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EFFICACY OF SPLENECTOMY IN PATIENTS WITH NON-HODGKIN'S LYMPHOMAS ASSOCIATED WITH AUTOIMMUNE HEMOLYTIC ANEMIA AND EVANS — FISHER SYNDROME

Objective: *to determine indications for surgical technique and outcomes of splenectomy in non-Hodgkin's lymphomas (NHL) associated with autoimmune hemolytic anemia (AIHA) or Evans — Fisher syndrome (EFS) based on our 20-year experience.* ***Subject and methods:*** *ten splenectomies in NHL associated with AIHA (group I) and 18 splenectomies in NHL associated with AIHA and immune thrombocytopenia — EFS (group II) have been performed. Outcomes were determined both post-operatively and over a long-term follow up observation during 3–201 months (median 68 months) and 1–290 months (median 195.5 months) in group I and group II, respectively.* ***Results:*** *splenectomy in NHL is indicated in those immune cytopenias refractory to steroids and cytotoxic therapy associated with massive splenomegaly, regional portal hypertension and hypersplenism. The surgical technique of splenectomy in large spleen is quite complicated and depends on both the spleen size and presence of adhesions. Postoperative mortality (progression of lymphoma, bleeding) reaches 7%. A favorable immediate outcome of surgery was observed in 93% of patients. Median value of postoperative event-free survival in NHL with AIHA reached 29.0 months (12.0–49.0 months), and median value of overall survival estimated 31.0 months (18.1–52.2 months), with a 3-year survival observed in 45% of patients and a 5-year survival in 22% of patients. Median event-free survival in patients with NHL and EFS reached 22 months (5.0–52.0 months), while median overall survival being 50 months (12.0–97.0 months), with a 3-year survival observed in as much as 62% of patients and a 5-year survival in 31% of patients. The lowest post-spenectomy life expectancy was stated in patients with aggressive lymphomas associated with immune cytopenias (diffuse large B-cell lymphoma, T-cell types).* ***Conclusions:*** *splenectomy has proved both an effective and quite safe treatment option and diagnostic tool in NHL complicated by immune cytopenias, particularly those associated with massive splenomegaly, regional portal hypertension and hypersplenism. Long-term results of splenectomy are mainly determined by a variant of NHL.*

INTRODUCTION

Non-Hodgkin's lymphomas (NHL) as other lymphoproliferative disorders (LPD) are accompanied with a high frequency of autoimmune processes among which the autoimmune cytopenias prevail [1, 2]. In particular, the autoimmune hemolytic anemia (AIHA), mostly due to warm antibodies (positive direct Coombs' test), accounts for 2.6–3.0% of all cases of NHL [3, 4]. It is frequently combined with an immune thrombocytopenia (ITP) and immune leukopenia, the immune characteristics of which are more difficult to confirm, since, thrombocytopenia and leukopenia may be a manifestation of hypersplenism in massive splenomegaly [5]. The pathogenesis of autoimmune processes in lymphoid proliferations remains a matter of considerable dispute and controversy, especially as a high frequency of LPD is also observed in AIHA [6]. It is believed that increased tendency to autoimmune antibodies formation in LPD is caused by rearrangements of the immunoglobulin V-region genes or T-cell receptor in the malignant B-/T-cells. It triggers the generation of autoreactive lymphocyte clones. Failure to eliminate these clones or the breakdown in the mechanisms that prevent their expansion may lead to the occurrence of autoimmune processes [4].

NHL with autoimmune cytopenias requires specific treatment approach that is caused by a whole range of conditions. It has been proved that the presence of AIHA in patients with NHL is an adverse prognostic sign [4]. Autoimmune process of such patients shows a poor response to corticosteroids and intravenous immunoglobulin, and slightly better response to cytostatic therapy of lymphoma [1, 3]. Finally, the massive splenomegaly with all possible consequences (abdominal discomfort, regional portal hypertension (RPH), hypersplenism) is

often observed in these NHL [5, 7, 8]. In such cases, the need for splenectomy arises having positive outcomes as well as some risk for a patient [7, 9].

The aim of this study was to specify the indications for surgical equipment and consequences of splenectomy in NHL associated with AIHA or Evans — Fisher syndrome (EFS) as based on twenty years' experience of performance of the surgery in our clinic.

MATERIALS AND METHODS

During the period of 1986–2015 at the Department of Surgery and Clinical Transfusion Medicine of the State Institution «Institute of Blood Pathology and Transfusion Medicine of National Academy of Medical Sciences of Ukraine» (Lviv) and at the premises of the Department of Surgery of Lviv City Communal Clinical Hospital No. 5 among 107 splenectomies in patients with NHL, 10 splenectomies were performed in patients with NHL and AIHA (group 1) and 18 splenectomies were performed in patients with NHL associated with AIHA and ITP — EFS (group 2).

The diagnostics of NHL and its variant was performed as based on the results of the clinical and instrumental examinations (Table 1), cytological examination of peripheral blood, bone marrow, aspirates and imprints of the affected organs, histological examination of biopsy specimens of the removed lymph nodes and/or spleen, immunophenotypic features of malignant cells of the investigated tissues in accordance with current classifications (WF, REAL with further specification pursuant to WHO classification) [10] (Table 2). The extending (stage) of the disease was estimated on grounds of clinical, X-ray, ultrasonographic examinations and computed tomography according to Ann Arbor staging system [11]. 15 patients were diagnosed with III-E or III-Es stage disease, and 13 patients were diagnosed with IV stage disease.

Splenectomy was performed under intubation anesthesia via the upper middle laparotomy. In patients with massive splenomegaly (spleen weight > 3 kg), marked perisplenitis and vascular anastomoses among organs resulting from RPH the laparotomy incision was extended towards pubic articulation or supplemented by a lateral incision on the left 2 cm above the umbilicus. The classical technique for splenectomy was applied. The enlarged spleen removal was started with mobilization of the inferior pole that technically allowed for a control of the splenic pedicle vessels, gradual visualization of splenic ligaments and junctions, and its dissection while systematically attaining hemostasis by virtue of vascular ligation or electrocoagulation. After releasing the spleen from ligaments and junctions and its exteriorization, the vascular pedicle and other vessels were ligated. Since 2002 all patients were immunized with vaccine Pneumo-24 and recently with Prevenar vaccine before splenectomy in order to prevent post-splenectomy infection.

The results of splenectomy were assessed in the immediate post-splenectomy period (on the fourteenth-sixteenth day) pursuant to criteria described in the references [12] and during follow-up control. The follow-up period after the surgery ranged between 3 and 201 months (median time 68 months) for group 1, and between 1 and 290 months (median time 195.5 months) for group 2.

The results were analyzed by means of descriptive statistical methods. The event-free survival (event — recurrence of immune cytopenia or when a patient died of lymphoma) and overall patients' survival were determined by the Kaplan — Meier method and described as a median survival (lower-

Table 1

Clinical and hematologic characteristics and results of splenectomy in patients with NHL associated with immune cytopenias

Criteria	NHL + AIHA	NHL + AIHA + ITP
Number of patients	10	18
Sex: male/female	6/4	12/6
Age > 60 years	2	5
Disease duration before splenectomy (months)	1–48	2–132
General condition according to ECOG ⩾ 2	1	2
Clinical signs		
Peripheral lymph nodes	4	5
Mediastinal lymph nodes	2	2
Intra-abdominal lymph nodes	10	14
Splenomegaly	10	18
Hepatomegaly	5	13
Bone marrow involvement ⩾ 30% of lymphoid cells	3	9
Stage of disease: III IV	 3 7	 12 6
Indices of peripheral blood		
Anemia < 100 g/l	8	10
Thrombocytopenia < 100 · 10^9/l	–	18
Leukocytosis > 10 · 10^9/l	3	7
Lymphocytosis 5–10 · 10^9/l	–	2
Lymphocytosis ⩾ 10 · 10^9/l	2	6
Leukopenia ⩽ 3.5 · 10^9/l	4	8
Reticulocytes > 20‰	10	13
Erythrocyte sedimentation rate > 20 mm/h	7	14
M-gradient	1	2
Therapy before splenectomy	6	9
Intraoperative indices		
Massive splenomegaly (weight > 1500 g)	10	12
Perisplenitis	1	6
Regional portal hypertension	6	12
Ascite	3	3
Bleeding during surgery	3	10
Blood loss > 500 ml	3	6
Response to splenectomy		
Remission > 12 months Remission 2–12 months Absence of remission (progression)	4 6 –	5 11 2
No need for treatment after splenectomy Received treatment after splenectomy	9 1	12 6

Table 2

Morphological variants of NHL with immune cytopenias

Types of NHLs	NHL + AIHA (number of patients)	NHL + AIHA + ITP (number of patients)
Splenic lymphoma with villous lymphocytes (SLVL)	–	5
Splenic marginal zone lymphoma (SMZL)	2	3
Nodal marginal zone lymphoma (NMZL)	1	–
Follicular lymphoma	–	1
Mantle cell lymphoma (MCL)	–	3
Diffuse large B-cell lymphoma (DLBCL)	6	5
B-cell NHL, unclassified	1	–
T-cell NHL, unclassified	–	1

upper quartiles) and 3-year and 5-year survival. The survival curves were compared using the log-rank test.

RESULTS AND DISCUSSION

Splenectomy was performed in 10 patients with NHL associated with warm-antibody AIHA. Among them there were 6 men and 4 women 25–68 years old (median age — 51.5 years). All patients, except for one of them, were in satisfactory clinical condition complaining of general weakness, easy fatigability and weight loss (grade 1–2 according to ECOG scale). The disease duration before splenectomy ranged from 1 to 48 months. Enlargement of peripheral lymph nodes occurred in 4 patients, mediastinal — in 2 patients, and enlargement of intra-abdominal lymph nodes was observed in all patients. Splenomegaly was found in all subjects, thereby, in 4 patients the spleen occupied all the left side of the abdomen, in 2 patients — it occupied the whole abdomen and its inferior pole descended into the small pelvis. Hepatomegaly (the liver protruded below the edge of the costal margin to 1–6 cm) was observed in 5 patients of the group. Bone marrow involvement (> 30% of lymphoid cells) was found in 3 patients with peripheral blood lymphocytosis > $10.0 \cdot 10^9$/l in 2 cases. M-gradient (see Table 1) appears on proteinogram of 1 patient with NMZL. Classification of patients according to NHL variants is presented in Table 2.

All patients showed signs of profound hemolysis: icteric skin and mucosa, anemia (8 patients showed hemoglobin level of 60–96 g/l), reticulocytosis 20–128‰ accompanied by increased total bilirubin due to indirect fraction, and in particular cases, followed by increased transaminase level, positive direct Coombs' test and warm agglutinins. Leukopenia ($1.0–3.5 \cdot 10^9$/l) occurred in 4 patients. In one patient, hemolysis was the first sign of disease, while in other patients it occurred after NHL manifestations. Abdominal manifestations (discomfort and pain in the left hypochondriac region) were noticed in 5 patients. RPH was sonographically diagnosed in 5 patients based on increased diameter of the splenic and portal veins.

Six patients administered corticosteroids, underwent chemotherapy, erythrocyte transfusions before surgery, however, that has not resulted in hemolysis cessation. Thus, the indications for splenectomy in the patients with NHL associated with AIHA were as follows: profound hemolysis which was refractory to drug therapy, leukopenia as a possible manifestation of hypersplenism, massive splenomegaly with abdominal symptoms, and presence of RPH.

In 3 patients splenectomy was followed by blood loss of more than 500 ml secondary to enlarged spleen, perisplenitis, excessive bleeding and RPH. In other cases (7 patients), the surgery was performed without complications with blood loss of less than 500 ml. The ascitic fluid was found in 3 patients. The weight of the removed spleens ranged from 1.5 to 10.0 kg. Abdominal lymphadenopathy was confirmed in all patients of group 1; enlarged lymph nodes only at splenic hilum were observed in 3 patients, in other 7 patients the lymph node packages were found along the lesser and greater curvatures of the stomach, in the hepatoduodenal ligament, at the splenic and renal hilums, along the upper edge of the pancreas, and enlarged mesenteric lymph nodes were also found. One patient had two accessory spleens removed, and another patient simultaneously underwent cholecystectomy for chronic calculous cholecystitis.

The histologic and immunohistochemical examinations of the removed spleens (including two accessory spleens) and abdominal lymph nodes confirmed the initial diagnosis of NHL variant in 5 patients. In another 5 patients who had no affected peripheral lymph nodes and/or leukemization available for morphological examination the variant of lymphoma was determined or specified that substantiates the diagnostic significance of splenectomy for these patients.

Complications occurred in 2 (20%) patients in the postoperative period. One patient developed a bilateral pneumonia that was resolved after proper antibacterial therapy. Another patient developed a lower extremity superficial thrombophlebitis in varicose veins secondary to post-splenectomy hyperthrombocytosis; the thrombectomy was performed (Table 3). The immediate result of splenectomy in all of the patients (100%) with NHL associated with AIHA was good: hemolysis ceased, hemoglobin level increased, in patients with leukopenia the leukocytes stabilized, bilirubin level reduced to the normal value, M-gradient disappeared, and no manifestations of abdominal discomfort were observed. Only one (10%) patient of group 1 required cytostatic therapy within the 1-year period after surgery.

Table 3

Complications after splenectomy in patients with NHL with immune cytopenias

Type of complications	NHL + AIHA	NHL + AIHA + ITP
Pneumonia	1	1
Acute postoperative hemorrhage	–	1
Acute thrombophlebitis of the lower extremity superficial veins	1	–
Postoperative pancreatitis	–	2
Acute adrenal insufficiency	–	1

While analyzing the long-term outcomes of splenectomy in patients with NHL associated with AIHA it has been defined that the median event-free survival was 29 months (12–49 months) (Fig. 1), and the median overall survival — 31 month (18.1–52.2 months) with the 3-year survival rate of 45% and 5-year survival rate of 22% (Fig. 2). The patient with NMZL had the shortest survival time after the surgery (3 months), and the best effect has been achieved in patient with mature B-cell NHL (low-grade malignancy according to WF). In this patient, NHL and massive splenomegaly has been associated with warm type AIHA (hemoglobin level — 50 g/l) and leukopenia ($1.4 \cdot 10^9$/l). Numerous blood transfusions, chemotherapy and corticosteroids therapy had no effect. The patient underwent splenectomy. The removed spleen weight constituted 10 kg. Splenectomy resulted in termination of hemolysis, leukocytes stabilization, and elimination of abdominal discomfort caused by giant spleen. The patient has been living for 201 months after the splenectomy having achieved complete clinical remission, without any additional treatment.

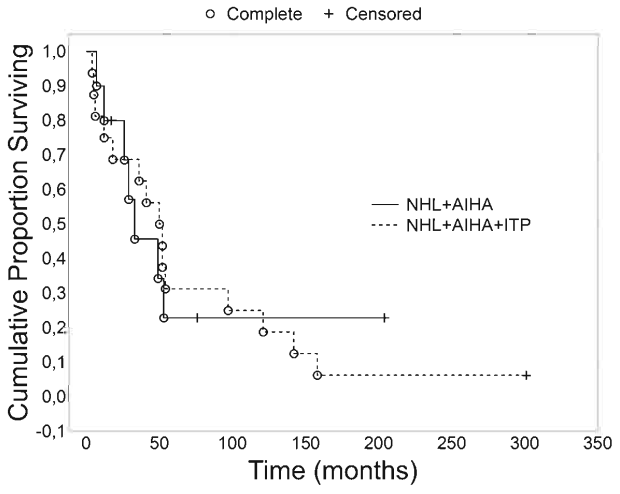

Fig. 1. The Kaplan — Meier curves of overall survival in patients with NHL, associated with AIHA, and NHL, associated with AIHA and ITP

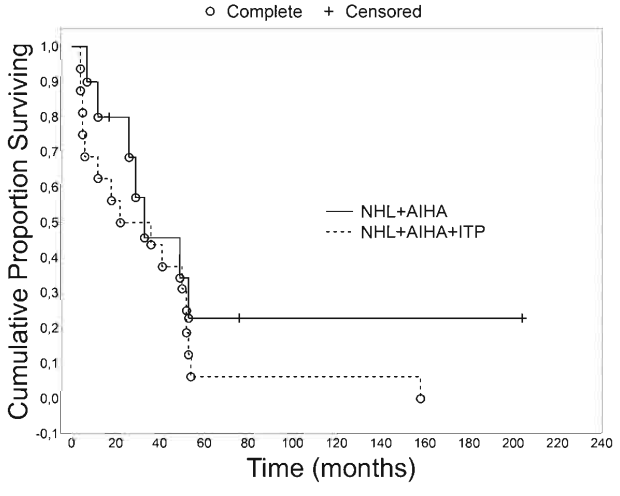

Fig. 2. The Kaplan — Meier curves of event-free survival in patients with NHL, associated with AIHA, and NHL, associated with AIHA and ITP

One patient with SMZL (who underwent surgery when there was no possibility to perform prophylactic vaccination) died 9 months after splenectomy due to untreated post-splenectomy infection (overwhelming postsplenectomy infection syndrome) that manifested as a septic shock. Antibiotic therapy and resuscitation at Intense Care Unit proved ineffective, and the patient died. In patients with DLBCL (n=6), despite good short-term results of splenectomy, the median overall survival was short — 26 months, wherein, five of them died of lymphoma progression, and one of them — died of myocardial infarction 64 months after the surgery.

In group 2, there were 18 patients with NHL associated with AIHA and ITP (EFS), 12 of them were men (25–65 years old) and 6 of them were women (56–69 years old), the median age — 53.5 months. General condition of 16 patients corresponded to grade 1–2 according to ECOG scale, and condition severity of two patients corresponded to grade 3. The disease duration before surgery ranged from 1 month to 11 years. Five patients were diagnosed with enlargement of peripheral lymph nodes. All of the patients suffered from a pronounced splenomegaly: in 10 patients the spleen occupied all the left side of the abdomen, in 4 patients it protruded beyond the median line and its inferior pole descended into the small pelvis. Hepatomegaly was observed in 13 cases. During instrumental examination of the chest and abdominal cavity all patients were diagnosed with splenomegaly, abdominal (14 patients) and mediastinal lymphadenopathy (2 patients). Bone marrow involvement was found in 9 patients, lymphoid cells count in the bone marrow exceeded 30%. M-gradient in blood serum was revealed in two subjects with lymphoma (see Table 1).

All patients showed signs of profound hemolysis, had positive direct Coombs' test and warm agglutinins. Reduced hemoglobin level of less than 100 g/l was observed in 10 patients, the number of reticulocytes varied from 22 to 138‰. Bilirubin concentration in blood increased due to indirect fraction. At the same time these patients were diagnosed with thrombocytopenia: number of thrombocytes ranged from minimum values to $92.0 \cdot 10^9$/l. However, moderate hemorrhages (skin petechiae, mucosal and abdominal hemorrhages) occurred only in one patient with DLBCL when thrombocytes number was less than $30 \cdot 10^9$/l. The number of leukocytes remained within normal range only in 3 patients, 8 patients were diagnosed with leukopenia, and another 7 were diagnosed with leukocytosis. Absolute lymphocytosis $5–10 \cdot 10^9$/l was noticed in 2 patients, and more than $10 \cdot 10^9$/l — was observed in 6 patients. In 5 patients with EFS, the atypical morphology of peripheral blood lymphocytes which corresponded to villous lymphocytes morphology was determined that constituted a ground for diagnosing SLVL [13, 14]. Marked manifestations of abdominal discomfort were noticed in 12 patients. 15 patients developed signs of RPH: increase in diameter of splenic vein (15 patients), increase in diameter of portal vein (9 patients), grade 1 esophageal varices determined by fibrogastroduodenoscopy (3 patients). Classification of patients according to NHL variants is presented in Table 2.

Nine patients of group 2 received treatment (chemotherapy, corticosteroids) before the surgery without possible effect on immune cytopenia. The indications for splenectomy in patients with NHL associated with AIHA and ITP were as follows: AIHA, thrombocytopenia, hemorrhagic syndrome, previous treatment failure, splenomegaly with abdominal manifestations and hypersplenism, RPH.

The spleen removal in patients of group 2 was technically difficult. In 6 patients the surgery was associated with marked perisplenitis in the form of adhesions of the spleen to the diaphragm, abdominal wall, colon and left kidney. 9 patients developed the increased bleeding, apparently secondary to thrombocytopenia, due to which the different hemostatic methods were applied: pharmacological method, electrocoagulation, tamping with hemostatic sponge, and in particular cases — with gauze pads. In one patient the upper middle laparotomy incision had to be supplemented by oblique incision in the left hypochondriac region due to marked perisplenitis, massive splenomegaly and excessive bleeding.

The weight of the removed spleens ranged from 1.5 to 6.0 kg, where in 12 cases the spleen was particularly large-sized (26–45 cm long). In one case the accessory spleens located at the hilum of the main spleen were detected and removed. The surgical blood loss constituted 200–1000 ml. The enlarged abdominal lymph nodes (14 patients) were detected mostly at the splenic hilum, along the greater curvature of the stomach, along the upper edge of the pancreas, less frequently — in the hepatoduodenal ligament, as well as enlarged paraaortic and mesenteric lymph nodes. In 10 patients the RPH was manifested by splenic, abdominal, diaphragmatic and omental varices; and the ascitic fluid was found in 3 patients.

The morphological and immunological examinations of the spleen and abdominal lymph nodes confirmed the diagnosis of NHL variant in 11 patients, enabled to determine or specify the lymphoma variant in 6 patients, and in one case it constituted a ground for changing the initial diagnosis of myelofibrosis for T-cell lymphoma (high-grade according to WF). Thus, the splenectomy was diagnostically significant for 7 patients.

The short-term results of splenectomy in 16 (89%) patients of group 2 were classified as good: hemolysis ceased, hemoglobin level has stabilized, number of thrombocytes increased or stabilized, in patients with leukopenia the leukocytes stabilized, in particular patients with leukocytosis the number of leukocytes reduced, and the abdominal discomfort syndrome was eliminated. The M-gradient disappeared in one patient with a MCL.

The splenectomy proved ineffective in two (11%) patients of group 2. In one patient with DLBCL associated with AIHA and ITP with severe hemorrhagic syndrome, leukopenia, massive (30×15 cm) spleen adjacent to the neighboring organs and abdominal wall, collateral varices in the abdominal cavity, the splenectomy was accompanied by great technical difficulties and excessive bleeding (blood loss — 1000 ml). The surgery has not resulted in hemolysis termination and increasing thrombocyte count, the patient died one month after splenectomy due to hemorrhagic syndrome. Another patient was admitted with a provisional diagnosis of myelofibrosis, splenomegaly, AIHA (hemoglobin — 51 g/l, positive Coombs' test), ITP (thrombocytes count — 34.0 • 10^9/l), and leukopenia (3.9 • 10^9/l). Due to splenomegaly, concomitant pancytopenia refractory to corticosteroids and for diagnosis confirmation the patient was assigned to undergo splenectomy. The surgery was accompanied by great technical difficulties, bleeding (blood loss — approximately 1000 ml) as a consequence of perisplenitis, thrombocytopenia and RPH. A high-grade (according to WF) malignant T-cell lymphoma was found in the removed spleen by means of morphological examination. On the twelfth day after splenectomy the peripheral blood indices improved (hemoglobin — 98 g/l, leukocytes — 27.0 • 10^9/l, thrombocytes — 589.0 • 10^9/l). However, the patient's condition remained unstable and he died one month after the surgery due to rapid progression of the lymphoma.

Complications after splenectomy (Table 3) occurred in 3 (17%) patients of group 2. The patient with SMZL developed pneumonia and postoperative pancreatitis after splenectomy. Both complications were successfully cured. The patient with SMZL and M-gradient in spite of pre- and perioperative bleeding prevention and unassociated with surgery developed intra-abdominal bleeding 2 hours after splenectomy, which was successfully suppressed with great difficulties without relaparotomy after consecutive administration of haemostatic agents, eptacog alfa, human prothrombin complex, fresh frozen plasma transfusion and finally, local administration of aprotinin. On the fifth day after the surgery the same patient developed postoperative pancreatitis that was timely diagnosed and treated. The acute adrenal insufficiency which was manifested by a sudden drop in blood pressure occurred in patient with MCL on the second day after the surgery. The patient's condition has stabilized after high corticosteroids dose administration. Six (33%) patients of group 2 underwent cytostatic therapy in the first year after the surgery.

While analyzing the long-term outcomes of splenectomy in patients with NHL associated with AIHA and ITP (Fig. 1, 2) it has been defined that the median event-free survival after the surgery was 22 months (5–52 months), and the median overall survival — 50 months (12–97 months) with the 3-year survival rate of 62% and 5-year survival rate of 31%. Depending on lymphoma's category the overall median survival time after splenectomy in patients of this group with SLVL constituted 39.8 months, with MCL — 159.7 months, with DLBCL — 21.4 months. The median event-free survival in patients with SLVL constituted 10.6 months, with MCL — 6.3 months and with DLBCL — 21.4 months. One patient with follicular lymphoma has lived 6 months after splenectomy and died due to the disease progression; another patient with SMZL has lived 143 months after the surgery without chemotherapeutic agents' administration.

Statistical comparison of overall and event-free survival after splenectomy showed no significant difference between the 2 groups (long-rank test for overall survival $p = 0.97607$, for event-free survival — $p = 0.21350$).

Thus, similar to other researchers [5, 8, 12, 15–19], we determined that splenectomy remains an effective and relatively safe method for treating NHL associated with immune cytopenias. Indications for splenectomy in patients of the represented groups were both diagnostic and therapeutic. Similar indications are discussed in the references [8, 16, 18, 20]. Most of patients showed more than one indication for the surgery that is mentioned in the references [16].

The splenectomy was diagnostically significant for 12 (43%) patients of both groups who suffered from isolated splenomegaly without involvement of accessible lymph nodes and bone marrow that is closely related to the issue of splenic lymphomas [20]. As a result of histological and immunophenotypic analysis of the affected splenic tissue, the diagnosis of NHL variant was determined or specified in 11 patients, and T-cell lymphoma with the initial diagnosis of myelofibrosis was found in one case.

An alternative to splenectomy in such patients (while there are no any other indications for the surgery) may be a punch biopsy of the spleen under ultrasound monitoring that, however, cannot be applied as a routine diagnostic method [20].

All patients of our group developed clear therapeutic indications for splenectomy: immune cytopenia (AIHA or

AIHA + ITP) which was refractory to previous therapy in 15 (54%) patients, and massive splenomegaly with abdominal signs and portal hypertension (in 6 patients of group 1 and in 14 patients of group 2, totally — 71% of patients). Some researchers qualify signs of hypersplenism as indications for the surgery in patients with NHL [5, 12, 19], which may include massive splenomegaly, thrombocytopenia, leukocytopenia, the immune origin of which is difficult to confirm in patients with NHL, and portal hypertension.

Splenectomy in case of massive splenomegaly is technically relatively difficult due to splenic adhesion to other organs of abdominal cavity and its vascularization [7, 8, 21]. We did not apply preliminary ligation of the splenic artery trunk, injection of adrenaline into the spleen for reducing its size, as it was recommended by some researchers. In our opinion, thereby we reduce the risk of ischemia of a pancreatic tail segment.

Different perioperative mortality rates in patients with NHL undergoing splenectomy are presented in the references — from 0% [16], 1% [8], 2.9% [17], 3.5% [18] to 3.8% [19], and the postoperative mortality within one month is reported in 9% of patients [12]. There were no incidences of perioperative mortality in patients of the group represented in the study (0%), however, 2 (7%) patients of group 2 died of T-cell lymphoma progression and hemorrhagic syndrome one month after the surgery. The postoperative complications (pneumonia, bleeding, thrombosis, pancreatitis) occurred in 5 (18%) patients that coincides with the data reported in the references (17% 37% [17], 29% [5], 21% [12], 19.2% [19], 17% [16]). The complications after splenectomy in patients with NHL can be divided into four types: those resulting from the disease severity; complications arising from technical difficulties during the surgery; suppurative septic and thrombotic complications.

The immediate clinical hematologic effect after the surgery achieved in 93% of patients: 100% in patients with NHL associated with AIHA and 89% in those with NHL associated with AIHA + ITP. The investigators confirm the high response rate to splenectomy in patients with NHL: 89% [5], 80% [16], 72% [17], 64% in patients with NHL associated with AIHA and 89% in patients with NHL associated with ITP [12] and report that 90–100% of patients became independent of red blood cell and platelet transfusions after the surgery [8].

The overall survival rate of patients with NHL after splenectomy was slightly better in patients of group 2, and the event-free survival rate — in patients of group 1, notwithstanding that the survival curves did not differ in both groups. The similar survival rates of the patients with NHL after splenectomy are reported by other researchers [5, 8, 12, 17]. The obtained results prove the statement of some investigators that operative treatment success depends mainly on NHL variant rather than presence or absence of concomitant cytopenia [8]. Among patients participating in the study, the shortest survival time after splenectomy was in those with aggressive lymphomas associated with immune cytopenias (DLBCL, T-cell). The simultaneous anemia, thrombocytopenia and leucopenia are the adverse prognostic signs of the splenectomy efficacy in patients with NHL associated with AIHA and ITP: 5 such patients of group 2 died 1 to 12 months after the surgery. Some researchers found the considerable survival time in patients with SMZL/SLVL [13, 14], however, in our group of patients it constituted on average only 39.8 months, only one patient with SMZL remained alive for 143 months after splenectomy. The particular splenic subtype of MCL with continuous remission after splenectomy is described in the references [19, 22]. We now follow one patient with MCL who had leukemic bone marrow and blood patterns and underwent lifesaving splenectomy due to massive splenomegaly, AIHA, and thrombocytopenia. He has been living without signs of lymphoma and therapy for 290 months after the surgery.

In case of massive splenomegaly, the spleen represents a great tumor mass. Five patients with a giant spleen underwent chemotherapy before the surgery without considerable effect: splenic size did not reduce, hemolysis and thrombocytopenia were preserved. Only one patient of group 1 and six patients of group 2 (25%) needed cytostatic therapy after splenectomy. The removal of a substantial tumor mass with spleen leads to improvement of the NHL course and response to treatment.

Those who had underwent splenectomy have 2 to 3 times higher risk of infection development (pneumonia, meningitis, sepsis), 2 times higher risk of deep vein thrombosis, including, 4.5 higher risk of pulmonary embolism [9] and portal venous thrombosis [8, 23]. We ascertain one (4%) case of post-splenectomy infection with fatal outcome in patient with SMZL + AIHA 9 months after the surgery. Smeltzer et al. [8] while examining 60 patients who had undergone splenectomy due to hematological pathology found the asymptomatic portal and splenic vein thrombosis in 38.3% of patients, whereby, in 5% of cases it as led to death.

Thus, despite considerable achievements in the field of modern hematology and surgery in treatment of NHL associated with immune cytopenias, splenectomy remains a serious challenge for specialists and requires a thorough approach in every clinical case.

CONCLUSIONS

1. Splenectomy remains an effective and relatively safe diagnostic and therapeutic method for treating NHL associated with immune cytopenias, particularly, in the presence of massive splenomegaly, hypersplenism and RPH.

2. Splenectomy in case of massive splenomegaly is technically relatively difficult depending on splenic size, adhesion to other organs of abdominal cavity and its vascularization. The perioperative mortality may be avoided under condition of proper pre- and intraoperative patient care, and the postoperative mortality rate (lymphoma progression, bleeding) equals to 7%.

3. As a result of splenectomy, the final diagnosis of NHL variant was specified or determined in 43% of patients, hemolysis relieved, hemoglobin and thrombocytes level stabilized, abdominal discomfort was eliminated, and the need for chemotherapy was reduced in 93% of patients.

4. The long-term outcomes of splenectomy and survival of patients with NHL depend mostly on NHL variant rather than presence or absence of concomitant cytopenia.

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ЕФЕКТИВНІСТЬ СПЛЕНЕКТОМІЇ ПРИ НЕХОДЖКІНСЬКИХ ЛІМФОМАХ, УСКЛАДНЕНИХ АУТОІМУННОЮ ГЕМОЛІТИЧНОЮ АНЕМІЄЮ ТА СИНДРОМОМ ЕВАНСА – ФІШЕРА

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Резюме. ***Мета:*** *визначити показання, хірургічну техніку і наслідки спленектомії при неходжкінських лімфомах (НХЛ), ускладнених аутоімунною гемолітичною анемією (АІГА) або синдромом Еванса — Фішера (СЕФ), на основі двадцятирічного досвіду виконання таких операцій.* ***Об'єкт і методи:*** *проведено 10 спленектомій при НХЛ, ускладненій АІГА (I група), та 18 спленектомій — при НХЛ, ускладненій АІГА та імунною тромбоцитопенією — СЕФ (II група). Результати оцінювали безпосередньо після операції та при тривалому спостереженні протягом 3–201 міс (медіана 68 міс) у I групі та 1–290 міс (медіана 195,5 міс) — у II групі.* ***Результати:*** *показання до спленектомії при НХЛ — наявність імунних цитопеній, резистентних до кортикостероїдів і цитостатичної терапії, які супроводжуються масивною спленомегалією, регіонарною портальною гіпертензією та гіперспленізмом. Операція спленектомії при масивній селезінці технічно досить складна, залежить від розміру органа та наявності прилягання. Післяопераційна смертність (прогресування лімфоми, кровотеча) становить 7%. У 93% хворих спостерігали позитивний безпосередній результат хірургічного втручання. При НХЛ, ускладненій АІГА, медіана безподійної виживаності після операції становила 29 міс (12–49 міс), а загальної виживаності — 31,0 міс (18,1–52,2 міс) з 3-річною виживаністю 45% пацієнтів і 5-річною — 22%. У хворих на НХЛ із СЕФ медіана безподійної виживаності сягала 22 міс (5–52 міс), а медіана загальної виживаності — 50 міс (12–97 міс), причому 3-річну виживаність відмічено у 62% хворих, а 5-річну — у 31%. Найменша тривалість життя після спленектомії зафіксована у хворих на агресивні лімфоми, ускладнені імунними цитопеніями (В-великоклітинна дифузна лімфома, Т-клітинні лімфоми).* ***Висновки:*** *спленектомія залишається ефективним і доволі безпечним діагностично-лікувальним методом при НХЛ, ускладнених імунними цитопеніями, особливо за наявності масивної спленомегалії, регіонарної портальної гіпертензії та гіперспленізму. Віддалені результати спленектомії значною мірою залежать від варіанта НХЛ.*

Ключові слова: неходжкінська лімфома, спленектомія, аутоімунна гемолітична анемія, імунна тромбоцитопенія.

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