Follicular lymphoma in children and adolescents: clinical, diagnostic and therapeutic features

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Abstract

Follicular lymphoma (FL) is one of the most common non-Hodgkin's lymphomas in adults, while it is a diagnosis of exclusion in adolescents and children. Clinical manifestations of FL in children are represented by long-term asymptomatic lymphadenopathy, less commonly by extranodal areas involvement. There are no standards for FL treatment in children, and therapy can vary from observational tactics (with the radical resection of a single focus during a biopsy) to the use of radiation therapy and polychemotherapy. Pediatric-type follicular lymphoma (PTFL) was first identified as a distinct variant in 2008 in the World Health Organization classification of hematopoietic and lymphoid tissue tumors. Clinical, morphological (cytological type 3A), immunohistochemical (absence of BCL2 expression in the center of the follicle) and cytogenetic (absence of t(14;18)(q32;q21)) features served as the reason for separation into an independent nosological variant. Despite the term "pediatric", cases of PTFL have been described in adults over 30 years of age. Most often, the disease is diagnosed in the early stages (I, II) and is characterized by a favorable prognosis.

In children and adolescents, FL occurs not only of the pediatric type. We present a clinical case of a typical “adult” type FL (Grade 1–2) in a 17-year-old patient. The

CHOP therapy with rituximab resulted in a complete remission, which lasted more than 2.5 years.

Keywords: follicular lymphoma, pediatric-type follicular lymphoma, oncology, hematology, diagnosis, treatment

Introduction. Follicular lymphoma (FL) accounts for up to 25-35% of all non-Hodgkin's lymphomas (NHL) in adults, and up to 70% of all indolent lymphomas. Median age at diagnosis is 65 years, but FL has been reported in young adults and in the pediatric population. [1].

FL is derived from B cells in the germinal centers of secondary lymphoid follicles. Tumor cells express surface immunoglobulins and B-linear markers such as CD19, CD20, CD22, CD79a. Up to 85% of FL are characterized by the presence of the t(14;18)(q32;q21) translocation, which leads to overexpression of the BCL 2 protein, which suppresses apoptosis.

It should be noted that other cytogenetic events are also characteristic of FL, since the t(14;18)(q32;q21) translocation may be present in patients with diffuse large B-cell lymphoma (DLBCL) and, in a small percentage of circulating B-lymphocytes, in healthy people. FL is also characterized by mutations in the *KMT2D, CREBBP*, and *EZH2* genes responsible for chromatin remodeling [2, 3].

Depending on the number of centroblasts in tumor follicles, 3 cytological types are distinguished: 1^{st} – up to 5 centroblasts in one tumor nodule, 2^{nd} – from 6 to 15, and 3^{rd} – more than 15. The 3^{rd} cytological type is subdivided into subvariants 3A, with the presence of centrocytes, and 3B, characterized by massive fields of centroblasts [4].

Clinical manifestations of FL are usually asymptomatic lymphadenopathy, which can last for years. Less than 20% of patients present with B-symptoms and increased LDH levels.

In 2-3% of cases, FL can transform into more aggressive variants of lymphomas – most often into DLBCL, but cases of transformation into lymphoblastic lymphoma, acute lymphoblastic leukemia, and, in rare cases, Hodgkin's lymphoma are described. The pathogenesis of transformation is based on additional mutations both in the genes regulating epigenetic events and in the genes controlling the cell cycle, proliferation, as well as mutations involving the *TP53* and *c-MYC* genes. It is necessary to exclude transformation in the case of disease progression, a rapid increase in lymph nodes size, the appearance of new extranodal lesions, B-symptoms, and LDH levels increase [3,5,6].

In patients with local stages, various approaches to treatment are used – from conservative "watch and wait" strategy to the use of radiation therapy, rituximab alone or in combination with bendamustine, as well as in R-CHOP and R-CVP regimens. The absolute criteria for starting therapy are a large tumor mass, the B-symptoms presence, signs of disease progression, and impaired vital functions.

Radiation therapy is effective and safe in patients with local FL stage. According to Pugh et al., 2010, radiation therapy in patients with stages I-II can achieve a

long-term remission of more than 90%. However, relapses occur in about half of patients within 10 years of starting treatment. As an alternative in patients with local FL stages, the tactics of "watch and wait" can be used, due to the indolent disease nature. When comparing two different treatment approaches, 10- and 20-year disease-free survival was found to be 79% and 63% in the group of patients who received radiation therapy, and in the group of patients who did not received radiation therapy – 66% and 51 % respectively. The 10- and 20-year overall survival in patients received radiation therapy was 62% and 35%, and for the group without radiation therapy – 48% and 23%. Thus, for patients with local stages of FL, the use of radiation therapy is more effective [7].

Ardeshna K.M., et al., 2014, evaluated the efficacy of rituximab monotherapy (with or without rituximab maintenance therapy for 2 years) compared to "watch and wait" strategy. The study included asymptomatic patients with a small tumor mass. 3-year progression-free survival in the observation group reached 36%, while in the group of patients who received rituximab therapy it was 60% (without maintenance therapy) and 82% (with maintenance therapy). However, when evaluating 3-year overall survival, there were no significant differences in the three groups: 94% in the observation group, 96% in the group with rituximab therapy without maintenance, and 97% in the group with maintenance. Treatment with rituximab did not result in an improvement in overall survival, but increased the interval to the start of specific anticancer treatment – only 46% of patients in the observation group did not start special therapy (follow-up interval – 3 years), compared with 80% of patients who received rituximab [8,9].

There is no standard of first-line therapy in patients with advanced stages of the disease. Mondello P. et al., 2018, conducted a comparative analysis of therapy efficacy for advanced FL stages according to R-B (rituximab + bendamustine) and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimens. The complete remission rate was 77% in the R-B group and 80% in the R-CHOP group. Overall survival rates were also comparable, but progression-free survival showed significant differences between the two treatment protocols, 15 years (R-B) and 11.7 years (R-CHOP). The relapse rate was 16% and 41%, respectively. The authors conclude that the R-B regimen is more effective and leads to an increase in progression-free survival [1,10].

In the 2008 WHO classification of hematopoietic and lymphoid tissues tumors, pediatric-type FL (PTFL) was first identified as a distinct FL variant, which was primarily due to the morphological, immunohistochemical and cytogenetic tumor features, and not age-related aspects of diagnosis, since this FL subvariant occurs not only in children and young adults (18 to 30 years of age), but also in the older age group. Although FL is quite common among the adult population and accounts for up to 25-35% of all NHL, pediatric-type FL is a rare disease and does not

exceed 2% of NHL in children and adolescents. It is more common in boys (the ratio of boys: girls is 3:1) over the age of 10 years [12].

PTFL in most cases is characterized by the 3rd cytological type with blastoid morphology. For a long time, specific FL diagnostic criteria have not been identified, however, at present, the absence of t(14;18)(q32;q21), CD10 and BCL 6expression, and absence of BCL 2, BCL 6 rearrangements are described as characteristic PTFL signs.

The most common are I and II stages of the disease. Typical involvement of the lymph nodes in the head and neck, Pirogov-Waldeyer ring, gastrointestinal tract, testicles. Not typical LDH increase and B-symptoms presence [11,12].

Treatment standards for pediatric-type FL, taking into account the rarity of this nosology, as well as the relatively benign disease, have not been developed.

Oschlies I. et al., 2009, described treatment results of 25 patients with PTFL according to the NHL-BFM 90, NHL-BFM 95 and B-NHL BFM-04 protocols. Most cases (76%) were represented by disease stages I-II, with a predominant neck lymph nodes involvement. A 5-year EFS of 96±4% was achieved. A relapse developed in 1 patient with stage IV, initial CNS and lymph nodes involvement, and Nijmegen syndrome [12].

Liu Q. et al., 2013 presented treatment approaches in 34 PTFL patients. All cases were represented by stage I-II with involvement of the Pirogov-Waldeyer ring, testicles, or single lymph nodes (mainly the head and neck). Treatment approaches were variable and could be limited to only a surgical approach, or include the use of polychemotherapy (mainly R-CHOP regimen) with the optional use of radiation therapy. All patients achieved complete remission with a median follow-up of 18 months (maximum 120 months) [1].

Attarbaschi A. et al., 2013, conducted a retrospective study evaluating treatment outcomes in 63 PTFL patients, according to data from two large study groups – EICNHL and i-BFM. In 87%, stages I-II of the disease was detected. In 70% of patients, treatment included only polychemotherapy, 1 patient (2%) received rituximab alone. Of the 26% of patients whose treatment was limited to surgical resection of a single disease focus, followed by dynamic monitoring, only 1 patient developed a relapse. 2-year EFS and OS were 94% and 100% with a median follow-up of 2.2 years [13].

The analysis of the literature did not reveal any clinical case reports of "adult" type FL (grade 1-2) stage III or IV in adolescents. Therapy approaches of this extremely rare group of patients, the amount of treatment required and the need for maintenance therapy remain relevant tasks for researchers. We present a clinical

case of FL grade 1-2 (“adult” type) in a 17-year-old patient with all lymph nodes groups and spleen involvement.

Clinical case. Patient K., 17 years old, with follicular lymphoma, grade 1-2, all lymph nodes groups and spleen involvement, III stage. She has been ill since July 23, 2020, when, after a viral infection caused by Herpes zoster, she complained of enlarged neck lymph nodes. On outpatient basis, conservative treatment (antibacterial therapy) was carried out, however, complaints persisted, and later fever appeared. In the complete blood count an ESR increase to 21 mm/h, anemia of the 2^{nd} degree and thrombocytopenia of the 1^{st} degree were revealed. Ultrasound revealed hepatosplenomegaly. To exclude lymphoma, she was referred to a pediatric oncohematological center at the place of residence.

Upon admission, the patient's condition was severe due to pronounced lymphoproliferative and intoxication syndrome. Enlarged submandibular, anterior and posterior neck, occipital, axillary, inguinal lymph nodes were palpated: multiple, painless, dense, and soldered to each other and surrounding tissues. On the right anterior-lateral neck surface, a conglomerate of lymph nodes measuring 9×5 cm was determined. The liver was palpated 6 cm and the spleen – 8-9 cm below the edge of the costal arch.

Examination carried out:

- Ultrasound of peripheral lymph nodes, abdominal cavity and retroperitoneal space: heterogeneous lymph nodes are noted in the neck, supra- and subclavian, axillary, inguinal areas, as well as in the abdominal cavity and retroperitoneal space;
- CT of the paranasal sinuses, neck, chest, abdominal cavity, retroperitoneal space, pelvis: lymphoproliferative process with neck, axillary, supraclavicular, para-aortic, iliac, inguinal lymph nodes involvement, severe hepatosplenomegaly;
- Trephine biopsy from 2 points: bone marrow tumor involvement not detected;
- Biochemical blood analysis: LDH – 157.4 U/L, other parameters within the reference values.

Taking into account the clinically pronounced lymphoproliferative syndrome, the absence of bone marrow involvement, a neck lymph nodes biopsy was performed to verify the diagnosis. The results of histological, immunohistochemical and cytogenetic studies of t(14;18)(q32;q21) were obtained: morphological picture of Grade 1-2 follicular lymphoma (**Fig. 1**).

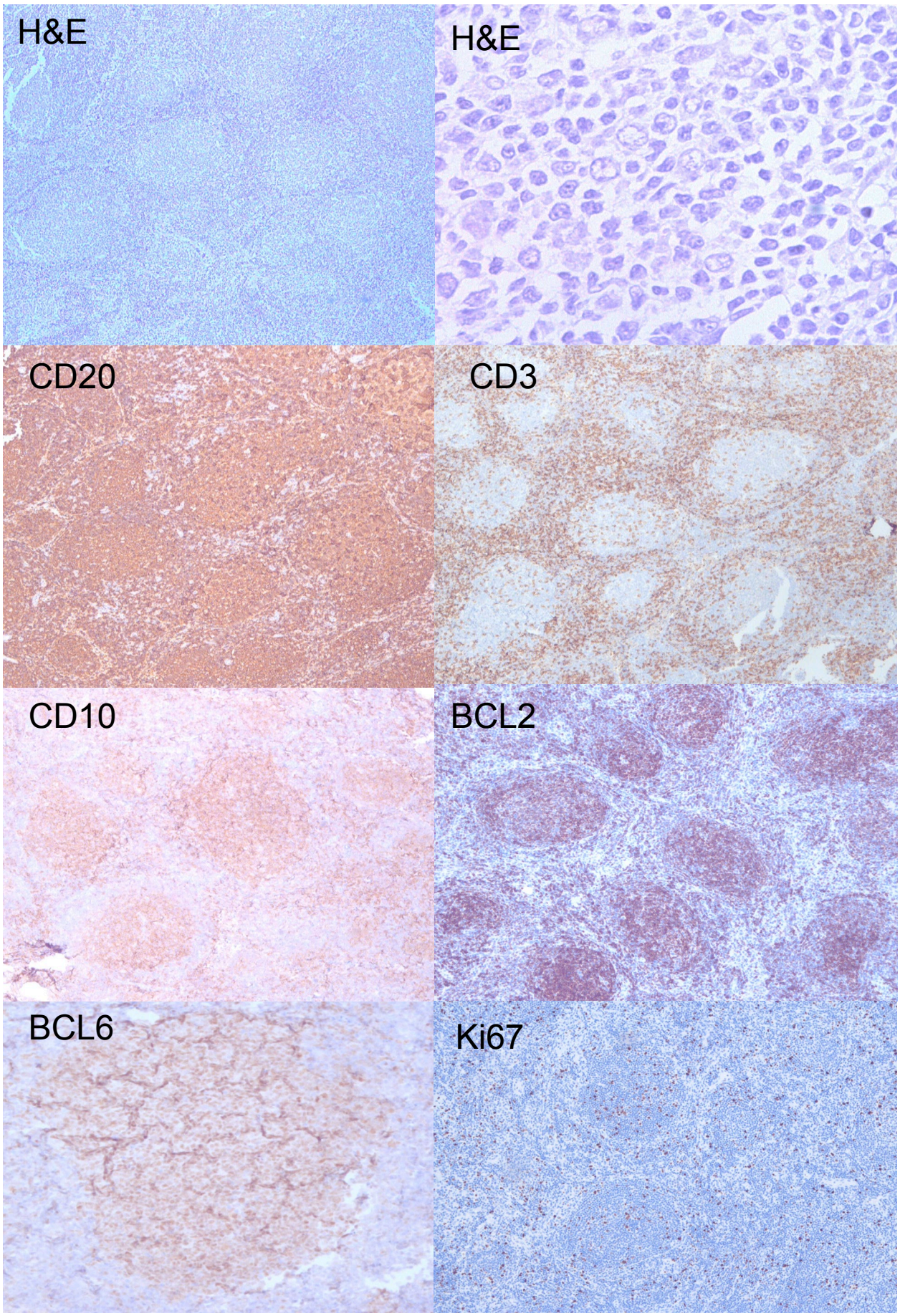
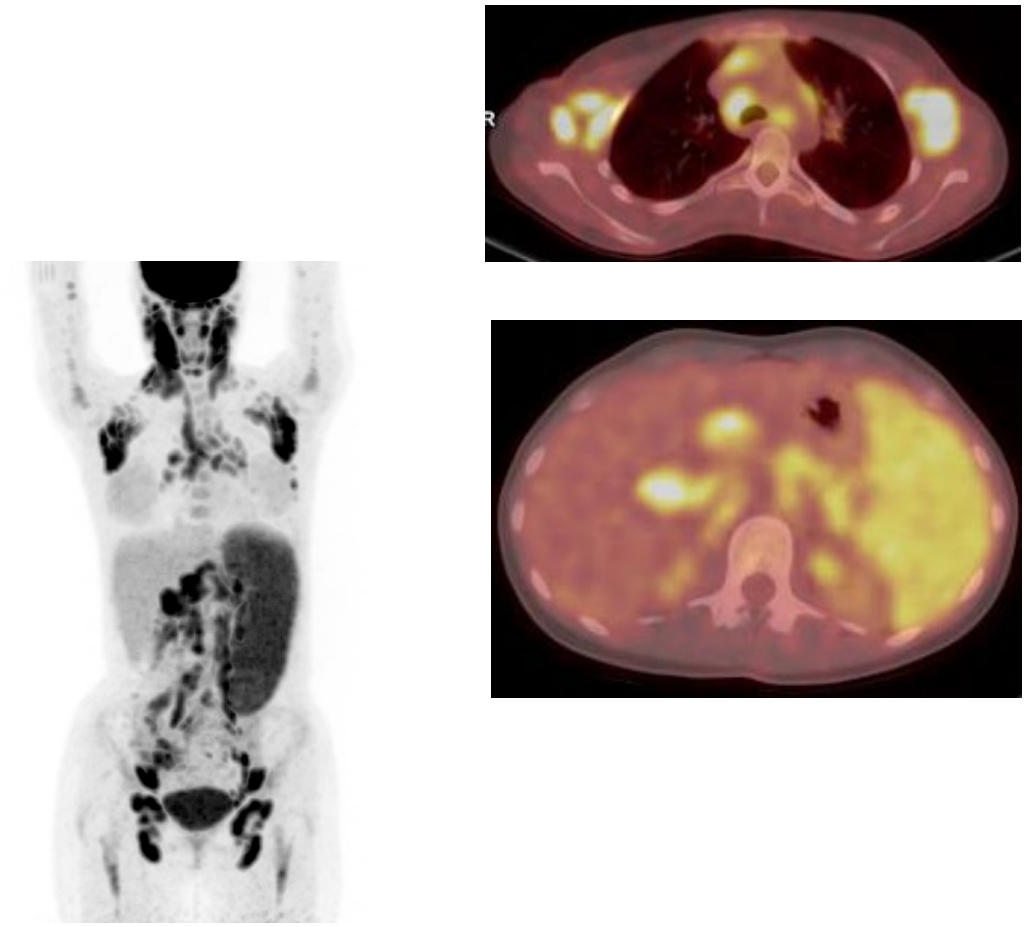


Fig. 1. Morphological picture of the lymph node. Multiple follicular structures represented by a mixture of large centroblasts. The follicles are represented by

CD20-positive B-lymphocytes, the cells of the parafollicular zones are represented by CD3-positive T-lymphocytes. Cells of germinal centers of lymphoid follicles have an intense expression of CD10 and BCL6. Tumor cells in follicles coexpress BCL2, Ki-67 expression level is low.

Additionally, in order to determine the tumor extent, PET/CT with ^{18}**F-FDG** was performed: metabolically altered lymph nodes of the submandibular groups, in the neck soft tissues, supraclavicular groups, prevascular group, parasternal group, paratracheal, bifurcation, bronchopulmonary, axillary groups, in the hepatic and lienis hilus, paraaortal, iliac and inguinal groups, and in the spleen are determined.

Fig. 2. A whole body positron emission tomography combined with computed tomography with intravenous contrast. Initial examination. Tumor lymph nodes are visualized on both sides of the diaphragm, spleen involvement.



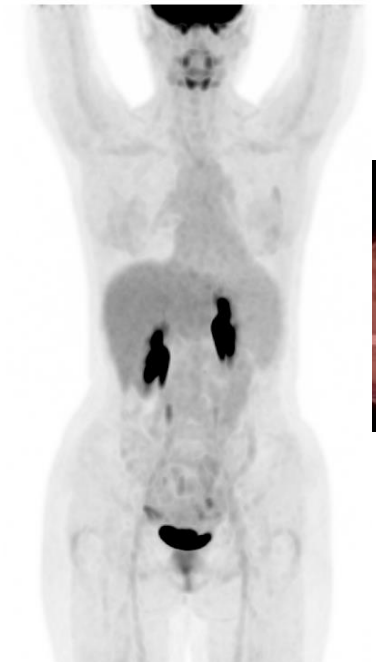
Special treatment was started: cytoreductive prephase, 2 polychemotherapy courses according to the R-CHOP:

- Rituximab 375 mg/m^2 IV, day 0;

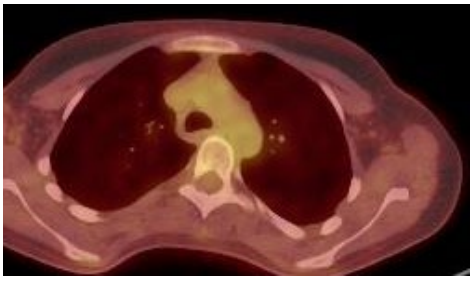
- Doxorubicin 50 mg/m^2 IV, day 1;
- Cyclophosphamide 750 mg/m^2 IV, day 1;
- Vincristine 1.4 mg/m^2 (total no more than 2 mg) IV, day 1;
- Prednisone 100 mg orally, days 1-5.

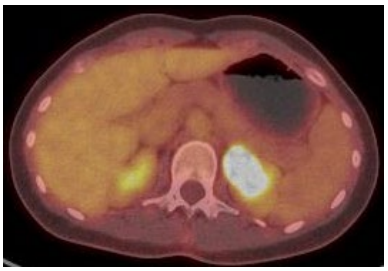
After two polychemotherapy courses, there was a significant decrease in the size of all previously determined foci. Control PET/CT of the whole body – DC3.

Fig. 3. A whole body positron emission tomography combined with computed tomography with intravenous contrast. Control during treatment (after 2 R-CHOP courses).



A complete metabolic response is noted, a significant decrease in the size of the tumor lymph nodes and spleen is determined.





The treatment was continued according to the previous scheme, patient received 4 more R-CHOP courses (6 in total), 3 rituximab infusions. During the control examination on PET/CT of the whole body (April 2023), there were **still no** data for pathological metabolic activity in previously identified lesions.

During treatment a complete response was achieved. Currently, the patient is in remission, the follow-up period from the end of treatment is more than 30 months.

Discussion. Despite that pediatric-type FL is a well-defined morpho-immunological nosological entity with “pediatric” in its name, this FL variant occurs not only in children. Similar cases have also been reported in adolescents and young adults [6, 14]. Most PTFL cases are stage I and II, for which, according

to some studies, tactics limited to surgical removal are successful [15]. The world literature also describes other treatment approaches, including the use of chemo- and radiation therapy. The "gold standard" of treatment, considering the rarity of this disease, as well as its relatively benign course, has not been developed. Nevertheless, despite the lack of unified therapy approaches, the amount and duration of treatment required, the survival rate for PTFL patients reaches 95-100% [13].

The uniqueness of the clinical observation we have described in an adolescent is the diagnosis of grade 1-2 FL, which is the most typical for adult patients and the systemic extent of the disease – in the analysis of both domestic and foreign literature, no similar cases were found with all groups of lymph nodes involvement. As a therapeutic option, R-CHOP chemotherapy was chosen with therapy efficacy evaluation after 2 courses. Considering the obtained pronounced positive effects, the treatment was continued as before. A total patient received 6 R-CHOP courses, after which rituximab maintenance therapy was carried out – 3 courses. Despite the initial disease extent, a complete metabolic response was achieved after two R-CHOP courses.

Conclusion. Thus, FL in children and adolescents can be represented not only by typical "pediatric" variants, but also, as in the clinical case described above, by the "adult" (grade 1-2) variant that required R-CHOP immunochemotherapy. This approach proved to be successful – a complete remission was achieved, which has lasted for more than 2.5 years.

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Authors' contributions

All the authors contributed equally to concept and design development, provision of research materials, data collection and processing, data analysis and interpretation, article writing, final article approval;

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The patient signed an informed consent for the publication of her data.