Clinical significance of soluble form of poliovirus receptor in newly diagnosed follicular lymphoma

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Background Follicular lymphoma (FL) remains an incurable malignancy with heterogeneous clinical outcomes that necessitate a better understanding of disease biology. Poliovirus receptor (PVR/CD155) is markedly overexpressed in several human malignant tumors and it has a unique dual oncoimmunoregulatory role. However, the role of the soluble form of PVR (sCD155) in FL has not been fully elucidated.

Methods Soluble PVR(sCD155) were measured in the sera of 50 patients newly diagnosed with FL by sandwich enzyme-linked immunosorbent assay and compared with those of 20 healthy control participants. Moreover, we evaluated its association with the clinicopathological parameters as well as response to chemotherapy in such patients.

Results Pretreatment level of sCD155 was significantly higher in patients with FL than in control participants ($P<0.001$). Higher levels of sCD155 were associated with aggressive high-risk clinicopathological parameters, sCD155 levels were significantly higher in FL patients with B symptoms, advanced Ann Arbor stage III and IV, bulky disease, and high-risk cytogenetic (*P*-value=0.01, 0.048, 0.028 and <0.001, respectively). In addition, of the 50 patients, 24 (48%) achieved CR after 4–6 courses of chemotherapy (R-CHOP), while 26 (52%) were not in remission, and higher levels of sCD155 were associated with poor response to chemotherapy (*P*-value<0.001). Receiver operating characteristic curve was applied. Serum level of sCD155 higher than 4.8 ng/ml is a good predictor for poor response to chemotherapy (area under the curve: 0.857, sensitivity and specificity 88.46% and 75%, respectively).

Conclusion PVR (CD155) is a potential therapeutic target that warrants further investigations and serum sCD155 may be used as a biomarker of treatment response and for predicting poor outcome in FL.

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Introduction

Follicular lymphoma (FL) is the second most common type of non-Hodgkin lymphoma characterized by indolent clinical course [1]. The disease course usually starts with an initial response to therapy, followed by frequent relapses [2]. The clinical outcome and overall survival of FL markedly improved over the past decades due to recent advances in diagnostic tools and the introduction of chemoimmunotherapy [3]. However, FL remains incurable malignancy with a heterogeneous clinical outcome; certain groups of patients have a poor prognosis due to progressive disease within 2 years after diagnosis, early relapse following treatment with chemoimmunotherapy, or due to transformation of FL to an aggressive high-grade lymphoma [4,5]. These variable outcomes clarify the need to gain further knowledge of disease biology and highlight the need for detection of predictable biomarkers of disease outcome and definitely the advent of new therapeutic targets. The immune checkpoint CD155, which was initially identified as a receptor for poliovirus, is an adhesion molecule belonging to the Nectin/Nectin-like family [6]. Although CD155 expression level in healthy tissues is low or absent, CD155 is markedly overexpressed in several human malignancies [7–9]. It has multiple contradicting roles in cancer development and progression; it plays important role in immune surveillance against cancer as it is a ligand for the activating receptor DNAM-1 expressed on cytotoxic T lymphocytes and natural killer (NK) cells rendering tumor cells more sensitive to elimination by immune cells [10]. On the other hand, CD155 expression is associated with poor prognosis and enhanced tumor progression through its biological involvement in important cellular processes, such as adhesion, contact inhibition, migration, and proliferation that promotes tumor cell invasion, migration, and proliferation [11]. Likewise, during tumor progression, inhibitory receptors of CD155 (TIGIT, CD96) are upregulated on the surface of immune cells leading to impairment of their cytotoxicity, mediating tumor immune escape [12].

In addition to membrane-bound CD155, human tissues express soluble CD155 (sCD155) encoded by splicing isoforms of CD155 that lack the transmembrane region [13]. The precise roles of sCD155/PVR in patients with cancer have not been fully elucidated [14]. Many studies have shown that CD155 is overexpressed in a variety of hematological malignancies, such as acute myeloid leukemia and multiple myeloma [15,16]. However, to the best of our knowledge, only scarce studies have investigated CD155 expression in FL [17]. In addition, no previous studies have examined the soluble form of CD155 in FL. In this study, we evaluated the serum level of the soluble immune checkpoint (PVR/sCD155) in patients newly diagnosed with FL and analyzed its association with clinicopathological parameters. In addition, we explored its impact on the treatment response in those patients.

Materials and methods

Patients

The current randomized, cross-sectional, comparative, case–control study was conducted at the Clinical Hematology and Bone Marrow Transplantation Unit, Department of Internal Medicine, Ain Shams University Hospitals, Cairo, Egypt. A total of 50 newly diagnosed adult patients with FL were recruited during the period between January 2019 and January 2020. A total of 20 healthy age- and sex-matched individuals were enrolled to serve as controls. The patients included 28 men and 22 women, with a mean age of 43.6±12.9 years, while the healthy controls included 11 men and 9 women, with a mean age of 40.9±7.2 years. This study was reviewed and approved by Ain Shams University Ethical Committee, and all patients provided written informed consent according to Declaration of Helsinki. The diagnosis of FL was made according to the criteria of World Health Organization [18] based mainly on histopathological examination, immunohistochemical examination, and cytogenetic analysis [19].

All patients were subjected to the following: detailed history and examination particularly for pallor, purpura, hepatosplenomegaly, and lymphadenopathy. In addition, the following investigations were also conducted: complete blood count using an automated coulter counter with examination of Leishman-stained peripheral blood, liver and kidney function tests, lactate dehydrogenase (LDH), serum uric acid, lymph node biopsy with histopathology, bone marrow aspirate and trephine biopsy with immunohistochemistry, cytogenetic study and computed tomography (CT) of the neck, chest, and pelvi-abdomen with contrast for staging and to confirm the presence or absence of bulky disease, which is defined as the presence of any nodal or extranodal tumor mass with a diameter >7 cm as per the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria [20]. Both patients, before receiving any treatment, and controls were subjected to measurement of serum level of sCD155. Patients were excluded from the study if they had any of the following conditions: previously treated FL, any other type of non-Hodgkin or Hodgkin lymphoma, and patients with any serious medical or psychiatric illness or any condition that would prevent the participant from signing the informed consent form.

Treatment and follow-up plane

All patients were treated and followed up after the end of chemotherapy courses for assessment of response to treatment. Although the initiation of treatment was in accordance with the GELF criteria [21], the choice of treating chemotherapy protocol was according to NCCN 2019 guidelines for FL; they received R-CHOP (Rituximab cyclophosphamide, Adriamycin, Vincristine, and prednisone) [22]. Follow-up after 6 months was by CT of the neck, chest, and pelvi-abdomen with contrast and bone marrow aspirate and trephine biopsy. Definitions of complete response (CR), partial response (PR), and progressive disease were the standard [23].

Enzyme-linked immunosorbent assay (ELISA) for human soluble PVR (CD155)

The RayBio® Human CD155 ELISA Kit (RayBiotech Company, Georgia, United States) is an *in vitro* ELISA for the quantitative measurement of human CD155 in serum. All reagents and samples were brought to room temperature (18–25°C) before use and it is recommended that all standards and samples be run at least in duplicate. In brief, purified CD155 antibody was adopted to coat microtiter plate. A solid-phase antibody was made, and then CD155 was added to the wells. CD155 antibody was combined with labeled horseradish peroxidase to form antibody–antigen–enzyme–antibody complex. After washing completely, the tetramethylbenzidine (TMB) substrate solution was added. The TMB substrate becomes blue in color. The reaction is terminated by the addition of a top solution and the color change is measured at a wave length of 450 nm. The concentration of CD155 in the samples was then determined by comparing the ordinary differential equations of the samples to the standard curve

Statistical analysis

Data were collected, revised, coded, and entered to the Statistical Package for Social Science (IBM SPSS)

version 23 (IBM Corp., Armonk, New York, USA). The quantitative data were presented as mean, SDs and ranges when their distribution was found to be parametric and median with interquartile range (IQR) when their distribution was found to be non-parametric and were compared using the Mann–Whitney *U*-test (for two-group comparison) while the comparison between two independent groups with quantitative data and parametric distribution were done by using unpaired t-test. Also qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using Chi-square test. Receiver operating characteristic curve (ROC) was used in the quantitative form to determine the diagnostic value of CD155. Area under the curve (AUC) values between 0.50 and 0.69 represent low accuracy, while values between 0.7 and 0.9 represent moderate accuracy and values >0.9 represent diagnostic tests with high accuracy. Two-sided $P<0.05$ was considered significant.

Results

Clinical characteristics of the patients

Demographic data and clinical characteristics of the 50 FL patients are summarized in Table 1.

sCD155 level in patients with FL and healthy controls

Compared with healthy controls, newly diagnosed FL patients had significantly higher sCD155 levels (median=1.09 ng/ml and 6.88 ng/ml, respectively, $P<0.001$; Table 2).

Association between serum sCD155 level and the clinicopathological characteristics of patients with FL

sCD155 levels in the sera of the 50 FL patients were significantly higher in men compared to women patients (*P*-value=0.027). As regards disease staging and the presence of bulky disease, sCD155 serum levels were significantly higher in patients with stage III and IV compared to stage I and II and higher in patients having bulky disease compared to others in whom disease is not bulky (*P*-value=0.048 and 0.028, respectively). Furthermore, sCD155 levels were significantly higher in patients with B symptoms vs patients without B symptoms (*P*-value=0.01) and poor risk cytogenetic vs others (*P*-value<0.001). sCD155 mean levels were higher in FL patients with other clinical variables, including presence of anemia, elevated LDH level, elevated B2 microglobulin level, and bone marrow infiltration than its mean levels in other FL patients with normal hemoglobin, LDH, B2 microglobulin levels, and without bone marrow infiltration; however the difference were statistically insignificant (*P*=0.6, 0.1,0.1 and 0.3, respectively; Table 3).

Table 1 Demographic data and clinical characteristics of patients with follicular lymphoma at diagnosis

Characteristics	Patients, No. (%)
Sex	
Male	28 (56)
Female	22 (44)
Age (years)[a]	43.68±12.87
Site of the affected LN group	
Cervical	1 (2)
Axillary	2 (4)
Mediastinal	1 (2)
Abdominal	3 (6)
Cervical and abdominal	4 (8)
Axillary and abdominal	2 (4)
Cervical and axillary and abdominal	7 (14)
All group	30 (60)
B symptoms	
Positive	35 (70)
Negative	15 (30)
Ann Arbor stage	
I–II	7 (14)
III–IV	43 (86)
Anemia (Hb<12 g/dl)	13 (26)
LDH	
Normal	21 (42)
Elevated	29 (58)
B2 microglobulin	
Normal	20 (40)
Elevated	30 (60)
BM infiltration	
Positive	37 (74)
Negative	13 (26)
Cytogentic risk	
High risk	18 (36)
Low risk	32 (64)
Bulky disease	
Yes	36 (72)
No	14 (28)

BM, bone marrow; LDH, lactate dehydrogenase; LN, lymph node.
[a]Mean±SD.

Table 2 CD155 expression level in follicular lymphoma patients and controls

Variable	Follicular lymphoma patients (*n*=50)		Control (*n*=20)		*P*-value*
	Median	Interquartile range	Median	Interquartile range	
CD155	6.88	2.25–17.25	1.09	0.86–1.15	<**0.001**

Data are median and interquartile range. *Mann–Whitney test. *P*-value <0.01: highly significant (HS).

sCD155 level in patients with FL and response to chemotherapy

Of the 50 patients, 24 (48%) achieved CR by the end of treatment courses (4–6 cycles of R-CHOP), while 26 (52%) were not in remission. FL patients who failed to achieve CR were 10 (20%) patients in PR, 8 (16%) patients with stationary disease, and 8 (16%) patients with disease progression; they were collectively labeled as poor responders. sCD155 serum level were significantly higher in patients with FL who are poor responders to chemotherapy than others who achieved CR (mean: 14.4 ng/ml and 2.871 ng/ml, respectively; *P*-value <0.001; Table 4 and Fig. 1).

Table 3 Correlations of CD155 expression level with clinicopathological parameters of the studied lymphoma patients

Age (*r* : 0.032)		CD155	*T*-test	
P-value=0.823	*N*	Mean±SD	*t*	*P*-value
Sex				
Male	28	11.104±8.606	2.285	0.027
Female	22	6.025±6.628		
Anemia				
No	37	8.593±7.952	−0.401	0.690
Yes	13	9.654±8.909		
B symptoms				
No	15	4.477±5.138	−2.650	0.011
Yes	35	10.751±8.501		
LDH				
Normal	21	6.679±7.638	−1.649	0.106
Elevated	29	10.455±8.236		
B2 microglobulin				
Normal	20	6.575±7.481	−1.658	0.104
Elevated	30	10.398±8.307		
Cytogenetic risk				
Low	32	5.509±6.512	−4.640	<0.001
High	18	14.842±7.364		
BM infiltration				
No	13	6.954±7.556	−0.987	0.329
Yes	37	9.542±8.317		
Staging				
Stage I–II	7	3.271±2.706	−2.025	0.048
Stage III–IV	43	9.780±8.368		
Bulky disease				
No	14	4.857±5.184	−2.265	0.028
Yes	36	10.429±8.582		

BM, bone marrow; LDH, lactate dehydrogenase.

Table 4 Correlations of CD155 expression level with remission status at 6 months of the studied lymphoma patients

CD155	Remission, No.=24 (48%)	Not remission, No.=26 (52%)	Test value (*t*)	*P*-value	Sig.
Mean ±SD	2.871±2.571	14.406±7.556	−7.104	<0.001	HS

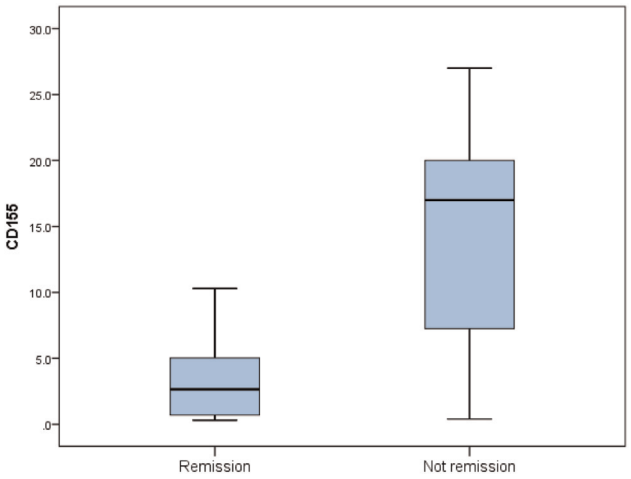
P-value >0.05: nonsignificant (NS). *P*-value <0.05: significant (S). *P*-value <0.01: highly significant (HS).

In addition, ROC curve was applied to determine the best cut-off value of sCD155 serum level for prediction of FL patients with poor response to treatment (AUC: 0.857 and the optimum cut-off level ≤4.8). sCD155 level had sensitivity (88.46%) and specificity (75%) as predictor of poor response to chemotherapy in patients with newly diagnosed FL (Fig. 2).

Discussion

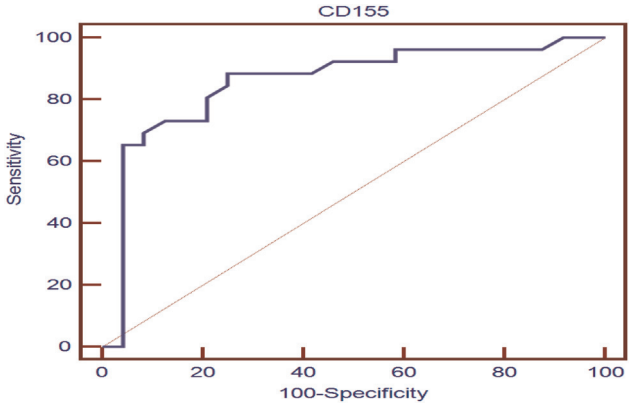
Despite the well-observed improvement in the outcome of patients with FL in the past 15 years with chemoimmunotherapy, which is the standard of care of these patients till now [24], the prognosis remains unsatisfactory. Poor response to

Figure 1



Box plot illustrating sCD155 serum level in cases of newly diagnosed FL with or without remission. Box represents the interquartile range. Line inside the box represents the median. Whiskers represent minimum and maximum values.

Figure 2



Receiver operating characteristic (ROC) curve was applied to determine the best cut-off value of sCD155 serum level for prediction of FL cases with poor response to treatment (AUC: 0.857 and the optimum cut-off level ?4.8). This had diagnostic sensitivity and specificity 88.46% and 75%, respectively as predictor of poor response.

chemotherapy, incurability with frequent relapses, and transformation to more aggressive subtypes remain the major challenges [25]. As a result, implementation of new treatment options including chemotherapy free regimens and immunoregulatory compounds with checkpoint blockade is indeed highly needed.

In addition to its protumorigenic properties, CD155 plays a dual immunoregulatory role in malignancy and is considered as a biological biomarker of tumor progression, which makes it a therapeutically attractive target [14]. Nevertheless, the role of soluble form of PVR (sCD155) in patients with FL has not been investigated.

The results of the current study demonstrated that, compared with healthy controls, patients with FL showed significantly higher level of serum sCD155. Consistently, Iguchi-Manaka *et al*. [26] reported that patients with various types of cancers, including lung, esophageal, gastric, colorectal, breast, pancreatic, cervical, and ovarian cancers, showed significantly higher level of serum sCD155 compared with healthy controls. This could be explained by what the researchers suggested that sCD155 might have an important immunoregulatory role in cancer same as the transmembrane CD155 isoform based on the previous studies supporting the roles of other soluble immune cell ligands [27,28]

Focusing more on FL, Josefsson *et al*. [29] investigated the surface expression of nine different coinhibitory receptors controlling T cell function in FL, including TIGIT that exerts its inhibitory function upon interacting with its ligands CD155 and CD112; the immunophenotypic analysis of FL samples showed that less than 5% of malignant lymphoma cells expressed CD155; however, it was strongly expressed by follicular dendritic cells and endothelial cells in the tumor microenvironment.

Moreover, the present study analyzed the association between sCD155 and clinicopathological parameters of the studied FL cohort. Notably, the results were consistent with previous findings of several studies which demonstrated that high CD155 in different types of tumors, either the membrane-bound form [8,9,30,31] or the soluble form of CD155 [32,33], is associated with aggressive clinicopathological features, which have negative prognostic impact.

FL typically has cytogenetic abnormality, t(14,18), which has no significant impact on the clinical outcome [34] (low-risk cytogenetic). On the other hand, other additional cytogenetic abnormalities as del (1), +18q, del(6), del(17p), +12, +21, and complex cytogenetic contribute to disease progression and is associated with poorer clinical outcome [35] (high-risk cytogenetic). In the current study, we found that patients with high-risk cytogenetic have higher serum level of sCD155 than others with low-risk cytogenetic. Ann Arbor staging system is one of the prognostic categories of FLIPI Score (follicular lymphoma international prognostic index); stage III and IV are strongly and independently associated with a poor clinical outcome [36] as well as the presence of bulky disease, which has long been associated with poor prognosis in patient with lymphoma [37]. Also the presence of B symptoms (fever >38°C, unintentional weight loss >10%, night sweats) is an established negative prognostic factor in patients with non-Hodgkin lymphoma, and its presence is a marker for more advanced disease, either as a widespread disease or as a disease of high histological grade [38]. The current study revealed that patients who have B symptoms have higher sCD155 in their sera than patients without B symptoms. In addition, the study demonstrated that the level of sCD155 in FL patients were positively correlated with disease stage and size of malignant lymphoid mass; those patients with advanced disease stage (Ann Arbor stage III, IV) and bulky disease tended to have higher serum level of sCD155 than others. This result suggests that the serum level of sCD155 correlates with the disease burden. These results were explained by several previous studies that demonstrated upregulated CD155 expression, either on tumor cells itself or on the immune cells infiltrating the tumor microenvironment, is correlated with promoted tumor growth, migration, proliferation, and distant metastasis through tumor-intrinsic mechanisms related to cell migration and survival besides the immune response inhibition by interacting CD155 with inhibitory receptors TIGIT leading to inhibition of T-cell and NK cell activity, including secretion of cytokines, such as interferon practice IFN. CD155 overexpression in tumor microenvironment skews the balance between the costimulatory CD155/DNAM-1 and coinhibitory CD155/TIGIT toward the immunosuppression side inducing tumor immune escape [11,39,40]. However, surprisingly, the results failed to detect any significant difference as regards sCD155 level between studied FL patients with and without anemia, elevated LDH, elevated B2 microglobulin, and bone marrow infiltration.

Finally, patients who poorly responded to chemotherapy and failed to achieve complete remission have higher sCD155 in their sera than others who responded well to chemotherapy and attain complete remission. The

results of the present study also demonstrated that serum level of sCD155 higher than 4.8 ng/ml is a good predictor for poor response to chemotherapy. These results are consistent with those reported by Gao *et al.* [12] who demonstrated that chemotherapeutic agents can induce CD155 expression on tumor cells and addressed the possibility that CD155 overexpression may counteract the efficiency of chemotherapeutic agents. On the contrary, Yoshida *et al.* [33] have reported that their studied esophageal cancer patients with high pretreatment level of sCD155, who received chemotherapy, showed a trend toward a better treatment response.

This was explained by Zingoni *et al.* [41], who agreed with Yoshida and co-workers, and suggested that several chemotherapeutic agents are used not only for their cytotoxic effect on the tumor cells but also for the recently discovered synergistic role of chemotherapy to the innate immunity through the release of stress molecules, called damage-associated molecular patterns (DAMPs), from dying tumor cells, which alert the immune system promoting the recognition of tumor cells by immune effector cells in addition to stimulating the activation ligands while downregulating the inhibitory ligands on the immune cells, contributing in cancer immune surveillance.

Despite that the current study had its limitations as it is a single-center study with a relatively small sample size and short observation period, which did not allow to conduct a prognostic evaluation, and also we did not evaluate the serum sCD155 at the end of the treatment course, we can conclude that, to the best of our knowledge, the current study is the first to report significantly elevated serum level of the soluble form of PVR (CD155) in patients newly diagnosed with FL relative to its level in healthy participants. Moreover, FL patients with higher sCD155 tend to have aggressive clinicopathological parameters that are well established to be associated with poor prognosis and showed poor response to chemotherapy.

Our data suggest that PVR (CD155) is a potential therapeutic target that warrants further investigations and serum sCD155 may be used as a biomarker of treatment response and for predicting poor outcome in FL.

Authors' contributions

All authors shared equally in this study. N.A.N. wrote the manuscript. N.A.N., A.M.K., and M.G.N. critically edited the manuscript. All authors shared in designing the study, performing the research, analyzing the data, and approving the final version of the article to be submitted.

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Conflicts of interest

There are no conflicts of interest.

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