PLATELETS AND COAGULATION IN
CHRONIC GRAFT VERSUS HOST DISEASE

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Summary

Chronic graft-versus-host disease (cGVHD) is a multi-organ alloimmune and autoimmune
disease occurring after allogeneic hematopoietic stem cell transplantation (alloHSCT). Due to
increasing safety of alloHSCT number of survivors is increasing and more patients are at risk of
developing cGVHD. Low platelet counts in cGVHD patients are predictors of poor survival acro-
ss many cGVHD studies; however, such association is still not well understood. Moreover, newer
studies found increased platelet counts and active thrombopoiesis associated with more active
and more severe cGVHD. Several acquired disorders of coagulation are described in cGVHD
patients as well. Hemostatic disorders in the setting of cGVHD have multifactorial etiology with
numerous interactions between inflammation and coagulation. Improved understanding of these
processes may lead to better understanding of pathophysiology of cGVHD and to improve pre-
vention and treatment of that severe disease.

Key words: platelets, thrombocytopenia, thrombopoiesis, coagulation disorders, chronic
graft versus host disease

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is an intensive
curative therapy used to treat numerous high-risk hematological malignant and
non-malignant diseases [1]. Over the past decade, the improvement were made
in supportive care, graft-versus-host disease (GVHD) prophylaxis, better mana-
gement of early complications, new stem cell sources, DNA-based tissue typing,
new conditioning regimens with less toxicity, resulting in improved outcomes.
The number of alloHSCT continues to increase with more than 25 000 performed
annually [1]. Recent study showed substantial reduction in early death related to alloHSCT and improved long-term survival after alloHSCT due to reduction in organ damage, infection and severe acute GVHD [2]. However, long-term survivors experience several long-term complications such as chronic GVHD, metabolic and endocrinology abnormalities, decreased quality of life and secondary malignances, and mortality rates remain twice as high as that of the general population among 15-year survivors of alloHSCT [3].

Chronic graft versus host disease (cGVHD) is a major late complication occurring in 25-80% of alloHSCT recipients [4]. It is a multi-organ alloimmune and autoimmune disease characterized by immune deregulation, immunodeficiency, development of signs and symptoms of different autoimmune or immunologic disorders, and is associated with decreased survival [4-7].

**Platelets and chronic GVHD**

Thrombocytopenia in cGVHD patients is among the most consistent and strongest negative survival predictors across many cGVHD studies, as it is extensively reviewed by Pulanic and colleagues [8]. One among the earliest studies which showed that cGVHD patients with low platelet counts had the worst survival and that thrombocytopenia may reflect more severe cGVHD was study by First and colleagues published in 1985 [9]. A few years later Sullivan with colleagues studied 179 patients with extensive cGVHD, and those with thrombocytopenia less than 100,000/μL had increased mortality [10]. Another important study was published in 1989 by Anasetti and colleagues [11]. This study concluded that persistent thrombocytopenia after alloHSCT is most often secondary to increased platelet destruction mediated by multiple mechanisms, and that increased mortality of patients with cGVHD and thrombocytopenia may be result of underlying immunodeficiency and immune deregulation [11]. Akpek with colleagues defined 3 risk factors at diagnosis of cGVHD that were significantly associated with increased non-relapse mortality: thrombocytopenia (platelets less than 100,000/μL), more than 50% body surface area skin involvement and progressive type of cGVHD onset [12]. Study of Przepiorka and colleagues validated risk stratification by platelet count in 116 alloHSCT patients [13]. Long term progression-free survival was 31% for patients without cGVHD, 51% for not thrombocytopenic cGVHD patients and just 16% for patients with cGVHD and thrombocytopenia [13]. Large multicenter study published by Akpek and colleagues in 2003 with a total of 1105 cGVHD patients from 4 different cohorts showed that thrombocytopenia (platelets less than 100,000/μL) was uniformly associated with increased risk of mortality acro-
ss all cohorts [14]. Arora and colleagues studied 159 cGVHD patients to identify predictors of response and long-term mortality [15]. In multivariate analysis age older than 20 years, progressive onset of cGVHD, gastrointestinal tract involvement and platelets less than 100,000/μL were associated with increased mortality [15]. Pavletic and colleagues identifies several independent prognostic risk factors for cGVHD incidence and severity comparing bone marrow (75 patients, alloBMT group) and peripheral blood alloHSCT (87 patients, alloPSCT group) recipients, suggesting that stem cell source may influence not just the incidence of cGVHD but also its characteristics [5]. Predictive factors for poor survival at 3 years after cGVHD diagnosis in alloPSCT patients were platelets below 100,000/μL and history of acute GVHD of the liver, and only low platelet count remained predictive for poor survival in alloBMT group [5]. Arora with colleagues in 2007 analyzed clinical presentation and response to treatment in 170 patients with cGVHD (123 after transplant from an unrelated donor and 47 from umbilical cord blood) (16). In both cohorts thrombocytopenia and not achieving complete or partial remission at 2 months were independently associated with increased mortality [16].

Several possible mechanisms of thrombocytopenia in the cGVHD setting were suggested: transplant-related thrombocytopenia, malignancy relapse, microangiopathic thrombocytopenia, drug-induced thrombocytopenia, immune-mediated thrombocytopenia, hypersplenism, infection, cytokine-induced thrombocytopenia (increased transforming growth factor-beta (TGF-β), low thrombopoietin level, other cytokines) [8].

In contrast, in the recent study by Grkovic and colleagues higher platelet counts were associated with more active and more severe chronic cGVHD [17]. In that study markers of inflammation were studied among 189 adult patients with chronic cGVHD and were correlated with disease activity and severity [17]. Higher platelets were associated with most severe skin (p=0.0016) and joint/fascia cGVHD involvement (p=0.0001) [17]. This relationship was hypothesized to be related to ongoing inflammation and reactive thrombocytosis mediated by IL-6, a strong stimulator of platelet production [17]. Moreover, platelets can contribute to pathogenesis of fibrosis as they are important source of fibrogenic cytokines such as TGF-β and platelet-derived growth factor (PDGF) [17]. In addition to that, Bat with colleagues recently found that active thrombopoiesis, measured by the absolute immature platelet number in the blood, was associated with worse severity and activity of chronic cGVHD, especially skin and joints/fascia manifestations, supporting hypothesis that ongoing inflammation in cGVHD stimulates increased thrombopoiesis in the most severe patients [18].
Acquired coagulation disorders and chronic GVHD

Patients with cGVHD may develop several other acquired coagulation disorders, including also an increased risk for venous thrombosis in spite of higher bleeding risk [8].

Pihusch et al [19] retrospectively analyzed hemostatic complications among 447 hematopoietic stem cell transplantation (HSCT) patients. The 364 alloHSCT patients had a higher incidence and severity of hemorrhagic complications than autologous HSCT patients, what was due to GVHD: patients with acute GVHD greater than grade I had a three-fold higher risk of bleeding, chronic GVHD patients had a four-fold higher risk, with an eleven-fold risk of severe hemorrhage. Such GVHD-associated bleeding was mostly localized in GVHD affected organs like skin and gastrointestinal tract and it correlated with an increased mortality. The authors concluded that acute and chronic GVHD strongly increase bleeding risk by destruction of epithelium and hyperperfusion and proliferation of the blood vessels [19]. In the same study, venous thromboembolism (VTE) occurred mostly later after transplantation and depended on the type of transplantation. Chronic GVHD and treatment with steroids were the most important risk factors for VTE [19]. The authors suggested that cytokines which modulate endothelial hemostatic function could be responsible for VTE in cGVHD. Other work from the same group of authors prospectively studied the impact of GVHD and of thrombophilic gene mutations in 89 alloHSCT patients [20]. They again reported increased risk for VTE among cGVHD patients [20]. In that work, thrombophilic gene mutations and polymorphisms did not influence either the incidence of any of the major transplant-related complications or the bleeding incidence [20]. Among patients with thromboembolic complications those with catheter thromboses and hepatic veno-occlusive disease showed an increased frequency of the 4G allele of the PAI-1 gene, while other tested thrombophilic gene mutations and polymorphisms had no impact on the incidence of VTE complications among alloHSCT patients [20].

Other acquired hemostatic disorders in chronic GVHD patients are rare and are described in several case reports [8]: acquired hemophilia A (acquired factor VIII inhibitor) [21], acquired von Willebrand’s disease [22], antiphospholipid syndrome (APS) [23], catastrophic APS [24], passive donor-to-recipient transfer of APS following the onset of cGVHD [25].

It is important to note the link between von Willebrand’s factor (vWF), endothelial injury and chronic GVHD described by Biedermann and colleagues [26]. They found that chronic GVHD patients have extensive loss of microvessels in affected tissues and increased circulating vWF concentrations, concluding that vWF was
released from vascular endothelial cells injured in process of cGVHD [26]. Since elevated vWF and factor VIII (FVIII) levels have been described as indicators of endothelial dysfunction and inflammation in different settings, our Zagreb’s cGVHD group assessed possible role of vWF and FVIII as potential biomarkers of cGVHD [27]. Preliminary results of this pilot study presented recently at the European Bone Marrow Transplantation meeting suggest that vWF and FVIII could represent interesting candidate biomarkers of cGVHD, what need to be further investigated in larger studies [27].

**CONCLUSION**

Platelet and coagulation disorders in the setting of chronic GVHD have multifactorial etiology with numerous interactions between inflammation and hemostasis. Improved understanding of these processes may lead to better understanding of pathophysiology of cGVHD and to improve prevention and treatment of that severe disease.

**References**


Sažetak

Trombociti i koagulacija u kroničnoj bolesti presatka protiv primatelja

Kronična bolest presatka protiv primatelja (eng. chronic graft-versus-host disease, cGVHD) je multiorganska aloimuna i autoimuna bolest koja nastaje nakon transplantacije alogeničnih krvotvornih matičnih stanica (aloTKMS). S obzirom na poboljšanje sigurnosti transplantacije i na porast preživljenja nakon aloTKMS, sve više osoba nakon aloTKMS ima rizik nastanka cGVHD. Trombocitopenija u cGVHD bolesnika je prediktor lošeg preživljenja u brojnim studijama cGVHD, iako ta povezanost još uvijek nije dobro objašnjena. Nove studije su utvrdile povezanost povišenih trombocita i aktivne trombocitopoeze s aktivnijim i težim cGVHD. Više stečenih poremećaja koagulacije opisano je u cGVHD bolesnika. Hemostatski poremećaji u cGVHD imaju multifaktorijalnu etiologiju s brojnim interakcijama između upale i koagulacije. Unaprijeđenje razumijevanja tih procesa dovest će do boljeg razumijevanja patofiziologije cGVHD, kao i prevencije i liječenja te teške bolesti.

Ključne riječi: trombociti, trombocitopenija, trombocitopoeza, poremećaji koagulacije, kronična bolest presatka protiv primatelja

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