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Markery zapalenia, aktywacja płytek krwi i zaburzenia krzepnięcia w chorobach zapalnych jelit

Markers of inflammation, activation of blood platelets and coagulation disorders in inflammatory bowel diseases

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Abstract

Inflammatory bowel disease (IBD) includes ulcerative colitis and Crohn's disease. It is a group of chronic disorders characterized by inflammation of the gastrointestinal track with unknown etiology. Currently applied biomarkers include CRP, ESR, pANCA, ASCA, and fecal calprotectin. The etiopathogenesis of IBD is multifactorial. In patients with IBD in inflamed alimentary tract mucosa the number of recruited monocytes and activated macrophages which are source of cytokines. In IBD, the exacerbation is accompanied by thrombocytosis. Platelets play a crucial role in the hemostasis and inflammatory response. Selectins, which regulates the hemostasis and inflammatory response, stimulates the secretion of many inflammatory mediators such as β -thromboglobuline, CD40L, fibrinogen, IL-1 β , platelet factor-4. In the course of IBD the following changes are observed: an increase in the number of platelets (reactive thrombocytosis), PDW and PCT, reduction in MPV, increased production and excretion of granular content products (P-selectin, GP53, β -TG, PF-4, vWF, fibrinolytic inhibitors).

Key words: markers of inflammation • blood platelet • MPV • inflammatory bowel disease • IBD • activation

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Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC) with unknown etiology [34]. Ulcerative colitis and Crohn's disease are chronic, relapsing inflammatory diseases of the intestine. The IBD diagnosis is usually based on the combination of clinical features, genetic predisposition, laboratory tests, radiology, endoscopy, and pathology [4, 12, 42]. In the pathogenesis of UC numerous mechanisms are involved. The chronic inflammation in UC results from: damage to the epithelial barrier, equilibrium between tolerance to commensal microflora, dietary antigens and suitable sensitivity to enteric pathogens maintained by intestinal immune systems, dysregulation of immunological responses, and genetic factors [1, 3, 8, 11, 40].

According to Fengming et al. [12], IBD is an immune-related disease, and some immune-associated markers have been explored for this disease. The differentiation of UC and CD is quite difficult for physicians especially when the clinical, endoscopic, and pathologic features are not typical or confused. However, some markers could help to resolve part of that problem.

SERUM MARKERS OF ACUTE PHASE RESPONSE

- C-reactive protein (CRP) and/or high-sensitivity C-reactive protein (hs-CRP) sharply increases, even reaching up to 350-400 mg/L, when acute inflammation occurs which is induced by interleukin 6 (IL-6), tumour necrosis factor- α (TNF- α), IL-1 β . Half-life of CRP is short (19 h); it increases rapidly and decreases sharply in acute inflammation. CRP level can be used with serum ghrelin as an important marker in establishing the mucosal damage in inflammatory bowel diseases [7, 18, 20].
- Erythrocyte sedimentation rate (ESR) indicates migration speed of red blood cells in plasma; it varies with concentration of plasma and the size of erythrocyte [8,12].
- Platelets Count (PLT) increase in patients with IBD [10, 12].
- Mean platelet volume (MPV) indicates average size of platelet; it could reflect the rate of platelet stimulation and production. MPV negatively correlated with some markers of inflammation, such as WBC, CRP and ESR [12].
- Red blood cell distribution (RDW) reflects the size and variability of erythrocytes in peripheral circulation. CRP, ESR and RDW increase in IBD [12].
- Albumin is a negative acute phase marker and decreased levels may be found during inflammation. Alpha 1-acid glycoprotein or orosomucoid is another hepatocyte derived acute phase protein related with IBD activity, but the long half-life (5 d) reduced its usefulness [8].
- Other acute phase markers include : sialic acid, fibrinogen [10], lactoferrin, β 2-microglobulin, serum amyloid A, alpha 1-antitrypsin [8].

The inflammation-associated cytokines include interleukins : IL-2, IL-4, IL-6, IL-1 β , TNF- α , IFN- β , TGF- β , IL-8, IL-10

(humoral immunity- IL-4, IL-6, IL-10 and cell-mediated immunity- IFN- γ , TNF- α , IL-2, IL-1 β) [11, 13, 33].

SEROLOGIC MARKERS OR ANTIBODIES

- ANCA (anti-neutrophil cytoplasmic antibodies) are antibodies for granules of neutrophil cytoplasm. The cytoplasmic (cANCA), the speckled (sANCA) and the perinuclear (pANCA) [12].
- Anti- β 2-Glycoprotein-I (anti- β 2-GPI IgA/IgM/IgG) [29].
- Anti-cardiolipin (ACA IgA/IgM/ IgG) [29].
- Anti-phosphatidylserine/prothrombin (anti-PS/PT IgA/IgM/IgG) [29].
- Anti-*Saccharomyces cerevisiae* antibodies (ASCAs) are antibodies for mannan in cell wall of *Saccharomyces cerevisiae*; it is homologous to cell wall of enterobacterias [12].
- Antibodies to outer membrane porin (Anti-OmpC), flagellin (Anti-Cbir1), *Pseudomonas fluorescens*-associated sequence I-2 and antibodies to flagellin A4-Fla2 and Fla-X [8].
- Anti-carbohydrate antibodies: anti-laminaribioside carbohydrate IgG (ALCA), anti-chitobioside carbohydrate IgA (ACCA), anti-synthetic mannoside antibodies (ASMA or AMCA) [8, 29].
- Pancreatic autoantibodies (PABs) [8,29].
- Serum p53 antibodies [8].

OTHER MARKERS IN IBD

- Fecal calprotectine is a protein in neutrophil granulocytes and macrophages; it consists of S100A8 and S100A9. It is released by activated innate immunity cells when cell stresses and damages, which also reflect the process of inflammation [12, 18].
- Fecal lactoferrin (FL) is an iron-binding protein; it covers most mucosal surface and interacts with exocrine organs (FL is helpful biomarker to the early diagnosis of pediatric IBD) [6, 20].
- Fecal neopterin (increases just in feces, not in serum and urine) [12].
- Advanced oxidation protein products (AOPPs) – novel protein markers of oxidative damage, accumulate in the plasma of patients with IBD (increased levels) [37, 38].
- S100A12 as a novel biomarker in proinflammation processes; it is a member of S100 calcium binding protein family, and is activated extracellularly similar to S100A8 and S100A9. S100A12 participates a lot in proinflammation processes; it stimulates proinflammation mediators by NF-kappaB or other similar pathways [12].
- MicroRNAs (miRNAs) are small noncoded single-stranded RNAs (18-24 nucleotides) [12].
- Adenosine deaminase (ADA) correlated with CRP [12].
- Lipopolysaccharide - binding protein (LBP) and CD14 - correlated with Hs-CRP,
- Abnormal lectin-based IgG glycosylation – it correlated with disease activity [12].



- Mopterin – a component of piperazine-[2,3-d]-pyrimidine, which is a metabolic product of cyclic guanosine monophosphate. Mopterin is released by T lymphocytes and macrophages stimulated by γ -interferon, serological mopterin also correlated with ESR [12].
- Soluble ST2 – a member of IL-1R superfamily; it consists of 2 parts (ST2L and sST2) and is coded by 2nd chromosome [12].
- Nitric oxide (NO) and trimethylamine-N-oxide (TMAO) [36].
- Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1),
- Substance P – serum substance P level sharply increases in UC and CD,
- Activated thrombin activatable fibrinolysis inhibitor (TAFIa) – correlated with WBC, CRP, fibrinogen, platelets,
- Quantitative fecal immunochemical test (FITs) – could detect fecal blood rapidly,
- Chitinase 3-like-1 (CHI3L1/YKL-40) – a protein excreted by endotheliocytes and macrophages in intestine,
- Angiogenin – increases significantly in IBD,
- Mucosal cytokine – IL-17A and IFN- γ , higher levels IL-17A and IFN- γ are significantly correlated with remission of IBD,
- Urine neopterin [12].

FUTURE BIOMARKERS

- Metabolome biomarkers – mucosal Indoleamine 2,3-dioxygenase-1 (IDO1), and L-arginine (L-Arg) [8],

PLATELETS AND COAGULATION IN IBD

Platelets are involved in the pathogenesis of chronic inflammations such as IBD. Thrombocyte activation observed in the active period of the disease not only regulates coagulation, but also enhances mucosal inflammation. Platelets initiate and support inflammatory processes by secretion of numerous biologically active substances such as PAF (platelet activation factor), PDGF (platelet-derived growth factor), platelet factor 4, beta-thromboglobulin, fibrinogen, von Willebrand factor (vWF), plasminogen, fibrinolytic inhibitors, coagulation V, VIII and XI factors, protein S, VEGF (vascular endothelial growth factor), P-selectin, ADP, serotonin, IL-1 β , chemokines, RANTES (regulated on activation, normal T-cell expressed and secreted), IL-8, COX (cyclooxygenase), TF (tissue factor), PAI-1 (plasminogen activator inhibitor -1) [27, 35].

According to Voudoukis et al. [32], during activation, platelets develop receptors for chemokines, cytokines, and complement components, enabling them to participate in various inflammatory cascades in IBD. Molecules released from the activated PLT induce an inflammatory phenotype in endothelial cells and leukocytes. Polymorphonuclear cells enhance their superoxide, PAF, leukotriene production, and endothelial cells stimulated by certain PLT factors (PAF, histamine, RANTES) increase vascular permeability.

MORPHOLOGICAL PARAMETERS OF BLOOD PLATELETS

Many PLT changes have been described in IBD, including morphological alterations (MPV, PDW – platelet distribution width, PCT – platelet crit), count increase, MPs release, over-excretion of granular content, and increased formation of PLT-PLT and PLT-leukocyte aggregates (PLA), which are all linked to PLT activation induced by inflammatory agonists. The first study reporting IBD reactive thrombocytosis (RT) in 1968 by Morowitz et al. [19] noted markedly-elevated concentration of circulating PLT during a period of increased clinical activity in a case of IBD patients. This effect is the result of aberrant bone marrow thrombopoiesis under the influence of inflammatory mediators and the aftermath of reduced PLT lifespan due to accelerated activation and consumption of thrombocytes at the sites of inflammation [35].

MPV is a machine-calculated measurement of the average size of platelets. MPV correlates with platelet function and activation. It can be influenced by inflammation. Larger platelets are metabolically and enzymatically more active and play an important role in inflammatory process. According to a study by Ozturk et al. [23] MPV levels were lowest in remission (UC and CD) and highest in the control group. Although Yuksel et al. [40] demonstrated a correlation between disease activity and MPV level, they did not find a significant link. MPV decrease in subjects with UC and CD can be associated with thrombopoiesis disturbance often observed in the early stages of systemic inflammatory processes [28]. Chronic inflammation in IBD increases the number of platelets and changes their morphology. While PCT is a measurement derived from the platelet count and the MPV, PDW is a direct flow cytometric measurement of platelet cell volume. According to a study by the Ozturk et al. [23] PDW was significantly lower in an active phase of UC and CD groups compared to a remission phase. PDW was positively and PCT negatively correlated with disease activity in UC. PCT percentage was also markedly correlated with ESR and WBC levels.

In their study, Liu et al. [14] demonstrated that the MPV level was significantly lower in CD patients than that in the healthy participants. Meanwhile, they also showed that CRP and ESR were both higher in CD patients compared with healthy controls, and higher in active compared with inactive CD patients. Even though the overall accuracy of CRP and ESR was lower than that of MPV in detecting CD patients, they were still effective in determination of active CD patients. The similar MPV in active and inactive CD patients observed in the study is not in agreement with the results of previous studies. The absence of any correlation between MPV and other inflammatory markers in their study supported the hypothesis that MPV was not in a close relationship with CD activity. There was a decline of MPV in CD patients compared with healthy controls. They also compared MPV with other inflammatory markers, including CRP, ESR and WBC, pointed to the discriminative talent of MPV and recommended MPV as the best marker for differentiating CD patients from

healthy subjects. Finally, they suggested caution when using MPV as a marker in determination of CD activity.

In the study by Tang et al. [31] in active CD, PLT and PCT levels were notably higher but P-LCR (large platelets) and PDW levels were lower than those in healthy controls and patients in remission. PLT, PDW, P-LCR and PCT were significantly correlated with active disease (CD). PCT may act as a specific and sensitive biomarker for determining active CD, especially in patients with an hs-CRP level lower than 10.0 mg/L.

ACTIVATION OF BLOOD PLATELETS

P-selectin is a member of the CAMs (cell adhesion molecules) family mainly produced in PLT. A soluble fraction of P-selectin is also detected in patients with inflammatory disorders, including IBD, and possibly serves as selectin binding inhibitor. The lectin containing N-terminal domain of P-selectin binds to PSGL-1 (P-selectin glycoprotein ligand) found in leukocytes mediating recruitment and rolling of infiltrating leukocytes in the gut mucosa, and initiating activation processes like chemokines production by monocytes and CD4(+) T cells, as well as superoxide over-excretion by neutrophils. CD40L (CD154) is a protein, strongly related to TNF and expressed on the surface of activated PLT and immune system cells. CD40L is produced and released only by activated PLT in IBD patients [26, 34]. In addition to increased levels of coagulation cascade proteins in IBD, CD40, CD40L, and soluble CD40L are increased in IBD [9, 22].

In our study [17], the platelet count and the level of soluble platelet selectin (sP-selectin) were found to increase with the disease progression. The level of sP-selectin was lowest in early cancer and was observed to increase after surgery in all the study patients. Irrespective of tumor stage, a statistically significant decrease was noted in the percentage of phagocytizing platelets and in the phagocytic index in gastric cancer patients as compared to healthy subjects. Despite an increased platelet count and stimulation of thrombocytopoiesis, the phagocytic functions of blood platelets were markedly impaired. Tumor development seems to impair metabolic processes. A decreasing phagocytic activity can promote both inflammatory processes (as in the course of IBD) and cancer growth.

In our other studies [25], the MPC, concentration of sP-selectin and IL-6 serum were significantly higher in subjects with ulcerative colitis compared to those in the healthy group. There was a decrease of MPV in patients with ulcerative colitis, which is statistically significant. Chronic inflammation in patients with ulcerative colitis causes an increase in the number of blood platelets, a change in their morphology and activation. Decreased MPV value reflects activation and the role blood platelets play in the inflammatory process of the mucous membrane of the colon. A high concentration of sP-se-

lectin, which is a marker of blood platelet activation, demonstrates their part in the inflammatory process. The increase in the concentration of sP-selectin correlated positively with the increase in concentration of IL-6. This is why it may be a useful marker of the activity of ulcerative colitis.

Platelet-derived microparticles (PDMPs) are active molecules involved in the hemostatic and inflammatory responses. To evaluate the changes in the platelet function in patients with inflammatory bowel disease, Andoh et al. [2] measured circulating PDMP levels. Their study showed PDMP levels of 17.2 ± 6.2 U/mL in the healthy controls. Significant differences were not observed between the healthy controls and inactive UC patients or between the healthy controls and inactive CD patients (17.6 ± 7.8 U/mL). In contrast, the PDMP levels were significantly higher in both active UC (49.2 ± 33.6 U/mL) and active CD (48.6 ± 42.8 U/mL) patients than in the healthy controls. Elevated PDMP levels in active patients were significantly reduced after remission. A significant correlation was observed between the PDMP levels and the sP-selectin levels. Elevated circulating PDMPs in active IBD patients suggest a role for platelets in the pathogenesis of IBD.

Circulating procoagulant microparticles (MPs) are thought to be involved in the pathogenesis of venous thromboembolism in patients with inflammatory bowel disease. Increased numbers of circulating TF(+) MPs represent a new facet of hemostatic abnormalities in IBD. However, the lack of association with activation of the coagulation system and disease activity questions their pathogenetic role for venous thromboembolism in this patient group [24].

In inactive Crohn's disease patient serum levels of (sP-selectin) sP-S, (plasma sE-selectin) sE-S, sVCAM-1 (human soluble vascular cell adhesion molecule-1) and sICAM-1 (human soluble intercellular adhesion molecule-1) were significantly lower than in controls. In active CD patients, only the sE-S values were higher than in controls. In UC patients, sP-S and sVCAM levels were lower than those in controls. Considering growth factors, CD patients in remission had levels of ANG (angiogenin) and VEGF lower than those found in controls [15].

BLOOD COAGULATION IN IBD

In contrast to hemostasis, which is a normal response to vascular injury, thrombosis is pathological coagulation occurring spontaneously or following a minimal vascular injury. The underlying cause of thrombosis is an imbalance between prothrombotic and antithrombotic mechanisms. The tendency towards thrombosis is related to three basic mechanisms, as defined by the Virchow's triad: vascular stasis, endothelial injury / vascular damage and hypercoagulability [43].

The possible association between inflammatory bowel disease and venous thrombosis (VTE) was first reported in 1936 by Bargen et al. [5], who described 18 patients with



thromboembolic diseases from among more than 1000 patients treated for IBD at the Mayo Clinic.

The secretion of tissue factor from damaged endothelium as well as the production of thrombin play a role in platelet activation [21, 30]. PAF, which is secreted from the inflamed bowel tissue, also contributes to the activation. The platelets not only play a role in hemostasis and thrombosis but also exhibit proinflammatory characteristics, since they secrete mediators such as platelet factor 4, platelet-activating factor, IL-8 and arachidonic acid metabolites. It was shown that production of these mediators was increased in IBD. In a study by Tekelioglu et al. [32], platelet activation was found to be statistically significantly higher in the active-phase patients group when compared with the control subjects group. On the other hand, it was insignificant in the inactive patients group. The results of their study might suggest that the elevation of CD62P expression in patients with IBD could be used as a criterion of disease activation. Furthermore, agents with properties to diminish platelet activation could prevent the development of thromboembolic complications in a patient with IBD.

Platelets are generally considered the first line of defense in sealing off injured blood vessels. The accumulation of activated platelets at sites of vessel injury is also associated with an increased expression of platelet receptors for coagulation proteases and cofactors, the release of a variety of bioactive substances from alpha- and dense granules that recruit additional platelets and activate other cell types and an amplification of the procoagulant response that is characterized by explosive thrombin generation [32]. The platelet dysfunction in IBD is also manifested as an increased expression of activation - dependent surface antigens on circulating platelets, including P-selectin, GP53, and CD40-ligand. Soluble CD40L levels are significantly higher in IBD patients (both CD and UC) compared to normal controls, which largely reflects the shedding of this proinflammatory signalling molecule from the surface of activated platelets. Alpha-granule derived platelet factors such as beta-thromboglobulin and platelet factor-4 are also increased in the plasma of IBD patients, although their appearance in plasma is not correlated with disease activity. Changes in platelet function during IBD are manifested as a tendency for platelets to spontaneously aggregate *in vitro* and to exhibit an increased sensitivity to endogenous pro-aggregation molecules such as collagen and adenosine diphosphate. Intravascular platelet aggregates have been detected in mucosal biopsies of patients with UC and there is an increased number of circulating platelet aggregates in the mesenteric venous circulation draining the inflamed bowel in UC. The increased expression of P-selectin on activated platelets enables these cells to bind to leukocytes,

which constitutively express PSGL-1, the major ligand for platelet P-selectin [16, 37].

The hypercoagulability of blood in IBD patients is associated with the appearance of thrombi in the vasculature of the intestine and extra-intestinal tissues. Platelet aggregates which stain positively for glycoprotein IIb/IIIa appear to occur at sites of granulomatous destruction of mesenteric blood vessels and there is evidence for intravascular fibrin deposition and complete thrombotic occlusion. The fibrin clots are within arteries supplying the inflamed gut and in capillaries and venules. The vessel obstruction that results from the formation of these clots likely contributes to the impaired tissue perfusion, cell necrosis, and organ dysfunction described in the colon of patients with IBD. Systemic thromboembolic events (TE) represent a major cause of morbidity and mortality associated with IBD. Thromboembolic complications in both Crohn's disease and UC appear to have at least 3-4 fold increased risk of developing compared to control patients [30]. The mortality rate from the thromboembolic complications of IBD ranges between 8-25% during the acute phase of the thrombotic events, with a two-year mortality of approximately 25%. Yoshida et al. found that no single biomarker of coagulation appears to reliably correlate with the occurrence of TE in IBD [35, 39].

Increased markers of coagulation include thrombin anti-thrombin complex, tissue factor and fibrinopeptide B, and can be described early in IBD. Factor XIIIa, a fibrin-stabilizing coagulation factor (and agonist for VEGF-2), is increased in IBD, while factor XIII TT has an increased number of mutations in IBD patients compared to controls suggesting links between thrombosis, angiogenesis and inflammation. Other authors reported that factor XIII activity is reduced in IBD patients [9].

CONCLUSION

Blood platelets are important key regulators in inflammatory disorders beyond haemostasis and thrombosis. In IBD pathogenesis, platelet activation could be the missing link between inflammation and coagulation. Thrombocytosis has been associated with IBD manifestations such as disease activity, whereas platelet parameters (MPV, PDW, PCT) have been suggested as surrogate markers for IBD [35]. In the course of IBD the following changes are observed: an increase in the number of platelets (reactive thrombocytosis), PDW and PCT, reduction in MPV, increased production and excretion of granular content products (P-selectin, β -TG, PF-4, vWF, fibrinolytic inhibitors). Additionally, the article by Zanoli et al. [41] provides of relationship between IBD and the risk of cardiovascular disease, particularly coronary artery disease.

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Table 1. Main biological markers in ulcerative colitis [8]

Serum markers of acute phase response		Response
C-reactive protein		Increased
Erythrocyte sediment rate		Increased
Platelet count		Increased
White blood cell count		Increased
Alpha 1-acid glycoprotein (orosomuroid)		Increased
B2-microglobulin		Increased
Sialic acid		Increased
Serum amyloid A		Increased
Ferritin		Increased
Serum albumin	Complement system	Decreased
Transferrin	Complement system	Decreased
C1s, C2, C3, C4, B	Complement system	Increased
Haptoglobin	Transport proteins	Increased
Haemopexin	Transport proteins	Increased
Caeruloplasmin	Transport proteins	Increased
Alpha1 Antitrypsin	Proteinase inhibitors	Increased
Alpha1 antichymotrypsin	Proteinase inhibitors	Increased
Fibrinogen	Coagulation and fibrinolytic proteins	Increased
Prothrombin	Coagulation and fibrinolytic proteins	Increased
Plasminogen	Coagulation and fibrinolytic proteins	Increased
Factor XII	Coagulation and fibrinolytic proteins	Decreased
IL-6, IL-1 β , TNF- α , IL-8, IL-10 IFN- β	Cytokines	Increased
Serologic markers/ antibodies		Positive rate
ANCA	Anti-neutrophil cytoplasmic antibodies (cANCA, sANCA, pANCA)	2-28% in CD 20-85% in UC

Serum markers of acute phase response		Response
ASCA	Anti-saccharomyces cerevisiae antibodies	39-69% in CD 5-15% in UC
Anti-OmpC	Antibodies to outer membrane porin	24-50% in CD 5-11% in UC
Anti-Cbir1	Flagellin related antigen	50% in CD 5-11% in UC
Anti-I2	Pseudomonas fluorescens-associated sequence I-2	30-50% in CD 2-10% in UC
Flagellin A4-Fla 2 and Fla-X antibodies	Newly identified	About 57% in CD
Antilaminaribioside carbohydrate IgG (ALCA)	Antiglycan antibody	17-28% in CD 4-7% in UC
Antichitobioside carbohydrate IgA (ACCA)	Antiglycan antibody	20-25% in CD 5-15% in UC
Anti-synthetic mannoside antibodies (ASMA or AMCA)	Antiglycan antibody	28% in CD 18% in UC
Pancreatic antibodies	Pancreatic secretion	30-40% in CD 2-6% in UC

CD – Crohn's disease, UC - ulcerative colitis

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