Oncohaematology

HIV-associated non-Hodgkin lymphoma

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Summary: In this article the clinical features, diagnosis and treatment of HIV-associated non-Hodgkin lymphoma are described. According to the WHO Classification (2008) most of the HIV-associated lymphoid tumors are diffuse large cell lymphoma. HIV-associated lymphomas are characterized by rapid growth of the tumor; occurrence of B symptoms in these patients is most commonly determined. Bone marrow affection is diagnosed in 25-40% of patients; gastrointestinal tract affection is diagnosed in 26% of patients. Central nervous system in involved into the tumor process in 12-57% HIV-infected patients. Patients with HIV-associated lymphoma and active immune function have a lower risk of infectious complication; therefore, an optimal and effective chemotherapy can be prescribed.

Key words: HIV-associated lymphoma, treatment, diagnosis.

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In accordance with the new classification of tumors of lymphoid tissue (WHO 2008), HIV-associated lymphomas are distinguished as a separate sub-group named "Lymphoproliferative disease associated with immunodeficiency" [1,50]. The research results advocated that immunodeficiency virus (HIV) significantly increases the risk of chronic lymphoproliferative disorders such as non-Hodgkin lymphomas (NHL) and Hodgkin's lymphoma (HL). It is epidemiologically demonstrated that HIV-infected patients have from 60 to 200-fold growth of NHL incidence. The number of NHL in HIV patients is increasing by 5.6%

annually as compared to 0.015% in general population. The risk of NHL or primary central nervous system lymphoma in HIV-infected patients is closely associated with the quantity of CD4. A research delivered an evidence that the incidence of NHL increased from 15.5 to 253.8 per 10,000 people per year, and the primary CNS lymphoma increased from 2 to 93.9 per 10,000 people per year among patients with more than 350 cells/mcl CD4 lymphocytes compared to those with fewer than 50 cells/mcl CD4 respectively [5].

Furthermore, it was argued that patients with lower CD4 quantity level are diagnosed with primary CNS lymphoma and primary lymphoma of exudates (PLE) more frequently while in HIV-infected patients with higher CD4 quantity level Burkitt's lymphoma and Hodgkin's lymphoma (LB) are diagnosed [10,32,50,55].

In lymphoid tissue cell ontogeny, most of the HIV-associated lymphoid tumors are diffuse large B-cell lymphoma (DLBCL), including primary CNS lymphoma. Burkitt's lymphoma (BL) in HIV-associated patients is diagnosed in 30-40% cases [1]. PLE, plasma-blast lymphoma and Hodgkin's lymphoma are much less likely to be diagnosed. Other subtypes of lymphoma, such as follicular lymphoma and peripheral T-cell lymphoma, may also rarely occur in this group of patients [1,55].

Pathogenesis of HIV-associated lymphomas

Pathogenesis of HIV-associated lymphoma involves a complex interaction of biological factors, such as the chronic stimulation with antigen, co-infection of oncogenic viruses, genetic abnormalities and deregulation of cytokines [22,35,39,50].

The chronic antigenicity stimulation that is related to HIV infection may first lead to increasing of the polyclonal B-cells quantity and, furthermore, likely to stimulate the emergence of monoclonal cells [18,55].

The increase of circulating free light immunoglobulin chains that can be a marker of polyclonal B-cell activation in patients with high risk of HIV-associated lymphoma has been recently established [31]. Actual researches seek to find the free light immunoglobulin chains which may be useful for detection of HIV-infected patients with high risk of lymphoma [31].

Most often, in about 40% of HIV-associated lymphomas, oncogenic Epstein-Barr virus (EBV) is detected [1,3,50]. Nearly all cases of primary CNS lymphoma and HL have EBV. In most HIV-associated PLE, the association of two EBV oncogenic viruses and herpes virus type 8 (HHV-8), found virtually in all patients, is detected [8].

EBV is determined in 30-50% of HIV-associated BL and in 50% of plasma-blast lymphoma (Table 1) [1,3,8]. EBV-positive HIV-associated lymphoma often express latent membrane protein 1 that activates cell proliferation by NF-kB activation path and induces hyperexpression *BCL2*, thereby, blocks apoptosis of tumor B-cells stimulating their survival [17,23,46].

Table 1
Association of oncogenic viruses in patient with HIV lymphoma

Histological variant	EBV +	HHV-8
DLBCL		
Centroblastic	30%	0
Immunoblastic	80-90%	0
Plasma-blast	More than 50%	80%
Primary Lymphoma of Exudates	100%	100
Burkitt's Lymphoma	30-50%	0
Primary CNS Lymphoma	100%	0
Hodgkin's Lymphoma	80-100%	0

Acceleration of cytokines, namely IL-6, IL-10 tumor necrosis factor-β, along with frequent aberrant somatic hypermutation of immunoglobulin genes reveal a role for immune stimulation in lymphooncogenesis in HIV-infected patients [1].

Polymorphism of chemokine paths also impacts the risk of HIV-associated lymphoma. For example, with HIV infection, stromal derived cells factor 1 variant 3'A doubles and, respectively, increases risk of NHL in heterozygote and homozygote by four times [43,55].

Molecular and genetic features of HIV-associated lymphoma

The studies identified a number of genetic abnormalities in HIV-associated lymphomas. A research by Carbone (2003) demonstrated that LB is associated with the activation of MYC gene. It is diverting that about 20% of HIV-positive DLBCL also have MYC translocation

[16,27]. BLC6 mutation occurs in 20% patients with HIV-associated lymphomas and centroblastic DLBCL and in 60% patients with HIV-associated lymphomas and PLE [24,25].

As a result of research, Lenz *et al* (2010) proved that the molecular profile of HIV-associated lymphoma is similar to DLBCL and LB of the HIV-negative patients [33].

Genes associated with a germinal centre of B-cell (GCB) DLBCL included germinal centre differentiation markers such as CD10 and BCL6 while genes associated with the activated B-cell (ABC) type of DLBCL contained IRF4/MUM1 [15].

Several studies have revealed that expression of *BCL2* gene was more than four times higher at ABC DLBCL than at DLBCL from GCB [2]. These results indicate that subtypes DLBCL GCB and ABC have derived from B-cells at various stages of differentiation. DLBCL with GCB arises from germinal centre of B-cells; DLBCL of ABC derives from post-germinal centre of B-cells at the stage of plasma lymphocyte differentiation.

Genetic analyses have shown that pathogenetic mechanisms at ABC and GCB DLBCL are different. DLBCL of GCB is exceptionally associated with translocation of t (14, 18) involving *BCL2* gene and immunoglobulin heavy chain gene, as well as amplification of c-rel locus of chromosome 2p. Furthermore, this lymphoma has amplification of oncogenic mir-17-92 of micro RNA cluster, deletion of tumor suppressors *PTEN* and frequent anomaly of *BLC6* gene [34,40].

Amplification of the oncogene *SPIB*, deletion of locus tumor suppressor *INK4a/ARF* and trisomy 3 are often determined at ABC DLBCL that leads to expression of abnormal *CARD11*, BCL10 and *A20*, that activates IkB kinase and NF-KB path of tumor lymphogenesis [17.34, 35.39].

Table 2 present histogenetic and genetic molecular features of lymphoma in HIV-infected patients depending on the histological origin of tumors.

Table 2

Features of HIV-associated lymphomas

		Histogenetic Markers (%)		Molecular genetic markers (%)				
Histogenetic origin	Histology	MUM1	Syn-1	BCL-2	BCL-6	P53	c-MYC	CD4 cells
Germinal (embryonic) Centre	Burkitt's lymphoma	<15	0	0	100	60	100	May be relatively well-preserved quantity
	DLBCL-GC	<30	0	0	>75	Rarely	0-50	Variable quantity
Post germinal Centre	DLBCL-ABC	100	>50	30	0	0	0-20	Usually low quantity
	Primary CNS lymphoma	>50	<60	90	<50	0	0	<50mm^3
	Primary lymphoma of exudates	100	>90	0	0	0	0	Variable quantity
	Plasma-blast lymphoma	100	100	0	0	Rarely	0	Variable quantity

Note: EBV Epstein-Barr virus; KSHV – Kaposhi's sarcoma-associated herpes virus; MUM1 – multiple myeloma-1; DLBCL - diffuse large B-cell lymphoma; GC – germinal centre; ABC – activated B-cell subtype.

Diagnosis of HIV-associated lymphomas [55]

A histological and immunohistochemical study of the material obtained by excision biopsy is the most important test for diagnostics.

In most cases, the histology of HIV-positive lymphoma is similar to those that develop in HIV-negative patients.

Histological features of HIV-associated lymphomas [1, 55]

Two histological variations are classified in HIV-associated DLBCL: centroblastic and immunoblastic. Centroblastic variant is about 25% of HIV-associated lymphomas; it is characterized by diffuse growth of large lymphoid cells with round or oval nuclei and prominent nucleoli. They often express markers of embryos follicle centre such as CD10 and BCL6; also, all tumor cells are CD20 positive, as a rule [9,50]. Immunoblastic variant of DLBCL contains more than 90% of immunoblasts and often exhibits traits of plasmacytoid differentiation [14,50,53]. This variant of DLBCL forms about 10% of all HIV-associated lymphomas. This tumor is CD10-negative, as it is a lymphoma

from post-follicular germinal centre of a lymph node. Frequently, positive expression in *MUM1/IRF4* and CD138/syndecan-1 markers is found at DLBCL immunoblastic type [9]. This tumor often has mitosis with high Ki-67/MIB-1 expression [36]. With immunoblastic lymphoma, the tumor cells may be CD20-negative due to co-expression of EBV.

Markers associated with activation, such as CD30, CD38, CD71, are often expressed at immunoblastic variant of DLBCL [10,50].

The tumor cell at PEL is a tumor of B-cell origin; however, tumor cells lacking expression of B-cell antigens, such as CD20 and CD79a. CD4, CD30, CD38, and CD138, are normally expressed and associated with KSHV/HHV-8 and EBV [30].

As a rule, with plasma-blast lymphoma, positive expression CD38, CD138 and MUM1/IRF4 antigens and also negative CD20 and CD 45 are diagnosed [53].

HIV-associated BL is divided into three separate subtypes: classic, plasmacydoid, atypical [50]. The classical type of BL is diagnosed in about 30% of all HIV-associated lymphomas. It morphologically resembles the classical BL of HIV-negative patients. Medium-size cells with abundant cytoplasm are typical for BL with plasmacytoid differentiation. It is more often observed in severe immunodeficiency. In other cases, the tumor cells have significant nuclear pleomorphism with smaller but more noticebly nucleous. In the past this type of BL was called atypical BL. All three types have very high mitotic indices with the expression of CD19, CD20, CD79a and CD10, and are negative for BCL2. EBV positive cases of BL range from 30% with classic BL and from 50% to 70% of BL cases associated with the second plasmacytoid differentiation [51]. Classic HIV-associated HL is largely represented by mixed-cell variant; EBV is detected in almost all cases of HL [51]. Notable that in the era of antiretroviral therapy a significant increase of nodular sclerosis of HL is registered due to the higher proportion of patients with high quantity of CD4 cells [6,30].

The research of gene expression is not used for the diagnosis of HIV-associated lymphoma. Although, in order to determine the origin of DLBCL, it is necessary to carry out the immunohistochemical studies using CD10, BCL6, and MUM1 [26]. In accordance with the latest diagnostic and prognostic algorithm, the additional study of GCET1 and FOXP1 markers is required [13]. Furthermore, according to the recent publications, the identification of *MYC*+ of tumor cells at DLBCL may

be used to determine the outcome of the therapy. It is argued that *MYC*-positive tumors poorly respond to the therapy with R-CHOP regime [16,26]. Thus, it is advisable to perform cytogenetic or FISH research of tumors in order to identify *MYC* translocations and prescribe the most efficient treatment.

Clinical features of HIV-associated non-Hodgkin's lymphomas

HIV-associated lymphomas are characterized by the rapid growth of the tumor; the presence of B-symptoms is most commonly detected in such patients (unexplained fever, night sweats, unexplained weight loss by more that 10% of normal bode weight). Bone marrow affection is diagnosed in 25-40% of patients; gastrointestinal tract affection is diagnosed in 26% of patients. Involvement of CNS in the tumor process in HIV-infected patients is determined in 12-57% of patients [11,53].

The complex of laboratory-instrumental examination for determination of the tumor process spread and detection of the prognostic group of patients with HIV-associated lymphoma is substantially similar to that of HIV-negative patients.

Diagnostic and prognostic role of positron emission tomography (FDG-PET) has been proved in patients with HIV-negative aggressive lymphomas. Nowadays, the role of FDG-PET in HIV-associated lymphomas is not well understood. Previous experience in evaluating FDG-PET in HIV-associated lymphoma is limited to the light retrospective analysis and requires further study. At conducting PET in patients with HIV-associated lymphomas, it is also necessary to perform differential diagnosis between tumor lesions, nodular reactive hyperplasia, lipodystrophy and infection [19,21].

Prognostic criteria for HIV-associated lymphomas

The International Prognostic Index (IPI) is a standard prognostic evaluation criterion in HIV-negative patients with DLBCL. However, the use of IPI in HIV-associated DLBCL is controversial. Several studies have shown that it is impossible to predict progression-free and common survival using IPI in patients with HIV-associated lymphomas [28,45].

Prognostic value in HIV-infected patients has a number of CD4 positive lymphocytes. It is proved that the patients with CD4 counts less than 100 cells/mcl are under high risk of serious opportunistic infections development and death. Furthermore, as noted before, patients with

severe immunosuppression are diagnosed with immunoblast subtype of DLBCL, which is more often ABC; they have worse results comparing to patients with immunocompetence, where GCB subtype is more common [21]. Although recently the studies proving that there is no association between the origin of the tumor's cells and the outcome of HIV-associated DBLCL [12,20,47].

CNS affection that has been increased in HIV-associated aggressive B-cell lymphomas also has unfavorable prognosis [1].

Treatment of HIV-associated non-Hodgkin's lymphomas

Treatment of HIV-associated lymphomas can be divided in two phases: before the antiretroviral therapy usage and after the widespread use of specific complex antiretroviral (ARV) therapy.

The results of treatment of HIV-associated lymphomas before the era of antiretroviral therapy were poor; the median of patient survival was average from 5 to 6 months and was mainly determined by the number of CD4 cells. These results were associated with the development of both hematological and non-hematological chemotherapy complications. In their study, Kaplan L.D. et al noted that high doses of cyclophosphamide correlated with poor patient survival [29]. Attempting to improve treatment outcomes and reduce the risk of infectious complications, a multicentre, randomize study was conducted; it compared the results of the therapy regime mBACOD at standard doses with reduced doses in 192 patients with HIV-associated lymphomas [29]. Table 3 shows in full answers that the survival median of comparing groups was not statistically different, whereas hematologic toxicity in the group of patients with low-dose of mBADOC regime was statistically lower. This led the authors to conclude that lower doses of chemotherapy were more preferable for HIV-associated lymphomas. However, the patients with low CD4-positive lymphocytes were involved in the study. In the era of widespread use of antiretroviral (ARV) treatment the number of patients with higher CD4 cells increased; this ultimately allows to increase the effectiveness of treatment and reduce the risk of infections at the use of standard doses of chemotherapy (Table 3) [36].

The beginning of using antiretroviral therapy about 15 years ago exerted a significant impact on the outcome of HIV-associated lymphomas with an increase of survival median; this explains the beneficence of the antiretroviral therapy on the immune system. Patients with HIV-associated lymphomas and safe immune system have lower risk of

infectious complications, which allows assigning them optimally effective and full chemotherapy [10,36]. One of the studies proved that common and progression-free survival of patients with HIV-associated lymphoma was largely dependent on ARV therapy, not the intensity of doses of cytostatic therapy [37].

Table 3 presents the results of randomized trials of studying different modes of cytostatic therapy in patients with HIV-associated lymphomas.

Table 3

The results of treatment of HIV-associated lymphomas in clinical trials

	Type of study, Number of patients, n	Lymphoma type	Therapy scheme		Number of CD4 cells/mm^3	Therapy outcome		
						Complete remission, %	Progression-free survival	Overall survival
Kaplan L.D., 1997 [29]	Multicentre, randomized, phase III (n=192)	Agressive NHL	m-BACOD+ GM-CSF		107	52	38 weeks	31 weeks
			m-BACOD low+ GM-CSF		100	41	56 weeks	35 weeks
Ratner l., 2001[44]	II (n=65)	DLBCL, immunoblastic NHL	m-CHOP		138	30	Response median to therapy is 65 weeks	
			CHOP		122	48	Response median to therapy is not reached	
Sparano J. A., 2004 [48]	II (n=98)	DLBCL, BL	didanosine		90	47	1-year - 42%, 2-year - 35%	6.8 months
			CDE		227	44	1-year - 40%, 2-year - 38%	13.7 months
Mounier N., 2006 [37]	III (n=485)	DLBCL	HIV (score 0)	ACVBP	239	61	5- year - 35,54%	5- year - 41,61%
				CHOP	239	51	5- year - 30,49%	5- year - 38,57%
			HIV (score 1)	CHOP	72	49	5- year - 16,35%	5- year - 18,37%
				CHOP low	72	32	5- year - 10,29%	5- year - 15,34%
			HIV (score 2-3)	CHOP low	21	20	5- year - 0,16%	5- year - 2,20%
				VS	21	5	5- year - 0%	5- year - 0,8%

Little R. F., 2003 [36].	II (n=39)	DLBCL, BL, PLE	EPOCH	198	74	4.4- year - 73%	4.4- year - 60%
Kaplan L.D., 2005 [28]	III (n=150)	DLBCL, BL	R-CHOP	130	49.5	45 weeks	139 weeks
			CHOP	147	41.2	38 weeks	110 weeks
Boue F., 2006 [7]	II (n=61)	DLBCL, BL, immunoblastic, plasmoblastic	R-CHOP	172	35	2- year - 69%	2- year - 75%
Spina M., 2005 [49]	II (n=74)	DLBCL, BL, anaplastic large cell lymphoma, immunoblastic	CDE-R	161	70	2- year - 59%	2- year - 64%
			CDE	227	45	2- year - 38%	2- year - 45%
Sparano J.A., 2010 [51]	II (n=101)	DLBCL, BL	R-DAEPOCH	181	73	1- year - 78%; 2- year - 66%	2- year - 70%
			DAEPOCH→ R	194	55	1- year - 66%; 2- year - 63%	2- year - 67%
Dunleavy K., 2010 [21]	II (n=33)	DLBCL	SC-EPOCH-RR	208		5- year - 84%	5- year - 68%

Note: m-BACOD – methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone; GM-CSF-колонистимулирующий factor; CDE-cyclophosphamide, doxorubicin, etoposide; R-Rituximab; CHOP-cyclophosphamide, vincristine, doxorubicin, prednisolone, ACVBP-doxorubicin, cyclophosphamide, vincristine, bleomycin, pnednisolone; EPOCH-etoposide, prednisolone, vincristine, doxorubicin, cuclophosphamide; SC-short course; DA-correlation dose.

Table 4 demonstrates the basic schemes for HIV-associated lymphomas treatment, while table 3 presented their efficiency.

Taking into account the risk of infection during and after chemotherapy, particularly in patients with a CD4 lymphocyte count less than 100 cells/mm^3, it is important to take preventive steps. All patients with HIV-associated lymphoma, irrespective of CD4 cell count at diagnosis and chemotherapy, should receive Pneumocystis jirall pneumonia prophylaxis, preferably with trimethoprim-sulfamethoxazole (1 tablet twice a day, three times a week during the therapy and up to restore of CD4 cell count to the number of more than 200 cells/ mm^3).

Patients with CD4 lymphocytes less than 50-100 cells/mm^3 also require prescription of azithromycin 1200 mg per week as the prevention of Mycobeacterium avium. Prescription of valacyclovir for preventing reactivation of herpes simplex virus is valid only in patients having herpes labialis and anogenital herpes in their past history. Patients with HIV-associated lymphoma and hepatitis B viremia require antiviral therapy. However, monotherapy using zidovudine (eg), will increase the probability of a specific mutation of HIV virus, M184V; this may lead to the development of resistance to antiretroviral drugs and increase the hematologic toxicity of chemotherapy. Patients with mucosal infections caused by Candida, should not receive chemotherapy concurrently with azoles.

The role of antiretroviral therapy during chemotherapy in patients with HIV-associated lymphoma

The risks and benefits of continuing ARV therapy during chemotherapy of aggressive lymphomas are contradictory. A lot of researchers are concerned about the fact that uncontrolled HIV replication during chemotherapy will lead to a immune function deterioration, and the continuation of antiretroviral therapy during chemotherapy and immune resumption mat prevent the development of infectious complications, especially in patients with low number of CD4. However, physicians should be ready for the potential pharmacokinetic interactions between ARV and chemotherapeutic medicines, especially first-generation antiretroviral drugs (zidovudine, stavudine, didanostine, and protease inhibitors).

Based on the result of the research of the integration of the first-generation antiretroviral drugs and cytostatic drugs, some authors recommend suspend antiretroviral therapy during chemotherapy. Several

researches are concerned about their pharmacokinetic and pharmacodynamic interaction that can reduce the required concentration of cytostatic and increase the toxicity of chemotherapeutic treatment [52]. Wilson *et al*., and Phenix demonstrated in their studies that some classes of first generation antiretroviral drugs decelerate apoptosis of lymphoid cells and facilitate an increased risk of new HIV mutations [41,42].

Nowadays, a new generation of antiretroviral drugs, such as tenofovir and emtricitabine-raltegravir, are widely used; they are well tolerated, do not cumulate side effects of chemotherapeutic treatment of lymphomas and do not affect on apoptosis of lymphocytes. Besides, in terms of acute opportunistic infections, 4-week delay in ARV therapy was associated with a significant increase of the risk of AIDS progression or death [54]. Patients with HIV-associated lymphoma usually have concominant opportunistic infections; average 7-week delay of ARV therapy during chemotherapy may have negative impact on general prognosis. At acute opportunistic infections, 4-week delay of ARV therapy was associated with a significant increase of AIDS progression risk or death. However, it is worth remembering that patients with HIV-associated lymphoma may be needed 4-6 cycles of chemotherapy; this may extend interruption of antiretroviral therapy and have negative impact on the patient survival in general. Bateganya and Mwanda proved in their study that there is a clear survival benefit of concominant prescription of ARV therapy and chemotherapy for the patients with HIV-associated lymphoma [4,38].

Clinical case

Patient A., 43 years old, complained on general weakness, aching stomach pain, heartburn, weight loss by 20 kg a year.

First, on 07 September 2012, the antibodies (Abs) to HIV were detected during the examination by clinical and epidemiological indications (weight loss, chronic active hepatitis C and injecting drugs consumer in past history).

From past history: has been ill for last year; in July 2011 was diagnosed with a stomach ulcer; recurrently held antiulcer therapy in outpatient and inpatient settings, had no improvement. EDG with biopsies has been performed 4 times. During one of the examinations (February 2012) esophageal candidiasis was detected. However, the suspicious for HIV infection or stomach cancer early diagnosis did not take place.

During the examination of **EDG** on 31 August 2012 a tumor formation on all the walls of the antrum was detected; it was deforming the stomach, stiffness, contact bleeding, partly with a touch of fibrin. These changes apply to the pylorus and the duodental cap. The pylorus is not identified, looks like tuberous mass.

The results of histopathological examination #4327-40, 06 September 2012. The material contains fragments of pyoinflammatory granulation tissue and necrotic detritus. Only the presence of ulcerative process can be reliably judged. The control after anti-ulcer therapy is recommended; repeated biopsy to obtain intact tissue.

On 13 September 2012 the patient goes to AIDS department of Gromashevskiy L.V. Institute of Epidemiology and Infectious Diseases.

The results of the additional examinations are the following: CD4 – 8.7% = 147 cells/mm^3; viral load of HIV – 1325 RNA cop/ml.

It was decided to lead a re-consultation in a specialized laboratory about histological specimens obtained by biopsy on 31 August 2012

The results of histological and immunohistochemical study #12CSD6049, 02 October 2012

The smooth muscular tissue is determined in the specimen (stomach muscular tissue) with a dense infiltration of large lymphocyte cells containing insignificant number of small lymphocytes. The nuclei of the tumor cells are vesicular and contains from 2 to 3 basophilic nuclei. There are a lot of pieces of mitosis and apoptosis in the tumor.
The morphological imaging mostly corresponds to the large-cell lymphoma. According to the immunohistochemical results, the tumor cells are positive for CD20, negative for CD3, CD30 and general cytokeratins. Also, the tumor cells are positive for CD10 and negative on BCL6 and MUM-1, which indicates about their origin from germinative centre. Conclusion: diffuse large B-cell stomach lymphoma, centroblastic variant with cell phenotype of germinative (embryonic) centre. Further treatment and observation is co-held with a hematologist. Further examination is conducted.

According to PET/CT, metabolically active and structural changes in the lower third of the stomach and bone-destructive changes were not detected. (Fig.1).

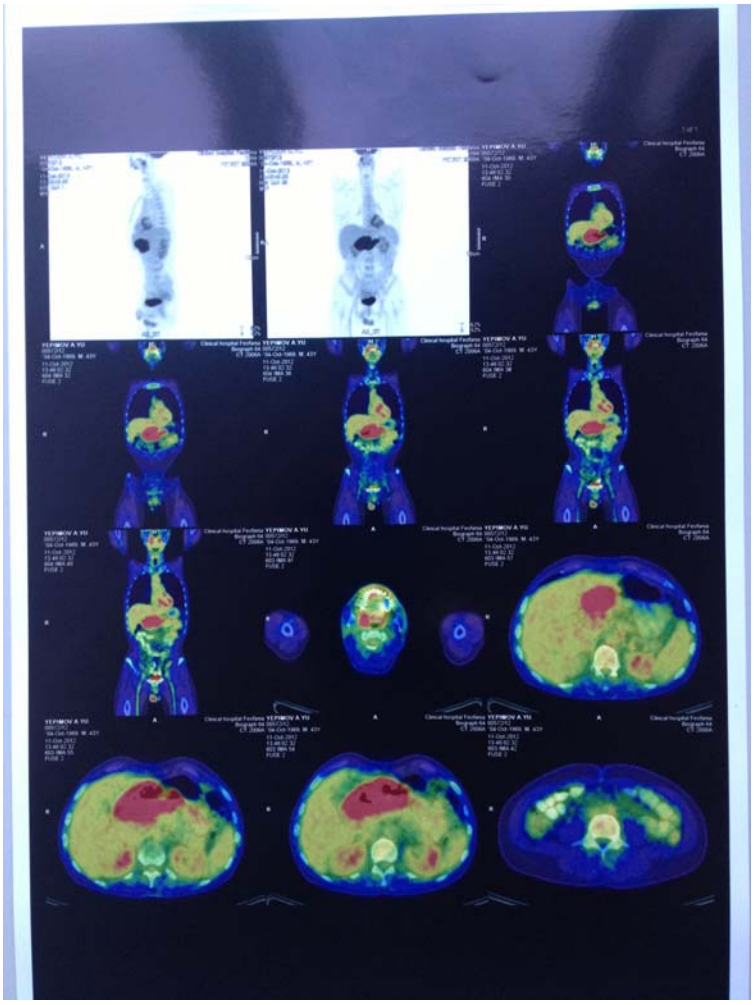

Figure 1. The results of PET / CT in the diagnosis of gastric lymphoma in a patient A

Analysis data of peripheral blood in the table

Erythrocytes	Hemoglobin	MCV	MCHC	Platelets	Leucocytes	Abs. lymphocytes	Abs. neutrophils	ESR
$4{,}58x10^{12}$/l	111 g/l	77	31.2	$125x10^{9}$/l	$5.8x10^{9}$/l	1,4x109/l	4.4x109/l	110 mm/hour

Data of chemical blood test in the table

Bilirubin	ALT	AST	urea	creatinine	glucose	albumin
10,4 mmol/l	19 U/l	30 U/l	5,8 mmol/l	7 4 mmol/l	5,5 mmol/l	34 g/l

The patient was genotyped by allele carriers of HLA-B*5701.

Basing on the results of the study, the diagnosis is as follows:
HIV infection is in clinical stage IV. HIV-associated non-Hodgkin's diffuse large B-cell stomach lymphoma II E of the germinal centre, T2N0M0. Candidosis of the oral cavity, esophagus.
Replicative form of chronic hepatitis C, RNA HCV +, genotype 3a, 1,2*10*6 copies. Prior to the chemotherapy, the patient was assigned

with antiretroviral therapy (ART): ABC/3TC+LPV/rit (combination of abcavir/lamivudine + combination of lopinavit/ritonavir).

A course of polychemotherapy R-CHOP-21 and two courses of CHOP21 of standard doses along with symptomatic therapy were conducted. Rituximab was canceled, as the number of CD4 lymphocytes with after its prescription decreased to 90 cells/mm and severe cytopenia developed.

After each course of chemotherapy, on day 7, fligrastim 5 mg/kg was injected to increase the absolute number of neutrophils to $1x10^9$/l and more. For the prevention of Pneumocystis jiroveci pneumonia, trimetorprim-sulfametoksol 960mg three times a week permanently was prescribed. To prevent bacterial infections, the patients took moxifloxacin 400mg twice a day for 10 days after each course of chemotherapy. Considering the risk of thrush of mouth (consequently after chemotherapy), the patient was prescribed with flucanazole 200-400mg daily for 10 days.

After the third course of chemotherapy, the patient was diagnosed with a complete remission, confirmed by the results of PET- CT study, 20 December 2012 (after 3 courses of chemotherapy). Comparing to the previous PET/CT (11 October 2012), the thickness of the stomach walls reduced to 0.75cm at the lesser and greater curvative. In the lower third of the stomach, the wall thickness decreased to 0.85cm. Increased metabolic activity was not observed. Conclusion: B-cell stomach lymphoma after 3 courses of polychemotherapy. PET/CT imaging of the complete and partly morphological regression. (Fig.2).

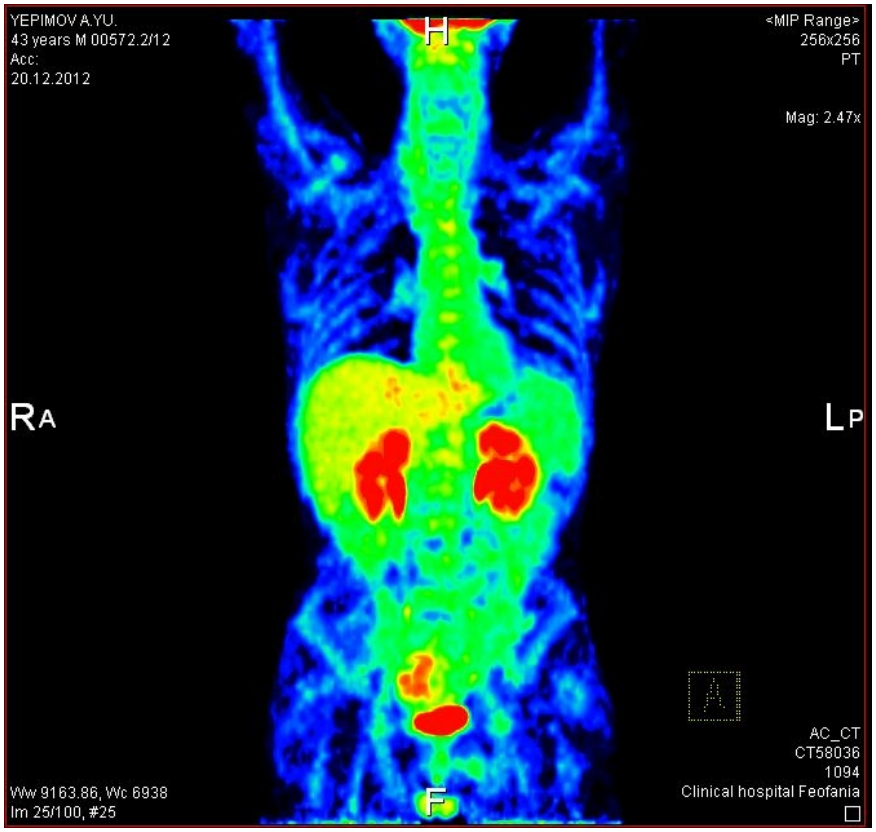

Figure 2. The results of PET-CT study after 3 cycles of chemotherapy in a patient A.

However, after chemotherapy, the patient happened to have a foul-smelling eructation, vomiting with indigested food, abdominal cramps in epigastric area. According to X-ray examination of the stomach (21 December 2012), a decompensated stenosis of the gastric outlet was installed. At EDG conducting (08 January 2013), the esophagus is passable; the mucosa is pale-pink and edematic; there are multiple linear undrainable erosions of up to 10mm. The stomach poorly straightens up with air; the volume of turbid fluid secretion, mucus and bile is increased fasting. Peristalsis is preserved. Folds are safe and elastic. The cardiac fold is of the second degree. There is a diffuse musocal erythema throughout the stomach. There is a bright speckled erythema and mosaic pattern mucosa. The folds are rough, thickened, twisted, having uneven surface. The pylorus is stenotic, it is impossible to input the apparatus of 9mm size into the duodenum. Conclusion: reflux esophagitis, stenosis of the gastric outlet (Fig.3)

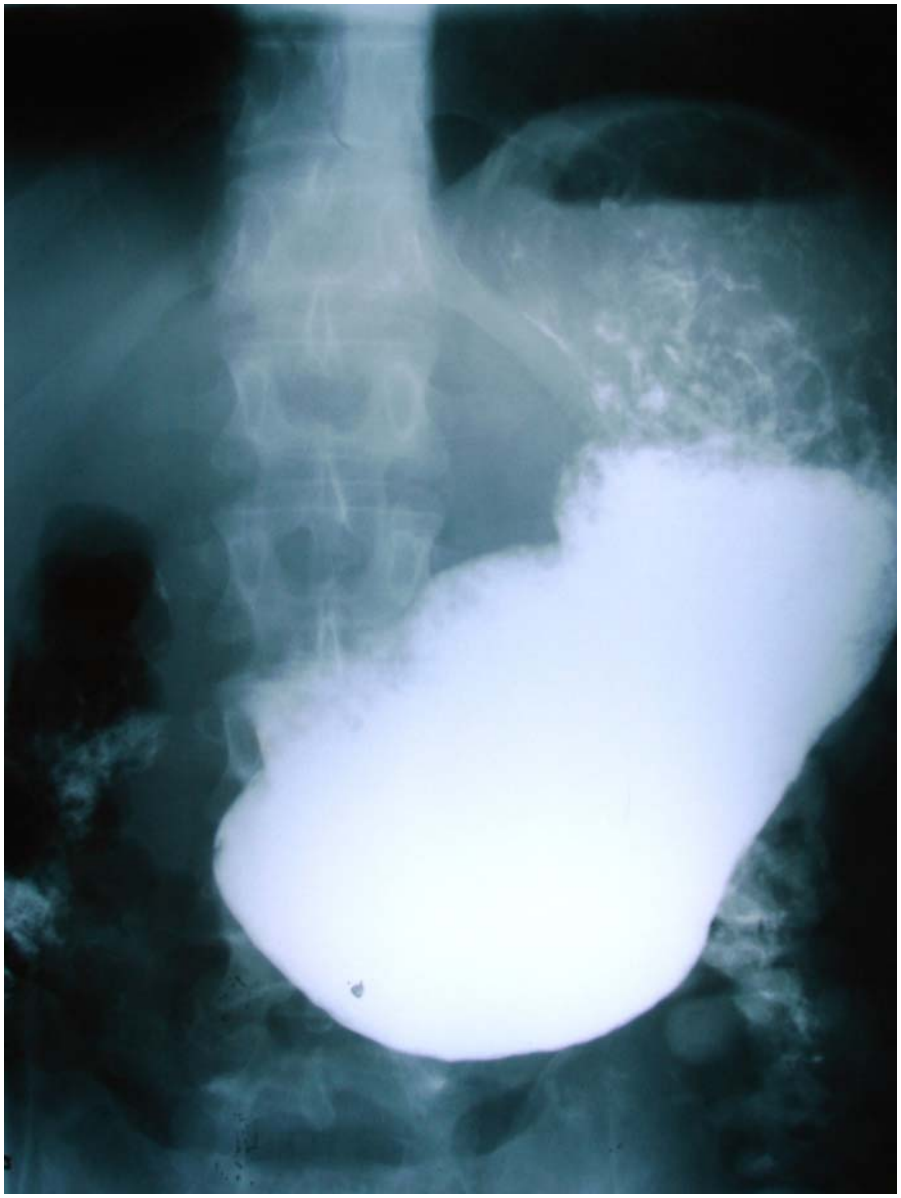

Figure 3. X-ray of the patient's stomach A.

Considering the scar deformity of the lower third of the stomach with decompensated stenosis of the pylorus, limophisis and ascites, it was decided to conduct palliative surgery. After adequate preoperative preparation (correction of water-protein-electrolyte metabolism, inserting nutrient nasointestinal tube), imposing of the bypass front cross-colon gastroenteroanastomosis with Brown's anastomosis (by Welver-Shalimov) and drainage of the absominal cavity were conducted. The postoperative period was relatively satisfactory, with no complications. The positive dynamic after gastric content evacuation along with adequate maintaining therapy was observed starting with the 10^{th} day; this allowed adding fractional oral infant nutrition feeding to parenteral and enteral feeding. The nasogastric decompression tube and nodal skin

sutures were removed on day 14 of the postoparational period. The patient was discharged on the 15th day of hospitalization.

Thus, a lot of patients may be diagnosed with lymphoma by the time of the diagnosis of HIV infection. In order to avoid a diagnostic mistake, the histological material should be sent to specialized histopathological laboratory. Clinical and treatment features of HIV-associated lymphomas as well as the high risk of both infectious and non-infectious complications during chemotherapy require further study for improving the prognosis of the disease in general.

Although many patients with immunodeficiency may have aggressive chemotherapy, it is accompanied by severe side effects and requires well-coordinated interactions between hematologist-oncologist and HIV-infection specialist along with often involving experts of different profiles into the treatment process.

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Table 4

Principle schemes of cytostatic maintenance therapy of HIV-associated lymphomas

Author	Type of NHL	Name of scheme	Drugs	Dose	Day of prescription	Preventioan of CNS affection	Maintenance therapy
Sparano J.A., 2010 [47]	DLBCL, BB, PLE, plasmablastic lymphoma	R-EPOCH-21	Rituximab	375 mg/m^2	Day 1, more than 3 hours	Intrathecal either cytarabine 50mg or methotrexate 12mg weekly for 4 weeks within one course	• Filgrastim 5mg/kg on day 6 after EPOCH • Trimetorprim-sulfametoksol 160-800 mg 3 times a week, permanently • Fluconazole 100 mg daily, permanently • Ciprofloxacin 500 mg twice a day, days 8-15 after EPOCH
			Etoposide	50 mg/m^2	Days 1-4 (96 hour infusion)		
			Doxorubicin	10 mg/m^2	Days 1-4 (96 hour infusion)		
			Vincristine	0.4 mg/m^2	Days 1-4 (96 hour infusion)		
			Prednisolone	60 mg/m^2	Days 1-5		
			Cyclophosphamide	1 course - 187 mg/m^2 if CD4 count less than 100 cells/m^3 и 375 mg/m^2 if CD4 count more than 100 cells/m^3	Day 5 (60 min. infusion)		
Dunleavy K., 2010 [21]	DLBCL, BB, PLE, plasmablastic lymphoma	SC-EPOCH-RR-21	Rituximab	375 mg/m^2	Days 1 and 5, more than 3 hours	Intrathecal methotrexate 12mg day 1 and day 5 starting with course 3-5	• Filgrastim 5mg/kg on day 6 after EPOCH • Prevention of Pneumocystis jiroveci pneumonia if CD4 count less than 100 cells/m^3
			Etoposide	50 mg/m^2	Days 1-4 (96 hour infusion)		
			Doxorubicin	10 mg/m^2	Days 1-4 (96 hour infusion)		
			Vincristine	0.4 mg/m^2	Days 1-4 (96 hour infusion)		
			Prednisolone	60 mg/m^2	Days 1-5		
			Cyclophosphamide	750 mg/m^2	Day 5 (60 min.		

					infusion)		
Mounier N., 2006 [37].	DLBCL	ACVBP-14	Doxorubicin	75 mg/m^2	Day 1	Intrathecal methotrexate 12mg before each course циклом (4 injections max.)	• Filgrastim 5mg/kg on day 6 after chemotherapy until the number of neutrophils is more than 0.5x10^9/l • Trimetorprim-sulfametoksol 160-800 mg 3 times a week, permanently
			Cyclophosphamide	1200 mg/m^2	Day 1		
			Vincristine	2 mg/m^2	Days 1, 5		
			Bleomycin	10 mg	Days 1, 5		
			Prednisolone	60 mg/m^2	Days 1, 5		
		CHOP-21	Doxorubicin	50 mg/m^2	Day 1	Intrathecal methotrexate 12mg before each course (4 injections max.)	
			Cyclophosphamide	750 mg/m^2	Day 1		
			Vincristine	1,4 mg/m^2	Day 1		
			Prednisolone	60 mg/m^2	Days 1 - 5		
		CHOP low-21	Doxorubicin	25 mg/m^2	Day 1	Intrathecal methotrexate 12mg before each course (4 injections max.)	
			Cyclophosphamide	400 mg/m^2	Day 1		
			Vincristine	1,4 mg/m^2	Day 1		
			Prednisolone	60 mg/m^2	Days 1 - 5		
		VS-14	Vincristine	2 mg	Day 1	Intrathecal methotrexate 12mg before each course (4 injections max.)	
			Prednisolone	60 mg/m^2	Days 1 - 5		
Spina M., 2005 [49]	DLBCL, BB, PLE, plasmablastic lymphoma	CDE+/-R-28	Rituximab	375 mg/m^2	Day 1, more than 3 hours	Intrathecal methotrexate 12mg before each course or cytrabine 50mg, days 1 and 4 of the first and second course of chemotherapy at BL or bone marrow affection	• Filgrastim 5mg/kg on day 6 after chemotherapy • Trimetorprim-sulfametoksol 160-800 mg 3 times a week, permanently • Fluconazole 100 mg daily, permanently
			Cyclophosphamide	185-200 mg/m^2	Days 1-4 (96 hour infusion)		
			Doxorubicin	12,5 mg/m^2	Days 1-4 (96 hour infusion)		
			Etoposide	60 mg/m^2	Days 1-4 (96 hour infusion)		

Note: DLBCL - diffuse large B-cell lymphoma; BL – Burkitt's lymphoma; PLE – primary lymphoma of exudates

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