., 2013; Mitelman et al., 2022). The most common numerical aberrations that are encountered in the malignant lymphadenopathies are trisomy 3, 7, 8 and 18 (Campbell, 2005). The chromosome bands 2p23, 6p23 and 14q32/IGH, which were the most common rearrangements in the present study, are frequently observed in B-cell lymphomas (Fleischman et al., 1989, Lasan-Trčić et al., 2013). For the comparison, chromosomal segments the most related with the oncological implications in head and neck SCC are: 1p, 3p, 4q, 5q, 7q, 8p, 10q, 11q, I8q, 20p. The frequent cytogenetic alterations include 3q, 8q, 9q, 20q, 7p and 11q13 rearrangements and losses of 3p, 9p, 21q, 5q, 13q, 18q, 18p (Pandey and Mishra, 2007; Mitelman et al., 2022).

Diagnosis of lymphoma can be made using bone marrow samples according to the cytogenetics patterns, but if we want to confirm the diagnosis and define lymphoma subtypes, immunohistochemistry, flow cytometry, FISH and additional laboratory tests using lymph node biopsy samples may be more helpful. The number of pathological karyotypes is particularly small in cases of extramedullary lymphomas in which bone marrow infiltration did not occur. In this way, it is more difficult to reach pathological cells. In these cases, the findings may be falsely negative. In comparison, this research revealed a large portion of bone marrow involved samples with a normal karyotype (Table 3). Data from other research indicate that even in patients with lymph node infiltration, the pathological cells also may be obscured by the more abundant normal hematopoietic cells (Čolović and Janković, 1999; Aurer et al., 2007; Kim et al., 2013).

Conclusion

The results of this research are representative in a term of the karyotype characteristics of patients with head and neck lymphoma who gravitated to UCC Tuzla. This is also the first work of its kind in Bosnia and Herzegovina that describes the cytogenetic characteristics of bone marrow cells that are involved in lymphomagenesis and represents initial cytogenetics investigations of malignant lymphoma using bone marrow specimens. Furthermore, it is necessary a larger sample size analysis to characterize and confirm our results. It would be also necessary to conduct a multicenter study to characterise the diagnostic and prognostic significance of cytogenetic abnormalities in lymphoma patients.

Conflict of interest

Authors declare no conflict of interest.

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