LYMPHOPROLIFERATION AT THE ONSET OF PID PATIENTS IN THE REPUBLIC OF BELARUS

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Lymphadenopathies and/or splenomegaly can be part of the clinical spectrum of several primary immunodeficiencies, including diseases with immune dysregulation, and autoinflammatory disorders. PID-associated lymphoproliferation is a serious diagnostic problem in clinical practice, especially in the field of oncology and hematology [1, 2, 3]. The finding of lymphadenopathy/splenomegaly in a patient with diagnosed immunodeficiency raises the question of the differential diagnosis between benign lymphoproliferation and malignancies. Non-malignant lymphoid hyperplasia is more common than malignant hyperplasia in PID patients. In some PID variants, lymphoid infiltration of non-lymphoid organs (lungs, liver, intestines) develops, which can be difficult to interpret. Establishing a genetic diagnosis today is becoming a necessity, as it provides genotype-specific patient management, influences the choice of therapeutic tactics, allowing for individual interventions and personalization of the observation strategy.

Results

We analyzed the clinical data of Belarusian patients with PID who had a lymphoproliferation as a manifestation of the disease.

According to the national register of the Republic of Belarus (№0761918200, registered May 4, 2019) at the beginning of 2022, the number of patients with PID was 621, of which 390 (62.8%) patients were genetically verified. Lymphoproliferative syndrome at the onset of the disease was observed in 29 patients (4.7% of the total number of PIDs). The diagnostic period varied from 1 month to 20 years (Mean age 7.8 years). Clinically significant consequences of diagnostic errors occurred in 3 (10.3%) patients: splenectomy (in a patient with ALPS), liver transplantation (in patient with STAT3 GOF mutation), chemotherapy (in a patient with ALPS). The following genetic defects were identified in 27 patients: FAS-TNFRSF6 (8), PIK3CD GOF (6), STAT3 GOF (3), LRBA (2), SH2D1A (2), XIAP (2), NFkB1 (1), NFkB2 (1), CTLA4 (1), C2 (1), CVID (2, genetic defect has not been established).

Treatment options and outcomes: mTOR inhibitor therapy was successfully applied in 7 patients (ALPS-FAS (3), APDS-PIK3CD GOF (4), inosine monophosphate dehydrogenase inhibitor in one patient with an established STAT3 GOF defect, phosphatidylinositol-3-kinase delta inhibitor in one patient with APDS-PIK3CD GOF, Rituximab in 3 patient with STAT3 GOF(1), ALPS-FAS (2), Abatacept in 1 patient with CTLA-4, 6 patients receive replacement therapy with IG (SH2D1A (1), NFkB1 (1), NFkB2 (1), CVID (2) STAT3 GOF (1).

One patient with ALPS developed B-cell lymphoma (age of onset 45 years), hematopoietic stem cell transplantation was performed in 3 patient (LRBA (2), XLPII (1) - alive 1, dead 2). One patient with XLPI (SH2D1A (1)) died before diagnosis. The median age of manifestation in patients with ALPS-FAS is 3 years, in patients with T-reg defects (STAT3 GOF, LRBA, CTLA4) - 2.3 years, in patients with XLPI/II - 1.8 years, in patients with APDS - 0.6 years.

	Gender m/f	Mean age of symptom onset (min/max), years	Mean age at diagnosis (min/max), years	Family case, no.
ALPS n=12	9/3	3 (0,5/11)	14,8 (1/35)	4
APDS n=6	3/3	0,6 (0,08/1)	7,7 (1/15)	1
T-reg defects STAT3 GOF (3), LRBA (2), CTLA4 (1) n=6	4/2	2,3	12,5 (5/17)	1
XLP I/II SH2D1A (2), XIAP (2) n=4	4/0	1,8 (0,5/4)	3,25 (0,6/8)	0
CVID/NFkB1 (1), NFkB2 (1), genetic defect has not been established (2) n=4	2/2	5 (1/24)	26 (4/57)	1
C2 deficiency n=1	0/1	14	15	0

The severity of non-malignant lymphoproliferation ranged from Grade I to Grade IV, no genotype-phenotype correlation was noted. Non-malignant lymphoproliferation was associated with autoimmune pathology significantly more often than in patients with PID, in whom non-malignant lymphoproliferation did not occur in the clinical picture ($p<0.001$). Autoimmune pathology was represented mainly by autoimmune cytopenias (AIHA, ITP). Proven EBV-associated non-malignant lymphoproliferation occurred in 6 patients: XIAP (2), STAT3 GOF (2), PIK3CD GOF (2).

Molecular structure/ Molecular target	Drug	PID use	Observation period or median of observation period, weeks (min/max)	Outcome
Phosphatidylinositol-3-kinase delta inhibitor	Leniolisib	APDS-PIK3CD GOF (1)	12	reduction in the size of the lymph nodes and spleen reduction in the volume of accompanying therapy
mTOR inhibitor	Rapamycin	ALPS-FAS (3), APDS-PIK3CD GOF(4)	108 (24/192)	marked improvement in symptoms of lymphoproliferation in all observed patients further hematological stabilization
CTLA-4 IgG fusion protein	Abatacept	CTLA-4 haploinsufficiency (1)	52	multidirectional dynamics - progression of splenomegaly and lymphadenopathy, but hematological stabilization
Inosine monophosphate dehydrogenase inhibitor	Cellcept	STAT3 GOF defect (1)	51	reduced symptoms of lymphoproliferation reduction in the volume of accompanying therapy
Anti-CD20 Agent	Rituximab	STAT3 GOF defect (1), ALPS-FAS (2)	4 (2/6)	relief of autoimmune cytopenia in all observed patients further hematological stabilization reduced symptoms of lymphoproliferation
Human Ig	Octagam Gammanorm	SH2D1A (1), NFkB1 (1), NFkB2 (1), CVID (2) STAT3 GOF (1)	208 (96/336)	reduction in the number of infectious episodes/hospitalizations reduction in the volume of accompanying therapy no effect on lymphoproliferation processes

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