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LYMPHOPROLIFERATIVE PROCESS ASSOCIATED WITH EBV INFECTION

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Abstract. *A clinical case of persistent lymphadenopathy associated with Epstein-Barr virus in a 14-year-old child is described. The peculiarity of the disease course was the indication for biopsy and histologic examination of the lymph nodes. The obtained immunohistochemical marker CD-30 determined the tactics of further observation of the patient.*

Key words: *Epstein-Barr virus (EBV), CD30-cells, lymphadenopathy, children*.

Introduction.

Epstein-Barr virus (EBV) is an extremely common pathogen, with more than 90% of adults being infected. In some cases, EBV infection can lead to clinically significant pathology, which can manifest in the form of prolonged lymphadenopathy. EBV plays a key role in the development of certain lymphomas and neoplastic diseases (B-, T-, NK-cell lymphomas, epithelial and mesenchymal malignancies) [1]. EBV-associated neoplastic diseases sometimes are diagnosed in patients without immunodeficiency. The lymphoproliferative process develops in conditions of interaction between EBV, immunogenetic factors, environmental factors, and the patient's immune system [2].

Aim: to study the clinical course of the disease with the risk of developing an EBV-associated lymphoproliferative process in a patient with generalized persistent lymphadenopathy.

Materials and methods. The results of the patient's tests were analyzed - clinical, laboratory, instrumental, pathomorphological - histological, immunohistochemical studies of the biopsy of the liver.

Clinical case description. Female patient M., 14 years old, with generalized lymphadenopathy syndrome was hospitalized in the Department of Oncohematology

and Intensive Chemotherapy with complaints of difficult nasal breathing, periodic fever up to 37.6 °C, enlarged cervical and axillary lymph nodes, general weakness.

At the age of 10, the girl had acute form of EBV infection of moderate severity. The diagnosis was confirmed by the presence of atypical mononuclear cells (18%) and lymphocytosis (61%) in the complete blood count, IgM VCA to EBV (ELISA), and positive results of PCR blood test. 9 months after the disease debut, a recurrence of EBV infection was confirmed, which clinically manifested with subfebrile body temperature, fatigue, and enlargement of the anterior and posterior cervical lymph nodes. Anti VCA IgM, EA IgG, anti EBNA IgG, and viral DNA were detected in saliva. In 2 months, EBV was not detected in blood and saliva. After 7 months and 11 months, 2 more episodes of reactivation of chronic EBV infection were registered. Until the time of the disease, the child developed and grew according to age.

On admission the general condition of the patient was of moderate severity. Anterior and posterior cervical lymph nodes were enlarged - on the left up to 1.5 - 2 cm in diameter, on the right - 2-3 cm in diameter, tender to palpation. Axillary lymph nodes on the right side were in the form of a 7x7 cm conglomerate (1 to 2 cm in diameter), on the left side - from 1.5 to 2 cm in diameter, sensitive to palpation, especially on the right side, densely elastic, mobile. There were no clinical signs of catarrhal syndrome, nasal breathing was difficult. Tonsils were hypertrophied (grade II), pink, without exudates. Respiratory rate - 20/min. Heart sounds were rhythmic, audible, heart rate was 98 beats/min, blood pressure - 110/60 mm Hg. The abdomen was soft, not painful to palpation. The liver and spleen were not enlarged. There were no peripheral edema. Meningeal signs were negative. No focal neurological symptoms were detected.

Diagnosis on admission: generalized lymphadenopathy syndrome.

The following tests were performed: complete blood count: Hb - 128 g/L, ESR - 4.0 x 10^{12}/L, CP - 0.9, hematocrit - 0.41, leukocytes - 2.6 x 10^{9}/L, band cells - 22%, segmented neutrophils - 29%, lymphocytes - 33%, monocytes - 7%, eosinophils - 9%, ESR - 15 mm/h, platelets - 183 x 10^{9}/L.

Biochemical blood test: total protein - 87.8 g/L, urea - 5.0 mmol/L, creatinine -

57.5 μmol/L, total bilirubin - 18.31 μmol/L, direct - 6.10 μmol/L, indirect - 12.21 μmol/L, iron (serum) - 4.6 μmol/l, ALT - 35 U/l, AST - 34 U/l.

Coagulogram: prothrombin index - 100%, plasma recalcification time - 80 seconds, fibrinogen - 355.2 mg/dL.

Results of the ELISA test and blood PCR: antiVCA IgG, antiEBNA IgG - 69,58 IU/mL, anti EA IgG, EBV DNA in serum – $4,94x10^5$ copies/mL; anti CMV IgM, anti CMV IgG -negative, anti Toxo IgM – negative, anti Toxo IgG> 8 IU/mL, anti HIV1/2 – not detected.

Immunological testing: Ig G - 17,5 U, IgA - 3,1 U, IgM - 2,30 U.

Ultrasonography of abdominal organs: the liver is located typically, does not protrude from the edge of the rib arch, the size of the right lobe is 120 mm, the left lobe is 60 mm, the parenchyma is of normal echogenicity, the bile ducts are not thickened, the gallbladder - the wall is thickened, the pancreas is visualized throughout, echogenicity is increased, spleen is not enlarged, structure is homogeneous, 120 x 50 mm, kidneys are typically located, contours are clear, smooth, differentiation of cortical and cerebral layers is preserved, parenchyma echogenicity is normal, medullary complex is not distended. Mesenteric lymph nodes are small, not enlarged.

Ultrasonography of lymph nodes: along the vascular bundles there are submandibular, posterior cervical lymph nodes with a diameter of 15-22-25 mm, hypoechoic, with a slight blood supply; supra- and subclavian lymph nodes - 12-19 mm, mediastinal lymph nodes - 10-12 mm; axillary lymph nodes on the right and left sides 10-15-25-35 mm; inguinal lymph nodes on both sides with a diameter of 10-16 mm, hypoechoic, with a slight blood supply.

The child was suspected of having Hodgkin's lymphoma, and therefore an excisional biopsy of the right axillary lymph node was performed. Its results: cytoarchitecture was erased in some places, there were areas of lymphocyte proliferation, partially histiocytes without fibrous strands, single large rounded lymphocytes with a large hyperchromic nucleus were observed. Conclusion: Hodgkin's lymphoma, lymphohistiocytic variant.

Histological specimens were sent to the reference laboratory (pathological

anatomy department of the Kyiv City Oncology Hospital). A microscopic description of the cervical lymph node was obtained: the structure is changed due to a large number of hypertrophied lymphoid follicles with active proliferation centers. The mantle zone around the follicles is thin. In the interfollicular space, there are macrophages in big amount, histiocytes, activated B-lymphocytes, as well as a large number of vessels with edematous endothelium. In one of the sections, there is some abrasion of the tissue pattern, the contours of the lymphoid follicles are not clear. This section was taken for immunohistochemical examination. Results of immunohistochemical examination: CD45 (PD7/26) positive membrane reaction in the majority of cells in the lymph node parenchyma. CD30 (Bcr-H2) - positive membrane reaction in some large cells that have Golgi staining, which makes them extremely similar to Hodgkin's cells, but there are few such cells. CD15 (BY87) is a negative reaction. Conclusion: the morphological structure of the examined lymph node indicates reactive hyperplasia with signs of severe immune blast transformation in lymphoid follicles and the presence of individual CD30-positive cells, possibly activated B lymphocytes. Since CD30 large cells are found in one of the lymph node sites, strict medical monitoring is recommended and, in the absence of positive dynamics, a repeated biopsy is recommended.

The patients was prescribed treatment: valacyclovir 1000 mg 3 p/day for 21 days, with a switch to suppressive doses of 500 mg 3 times a day for a month.

Ultrasonography of the lymph nodes 1 month after completion of antiviral therapy: submandibular, posterior neck lymph nodes 10-15 mm in diameter, hypoechoic, with insignificant blood supply; supra- and subclavian lymph nodes 12-15 mm, mediastinal lymph nodes 10-12 mm; axillary lymph nodes on the right and left sides 10-12 mm; inguinal lymph nodes on both sides 10-12 mm in diameter, hypoechoic, with insignificant blood supply.

The child was observed on an outpatient basis by a pediatrician and an infectious diseases specialist. Every 3 months, she undergoes medical examinations by a pediatrician with EBV markers detection and lymph node ultrasound to determine the need for further imaging methods of examination.

Conclusion.

The presence of CD30 can indicate both reactive changes and malignant process, in particular Hodgkin's lymphoma. Therefore, it is recommended to analyze histological, immunohistochemical and molecular genetic data in the dynamics of the disease. Antiviral therapy (valacyclovir) had a positive clinical effect in the patient. Given the ambiguous efficacy of antiviral drugs, it is advisable to decide on their prescription taking into account all possible factors and risks for a particular patient. In children with persistent generalized lymphadenopathy associated with EBV, careful monitoring of the clinical condition and laboratory parameters is necessary for early detection of possible complications or relapses of the disease. In the presence of persistent lymphadenopathy, a biopsy should be considered.

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