News Release

Title

Clinicopathological features of graft versus host disease-associated myositis

Key Points

•Chronic graft versus host disease (GVHD)-associated myositis targeting skeletal muscle is a relatively rare but potentially debilitating complication following allogeneic hematopoietic stem cell transplantation (HSCT).

• We reviewed the clinicopathological features of GVHD-associated myositis among patients receiving allogeneic HSCT to elucidate the cellular pathogenesis.

• In this study, these clinical and histopathological examinations reveal leukocyte and macrophage infiltration into the muscle interstitium of GVHD-associated myositis patients. These infiltrating cells express Programmed death-1 (PD-1) and are associated with elevated human leukocyte antigen (HLA)-DR and Programmed death- ligand1 (PD-L1) in adjacent myofibers.

• A similar expression pattern was found in anti-tRNA-synthetase antibody-associated myopathy (ASM) but not dermatomyositis (DM). The result suggests that these findings can aid in differential diagnosis between GVHD-associated myositis and DM.

Summary

GVHD is a potentially serious complication of organ transplantation in which immune cells from the donor organ induce an immune response in the host. In GVHD following HSCT, there may be varying degrees of damage to multiple organs, including the skin and viscera, while damage to muscle and nervous tissues is relatively rare. GVHD of the muscles, termed GVHD-associated myositis, is difficult to distinguish from other myositis based on clinicopathological features, and there is currently insufficient knowledge of the unique pathological characteristics of GVHD-associated myositis for timely diagnosis and treatment.

Expression of HLA-DR molecules in muscle tissue is a marker of inflammation used in the diagnosis of muscle pathology. In contrast to the widely used HLA-ABC, it is less sensitive. Still, it has been reported to be useful in the diagnosis of specific myositis, such as anti-tRNA synthetase (ARS)-associated myositis and inclusion body myositis. Programmed death-1 (PD-1) is expressed on immune cells and interacts with its cognate ligand, programmed death-ligand 1 (PD-L1), to provide inhibitory signals that control T cell activation. In lung and

liver tissues of GVHD patients, the PD-L1 pathway has been reported to be activated by interferon-γ (IFN-γ) to suppress immune responses. IFN-γ has also been shown to induce the expression of HLA-DR molecules in myositis tissues. However, the functions of PD-1 and IFN-γ and their associations with HLA-DR have yet to be elucidated in GVHD-associated myositis.

Research Background

Chronic graft versus host disease (GVHD)-associated myositis targeting skeletal muscle is a relatively rare but potentially debilitating complication following allogeneic hematopoietic stem cell transplantation (HSCT). We reviewed the clinicopathological features of GVHD-associated myositis among patients receiving allogeneic HSCT to elucidate the cellular pathogenesis.

Methods

We retrospectively reviewed clinical data and muscle biopsy results from 17 consecutive patients diagnosed with GVHD-associated myositis at our institution between 1995 and 2019. Immunostaining findings of GVHD-associated myositis were compared to those of patients with anti-tRNA-synthetase antibody-associated myopathy (ASM) (n =13) and dermatomyositis (DM) (n = 12).

Research Results

The majority of patients with GVHD-associated myositis exhibited subacute or chronic progression of mild to moderate limb weakness. The clinical course was benign in all patients, and myositis was not a direct cause of death in any case. In pathology, the degree of inflammation varied from relatively few necrotic fibers and infiltrating cells to numerous infiltrating cells and connective tissue growth areas observed in some muscle bundles. Cells positive for PD-1 infiltrated within the endomysium were colocalized with the HLA-DR-positive interstitium and PD-L1 immunoreactivity was detected in PD-1- and HLA-DR-positive interstitium (Figure 1).

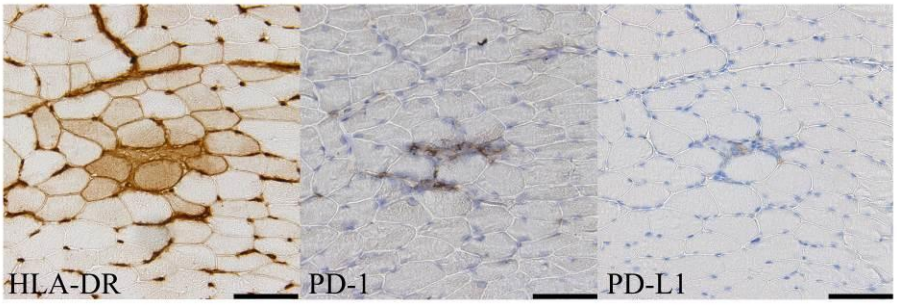

Figure 1. Pathology of GVHD-associated myositis

Next, we compared the histopathological findings of GVHD-associated myositis to anti-tRNA-synthetase antibody-associated myopathy (ASM) and dermatomyositis (DM). Similar to GVHD-associated myositis, the muscle specimens from ASM patients also demonstrated PD-1-positive cells colocalized with HLA-DR-positive interstitium. By contrast, PD-1-positive cells and HLA-DR-positive interstitium were less frequently observed in DM, though perifascicular myofibers in DM were often positive for HLA-DR without adjacent interstitium proliferation or PD-1-positive cells (Figure 2).

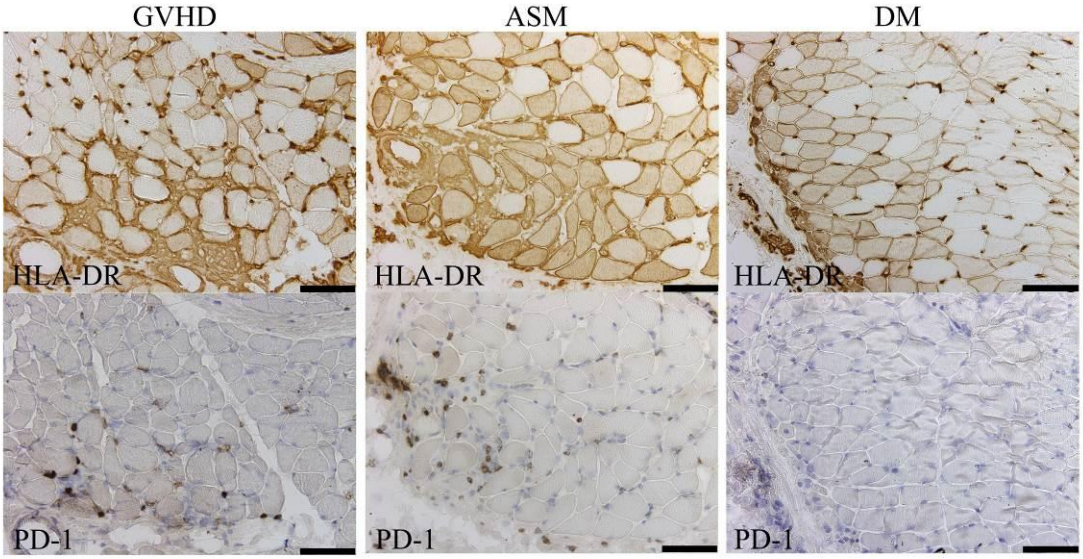

Figure 2. Differences in histopathological features among GVHD-associated myositis, ASM, and DM

The proportion of HLA-DR-positive myofibers was higher in GVHD and ASM than in DM (Figure 3A), and the number of PD-1-positive cells infiltrating into muscle bundles was also significantly larger in GVHD and ASM than in DM (Figure 3B).

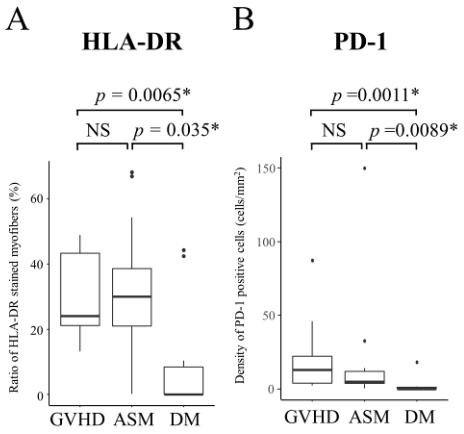

Figure 3. The proportion of HLA-DR-positive myofibers and the density of PD-1-positive cells in each disorder

Research Summary and Future Perspective

The results of this study aid in the differential diagnosis of GVHD-associated myositis and suggest a pathophysiologic link between GVHD-associated myositis and ASM. In the future, we would like to analyze the IFN-γ expression and related molecules using genetic analysis to elucidate these mechanisms.

Publication

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