Vascular endothelial syndromes after HCT: 2020 update

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Given that it is several years since the publication in *Bone Marrow Transplantation* of our first editorial focusing on the endothelial complications shortly after hematopoietic cell transplantation (HCT) [1], we felt it is of utmost importance to update the topic. Several advances have been made since that publication to justify such an update and a recent review on the subject by Pagliuca et al. [2], suggested that an update is now timely. The current contribution aims to offer a thorough review of the current knowledge of the main vascular endothelial syndromes (VES) and at the same time introduces some new concepts and suggests several changes to the classification that we think deserve in-depth comment.

The first aspect of the above mentioned review article [2] that may lead to confusion is the title “Allogeneic reactivity-mediated endothelial cell complications,” since all VES, except the recently introduced graft-versus-host disease (GVHD) (see below), can also be observed after autologous HCT. Allogeneic reactivity is only one of the factors that induces endothelial dysfunction. In fact, one of these complications, the engraftment syndrome [3], is almost exclusively seen after auto-HCT; others, such as diffuse alveolar hemorrhage (DAH) or peri-engraftment respiratory distress syndrome (PERDS), may be observed in both modalities of transplantation [4, 5], and transplant-associated thrombotic microangiopathy (TA-TMA) despite being observed mainly after allo-HCT, can occasionally be diagnosed after auto-HCT [6]. An excellent example of the impact of the alloreactivity in VES is offered by sinusoidal

obstruction syndrome (SOS) as its incidence correlates perfectly with the intensity of alloreactivity. Thus, a higher incidence of SOS will occur after allogeneic (versus autologous), unrelated (versus sibling), mismatched (versus matched) or unmanipulated (versus T-cell depleted) HCT [7]. Consequently, *sensu strictu*, we should not speak of VES mediated by alloreactivity but of the impact of alloreactivity on VES.

The second questionable aspect of the review article [2] is the proposal to remove SOS from VES list because “its pathogenesis is not entirely endothelial.” The question immediately arises: is there any evidence that the remaining VES are entirely endothelial? If we analyze, for example, one of the most important VES, that of TA-TMA, we can observe that in addition to the initial endothelial dysfunction, many other pathogenetic events occur: thrombus formation in microcirculation (origin of the classic manifestations of this disease); activation of antigen-presenting cells (with the possible production of antibodies against factor H and recipient-specific antibodies); overproduction of neutrophil extracellular traps that facilitate (together with some gene polymorphisms) the activation of the classical and alternative complement pathway with deposition of C4d and C5b-9 or membrane attack complex in the renal arterioles [6, 8]. Therefore, TA-TMA is also not an entirely endothelial complication. A final argument against the exclusion of SOS from the VES is to recognize the historical fact that after knowing the endothelial origin of SOS [9] and observing that other early complications of HCT had a close relationship with the microvascular tree and overlapping clinical manifestations, all these syndromes were grouped under the designation of VES [10]. Therefore, the exclusion of SOS would render the classical VES classification meaningless.

Despite it being usual to include idiopathic pneumonia syndromes (IPS) among the VES, this isn't entirely correct. Most IPS do not have a well-known/understood pathogenesis but the fact that cannot be denied is that only a small subgroup of IPS affect the vascular tree, including DAH,

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Table 1 Vascular endothelial syndromes after HCT.

Sinusoidal obstruction syndrome (SOS)
Capillary leak syndrome (CLS)
Pre-engraftment syndrome (pre-ES)
Engraftment syndrome (ES)
Transplant-associated thrombotic microangiopathy (TA-TMA)
Vascular idiopathic pneumonia syndromes:
Diffuse alveolar hemorrhage (DAH)
Capillary leak syndrome (CLS)
Peri-engraftment respiratory distress syndrome (PERDS)
Posterior reversible encephalopathy syndrome (PRES)
Acute-graft-versus-host disease (aGVHD) (provisional entity)

PERDS, and capillary leak syndrome (CLS) [5]. Consequently, the correct way of classifying these VES that affect the lungs is with the designation “Vascular IPS”.

A common origin shared between VES and acute GVHD had already been proposed several years ago. Initial observations suggested the hypothesis of vascular endothelium as a target of GVHD [11]. Nowadays, there is enough evidence indicating that endothelial damage is not only a consequence of GVHD but the possible triggering event of this complication [12]. In addition, it has been observed that angiogenesis observed in GVHD occurs exclusively in target organs and precedes leukocyte infiltration during GVHD [13]. Despite all these relationships, it is difficult to accept the sentence “VES may overlap with acute GVHD and, sometimes, the clinical distinction among these forms and GVHD can be challenging” as the clinical manifestations of GVHD differ completely, even in the hyperacute forms [14], from those observed in VES, except in some cases of intestinal TA-TMA and GVHD [15]. In fact, this observation is one of the main reasons for reluctance to include GVHD among VES, since its clinical behavior does not overlap with those of the rest of VES.

The last aspect to comment on in a manuscript dedicated to VES and its treatment is the absence of some detailed references on the protective and therapeutic effect of defibrotide on the endothelium. This agent has demonstrated its effectiveness in: treatment of severe SOS [16]; prevention of SOS and GVHD in a randomized study in children [17] (basis of the current randomized study of GVHD prevention with defibrotide ClinicalTrials.gov-NCT03339297); treatment of TA-TMA [18]; prevention and treatment of GVHD in vitro [19] and in animal models (manuscript submitted). If this effect is confirmed in the ongoing studies, we will have the first agent preventing GVHD without causing immunosuppression.

In conclusion, we propose only minor changes to the original classification of VES (see Table 1).

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Compliance with ethical standards

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