# Thrombotic risk in paroxysmal nocturnal hemoglobinuria-like (PNH-like) phenotype

**Authors: Melania Carlisi[1], Salvatrice Mancuso[2], Gregorio Caimi[3], Sergio Siragusa[4].**

*(1) Department of Surgical, Oncological and Stomatological Disciplines, University of Palermo, Palermo, Italy. Mail address: melania.carlisi@unipa.it*

*(2) Health Promotion Sciences, Maternal and Infant Care, Internal Medicine and Medical Specialties (PROMISE) Department, University of Palermo, 90127 Palermo, Italy. Mail address: salvatrice.mancuso@unipa.it*

*(3) Health Promotion Sciences, Maternal and Infant Care, Internal Medicine and Medical Specialties (PROMISE) Department, University of Palermo, 90127 Palermo, Italy. Mail address: gregorio.caimi@unipa.it*

*(4) Health Promotion Sciences, Maternal and Infant Care, Internal Medicine and Medical Specialties (PROMISE) Department, University of Palermo, 90127 Palermo, Italy. Mail address: sergio.siragusa@unipa.it.*

**Corresponding author**: Melania Carlisi, Department of Surgical, Oncological and Stomatological Disciplines, University of Palermo, Italy, Via del Vespro 129, 90127, Palermo, Italy; Phone/Fax: +39 0916554410/0916554402; e-mail: melania.carlisi@unipa.it

**Abstract**

The complement system is an essential component of the innate immune defence that, if overly activated, may damage organs and tissues. For this reason, there is a fine complement regulatory system. The complement modulation system includes two proteins with important regulatory activity, CD55 or decay accelerating factor (DAF) and CD59 or membrane inhibitor of reactive lysis (MIRL).

The paroxysmal nocturnal hemoglobinuria (PNH) is a clonal and non-neoplastic disease characterized by intravascular haemolysis, occurrence of thrombosis and bone marrow failure.

In clinical practice, in opposition to PNH, a variety of pathological conditions have been observed with an acquired and non-genetic deficiency of the regulatory proteins CD55 and CD59. This abnormal, non-clonal, reduced expression of complement regulatory proteins configures what we may define as PNH-like phenotype.

Similarly to PNH, even in the PNH-like phenotype diseases there has been a greater exposure to the mediated complement cellular lysis and, a likely increased risk of thromboembolic events.

Therefore, the knowledge of the potential roles of the complement system becomes necessary for a deeper understanding of several pathological conditions and for an improved clinical management of the patients.

**Keywords**: paroxysmal nocturnal hemoglobinuria, complement system, CD55, CD59, thromboembolic risk.

# 1. Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal disorder of the stem cell that often is associated with bone marrow failure, hemolytic anemia and thrombosis. It is due to somatic mutations in phosphatidylinositol glycan class A (PIGA), a gene involved in GPI anchor biosynthesis, with subsequent deficiency of several glycosylphosphatidylinositol (GPI)-anchored proteins. The deficiency of CD55 and CD59 leads to uncontrolled complement activation that accounts for hemolysis and other PNH manifestations [1].

Apart from PNH, literature underlines the presence of a cellular PNH-like phenotype in several clinical conditions, including autoimmune diseases, diabetes mellitus, HIV infectious and treatment regimens immunotherapy-based [2]. There is yet a lack of indepth knowledge regarding the development in terms of the PNH-like cellular phenotype, however it is important to identify and distinguish these from the effective PNH clone.

In this review, the differences between PNH and PNH-like phenotype will be analysed. Furthermore, the clinical impact of the reduced/absent GPI-linked proteins expression, especially in terms of thrombotic risk, will be discussed. These notions are to be considered helpful to increase the awareness about these occurring diseases to improve clinical management of patients.

# 2. The complement system

The complement system was first recognized in the 19th century. It acts upon the control of local inflammation and the adaptive immune response. The complement system consists of several soluble and membrane proteins that interact both with each other and with other immune system molecules [3]. The soluble proteins are usually defined "components" and they are present in an inactive form in the plasma. Under specific conditions, the components are activated, producing activation products with different effector functions. Despite having a specific role in the

immunological defence processes, a rapid and extensive activation of the complement system could have a damaging effect on the host cells. For this reason, the activity of complement system is modulated and inhibited by proteins expressed on the membrane surface of the normal host cells [4].

Two distinct circuits, the alternative and the classical pathways may activate the complement. There is also a third pathway triggered by the link with the "Mannose-Binding lectin" (MBL), called "lectinic pathway". Although the different activation mechanisms, all these lead to cleavage of C3; the C3 proteolysis represents the main event of the activation complement, with generating downstream biological products active against pathogens [5].

The alternative pathway of complement leads to the C3 proteolysis in the absence of immune complexes. In the classical pathway, the complement activation requires IgG or IgM antibodies associated with their specific antigens. The lectinic way is activated without antibodies, by the interaction of microbial polysaccharides with circulating lectins such as MBL.

The C5 convertase, created by the alternative and classical pathways, activates the complement terminal components forming the "membrane attack complex: MAC" with the subsequent distruction of the cells [6].


## 3. Modulation of the complement activation: regulatory proteins

Even when it is properly activated and regulated, the complement system activation may cause serious damage to organs and tissues [7-9]. For this reason there is a fine adjustment of this system. The complement modulation system includes two proteins with specific regulatory activity, CD55 or decay accelerating factor (DAF) and CD59 or membrane inhibitor of reactive lysis (MIRL).

CD55 is a glycosylphosphatidylinositol (GPI)-linked protein that binds C3b and C4b with the inhibition of C3 convertase formation [10].

Instead, CD 59 is a cell surface protein anchored in a single GPI chain; it is widely expressed on the cells of all tissues. Its expression on erythrocytes is essential for their survival as it inhibits the

incorporation of C5b-9 by preventing MAC polymerization in plasma membranes and thus protecting cells from complement-mediated lysis.

## 4. Genetic defects of complement regulatory proteins: PNH-model

PNH is a clonal, non-neoplastic acquired disorder of the stem cell, characterized by intravascular haemolysis, occurrence of thrombosis and bone marrow failure [11]. The PNH cells were characterized by the lack of a group of proteins, expressed along the cell membrane, mediating the GPI-anchor due to the genetic mutation of PIG-A [12]. Among the proteins anchored by the GPI a pivotal role is played by CD55 and CD59. The latter belong to the family of regulatory complement proteins (Creg proteins) with inhibitory functions [13].

In the cases of massive activation of the complement by the alternative pathway, the CD55 and CD59 preserve the cellular elements on which they are expressed (in particular the red blood cells) by the lysis complement induced [14].

The haemolysis observed in PNH cases is especially intravascular, but a small part also consists of extra-vascular haemolysis. The fragments that derive from the hydrolysis of the complement proteins (especially C3d), in the absence of the protection mediated by CD55, opsonize the erythrocytes, favouring an antibody-mediated removal through a process occurring in the extra-vascular district.

Clinically, we distinguish three main kinds of PNH:

- Classical PNH, with clinical manifestations of hemolytic and thrombotic type;

-PNH in the context of bone marrow failure conditions (aplastic anemia or myelodysplastic syndromes);

- Subclinical PNH, in which patients have small EPN clones but not clinical or laboratory evidence of haemolysis and/or thrombotic events; these latter are one of the main causes of morbidity and mortality of PNH subjects.

Epidemiologically, the risk of thrombotic events correlates with the size of the PNH clone.

Thrombosis may occur in any site; the venous sites are more common than arterial ones. The most commonly involved sites include the intra-abdominal regions (hepatic, portal, mesenteric, splenic, etc.) and cerebral regions (sagittal and cavernous sinus). Budd-Chiari syndrome is the most frequent thrombotic form observed in PNH subjects; deep vein thrombosis and pulmonary embolism are also relatively prevailing.

In regard to pathophysiological mechanisms, the thrombophilic status in patients with PNH is multifactorial; many mechanisms have been proposed, but none of these alone may explain the high thrombotic risk that characterizes these subjects [15].

The absence of regulatory proteins CD55 and CD59 on platelets leads to the formation of microparticles with prothrombotic activity. High levels of free hemoglobin promote "scavenging" of nitric oxide (NO), implicated in platelet activation and aggregation.

In addition, even an impaired platelet function could be implicated in the pathophysiology of thrombotic events. In fact, as emerged from some papers in the literature, the adhesion and aggregation of platelets, especially of CD59 + platelets, were compensatively decreased in patients with PNH clone [16].

Finally, the complement activation contributes to the determination of a thrombophilic state. C5a may cause a proinflammatory state generating some cytokines such as interleukin-6, interleukin-8 and TNF-alpha. Moreover, the lack or absence of other GPI-related proteins, such as urokinase-type plasminogen receptor inhibitor, heparan sulfate and tissue factor pathway inhibitor, induce a defective fibrinolysis [17].

There is no evidence of genetic increased thrombophilic risk factors in PNH patients. In fact, the frequency of mutations in the gene for the factor V Leiden examined in these patients is the same as the one observed in the general population.

## 5. Acquired defects of regulatory complement proteins: PNH-like phenotype

The PNH is a pathological condition that is fully part of the rare diseases and, to date, the diagnostic investigation is justified in the presence of some clinical and laboratory criteria. However, in clinical practice, a variety of pathological conditions have been observed with an acquired and non-genetic deficiency of the regulatory proteins CD55 and CD59 [18].

In fact, the altered expression of CD55 and CD59 on the surface of erythrocytes is not exclusive to PNH, but it is possible to observe it in other clinical conditions such as: hemolytic anemia on autoimmune basis, infection from HIV, type 2 diabetes mellitus, systemic lupus erythematosus, chronic renal failure, autoimmune-induced thrombocytopenia, aplastic anemia, haematological diseases and poly-transfusion patients with beta-thalassemia major [19-21]. This abnormal expression of complement regulatory proteins defines a PNH-like phenotype, observed in different clinical settings, included some case of critically ill patients. [22].

As in the case of PNH, even in the PNH-like conditions, greater exposure to the mediated complement lysis and, probably, also an increased risk of thromboembolic events may be observed.

Therefore, the complement system and regulatory proteins play a role not only in mechanisms of immunological defence, but also in the clinical picture of various diseases. Moreover, the knowledge of the potential roles of the complement system becomes necessary for a deeper understanding of several pathological conditions and for a better clinical management of the patients.

### 5.1 Autoimmune diseases

CD55 and CD59 are cellular proteins of type I inhibiting the formation of C3 convertase and terminal polymerization of membrane attachment complexes, respectively. Several papers have reported that the reduced expression of these cell surface proteins are not specific to PNH and may be found in patients with autoimmune disorders [23-26].

The pathophysiological mechanisms behind the determination of this PNH-like phenotype are yet to

be understood, however this immunological disorder might play a pivotal role in the pathogenesis of autoimmune hemocytopenias. This event might be associated to an increase in thrombotic risk. The presence of a PNH-like phenotype has been demonstrated in some autoimmune disease as stated in the following sections.

### 5.1.1. Autoimmune hemolytic anemia (AIHA)

Certain studies highlighted a reduced expression of the CD55 and CD59 in erythrocytes. Ruiz-Argüelles et al. have examined the membrane density of CD55 and CD59 in erythrocytes from 19 patients with AIHA and also its possible association with the presence of antiphospholipid antibodies (APLA) [27]. They found this disorder in several SLE patients with secondary AIHA, and in few patients with primary AIHA.

Although many of the patients examined showed positive tests for APLA, no correlation was found between the antibodies detected - IgG, IgM or both isotypes - and CD55 or CD59 expression in erythrocytes. In fact, the presence of such antibodies is not necessarily associated to an autoimmune disease; these antibodies may be operative in idiotypic networks, opsonization and also from exposure to several infectious agents.

The PNH-like phenotype, with a more frequent decreased expression of CD59, may be due to defects in the GPI anchor synthesis but also to the conjugation defect of proteins into cell membrane.

It is important to underline that the decreased expression of CD55 and CD59 in AIHA does not mime the PNH patterns, but instead, as it has been observed, there was a shift in fluorescence of all red cells, indicating the non-clonal nature of this acquired defect.

### 5.1.2. Immune thrombocytopenia (ITP)

It is generally accepted that immune thrombocytopenia derives from sensitization of platelets with specific antibodies, with subsequent platelets destruction or sequestration by the mononuclear phagocytic system. Autoantibodies in the ITP are directed to the platelet glycoprotein GPIIb / IIIa and GPIb / IX complex, although antibodies directed to β-2 glycoprotein 1 have been found [28]. Despite the pathogenetic role, the detection of these antibodies is not simple and many patients have been found to be negative. Furthermore, the positive test for the detection of platelet antibodies has no prognostic value and does not change the therapeutic approach [29].

In regard to the expression of complement regulatory proteins, Ruiz-Argüelles et al. have examined 30 patients with the diagnosis of ITP, observing that the deficient expression of CD59 was more common than that of CD55. Furthermore, the lack of CD59 has been associated with severity of thrombocytopenia, while the same association has not been demonstrated with the deficiency of CD55 [27].

Furthermore, to understand whether the PNH-like phenotype could also be present in the megakaryocyte precursors, an evaluation was also performed on young platelets. In the latter, the expression of CD55 and CD59 was normal, while a reduced expression of CD55 and CD59 was observed in mature platelets. This finding excludes that the deficiency of these proteins affects the medullary platelet precursors confirming, on the contrary, it is an acquired disorder.

### 5.1.3 Systemic lupus erythematosus  (SLE)

Lymphopenia is a haematological abnormality present in SLE patients. It seems related to the acute phase of the disease, and at the same time during remission. Antibodies to lymphocytes are believed to be responsible of this haematological finding, probably through a mechanism regarding antibody-dependent cell cytotoxicity, opsonization, blockage of surface receptors and apoptosis. The mediated complement lysis is, perhaps, the most frequent and plausible explanation of the cytopenia [30-32].

Ruiz-Argüelles et al. have examined the membrane density of CD55 and CD59 also in lymphocytes of SLE patients, with and without lymphopenia. Both T and B cells of LSE patients with lymphopenia manifested a reduced expression of CD55 and CD59 compared to cells of healthy individuals; LSE patients with normal lymphocyte counts did not show this alteration [27].

Therefore, the decreased expression of complement regulatory proteins, perhaps secondary to the effect of autoantibodies, might facilitate lysis, favouring the development of cytopenia in SLE patients [33]


## 5.2 Chronic kidney disease (CKD)

Altered expression of CD55 and CD59 has also been observed in CKD patients [34]. In this context, Lama Al-Faris et al. have evaluated the expression pattern of CD55 and CD59 proteins on erythrocyte of patients with CKD [2, 35].

The aim of their research was to evaluate the possible cause of this phenotype, to evaluate a possible association with erythropoietin values and an inflammatory condition of this clinical disorder; thereafter to consider the role of this PNH-like phenotype in the pathogenesis of the anemic condition. The results of the research have showed that CKD patients had a significant decrease in the expression of CD55 and CD59 along the membrane surface, with a predominance of CD59 deficiency. Moreover, the study highlighted a strong correlation between the expression of CD55 and CD59, and the associated erythropoietin therapy; moreover, high values of PCR were correlated to the CD55 and CD59 levels.

In conclusion, the reduced levels of erythropoietin as well as the degree of inflammation, measured by PCR, influenced negatively the expression of CD55 and CD59 in CKD patients, increasing susceptibility to haemolysis, worsening the anemia [36-38].


## 5.3 HIV infection

The complement system contributes to the pathogenesis of HIV-mediated infection. In order to survive at the complement-mediated lysis, this virus has developed many mechanisms of resistance, including the opsonization with the complement fragments used to its own advantage. A diminished expression of CD55 and CD59 in lymphocytes in HIV-1 patients has been demonstrated, and this data seems associated with a higher sensitivity of lymphocytes to the lithic action of the complement. This is one of the main mechanisms of anti-cytotoxicity mediated against CD4+ T cells, which makes them more susceptible to apoptosis.

Furthermore, a reduction of CD59 was also observed on CD4+ alveolar lymphocytes from individuals infected with HIV-1, contributing to the local immunodeficiency present also in the pulmonary tissue [39, 40].

### 5.4 Diabetes mellitus

Diabetes and pre-diabetic status are the main independent risk factors for cardiovascular diseases. Diabetic subjects have a higher risk of heart attacks, strokes and occlusive peripheral vascular disease caused by an accelerated form of atherosclerosis [41]. Several experimental and clinical studies have supported the existence of a link between the complement system, complement regulatory proteins and pathogenesis of cardiovascular disease [42, 43].

In diabetes mellitus, the presence of this link has been provided by the identification of activated complement proteins such as C1q, C4d, C3d and MAC in the kidney [44] and retina [45].

Liu et al. have advanced the hypothesis that the functional inactivation of human CD59 by glycation process increases the pathological cellular responses induced by the formation of MAC, thus contributing to the highest risk of cardiovascular diseases in diabetic subjects. In support of this hypothesis, it has been reported that the erythrocyte of diabetic subjects show reduced CD59 activity and are more sensitive to MAC-mediated lysis. These findings underline a particular evidence for the hypothesis that the complement activation, with secondary reduced expression of CD59 in diabetic subjects, might contribute to the development of vascular complications [46].

Other authors have also demonstrated that in endothelial cells incubated with high concentration of glucose the expression of CD55 and CD59 decreased [47].

### 5.5 Haematological diseases

The PNH-like phenotype has been observed also in several haematological diseases, including aplastic anemia (AA), myelodysplastic syndromes (MDS), acute leukemias, lymphoproliferative syndromes (LPSs), myeloproliferative syndromes and *β*-Thalassemia. Some information about the PNH-like phenotype in plasma cell dyscrasias (PCDs) is also available, but no specific link between this phenotype and the pathogenesis has been provided. In consideration of the few data available in the literature, we are interested in describing the PNH-like phenotype in *β*-Thalassemia and PCDs.

### 5.5.1 β-Thalassemia

β-thalassemia is a genetic hemolytic disease due to the absence or the reduced synthesis of β-chains of hemoglobin A. The clinical picture of β-thalassemia is extremely varied, and range from the transfusion-dependent forms of beta-thalassemia major (β-TM) to the asymptomatic state of the thalassaemic trait. Chronic transfusions are the mainstay of treatment for severe β-TM patients but at the same time the iron overload is an important source of morbidity and mortality in these subjects.

Iron overload increases the risk of cirrhosis, heart failure and endocrinopathies, while ineffective erythropoiesis and haemolysis contribute to several complications such as splenomegaly, extramedullary hematopoiesis, pulmonary hypertension and thrombosis. Haemolysis is a common feature in β-TM patients. In order to study the haemolytic status in these patients, several researches were conducted to evaluate the role of CD55 and CD59, deducing that the low expression of CD55 favours the complement deposition on RBCs and enhances or promotes their lysis [48, 49].

In another paper, from the cytofluorimetric analysis, Kurtoğllu and colleagues observed that in β-TM patients the levels of CD55 were decreased compared to patients with intermediate β-T (β-TI),

while CD59 levels in β-TM patients were not significantly different than β-TI patients and controls. Low CD55 levels in patients with β-TM indicate a role of the complement regulatory proteins, in the pathogenesis of haemolysis in this disorder, and therefore, a crucial role in the development of chronic complications described in these patients [50].

### 5.5.2 Plasma cell dyscrasias (PCDs)

Some data are available in the literature regarding the presence of PNH phenotype in red blood cells of patients with PCD diagnosis [51, 52].

Meletis et al. described the presence of CD55/CD59- deficient red cells in patients with PCD, including monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma with IgA, IgG, IgD, BJ, Non-secretory isotypes and Heavy chain disease (HCD) [53]. In this research they found that frequency of simultaneous CD55 and CD59 deficiency was about 13% in these patients but without signs of hemolysis. Therefore, it is possible that CD55 or CD59 deficiency, alone is not sufficient to cause hemolysis. The patients with MM represented a greater proportion of red cells deficient in the CD55 antigen compared to patients with other types of PCD.

No correlation was found between the infiltration of plasma cells in bone marrow, the stage or isotype of MM, the presence of anemia, the levels of paraprotein and β2-microglobulin in MM patients with the PNH phenotype. Instead, in another paper from Terpos E. et al, has been observed an association between existence of the PNH phenotype and myeloma bone disease [54]. These results suggest that there is a possible link between PNH phenotype and increased osteoclastic activity in MM owing to a potential effect of myeloma microenvironment.

Several hypotheses may be proposed to explain the PNH phenotype in PCDs. The neoplastic cells in PCDs may be prone to somatic mutations or it is possible that in the context of PCDs could be a survival advantage to PNH cells.

It is important to distinguish PNH as a disease entity from the PNH-like defect observed in PCDs and a deeper knowledge of the link between the PNH phenotype and these disorders, can allow for

a best disease understanding and the formulation of therapeutic strategies to individual patients.

## 6. Thrombotic risk in PNH-like phenotype

Complement system and blood coagulation system represent two types of enzymatic cascades acting as protectors. In fact, both the complement and the coagulative cascades are associated with different functions of the immune and cardiovascular system. The specific components of the complement and coagulation systems are finely arranged to form two distinct multi-protein networks, with several crossover points [55].

The hemostasis involves a mix of processes supporting blood clotting (coagulation) in sites with altered vascular integrity and a subsequent dissolution of blood clots (fibrinolysis). The hemostasic system depends on the functions of: blood cells, vascular system, different soluble plasma proteins and low molecular weight components, all rigorously organized. A key role is played by platelets; these cells, once activated, provide a cell surface useful for starting the coagulation cascade, with consequent regulation of mediators essential for effective haemostatic responses. The haemostatic system is the result of two different pathways, identified as extrinsic and intrinsic coagulation pathways. Both pathways lead to the release of activated X-factor (Xa), with subsequent proteolytic activation and conversion of prothrombin into thrombin. Following the formation of the clot, fibrinolysis, with a distinct enzymatic cascade, leads to the removal of fibrin deposits.

As above stated, coagulation and complement are two systems with many points of interlinked and affinity. There are different elements in common: 1) both systems act as innate defences against external warnings; 2) the presence of foreign or altered cell surfaces is required for the beginning of biological processes; 3) the cascade reactions are generally organized in three phases: initiation, amplification and propagation; 4) there are several regulatory molecules (i.e. natural inhibitors) able to orchestrate the activity of both systems; 5) different components of each cascade interact with cell-surface receptors with the downstream biological effects.

These common characteristics of the coagulation and complement systems may explain the possible role of complement dysregulation in the development of thrombotic events, as well as, the hyperactivation of the complement system during thromboembolic events [56-62].


### 6.1 Complement activity and thrombotic risk: pathophysiological bases

Several data underline the procoagulant effect of complement on the coagulation cascade, either directly or indirectly. Its direct procoagulant activity may be performed at different levels. For example, MASP-2, a component of the complement lectin pathway, acts upon the activation of thrombin and subsequent generation of the fibrin network. The effector proteins of the complement may also induce morphological and functional changes in the endothelium, stimulating the activation of the coagulation cascade. Specifically, for example, C5a in combination with antibodies against endothelial cells may trigger the release of heparan sulfate from the endothelial surface, with a negative regulation of conformational antithrombin activation, an inhibitor of the coagulation system.

The complement activation may also modulate the aggregative platelets properties [63]. For example, the formation of the C5b-9 complex on cell surfaces may trigger changes in some cell membrane structures, inducing platelet activation or activating the coagulation. Moreover, in some experimental studies, it has been observed that stimulation of platelets with MAC may cause the depolarization of the cell membrane, the secretion of granules with subsequent activation of the coagulation cascade. Furthermore, MAC formation stimulates the release of membrane microparticles from platelet surface and endothelial cells, which may expose binding sites for the Va factor and support the proteolytic generation of thrombin. Platelet activation may also be mediated by the binding of C1q to its receptor on platelet surfaces. This process may result in platelet aggregation via a P-selectin-dependent pathway. C3 activation products may also directly induce platelet activation and aggregation [64].

The complement system capacity in inducing activation of the coagulation cascade are further supported by recent studies that have shown delayed thrombosis in mice with C3 deficiency and platelet hyperreactivity in mice deficient in the negative regulator (CD59b) of MAC (a mouse variant of human CD59) [65].

Another way through which the complement system may activate the coagulation cascade is the interaction between multimeric von Willebrand factor [66] and the regulation of tissue factor (TF) expression on endothelial cells [67].

Under conditions with compromised integrity of blood vessels, the induction of TF on endothelial cell surfaces may activate the extrinsic coagulation pathway. C5a may promote increased expression and activity of tissue factor in human and neutrophil endothelial cells.

Indirect actions of complement activation on hemostasis have also been described. These may occur through the regulation of specific cytokines, with a role in the maintenance of the haemostatic balance. For example, the anaphylatoxins C5a and C3a influence the production and secretion of TNF-α and IL-6 [68]. TNF-α and IL-6 may promote TF expression from blood cells and endothelial cells, while IL-6 may influence coagulation by acting upon platelet activity [69]. Finally, pro-inflammatory cytokines may also modulate the levels of antithrombotic proteins, such as thrombomodulin, reducing its activity [70].


*6.2 Complement activity and thrombotic risk: the clinical settings*

The link between the complement system activation and the development of thrombotic events may occur in different clinical conditions. Significant instances are represented by autoimmune disease [71], including systemic lupus erythematosus; they are also associated with thrombotic disturbances, especially in the presence of a PNH-like phenotype [72].

In these pathological settings, as described above, the reduced expression of some of the complement regulatory proteins (i.e. CD55 and CD59) could lead to a hyperactivation of this

system with the consecutive development of all the conditions capable of favouring the development of thrombotic events.

Moreover, the activation of the complement in these conditions may facilitate the release of proinflammatory modulators such as C5a and TNF-a, which in turn may also induce coagulation-dependent initiation of TF.

Remarkably, the aforementioned clinical conditions have demonstrated a strong correlation between the complement and coagulation systems; and such discovery will support and improve the management of patients.


## 7. Conclusions

Inflammation and thrombosis are closely linked by numerous mechanisms; recent clinical and laboratory data have demonstrated that complement and coagulation systems are "in vivo" interconnected at various levels.

In several acquired diseases, and thus distinct from PNH, different anomalies have been observed in the cellular expression of CD55 and CD59, with the development of PNH-like phenotype.

The pathophysiological mechanisms behind this phenotype have not been fully elucidated but it is characterized by a non-controlled activation of the complement system with following biochemical changes necessary for the coagulation cascade activation, with subsequent increased thrombotic risk. The development of thromboembolic events is one of the main determinants of morbidity and mortality in all clinical settings. Therefore, a specific understanding of the balance between complement and coagulation components and their reciprocal inhibitors may be useful for a better clinical management of patients.

Lastly, an understanding of such balance between the two at different levels may provide the basis for the development of possible diagnostic or prognostic markers and for the planning of more effective therapeutic strategies.

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