

## IMMUNODEFICIENCY-ASSOCIATED LYMPHOPROLIFERATIVE DISORDERS AND LYMPHOID NEOPLASMS IN POST-COVID-19 PANDEMIC ERA

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The 2017 revision of WHO Classification of tumors of hematopoietic and lymphoid tissues contains separate chapters on the immunodeficiency-associated lymphoproliferative disorders. In this mini-review, the brief description of pathological, immunophenotypical and clinical features of lymphoid neoplasms associated with primary immune disorders, HIV infection, those arising in post-transplant setting and other lymphoproliferative disorders (excluding those induced by radiation) is given. The heterogeneous spectrum of these lymphoid malignancies is specified by the nature of those factors that are capable to induce immune suppression or chronic antigenic stimulation of immune system. Taking into account the full swing of SARS-CoV-2 pandemic and our ignorance of the ability of this virus to induce the sustained stimulation of immune system, we could not exclude the high risk of autoimmune diseases and lymphoid neoplasms in the long-term post-pandemic period. In this context, the role of angiotensin-converting enzyme 2 as well as some recently reported cell receptors for SARS-CoV-2 cell entry should be considered as far as some of them (CD147, CD26) could be tumor-associated antigens.

**Key Words:** lymphoproliferative disorders, lymphoid neoplasms, immunodeficiency, SARS-CoV-2.

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Since December 2019, the humankind is facing a global pandemic caused by newly emerging SARS-CoV-2. According to WHO data, as of February 2021, more than 2.3 million patients with COVID-19 died worldwide. Each wave of the global persistence of any viral and bacterial infection challenges immune system of human population with possible long-term effects that are inherent to the chronic antigenic stimulation, persistence of the foreign genetic material in the body, impairment of the different types of immunocompetent cells, etc. The pandemics caused by SARS-CoV-2 will be no exception. In this respect, the infection-associated lymphoid neoplasms come to the fore and are worthy of consideration. The general aspects of SARS-CoV-2 pathogenesis in the context of its relation to the origin of lymphoproliferative disorders (LPD) and probable increase in the incidence of lymphoid neoplasms are briefly reviewed.

**The heterogeneity of the immunodeficiency-associated lymphoproliferative disorders.** Among the lymphoid neoplasms, the modern WHO Classification of tumors of hematopoietic and lymphoid tissues (2017) [1, 2] as well as the preceding classifications (2001, 2008) delineates immunodeficiency-associated LPD. In particular, the corresponding chapter includes the following headings: LPD associated with primary immune disorders (PID), lymphomas associated with HIV infection, post-transplant lymphoproliferative disorders (PTLPD), and other iatrogenic immunodeficiency-associated LPD (e.g. methotrexate-associat-

ed). We believe that in future LPD sub-classifications, the category of immunodeficiency-associated LPD could include the tumors of lymphoid tissue originating in the patients having been exposed to the ionizing radiation [3–6].

LPD associated with PID are heterogeneous that is not surprising taking into account the nature of the underlying immune impairments. The PIDs that are most frequently associated with LPD comprise ataxia-telangiectasia, Wiskott-Aldrich syndrome, common variable immunodeficiency, severe combined immunodeficiency, X-linked lymphoproliferative disease, Nijmegen breakage syndrome, hyper-IgM syndrome resulting from mutations in the *CD40* or *CD40LG* genes, autoimmune lymphoproliferative syndrome. The patients with Nijmegen breakage syndrome and ataxia-telangiectasia are characterized by the increased susceptibility to the exposure to ionizing radiation [2, 7]. Most commonly, PID-associated LPD are extranodal affecting gastrointestinal tract, lungs, CNS. In most cases, it is not possible to distinguish PID-associated LPD from those originating in immunocompetent persons based on pathological and immunohistochemical features. The prognosis and the treatment outcome depend on the histological type of lymphoid neoplasm and the underlying PID.

The PTLPD in patients who had been subjected to organ transplantation or stem cell allograft seem to be a consequence of immunosuppressive therapy or the chronic antigenic stimulation triggered by the graft [8, 9]. Most PTLPD are associated with the concomitant EBV infection. The majority of PTLPD cases are presented as proliferation of monomorphic lymphoid or plasmacytic cells localized in lymph nodes, gastrointestinal tract, lungs or liver. One could expect that in near future the number of PTLPD cases will

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**Abbreviations used:** ACE2 – angiotensin-converting enzyme 2; IL – interleukin; LPD – lymphoproliferative disorders; PID – primary immune disorders; PTLPD – post-transplant lymphoproliferative disorders.

be growing in many countries due to the increased organ transplantations including stem cell therapy.

In accordance to WHO classification [2, 10], the category of other iatrogenic immunodeficiency-associated LPD comprises lymphomas arising in patients treated with immunosuppressive drugs for autoimmune diseases rather than post transplantation. The frequency of the disorders falling into this category is not well known [2, 10]. The risk and type of these LPD depends on the nature of the underlying pathological process (e.g. rheumatoid arthritis, systemic lupus erythematosus, etc.), the duration of the treatment and the specific immunosuppressive drug being used. Iatrogenic LPD in about half of the cases is extranodal with the lesions detected in gastrointestinal tract, spleen, liver, bone marrow, soft tissues. In patients treated with methotrexate, most frequent is diffuse large B-cell lymphoma and mixed cellularity Hodgkin lymphoma.

Among the tumors of lymphoid tissue included in WHO classification, there are HIV-associated lymphomas. Several forms of lymphoma are believed to be most frequently associated with HIV. Among them are diffuse large B-cell lymphoma, primary effusion lymphoma, plasmablastic lymphoma, Burkitt lymphoma, and classic Hodgkin lymphoma. The incidence of these types of lymphoma even in HIV-infected persons receiving antiretroviral therapy is ten times higher than in general population [11–13]. In fact, in our practical activity in the Reference Laboratory of IEPOR, we have observed more than a few cases falling under this category of LPD. The comorbidity of lymphoid malignancies and COVID-19 also deserves close attention.

Today, there are approximately 38 million HIV-infected people worldwide. All those people have high risk of developing comorbid conditions besides HIV-associated lymphomas. The heterogeneous clinical manifestations and laboratory findings in HIV-associated lymphomas may be attributable in part to chronic antigenic stimulation, genetic abnormalities and the disruption of cytokine network [2]. In HIV-infected persons, the risk of COVID-19 lethality seems also to be higher although this question has not been yet elucidated [14]. It should be speculated that despite of the structural dissimilarity, HIV and SARS-CoV-2 possess some similar signs. For example, they both target T cells and cause lymphopenia in the peripheral blood [14, 15]. It could be suggested that both HIV and SARS-CoV-2 share some related pathways for entering the cells [16]. Moreover, both viruses generate an increase in the cytokine production and aberrant formation of neutrophil extracellular traps that is related to complications in the infected patients. Several systematic reviews have been already published analyzing the cases of HIV and SARS-CoV-2 coinfection [14].

Apart from HIV-associated lymphomas, one more quite distinct category of infection-associated lymphoid malignancies exists. In these cases, the lymphoid cells are not directly transformed by infec-

tious agents. The origin of several types of lymphoid neoplasms such as gastric lymphoma, immunoproliferative small intestinal disease, spleen and cutaneous lymphoma is clearly connected with chronic stimulation of the immune system resulting from the infections caused by *H. pylori*, *C. jejuni*, *B. burgdorferi* as well as hepatitis C virus [17].

**Immunological and hematological findings in patients with COVID-19.** Human coronaviruses (CoV) recognized as early as in 1960 include seven viruses that cause mild respiratory infections as well as the novel viruses appearing in the 21<sup>st</sup> century and resulting in severe and potentially dangerous infections (SARS-CoV, MERS-CoV, SARS-CoV-2) [14, 18].

SARS-CoV-2 infection is associated with an intensive pathological hyperinflammatory response with accompanying excess activation of host immune mechanisms resulting in the overproduction of inflammatory cytokines giving rise to the extensive neutrophil and macrophage infiltration of the tissues. SARS-CoV-2 infection is accompanied by the lymphopenia with decreasing count of CD4<sup>+</sup> and CD8<sup>+</sup> T cells, B cells and NK cells [18–20]. Moreover, it was proved that the absolute number of total T cells as well as CD4<sup>+</sup> and CD8<sup>+</sup> subsets inversely correlate with patients survival rate [21]. The prognostic significance of thrombocytopenia in COVID-19 was also demonstrated [22]. In patients with severe course of COVID-19, neutrophil count and neutrophil to lymphocyte ratio increase while the percentage of eosinophils, basophils and monocytes in leukogram are reduced [20]. It is important to note that upon recovery, the absolute number of T and B cells returns to normal values.

In most patients with severe course of COVID-19, the levels of the inflammatory proteins such as interleukin (IL)-6, IL-1 $\beta$ , IL-2, IL-8, IL-10, IL-17, tumor necrosis factor- $\alpha$ , interferon- $\gamma$  inducible protein 10 kD, monocyte chemoattractant protein-1, macrophage inflammatory proteins 1- $\alpha$ , GM-CSF, G-CSF increase [21–25]. This cytokine storm damages seriously multiple organs of the body resulting, in particularly, to the extremely dangerous lung damage accompanied with infiltration with polymorphonuclear neutrophils and macrophages. Finally, the hyaline membranes are formed with thickening of the alveolar walls. Lymph node necrosis and spleen atrophy represent the characteristic features of the immune-mediated injuries in COVID-19 [23–25]. In some patients with severe course of COVID-19, on the background of the increased IgG response, antibody-dependent enhancement of SARS-CoV-2 occurs [21]. To sum up the available data, the ability of SARS-CoV-2 to induce a hyperstimulated state of the immune system leading to the synthesis of autoantibodies is doubtless.

**The COVID-19 pandemic, could it be associated with the increasing rate of lymphoid malignancies?** At present, the efforts of the scientists and physicians worldwide are focused on curbing COVID-19 pandemic and search for the effective therapeutics for decreasing the rate of complication

in early period. Nevertheless, taking into account the scale of the pandemic, one cannot but think of the probable long-term consequences, in particular, the increasing rate of immunodeficiency-associated lymphoproliferative diseases in convalescents. One cannot exclude the probable increasing rate of tumors of other organs and systems. The aspects of epidemiology of lymphoid malignancies, their latency, immunophenotypic features and genetic profile may come into limelight some time later.

The development of immunodeficiency-associated lymphoproliferative diseases in persons who came through COVID-19 could be considered from the stochastic point of view. Nevertheless, the early viral and host-related factors affecting COVID-19 pathogenesis and having a bearing to the development of immune impairments should attract our attention. It is known that binding of SARS-CoV-2 to host cell receptors such as angiotensin-converting enzyme 2 (ACE2) via spike protein represents a critical step for virus entry [25, 26]. At the same time, we are well aware of ACE2 involvement in the pathogenesis of certain tumors. For example, ACE2 enzymatic activity is reduced in renal tumors [27]. There are some findings indicating the role of ACE2 in the development of pancreatic cancer [28]. ACE2 overexpression suppresses invasion, angiogenesis and metastasis in non-small cell lung cancer [29, 30].

Recently, CD147 has been recognized as a novel cell receptor used for SARS-CoV-2 entry into the cell [31–33]. Several other receptors are supposed to play that role, such as CD26 [34] and CD209 [35]. In this respect, it is worth noting that CD147, CD26 and CD209 are expressed on cells of a large number of solid and hematological neoplasms.

CD147 (also called as Basigin and extracellular inducer of matrix metalloproteinases) is expressed by many types of cells including epithelial cells, cells of vascular endothelium, platelets, erythrocytes, leukocytes, activated T cells. This protein plays important role in the intercellular interactions in various physiological and pathological processes. CD147 expression is detected on neoplastic cells in several forms of cancer (lung cancer, breast cancer, pancreatic cancer, hepatocellular carcinoma, melanoma). CD147 participates in regulation of proliferative activity and is involved in invasion and metastasizing of cancer cells. Also, it is involved in the epithelial-mesenchymal transition.

Several papers, including those published before the discovery of CD147 involvement in SARS-CoV-2 entry into the cell, disclose the data about the role of CD147 in pathogenesis of several forms of hematological malignancies. In particular, CD147 expression is known in several LPD such as anaplastic large cell lymphoma and Hodgkin's lymphoma [36]. The increase in CD147 and the elevation of its glycosylation were found in the relapsed B-cell acute lymphoblastic leukemia [37, 38]. CD147 expression was higher in the cells of cerebrospinal fluid as compared

with leukemic cells of bone marrow. The authors suggest that CD147 may be important for the formation of extramedullary foci of infiltration with leukemic cells. In several studies, the role of CD147 in the pathogenesis of anaplastic large cell lymphoma and multiple myeloma was analyzed [39, 40]. Some evidence suggests the role of CD147 in the development of chronic lymphocytic leukemia [41].

CD26 (dipeptidyl peptidase-4, DPP4) is 110-kD transmembrane glycoprotein normally expressed in different cells of the immune system [42, 43]. Originally, it was described as a marker of T cells [44]. CD26 is also expressed by endothelial cells and epithelial cells of lung, small intestine, pancreas and in hepatocytes [45]. The recent evidence demonstrates the binding of SARS-CoV-2 with CD26 for entering the host cells. The co-expression of CD26 and ACE2 as receptors for SARS-CoV-2 binding could not be excluded. The host CD26 cleaves amino-terminal dipeptides that results in T-cell activation as a key immunoregulatory factor in viral infection [46].

CD26 expression is detected in cells of several types of malignant tumors playing a role in carcinogenesis [45]. In hematological malignancies CD26 is expressed on cells of T-cell lymphoblastic lymphoma/leukemia [47], T-large granular LPD [48] and in a large group of B-CLL patients with unfavorable prognosis [49].

CD209L (also known as L-SIGN) and CD209 (also known as DC-SIGN) also seem to represent the alternative receptors for SARS-CoV-2 entry [35]. CD209L and CD209 are members of C-type lectin superfamily [50]. CD209L is expressed in human type II alveolar cells, alveolar macrophages and mononuclear cells of peripheral blood [51]. C-type lectin moiety of CD209L and CD209 functions as calcium-dependent glycan-recognition domain [49]. Binding to mannose-like carbohydrates of ICAM2 and ICAM3, CD209 represents the high-affinity receptor of these cell adhesion molecules regulating T-cell proliferation induced by dendritic cells. Of special importance, CD209 serves as receptor for HIV-1, HIV-2, Ebola virus, cytomegalovirus, measles virus, HCV and SARS-CoV [51]. Contrary to CD147, CD26 or ACE2, CD209 have not been yet detected on cancer cells of various origin [35].

**Future outlook.** The pandemic of COVID-19 caused by SARS-CoV-2 gains momentum. COVID-19 pathogenesis has not been studied in details especially for the severe forms of this disease involving multiple organs and systems. The immunological impairments play undoubtedly important role as evidenced by the shifts in the functional properties of the various types of lymphoid cells as well as the changed ratio between different lymphocyte subpopulations. The same holds true for the system of mononuclear phagocytes circulating in the peripheral blood. Unfortunately, due to the lack of time, the analysis of the immunocompetent cells in bone marrow at the early stages of antigen-independent differentiation and histiocytes/macro-

phages and dendritic cells interacting with lymphoid cells in the organs of lymphopoiesis escaped the reach of scientists.

At present, the possibility of the repeated disease in the COVID-19 convalescents and the complex of the serious disturbances in the function of the internal organs in such patients raise serious concerns.

The vaccination is undoubtedly the only existing means enabling the spread of SARS-CoV-2 infection [52]. Nevertheless, the seemingly short duration of the immunity and possible secondary effects of several vaccines in the long-term perspective should be carefully considered.

The problems of the long-term oncological consequences, firstly the risk of immunodeficiency-associated lymphoproliferative diseases in the persons who suffered from COVID-19 are challenging for the future. Nevertheless, it is high time now to think of them and to start the development of the epidemiological aspects of the possible increasing incidence of different types of the acute and chronic lymphocytic leukemia, non-Hodgkin and Hodgkin lymphomas, their peculiar features (localization, histomorphology, genetic profile, immunophenotype, prognosis and predictive factors).

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### ЛІМФОПРОЛІФЕРАТИВНІ ЗАХВОРЮВАННЯ, АСОЦІЙОВАНІ З ІМУНОДЕФІЦИТАМИ, ТА ЛІМФОЇДНІ НОВОУТВОРЕННЯ ПІСЛЯ ПАНДЕМІЇ COVID-19

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У переглянутій класифікації ВООЗ пухлин кровотворної та лімфоїдної тканин від 2017 р. містяться кілька окремих розділів, присвячених лімфопроліферативним захворюванням, асоційованим з імунodefіцитами. У представленому мініогляді наведено стислий опис патологічних, імунотипових і клінічних особливостей лімфоїдних новоутворень, асоційованих з первинними імунними розладами, інфекцією ВІЛ, а також таких, що виникають після трансплантації та інших лімфопроліферативних захворювань (виключаючи індуковані радіацією). Гетерогенний спектр цих лімфоїдних злоякісних новоутворень обумовлений природою факторів, здатних спричиняти імуносупресію або хронічну антигенну стимуляцію імунної системи. З огляду на те, що пандемія, спричинена SARS-CoV-2, перебуває в розпалі, і ми ще не до кінця усвідомлюємо здатність цього вірусу індукувати тривалу стимуляцію імунної системи, не можна виключати високого ризику автоімунних захворювань та лімфоїдних новоутворень, що можуть виникнути через тривалий час після пандемії. У цьому контексті, слід розглянути роль ангіотензинперетворювального ферменту 2 та інших клітинних рецепторів для потрапляння SARS-CoV-2 всередину клітини. Також слід звернути увагу на те, що деякі з цих клітинних рецепторів (CD147, CD26) є пухлино-асоційованими антигенами.