UDC: 616-006.441:616-08:617-089

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Results of surgical treatment and immunochemotherapy of primary non-Hodgkin's lymphomas of the orbit

Relevance: *Treatment of non-Hodgkin's lymphomas (NHL) of the orbit is an acute problem in oncophthalmology. In recent years, much importance in developing the tactics of treating lymphomas of the orbit is given to prognostic factors that influence the effectiveness of treatment and total survival of patients.*

Purpose of the study *was to assess the effectiveness of surgical treatment in combination with immune chemotherapy in patients with lymphoma of the orbit depending on prognostic factors and to achieve a better quality of life of patients.*

Results: *The results of histological and IHC verification of diagnosis and combination treatment of 17 patients with malignant lymphomas of the orbit were analyzed. The treatment outcome was compared by stage of the disease and the methods of treatment (surgery, immune chemotherapy). Surgery and immune chemotherapy of advanced stages of primary lymphomas of the orbit proved to be more effective; the remission amounted to 80%. The quality of life by ECOG scale has improved from 3-4 before treatment to 1 after treatment. Also, the predictors influencing the treatment effectiveness were identified. The total 3-years survival of patients after combination treatment amounted to 98.6%.*

Conclusion: *All studied tumors had a high proliferative index (above 80%) what dictated the use of adjuvant immunochemotherapy in all cases of B-cell lymphoma. In all patients with advanced stages, the use of combination therapy (surgery + immune PCT) allowed achieving a better effect compared with surgery alone, what has proven the adequacy of the chosen treatment tactics.*

Keywords: *primary malignant lymphoma of the orbit, surgical treatment, chemotherapy, and therapy prognosis.*

Introduction. Non-Hodgkin lymphomas (NHL) of the eye orbit make up from 8 to 12% of all primary extranodal NHLs [1]. According to other authors, primary NHL of the orbit account for 2 to 4% [2], 5 to 14% [3] of all extranodal lymphomas and 37.3% of all malignant orbit tumors [4]. The share of lymphomas in primary tumors of the orbit is also controversial. Academician A.F. Brovkina et al. report that they constitute more than half of primary orbit tumors [4], the other sources – no more than 10% [5].

NHLs of the orbit belong to extranodal lymphomas. They most often have a B-cell origin with a predominantly indolent course [1]. In the literature, extranodal NHLs range from 24% to 40.7% of all NHLs [6]. Poddubnaya et al. [7] report that extranodal NHLs account for 24-48% of all NHLs, while NHL of the orbit, the eye, and its sinus make 4.1 to 8% of all extranodal lymphomas [6]. In all disseminated forms, the involvement of orbit and conjunctive tissues is limited to 5.3% of patients [2]. Lymphomas make 37.3-40 % of all malignant neoplasms of the orbit [4].

WHO has classified a new variant of lymphomas, including B-cell lymphomas from MALT-type marginal cells, i.e., tumors developing from lymphoid tissue associated with mucous membranes. Among primary NHL of visual organs, the most frequent are indolent MALT lymphomas that make up to 54.4% [2, 8] and tumors from the cells of the mantle zone - up to 23.5% [7, 9, 10]. Diffuse large B-cell lymphoma (DLBCL) of the orbit ranks third in incidence among other lymphomas.

Lately, prognostic factors affecting treatment efficacy and patient survival are of particular importance when developing tactics for treating lymphomas of the orbit. The disease prognosis for NHL of the orbit was estimated by International Prognostic Index (IPI), which considers the patient's age (over 60 years old), general status by ECOG, LDH in serum (over 450 IU / l), Ki 67 proliferative index, IHC data, and Ann Arbor classification stage.

Purpose of the study was to assess the efficacy of combination therapy of patients with orbital lymphoma depending on prognostic factors.

Materials and Methods: We have analyzed the literature data and the results of our own study when conducting combination treatment in patients with lymphoma of the orbit.

The inclusion criteria: primary patients above 18 years with B-cell lymphoma, verified by histology and IHC tests, regardless of proliferative activity (Ki 67) and tumor stage; ECOG performance status – NMT 3. Other inclusion criteria included: ANC ≥1,000/μL, PLT CNT ≥50,000/μL, serum creatinine and urea levels ≤1.5x ULN, ALT and AST ≤2.5x ULN. Overall 3-year survival rate.

All surgery interventions were planned individually based on the findings of radiological examinations. Ultrasonography before the operation was performed using ex-

pert class "Logiq-7" ultrasonographer. We used multi-frequency transducers: linear with a frequency of 5-7.5 MHz and convex with a frequency of 3.5-5 MHz. Additionally, to assess the vascularization of the DDC, Power Doppler Mapping and SD in real-time, when the second tissue harmonic mode is activated.

All 17 patients received treatment and diagnostic orbitotomy with the removal of the orbit tumor and rapid histological examination of the surgical material. A rapid survey was conducted to exclude other morphological forms of neoplasms, which could affect surgical tactics.

Killian's transcutaneous orbitotomy was performed in 11 (64.7%) patients, transpalpebral orbitotomy – in 3 (17.6%), external orbitotomy by bone-temporal access – in 2 (11.7%), and by Smith access – in 1 (5.8%) patient.

After surgery, the patients received polychemotherapy (PCT) in different regimens depending on the prognostic factors (stage of the process, IHC data, proliferative index, etc.). The patients with B-cell lymphomas and CD 20 (+) antigene expression received PCT in the R-CHOP regimen (6 to 8 courses): Rituximab 375 mg/m^2 on Day 1, IV, Cyclophosphamide 750 mg/m^2, Doxorubicin 50 mg/m^2, Vincristine 1.4 mg/m^2, all i / v on Day 2, prednisolone 40 mg/m^2 on Days 1-5. The patients with T-cell NHL received PCT in the CHOEP regimen (Cyclophosphamide 750 mg/m^2, Doxorubicin 50 mg/m^2, Vincristine 1.4 mg/m^2 - all i / v on Day 2, Etoposide 100 mg/m^2 on Days 1-3 i.v., and Prednisone 40 mg/m^2 i.v. on Days 1-5), 6 courses in total. Five patients with stage IV of the process underwent an orbitotomy and partial removal of the tumor and subsequent immune PCT in the R-CHOP scheme up to 3-4 courses.

The effectiveness of treatment was assessed by the results of clinical, laboratory and instrumental studies (full blood count (FBC), lactate dehydrogenase (LDH), alkaline phosphates (ALP), radiation methods).

The primary points of assessment included: size and localization of the primary tumor according to radiology examination, FBC, blood chemistry (LDH and ALP), tumor biopsy IHC, myelogram, cytogenetic test results, immunological studies and the patient's activity by ECOG scale. The primary points were assessed by ophthalmoscopy, FBC, blood chemistry (LDH and ALP), tumor needle biopsy, orbitotomy with subsequent histological examination of the tumor, IHC-test to determine the CD 20 antigene expression.

The secondary endpoints of assessment included: tumor regression rate (complete, partial regression) based on the tumor size reduction data, intoxication symptoms relief, the improvement of results of radiology examination, blood biochemistry (LDH and ALP), the myelogram data after 4-6 PCT courses, as well as the EGOC performance status and 3-year total survival of the patients.

Results and Discussion: We analyzed the results of a combination treatment of 17 patients with NHL of the orbit, of them, 8 men and 9 women. The patients were aged 23 to 92, average age – 57 years. Distribution of disease stage: stage III – 12 (70.5%), stage IV – 5 (29.4%). Unilateral damage to the orbit – in 15 (88.2%) patients, bilateral – in 2 (11.7%) patients. In 12 (70.5%) patients, the process was localized in the anterior parts of the orbit, in 5 (29.4%) – in the middle and deep parts of the orbit with distribution to the maxillary sinus. All patients had the EGOC performance status 3-4 before the treatment.

The clinical picture of the NHL of the orbit was characterized by different degrees of exophthalmos, the difficulty of reposition, ptosis of the upper eyelid, diplopia, displacement of the eyeball, restriction of its mobility.

Radiation examination (figure 1) showed the process localization in the orbit, namely, nodular form of NHL and allowed to determine the damage to the lacrimal gland. Twelve patients (70.5%) with frontal localization of the process in the orbit underwent cytological verification of the process. The cytological sign of lymphoma was the detection of the proliferation of abnormal lymphoid elements in the resulting biopsy. Five (29.4%) patients with deep localization of the tumor underwent orbitotomy with subsequent histological and IHC examination.

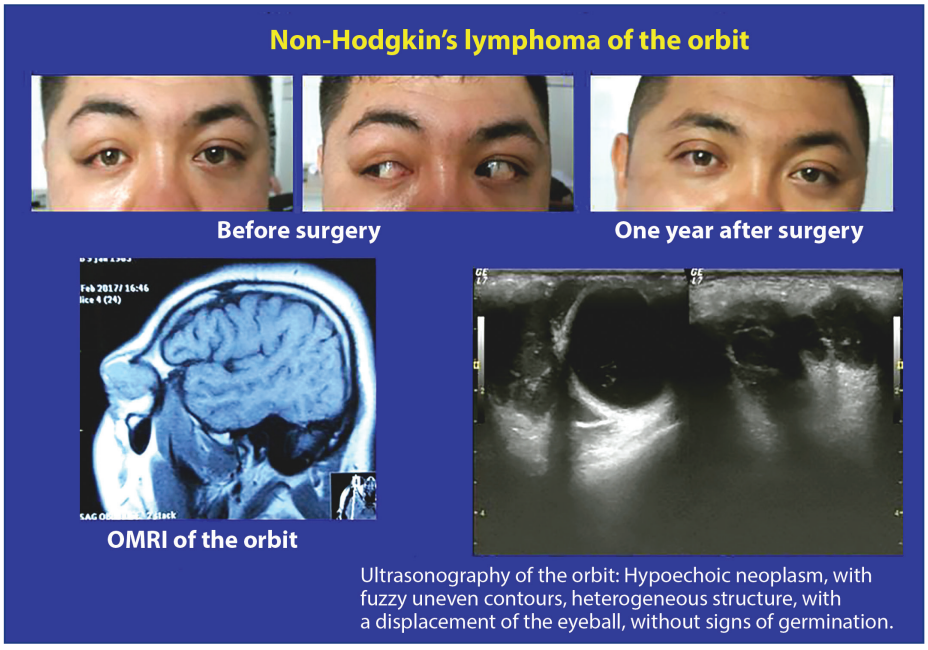

Figure 1 – Patient A., 45 years (episodes before and after treatment)

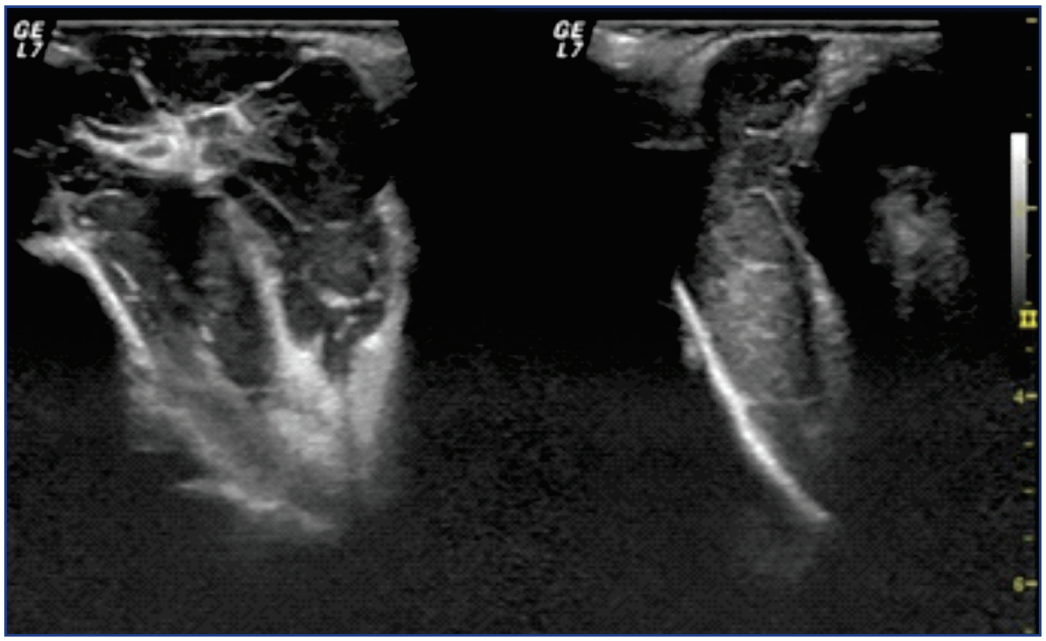

Figure 2 – Ultrasonography, Patient A., 67 years. Lymphoma of the orbit

The study of the incidence of morpho-immunological variants of primary NHL has shown the prevalence of DLBCL (8 cases, 47.0%) and MALT lymphoma (4 cases, 23.5%). Other cases included lymphomas from the mantle zone (2 cases, 11.7%), follicular lymphoma (2 cases, 11.7%), and T-cell lymphoma (1 case, 5.8%).

Saakyan et al. [10] reported the number of primary B-cell lymphomas of the orbit not to exceed 50% what is fully consistent with our data.

In most cases (16 out of 17), the tumor had high proliferative activity: Ki 67 varied from 56 to 80%. Besides, IHC examination has shown the CD20 antigene expression in all but one patient.

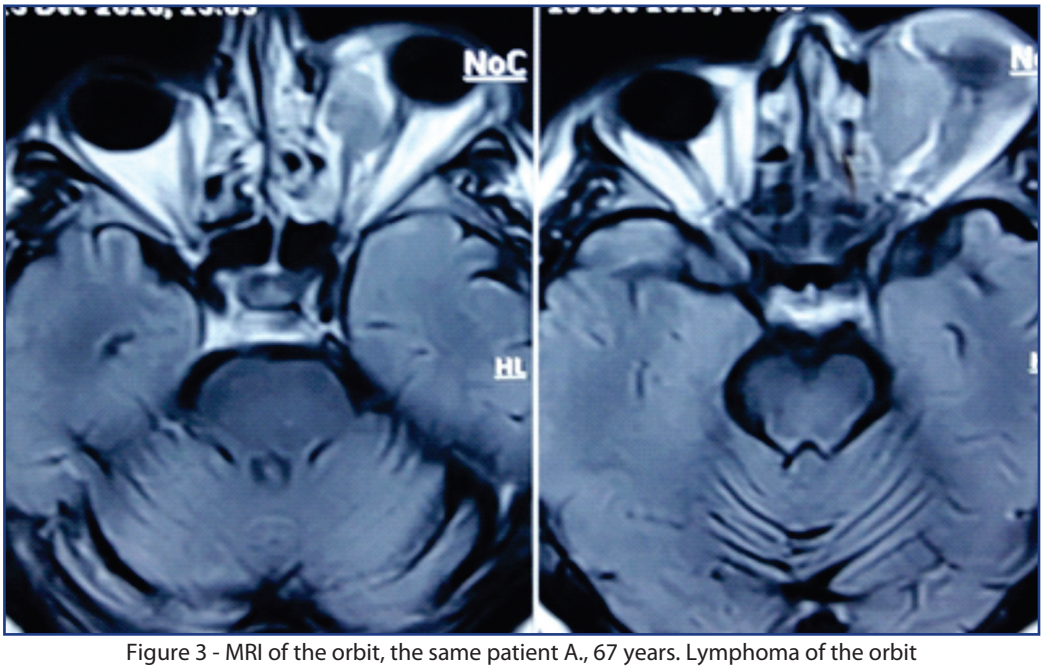

Figure 3 - MRI of the orbit, the same patient A., 67 years. Lymphoma of the orbit

Lymphoproliferative diseases of the orbit suggest conservative surgery. It is essential not only to preserve the vision but to avoid, as much as possible, such violations of the organ of vision, as squint, ptosis, coarse postoperative scars. Individual planning of operations and use of microsurgical equipment, careful hemostasis when performing orbital operations allowed to reduce the percentage of postoperative complications in this category of patients by 2-2.5 times compared to the results without individual planning of operations.

After immune PCT, all patients had remission of the disease, confirmed by radiation examination (more than 80%).

Only in one case, due to the residual tumor in the maxillary sinus, the patient had to undergo additional remote gamma therapy in the single boost dose 2 Gr to total boost dose 36 Gr after 4 PCT courses. One month after the radiation therapy radiation examination shows partial regression of the tumor in the maxillary sinuses. It is worth noting that before treatment all the patients, especially those with stage IV of the disease, had high LDH (560 to 645 U / L) and ALP (270 to 320 U / L) levels. After the conducted combination therapy, the LDH and ALP levels approached normal values: LDH varied in the range of 259 - 332 U / L and ALP – 132 to 143 U / L. FBC values were also normalized after their treatment.

After surgery and immune PCT, the ECOG performance status was equal to 1. All patients are currently in remission and under surveillance at the place of residence. Regardless of the effectiveness of treatment, 6-7 months later, they should pass PET-CT to evaluate the effectiveness of treatment and predict further therapy.

Analysis of data obtained in the limited cohort of patients with tumors of B-cell origin stages III-IV, leads to the following conclusion: the scope of surgery and the PCT regimens depended mainly on the stage and localization of the process, whereas the immune PCT was administered depending on the cell origin of the tumor and the proliferative index. Nearly all tumors had a high proliferative index, which dictated the use of adjuvant immune PCT in all cases of B-cell lymphoma. In all patients at terminal stages, the combination therapy (surgery + immune PCT) allowed to achieve a better effect compared with the surgical method, which indicates the adequacy of the choice of treatment tactics.

It should be noted that the effectiveness of treatment and the disease forecast did not significantly depend on the patient age. The liver enzymes (LDH and ALP) were back to normal levels after surgery and immune PCT what indicates their prognostic value.

The quality of life of patients has improved after treatment; the ECOG performance status was equal to 1.

Conclusions:

1. The orbit of the eye is most often affected by B-cell NHL. In our study, 16 out of 17 patients (94%) had B-cell lymphoma vs. 8 (47%) patients with DLBCL.

2. Combination therapy (surgery + immune PCT) has proven its high efficacy against advanced stages of the disease. Remission has exceeded 80%.

3. The proliferation index of tumors, the expression of CD 20 (+) antigen, as well as the LDH and ALP levels have a more significant effect on the prognosis of the disease compared with other prognostic signs.

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