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Intestinal Thrombotic Microangiopathy After Hematopoietic Stem Cell Transplantation

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1. Introduction

Thrombotic microangiopathy (TMA) is a significant complication following hematopoietic stem-cell transplantation (HSCT), which is also described as transplant-associated microangiopathy (TAM). Endothelial injuries from multiple factors contribute to the formation of widespread platelet thrombi within the microvasculature, causing hemolytic anemia and damage to various organs(Daly *et al*, 2002a; Daly *et al*, 2002b; Nishida *et al*, 2004; Pettitt & Clark, 1994; Shimoni *et al*, 2004; Zeigler *et al*, 1996; Zeigler *et al*, 1995). Owing to the difficulty in making a definitive diagnosis of TMA in HSCT recipients, it is usually diagnosed based on clinical and laboratory findings, such as serum lactic dehydrogenase (LD) levels and the percentage of fragmented erythrocytes (Martinez *et al*, 2005; Oran *et al*, 2007; Zeigler *et al*, 1995).

However, these findings are frequently nonspecific, because they are influenced by many other clinical events. Some research group has been reported case series involving TMA with steroid-refractory diarrhea. They showed that TMA frequently involves the gastrointestinal tract in HSCT recipients (Inamoto *et al*, 2009; Narimatsu *et al*, 2005; Nishida *et al*, 2004).

The transplantation-related TMA has different clinical features and outcomes from TMA in the patients with other situations. In this chapter, I describe clinical feature and treatment of the transplantation-related TMA.

2. Classic and intestinal TMA – Clinical manifestations

The most common criteria for classic TMA diagnosis following HSCT are the signs of microangiopathic hemolysis (Martinez *et al*, 2005; Oran *et al*, 2007). On the other hand, in the patients with intestinal TMA, red cell fragmentation and serum LD elevation were usually mild or absent, and serum haptoglobin levels were detectable(Inamoto *et al*, 2009; Narimatsu *et al*, 2005; Nishida *et al*, 2004). Postmortem studies failed to find any evidence of TMA other than in the intestine(Narimatsu *et al*, 2005). Neither renal dysfunction nor neurologic abnormalities were not usually present in those patients. Based on the conventional pentad of HUS/TTP, TMA was not diagnosed in any of them in intestinal TMA. These findings suggest a difference in pathogenesis between intestinal TMA(Inamoto *et al*, 2009; Narimatsu

et al, 2005; Nishida *et al*, 2004) following HSCT and either classic TTP (Furlan *et al*, 1998) or classic TMA following HSCT(Allford *et al*, 2002; Nishida *et al*, 2004).

The differences in the observations between classic TMA and intestinal TMA can be explained by several reasons, such as the conditioning agents and patients' backgrounds. It may be also explained by following reasons. Clinicians and pathologists might not be commonly aware of TMA and could possibly have misinterpreted it as GVHD or infectious colitis. A pathological diagnosis of TMA can be difficult to make. Thrombolysis, which might occur after death, might have masked the pathological findings of TMA at autopsy (Iwata *et al*, 2001). However, those explanations failed to explain this reason. Thus, further investigation can allow a proper interpretation of the various published reports.

3. Diagnosis of intestinal TMA

Total colonoscopy from the rectum to the terminal ileum with biopsy is required for the diagnosis of intestinal TMA. The patients had focal TMA lesions of various distributions. Thus, biopsy of the rectum alone might have missed the diagnosis of TMA. Colonoscopic findings of TMA were diverse (Narimatsu *et al*, 2005). It was difficult to differentiate TMA from intestinal GVHD (Iqbal *et al*, 2000; Martin *et al*, 2004) and CMV colitis.(Meyers *et al*, 1986) Furthermore, TMA was complicated with GVHD and CMV colitis in many patients (Inamoto *et al*, 2009; Narimatsu *et al*, 2005). Macroscopic observation alone is not sufficient to make a diagnosis of TMA. Laboratory findings alone are also not useful in previous studies (Inamoto *et al*, 2009; Narimatsu *et al*, 2005; Nishida *et al*, 2004). Clinically available risk factors were also not identified in previous studies; laboratory data such as LD at the time of colonoscopy were not significantly different between patients with and without TMA. Thus, a biopsy and a pathological examination extending from the rectum to the terminal ileum are probably necessary to make a definite diagnosis in patients with diarrhea.

4. Pathological features

Suggested mechanisms on onset of intestinal TMA was shown in Figure 1; there is limited information on the pathogenesis of intestinal TMA(Inamoto *et al*, 2009; Narimatsu *et al*, 2005; Nishida *et al*, 2004). Classic TMA after myeloablative HSCT has a multifactorial etiology that includes immunosuppressive agents,(Pham *et al*, 2000; Trimarchi *et al*, 1999) total body irradiation (TBI) (Ballermann, 1998), CMV infection (Takatsuka *et al*, 2003), and acute GVHD (Ertault-Daneshpouy *et al*, 2004). These factors injure the vascular endothelium of many organs (Pettitt & Clark, 1994). In contrast, particular factors specifically affecting the gastrointestinal system are largely involved in the etiology of intestinal TMA after HSCT. It should be noted that most patients with intestinal TMA had overlapping gastrointestinal GVHD and/or CMV colitis(Narimatsu *et al*, 2005). An animal study has demonstrated that the vascular endothelium is a target of alloimmunity (Ertault-Daneshpouy *et al*, 2004). The previous report by us supports this hypothesis(Narimatsu *et al*, 2005). GVHD was associated with gastrointestinal TMA, and the association could partly explain why TMA was located in the gut. It is reasonable to assume that GVHD damages the gastrointestinal endothelium, leading to the development of intestinal TMA. Regimen-related toxicity (RRT) of the gut is known to increase the risk of intestinal GVHD.(Goldberg *et al*, 2005) Gastrointestinal damage due to preparative regimens might contribute to the development of intestinal TMA. In our

previous study, CMV infection, which is another putative etiology of TMA,(Takatsuka *et al*, 2003) was documented in 4 patients, and all were located in the gut. (Narimatsu et al, 2005) CMV colitis might be associated with intestinal TMA following HSCT.
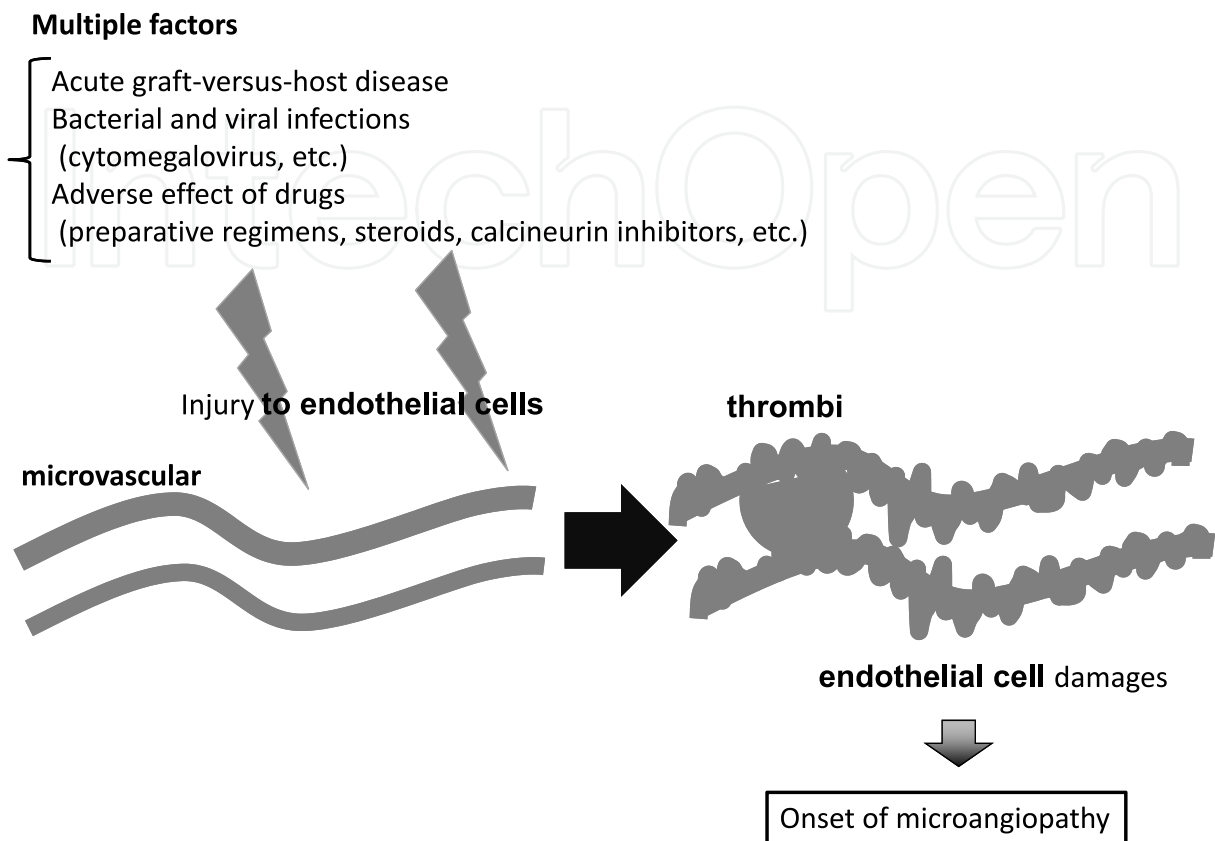
Multiple factors

Acute graft-versus-host disease
Bacterial and viral infections
 (cytomegalovirus, etc.)
Adverse effect of drugs
 (preparative regimens, steroids, calcineurin inhibitors, etc.)

Injury **to endothelial cells**   **thrombi**

microvascular

endothelial cell damages

Onset of microangiopathy

Fig. 1. Suggested mechanisms on onset of intestinal TMA

Inamoto et al presented the usefulness of Immunostainings(Inamoto *et al*, 2009). They made histopathological diagnosis of "intestinal TAM" by the presence of microangiopathy with ischemic (noninflammatory) crypt loss. Microangiopathy was confirmed by hematoxylin–eosin staining and CD34 immunostaining. The clues for endothelial injury are swollen endothelial cells and denuded endothelial cells. Ischemic changes followed by microangiopathy included individual non-inflammatory crypt degeneration with detachment and apoptosis of epithelial cells, wedge-shaped segmental injury and interstitial edema with hemorrhage or fragmented RBCs. Although, pathological definition of intestinal TMA is uncertain, these pathological findings are worth investigating.

5. Treatment

While the appropriate treatment of intestinal TMA is unknown, a published series of cases suggests that reducing the dose of immunosuppressants may be effective for intestinal TMA as well as classic TMA.(Inamoto *et al*, 2009; Nishida *et al*, 2004) On the other hand, our study group suggested that patients with intestinal GVHD and TMA could be improved without immunosuppressant reduction. This observation would indicate that the management of GVHD, rather than immunosuppressant reduction, is important in the treatment of intestinal TMA. In fact, the reduction of immunosuppressants to prevent vascular

endothelial damage would aggravate GVHD, and increase the risk of TMA progression. (Narimatsu et al, 2005) Considering these possibilities, one should be vigilant when deciding on the dose of immunosuppressant for TMA after HSCT.

The treatments used for classic TTP, such as fresh frozen plasma and plasma exchange, have been tried for TMA after bone marrow transplantation.(Allford *et al*, 2002) However, the efficacy of these treatments in patients with intestinal TMA remains unclear. Minimizing the damage to the intestinal mucosa and the vascular endothelium would be more desirable for the management of intestinal TMA than the treatments designed for classic TTP.

6. Conclusion and future direction

The intestinal TMA is a significant complication after HSCT. When transplant recipients develop refractory diarrhea, Intestinal TMA needs to be included in the differential diagnoses. However, conventional diagnostic criteria can overlook TMA. Thus, the diagnosis of intestinal TMA after HSCT requires endoscopy with biopsy.

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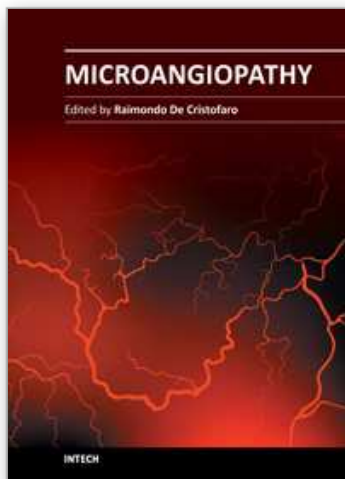
Microangiopathy

Edited by Prof. Raimondo De Cristofaro

Microangiopathies are pathological processes causing degenerative disorders of small vessels. The circulatory problems caused by microangiopathies may be responsible for failure of individual or multiple organs. These pathological processes are indeed one of the most common disorders characterized by high morbility and mortality in the affected patients. Many studies have revealed very complicated processes both at cellular and molecular level. However, much work remains to define the diversity of different pathogenetic mechanisms leading to microangiopathic disorders to provide appropriate prevention and treatment strategies. The aim of this volume is providing illustrative examples of relevant mechanisms responsible for different forms of microangiopathies and how this body of evidences can be harnessed to define new strategies of therapeutic intervention.

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